テセントリク点滴静注1200mg
に関する資料

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目次

1.5 起原又は発見の経緯及び開発の経緯 2

図一覧

図 1.5-1 開発の経緯図 2

1.5 起原又は発見の経緯及び開発の経緯

起原又は発見の経緯及び開発の経緯については2.5項に記載した。開発の経緯図は図 1.5-1に示す。

図 1.5-1 開発の経緯図

試験項目		国内	海外	試験の内容	2022	2023	2024	2025
	第II相	○		JTD2101	⑥			*

図中の算用数字は当該試験の開始月または終了月

*試験継続中

目次

1.6 外国における使用状況等に関する資料 2
1.6.1 外国における承認申請状況 2
1.6.2 代表的な添付文書の和訳概要 2
1.6.2.1 米国添付文書の和訳概要 2
1.6.2.2 欧州添付文書の和訳概要 6
1.6.3 米国における添付文書 15
1.6.4 欧州における添付文書 87
1.6.5 Core Data Sheet 260

1.6 外国における使用状況等に関する資料

1.6.1 外国における承認申請状況

2025年5月時点で，テセントリク点滴静注1200mg は非小細胞肺癌，尿路上皮癌，小細胞肺癌，乳癌，肝細胞癌，胞巣状軟部肉腫，節外性 NK/T 細胞リンパ腫・鼻型のいずれかに対して，欧米を含む世界125カ国で承認を取得している。

胸腺癌に対しては，2025年8月時点で，承認を取得している国又は地域はない。

テセントリク点滴静注の代表的な外国添付文書として，米国添付文書及び欧州添付文書の和訳の概要を1.6.2に示し，米国添付文書の原文，欧州添付文書の原文及びテセントリク点滴静注の企業中核データシート（Core Data Sheet）をそれぞれ1.6.3，1.6.4及び1.6.5に添付する。

1.6.2 代表的な添付文書の和訳概要

1.6.2.1 米国添付文書の和訳概要

テセントリク点滴静注の代表的な外国添付文書として，米国の添付文書（2025年10月版）の和訳概要を以下に示す。

1 効能・効果

1.1 非小細胞肺癌

- テセントリクは，単剤として，切除及びプラチナベース化学療法施行後の術後補助療法として，ステージ II から IIIA*[臨床試験（14.1）を参照]*であり，FDA 承認検査で特定される PD-L1発現が腫瘍細胞の1%以上で認められる非小細胞肺癌（NSCLC）成人患者を適応とする*[用法・用量（2.1）を参照]*。
- テセントリクは，単剤として，腫瘍の EGFR 及び ALK 遺伝子に異常がなく，FDA 承認検査で特定される PD-L1高発現（腫瘍細胞の50%以上が染色される[TC≥50%]又は染色される腫瘍浸潤免疫細胞[IC]が腫瘍領域の10%以上を占める[IC≥10%]）の化学療法未治療の転移性 NSCLC 成人患者を適応とする*[用法・用量（2.1）を参照]*。
- テセントリクは，腫瘍の EGFR 及び ALK 遺伝子に異常のない転移性非扁平上皮 NSCLC 成人患者に対する1次治療としての，ベバシズマブ，パクリタキセル及びカルボプラチンとの併用療法を適応とする。
- テセントリクは，腫瘍の EGFR 及び ALK 遺伝子に異常のない転移性非扁平上皮 NSCLC 成人患者に対する1次治療としての，nab-パクリタキセル，カルボプラチンとの併用療法を適応とする。
- テセントリクは，単剤として，白金製剤を含む化学療法の施行中又は施行後に病勢進行に至った転移性 NSCLC 成人患者を適応とする。腫瘍の EGFR 又は ALK 遺伝子に異常がある場合は，これら異常を有する NSCLC に対して FDA が承認した治療がテセントリクの投与前に施行され，その施行下で病勢進行に至った患者であること。

1.2 小細胞肺癌

- テセントリクは進展型小細胞肺癌（ES-SCLC）の成人患者に対する1次治療としての，カルボプラチン及びエトポシドとの併用療法を適応とする。
- テセントリクはテセントリクまたはアテゾリズマブおよびヒアルロニダーゼ-tqjs、カルボプラチンおよびエトポシドによる一次治療導入療法後に疾患が進行していない ES-SCLC の成人患者に対する維持治療としての，ルルビネクテジンとの併用療法を適応とする。

1.3 肝細胞癌

テセントリクは全身化学療法未治療の切除不能又は転移性肝細胞癌（HCC）の成人患者に対

するベバシズマブとの併用療法を適応とする。

1.4 悪性黒色腫

テセントリクはBRAF V600変異陽性の切除不能又は転移性悪性黒色腫の成人患者に対するコビメチニブとベムラフェニブの併用療法を適応とする*［用法・用量（2.1）を参照］*。

1.5 胞巣状軟部肉腫

テセントリクは，単剤として，切除不能又は転移性胞巣状軟部肉腫（ASPS）の2歳以上の小児及び成人患者を適応とする。

2 用量・用法

2.1 非小細胞肺癌及び悪性黒色腫の治療に対する患者の選択

腫瘍細胞における PD-L1発現レベルに基づき，ステージ II から IIIA の非小細胞肺癌の治療として，テセントリクの投与対象として選択する*［臨床試験（14.1）を参照］*。

腫瘍細胞又は腫瘍浸潤免疫細胞における PD-L1発現レベルに基づき，非小細胞肺癌患者の一次治療として，テセントリクの投与対象として選択する*［臨床試験（14.1）を参照］*。

FDA が承認した，転移性非小細胞肺癌における PD-L1の発現を調べる検査法の情報は，http://www.fda.gov/CcompanionDiagnostics で提供されている。

BRAF V600変異に基づき，テセントリクとコビメチニブ及びベムラフェニブの併用療法を切除不能又は転移性悪性黒色腫患者に対して選択する*［臨床試験（14.4）を参照］*。FDA が承認した悪性黒色腫における BRAF V600変異を調べる検査法の情報は，http://www.fda.gov/CompanionDiagnostics で提供されている。

2.2 推奨用量

単剤療法としてのテセントリク静脈内投与の推奨用量を表1に示す。

表1：単剤療法としてのテセントリクの推奨用量

適応症	テセントリクの推奨投与量*	治療継続期間
転移性 NSCLC	840mg を2週間間隔　又は 1200mg を3週間間隔　又は 1680mg を4週間間隔	病勢進行に至るまで，又は許容できない毒性が発現するまで
NSCLC の術後補助療法	840mg を2週間間隔　又は 1200mg を3週間間隔　又は 1680mg を4週間間隔	疾患の再発又は許容できない毒性が発生しない限り，1年まで
ASPS（成人）	840mg を2週間間隔　又は 1200mg を3週間間隔　又は 1680mg を4週間間隔	病勢進行に至るまで，又は許容できない毒性が発現するまで
ASPS（2歳以上の小児）	15mg/kg（1200mg を上限）を3週間間隔	

*60分間かけて点滴静注する。初回投与の忍容性に問題がなければ，その後は全ての投与を30分間で行っても良い。

他剤との併用療法としてのテセントリクの推奨静注投与用量を表2に示す。テセントリクと併用で使用される各治療薬の推奨用量は，必要に応じてそれぞれの処方情報を参照すること。

表2：他剤との併用療法としてのテセントリクの推奨用量

適応症	テセントリクの推奨投与量*	治療継続期間
NSCLC	840mg を2週間間隔　又は 1200mg を3週間間隔　又は 1680mg を4週間間隔 同日に投与する際には化学療法やベバシズマブの前にテセントリクを投与する。	病勢進行に至るまで，又は許容できない毒性が発現するまで
SCLC	840mg を2週間間隔　又は 1200mg を3週間間隔　又は 1680mg を4週間間隔 同日に投与する際には化学療法の前にテセントリクを投与する。	
HCC	840mg を2週間間隔　又は 1200mg を3週間間隔　又は 1680mg を4週間間隔 同日に投与する際にはベバシズマブの前にテセントリクを投与する。 ベバシズマブは15mg/kg を3週間隔で投与する。	
悪性黒色腫	840mg を2週間間隔　又は 1200mg を3週間間隔　又は 1680mg を4週間間隔 テセントリクと共にコビメチニブは60mg を1日1回経口投与（21日間投与したのち7日間休薬）し，ベムラフェニブは720mg を1日2回経口投与する。 テセントリクの初回投与前に，患者はコビメチニブ60mg を1日1回経口投与（21日間投与したのち7日間休薬）し，ベムラフェニブ960mg を1~21日目は1日2回経口投与し，22~28日目は720mg を1日2回経口投与する28日サイクルの治療を受けなければならない。	

*60分間かけて点滴静注する。初回投与の忍容性に問題がなければ，その後は全ての投与を30分間で行っても良い。

2.3 副作用に対する用量の変更

テセントリクの用量減量は推奨されない。一般的に，重症な（Grade 3）免疫関連事象についてはテセントリクを休薬する。生命を脅かす（Grade 4）免疫関連事象，全身性免疫抑制治療を必要とする再発性の重症な（Grade 3）免疫関連事象，又はステロイドを開始してから12週以内に副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量できない場合にはテセントリクの投与を永久に中止する。

これらの一般的なガイドラインと異なる管理を必要とするテセントリクの副作用に対する用量の変更は表3に示す。

表3：副作用発現時に推奨される用量変更の方法

副作用	重症度 [a]	用量変更
免疫介在性の副作用 *［警告及び使用上の注意（5.1）参照］*		
肺臓炎	Grade 2	休薬する [b]
	Grade 3又は4	投与を永久に中止する
大腸炎	Grade 2又は3	休薬する [b]
	Grade 4	投与を永久に中止する

副作用	重症度 [a]	用量変更
免疫介在性の副作用 *［警告及び使用上の注意（5.1）参照］*		
肝臓に腫瘍病変がない肝炎	AST若しくはALTがULNの3倍超かつ8倍以下 又は 総ビリルビンが ULN の1.5倍超かつ3倍以下の増加	休薬する [b]
	AST若しくはALTがULNの8倍超 又は 総ビリルビンが ULN の3倍超に増加	投与を永久に中止する
肝臓に腫瘍病変を有する肝炎 [c]	ベースラインの AST 若しくは ALT が ULN の1倍超かつ3倍以下であり，ULNの5倍超かつ10倍以下に増加 又は ベースラインの AST 若しくは ALT が ULN の3倍超かつ5倍以下であり，ULNの8倍超かつ10倍以下に増加の場合	休薬する [b]
	AST若しくはALTがULNの10倍超 又は 総ビリルビンが ULN の3倍超に増加の場合	投与を永久に中止する
内分泌障害	Grade 3又は4	重症度に応じて，臨床的に安定するまで休薬する又は投与を永久に中止する
腎機能障害を伴う腎炎	血中クレアチニン増加を伴う Grade 2又は Grade 3	休薬する [b]
	血中クレアチニン増加を伴う Grade 4	投与を永久に中止する
剥離性皮膚症状	SJS，TEN 又は DRESS の疑い	休薬する
	SJS，TEN，DRESS の確定診断	投与を永久に中止する
心筋炎又は心膜炎	Grade 2，3又は4	投与を永久に中止する
神経毒性	Grade 2	休薬する [b]
	Grade 3又は4	投与を永久に中止する
その他の副作用		
Infusion-Related Reaction *［警告及び使用上の注意（5.2）参照］*	Grade 1又は2	投与を中断するか，点滴速度を遅らせる
	Grade 3又は4	投与を永久に中止する

[a] 有害事象共通用語規準（CTCAE）第4.0版に基づく。

[b] 副腎皮質ステロイドの漸減後，完全又は部分的な回復（Grade 0から1）した患者で再開する。ステロイドを開始してから12週以内に完全又は部分的な回復が認められない又は，ステロイドを開始してから12週以内にプレドニゾン1日10mg 相当以下に減量できない場合にはテセントリクの投与を永久に中止する。

[c] ベースラインの AST 若しくは ALT が ULN より低い又は同等の場合，肝臓に病変のない肝炎に対する推奨に基づきテセントリクを休薬又は投与を永久に中止する。

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal（基準値上限）, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms（薬物性過敏症症候群）, SJS = Stevens Johnson syndrome（スティーブンス・ジョンソン症候群）, TEN = toxic epidermal necrolysis（中毒性表皮壊死症）

2.4 調製及び投与

調製

溶液及び容器を可能な限り，投与前に微粒子や変色がないかどうか製剤を目視検査する。溶液が濁っている，変色している，又は可視的微粒子が認められる場合，そのバイアルは廃棄すること。バイアルを振り混ぜないこと。

輸液は次の通り調製する：

- 処方する用量に基づいて，適切なバイアルを選択する。
- 滅菌針と注射器を使用してバイアルから必要量のテセントリクを抜き取る。
- 最終濃度が3.2mg/ml から16.8mg/ml の間になる様，USP に準拠した注射用0.9%塩化ナトリウム輸液バッグ[ポリ塩化ビニル（PVC），ポリエチレン（PE）又はポリオレフィン（PO）製]に注入し，希釈する。
- 希釈は USP に準拠した注射用0.9%塩化ナトリウム以外で行わないこと。
- バッグを静かに反転させて混合する。振り混ぜないこと。
- 使用した，又は空のテセントリクのバイアルは廃棄する。

輸液の保存

本剤に保存剤は添加されていない。

調製後は直ちに投与すること。希釈後のテセントリク輸液をすぐ使用しない場合は，次のいずれかの条件で保存できる。

- 室温保存する場合は，調製時点から6時間までとする。この時間には，輸液バッグでの室温保存時間と点滴投与時間が含まれる。
- 2℃～8℃（36°F～46°F）で冷蔵保存する場合は，調製時点から24時間までとする。

凍結させないこと。

振り混ぜないこと。

投与

初回投与は60分間をかけて点滴静脈内投与する。静注ラインには，発熱物質不含で蛋白結合性の低い滅菌インラインフィルター（孔径0.2～0.22μm）を使用すること。初回投与の忍容性が良好であれば，その後の全て投与を30分間で行ってよい。

同じ静注ラインで他剤を同時に投与しないこと。

静脈内大量投与や急速静脈内投与は行わないこと。

1.6.2.2 欧州添付文書の和訳概要

テセントリク点滴静注の代表的な外国添付文書として，欧州の添付文書（2025年6月版）の和訳概要を以下に示す。

4. 臨床関連事項

4.1 適応症

尿路上皮癌（UC）

テセントリク単剤療法は，局所進行又は転移性 UC の成人患者の内，以下の患者を適応とする。

- 白金製剤を含む化学療法の施行歴がある。又は
- シスプラチン不適と考えられ，かつ，腫瘍に PD-L1の発現（≧5%）を認める（5.1項参照）。

早期非小細胞肺癌（NSCLC）
テセントリク単剤療法は，完全切除及びプラチナベース化学療法施行後の術後補助療法として，腫瘍における PD-L1発現が50%以上の腫瘍細胞（TC）を有し，かつ EGFR 遺伝子変異又は ALK 融合遺伝子の変異を持たない再発リスクの高い NSCLC の成人患者に適応される（選択基準は5.1項参照）。

進行性 NSCLC
テセントリクは，ベバシズマブ，パクリタキセル，カルボプラチンとの併用で，転移性非扁平上皮 NSCLC 一次治療の成人患者に適応される。EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性の NSCLC 患者では，ベバシズマブ，パクリタキセル，カルボプラチンと併用するテセントリクは，適切な分子標的治療に増悪した後にのみ適応となる（5.1項参照）。

テセントリクは, nab-パクリタキセル, カルボプラチンとの併用で, EGFR 遺伝子変異又は ALK 融合遺伝子の変異を持たない転移性非扁平上皮 NSCLC 一次治療の成人患者に適応される（5.1項参照）。

テセントリク単剤療法は，腫瘍における PD-L1発現が50%以上の TC 又は10%以上の腫瘍浸潤免疫細胞（IC）を有し，かつ EGFR 遺伝子変異又は ALK 融合遺伝子の変異を持たない転移性 NSCLC 一次治療の成人患者に適応される（5.1項参照）。

テセントリク単剤療法は，プラチナ製剤による治療が適応とならない進行性非小細胞肺癌の一次治療の成人患者に適応される（選択基準は5.1項参照）。

テセントリク単剤療法は，化学療法後の局所進行性又は転移性 NSCLC の成人患者の治療に適応される。EGFR 遺伝子変異陽性又は ALK 融合遺伝子陽性の NSCLC の患者も，テセントリクによる治療を受ける前に標的療法を受けている必要がある（5.1項参照）。

小細胞肺癌（SCLC）
テセントリクは，カルボプラチン，エトポシドとの併用で，進展型小細胞肺癌（ES-SCLC）一次治療の成人患者に適応される（5.1項参照）。

トリプルネガティブ乳癌（TNBC）
テセントリクは，nab-パクリタキセルとの併用で，切除不能な局所進行又は転移性 TNBC の治療で，PD-L1発現（≧1%）が認められ，転移性疾患に対する化学療法の施行歴がない成人患者に適応される。

肝細胞癌（HCC）
テセントリクは，ベバシズマブとの併用で，全身化学療法未治療の進行又は切除不能な HCC の成人患者に適応される（5.1項参照）。

4.2 用法・用量

テセントリク投与は，癌治療の経験豊富な医師が開始し，監督しなければならない。

UC 患者，TNBC 患者，又は NSCLC 患者に対する PD-L1検査
単剤療法におけるテセントリク

適応症に明記されている場合，腫瘍の PD-L1発現レベルに基づいて患者を選択する際は、バリデートされた検査によって確認すること（4.1項及び5.1項参照）。

併用療法におけるテセントリク

未治療の TNBC 患者の場合，バリデートされた検査法で確認した腫瘍の PD-L1発現レベルに基づき，投与すべき患者を選択する（5.1項参照）。

用量

テセントリクの推奨用量としては，表1で示されるように，840 mg の2週間間隔での静脈内投与，1200 mg の3週間間隔での静脈内投与，又は1680mg の4週間間隔での静脈内投与である。

併用療法においてテセントリクを投与する場合には，併用薬の全処方情報も参照すること（5.1項参照）。

表1：推奨されるテセントリクの静脈内投与量

適応症	推奨投与量とスケジュール	治療継続期間
テセントリク単剤療法		
1L UC 1L 転移性 NSCLC 1L プラチナ製剤不適格の NSCLC	• 840mg を 2 週間間隔又は • 1200mg を 3 週間間隔又は • 1680mg を 4 週間間隔	病勢進行，又は管理できない毒性が発現するまで
早期 NSCLC	• 840mg を 2 週間間隔又は • 1200mg を 3 週間間隔又は • 1680mg を 4 週間間隔	病勢進行，又は管理できない毒性が発現しない限り1年まで。1年以上の治療期間については検証されていない。
2L UC 2L NSCLC	• 840mg を 2 週間間隔又は • 1200mg を 3 週間間隔又は • 1680mg を 4 週間間隔	臨床的有用性がなくなるまで，又は管理できない毒性が発現するまで
テセントリク併用療法		
1L 非扁平上皮 NSCLC，ベバシズマブ，パクリタキセル，カルボプラチンとの併用	導入及び維持期： • 840mg を 2 週間間隔又は • 1200mg を 3 週間間隔又は • 1680mg を 4 週間間隔 同日に投与する場合にはテセントリクをはじめに投与すること。 併用薬の導入期（4又は6サイクル）： ベバシズマブ，パクリタキセル，そしてカルボプラチンは3週間間隔で投与すること。 維持期（化学療法なし）： ベバシズマブ3週間間隔。	病勢進行，又は管理できない毒性が発現するまで。非定型反応（すなわち，初期の疾患進行とそれに続く腫瘍縮小）が，疾患進行後の継続的なテセントリク治療で観察されている。疾患の進行以降の治療については，医師の裁量で考慮される。
1L 非扁平上皮 NSCLC，nab-パクリタキセル，カルボプラチンとの併用	導入及び維持期： • 840mg を 2 週間間隔又は • 1200mg を 3 週間間隔又は • 1680mg を 4 週間間隔	病勢進行，又は管理できない毒性が発現するまで。非定型反応（すなわち，初期の疾患進行とそれに続く腫瘍縮小）が，疾患進行後の継続的なテセントリク治療で観察されている。疾患の

適応症	推奨投与量とスケジュール	治療継続期間
	同日に投与する場合にはテセントリクをはじめに投与すること。 併用薬の導入期（4又は6サイクル）： nab-パクリタキセル，そしてカルボプラチンを1日目に投与すること；加えてnab-パクリタキセルを3週サイクルの8，15日目に投与すること。	進行以降の治療については，医師の裁量で考慮される。
1L ES-SCLC，カルボプラチンとエトポシドとの併用	導入及び維持期： • 840mgを2週間間隔又は • 1200mgを3週間間隔又は • 1680mgを4週間間隔 同日に投与する場合にはテセントリクをはじめに投与すること。 併用薬の導入期（4サイクル）： カルボプラチン，そしてエトポシドを1日目に投与すること；加えてエトポシドを3週サイクルの2，3日目に投与すること。	病勢進行，又は管理できない毒性が発現するまで。非定型反応（すなわち，初期の疾患進行とそれに続く腫瘍縮小）が，疾患進行後の継続的なテセントリク治療で観察されている。疾患の進行以降の治療については，医師の裁量で考慮される。
1L 切除不能な局所進行又は転移性 TNBC，nab-パクリタキセルとの併用	• 840mgを2週間間隔又は • 1200mgを3週間間隔又は • 1680mgを4週間間隔 同日に投与する場合にはnab-パクリタキセルの前にテセントリクを投与すること。nab-パクリタキセルは100 mg/m^{2}を28日サイクルの1，8，15日目に投与すること。	病勢進行，又は管理できない毒性が発現するまで。
進行又は切除不能な HCC，ベバシズマブとの併用	• 840mgを2週間間隔又は • 1200mgを3週間間隔又は • 1680mgを4週間間隔 同日に投与する場合にはベバシズマブの前にテセントリクを投与すること。ベバシズマブは15mg/kg body weight (bw)を3週間間隔で投与すること。	臨床的有用性がなくなるまで，又は管理できない毒性が発現するまで

投与が遅れた場合又は投与を忘れた場合

予定したテセントリク投与を忘れた場合，忘れた分は可及的速やかに投与する。適切な投与間隔が維持されるよう，投与スケジュールを調節しなければならない。

投与中の用量調節

テセントリクの用量減量は推奨されない。

投与の延期又は中止（4.4項及び4.8項も参照）

表2：推奨されるテセントリクの用量調節法

免疫関連副作用	重症度	投与の調節
肺臓炎	Grade 2	テセントリクの投与を保留 当該事象が12週以内に Grade 0 又は Grade 1に改善され，副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量されたら，投与を再開して差し支えない。
	Grade 3又は4	テセントリクの投与を永続的に中止
肝炎（HCC 患者を除く）	Grade 2： （ALT 又は AST > 3～5×基準値上限 [ULN] *又は* 血中ビリルビン> 1.5～3×ULN）	テセントリクの投与を保留 当該事象が12週以内に Grade 0 又は Grade 1に改善され，副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量されたら，投与を再開して差し支えない。
	Grade 3又は4： （ALT 又は AST > 5×ULN *又は* 血中ビリルビン> 3×ULN）	テセントリクの投与を永続的に中止
肝炎（HCC 患者）	ベースライン時は AST/ALT が基準値内の患者で，基準値上限の3倍超かつ10倍以下に増加した場合 又は ベースライン時は AST/ALT が基準値上限の1倍超かつ3倍以下の患者で，基準値上限の5倍超かつ10倍以下に増加した場合 又は ベースライン時は AST/ALT が基準値上限の3倍超かつ5倍以下の患者で，基準値上限の8倍超かつ10倍以下に増加した場合	テセントリクの投与を保留 当該事象が12週以内に Grade 0 又は Grade 1に改善され，副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量されたら，投与を再開して差し支えない。
	AST/ALT が基準値上限の10倍超に増加した場合 又は 総ビリルビンが基準値上限の3倍超に増加した場合	テセントリクの投与を永続的に中止
大腸炎	Grade 2又は3の下痢（1日あたり排	テセントリクの投与を保留

免疫関連副作用	重症度	投与の調節
	便回数のベースラインから4回以上の増加） *又は* 症候性大腸炎	当該事象が12週以内に Grade 0又は Grade 1に改善され, 副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量されたら，投与を再開して差し支えない。
	Grade 4の下痢又は大腸炎（生命を脅かすもの，緊急介入の適応）	テセントリクの投与を永続的に中止
甲状腺機能低下症又は甲状腺機能亢進症	症候性	テセントリクの投与を保留 *甲状腺機能低下症：* 症状が甲状腺補充療法によりコントロールされ TSH 値が低下したら，投与を再開して差し支えない。 *甲状腺機能亢進症：* 症状が抗甲状腺薬によりコントロールされ甲状腺機能が改善されたら，投与を再開して差し支えない。
副腎機能不全	症候性	テセントリクの投与を保留 症状が12週以内に Grade 0又は Grade 1に改善され，副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量され, 補充療法で患者が安定化したら，投与を再開して差し支えない。
下垂体炎	Grade 2又は3	テセントリクの投与を保留 症状が12週以内に Grade 0又は Grade 1に改善され，副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量され, 補充療法で患者が安定化したら，投与を再開して差し支えない。
	Grade 4	テセントリクの投与を永続的に中止
1型糖尿病	Grade 3又は4の高血糖（空腹時血糖 値> 250 mg/dL 又は 13.9 mmol/L）	テセントリクの投与を保留 インスリン補充療法で代謝コントロールが達成されたら投与を再開して差し支えない。
発疹/重大な皮膚の副作用	Grade 3 又はスティーブンス・ジョンソン症候群（SJS），中毒性表皮壊死症	テセントリクの投与を保留 症状が12週以内に Grade 0又は

免疫関連副作用	重症度	投与の調節
	（TEN）[1]の疑い	Grade 1に改善され，副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量された場合，投与を再開して差し支えない。
	Grade 4 又はスティーブンス・ジョンソン症候群（SJS），中毒性表皮壊死症（TEN）[1]の確定診断	テセントリクの投与を永続的に中止
筋無力症候群/重症筋無力症, ギラン・バレー症候群, 髄膜脳炎及び顔面不全麻痺	Grade 1又は2の顔面不全麻痺	テセントリクの投与を保留 症状が完全に回復した場合，投与を再開して差し支えない。テセントリクの投与を保留しても症状が完全に回復しない場合は，テセントリクの投与を永続的に中止する。
	全 Grade の筋無力症候群/重症筋無力症，ギラン・バレー症候群及び髄膜脳炎 又は Grade 3又は4の顔面不全麻痺	テセントリクの投与を永続的に中止
脊髄炎	Grade 2，3又は4	テセントリクの投与を永続的に中止
膵炎	Grade 3又は4の血清アミラーゼ又はリパーゼ増加（> 2×ULN） 又は Grade 2又は3の膵炎	テセントリクの投与を保留 血清アミラーゼ値とリパーゼ値が12週以内に Grade 0又は Grade 1に改善され, 又は膵炎症状が消失し，かつ副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量されたら，投与を再開して差し支えない。
	Grade 4又は再発性膵炎（Grade を問わない）	テセントリクの投与を永続的に中止
心筋炎	Grade 2以上	テセントリクの投与を永続的に中止
腎炎	Grade 2： （クレアチニン値＞1.5～3.0×ベースライン又は＞1.5～3.0×ULN）	テセントリクの投与を保留 当該事象が12週間以内に Grade 0又は Grade 1に改善され，副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量されたら，投与を再開して差し支えない
	Grade 3又は4： （クレアチニン値＞3.0×ベースライン又は＞3.0×ULN）	テセントリクの投与を永続的に中止

免疫関連副作用	重症度	投与の調節
筋炎	Grade 2又は3	テセントリクの投与を保留
	Grade 4又は再発性筋炎での Grade 3	テセントリクの投与を永続的に中止
心膜障害	Grade1の心膜炎	テセントリクの投与を保留[2]
	Grade2以上	テセントリクの投与を永続的に中止
血球貪食性リンパ組織球症	血球貪食性リンパ組織球症疑い[1]	テセントリクの投与を永続的に中止
その他の免疫関連副作用	Grade 2又は3	副作用が12週以内に Grade 0～1に回復し，副腎皮質ステロイドがプレドニゾン1日10mg 相当以下に減量されるまで投与を保留。
	Grade 4又は再発性の Grade 3	テセントリクの投与を永続的に中止（ホルモン補充療法でコントロールされた内分泌障害を除く）
その他の副作用	**重症度**	**投与の調節**
Infusion-related reactions	Grade 1又は2	点滴速度を遅らせる，又は投与を中断する。事象が消失したら投与を再開して差し支えない。
	Grade 3又は4	テセントリクの投与を永続的に中止

ALT = アラニンアミノトランスフェラーゼ; AST = アスパラギン酸アミノトランスフェラーゼ; ULN = 基準値上限.
注：毒性の Grade は米国国立がん研究所の有害事象共通用語規準（NCI-CTCAE）の現行版に従う。
[1]重症度にかかわらず
[2]詳細な心機能評価を実施して原因を特定し，適切に管理する

特別な集団

小児患者

小児及び18歳未満の青年におけるテセントリクの安全性と有効性は確立されていない。現在入手可能なデータはセクション4.8，5.1，および5.2で説明されているが，推奨用量の設定はない。

高齢者

母集団薬物動態解析に基づき，65歳以上の患者でテセントリクの用量調節の必要はない（4.8項，5.1項参照）。

アジア人の患者

IMpower150試験におけるアジア人患者で認められた血液毒性増加のために，パクリタキセルの開始用量は3週間ごとに175mg/m^{2}を投与することが推奨される。

腎機能障害

母集団薬物動態解析に基づき，軽度及び中等度腎機能障害患者で用量調節の必要はない（5.2項参照）。重度腎機能障害患者については，データが限られているため結論を導くことはできない。

肝障害

母集団薬物動態解析に基づき，軽度又は中等度肝障害患者で用量調節の必要はない。重度肝障害患者を対象とした試験は行われていない（5.2項参照）。

Eastern Cooperative Oncology Group（ECOG）全身状態（PS）2以上

ECOG PS 2以上の患者は，TNBC，ES-SCLC，UC の二次治療及び HCC に対する臨床試験から除外された（4.4項及び5.1項参照）。

投与方法

製品ラベルを確認し，正しい製剤（点滴静注又は皮下注）が処方通りに患者に投与されていることを確認することが重要である。

テセントリク点滴静注は皮下投与を目的としていないため，点滴静脈内投与のみで使用すること。静脈内注射やボーラス投与を行ってはならない。

現在テセントリク点滴静注の投与を受けている患者は、アテゾリズマブ皮下注に切り替えることができ、その逆も可能である。

テセントリク点滴静注の初回投与は60分かけて行わなければならない。初回投与の忍容性に問題がなければ，その後の点滴投与は全て30分で行って差し支えない。

投与前の製剤の希釈及び取り扱い方法については，6.6項を参照。

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TECENTRIQ safely and effectively. See full prescribing information for TECENTRIQ.

TECENTRIQ® (atezolizumab) injection, for intravenous use
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Warnings and Precautions (5.2)	08/2025
Indications and Usage (1.2)	10/2025

INDICATIONS AND USAGE

TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated:

Non-Small Cell Lung Cancer (NSCLC)

- as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test. (1.1, 14.1)
- for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. (1.1)
- in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. (1.1)
- in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations (1.1)
- for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ. (1.1)

Small Cell Lung Cancer (SCLC)

- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). (1.2)
- in combination with lurbinectedin, for the maintenance treatment of adult patients with ES-SCLC whose disease has not progressed after first-line induction therapy with TECENTRIQ or atezolizumab and hyaluronidase-tqjs, carboplatin and etoposide. (1.2)

Hepatocellular Carcinoma (HCC)

- in combination with bevacizumab for the treatment of adult patients with unresectable or metastatic HCC who have not received prior systemic therapy. (1.3)

Melanoma

- in combination with cobimetinib and vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. (1.4)

Alveolar Soft Part Sarcoma (ASPS)

- for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS. (1.5)

DOSAGE AND ADMINISTRATION

Administer TECENTRIQ intravenously over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

NSCLC

- In the adjuvant setting, administer TECENTRIQ following resection and up to 4 cycles of platinum-based chemotherapy as 840 mg every 2 weeks, 1200 mg every 3 weeks or 1680 mg every 4 weeks for up to 1 year. (2.2)
- In the metastatic setting, administer TECENTRIQ as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. (2.2)
- When administering with chemotherapy with or without bevacizumab, administer TECENTRIQ prior to chemotherapy and bevacizumab when given on the same day. (2.2)

Small Cell Lung Cancer

- Administer TECENTRIQ as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. Administer TECENTRIQ prior to chemotherapy when given on the same day. (2.2)

Hepatocellular Carcinoma

- Administer TECENTRIQ as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. Administer TECENTRIQ prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg every 3 weeks. (2.2)

Melanoma

- Following completion of a 28-day cycle of cobimetinib and vemurafenib, administer TECENTRIQ 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks with cobimetinib 60 mg orally once daily (21 days on /7 days off) and vemurafenib 720 mg orally twice daily. (2.2)

ASPS

- Adults: Administer TECENTRIQ as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. (2.2)
- Pediatric patients 2 years of age and older: 15 mg/kg (up to a maximum of 1200 mg), every 3 weeks (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Mediated Adverse Reactions
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection. (5.1)
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. (5.1)
  - Withhold or permanently discontinue based on severity and type of reaction. (5.1).
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of infusion reactions. (5.2)
- Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

TECENTRIQ as a single-agent

- Most common adverse reactions (≥ 20%) with TECENTRIQ as a single-agent are fatigue/asthenia, decreased appetite, nausea, cough, and dyspnea. (6.1)

TECENTRIQ in combination with other antineoplastic drugs

- Most common adverse reactions (≥ 20%) in patients with NSCLC and SCLC are fatigue/asthenia, nausea, alopecia, constipation, diarrhea, and decreased appetite. (6.1)

TECENTRIQ in combination with bevacizumab

- Most common adverse reactions (≥ 20%) in patients with HCC are hypertension, fatigue and proteinuria. (6.1)

TECENTRIQ in combination with cobimetinib and vemurafenib

- Most common adverse reactions (≥ 20%) with TECENTRIQ in patients with melanoma are rash, musculoskeletal pain, fatigue, hepatotoxicity, pyrexia, nausea, pruritus, edema, stomatitis, hypothyroidism, and photosensitivity reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Non-Small Cell Lung Cancer
- 1.2 Small Cell Lung Cancer
- 1.3 Hepatocellular Carcinoma
- 1.4 Melanoma
- 1.5 Alveolar Soft Part Sarcoma

2 DOSAGE AND ADMINISTRATION
- 2.1 Patient Selection for Treatment of Non-Small Cell Lung Cancer and Melanoma
- 2.2 Recommended Dosage
- 2.3 Dosage Modifications for Adverse Reactions
- 2.4 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Severe and Fatal Immune-Mediated Adverse Reactions
- 5.2 Infusion-Related Reactions
- 5.3 Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors
- 5.4 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.6 Immunogenicity

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 Non-Small Cell Lung Cancer
- 14.2 Small Cell Lung Cancer
- 14.3 Hepatocellular Carcinoma
- 14.4 Melanoma
- 14.5 Alveolar Soft Part Sarcoma

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer

- TECENTRIQ, as a single-agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA *[see Clinical Studies (14.1)]* non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.
- TECENTRIQ, as a single agent, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations *[see Dosage and Administration (2.1)]*.
- TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ.

1.2 Small Cell Lung Cancer

- TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- TECENTRIQ, in combination with lurbinectedin, is indicated for the maintenance treatment of adult patients with ES-SCLC whose disease has not progressed after first-line induction therapy with TECENTRIQ or atezolizumab and hyaluronidase-tqjs, carboplatin and etoposide.

1.3 Hepatocellular Carcinoma

TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

1.4 Melanoma

TECENTRIQ, in combination with cobimetinib and vemurafenib, is indicated for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma *[see Dosage and Administration (2.1)]*.

1.5 Alveolar Soft Part Sarcoma

TECENTRIQ, as a single agent, is indicated for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of Non-Small Cell Lung Cancer and Melanoma

Select patients with Stage II to IIIA non-small cell lung cancer for treatment with TECENTRIQ as a single agent based on PD-L1 expression on tumor cells *[see Clinical Studies (14.1)]*.

Select patients with first-line metastatic non-small cell lung cancer for treatment with TECENTRIQ as a single agent based on the PD-L1 expression on tumor cells or on tumor-infiltrating immune cells *[see Clinical Studies (14.1)]*.

Information on FDA-approved tests for the determination of PD-L1 expression in metastatic non-small cell lung cancer are available at: http://www.fda.gov/CcompanionDiagnostics.

Select patients with unresectable or metastatic melanoma for treatment with TECENTRIQ in combination with cobimetinib and vemurafenib after confirming the presence of a BRAF V600 mutation *[see Clinical Studies (14.4)]*. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosages of TECENTRIQ are presented in Table 1. Administer TECENTRIQ as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Table 1: Recommended Dosage of TECENTRIQ as a Single Agent

Indication	**Recommended Dosage of TECENTRIQ**	**Duration of Therapy**
Metastatic NSCLC	● 840 mg every 2 weeks or ● 1200 mg every 3 weeks or ● 1680 mg every 4 weeks	Until disease progression or unacceptable toxicity
Adjuvant Treatment of NSCLC	● 840 mg every 2 weeks or ● 1200 mg every 3 weeks or ● 1680 mg every 4 weeks	Up to one year, unless there is disease recurrence or unacceptable toxicity
ASPS (adult)	● 840 mg every 2 weeks or ● 1200 mg every 3 weeks or ● 1680 mg every 4 weeks	Until disease progression or unacceptable toxicity
ASPS (pediatric, 2 years of age and older)	15 mg/kg (up to a maximum 1200 mg) every 3 weeks	

The recommended intravenous dosages of TECENTRIQ in combination with other therapeutic agents are presented in Table 2. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with TECENTRIQ for the recommended dosage information, as appropriate.

Table 2: Recommended Dosage of TECENTRIQ in Combination with Other Therapeutic Agents

Indication	Recommended Dosage of TECENTRIQ	Duration of Therapy
NSCLC	● 840 mg every 2 weeks or ● 1200 mg every 3 weeks or ● 1680 mg every 4 weeks Administer TECENTRIQ prior to chemotherapy and bevacizumab when given on the same day.	Until disease progression or unacceptable toxicity
SCLC	● 840 mg every 2 weeks or ● 1200 mg every 3 weeks or ● 1680 mg every 4 weeks Administer TECENTRIQ prior to chemotherapy when given on the same day.	
HCC	● 840 mg every 2 weeks or ● 1200 mg every 3 weeks or ● 1680 mg every 4 weeks Administer TECENTRIQ prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg every 3 weeks.	
Melanoma	● 840 mg every 2 weeks or ● 1200 mg every 3 weeks or ● 1680 mg every 4 weeks Administer TECENTRIQ with cobimetinib 60 mg orally once daily (21 days on and 7 days off) and vemurafenib 720 mg orally twice daily. Prior to initiating TECENTRIQ, patients should receive a 28-day treatment cycle of cobimetinib 60 mg orally once daily (21 days on and 7 days off) and vemurafenib 960 mg orally twice daily from Days 1-21 and vemurafenib 720 mg orally twice daily from Days 22-28.	

2.3 Dosage Modifications for Adverse Reactions

No dose reduction for TECENTRIQ is recommended. In general, withhold TECENTRIQ for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TECENTRIQ for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability

to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for TECENTRIQ for adverse reactions that require management different from these general guidelines are summarized in Table 3.

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity[a]**	**Dosage Modification**
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[b]
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grades 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue

Adverse Reaction	Severity[a]	Dosage Modification
Myocarditis or Pericarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue

[a] Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4

[b] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids

[c] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue TECENTRIQ based on recommendations for hepatitis with no liver involvement

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson syndrome, TEN = toxic epidermal necrolysis

2.4 Preparation and Administration

Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed. Do not shake the vial.

Prepare the solution for infusion as follows:

- Select the appropriate vial(s) based on the prescribed dose.
- Withdraw the required volume of TECENTRIQ from the vial(s) using sterile needle and syringe.
- Dilute to a final concentration between 3.2 mg/mL and 16.8 mg/mL in a polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with only 0.9% Sodium Chloride Injection, USP.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard used or empty vials of TECENTRIQ.

Storage of Infusion Solution

This product does not contain a preservative.

Administer immediately once prepared. If diluted TECENTRIQ infusion solution is not used immediately, store solution either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or

- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

Do not freeze.

Do not shake.

Administration

Administer the initial infusion over 60 minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Do not coadminister other drugs through the same intravenous line.

Do not administer as an intravenous push or bolus.

3 DOSAGE FORMS AND STRENGTHS

Injection: 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

TECENTRIQ is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*. In general, if TECENTRIQ requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic

immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

TECENTRIQ as a Single Agent:

Immune-mediated pneumonitis occurred in 3% (83/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.8%), and Grade 2 (1.1%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 0.5% and withholding of TECENTRIQ in 1.5% of patients.

Systemic corticosteroids were required in 55% (46/83) of patients with pneumonitis. Pneumonitis resolved in 69% of the 83 patients. Of the 39 patients in whom TECENTRIQ was withheld for pneumonitis, 25 reinitiated TECENTRIQ after symptom improvement; of these, 4% had recurrence of pneumonitis.

In IMpower010 immune-mediated pneumonitis occurred in 3.8% (19/495) of patients receiving TECENTRIQ as a single agent, including fatal (0.2%), Grade 4 (0.2%), and Grade 3 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 2.2% and withholding of TECENTRIQ in 0.8% of patients.

Systemic corticosteroids were required in 63% (12/19) of patients with pneumonitis. Pneumonitis resolved in 84% of the 19 patients.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated pneumonitis occurred in 13% (29/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 3 (1.3%) and Grade 2 (7%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 2.6% and withholding of TECENTRIQ in 7.4% of patients.

Systemic corticosteroids were required in 55% (16/29) of patients with pneumonitis. Pneumonitis resolved in 97% of the 29 patients. Of the 17 patients in whom TECENTRIQ was withheld for pneumonitis, 10 reinitiated TECENTRIQ after symptom improvement; of these, 50% had recurrence of pneumonitis.

Immune-Mediated Colitis

TECENTRIQ can cause immune-mediated colitis. Colitis can present with diarrhea, abdominal pain, and lower gastrointestinal (GI) bleeding. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

TECENTRIQ as a Single Agent:

Immune-mediated colitis occurred in 1% (26/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%) and Grade 2 (0.3%) adverse reactions. Colitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.5% of patients.

Systemic corticosteroids were required in 50% (13/26) of patients with colitis. Colitis resolved in 73% of the 26 patients. Of the 12 patients in whom TECENTRIQ was withheld for colitis, 8

reinitiated treatment with TECENTRIQ after symptom improvement; of these, 25% had recurrence of colitis.

Immune-Mediated Hepatitis

TECENTRIQ can cause immune-mediated hepatitis.

Immune-mediated hepatitis occurred in 1.8% (48/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.5%), and Grade 2 (0.5%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 25% (12/48) of patients with hepatitis. Hepatitis resolved in 50% of the 48 patients. Of the 6 patients in whom TECENTRIQ was withheld for hepatitis, 4 reinitiated treatment with TECENTRIQ after symptom improvement; of these, none had recurrence of hepatitis.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated hepatitis occurred in 6.1% (14/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 4 (1.3%), Grade 3 (1.7%) and Grade 2 (1.3%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 2.2% and withholding of TECENTRIQ in 1.7% of patients.

Systemic corticosteroids were required in 50% (7/14) of patients with hepatitis. Hepatitis resolved in 93% of the 14 patients. Of the 4 patients in whom TECENTRIQ was withheld for hepatitis, 3 reinitiated TECENTRIQ after symptom improvement; of these, 33% had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TECENTRIQ can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Adrenal insufficiency occurred in 0.4% (11/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in one patient and withholding of TECENTRIQ in one patient.

Systemic corticosteroids were required in 82% (9/11) of patients with adrenal insufficiency; of these, 3 patients remained on systemic corticosteroids. The single patient in whom TECENTRIQ was withheld for adrenal insufficiency did not reinitiate TECENTRIQ.

In IMpower010 immune-mediated adrenal insufficiency occurred in 1.2% (6/495) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 0.6% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 83% (5/6) of patients with adrenal insufficiency; of these, 4 patients remained on systemic corticosteroids.

Hypophysitis

TECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated.

Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Hypophysitis occurred in <0.1% (2/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (1 patient, <0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of TECENTRIQ in one patient and no patients required withholding of TECENTRIQ.

Systemic corticosteroids were required in 50% (1/2) of patients with hypophysitis. Hypophysitis did not resolve in these 2 patients.

Thyroid disorders

TECENTRIQ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or medical management for hyperthyroidism as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Thyroiditis:

Thyroiditis occurred in 0.2% (4/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (<0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in one patient.

Hormone replacement therapy was required in 75% (3/4) of patients with thyroiditis. Systemic corticosteroids were required in 25% (1/4) of patients with thyroiditis. Thyroiditis resolved in 50% of patients. The single patient in whom TECENTRIQ was withheld for thyroiditis reinitiated TECENTRIQ; this patient did not have recurrence of thyroiditis.

In IMpower010, thyroiditis occurred in 1.2% (6/495) of patients receiving TECENTRIQ as a single agent, including Grade 2 (0.4%) adverse reactions. Thyroiditis led to withholding of TECENTRIQ in one patient.

Hormone replacement therapy was required in 67% (4/6) of patients with thyroiditis. Systemic corticosteroids were required in 33% (2/6) of patients with thyroiditis. Thyroiditis resolved in 50% of patients.

Hyperthyroidism:

TECENTRIQ as a Single Agent:

Hyperthyroidism occurred in 0.8% (21/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (0.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.1% of patients.

Antithyroid therapy was required in 29% (6/21) of patients with hyperthyroidism. Of these 6 patients, the majority remained on antithyroid treatment. Of the 3 patients in whom TECENTRIQ was withheld for hyperthyroidism, one patient reinitiated TECENTRIQ; this patient did not have recurrence of hyperthyroidism.

In IMpower010 hyperthyroidism occurred in 6% (32/495) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.4%) adverse reactions. Hyperthyroidism led to permanent discontinuation of TECENTRIQ in 0.8% and withholding of TECENTRIQ in 2.8% of patients.

Antithyroid therapy was required in 38% (12/32) of patients with hyperthyroidism. Of these 12 patients, the majority remained on antithyroid treatment. Of the 14 patients in whom TECENTRIQ was withheld for hyperthyroidism, 9 patients reinitiated TECENTRIQ.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Hyperthyroidism occurred in 19% (43/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 3 (0.9%) and Grade 2 (7.8%) adverse reactions. Hyperthyroidism led to permanent discontinuation of TECENTRIQ in 0.4% and withholding of TECENTRIQ in 10% of patients.

Antithyroid therapy was required in 53% (23/43) of patients with hyperthyroidism. Of these 23 patients, the majority remained on antithyroid treatment. Of the 24 patients in whom TECENTRIQ was withheld for hyperthyroidism, 18 patients reinitiated TECENTRIQ; of these, 28% had recurrence of hyperthyroidism.

Hypothyroidism:

TECENTRIQ as a Single Agent:

Hypothyroidism occurred in 4.9% (128/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) and Grade 2 (3.4%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.6% of patients.

Hormone replacement therapy was required in 81% (104/128) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 17 patients in whom TECENTRIQ was withheld for hypothyroidism, 8 reinitiated TECENTRIQ after symptom improvement.

In IMpower010 hypothyroidism occurred in 17% (86/495) of patients receiving TECENTRIQ as a single agent. Hypothyroidism led to permanent discontinuation of TECENTRIQ in 1.6% and withholding of TECENTRIQ in 1.6% of patients.

Hormone replacement was required in 57% (49/86) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 8 patients in whom TECENTRIQ was withheld for hypothyroidism, 3 reinitiated TECENTRIQ after symptom improvement.

TECENTRIQ in Combination with Platinum-based Chemotherapy:

Hypothyroidism occurred in 11% (277/2421) of patients with NSCLC and SCLC receiving TECENTRIQ in combination with platinum-based chemotherapy, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (5.7%) adverse reactions. Hypothyroidism led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 1.6% of patients.

Hormone replacement therapy was required in 71% (198/277) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 39 patients in whom TECENTRIQ was withheld for hypothyroidism, 9 reinitiated TECENTRIQ after symptom improvement.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Hypothyroidism occurred in 26% (60/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 2 (9.1%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 2.6% of patients.

Hormone replacement therapy was required in 52% (31/60) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 6 patients in whom TECENTRIQ was withheld for hypothyroidism, 4 reinitiated TECENTRIQ after symptom improvement. The majority of patients with hypothyroidism required long term thyroid replacement.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Type 1 diabetes mellitus occurred in 0.3% (7/2616) of patients receiving TECENTRIQ, including Grade 3 (0.2%) and Grade 2 (<0.1%) adverse reactions. Type 1 diabetes mellitus led to permanent discontinuation of TECENTRIQ in one patient and withholding of TECENTRIQ in two patients.

Treatment with insulin was required for all patients with confirmed Type 1 diabetes mellitus and insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both re-initiated TECENTRIQ treatment.

Immune-Mediated Nephritis with Renal Dysfunction

TECENTRIQ can cause immune-mediated nephritis.

TECENTRIQ as a Single Agent:

Immune-mediated nephritis with renal dysfunction occurred in <0.1% (1/2616) of patients receiving TECENTRIQ as a single agent, and this adverse reaction was a Grade 3 (<0.1%) adverse reaction. Nephritis led to permanent discontinuation of TECENTRIQ in this patient.

This patient required systemic corticosteroids. In this patient, nephritis did not resolve.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated nephritis with renal dysfunction occurred in 1.3% (3/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 2 (1.3%) adverse reactions. Nephritis led to permanent discontinuation of TECENTRIQ in 0.4% and withholding of TECENTRIQ in 0.9% of patients.

Systemic corticosteroids were required in 67% (2/3) of patients with nephritis. Nephritis resolved in all 3 of these patients. Of the 2 patients in whom TECENTRIQ was withheld for nephritis, both reinitiated TECENTRIQ after symptom improvement and neither had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Immune-mediated dermatologic adverse reactions occurred in 0.6% (15/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 20% (3/15) of patients with dermatologic adverse reactions. Dermatologic adverse reactions resolved in 87% of the 15 patients. Of the 4 patients in whom TECENTRIQ was withheld for immune-mediated dermatologic adverse reactions, none re-initiated TECENTRIQ.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% (unless otherwise noted) in patients who received TECENTRIQ or were

reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis.

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

5.2 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions, including anaphylaxis. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.3)]*. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%). The frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers, in combination with other antineoplastic drugs in NSCLC and SCLC, and across the recommended dose range (840 mg Q2W to 1680 mg Q4W).

5.3 Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockage and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in WARNINGS AND PRECAUTIONS reflect exposure to TECENTRIQ as a single-agent in 2616 patients in two randomized, active-controlled studies (POPLAR, OAK) and three open-label, single arm studies (PCD4989g, BIRCH, FIR) which enrolled 1636 patients with metastatic NSCLC, and 980 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2616 patients who received a single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months. Using the dataset described for patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (48%), decreased appetite (25%), nausea (24%), cough (22%), and dyspnea (22%). In addition, the data reflect exposure to TECENTRIQ as a single agent as adjuvant therapy in 495 patients with early-stage NSCLC enrolled in a randomized study (IMpower010).

In addition, the data reflect exposure to TECENTRIQ in combination with other antineoplastic drugs in 2421 patients with NSCLC (N = 2223) or SCLC (N = 198) enrolled in five randomized, active-controlled trials, including IMpower150, IMpower130 and IMpower133. Among the 2421 patients, 53% were exposed to TECENTRIQ for longer than 6 months and 29% were exposed to TECENTRIQ for longer than 12 months. Among the 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with other antineoplastic drugs, the most common adverse reactions in ≥20% of patients were fatigue/asthenia (49%), nausea (38%), alopecia (35%), constipation (29%), diarrhea (28%) and decreased appetite (27%).

The data also reflect exposure to TECENTRIQ administered in combination with cobimetinib and vemurafenib in 230 patients enrolled in IMspire150. Among the 230 patients, 62% were exposed to TECENTRIQ for longer than 6 months and 42% were exposed to TECENTRIQ for longer than 12 months.

Non-Small Cell Lung Cancer (NSCLC)

Adjuvant Treatment of Early-stage NSCLC

IMpower010

The safety of TECENTRIQ was evaluated in IMpower010, a multicenter, open-label, randomized trial for the adjuvant treatment of patients with stage IB (tumors ≥ 4 cm) - IIIA NSCLC who had complete tumor resection and received up to 4 cycles of cisplatin-based adjuvant chemotherapy. Patients received TECENTRIQ 1200 mg every 3 weeks (n=495) for 1 year (16 cycles), unless disease progression or unacceptable toxicity occurred, or best supportive care *[see Clinical Studies (14.1)]*. The median number of cycles received was 16 (range: 1, 16).

Fatal adverse reactions occurred in 1.8% of patients receiving TECENTRIQ; these included multiple organ dysfunction syndrome, pneumothorax, interstitial lung disease, arrhythmia, acute cardiac failure, myocarditis, cerebrovascular accident, death of unknown cause, and acute myeloid leukemia (1 patient each).

Serious adverse reactions occurred in 18% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>1%) were pneumonia (1.8%), pneumonitis (1.6%), and pyrexia (1.2%).

TECENTRIQ was discontinued due to adverse reactions in 18% of patients*;* the most common adverse reactions (≥1%) leading to TECENTRIQ discontinuation were pneumonitis (2.2%), hypothyroidism (1.6%), increased aspartate aminotransferase (1.4%), arthralgia (1.0%), and increased alanine aminotransferase (1.0%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 29% of patients; the most common (>1%) were rash (3.0%), hyperthyroidism (2.8%), hypothyroidism (1.6%), increased AST (1.6%), pyrexia (1.6%), increased ALT (1.4%), upper respiratory tract infection (1.4%), headache (1.2%), peripheral neuropathy (1.2%), and pneumonia (1.2%).

Tables 4 and 5 summarize adverse reactions and selected laboratory abnormalities in patients receiving TECENTRIQ in IMpower010.

Table 4: Adverse Reactions Occurring in ≥10% of Patients with Early-Stage NSCLC Receiving TECENTRIQ in IMpower010

Adverse Reaction*	TECENTRIQ N = 495		Best Supportive Care N = 495	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Skin and Subcutaneous Tissue				
Rash[1]	17	1.2	1.4	0
Pruritus	10	0	0.6	0
Endocrine Disorders				
Hypothyroidism[2]	14	0	0.6	0
Respiratory, Thoracic and Mediastinal				
Cough[3]	16	0	11	0
General				
Pyrexia[4]	14	0.8	2.2	0.2
Fatigue[5]	14	0.6	5	0.2
Nervous System Disorders				
Peripheral neuropathy[6]	12	0.4	7	0.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[7]	14	0.8	9	0.2
Arthralgia[8]	11	0.6	6	0

*Graded per NCI CTCAE v4.0

[1] Includes rash, dermatitis, genital rash, skin exfoliation, rash maculo-papular, rash erythematous, rash papular, lichen planus, eczema asteatotic, dermatitis exfoliative, palmar-plantar erythrodysaesthesia syndrome, dyshidrotic eczema, eczema, drug eruption, rash pruritic, toxic skin eruption, dermatitis acneiform

[2] Includes hypothyroidism, autoimmune hypothyroidism, primary hypothyroidism, blood thyroid stimulating hormone increased

[3] Productive cough, upper airway cough syndrome, cough

[4] Includes pyrexia, body temperature increased, hyperthermia

[5] Includes fatigue, asthenia

[6] Includes paraesthesia, neuropathy peripheral, peripheral sensory neuropathy, hypoaesthesia, polyneuropathy, dysaesthesia, neuralgia, axonal neuropathy

[7] Includes myalgia, bone pain, back pain, spinal pain, musculoskeletal chest pain, pain in extremity, neck pain, non-cardiac chest pain, musculoskeletal discomfort, musculoskeletal stiffness, musculoskeletal pain

[8] Includes arthralgia, arthritis

Table 5: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with Early-Stage NSCLC Receiving TECENTRIQ in IMpower010

Laboratory Abnormality[1]	TECENTRIQ[2]		Best Supportive Care[2]	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased aspartate aminotransferase	34	2.5	18	0
Increased alanine aminotransferase	30	3.3	19	0.4
Hyperkalemia	24	3.5	15	2.5
Increased blood creatinine	31	0.2	23	0.2

[1] Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).
[2] The denominators used to calculate the rate varied from 78-480 for BSC arm and 483 for TECENTRIQ are for all tests of interest based on the number of patients with a baseline value and at least one post-treatment value.

Metastatic Chemotherapy-Naïve NSCLC

IMpower110

The safety of TECENTRIQ was evaluated in IMpower110, a multicenter, international, randomized, open-label study in 549 chemotherapy-naïve patients with stage IV NSCLC, including those with EGFR or ALK genomic tumor aberrations. Patients received TECENTRIQ 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin with either pemetrexed or gemcitabine (n=263) until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*. IMpower110 enrolled patients whose tumors express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area). The median duration of exposure to TECENTRIQ was 5.3 months (0 to 33 months).

Fatal adverse reactions occurred in 3.8% of patients receiving TECENTRIQ; these included death (reported as unexplained death and death of unknown cause), aspiration, chronic obstructive pulmonary disease, pulmonary embolism, acute myocardial infarction, cardiac arrest, mechanical ileus, sepsis, cerebral infarction, and device occlusion (1 patient each).

Serious adverse reactions occurred in 28% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>2%) were pneumonia (2.8%), chronic obstructive pulmonary disease (2.1%) and pneumonitis (2.1%).

TECENTRIQ was discontinued due to adverse reactions in 6% of patients*;* the most common adverse reactions (≥2 patients) leading to TECENTRIQ discontinuation were peripheral neuropathy and pneumonitis.

Adverse reactions leading to interruption of TECENTRIQ occurred in 26% of patients; the most common (>1%) were ALT increased (2.1%), AST increased (2.1%), pneumonitis (2.1%), pyrexia (1.4%), pneumonia (1.4%) and upper respiratory tract infection (1.4%).

Tables 6 and 7 summarize adverse reactions and selected laboratory abnormalities in patients receiving TECENTRIQ in IMpower110.

Table 6: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in IMpower110

Adverse Reaction	TECENTRIQ N = 286		Platinum-Based Chemotherapy N = 263	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Gastrointestinal				
Nausea	14	0.3	34	1.9
Constipation	12	1.0	22	0.8
Diarrhea	11	0	12	0.8
General				
Fatigue/asthenia	25	1.4	34	4.2
Pyrexia	14	0	9	0.4
Metabolism and Nutrition				
Decreased appetite	15	0.7	19	0
Respiratory, Thoracic and Mediastinal				
Dyspnea	14	0.7	10	0
Cough	12	0.3	10	0

Graded per NCI CTCAE v4.0

Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower110

Laboratory Abnormality	TECENTRIQ		Platinum-Based Chemotherapy	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	69	1.8	94	20
Lymphopenia	47	9	59	17
Chemistry				
Hypoalbuminemia	48	0.4	39	2
Increased alkaline phosphatase	46	2.5	42	1.2
Hyponatremia	44	9	36	7
Increased ALT	38	3.2	32	0.8
Increased AST	36	3.2	32	0.8
Hyperkalemia	29	3.9	36	2.7
Hypocalcemia	24	1.4	24	2.7
Increased blood creatinine	24	0.7	33	1.5
Hypophosphatemia	23	3.6	21	2

Each test incidence is based on the number of patients who had at least one on-study laboratory measurement available: TECENTRIQ (range: 278-281); platinum-based chemotherapy (range: 256-260). Graded per NCI CTCAE v4.0. Increased blood creatinine only includes patients with test results above the normal range.

IMpower150

The safety of TECENTRIQ with bevacizumab, paclitaxel and carboplatin was evaluated in IMpower150, a multicenter, international, randomized, open-label trial in which 393 chemotherapy-naïve patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m^2 or 200 mg/m^2, and carboplatin AUC 6 mg/mL/min intravenously every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

Fatal adverse reactions occurred in 6% of patients receiving TECENTRIQ; these included hemoptysis, febrile neutropenia, pulmonary embolism, pulmonary hemorrhage, death, cardiac arrest, cerebrovascular accident, pneumonia, aspiration pneumonia, chronic obstructive pulmonary disease, intracranial hemorrhage, intestinal angina, intestinal ischemia, intestinal obstruction and aortic dissection.

Serious adverse reactions occurred in 44%. The most frequent serious adverse reactions (>2%) were febrile neutropenia, pneumonia, diarrhea, and hemoptysis.

TECENTRIQ was discontinued due to adverse reactions in 15% of patients; the most common adverse reaction leading to discontinuation was pneumonitis (1.8%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common (>1%) were neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea, hypothyroidism, anemia, pneumonia, pyrexia, hyperthyroidism, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria.

Tables 8 and 9 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin in IMpower150.

Table 8: Adverse Reactions Occurring in ≥15% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

Adverse Reaction	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Nervous System				
Neuropathy[1]	56	3	47	3
Headache	16	0.8	13	0
General				
Fatigue/Asthenia	50	6	46	6
Pyrexia	19	0.3	9	0.5
Skin and Subcutaneous Tissue				
Alopecia	48	0	46	0
Rash[2]	23	2	10	0.3
Musculoskeletal and Connective Tissue				
Myalgia/Pain[3]	42	3	34	2
Arthralgia	26	1	22	1
Gastrointestinal				

Adverse Reaction	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Nausea	39	4	32	2
Diarrhea[4]	33	6	25	0.5
Constipation	30	0.3	23	0.3
Vomiting	19	2	18	1
Metabolism and Nutrition				
Decreased appetite	29	4	21	0.8
Vascular				
Hypertension	25	9	22	8
Respiratory				
Cough	20	0.8	19	0.3
Epistaxis	17	1	22	0.3
Renal				
Proteinuria[5]	16	3	15	3

Graded per NCI CTCAE v4.0

[1] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paraesthesia, dysesthesia, polyneuropathy

[2] Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, contact dermatitis, rash erythematous, rash macular, pruritic rash, seborrheic dermatitis, dermatitis psoriasiform

[3] Includes pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain, back pain, myalgia, and bone pain

[4] Includes diarrhea, gastroenteritis, colitis, enterocolitis

[5] Data based on Preferred Terms since laboratory data for proteinuria were not systematically collected

Table 9: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

Laboratory Abnormality	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	83	10	83	9
Neutropenia	52	31	45	26
Lymphopenia	48	17	38	13
Chemistry				
Hyperglycemia	61	0	60	0
Increased BUN	52	NA[1]	44	NA[1]
Hypomagnesemia	42	2	36	1
Hypoalbuminemia	40	3	31	2
Increased AST	40	4	28	0.8
Hyponatremia	38	10	36	9

Laboratory Abnormality	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Increased Alkaline Phosphatase	37	2	32	1
Increased ALT	37	6	28	0.5
Increased TSH	30	NA[1]	20	NA[1]
Hyperkalemia	28	3	25	2
Increased Creatinine	28	1	19	2
Hypocalcemia	26	3	21	3
Hypophosphatemia	25	4	18	4
Hypokalemia	23	7	14	4
Hyperphosphatemia	25	NA[1]	19	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ with bevacizumab, paclitaxel, and carboplatin range: 337-380); bevacizumab, paclitaxel, and carboplatin (range: 337-382). Graded per NCI CTCAE v4.0
[1] NA = Not applicable. NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

IMpower130

The safety of TECENTRIQ with paclitaxel protein-bound and carboplatin was evaluated in IMpower130, a multicenter, international, randomized, open-label trial in which 473 chemotherapy-naïve patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg and carboplatin AUC 6 mg/mL/min intravenously on Day 1 and paclitaxel protein-bound 100 mg/m^2 intravenously on Day 1, 8, and 15 of each 21-day cycle for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*. Among patients receiving TECENTRIQ, 55% were exposed for 6 months or longer and 3.5% were exposed for greater than one year.

Fatal adverse reactions occurred in 5.3% of patients receiving TECENTRIQ; these included pneumonia (1.1%), pulmonary embolism (0.8%), myocardial infarction (0.6%), cardiac arrest (0.4%), pneumonitis (0.4%) and sepsis, septic shock, staphylococcal sepsis, aspiration, respiratory distress, cardiorespiratory arrest, ventricular tachycardia, death (not otherwise specified), and hepatic cirrhosis (0.2% each).

Serious adverse reactions occurred in 51% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (≥2%) were pneumonia (6%), diarrhea (3%), lung infection (3%), pulmonary embolism (3%), chronic obstructive pulmonary disease exacerbation (2.5%), dyspnea (2.3%), and febrile neutropenia (1.9%).

TECENTRIQ was discontinued due to adverse reactions in 13% of patients; the most common adverse reactions leading to discontinuation were pneumonia (0.8%), pulmonary embolism (0.8%), fatigue (0.6%), dyspnea (0.6%), pneumonitis (0.6%), neutropenia (0.4%), nausea (0.4%), renal failure (0.4%), cardiac arrest (0.4%), and septic shock (0.4%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 62% of patients; the most common (>1%) were neutropenia, thrombocytopenia, anemia, diarrhea, fatigue/asthenia, pneumonia, dyspnea, pneumonitis, pyrexia, nausea, acute kidney injury, vomiting, pulmonary embolism, arthralgia, infusion-related reaction, abdominal pain, chronic obstructive pulmonary disease exacerbation, dehydration, and hypokalemia.

Tables 10 and 11 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with paclitaxel protein-bound and carboplatin in IMpower130.

Table 10: Adverse Reactions Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower130

Adverse Reaction	TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin N = 473		Paclitaxel Protein-Bound and Carboplatin N = 232	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General				
Fatigue/Asthenia	61	11	60	8
Gastrointestinal				
Nausea	50	3.4	46	2.2
Diarrhea [1]	43	6	32	6
Constipation	36	1.1	31	0
Vomiting	27	2.7	19	2.2
Musculoskeletal and Connective Tissue				
Myalgia/Pain [2]	38	3	22	0.4
Nervous System				
Neuropathy [3]	33	2.5	28	2.2
Respiratory, Thoracic and Mediastinal				
Dyspnea [4]	32	4.9	25	1.3
Cough	27	0.6	17	0
Skin and Subcutaneous Tissue				
Alopecia	32	0	27	0
Rash [5]	20	0.6	11	0.9
Metabolism and Nutrition				
Decreased appetite	30	2.1	26	2.2

Graded per NCI CTCAE v4.0

[1] Includes diarrhea, colitis, and gastroenteritis

[2] Includes back pain, pain in extremity, myalgia, musculoskeletal chest pain, bone pain, neck pain and musculoskeletal discomfort

[3] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

[4] Includes dyspnea, dyspnea exertional and wheezing

[5] Includes rash, rash maculo-papular, eczema, rash pruritic, rash erythematous, dermatitis, dermatitis contact, drug eruption, seborrheic dermatitis and rash macular.

Table 11: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower130

Laboratory Abnormality	TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin N = 473		Paclitaxel Protein-Bound and Carboplatin N = 232	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	92	33	87	25
Neutropenia	75	50	67	39
Thrombocytopenia	73	19	59	13
Lymphopenia	71	23	61	16
Chemistry				
Hyperglycemia	75	8	66	8
Hypomagnesemia	50	3.4	42	3.2
Hyponatremia	37	9	28	7
Hypoalbuminemia	35	1.3	31	0
Increased ALT	31	2.8	24	3.9
Hypocalcemia	31	2.6	27	1.8
Hypophosphatemia	29	6	20	3.2
Increased AST	28	2.2	24	1.8
Increased TSH	26	NA[1]	5	NA[1]
Hypokalemia	26	6	24	4.4
Increased Alkaline Phosphatase	25	2.6	22	1.3
Increased Blood Creatinine	23	2.8	16	0.4
Hyperphosphatemia	21	NA[1]	13	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ with paclitaxel protein-bound and carboplatin (range: 423 - 467); paclitaxel protein-bound and carboplatin (range: 218 - 229). Graded per NCI CTCAE v4.0.
[1] NA = Not applicable. NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

Previously Treated Metastatic NSCLC

OAK

The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression *[see Clinical Studies (14.1)]*. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The median duration of exposure was 3.4 months (0 to 26 months) in TECENTRIQ-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients.

The study population characteristics were: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 68% former smoker, 16% current smoker, and 63% had Eastern Cooperative Oncology Group (ECOG) performance status of 1.

Fatal adverse reactions occurred in 1.6% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure.

Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions (>1%) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

TECENTRIQ was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common (>1%) were pneumonia, liver function test abnormality, dyspnea, fatigue, pyrexia, and back pain.

Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in OAK.

Table 12: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in OAK

Adverse Reaction	TECENTRIQ N = 609		Docetaxel N = 578	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue/Asthenia[1]	44	4	53	6
Pyrexia	18	<1	13	<1
Respiratory				
Cough[2]	26	<1	21	<1
Dyspnea	22	2.8	21	2.6
Metabolism and Nutrition				
Decreased appetite	23	<1	24	1.6
Musculoskeletal				
Myalgia/Pain[3]	20	1.3	20	<1
Arthralgia	12	0.5	10	0.2
Gastrointestinal				
Nausea	18	<1	23	<1
Constipation	18	<1	14	<1
Diarrhea	16	<1	24	2
Skin				
Rash[4]	12	<1	10	0

Graded per NCI CTCAE v4.0

[1] Includes fatigue and asthenia

[2] Includes cough and exertional cough

[3] Includes musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia

[4] Includes rash, erythematous rash, generalized rash, maculopapular rash, papular rash, pruritic rash, pustular rash, pemphigoid

Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in OAK

Laboratory Abnormality	TECENTRIQ		Docetaxel	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21
Chemistry				
Hypoalbuminemia	48	4	50	3
Hyponatremia	42	7	31	6
Increased Alkaline Phosphatase	39	2	25	1
Increased AST	31	3	16	0.5
Increased ALT	27	3	14	0.5
Hypophosphatemia	27	5	23	4
Hypomagnesemia	26	1	21	1
Increased Creatinine	23	2	16	1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 546-585) and docetaxel (range: 532-560). Graded according to NCI CTCAE version 4.0

Small Cell Lung Cancer (SCLC)

IMpower133

The safety of TECENTRIQ with carboplatin and etoposide was evaluated in IMpower133, a randomized, multicenter, double-blind, placebo-controlled trial in which 198 patients with ES-SCLC received TECENTRIQ 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles, followed by TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. Among 198 patients receiving TECENTRIQ, 32% were exposed for 6 months or longer and 12% were exposed for 12 months or longer.

Fatal adverse reactions occurred in 2% of patients receiving TECENTRIQ. These included pneumonia, respiratory failure, neutropenia, and death (1 patient each).

Serious adverse reactions occurred in 37% of patients receiving TECENTRIQ. Serious adverse reactions in >2% were pneumonia (4.5%), neutropenia (3.5%), febrile neutropenia (2.5%), and thrombocytopenia (2.5%).

TECENTRIQ was discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction requiring permanent discontinuation in >2% of patients was infusion-related reactions (2.5%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 59% of patients; the most common (>1%) were neutropenia (22%), anemia (9%), leukopenia (7%), thrombocytopenia (5%), fatigue (4.0%), infusion-related reaction (3.5%), pneumonia (2.0%), febrile neutropenia (1.5%), increased ALT (1.5%), and nausea (1.5%).

Tables 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with carboplatin and etoposide in IMpower133.

Table 14: Adverse Reactions Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

Adverse Reaction	TECENTRIQ with Carboplatin and Etoposide N = 198		Placebo with Carboplatin and Etoposide N = 196	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General				
Fatigue/asthenia	39	5	33	3
Gastrointestinal				
Nausea	38	1	33	1
Constipation	26	1	30	1
Vomiting	20	2	17	3
Skin and Subcutaneous Tissue				
Alopecia	37	0	35	0
Metabolism and Nutrition				
Decreased appetite	27	1	18	0

Graded per NCI CTCAE v4.0

Table 15: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

Laboratory Abnormality	TECENTRIQ with Carboplatin and Etoposide		Placebo with Carboplatin and Etoposide	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	94	17	93	19
Neutropenia	73	45	76	48
Thrombocytopenia	58	20	53	17
Lymphopenia	46	14	38	11
Chemistry				
Hyperglycemia	67	10	65	8
Increased Alkaline Phosphatase	38	1	35	2
Hyponatremia	34	15	33	11
Hypoalbuminemia	32	1	30	0
Decreased TSH[2]	28	NA[1]	15	NA[1]
Hypomagnesemia	31	5	35	6
Hypocalcemia	26	3	28	5
Increased ALT	26	3	31	1
Increased AST	22	1	21	2
Increased Blood Creatinine	22	4	15	1
Hyperphosphatemia	21	NA[1]	23	NA[1]
Increased TSH[2]	21	NA[1]	7	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 181-193); Placebo (range: 181-196). Graded per NCI CTCAE v4.0
[1] NA = Not applicable. [2] TSH = thyroid-stimulating hormone. NCI CTCAE v4.0 does not include these laboratories.

IMforte

The safety of TECENTRIQ in combination with lurbinectedin was evaluated in IMforte *[see Clinical Studies (14.2)].* Patients received TECENTRIQ 1200 mg IV and lurbinectedin 3.2 mg/m^2 IV, on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity. Primary prophylaxis of G-CSF was administered to 84% of patients. Among 242 patients receiving TECENTRIQ with lurbinectedin, the median duration of exposure to TECENTRIQ was 4.2 months, with 34% of patients exposed for 6 months or longer and 8% of patients exposed for 12 months or longer.

Serious adverse reactions occurred in 31% of patients receiving TECENTRIQ with lurbinectedin. Serious adverse reactions in >2% of patients were pneumonia (2.5%), respiratory tract infection (2.1%), dyspnea (2.1%), and decreased platelet count (2.1%). Fatal adverse reactions occurred in 5% of patients receiving TECENTRIQ with lurbinectedin including pneumonia (3 patients), sepsis (3 patients), cardio-respiratory arrest (2 patients), myocardial infarction (2 patients) and febrile neutropenia (1 patient).

Permanent discontinuation of TECENTRIQ due to an adverse reaction occurred in 2.5% of patients. The adverse reactions requiring permanent discontinuation in ≥ 1% of patients who received TECENTRIQ were immune-mediated nephritis, peripheral neuropathy, nephropathy, pneumonitis, anemia, neutropenia, and thrombocytopenia.

Dosage interruptions of TECENTRIQ due to an adverse reaction occurred in 29% of patients. Adverse reactions which required dosage interruption in ≥ 2% of patients included anemia, fatigue, decreased neutrophil count, pneumonitis, and decreased platelet count.

Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with lurbinectedin in IMforte.

Table 16: Adverse Reactions (≥10%) in Patients with ES-SCLC Who Received TECENTRIQ with Lurbinectedin in IMforte

Adverse Reaction	TECENTRIQ with Lurbinectedin N = 242		TECENTRIQ N = 240	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal				
Nausea	36	3	4	1
Diarrhea[1]	15	0	8	0
Vomiting	14	1	3	0
Constipation	12	0	6	1
General disorders and administration site conditions				
Fatigue[2]	32	5	13	2
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[3]	19	2	16	1
Metabolism and Nutrition				
Decreased appetite	17	0	7	0
Respiratory, thoracic and mediastinal disorders				
Cough[4]	12	0	8	0
Dyspnea[5]	11	2	10	2

Graded per NCI CTCAE v5.0

[1] Includes diarrhea and colitis.

[2] Includes fatigue and asthenia.

[3] Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, and pain in extremity.

[4] Includes cough, productive cough, and upper-airway cough syndrome.

[5] Includes dyspnea and dyspnea exertional.

Clinically relevant adverse reactions in < 10% of patients who received TECENTRIQ in combination with lurbinectedin included pneumonia, phlebitis, extravasation resulting in skin necrosis, hypersensitivity and increased creatine phosphokinase.

Table 17: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with ES-SCLC Who Received TECENTRIQ in Combination with Lurbinectedin in IMforte

Laboratory Abnormality	TECENTRIQ with Lurbinectedin N = 242		TECENTRIQ N = 240	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Lymphopenia	55	17	31	11
Thrombocytopenia	54	15	15	3
Anemia	51	13	12	3
Neutropenia	36	18	7	4
Chemistry				
Increased alkaline phosphatase	29	1	14	0
Decreased sodium	27	4	30	5
Increased ALT	25	3	18	2
Increased AST	24	3	22	1
Decreased calcium	24	3	8	1
Increased creatinine	21	3	14	0

Graded per NCI CTCAE v5.0

Hepatocellular Carcinoma (HCC)

IMbrave150

The safety of TECENTRIQ in combination with bevacizumab was evaluated in IMbrave150, a multicenter, international, randomized, open-label trial in patients with locally advanced or metastatic or unresectable hepatocellular carcinoma who have not received prior systemic treatment *[see Clinical Studies (14.3)]*. Patients received 1,200 mg of TECENTRIQ intravenously followed by 15 mg/kg bevacizumab (n=329) every 3 weeks, or 400 mg of sorafenib (n=156) given orally twice daily, until disease progression or unacceptable toxicity. The median duration of exposure to TECENTRIQ was 7.4 months (range: 0-16 months) and to bevacizumab was 6.9 months (range: 0-16 months).

Fatal adverse reactions occurred in 4.6% of patients in the TECENTRIQ and bevacizumab arm. The most common adverse reactions leading to death were gastrointestinal and esophageal varices hemorrhage (1.2%) and infections (1.2%).

Serious adverse reactions occurred in 38% of patients in the TECENTRIQ and bevacizumab arm. The most frequent serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 9% of patients in the TECENTRIQ and bevacizumab arm. The most common adverse reactions leading to TECENTRIQ discontinuation were hemorrhages (1.2%), including gastrointestinal, subarachnoid, and pulmonary hemorrhages; increased transaminases or bilirubin (1.2%); infusion-related reaction/cytokine release syndrome (0.9%); and autoimmune hepatitis (0.6%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 41% of patients in the TECENTRIQ and bevacizumab arm; the most common (≥ 2%) were liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatase (8%);

infections (6%); gastrointestinal hemorrhages (3.6%); thrombocytopenia/decreased platelet count (3.6%); hyperthyroidism (2.7%); and pyrexia (2.1%).

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 12% of patients in the TECENTRIQ and bevacizumab arm.

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ and bevacizumab in IMbrave150.

Table 18: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving TECENTRIQ in IMbrave150

Adverse Reaction	TECENTRIQ in combination with Bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[2] (%)	Grades 3–4[2] (%)	All Grades[2] (%)	Grades 3–4[2] (%)
Vascular Disorders				
Hypertension	30	15	24	12
General Disorders and Administration Site Conditions				
Fatigue/asthenia[1]	26	2	32	6
Pyrexia	18	0	10	0
Renal and Urinary Disorders				
Proteinuria	20	3	7	0.6
Investigations				
Weight Decreased	11	0	10	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	19	0	10	0
Rash	12	0	17	2.6
Gastrointestinal Disorders				
Diarrhea	19	1.8	49	5
Constipation	13	0	14	0
Abdominal Pain	12	0	17	0
Nausea	12	0	16	0
Vomiting	10	0	8	0
Metabolism and Nutrition Disorders				
Decreased Appetite	18	1.2	24	3.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	12	0	10	0
Epistaxis	10	0	4.5	0
Injury, Poisoning and Procedural Complications				
Infusion-Related Reaction	11	2.4	0	0

[1] Includes fatigue and asthenia
[2] Graded per NCI CTCAE v4.0

Table 19: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving TECENTRIQ in IMbrave150

Laboratory Abnormality	TECENTRIQ in combination with Bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Chemistry				
Increased AST	86	16	90	16
Increased Alkaline Phosphatase	70	4	76	4.6
Increased ALT	62	8	70	4.6
Decreased Albumin	60	1.5	54	0.7
Decreased Sodium	54	13	49	9
Increased Glucose	48	9	43	4.6
Decreased Calcium	30	0.3	35	1.3
Decreased Phosphorus	26	4.7	58	16
Increased Potassium	23	1.9	16	2
Hypomagnesemia	22	0	22	0
Hematology				
Decreased Platelet	68	7	63	4.6
Decreased Lymphocytes	62	13	58	11
Decreased Hemoglobin	58	3.1	62	3.9
Increased Bilirubin	57	8	59	14
Decreased Leukocyte	32	3.4	29	1.3
Decreased Neutrophil	23	2.3	16	1.1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ plus bevacizumab (222-323) and sorafenib (90-153)
[1] Graded per NCI CTCAE v4.0

Melanoma

IMspire150

The safety of TECENTRIQ, administered with cobimetinib and vemurafenib was evaluated in IMspire150, a double-blind, randomized (1:1), placebo-controlled study conducted in patients with previously untreated BRAF V600 mutation-positive metastatic or unresectable melanoma *[see Clinical Studies (14.4)]*. Patients received TECENTRIQ with cobimetinib and vemurafenib (N=230) or placebo with cobimetinib and vemurafenib (n=281).

Among the 230 patients who received TECENTRIQ administered with cobimetinib and vemurafenib, the median duration of exposure to TECENTRIQ was 9.2 months (range: 0-30 months) to cobimetinib was 10.0 months (range: 1-31 months) and to vemurafenib was 9.8 months (range: 1-31 months).

Fatal adverse reactions occurred in 3% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. Adverse reactions leading to death were hepatic failure, fulminant hepatitis, sepsis, septic shock, pneumonia, and cardiac arrest.

Serious adverse reactions occurred in 45% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) serious adverse reactions were hepatotoxicity (7%), pyrexia (6%), pneumonia (4.3%), malignant neoplasms (2.2%), and acute kidney injury (2.2%).

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 21% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) adverse reactions leading to TECENTRIQ discontinuation were increased ALT (2.2%) and pneumonitis (2.6%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 68% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) adverse reactions leading to TECENTRIQ interruption were pyrexia (14%), increased ALT (13%), hyperthyroidism (10%), increased AST (10%), increased lipase (9%), increased amylase (7%), pneumonitis (5%), increased CPK (4.3%), diarrhea (3.5%), pneumonia (3.5%), asthenia (3%), rash (3%), influenza (3%), arthralgia (2.6%), fatigue (2.2%), dyspnea (2.2%), cough (2.2%), peripheral edema (2.2%), uveitis (2.2%), bronchitis (2.2%), hypothyroidism (2.2%), and respiratory tract infection (2.2%).

Tables 20 and 21 summarize the incidence of adverse reactions and laboratory abnormalities in Study IMspire150.

Table 20: Adverse Reactions Occurring in ≥10% of Patients on the TECENTRIQ plus Cobimetinib and Vemurafenib Arm or the Placebo plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4 TECENTRIQ in IMspire150)

Adverse Reaction	TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)		Placebo with Cobimetinib and Vemurafenib (n=281)	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Skin and Subcutaneous Tissue Disorders				
Rash [1]	75	27	72	23
Pruritus	26	<1	17	<1
Photosensitivity reaction	21	<1	25	3.2
General Disorders and Administration Site Conditions				
Fatigue [2]	51	3	45	1.8
Pyrexia [3]	49	1.7	35	2.1
Edema [4]	26	<1	21	0
Gastrointestinal Disorders				
Hepatotoxicity [5]	50	21	36	13
Nausea	30	<1	32	2.5
Stomatitis [6]	23	1.3	15	<1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain [7]	62	4.3	48	3.2
Endocrine Disorders				
Hypothyroidism [8]	22	0	10	0
Hyperthyroidism	18	<1	8	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction [9]	10	2.6	8	<1
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonitis [10]	12	1.3	6	<1
Vascular Disorders				
Hypertension [11]	17	10	18	7

[1] Includes rash, rash maculo-papular, dermatitis acneiform, rash macular, rash erythematous, eczema, skin exfoliation, rash papular, rash pustular, palmar-plantar erythrodysesthesia syndrome, dermatitis, dermatitis contact, erythema multiforme, rash pruritic, drug eruption, nodular rash, dermatitis allergic, exfoliative rash, dermatitis exfoliative generalized and rash morbilliform

[2] Includes fatigue, asthenia and malaise

[3] Includes pyrexia and hyperpyrexia

[4] Includes edema peripheral, lymphoedema, edema, face edema, eyelid edema, periorbital edema, lip edema and generalized edema

[5] Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, transaminases increased, hepatitis, hepatic enzyme increased, hepatotoxicity, hypertransaminasemia, bilirubin conjugated increased, hepatocellular injury, hyperbilirubinemia, liver function test increased, hepatic failure, hepatitis fulminant and liver function test abnormal

[6] Includes stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, cheilitis and glossitis

[7] Includes arthralgia, myalgia, pain in extremity, back pain, musculoskeletal pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, bone pain, spinal pain, immune-mediated arthritis, joint stiffness and non-cardiac chest pain

[8] Includes hypothyroidism and blood thyroid stimulating hormone increased

[9] Includes infusion related reaction and hypersensitivity

[10] Includes pneumonitis and interstitial lung disease

[11] Includes hypertension, blood pressure increased, hypertensive crisis

Clinically important adverse reactions in < 10% of patients who received TECENTRIQ plus cobimetinib and vemurafenib were:

Cardiac Disorders: Arrhythmias, ejection fraction decreased, electrocardiogram QT prolonged

Eye Disorders: Uveitis

Gastrointestinal disorders: Pancreatitis

Infections and infestations: Pneumonia, urinary tract infection

Metabolism and nutrition disorders: Hyperglycemia

Nervous system Disorders: Dizziness, dysgeusia, syncope

Respiratory, thoracic and mediastinal disorders: Dyspnea, oropharyngeal pain

Skin and Subcutaneous Tissue Disorders: Vitiligo

Table 21: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients Receiving TECENTRIQ Plus Cobimetinib and Vemurafenib Arm or the Placebo Plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4) in IMspire150

Laboratory Abnormality	TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)		Placebo with Cobimetinib and Vemurafenib (n=281)	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Hematology				
Decreased Lymphocytes	80	24	72	17
Decreased Hemoglobin	77	2.6	72	2.2
Decreased Platelet	34	1.3	24	0.4
Decreased Neutrophils	26	2.2	19	1.5
Chemistry				
Increased Creatine Kinase	88	22	81	18
Increased AST	80	13	68	6
Increased ALT	79	18	62	12
Increased Triacylglycerol Lipase	75	46	62	35
Increased Alkaline Phosphatase	73	6	63	2.9
Decreased Phosphorus	67	22	64	14
Increased Amylase	51	13	45	13
Increased Blood Urea Nitrogen	47	NA[1]	37	NA[1]
Decreased Albumin	43	0.9	34	1.5
Increased Bilirubin	42	3.1	33	0.7
Decreased Calcium	41	1.3	28	0
Decreased Sodium	40	5	34	7
Decreased Thyroid-Stimulating Hormone	38	NA[1]	23	NA[1]
Increased Thyroid-Stimulating Hormone [2]	37	NA[1]	33	NA[1]
Decreased Potassium	36	5	22	4.3
Increased Triiodothyronine	33	NA[1]	18	NA[1]
Increased Free Thyroxine	32	NA[1]	21	NA[1]
Decreased Total Triiodothyronine	32	NA[1]	8	NA[1]
Increased Potassium	29	1.3	19	1.4
Decreased Triiodothyronine	27	NA[1]	21	NA[1]
Increased Sodium	20	0	13	0.4

Graded per NCI CTCAE v4.0.
Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ plus cobimetinib and vemurafenib (28-277), placebo plus cobimetinib and vemurafenib arm (25-230).
[1] NA= Not applicable. NCI CTCAE v4.0 does not include these laboratories.
[2] Increased Thyroid Stimulating Hormone has a difference <5% (All Grades) between arms and is included for clinical completeness.

Unresectable or Metastatic Alveolar Soft Part Sarcoma (ASPS)

ML39345 Study

The safety of TECENTRIQ was evaluated in 47 adult and 2 pediatric patients enrolled in Study ML39345 *[see Clinical Studies (14.5)]*. Adult patients received TECENTRIQ 1200 mg every 3 weeks and pediatric patients received 15 mg/kg up to a maximum 1200 mg every 3 weeks until disease progression or unacceptable toxicity. The median duration of exposure to TECENTRIQ was 8.9 months (1 to 40 months).

Serious adverse reactions occurred in 41% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>2%) were fatigue, pain in extremity, pulmonary hemorrhage, and pneumonia (4.1% each).

Dosage interruptions of TECENTRIQ due to an adverse reaction occurred in 35% of patients. The most common adverse reactions (≥3%) leading to dose interruptions were pneumonitis and pain in extremity (4.1% each).

Tables 22 and 23 summarize adverse reactions and laboratory abnormalities in Study ML39345.

Table 22: Adverse Reactions Occurring in ≥15% of Patients with ASPS Receiving TECENTRIQ in ML39345

Adverse Reaction	TECENTRIQ N = 49	
	All Grades (%)	Grades 3–4 (%)
General disorders and administration site conditions		
Fatigue	55	2
Pyrexia	25	2
Influenza like illness	18	0
Gastrointestinal disorders		
Nausea	43	0
Vomiting	37	0
Constipation	33	0
Diarrhea	27	2
Abdominal pain[1]	25	0
Metabolism and nutrition disorders		
Decreased appetite	22	2
Respiratory, Thoracic and Mediastinal		
Cough[2]	45	0
Dyspnea	33	0
Rhinitis allergic	16	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[3]	67	8
Skin and subcutaneous tissue disorders		
Rash[4]	47	2
Nervous system disorders		
Headache	43	4
Dizziness[5]	29	4
Vascular disorders		
Hypertension	43	6
Hemorrhage[6]	29	2
Psychiatric disorders		
Insomnia	27	0
Anxiety	25	0
Cardiac Disorders		
Arrhythmia[7]	22	2
Endocrine disorders		
Hypothyroidism[8]	25	0
Investigations		
Weight decreased	18	0

Weight increased	16	6

Graded per NCI CTCAE v4.0

[1]Includes abdominal pain and abdominal pain upper
[2]Includes cough, upper-airway cough syndrome, and productive cough
[3]Includes arthralgia, pain in extremity, myalgia, non-cardiac chest pain, neck pain, musculoskeletal chest pain, and back pain
[4]Includes rash maculo-papular, rash, dermatitis acneiform, eczema, skin exfoliation, and drug eruption
[5]Includes vertigo and dizziness
[6]Includes pulmonary hemorrhage, hemoptysis, conjunctival hemorrhage, epistaxis, hematuria, rectal hemorrhage, and laryngeal hemorrhage
[7]Includes atrial fibrillation, sinus bradycardia, ventricular tachycardia, and sinus tachycardia
[8]Includes hypothyroidism and blood thyroid stimulating hormone increased

Table 23: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with ASPS Receiving TECENTRIQ in ML39345

Laboratory Abnormality [1]	**TECENTRIQ[2]**	
	All Grades (%)	**Grades 3–4 (%)**
Hematology		
Decreased Hemoglobin	63	0
Decreased Platelets	27	0
Increased Platelets	29	0
Chemistry		
Increased Alkaline Phosphatase	29	0
Decreased Amylase	40	0
Increased Amylase	20	20
Decreased Bilirubin	49	0
Decreased Calcium	47	0
Increased Calcium	25	14
Decreased Glucose	33	0
Increased Glucose	78	0
Decreased Glucose (fasting)	25	0
Decreased Magnesium	21	0
Increased Magnesium	26	26
Increased AST	39	2
Increased ALT	33	2
Decreased Sodium	43	0
Increased Lipase	25	25

[1] Laboratory tests which do not have NCI CTCAE grading criteria are also included for All Grade assessments, which were performed by comparing to respective lab normal ranges.
[2] The denominators used to calculate the rate varied from 4-49 for all tests of interest based on the number of patients with a baseline value and at least one on-study laboratory measurement available.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TECENTRIQ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cardiac: pericarditis, pericardial effusion, cardiac tamponade

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]*, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death *(see Data)*. Advise females of reproductive potential of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

Infertility

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Alveolar Soft Part Sarcoma

The safety and effectiveness of TECENTRIQ for unresectable or metastatic ASPS have been established in pediatric patients aged 2 years and older. Use of TECENTRIQ for this indication is supported by evidence from an adequate and well controlled study of TECENTRIQ in adults and 2 adolescent pediatric patients (≥12 years of age) with ASPS with additional pharmacokinetic and safety data in pediatric patients 2 years to <17 years. These data suggest that atezolizumab exposure in pediatric patients aged 2 years and older is comparable with that of adults and is expected to result in similar safety and efficacy to that of adults *[see Adverse Reactions (6.1), Pharmacokinetics (12.3), Clinical Studies (14.5)]*. The course of unresectable or metastatic ASPS is sufficiently similar between pediatric patients 2 to 11 years old and that of adults and adolescent patients to allow extrapolation of efficacy and safety to pediatric patients 2 years and older.

The safety and effectiveness of TECENTRIQ for ASPS have not been established in pediatric patients younger than 2 years of age.

Solid Tumors and Lymphomas

The safety and effectiveness of TECENTRIQ in pediatric patients have not been established in non-small cell lung cancer, small-cell lung cancer, hepatocellular carcinoma, or melanoma.

The safety and effectiveness of TECENTRIQ were assessed, but not established in a single-arm, multi-center, multi-cohort trial (NCT02541604) in 60 pediatric patients aged 7 months to <17 years with relapsed or progressive solid tumors and lymphomas. No new safety signals were observed in pediatric patients in this study.

8.5 Geriatric Use

TECENTRIQ as a Single-Agent

Of 2616 patients with metastatic NSCLC and other tumor types treated with single agent TECENTRIQ in clinical studies, 49% were 65 years and over and 15% were 75 years and over. No overall differences in safety or effectiveness were observed between patients aged 65 years or older and younger patients.

TECENTRIQ in Combination with Other Antineoplastic Drugs

Of 2421 patients with NSCLC and SCLC treated with TECENTRIQ in combination with other antineoplastic drugs in clinical studies, 48% were 65 years and over and 10% were 75 years and over. No overall differences in safety or effectiveness were observed between patients aged 65 years or older and younger patients.

TECENTRIQ in Combination with Lurbinectedin

Of the 242 patients with ES-SCLC treated with TECENTRIQ in combination with lurbinectedin in IMforte, 124 (51%) patients were 65 years of age and older, while 29 (12%) patients were 75 years of age and older. No overall differences in effectiveness were observed between older and younger patients. There was a higher incidence of Grade 3 or 4 adverse reactions (45% vs 31%) and treatment discontinuation (11% vs 0.8%) in patients ≥ 65 years of age compared to younger patients, respectively.

11 DESCRIPTION

Atezolizumab is a programmed cell death ligand 1 (PD-L1) blocking antibody. Atezolizumab is an Fc-engineered, humanized, non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

TECENTRIQ (atezolizumab) injection for intravenous use is a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. Each 14 mL vial contains 840 mg of atezolizumab and is formulated in glacial acetic acid (11.5 mg), L-histidine (43.4 mg), polysorbate 20 (5.6 mg), and sucrose (575.1 mg) with a pH of 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PD L1 may be expressed on tumor cells and/or tumor infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD L1 to the PD 1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is a monoclonal antibody that binds to PD L1 and blocks its interactions with both PD 1 and B7.1 receptors. This releases the PD L1/PD 1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD L1 activity resulted in decreased tumor growth.

In mouse models of cancer, dual inhibition of the PD-1/PD-L1 and MAPK pathways suppresses tumor growth and improves tumor immunogenicity through increased antigen presentation and T cell infiltration and activation compared to targeted therapy alone.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of atezolizumab have not been fully characterized.

12.3 Pharmacokinetics

Atezolizumab exposure increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg (0.07 to 1.33 times of the approved recommended doses), including a dose of 1200 mg administered every 3 weeks. Steady state was achieved after 6 to 9 weeks following multiple doses. The systemic accumulation ratio for every 2 weeks administration and every 3 weeks administration is 3.3- and 1.9- fold, respectively.

Distribution

The volume of distribution at steady state is 6.9 L.

Elimination

The clearance (CV%) is 0.2 L/day (29%) and the terminal half-life is 27 days. Atezolizumab clearance was found to decrease over time, with a mean maximal reduction (CV%) from baseline value of 17% (41%); however, the decrease in clearance was not considered clinically relevant.

Specific Populations

The following factors had no clinically significant effect on the systemic exposure of atezolizumab: age (2 to 89 years), body weight, sex, albumin levels, tumor burden, region or race, mild or moderate renal impairment [estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m^2], mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 x ULN and any AST), moderate hepatic impairment (bilirubin >1.5 to 3 x ULN and any AST), level of PD-L1 expression, or performance status.

Pediatric Patients

Atezolizumab serum concentrations with weight-based dosing at 15 mg/kg up to a maximum of 1200 mg every 3 weeks, in pediatric patients (2 years to <17 years) with relapsed or progressive solid tumors and lymphomas, are comparable to those of adult patients receiving 1200 mg every 3 weeks; while the exposure tended to be lower in pediatric patients less than 12 years old, this is not considered to be clinically relevant.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other products.

During the first year of treatment with TECENTRIQ across 8 clinical studies, 13% to 36% of patients developed anti-atezolizumab antibodies. Median atezolizumab clearance in patients who tested positive for ADA was 19% (minimum 18%, maximum 49%) higher as compared to atezolizumab clearance in patients who tested negative for ADA; this change in clearance is not expected to be clinically significant.

In OAK and IMbrave150, exploratory analyses showed that the subset of patients who were ADA-positive appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for ADA *[see Clinical Studies (14.1, 14.3)]*. In study IMpower150 and IMforte, the impact of ADA on efficacy did not appear to be clinically significant *[see Clinical Studies (14.1)]*. In the remaining studies, there is insufficient information to characterize the effect of ADA on efficacy.

The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Across clinical studies, the incidence of neutralizing antibodies (NAb) in ADA-positive patients was 24% to 83%. The effect of NAb on atezolizumab exposure and safety did not appear to be clinically significant. The effect of NAb on key efficacy endpoints is uncertain due to small sample sizes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of atezolizumab for carcinogenicity or genotoxicity.

Animal fertility studies have not been conducted with atezolizumab; however, an assessment of the male and female reproductive organs was included in a 26-week, repeat-dose toxicity study in cynomolgus monkeys. Weekly administration of atezolizumab to female monkeys at the highest dose tested caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries. This effect occurred at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible. There was no effect on the male monkey reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer

Adjuvant Treatment of Stage II-IIIA NSCLC with PD-L1 Expression ≥ 1%

The efficacy of TECENTRIQ was evaluated in IMpower010 (NCT02486718), a multi-center, randomized, open-label trial for the adjuvant treatment of patients with NSCLC who had complete tumor resection and were eligible to receive cisplatin-based adjuvant chemotherapy. Eligible patients were required to have Stage IB (tumors ≥ 4 cm) – Stage IIIA NSCLC per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition. Patients were excluded if they had a history of autoimmune disease; a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

A total of 1005 patients who had complete tumor resection and received cisplatin-based adjuvant chemotherapy were randomized (1:1) to receive TECENTRIQ 1200 mg intravenous infusion every 3 weeks for 16 cycles, unless disease recurrence or unacceptable toxicity occurred, or best supportive care (BSC). Randomization was stratified by sex, stage of disease, histology, and PD-L1 expression.

Tumor assessments were conducted at baseline of the randomization phase and every 4 months for the first year following Cycle 1, Day 1 and then every 6 months until year five, then annually thereafter.

The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%) and Asian (24%). Most patients were current or previous smokers (78%) and baseline Eastern Cooperative Oncology Group (ECOG) performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had Stage IB, 47% had Stage II and 41% had Stage IIIA disease. PD-L1 expression, defined as the percentage of tumor cells expressing PD-L1 as measured by the VENTANA PD-L1 (SP263) assay, was ≥ 1% in 53% of patients, <1% in 44% and unknown in 2.6%.

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. The primary efficacy analysis population (n = 476) was patients with Stage II – IIIA NSCLC with PD-L1 expression on ≥ 1% of tumor cells (PD-L1 ≥ 1% TC). DFS was defined as

the time from the date of randomization to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. A key secondary efficacy outcome measure was overall survival (OS) in the intent-to-treat population.

At the time of the interim DFS analysis, the study demonstrated a statistically significant improvement in DFS in the PD-L1 ≥ 1% TC, Stage II – IIIA patient population.

Efficacy results are presented in Table 24 and Figure 1.

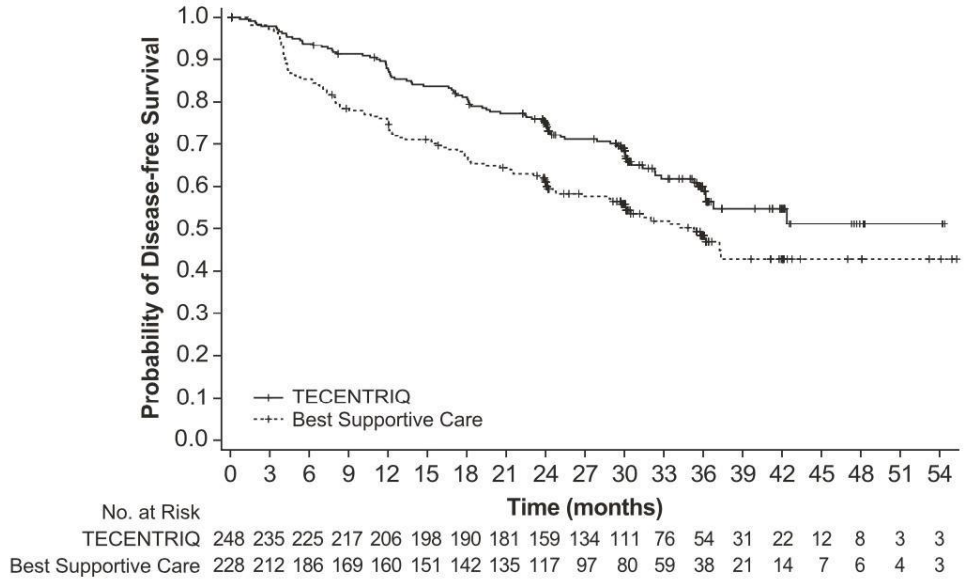
Table 24: Efficacy Results from IMpower010 in Patients with Stage II - IIIA NSCLC with PD-L1 expression ≥ 1% TC

	Arm A: TECENTRIQ N = 248	Arm B: Best Supportive Care N = 228
Disease-Free Survival		
Number of events (%)	88 (35)	105 (46)
Median, months	NR	35.3
(95% CI)	(36.1, NE)	(29.0, NE)
Hazard ratio[1] (95% CI)	0.66 (0.50, 0.88)	
p-value	0.004	

CI = Confidence interval, NE = Not estimable, NR = Not reached
[1] Stratified by stage, sex, and histology

In a pre-specified secondary subgroup analysis of patients with PD-L1 TC ≥ 50% Stage II – IIIA NSCLC (n=229), the median DFS was not reached (95% CI: 42.3 months, NE) for patients in the TECENTRIQ arm and was 35.7 months (95% CI: 29.7, NE) for patients in the best supportive care arm, with a HR of 0.43 (95% CI: 0.27, 0.68). In an exploratory subgroup analysis of patients with PD-L1 TC 1-49% Stage II – IIIA NSCLC (n=247), the median DFS was 32.8 months (95% CI: 29.4, NE) for patients in the TECENTRIQ arm and 31.4 months (95% CI: 24.0, NE) for patients in the best supportive care arm, with a HR of 0.87 (95% CI: 0.60, 1.26).

Figure 1: Kaplan-Meier Plot of Disease-Free Survival in IMpower010 in Patients with Stage II – IIIA NSCLC with PD-L1 expression ≥ 1% TC



At the time of the DFS interim analysis, 19% of patients in the PD-L1 ≥1% TC Stage II – IIIA patient population had died. An exploratory analysis of OS in this population resulted in a stratified HR of 0.77 (95% CI: 0.51, 1.17).

Metastatic Chemotherapy-Naïve NSCLC with High PD-L1 Expression

The efficacy of TECENTRIQ was evaluated in IMpower110 (NCT02409342), a multicenter, international, randomized, open-label trial in patients with stage IV NSCLC whose tumors express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC ≥ 1%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area [IC ≥ 1%]), who had received no prior chemotherapy for metastatic disease. PD-L1 tumor status was determined based on immunohistochemistry (IHC) testing using the VENTANA PD-L1 (SP142) Assay. The evaluation of efficacy is based on the subgroup of patients with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%), excluding those with EGFR or ALK genomic tumor aberrations. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

Randomization was stratified by sex, ECOG performance status, histology (non-squamous vs. squamous) and PD-L1 expression (TC ≥ 1% and any IC vs. TC < 1% and IC ≥ 1%). Patients were randomized (1:1) to receive one of the following treatment arms:

- Arm A: TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity
- Arm B: Platinum-based chemotherapy

Arm B platinum-based chemotherapy regimens for non-squamous NSCLC consisted of cisplatin (75 mg/m²) and pemetrexed (500 mg/m²) OR carboplatin (AUC 6 mg/mL/min) and pemetrexed (500 mg/m²) on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by pemetrexed (500 mg/m²) until disease progression or unacceptable toxicity.

Arm B platinum-based chemotherapy regimens for squamous NSCLC consisted of cisplatin (75 mg/m²) on Day 1 with gemcitabine (1250 mg/m^2) on Days 1 and 8 of each 21-day cycle OR carboplatin (AUC 5 mg/mL/min) on Day 1 with gemcitabine (1000 mg/m^2) on Days 1 and 8 of each 21-day cycle for a maximum of 4 or 6 cycles followed by best supportive care until disease progression or unacceptable toxicity.

Administration of TECENTRIQ was permitted beyond RECIST-defined disease progression. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses.

The major efficacy outcome measure was overall survival (OS) sequentially tested in the following subgroups of patients, excluding those with EGFR or ALK genomic tumor aberrations: TC ≥50% or IC ≥10%; TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%.

Among the 205 chemotherapy-naïve patients with stage IV NSCLC with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) excluding those with EGFR or ALK genomic tumor aberrations, the median age was 65.0 years (range: 33 to 87), and 70% of patients were male. The majority of patients were White (82%) and Asian (17%). Baseline ECOG performance status was 0 (36%) or 1 (64%); 88% were current or previous smokers; and 76% of patients had non-squamous disease while 24% of patients had squamous disease.

The trial demonstrated a statistically significant improvement in OS for patients with high PD-L1 expression (TC ≥50% or IC ≥10%) at the time of the OS interim analysis. There was no statistically significant difference in OS for the other two PD-L1 subgroups (TC ≥5% or IC ≥5%;

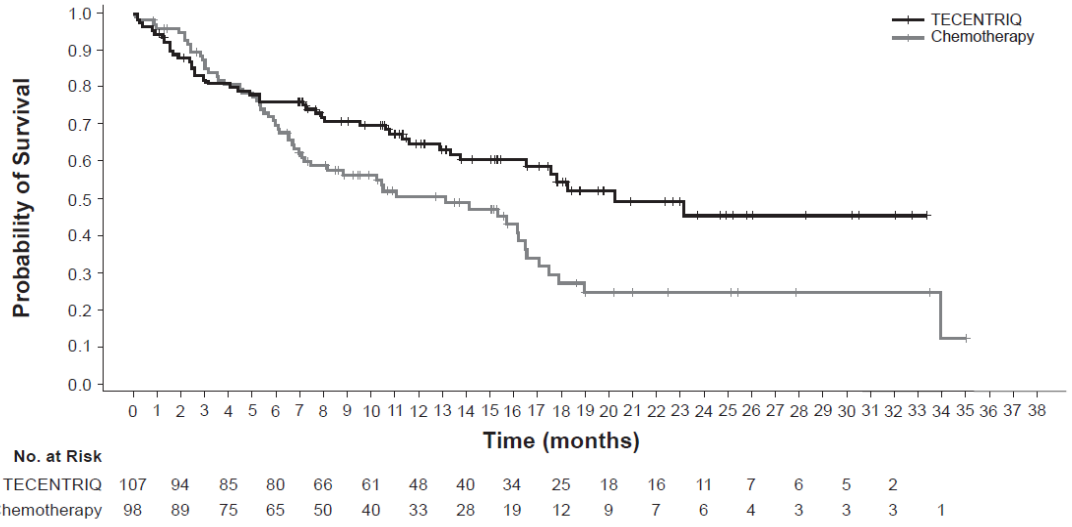
and TC ≥1% or IC ≥1%) at the interim or final analyses. Efficacy results for patients with NSCLC with high PD-L1 expression are presented in Table 25 and Figure 2.

Table 25: Efficacy Results from IMpower110 in Patients with NSCLC with High PD-L1 Expression (TC ≥ 50% or IC ≥ 10%) and without EGFR or ALK Genomic Tumor Aberrations

	Arm A: TECENTRIQ N = 107	Arm B: Platinum-Based Chemotherapy N = 98
Overall Survival[1]		
Deaths (%)	44 (41%)	57 (58%)
Median, months	20.2	13.1
(95% CI)	(16.5, NE)	(7.4, 16.5)
Hazard ratio[2] (95% CI)	0.59 (0.40, 0.89)	
p-value[3]	0.0106[4]	

[1]Based on OS interim analysis. The median survival follow-up time in patients was 15.7 months.
[2]Stratified by sex and ECOG performance status
[3]Based on the stratified log-rank test compared to Arm A
[4]Compared to the allocated alpha of 0.0413 (two-sided) for this interim analysis.
CI=confidence interval; NE=not estimable

Figure 2: Kaplan-Meier Plot of Overall Survival in IMpower110 in Patients with NSCLC with High PD-L1 Expression (TC ≥ 50% or IC ≥ 10%) and without EGFR or ALK Genomic Tumor Aberrations



Investigator-assessed PFS showed an HR of 0.63 (95% CI: 0.45, 0.88), with median PFS of 8.1 months (95% CI: 6.8, 11.0) in the TECENTRIQ arm and 5 months (95% CI: 4.2, 5.7) in the platinum-based chemotherapy arm. The investigator-assessed confirmed ORR was 38% (95% CI: 29%, 48%) in the TECENTRIQ arm and 29% (95% CI: 20%, 39%) in the platinum-based chemotherapy arm.

Metastatic Chemotherapy-Naive Non-Squamous NSCLC

IMpower150

The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial

in patients with metastatic non-squamous NSCLC. Patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (tGE) status and ECOG performance status 0 or 1 were eligible. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, or clear tumor infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions as seen on imaging. Randomization was stratified by sex, presence of liver metastases, and PD-L1 expression status on tumor cells (TC) and tumor-infiltrating immune cells (IC) as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following three treatment arms:

- Arm A: TECENTRIQ 1200 mg, paclitaxel 175 mg/m² or 200 mg/m² and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm B: TECENTRIQ 1200 mg, bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm C: bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

Patients who had not experienced disease progression following the completion or cessation of platinum-based chemotherapy, received:

- Arm A: TECENTRIQ 1200 mg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity
- Arm B: TECENTRIQ 1200 mg and bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity
- Arm C: bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity

Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prior to randomization for PD-L1 tumor expression using the VENTANA PD-L1 (SP142) assay at a central laboratory. Tumor tissue was collected at baseline for expression of tGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures.

Major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-WT (patients with high expression of T-effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT-WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the tGE-WT subpopulation, and ORR/DoR in the tGE-WT and ITT-WT subpopulations.

A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the tGE-WT subpopulation. The demographic information is limited to the 800 patients enrolled in Arms B and C where efficacy has been demonstrated. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were White (82%), 13% of patients were Asian, 10% were Hispanic, and 2% of patients were Black. Clinical sites in Asia (enrolling 13% of the study population) received paclitaxel at a dose of 175 mg/m^2 while the remaining 87% received paclitaxel at a dose of 200 mg/m^2. Approximately 14% of patients had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1

was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK- positive NSCLC.

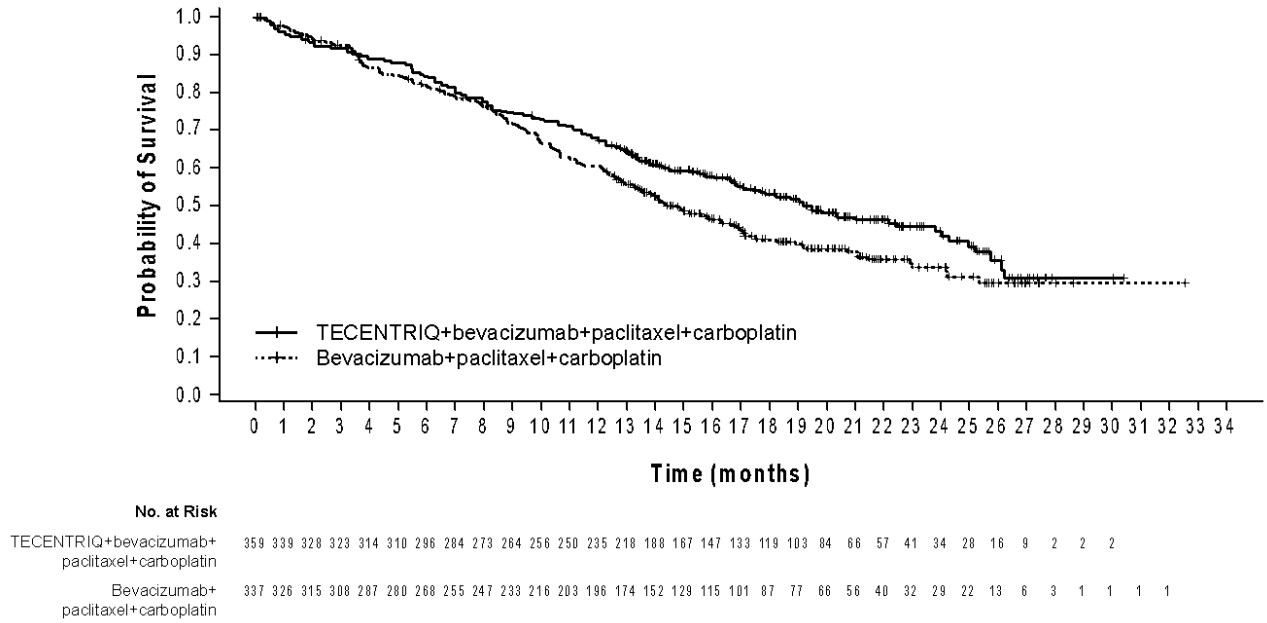
The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 26 and Figure 3.

Table 26: Efficacy Results in ITT-WT Population in IMpower150

	Arm C: Bevacizumab, Paclitaxel and Carboplatin N = 337	Arm B: TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 359	Arm A: TECENTRIQ with Paclitaxel, and Carboplatin N = 349
Overall Survival[1]			
Deaths (%)	197 (59%)	179 (50%)	179 (51%)
Median, months	14.7	19.2	19.4
(95% CI)	(13.3, 16.9)	(17.0, 23.8)	(15.7, 21.3)
Hazard ratio[2] (95% CI)	---	0.78 (0.64, 0.96)	0.84 (0.72, 1.08)
p-value[3]	---	0.016[4]	0.204[5]
Progression-Free Survival[6]			
Number of events (%)	247 (73%)	247 (69%)	245 (70%)
Median, months	7.0	8.5	6.7
(95% CI)	(6.3, 7.9)	(7.3, 9.7)	(5.6, 6.9)
Hazard ratio[2] (95% CI)	---	0.71 (0.59, 0.85)	0.94 (0.79, 1.13)
p-value[3]	---	0.0002[7]	0.5219
Objective Response Rate[6]			
Number of responders (%)	142 (42%)	196 (55%)	150 (43%)
(95% CI)	(37, 48)	(49, 60)	(38, 48)
Complete Response	3 (1%)	14 (4%)	9 (3%)
Partial Response	139 (41%)	182 (51%)	141 (40%)
Duration of Response[6]	n = 142	n = 196	n = 150
Median, months	6.5	10.8	9.5
(95% CI)	(5.6, 7.6)	(8.4, 13.9)	(7.0, 13.0)

[1]Based on OS interim analysis
[2]Stratified by sex, presence of liver metastases, and PD-L1 expression status on TC and IC
[3]Based on the stratified log-rank test compared to Arm C
[4]Compared to the allocated α=0.0174 (two sided) for this interim analysis
[5]Compared to the allocated α=0.0128 (two sided) for this interim analysis
[6]As determined by independent review facility (IRF) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[7]Compared to the allocated α=0.006 (two sided) for the final PFS analysis
CI=confidence interval

Figure 3: Kaplan-Meier Curves for Overall Survival in ITT-WT Population in IMpower150



Exploratory analyses showed that the subset of patients in the four drug regimen arm who were ADA positive by week 4 (30%) appeared to have similar efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (70%) *[see Clinical Pharmacology (12.6)]*. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Similarly ADA negative patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm were compared with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, tobacco history, metastatic site, TC level, and IC level. The hazard ratio comparing the ADA-positive subgroup with its matched control was 0.69 (95% CI: 0.44, 1.07). The hazard ratio comparing the ADA-negative subgroup with its matched control was 0.64 (95% CI: 0.46, 0.90).

IMpower130

The efficacy of TECENTRIQ with paclitaxel protein-bound and carboplatin was evaluated in IMpower130 (NCT02367781), a multicenter, randomized (2:1), open-label trial in patients with stage IV non-squamous NSCLC. Patients with Stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor, if appropriate, were eligible. The trial excluded patients with history of autoimmune disease, administration of live attenuated vaccine within 28 days prior to randomization, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, and active or untreated CNS metastases. Randomization was stratified by sex, presence of liver metastases, and PD-L1 tumor expression according to the VENTANA PD-L1 (SP142) assay as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following treatment regimens:

- TECENTRIQ 1200 mg on Day 1, paclitaxel protein-bound 100 mg/m² on Days 1, 8, and 15, and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by TECENTRIQ 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or
- Paclitaxel protein-bound 100 mg/m² on Days 1, 8 and 15 and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by best supportive care or pemetrexed.

Tumor assessments were conducted every 6 weeks for the first 48 weeks, then every 9 weeks thereafter. Major efficacy outcome measures were PFS by RECIST v1.1 and OS in the subpopulation of patients evaluated for and documented to have no EGFR or ALK genomic tumor aberrations (ITT-WT).

A total of 724 patients were enrolled; of these, 681 (94%) were in the ITT-WT population. The median age was 64 years (range: 18 to 86) and 59% were male. The majority of patients were white (90%), 2% of patients were Asian, 5% were Hispanic, and 4% were Black. Baseline ECOG performance status was 0 (41%) or 1 (58%). Most patients were current or previous smokers (90%). PD-L1 tumor expression was TC0/1/2 and IC0/1 in 73%; TC3 and any IC in 14%; and TC0/1/2 and IC2/3 in 13%.

Efficacy results for the ITT-WT population are presented in Table 27 and Figure 4.

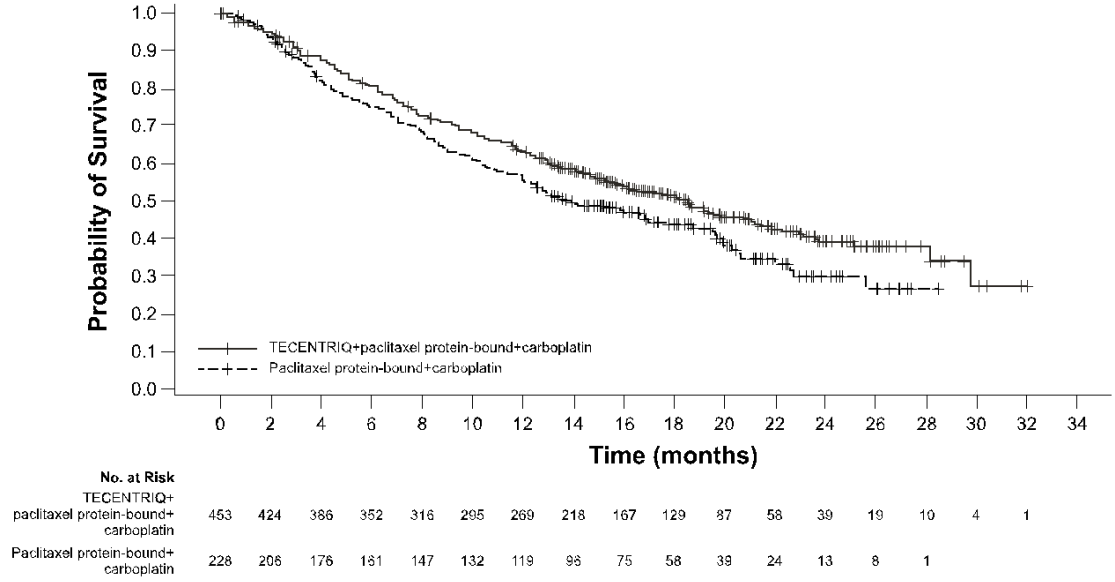
Table 27: Efficacy Results from IMpower130

	TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin	**Paclitaxel Protein-Bound and Carboplatin**
Overall Survival[1]	n=453	n=228
Deaths (%)	228 (50%)	131 (57%)
Median, months	18.6	13.9
(95% CI)	(15.7, 21.1)	(12.0, 18.7)
Hazard ratio[2] (95% CI)	0.80 (0.64, 0.99)	
p-value[3]	0.0384[4]	
Progression-Free Survival[6]	n=453	n=228
Number of events (%)	330 (73%)	177 (78%)
Median, months	7.2	6.5
(95% CI)	(6.7, 8.3)	(5.6, 7.4)
Hazard ratio[2] (95% CI)	0.75 (0.63, 0.91)	
p-value[3]	0.0024[5]	
Overall Response Rate[6,7]	n=453	n=228
Number of responders (%)	207 (46%)	74 (32%)
(95% CI)	(41, 50)	(26, 39)
Complete Response	22 (5%)	2 (1%)
Partial Response	185 (41%)	72 (32%)
Duration of Response[6,7]	n=207	n=74
Median, months	10.8	7.8
(95% CI)	(9.0, 14.4)	(6.8, 10.9)

[1]Based on OS interim analysis
[2]Stratified by sex and PD-L1 tumor expression on tumor cells (TC) and tumor infiltrating cells (IC)

[3]Based on the stratified log-rank test
[4]Compared to the allocated α=0.0428 (two sided) for this interim analysis
[5]Compared to the allocated α=0.006 (two sided) for the final PFS analysis
[6]As determined by independent review facility (IRF) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[7]Confirmed response
CI=confidence interval

Figure 4: Kaplan-Meier Curves for Overall Survival in IMpower130



Previously Treated Metastatic NSCLC

OAK

The efficacy of TECENTRIQ was evaluated in a multicenter, international, randomized (1:1), open-label study (OAK; NCT02008227) conducted in patients with locally advanced or metastatic NSCLC whose disease progressed during or following a platinum-containing regimen. Patients with a history of autoimmune disease, symptomatic or corticosteroid-dependent brain metastases, or requiring systemic immunosuppression within 2 weeks prior to enrollment were ineligible. Randomization was stratified by PD-L1 expression tumor-infiltrating immune cells (IC), the number of prior chemotherapy regimens (1 vs. 2), and histology (squamous vs. non-squamous).

Patients were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 36 weeks and every 9 weeks thereafter. Major efficacy outcome measure was overall survival (OS) in the first 850 randomized patients and OS in the subgroup of patients with PD-L1-expressing tumors (defined as ≥ 1% PD-L1 expression on tumor cells [TC] or immune cells [IC]). Additional efficacy outcome measures were OS in all randomized patients (n = 1225), OS in subgroups based on PD-L1 expression, overall response rate (ORR), and progression free survival as assessed by the investigator per RECIST v.1.1.

Among the first 850 randomized patients, the median age was 64 years (33 to 85 years) and 47% were ≥ 65 years old; 61% were male; 70% were White and 21% were Asian; 15% were current smokers and 67% were former smokers; and 37% had baseline ECOG performance status (PS) of 0 and 63% had a baseline ECOG PS of 1. Nearly all (94%) had metastatic disease, 74% had

non-squamous histology, 75% had received only one prior platinum-based chemotherapy regimen, and 55% of patients had PD-L1-expressing tumors.

Efficacy results are presented in Table 28 and Figure 5.

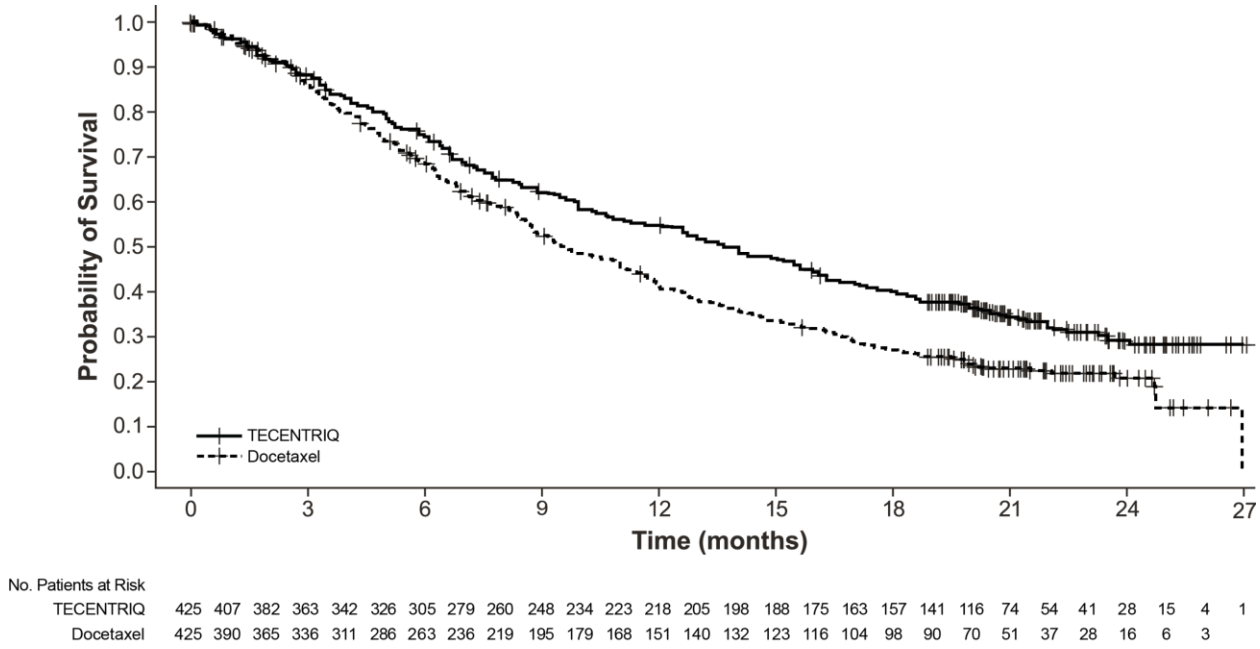
Table 28: Efficacy Results in OAK

	TECENTRIQ	Docetaxel
Overall Survival in first 850 patients		
Number of patients	N=425	N=425
Deaths (%)	271 (64%)	298 (70%)
Median, months	13.8	9.6
(95% CI)	(11.8, 15.7)	(8.6, 11.2)
Hazard ratio[1] (95% CI)	0.74 (0.63, 0.87)	
p-value[2]	0.0004[3]	
Progression-Free Survival		
Number of Patients	N=425	N=425
Events (%)	380 (89%)	375 (88%)
Progression (%)	332 (78%)	290 (68%)
Deaths (%)	48 (11%)	85 (20%)
Median, months	2.8	4.0
(95% CI)	(2.6, 3.0)	(3.3, 4.2)
Hazard ratio[1] (95% CI)	0.95 (0.82, 1.10)	
Overall Response Rate [4]		
Number of Patients	N=425	N=425
ORR, n (%)	58 (14%)	57 (13%)
(95% CI)	(11%, 17%)	(10%, 17%)
Complete Response	6 (1%)	1 (0.2%)
Partial Response	52 (12%)	56 (13%)
Duration of Response[3]	N=58	N=57
Median, months	16.3	6.2
(95% CI)	(10.0, NE)	(4.9, 7.6)
Overall Survival in all 1225 patients		
Number of patients	N=613	N=612
Deaths (%)	384 (63%)	409 (67%)
Median, months	13.3	9.8
(95% CI)	(11.3, 14.9)	(8.9, 11.3)
Hazard ratio[1] (95% CI)	0.79 (0.69, 0.91)	
p-value[2]	0.0013[5]	

[1] Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] Based on the stratified log-rank test
[3] Compared to the pre-specified allocated α of 0.03 for this analysis
[4] Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)

	TECENTRIQ	Docetaxel
[5] Compared to the allocated α of 0.0177 for this interim analysis based on 86% information using O'Brien-Fleming boundary CI=confidence interval; NE=not estimable		

Figure 5: Kaplan-Meier Curves of Overall Survival in the First 850 Patients Randomized in OAK



No. Patients at Risk

TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3	

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (79%) *[see Clinical Pharmacology (12.6)]*. ADA positive patients by week 4 appeared to have similar OS compared to docetaxel-treated patients. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the TECENTRIQ arm with a matched population in the docetaxel arm and ADA negative patients in the TECENTRIQ arm with a matched population in the docetaxel arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, histology (squamous vs. non-squamous), baseline albumin, baseline LDH, gender, tobacco history, metastases status (advanced or local), metastatic site, TC level, and IC level. The hazard ratio comparing the ADA positive subgroup with its matched control was 0.89 (95% CI: 0.61, 1.3). The hazard ratio comparing the ADA negative subgroup with its matched control was 0.68 (95% CI: 0.55, 0.83).

14.2 Small Cell Lung Cancer

IMpower133

The efficacy of TECENTRIQ with carboplatin and etoposide was investigated in IMpower133 (NCT02763579), a randomized (1:1), multicenter, double-blind, placebo-controlled trial in 403 patients with ES-SCLC. IMpower133 enrolled patients with ES-SCLC who had received no prior chemotherapy for extensive stage disease and ECOG performance status 0 or 1. The trial excluded patients with active or untreated CNS metastases, history of autoimmune disease, administration of a live, attenuated vaccine within 4 weeks prior to randomization, or administration of systemic immunosuppressive medications within 1 week prior to randomization. Randomization was stratified by sex, ECOG performance status, and presence of brain metastases. Patients were randomized to receive one of the following two treatment arms:

- TECENTRIQ 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles followed by TECENTRIQ 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or
- placebo and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles followed by placebo once every 3 weeks until disease progression or unacceptable toxicity.

Administration of TECENTRIQ was permitted beyond RECIST-defined disease progression. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients treated beyond disease progression had tumor assessment conducted every 6 weeks until treatment discontinuation.

Major efficacy outcome measures were OS and PFS as assessed by investigator per RECIST v1.1 in the intent-to-treat population. Additional efficacy outcome measures included ORR and DoR as assessed by investigator per RECIST v1.1.

A total of 403 patients were randomized, including 201 to the TECENTRIQ arm and 202 to the chemotherapy alone arm. The median age was 64 years (range 26 to 90) and 65% were male. The majority of patients were White (80%); 17% were Asian, 4% were Hispanic and 1% were Black. Baseline ECOG performance status was 0 (35%) or 1 (65%); 9% of patients had a history of brain metastases, and 97% were current or previous smokers.

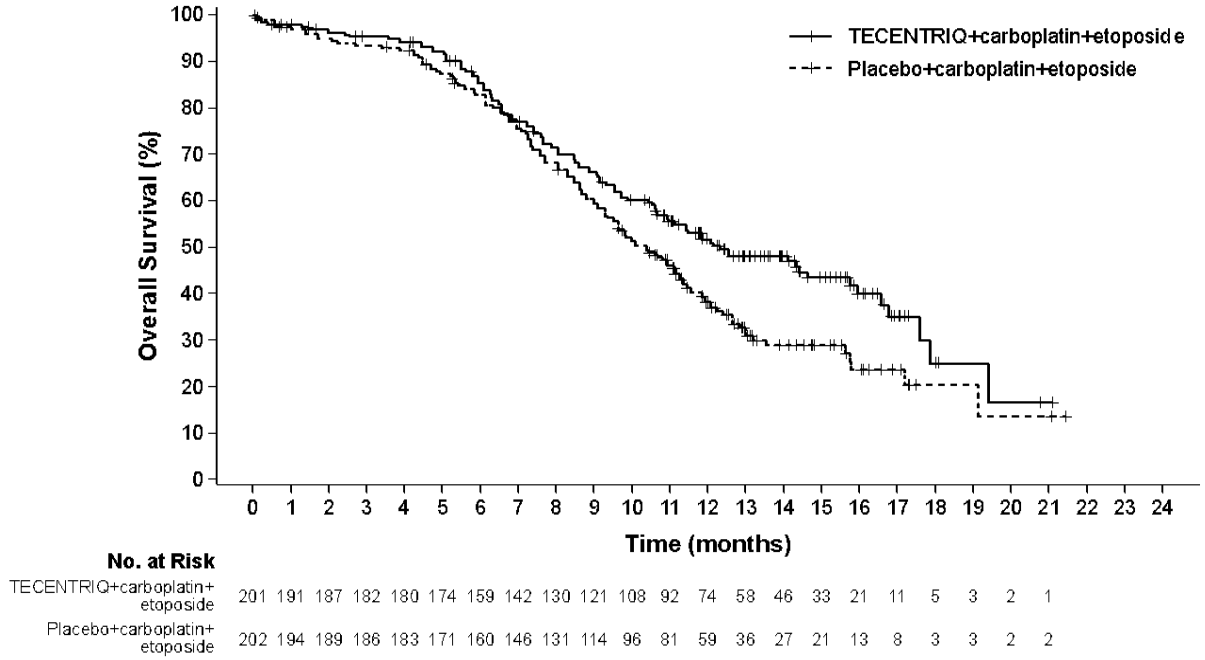
Efficacy results are presented in Table 29 and Figure 6.

Table 29: Efficacy Results from IMpower133

	TECENTRIQ with Carboplatin and Etoposide	Placebo with Carboplatin and Etoposide
Overall Survival	N=201	N=202
Deaths (%)	104 (52%)	134 (66%)
Median, months	12.3	10.3
(95% CI)	(10.8, 15.9)	(9.3, 11.3)
Hazard ratio[3] (95% CI)	0.70 (0.54, 0.91)	
p-value[4, 5]	0.0069	
Progression-Free Survival[1,2]	N=201	N=202
Number of events (%)	171 (85%)	189 (94%)
Median, months	5.2	4.3
(95% CI)	(4.4, 5.6)	(4.2, 4.5)
Hazard ratio[3] (95% CI)	0.77 (0.62, 0.96)	
p-value[4, 6]	0.0170	
Objective Response Rate[1,2,7]	N=201	N=202
Number of responders (%)	121 (60%)	130 (64%)
(95% CI)	(53, 67)	(57, 71)
Complete Response (%)	5 (2%)	2 (1%)
Partial Response (%)	116 (58%)	128 (63%)
Duration of Response[1,2,7]	N=121	N=130
Median, months	4.2	3.9
(95% CI)	(4.1, 4.5)	(3.1, 4.2)

[1]As determined by investigator assessment
[2] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[3]Stratified by sex and ECOG performance status
[4]Based on the stratified log-rank test
[5]Compared to the allocated α of 0.0193 for this interim analysis based on 78% information using O'Brien-Fleming boundary
[6]Compared to the allocated α of 0.05 for this analysis
[7]Confirmed response
CI=confidence interval

Figure 6: Kaplan-Meier Plot of Overall Survival in IMpower133



IMforte

The efficacy of TECENTRIQ in combination with lurbinectedin as maintenance treatment was evaluated in IMforte (NCT05091567), a randomized, multicenter, open-label study in patients with ES-SCLC. Patients were eligible if their disease had not progressed after completion of four cycles of TECENTRIQ, carboplatin and etoposide (induction treatment) and they had an ECOG performance status of 0 or 1. The trial excluded patients with CNS metastases, history of autoimmune disease, or administration of systemic immunosuppressive medications within 1 week prior to enrollment. Unless contraindicated, primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was mandated for patients assigned to the TECENTRIQ with lurbinectedin arm.

The trial randomized 483 patients who had not experienced disease progression following the completion of four cycles of TECENTRIQ with carboplatin and etoposide to one of the following two treatment arms:

- TECENTRIQ 1200 mg IV in combination with lurbinectedin 3.2 mg/m^2 IV once every 3 weeks until disease progression or unacceptable toxicity, or
- TECENTRIQ 1200 mg IV once every 3 weeks until disease progression or unacceptable toxicity

Randomization was stratified by ECOG performance status prior to randomization (0 vs. 1), lactate dehydrogenase (LDH) (≤ ULN vs. > ULN) prior to randomization, presence of liver metastases prior to initial study enrollment (yes vs. no), and prior receipt of prophylactic cranial irradiation (yes vs. no).

The major efficacy outcome measures were OS and PFS by Independent Review Facility (IRF) per RECIST v1.1.

A total of 483 patients were randomized, including 242 to the TECENTRIQ with lurbinectedin arm and 241 to the TECENTRIQ arm. The median age was 66 years (range 35 to 85 years); 63% male; 82% White; 13% Asian; 0.8% were Black or African American; 7% were of Hispanic or Latino ethnicity and 98% were current or previous smokers. Baseline ECOG performance status was 0 (43%) or 1 (57%).

Efficacy results are presented in Table 30 and Figures 7 and 8.

Table 30: Efficacy Results from IMforte

	TECENTRIQ with Lurbinectedin N=242	TECENTRIQ N=241
Overall Survival [1]		
Deaths (%)	113 (47%)	136 (56%)
Median, months	13.2	10.6
(95% CI)	(11.9, 16.4)	(9.5, 12.2)
Hazard ratio[2] (95% CI)	0.73 (0.57, 0.95)	
p-value[3, 6]	0.0174	
Progression-Free Survival [1, 4, 5]		
Number of events (%)	174 (72%)	202 (84%)
Median, months	5.4	2.1
(95% CI)	(4.2, 5.8)	(1.6, 2.7)
Hazard ratio[2] (95% CI)	0.54 (0.43, 0.67)	
p-value[3, 7]	<0.0001	

[1]Measured from the time of randomization
[2]Stratified by ECOG performance status, LDH level, presence of liver metastases and prior receipt of prophylactic cranial irradiation
[3]Based on the stratified log-rank test
[4]As determined by an IRF
[5]per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[6]Compared to the allocated alpha of 0.0313 (two-sided) for this interim OS analysis.
[7]Compared to the allocated alpha of 0.001 (two- sided) for this final PFS analysis.
CI=confidence interval

Figure 7: Kaplan-Meier Plot of IRF-assessed Progression-Free Survival in IMforte

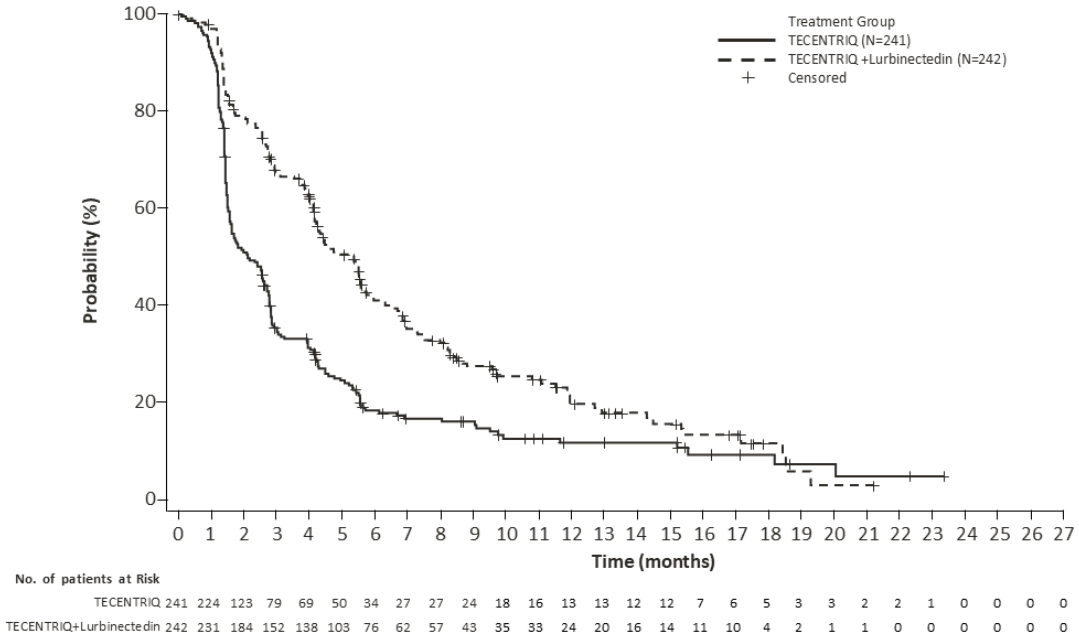
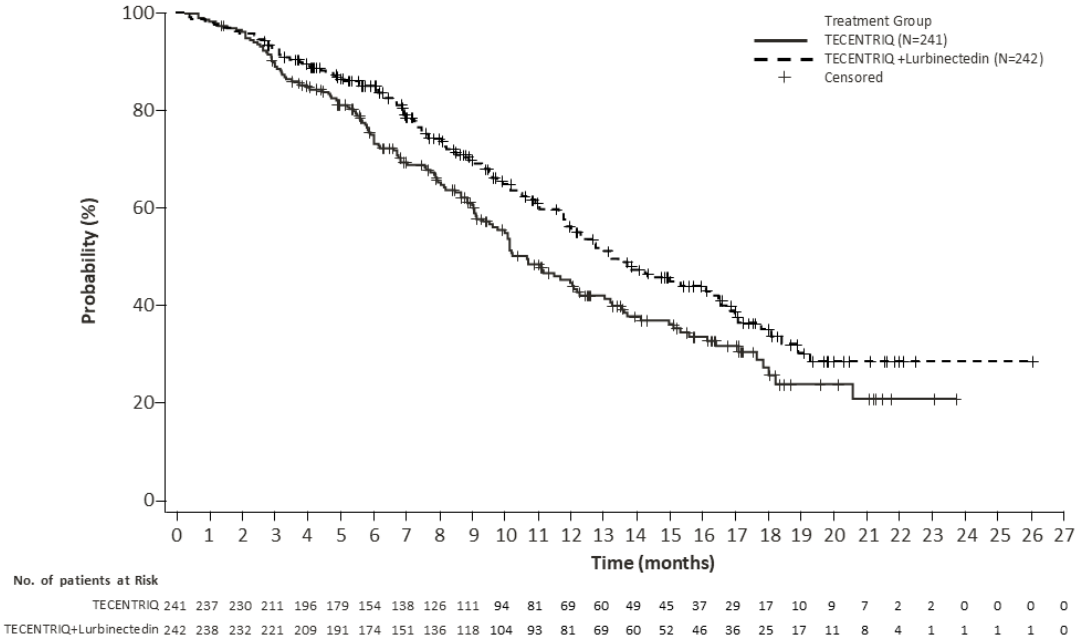


Figure 8: Kaplan-Meier Plot of Overall Survival in IMforte



14.3 Hepatocellular Carcinoma

The efficacy of TECENTRIQ in combination with bevacizumab was investigated in IMbrave150 (NCT03434379), a multicenter, international, open-label, randomized trial in patients with locally advanced unresectable and/or metastatic hepatocellular carcinoma who have not received prior systemic therapy. Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline AFP (<400 vs. ≥400 ng/mL), and by ECOG performance status (0 vs. 1).

A total of 501 patients were randomized (2:1) to receive either TECENTRIQ as an intravenous infusion of 1200 mg, followed by 15 mg/kg bevacizumab, on the same day every 3 weeks or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. Patients could discontinue either TECENTRIQ or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until disease progression or unacceptable toxicity associated with the single-agent.

The study enrolled patients who were ECOG performance score 0 or 1 and who had not received prior systemic treatment. Patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding. Patients with Child-Pugh B or C cirrhosis, moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; or untreated or corticosteroid-dependent brain metastases were excluded. Tumor assessments were performed every 6 weeks for the first 54 weeks and every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 65 years (range: 26 to 88) and 83% of patients

were male. The majority of patients were Asian (57%) or White (35%); 40% were from Asia (excluding Japan). Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). HCC risk factors were Hepatitis B in 48% of patients, Hepatitis C in 22%, and 31% of patients had non-viral liver disease. The majority of patients had BCLC stage C (82%) disease at baseline, while 16% had stage B, and 3% had stage A.

The major efficacy outcome measures were overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) per RECIST v1.1. Additional efficacy outcome measures were IRF-assessed overall response rate (ORR) per RECIST and mRECIST.

Efficacy results are presented in Table 31 and Figure 9.

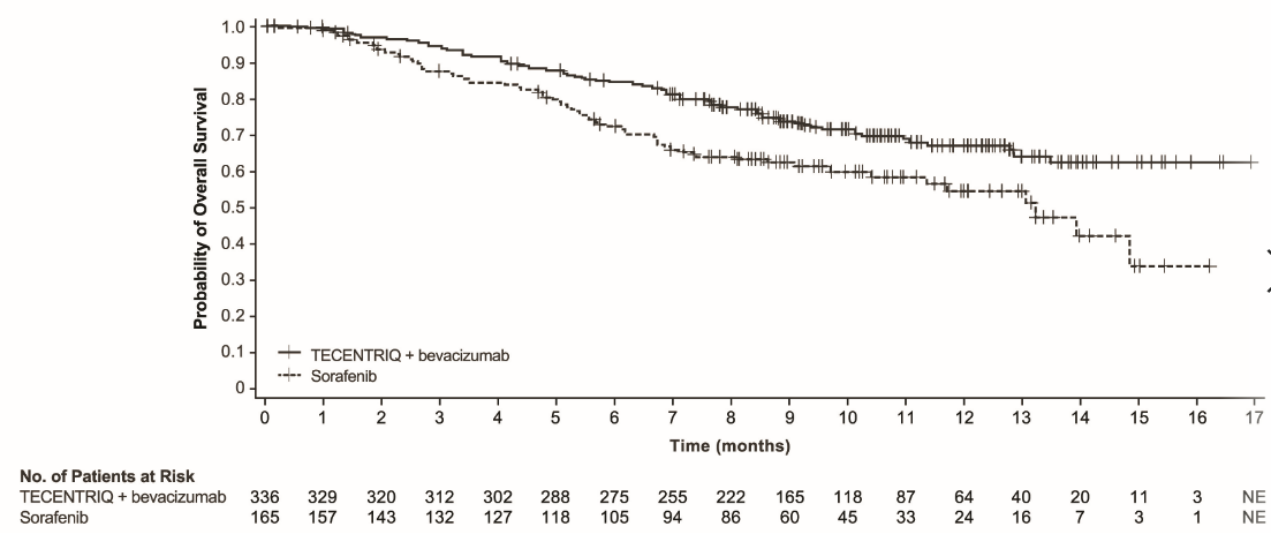
Table 31: Efficacy Results from IMbrave150

	TECENTRIQ in combination with Bevacizumab (N= 336)	**Sorafenib (N=165)**
Overall Survival		
Number of deaths (%)	96 (29)	65 (39)
Median OS in months (95% CI)	NE (NE, NE)	13.2 (10.4, NE)
Hazard ratio[1] (95% CI)	0.58 (0.42, 0.79)	
p-value[2]	0.0006[2]	
Progression-Free Survival[3]		
Number of events (%)	197 (59)	109 (66)
Median PFS in months (95% CI)	6.8 (5.8, 8.3)	4.3 (4.0, 5.6)
Hazard ratio[1] (95% CI)	0.59 (0.47, 0.76)	
p-value	<0.0001	
Overall Response Rate[3,5](ORR), RECIST 1.1		
Number of responders (%)	93 (28)	19 (12)
(95% CI)	(23, 33)	(7,17)
p-value[4]	<0.0001	
Complete responses, n (%)	22 (7)	0
Partial responses, n (%)	71 (21)	19 (12)
Duration of Response[3,5] (DOR) RECIST 1.1		
	(n=93)	(n=19)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.7, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)
Overall Response Rate[3,5] (ORR), HCC mRECIST		
Number of responders (%)	112 (33)	21 (13)
(95% CI)	(28, 39)	(8, 19)
p-value[4]	<0.0001	
Complete responses, n (%)	37 (11)	3 (1.8)
Partial responses, n (%)	75 (22)	18 (11)
Duration of Response[3,5] (DOR) HCC mRECIST		
	(n=112)	(n=21)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.9, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)

[1] Stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)
[2] Based on two-sided stratified log-rank test; as compared to significance level 0.004 (2-sided) based on 161/312=52% information using the OBF method
[3] Per independent radiology review
[4] Based on two-sided Cochran-Mantel-Haesnszel test

[5] Confirmed responses
+ Denotes a censored value
CI=confidence interval; HCC mRECIST=Modified RECIST Assessment for Hepatocellular Carcinoma; NE=not estimable; RECIST 1.1=Response Evaluation Criteria in Solid Tumors v1.1

Figure 9: Kaplan-Meier Plot of Overall Survival in IMbrave150



Exploratory analyses showed that the subset of patients (20%) who were ADA-positive by week 6 appeared to have reduced efficacy (effect on OS) as compared to patients (80%) who tested negative for treatment-emergent ADA by week 6 *[see Clinical Pharmacology (12.6)]*. ADA-positive patients by week 6 appeared to have similar overall survival compared to sorafenib-treated patients. In an exploratory analysis, inverse probability weighting was conducted to compare ADA-positive patients and ADA-negative patients in the TECENTRIQ and bevacizumab arm to the sorafenib arm. Inverse probability weighting factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, age, race, geographic region, weight, neutrophil-to-lymphocyte ratio, AFP (<400 ng/mL vs ≥400 ng/mL), number of metastatic sites, MVI and/or EHS present at study entry, etiology (HBV vs. HCV vs. non-viral) and Child-Pugh Score (A5 vs. A6). The OS hazard ratio comparing the ADA-positive subgroup of the TECENTRIQ and bevacizumab arm to sorafenib was 0.93 (95% CI: 0.57, 1.53). The OS hazard ratio comparing the ADA-negative subgroup to sorafenib was 0.39 (95% CI: 0.26, 0.60).

14.4 Melanoma

The efficacy of TECENTRIQ in combination with cobimetinib and vemurafenib was evaluated in a double-blind, randomized (1:1), placebo-controlled, multicenter trial (IMspire150; NCT02908672) conducted in 514 patients. Randomization was stratified by geographic location (North America vs. Europe vs. Australia, New Zealand, and others) and baseline lactate dehydrogenase (LDH) [less than or equal to upper limit of normal (ULN) vs. greater than ULN]. Eligible patients were required to have previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma as detected by a locally available test and centrally confirmed with the FoundationOne™ assay. Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic

immunosuppressive medications within 2 weeks prior to randomization; and active or untreated CNS metastases.

TECENTRIQ was initiated after patients received a 28-day treatment cycle of cobimetinib 60 mg orally once daily (21 days on / 7 days off) and vemurafenib 960 mg orally twice daily Days 1-21 and 720 mg orally twice daily Days 22-28. Patients received TECENTRIQ 840 mg intravenous infusion over 60 minutes every 2 weeks in combination with cobimetinib 60 mg orally once daily and vemurafenib 720 mg orally twice daily, or placebo in combination with cobimetinib 60 mg orally once daily and vemurafenib 960 mg orally twice daily. Treatment continued until disease progression or unacceptable toxicity. There was no crossover at the time of disease progression. Tumor assessments were performed every 8 weeks (± 1 week) for the first 24 months and every 12 weeks (± 1 week) thereafter.

The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) per RECIST v1.1. Additional efficacy outcomes included PFS assessed by an independent central review, investigator-assessed ORR, OS, and DOR.

The median age of the study population was 54 years (range: 22-88), 58% of patients were male, 95% were White, a baseline ECOG performance status of 0 (77%) or 1 (23%), 33% had elevated LDH, 94% had metastatic disease, 60% were Stage IV (M1C), 56% had less than three metastatic sites at baseline, 3% had prior treatment for brain metastases, 30% had liver metastases at baseline, and 14% had received prior adjuvant systemic therapy. Based on central testing, 74% were identified as having a V600E mutation, 11% as having V600K mutation, and 1% as having V600D or V600R mutations.

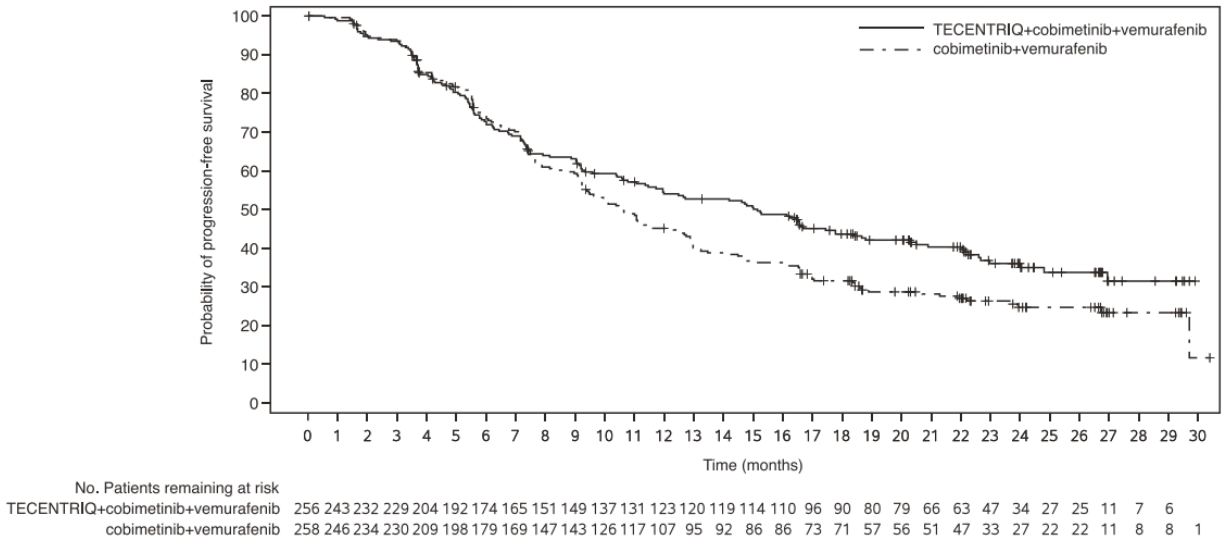
Efficacy results are summarized in Table 32 and Figure 10. Patients had a median survival follow up time of 18.9 months.

Table: 32 Efficacy Results from IMspire150

	TECENTRIQ + Cobimetinib + Vemurafenib N=256	Placebo + Cobimetinib + Vemurafenib N=258
Progression-Free Survival[1]		
Number of events (%)	148 (58)	179 (69)
Median, months	15.1	10.6
(95% CI)	(11.4, 18.4)	(9.3, 12.7)
Hazard ratio[2] (95% CI)	0.78 (0.63, 0.97)	
p-value[3]	0.0249	
Overall Response Rate[1,4]		
Number of responders (%)	170 (66)	168 (65)
(95% CI)	(60, 72)	(59, 71)
Complete responses, n (%)	41 (16)	46 (18)
Partial response, n (%)	129 (50)	122 (47)
Duration of Response[1,4]	n=170	n=168
Median, months	20.4	12.5
(95% CI)	(15.1, NE)	(10.7, 16.6)

[1] As determined by investigator assessment with Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval
[2] Stratified by baseline LDH
[3] Based on the stratified log-rank test
[4] Confirmed Responses

Figure 10: Kaplan-Meier Plot for Progression-Free Survival in IMspire150



At a pre-specified analysis at the time of the primary analysis of PFS, the OS data were not mature. The median OS was 28.8 months with 93 (36%) deaths in the TECENTRIQ plus cobimetinib and vemurafenib arm, and 25.1 months with 112 (43%) deaths in the placebo plus

cobimetinib and vemurafenib arm. The hazard ratio for OS was 0.85 (95% CI: 0.64, 1.11) and the p-value was 0.2310.

14.5 Alveolar soft part sarcoma (ASPS)

The efficacy of TECENTRIQ was evaluated in study ML39345 (NCT03141684), an open-label, single-arm study, in 49 adult and pediatric patients aged 2 years and older with unresectable or metastatic ASPS. Eligible patients were required to have histologically or cytologically confirmed ASPS that was not curable by surgery, and an ECOG performance status of ≤ 2.

Patients were excluded if they had known primary central nervous system (CNS) malignancy or symptomatic CNS metastases, known clinically significant liver disease, or history of idiopathic pulmonary fibrosis, pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.

Adult patients received 1200 mg intravenously and pediatric patients received 15 mg/kg (up to a maximum of 1200 mg) intravenously once every 21 days until disease progression or unacceptable toxicity.

The major efficacy outcomes were Overall Response Rate (ORR) and Duration of Response (DOR) by Independent Review Committee according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

A total of 49 patients were enrolled. The median age of patients was 31 years (range: 12-70); 2% of adult patients (n=47) were ≥65 years of age and the pediatric patients (n=2) were ≥12 years of age; 51% of patients were female, 55% White, 29% Black or African American, 10% Asian; 53% had an ECOG performance status of 0 and 45% had an ECOG performance status of 1. All patients had prior surgery for ASPS and 55% received at least one prior line of treatment for ASPS; 55% received radiotherapy and 53% received chemotherapy. Of the patients who reported staging at initial diagnosis, all were Stage IV.

Efficacy results of this study are summarized in Table 33.

Table 33: Efficacy Results from Study ML39345

Endpoint	**All Patients** (N=49)
Overall response rate (95% CI)[a]	24% (13, 39)
Complete Responses, n	0
Partial Responses, n (%)	12 (24)
Duration of response	
Median, month	NE
(95% CI)	(17.0, NE)
Range	1+, 41+
Durability of Response	
≥6 months, n (%)	8 (67%)
≥12 months, n (%)	5 (42%)

CI: confidence interval; N: number of patients; +: Censored

[a] 95% CI based on Clopper–Pearson exact method.

16 HOW SUPPLIED/STORAGE AND HANDLING

TECENTRIQ injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion supplied as a carton containing one 840 mg/14 mL single-dose vial (NDC 50242-918-01) or 1,200 mg/20 mL single-dose vial (NDC 50242-917-01).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of TECENTRIQ, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis *[see Warnings and Precautions (5.1)]*.
- Nephritis: Advise patients to contact their healthcare provider immediately for pelvic pain, frequent urination, or unusual swelling. *[see Warnings and Precautions (5.1)]*.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately for generalized rash, skin eruption, or painful skin and mucous membrane lesions *[see Warnings and Precautions (5.1)]*.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT after PD-1/PD-L1 inhibitors

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

U.S. License No.: 1048

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MEDICATION GUIDE
TECENTRIQ® (te-SEN-trik)
(atezolizumab)
Injection

What is the most important information I should know about TECENTRIQ?

TECENTRIQ is a medicine that may treat certain cancers by working with your immune system. TECENTRIQ can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during your treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worse signs or symptoms, including:

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heart beat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

Problems can also happen in other organs. These are not all of the signs and symptoms of immune system problems that can happen with TECENTRIQ. Call or see your healthcare provider right away for any new or worse signs or symptoms, including:

- chest pain, irregular heartbeat, shortness of breath, or swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

Infusion reactions that can sometimes be severe or life-threatening. Signs and symptoms of infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness
- feeling like passing out
- fever
- back or neck pain

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These

complications may happen if you underwent transplantation either before or after being treated with TECENTRIQ. Your healthcare provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious.
Your healthcare provider will check you for these problems during your treatment with TECENTRIQ. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with TECENTRIQ if you have severe side effects.

What is TECENTRIQ?

TECENTRIQ is a prescription medicine used to treat:

- **adults with a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - **TECENTRIQ may be used alone as a treatment for your lung cancer:**
    - to help prevent your lung cancer from coming back after your tumor(s) has been removed by surgery and you have received platinum-based chemotherapy, **and**
    - you have stage 2 to stage 3A NSCLC (talk to your healthcare provider about what these stages mean), **and**
    - your cancer tests positive for "PD-L1".
  - **TECENTRIQ may be used alone as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - your cancer tests positive for "high PD-L1", **and**
    - your tumor does not have an abnormal "EGFR" or "ALK" gene.
  - **TECENTRIQ may be used with the medicines bevacizumab, paclitaxel, and carboplatin as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - is a type called "non-squamous NSCLC", **and**
    - your tumor does not have an abnormal "EGFR" or "ALK" gene.
  - **TECENTRIQ may be used with the medicines paclitaxel protein-bound and carboplatin as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - is a type called "non-squamous NSCLC", **and**
    - your tumor does not have an abnormal "EGFR" or "ALK" gene.
  - **TECENTRIQ may also be used alone when your lung cancer:**
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
    - if your tumor has an abnormal "EGFR" or "ALK" gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, and it did not work or is no longer working.
- **adults with a type of lung cancer called "extensive-stage small cell lung cancer (SCLC)", which is SCLC that has spread or grown.**
  - **TECENTRIQ may be used with the chemotherapy medicines carboplatin and etoposide as your first treatment.**
  - **TECENTRIQ may be used with the medicine lurbinectedin as maintenance treatment when your lung cancer:**
    - has not progressed after first treatment with TECENTRIQ or atezolizumab and hyaluronidase-tqjs and the chemotherapy medicines carboplatin and etoposide.
- **adults with a type of liver cancer called hepatocellular carcinoma (HCC). TECENTRIQ may be used with the medicine bevacizumab when your liver cancer:**
  - has spread or cannot be removed by surgery, **and**
  - you have not received other medicines by mouth or injection through your vein (IV) to treat your cancer.
- **adults with a type of skin cancer called melanoma. TECENTRIQ may be used with the medicines cobimetinib and vemurafenib when your melanoma:**
  - has spread to other parts of the body or cannot be removed by surgery, **and**
  - has a certain type of abnormal "BRAF" gene. Your healthcare provider will perform a test to make sure this TECENTRIQ combination is right for you.
- **adults and children 2 years of age and older with a type of soft tissue tumor (cancer) called alveolar soft part sarcoma (ASPS). TECENTRIQ may be used when your sarcoma:**
  - has spread to other parts of the body or cannot be removed by surgery.

It is not known if TECENTRIQ is safe and effective when used:

- in children younger than 2 years of age for the treatment of ASPS.
- in children for the treatment of NSCLC, SCLC, HCC, or melanoma.

Before receiving TECENTRIQ, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. TECENTRIQ can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with TECENTRIQ.

Females who are able to become pregnant:

  - Your healthcare provider should do a pregnancy test before you start treatment with TECENTRIQ.
  - You should use an effective method of birth control during your treatment and for at least 5 months after the last dose of TECENTRIQ.

- are breastfeeding or plan to breastfeed. It is not known if TECENTRIQ passes into your breast milk. Do not breastfeed during treatment and for at least 5 months after the last dose of TECENTRIQ.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive TECENTRIQ?

- Your healthcare provider will give you TECENTRIQ into your vein through an intravenous (IV) line over 30 to 60 minutes.
- TECENTRIQ is usually given every 2, 3, or 4 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will test your blood to check you for certain side effects.
- For treatment of a type of skin cancer called melanoma, your healthcare provider will also prescribe you cobimetinib and vemurafenib. Take cobimetinib and vemurafenib exactly as your healthcare provider tells you.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of TECENTRIQ?

TECENTRIQ can cause serious side effects, including:

- **See "What is the most important information I should know about TECENTRIQ?"**

The most common side effects of TECENTRIQ when used alone include:

- feeling tired or weak
- decreased appetite
- nausea
- cough
- shortness of breath

The most common side effects of TECENTRIQ when used in lung cancer with other anti-cancer medicines include:

- feeling tired or weak
- nausea
- hair loss
- constipation
- diarrhea
- decreased appetite

The most common side effects of TECENTRIQ when used in hepatocellular carcinoma with bevacizumab include:

- high blood pressure
- feeling tired or weak
- too much protein in the urine

The most common side effects of TECENTRIQ when used in melanoma with cobimetinib and vemurafenib include:

- skin rash
- joint, muscle, or bone pain
- feeling tired or weak
- liver injury
- fever
- nausea
- itching
- swelling of legs or arms
- mouth swelling (sometimes with sores)
- low thyroid hormone levels
- sunburn or sun sensitivity

TECENTRIQ may cause fertility problems in females, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of TECENTRIQ.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TECENTRIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about TECENTRIQ that is written for health professionals.

What are the ingredients in TECENTRIQ?

Active ingredient: atezolizumab

Inactive ingredients: glacial acetic acid, L-histidine, polysorbate 20 and sucrose

Manufactured by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990 USA
U.S. License No.: 1048 TECENTRIQ is a registered trademark of Genentech, Inc.
For more information, call 1-844-832-3687 or go to www.TECENTRIQ.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: 10/2025

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tecentriq 840 mg concentrate for solution for infusion
Tecentriq 1 200 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tecentriq 840 mg concentrate for solution for infusion

One 14 mL vial of concentrate contains 840 mg of atezolizumab*

Tecentriq 1 200 mg concentrate for solution for infusion

One 20 mL vial of concentrate contains 1 200 mg atezolizumab*

After dilution (see section 6.6), the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL.

*Atezolizumab is an Fc-engineered, humanised IgG1 anti-programmed death-ligand 1 (PD-L1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient with known effect
Each 840 mg vial of Tecentriq contains 5.6 mg of polysorbate 20.
Each 1 200 mg vial of Tecentriq contains 8 mg of polysorbate 20.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly yellowish liquid. The solution has a pH of 5.5 - 6.1 and an osmolality of 129 - 229 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Urothelial carcinoma (UC)

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC:

- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% (see section 5.1).

Early-stage non-small cell lung cancer (NSCLC)

Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR-mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).

Advanced NSCLC

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR-mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1).

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR-mutant or ALK-positive NSCLC (see section 5.1).

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR-mutant or ALK-positive NSCLC (see section 5.1).

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy (see section 5.1 for selection criteria).

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq (see section 5.1).

Small cell lung cancer (SCLC)

Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (see section 5.1).

Triple-negative breast cancer (TNBC)

Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

Hepatocellular carcinoma (HCC)

Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy (see section 5.1).

4.2 Posology and method of administration

Tecentriq must be initiated and supervised by physicians experienced in the treatment of cancer.

PD-L1 testing for patients with UC or TNBC or NSCLC

Tecentriq monotherapy

If specified in the indication, patient selection for treatment with Tecentriq based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1 and 5.1).

Tecentriq in combination therapy

Patients with previously untreated TNBC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology

The recommended dose of Tecentriq is either 840 mg administered intravenously every two weeks, or 1 200 mg administered intravenously every three weeks, **or** 1 680 mg administered intravenously every four weeks, as presented in Table 1.

When Tecentriq is administered in combination therapy please also refer to the full prescribing information for the combination products (see also section 5.1).

Table 1: Recommended dose for Tecentriq by intravenous administration

Indication	**Recommended dose and schedule**	**Duration of treatment**
Tecentriq monotherapy		
1L UC 1L metastatic NSCLC 1L platinum-ineligible NSCLC	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks	Until disease progression or unmanageable toxicity.
Early-stage NSCLC	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks	For 1 year unless disease recurrence or unacceptable toxicity. Treatment duration for more than 1 year was not studied.
2L UC 2L NSCLC	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks	Until loss of clinical benefit or unmanageable toxicity.
Tecentriq combination therapy		
1L non-squamous NSCLC with bevacizumab, paclitaxel, and carboplatin	Induction and maintenance phases: • 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four or six cycles): Bevacizumab, paclitaxel, and then carboplatin are administered every three weeks. Maintenance phase (without chemotherapy): Bevacizumab every 3 weeks.	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be considered at the discretion of the physician.
1L non-squamous NSCLC with nab-paclitaxel and carboplatin	Induction and maintenance phases: • 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four or six cycles): Nab-paclitaxel, and carboplatin are administered on day 1; in addition,	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be

Indication	Recommended dose and schedule	Duration of treatment
	nab-paclitaxel is administered on days 8 and 15 of each 3-weekly cycle.	considered at the discretion of the physician.
1L ES-SCLC with carboplatin and etoposide	Induction and maintenance phases: • 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four cycles): Carboplatin, and then etoposide are administered on day 1; etoposide is also administered on days 2 and 3 of each 3-weekly cycle.	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be considered at the discretion of the physician.
1L unresectable locally advanced or metastatic TNBC with nab-paclitaxel	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered prior to nab-paclitaxel when given on the same day. Nab-paclitaxel should be administered at 100 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.	Until disease progression or unmanageable toxicity.
Advanced or unresectable HCC with bevacizumab	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg body weight (bw) every 3 weeks.	Until loss of clinical benefit or unmanageable toxicity.

Delayed or missed doses

If a planned dose of Tecentriq is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses.

Dose modifications during treatment

Dose reductions of Tecentriq are not recommended.

Dose delay or discontinuation (see also sections 4.4 and 4.8)

Table 2: Dose modification advice for Tecentriq

Immune-mediated adverse reaction	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue Tecentriq
Hepatitis in patients without HCC	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 x ULN)	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x ULN)	Permanently discontinue Tecentriq
Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3 x to ≤ 10x ULN *or* If AST/ALT is > 1 to ≤ 3 x ULN at baseline and increases to > 5x to ≤ 10x ULN *or* If AST/ALT is > 3 x to ≤ 5 x ULN at baseline and increases to >8 x to ≤ 10x ULN	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	If AST/ALT increases to > 10 x ULN or total bilirubin increases to > 3 x ULN	Permanently discontinue Tecentriq

Immune-mediated adverse reaction	Severity	Treatment modification
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic Colitis	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue Tecentriq
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold Tecentriq *Hypothyroidism:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism:* Treatment may be resumed when symptoms are controlled by anti-thyroid medicinal product and thyroid function is improving
Adrenal insufficiency	Symptomatic	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue Tecentriq

Immune-mediated adverse reaction	Severity	Treatment modification
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold Tecentriq Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Permanently discontinue Tecentriq
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, Meningoencephalitis and Facial paresis	Facial paresis Grade 1 or 2	Withhold Tecentriq Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding Tecentriq, permanently discontinue Tecentriq
	All Grades Myasthenic syndrome/myasthenia gravis, Guillain Barré syndrome and Meningoencephalitis or Facial paresis Grade 3 or 4	Permanently discontinue Tecentriq
Myelitis	Grade 2, 3, or 4	Permanently discontinue Tecentriq
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold Tecentriq Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue Tecentriq

Immune-mediated adverse reaction	Severity	Treatment modification
Myocarditis	Grade 2 or above	Permanently discontinue Tecentriq
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue Tecentriq
Myositis	Grade 2 or 3	Withhold Tecentriq
	Grade 4 or Grade 3 recurrent myositis	Permanently discontinue Tecentriq
Pericardial disorders	Grade 1 pericarditis	Withhold Tecentriq[2]
	Grade 2 or above	Permanently discontinue Tecentriq
Haemophagocytic lymphohistiocytosis	Suspected haemophagocytic lymphohistiocytosis[1]	Permanently discontinue Tecentriq
Other immune-mediated adverse reactions	Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or recurrent Grade 3	Permanently discontinue Tecentriq (except endocrinopathies controlled with replacement hormones)
Other adverse reactions	**Severity**	**Treatment modification**
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue Tecentriq

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
Note: Toxicity should be graded with the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).
[1] Regardless of severity
[2] Conduct a detailed cardiac evaluation to determine the aetiology and manage appropriately

Special populations

Paediatric population

The safety and efficacy of Tecentriq in children and adolescents aged below 18 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections 4.8 and 5.1).

Asian patients

Due to increased haematologic toxicities observed in Asian patients in IMpower150, it is recommended that the starting dose of paclitaxel should be 175 mg/m^2 every three weeks.

Renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild or moderate hepatic impairment. Tecentriq has not been studied in patients with severe hepatic impairment (see section 5.2).

Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2

Patients with ECOG performance status ≥ 2 were excluded from the clinical trials in TNBC, ES-SCLC, 2nd line UC and HCC (see sections 4.4 and 5.1).

Method of administration

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed.

Tecentriq intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only. The infusions must not be administered as an intravenous push or bolus.

Patients currently receiving intravenous Tecentriq can switch to atezolizumab solution for injection or vice versa.

The initial dose of intravenous Tecentriq must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

For instructions on dilution and handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to atezolizumab or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immune-mediated adverse reactions

Most immune-mediated adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system have been observed. Immune-mediated adverse reactions with atezolizumab may occur after the last dose of atezolizumab.

For suspected immune-mediated adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical trials in patients whose immune-mediated adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Immune-mediated pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-mediated pneumonitis should be ruled out.

Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg body weight (bw)/day prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

Immune-mediated hepatitis

Cases of hepatitis, some leading to fatal outcomes have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be monitored prior to initiation of treatment, periodically during treatment with atezolizumab and as indicated based on clinical evaluation.

For patients without HCC, treatment with atezolizumab should be withheld if Grade 2 event (ALT or AST > 3 to 5 x ULN or blood bilirubin > 1.5 to 3 x ULN) persists for more than 5 to 7 days, and 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month.

Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 3 x ULN).

For patients with HCC, treatment with atezolizumab should be withheld if ALT or AST increases to > 3 to ≤ 10 x ULN from normal limits at baseline, or > 5 to ≤ 10 x ULN from > 1 ULN to ≤ 3 x ULN

at baseline, or > 8 to ≤ 10 x ULN from > 3 ULN to ≤ 5 x ULN at baseline, and persists for more than 5 to 7 days, and 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month.

Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued if ALT or AST increases to > 10 x ULN or total bilirubin increases > 3 x ULN).

Immune-mediated colitis

Cases of diarrhoea or colitis have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis.

Treatment with atezolizumab should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, treatment with 1 to 2 mg/kg bw/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis. The potential complication of gastrointestinal perforation associated with colitis should be taken into consideration.

Immune-mediated endocrinopathies

Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, including diabetic ketoacidosis have been observed in clinical trials with atezolizumab (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies. Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered.

Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab. For symptomatic hypothyroidism, atezolizumab should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, atezolizumab should be withheld and an anti-thyroid medicinal product should be initiated as needed. Treatment with atezolizumab may be resumed when symptoms are controlled and thyroid function is improving.

For symptomatic adrenal insufficiency, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).

For Grade 2 or Grade 3 hypophysitis, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started, and hormone replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent

per day and the patient is stable on replacement therapy (if required). Treatment with atezolizumab should be permanently discontinued for Grade 4 hypophysitis.

Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

Immune-mediated meningoencephalitis

Meningoencephalitis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis.

Treatment with atezolizumab must be permanently discontinued for any grade of meningitis or encephalitis. Treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow.

Immune-mediated neuropathies

Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, and facial paresis were observed in patients receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy.

Myelitis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of myelitis.

Treatment with atezolizumab must be permanently discontinued for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Initiation of systemic corticosteroids (at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent) should be considered.

Treatment with atezolizumab should be withheld for Grade 1 or 2 facial paresis, and treatment with systemic corticosteroids (1 to 2 mg/kg bw/day prednisone or equivalent) should be considered. Treatment may be resumed only if the event fully resolves. Treatment with atezolizumab should be permanently discontinued for Grade 3 or Grade 4 facial paresis, or any other neuropathy that does not fully resolve while withholding atezolizumab.

Treatment with atezolizumab must be permanently discontinued for Grade 2, 3 or 4 myelitis.

Immune-mediated pancreatitis

Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.

Treatment with atezolizumab should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Immune-mediated myocarditis

Cases of myocarditis, including fatal cases, have been observed with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.

Patients with cardiac or cardiopulmonary symptoms should be assessed for potential myocarditis, to ensure the initiation of appropriate measures at an early stage. If myocarditis is suspected, treatment with atezolizumab should be withheld, prompt initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started, and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, treatment with atezolizumab must be permanently discontinued for Grade ≥ 2 myocarditis (see section 4.2).

Immune-mediated nephritis

Nephritis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for changes in renal function.

Treatment with atezolizumab should be withheld for Grade 2 nephritis, and treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 nephritis.

Immune-mediated myositis

Cases of myositis, including fatal cases, have been observed with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myositis. Patients with possible myositis should be monitored for signs of myocarditis.

If a patient develops signs and symptoms of myositis, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Treatment with atezolizumab should be withheld for Grade 2 or 3 myositis and corticosteroid therapy (1-2 mg/kg bw/day prednisone or equivalent) should be initiated. If symptoms improve to ≤ Grade 1, taper corticosteroids as clinically indicated. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4 or grade 3 recurrent myositis, or when unable to reduce the corticosteroid dose to the equivalent of ≤ 10 mg prednisone per day within 12 weeks after onset.

Immune-mediated severe cutaneous adverse reactions

Immune-mediated severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. For suspected SCARs, patients should be referred to a specialist for further diagnosis and management.

Based on the severity of the adverse reaction, atezolizumab should be withheld for Grade 3 skin reactions and treatment with systemic corticosteroids at a dose of 1-2 mg/kg bw/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered.

Atezolizumab should be withheld for patients with suspected SJS or TEN. For confirmed SJS or TEN, atezolizumab should be permanently discontinued.

Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Immune-mediated pericardial disorders

Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some leading to fatal outcomes, have been observed with atezolizumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of pericardial disorders.

For suspected Grade 1 pericarditis, treatment with atezolizumab should be withheld and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. For suspected Grade ≥ 2 pericardial disorders, treatment with atezolizumab should be withheld, prompt treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of a pericardial disorder event is established, treatment with atezolizumab must be permanently discontinued for Grade ≥ 2 pericardial disorders (see section 4.2).

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has been reported in patients receiving atezolizumab (see section 4.8). HLH should be considered when the presentation of cytokine release syndrome is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH. For suspected HLH, atezolizumab must be permanently discontinued and patients should be referred to a specialist for further diagnosis and management.

Other immune-mediated adverse reactions

Given the mechanism of action of atezolizumab, other potential immune-mediated adverse reactions may occur, including noninfective cystitis.

Evaluate all suspected immune-mediated adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and, based on the severity of the reaction, managed with treatment modifications and corticosteroids as clinically indicated (see section 4.2 and section 4.8).

Infusion-related reactions

Infusion-related reactions have been observed with atezolizumab, including anaphylaxis (see section 4.8). The rate of infusion should be reduced, or treatment should be interrupted, in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion-related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

Disease-specific precautions

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in metastatic non-squamous NSCLC

Physicians should carefully consider the combined risks of the four-drug regimen of atezolizumab bevacizumab, paclitaxel, and carboplatin before initiating treatment (see section 4.8).

Use of atezolizumab in combination with nab-paclitaxel in metastatic TNBC

Neutropenia and peripheral neuropathies occurring during treatment with atezolizumab and nab-paclitaxel may be reversible with interruptions of nab-paclitaxel. Physicians should consult the nab-paclitaxel summary of product characteristics (SmPC) for specific precautions and contraindications of this medicine.

Use of atezolizumab in UC for previously untreated patients who are considered cisplatin ineligible

The baseline and prognostic disease characteristics of the IMvigor210 Cohort 1 study population were overall comparable to patients in the clinic who would be considered cisplatin ineligible but would be eligible for a carboplatin-based combination chemotherapy. There are insufficient data for the subgroup of patients that would be unfit for any chemotherapy; therefore, atezolizumab should be used with caution in these patients, after careful consideration of the potential balance of risks and benefits on an individual basis.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

Patients with NSCLC that had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were excluded from the pivotal clinical trial IMpower150 after several cases of fatal pulmonary haemorrhage were observed, which is a known risk factor of treatment with bevacizumab.

In the absence of data, atezolizumab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients with NSCLC who have progressed on erlotinib+bevacizumab

In study IMpower150, there are no data on the efficacy of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients who have progressed previously on erlotinib+bevacizumab.

Use of atezolizumab in combination with bevacizumab in HCC

Data in HCC patients with Child-Pugh B liver disease treated with atezolizumab in combination with bevacizumab are very limited and there are currently no data available in HCC patients with Child-Pugh C liver disease.

Patients treated with bevacizumab have an increased risk of haemorrhage, and cases of severe gastrointestinal haemorrhage, including fatal events, were reported in patients with HCC treated with atezolizumab in combination with bevacizumab. In patients with HCC, screening for and subsequent treatment of oesophageal varices should be performed as per clinical practice prior to starting treatment with the combination of atezolizumab and bevacizumab. Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding with the combination treatment. Please refer to the bevacizumab Summary of Product Characteristics.

Diabetes mellitus can occur during treatment with atezolizumab in combination with bevacizumab. Physicians should monitor blood glucose levels prior to and periodically during treatment with atezolizumab in combination with bevacizumab as clinically indicated.

Use of atezolizumab as monotherapy for first-line treatment in metastatic NSCLC

Physicians should consider the delayed onset of atezolizumab effect before initiating first-line treatment as monotherapy in patients with NSCLC. A higher number of deaths within 2.5 months after randomisation followed by a long-term survival benefit was observed with atezolizumab compared with chemotherapy. No specific factor(s) associated with early deaths could be identified (see section 5.1).

Patients excluded from clinical trials

Patients with the following conditions were excluded from clinical trials: a history of autoimmune disease, history of pneumonitis, active brain metastasis, ECOG PS ≥ 2 (except for patients with advanced NSCLC ineligible for a platinum-based therapy), HIV, hepatitis B or hepatitis C infection (for non-HCC patients), significant cardiovascular disease and patients with inadequate hematologic and end-organ function. Patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry; therapeutic oral or intravenous antibiotics within 2 weeks prior to initiation of study treatment were excluded from clinical trials.

Excipients with known effect

This medicinal product contains polysorbate 20. Each vial of Tecentriq 840 mg concentrate for solution for infusion contains 5.6 mg of polysorbate 20, which is equivalent to 0.4 mg/mL. Each vial of Tecentriq 1 200 mg concentrate for solution for infusion contains 8 mg of polysorbate 20, which is equivalent to 0.4 mg/ml. Polysorbate 20 may cause allergic reactions.

Patient card

The prescriber must discuss the risks of Tecentriq therapy with the patient. The patient will be provided with the patient card and instructed to carry the card at all times.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-mediated adverse reactions after starting atezolizumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab.

Pregnancy

There are no data from the use of atezolizumab in pregnant women. No developmental and reproductive studies were conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway in murine pregnancy models can lead to immune-mediated rejection of the developing foetus resulting in foetal death (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of atezolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

Human immunoglobulins G1 (IgG1) are known to cross the placental barrier and atezolizumab is an IgG1; therefore, atezolizumab has the potential to be transmitted from the mother to the developing foetus.

Atezolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with atezolizumab.

Breast-feeding

It is unknown whether atezolizumab is excreted in human milk. Atezolizumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Tecentriq therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data are available on the possible effects of atezolizumab on fertility. No reproductive and development toxicity studies have been conducted with atezolizumab; however, based on the 26-week repeat dose toxicity study, atezolizumab had an effect on menstrual cycles at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible (see section 5.3). There were no effects on the male reproductive organs.

4.7 Effects on ability to drive and use machines

Tecentriq has minor influence on the ability to drive and use machines. Patients experiencing fatigue should be advised not to drive and use machines until symptoms abate (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of atezolizumab as monotherapy is based on pooled data in 5 039 patients across multiple tumour types. The most common adverse reactions (> 10%) were fatigue (29.3%), decreased appetite (20.1%), rash (19.7%), nausea (18.8%), cough (18.2%), diarrhoea (18.1%), pyrexia (17.9%), dyspnoea (16.6%), arthralgia (16.2%), pruritus (13.3%), asthenia (13%), back pain (12.2%), vomiting (11.7%), urinary tract infection (11%) and headache (10.2%).

The safety of atezolizumab given in combination with other medicinal products, has been evaluated in 4 535 patients across multiple tumour types. The most common adverse reactions (≥ 20%) were anaemia (36.8%), neutropenia (36.6%), nausea (35.5%), fatigue (33.1%), alopecia (28.1%), rash (27.8%), diarrhoea (27.6%), thrombocytopenia (27.1%), constipation (25.8%), decreased appetite (24.7%) and peripheral neuropathy (24.4%).

Use of atezolizumab in the adjuvant NSCLC setting

The safety profile of atezolizumab in the adjuvant setting in the non-small cell lung cancer (NSCLC) patient population (IMpower010) was generally consistent with the overall pooled monotherapy safety

profile in the advanced setting. Nevertheless, the incidence of immune-mediated adverse reactions of atezolizumab in IMpower010 was 51.7% compared to 38.4% in the pooled monotherapy population with advanced disease. No new immune-mediated adverse reactions were identified in the adjuvant setting.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

In the first-line NSCLC study (IMpower150), an overall higher frequency of adverse events was observed in the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin compared to atezolizumab, paclitaxel and carboplatin, including Grade 3 and 4 events (63.6% compared to 57.5%), Grade 5 events (6.1% compared to 2.5%), adverse events of special interest to atezolizumab (52.4% compared to 48.0%), as well as adverse events leading to withdrawal of any study treatment (33.8% compared to 13.3%). Nausea, diarrhoea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria were reported higher (≥5% difference) in patients receiving atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, haemoptysis, cerebrovascular accident, including fatal events.

Further details on serious adverse reactions are provided in section 4.4.

Tabulated list of adverse reactions

The adverse reactions (ARs) are listed by MedDRA system organ class (SOC) and categories of frequency in Table 3 for atezolizumab given as monotherapy or as combination therapy. Adverse reactions known to occur with atezolizumab or chemotherapies given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy. The following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Summary of adverse reactions occurring in patients treated with atezolizumab

Atezolizumab monotherapy		Atezolizumab in combination therapy
Infections and infestations		
Very common	urinary tract infection[a]	lung infection[b]
Common		sepsis[aj]
Blood and lymphatic system disorders		
Very common		anaemia, thrombocytopenia[d], neutropenia[e], leukopenia[f]
Common	thrombocytopenia[d]	lymphopenia[g]
Rare	haemophagocytic lymphohistiocytosis	haemophagocytic lymphohistiocytosis
Immune system disorders		
Common	infusion-related reaction[h]	infusion-related reaction[h]
Endocrine disorders		
Very common		hypothyroidism[i]
Common	hypothyroidism[i], hyperthyroidism[j]	hyperthyroidism[j]
Uncommon	diabetes mellitus[k], adrenal insufficiency[l], hypophysitis[m]	hypophysitis[m]

Atezolizumab monotherapy		Atezolizumab in combination therapy
Metabolism and nutrition disorders		
Very common	decreased appetite	decreased appetite
Common	hypokalaemia[ae], hyponatraemia[af], hyperglycaemia	hypokalaemia[ae], hyponatraemia[af], hypomagnesaemia[n]
Nervous system disorders		
Very common	headache	peripheral neuropathy[o], headache
Common	peripheral neuropathy[o]	syncope, dizziness
Uncommon	Guillain-Barré syndrome[p], meningoencephalitis[q]	
Rare	myasthenic syndrome[r], facial paresis, myelitis	facial paresis
Eye disorders		
Rare	uveitis	
Cardiac disorders		
Common	pericardial disorders[ao]	
Uncommon		pericardial disorders[ao]
Rare	myocarditis[s]	
Vascular disorders		
Very common		hypertension[ai]
Common	hypotension	
Respiratory, thoracic, and mediastinal disorders		
Very common	dyspnoea, cough	dyspnoea, cough, nasopharyngitis[am]
Common	pneumonitis[t], hypoxia[ag], nasopharyngitis[am]	dysphonia
Gastrointestinal disorders		
Very common	nausea, vomiting, diarrhoea[u]	nausea, vomiting, diarrhoea[u], constipation
Common	colitis[v], abdominal pain, dysphagia, oropharyngeal pain[w], dry mouth	stomatitis, dysgeusia, colitis[v]
Uncommon	pancreatitis[x]	
Rare	coeliac disease	coeliac disease
Hepatobiliary disorders		
Common	AST increased, ALT increased, hepatitis[y]	AST increased, ALT increased
Skin and subcutaneous tissue disorders		
Very common	rash[z], pruritus	rash[z], pruritus, alopecia[ah]
Common	dry skin[ap]	
Uncommon	severe cutaneous adverse reactions[ak], psoriasis[an], lichen disorders[aq]	severe cutaneous adverse reactions[ak], psoriasis[an]

Atezolizumab monotherapy		Atezolizumab in combination therapy
Rare	pemphigoid	pemphigoid, lichen disorders[aq]
Musculoskeletal and connective tissue disorders		
Very common	arthralgia, back pain	arthralgia, musculoskeletal pain[aa], back pain
Common	musculoskeletal pain[aa]	
Uncommon	myositis[ab]	
Renal and urinary disorders		
Common	blood creatinine increased[c]	proteinuria[ac], blood creatinine increased[c]
Uncommon	nephritis[ad]	
Not known	cystitis noninfective[al]	
General disorders and administration site conditions		
Very common	pyrexia, fatigue, asthenia	pyrexia, fatigue, asthenia, oedema peripheral
Common	influenza like illness, chills	
Investigations		
Common		blood alkaline phosphatase increased
Uncommon	blood creatine phosphokinase increased	

[a] Includes reports of urinary tract infection, cystitis, pyelonephritis, escherichia urinary tract infection, urinary tract infection bacterial, kidney infection, pyelonephritis acute, pyelonephritis chronic, pyelitis, renal abscess, streptococcal urinary tract infection, urethritis, urinary tract infection fungal, urinary tract infection pseudomonal.
[b] Includes reports of pneumonia, bronchitis, lower respiratory tract infection, infectious pleural effusion, tracheobronchitis, atypical pneumonia, lung abscess, infective exacerbation of chronic obstructive airways disease, paracancerous pneumonia, pyopneumothorax, pleural infection, post procedural pneumonia.
[c] Includes reports of blood creatinine increased, hypercreatininaemia.
[d] Includes reports of immune thrombocytopenia, thrombocytopenia, platelet count decreased.
[e] Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis, granulocytopenia.
[f] Includes reports of white blood cell count decreased, leukopenia.
[g] Includes reports of lymphopenia, lymphocyte count decreased.
[h] Includes reports of infusion-related reaction, cytokine release syndrome, hypersensitivity, anaphylaxis.
[i] Includes reports of anti-thyroid antibody positive, autoimmune hypothyroidism, autoimmune thyroiditis, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, euthyroid sick syndrome, goitre, hypothyroidism, immune-mediated hypothyroidism, immune-mediated thyroiditis, myxoedema, primary hypothyroidism, thyroid disorder, thyroid hormones decreased, thyroid function test abnormal, thyroiditis, thyroiditis acute, thyroxine decreased, thyroxine free decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine decreased, tri-iodothyronine increased, tri-iodothyronine free abnormal, tri-iodothyronine free decreased, tri-iodothyronine free increased, silent thyroiditis.
[j] Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos.
[k] Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis, ketoacidosis.
[l] Includes reports of adrenal insufficiency, blood corticotropin decreased, glucocorticoid deficiency, primary adrenal insufficiency, secondary adrenocortical insufficiency.
[m] Includes reports of hypophysitis, hypopituitarism, secondary adrenocortical insufficiency, temperature regulation disorder.

[n] Includes reports of hypomagnesaemia, blood magnesium decreased.
[o] Includes reports of neuropathy peripheral, autoimmune neuropathy, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy, axonal neuropathy, lumbosacral plexopathy, neuropathic arthropathy, peripheral nerve infection, neuritis, immune-mediated neuropathy.
[p] Includes reports of Guillain-Barré syndrome, ascending flaccid paralysis, demyelinating polyneuropathy.
[q] Includes reports of encephalitis, encephalitis autoimmune, meningitis, meningitis aseptic, photophobia.
[r] Includes reports of myasthenia gravis.
[s] Includes reports of myocarditis, autoimmune myocarditis, and immune-mediated myocarditis.
[t] Includes reports of pneumonitis, lung infiltration, bronchiolitis, immune-mediated lung disease, immune-mediated pneumonitis, interstitial lung disease, alveolitis, lung opacity, pulmonary fibrosis, pulmonary toxicity, radiation pneumonitis.
[u] Includes reports of diarrhoea, defaecation urgency, frequent bowel movements, gastrointestinal hypermotility.
[v] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative, diversion colitis, eosinophilic colitis, immune-mediated enterocolitis.
[w] Includes reports of oropharyngeal pain, oropharyngeal discomfort, throat irritation.
[x] Includes reports of autoimmune pancreatitis, pancreatitis, pancreatitis acute, lipase increased, amylase increased.
[y] Includes reports of ascites, autoimmune hepatitis, hepatic cytolysis, hepatitis, hepatitis acute, hepatitis toxic, hepatotoxicity, immune-mediated hepatitis, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, liver injury, oesophageal varices haemorrhage, varices oesophageal, spontaneous bacterial peritonitis.
[z] Includes reports of acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, eczema infected, erythema, erythema of eyelid, eyelid rash, fixed eruption, folliculitis, furuncle, hand dermatitis, immune-mediated dermatitis, lip blister, oral blood blister, palmar-plantar erythrodysaesthesia syndrome, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash vesicular, scrotal dermatitis, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, vascular access site rash.
[aa] Includes reports of musculoskeletal pain, myalgia, bone pain.
[ab] Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present, myopathy, polymyositis.
[ac] Includes reports of proteinuria, protein urine present, haemoglobinurea, urine abnormality, nephrotic syndrome, albuminuria.
[ad] Includes reports of nephritis, autoimmune nephritis, Henoch-Schonlein purpura nephritis, paraneoplastic glomerulonephritis, tubulointerstitial nephritis.
[ae] Includes reports of hypokalaemia, blood potassium decreased.
[af] Includes reports of hyponatraemia, blood sodium decreased.
[ag] Includes reports of hypoxia, oxygen saturation decreased, pO2 decreased.
[ah] Includes reports of alopecia, madarosis, alopecia areata, alopecia totalis, hypotrichosis.
[ai] Includes reports of hypertension, blood pressure increased, hypertensive crisis, blood pressure systolic increased, diastolic hypertension, blood pressure inadequately controlled, retinopathy hypertensive, hypertensive nephropathy, essential hypertension, orthostatic hypertension.
[aj] Includes reports of sepsis, septic shock, urosepsis, neutropenic sepsis, pulmonary sepsis, bacterial sepsis, klebsiella sepsis, abdominal sepsis, candida sepsis, escherichia sepsis, pseudomonal sepsis, staphylococcal sepsis.
[ak] Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative, dermatitis exfoliative generalised, toxic skin eruption, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, cutaneous vasculitis.
[al] Includes reports of cystitis noninfective and immune-mediated cystitis.
[am] Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea.
[an] Includes reports of psoriasis, dermatitis psoriasiform.
[ao] Includes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive.
[ap] Includes reports of dry skin, xerosis.

[aq] Includes reports of lichenoid keratosis, lichen sclerosus and lichen planus.

Description of selected adverse reactions

The data below reflect information for significant adverse reactions for atezolizumab as monotherapy in clinical trials (see section 5.1). Details for the significant adverse reactions for atezolizumab when given in combination are presented if clinically relevant differences were noted in comparison to atezolizumab monotherapy. The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Immune-mediated pneumonitis

Pneumonitis occurred in 3.0% (151/5 039) of patients who received atezolizumab monotherapy. Of these patients, three experienced fatal events. The median time to onset was 3.7 months (range: 3 days to 29.8 months). The median duration was 1.7 months (range: 0 days to 27.8+ months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 41 (0.8%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.8% (92/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated hepatitis

Hepatitis occurred in 1.7% (88/5 039) of patients who received atezolizumab monotherapy. Of the 88 patients, three experienced fatal events. The median time to onset was 1.4 months (range: 0 days to 26.3 months). The median duration was 1 month (range: 0 day to 52.1+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 46 (0.9%) patients. Hepatitis requiring the use of corticosteroids occurred in 2.6% (130/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated colitis

Colitis occurred in 1.2% (62/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 4.5 months (range: 15 days to 36.4 months). The median duration was 1.4 months (range: 3 days to 50.2+ months; + denotes a censored value). Colitis led to discontinuation of atezolizumab in 24 (0.5%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (30/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated endocrinopathies

Thyroid disorders

Hypothyroidism occurred in 8.5% (427/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 4.2 months (range: 0 days to 38.5 months). Hypothyroidism occurred in 17.4% (86/495) of patients who received atezolizumab monotherapy in the adjuvant NSCLC setting. The median time to onset was 4.0 months (range: 22 days to 11.8 months).

Hyperthyroidism occurred in 2.4% (121/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 2.7 months (range: 0 days to 24.3 months). Hyperthyroidism occurred in 6.5% (32/495) of patients who received atezolizumab monotherapy in the adjuvant NSCLC setting. The median time to onset was 2.8 months (range: 1 day to 9.9 months).

Adrenal insufficiency

Adrenal insufficiency occurred in 0.5% (25/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 6.2 months (range: 3 days to 21.4 months). Adrenal insufficiency led to discontinuation of atezolizumab in 5 (0.1%) patients. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.4% (20/5 039) of patients receiving atezolizumab monotherapy.

Hypophysitis

Hypophysitis occurred in 0.2% (9/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 5.3 months (range: 21 days to 13.7 months). Six (0.1%) patients required the use of corticosteroids and treatment with atezolizumab was discontinued in 1 (< 0.1%) patient.

Hypophysitis occurred in 1.4% (15/1 093) of patients who received atezolizumab in combination with paclitaxel followed by atezolizumab, dose-dense doxorubicin or epirubicin, and cyclophosphamide. The median time to onset was 3.8 months (range: 2.4 to 10.7 months). Eleven patients (1.0%) required the use of corticosteroids. Treatment with atezolizumab was discontinued in 7 (0.6%) patients.

Hypophysitis occurred in 0.8% (3/393) of patients who received atezolizumab with bevacizumab, paclitaxel, and carboplatin. The median time to onset was 7.7 months (range: 5.0 to 8.8 months). Two patients required the use of corticosteroids.

Hypophysitis occurred in 0.4% (2/473) of patients who received atezolizumab in combination with nab-paclitaxel and carboplatin. The median time to onset was 5.2 months (range: 5.1 to 5.3 months). Both patients required the use of corticosteroids.

Diabetes mellitus

Diabetes mellitus occurred in 0.6% (30/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 5.5 months (range: 3 days to 29.0 months). Diabetes mellitus led to the discontinuation of atezolizumab in < 0.1% (3/5 039) patients. Four (< 0.1%) patients required the use of corticosteroids.

Diabetes mellitus occurred in 2.0% (10/493) of HCC patients who received atezolizumab in combination with bevacizumab. The median time to onset was 4.4 months (range: 1.2 months - 8.3 months). No events of diabetes mellitus led to atezolizumab withdrawal.

Immune-mediated meningoencephalitis

Meningoencephalitis occurred in 0.4% (22/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 15 days (range: 0 days to 12.5 months). The median duration was 24 days (range: 6 days to 14.5+ months; + denotes a censored value).

Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (12/5 039) of patients receiving atezolizumab and eight patients (0.2%) discontinued atezolizumab.

Immune-mediated neuropathies

Guillain-Barré syndrome and demyelinating polyneuropathy

Guillain-Barré syndrome and demyelinating polyneuropathy occurred in 0.1% (6/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 4.1 months (range: 18 days to 8.1 months). The median duration was 8.0 months (range: 18 days to 24.5+ months; + denotes a censored value). Guillain-Barré syndrome led to discontinuation of atezolizumab in 1 patient (< 0.1%). Guillain-Barré syndrome requiring the use of corticosteroids occurred in < 0.1% (3/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated facial paresis

Facial paresis occurred in < 0.1% (1/5 039) of patients who received atezolizumab monotherapy. The time to onset was 29 days. The duration was 1.1 months. The event did not require the use of corticosteroids and the event did not lead to discontinuation of atezolizumab.

Immune-mediated myelitis

Myelitis occurred in < 0.1% (1/5 039) of patients who received atezolizumab monotherapy. The time to onset was 3 days. The event required the use of corticosteroids but did not lead to discontinuation of atezolizumab.

Myasthenic syndrome

Myasthenia gravis occurred in < 0.1% (2/5 039) of patients (including 1 fatal case) who received atezolizumab monotherapy. The median time to onset was 2.6 months (range: 1.2 months to 4 months).

Immune-mediated pancreatitis

Pancreatitis, including amylase increased and lipase increased, occurred in 0.8% (40/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 5 months (range: 0 days to 24.8 months). The median duration was 24 days (range: 3 days to 40.4+ months; + denotes a censored value). Pancreatitis led to the discontinuation of atezolizumab in 3 (< 0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in 0.2% (8/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated myocarditis

Myocarditis occurred in < 0.1% (5/5 039) of patients who received atezolizumab monotherapy. Of the 5 patients, one experienced a fatal event in the adjuvant NSCLC setting. The median time to onset was 3.7 months (range: 1.5 to 4.9 months). The median duration was 14 days (range: 12 days to 2.8 months). Myocarditis led to the discontinuation of atezolizumab in 3 (< 0.1%) patients. Three (<0.1%) patients required the use of corticosteroids.

Immune-mediated nephritis

Nephritis occurred in 0.2% (11/5 039) of patients who received atezolizumab. The median time to onset was 5.1 months (range: 3 days to 17.5 months). Nephritis led to discontinuation of atezolizumab in 5 (≤ 0.1%) patients. Five (0.1%) patients required the use of corticosteroids.

Immune-mediated myositis

Myositis occurred in 0.6% (32/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 3.5 months (range: 12 days to 11.5 months). The median duration was 3.2 months (range: 9 days to 51.1+ months; + denotes a censored value). Myositis led to discontinuation of atezolizumab in 6 (0.1%) patients. Ten (0.2%) patients required the use of corticosteroids.

Immune-mediated severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) occurred in 0.6% (30/5 039) of patients who received atezolizumab monotherapy. Of the 30 patients, one experienced a fatal event. The median time to onset was 4.8 months (range: 3 days to 15.5 months). The median duration was 2.4 months (range: 1 day to 37.5+ months; + denotes a censored value). SCARs led to discontinuation of atezolizumab in 3 (< 0.1%) patients. SCARs requiring the use of systemic corticosteroids occurred in 0.2% (9/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated pericardial disorders

Pericardial disorders occurred in 1% (49/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 1.4 months (range: 6 days to 17.5 months). The median duration was 2.5 months (range: 0 to 51.5+ months; + denotes a censored value). Pericardial disorders led to

discontinuation of Tecentriq in 3 (< 0.1%) patients. Pericardial disorders requiring the use of corticosteroids occurred in 0.2% (7/5 039) of patients.

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reaction(s) reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with atezolizumab: pancreatic exocrine insufficiency.

Immunogenicity

Across multiple phase II and III studies, 13.1% to 54.1% of patients developed treatment-emergent anti-drug antibodies (ADAs). Patients who developed treatment-emergent ADAs tended to have overall poorer health and disease characteristics at baseline. Those imbalances in health and disease characteristics at baseline can confound the interpretation of pharmacokinetic (PK), efficacy and safety analyses. Exploratory analyses adjusting for imbalances in baseline health and disease characteristics were conducted to assess the effect of ADA on efficacy. These analyses did not exclude possible attenuation of efficacy benefit in patients who developed ADA compared to patients who did not develop ADA. The median time to ADA onset ranged from 3 weeks to 5 weeks.

Across pooled datasets for patients treated with atezolizumab monotherapy (N=3 460) and with combination therapies (N= 2 285), the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: Grade 3-4 AEs 46.2% vs. 39.4%, Serious Adverse Events (SAEs) 39.6% vs. 33.3%, AEs leading to treatment withdrawal 8.5% vs 7.8% (for monotherapy); Grade 3-4 AEs 63.9% vs. 60.9%, SAEs 43.9% vs. 35.6%, AEs leading to treatment withdrawal 22.8% vs 18.4% (for combination therapy). However, available data do not allow firm conclusions to be drawn on possible patterns of adverse reactions.

Paediatric population

The safety of atezolizumab in children and adolescents has not been established. No new safety signals were observed in a clinical trial with 69 paediatric patients (< 18 years) and the safety profile was comparable to adults.

Elderly

No overall differences in safety were observed between patients < 65, 65-74, and 75-84 years of age receiving atezolizumab monotherapy. The data for patients ≥ 85 years of age are too limited to draw meaningful conclusions about this population.

In study IMpower150, age ≥ 65 was associated with an increased risk of developing adverse events in patients receiving atezolizumab in combination with bevacizumab, carboplatin and paclitaxel. In studies IMpower150, IMpower133 and IMpower110, data for patients ≥ 75 years of age were too limited to draw conclusions. In the IPSOS study in 1L platinum-ineligible NSCLC patients, there were no overall differences in the safety profile for 1L atezolizumab monotherapy between the patient age subgroups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with atezolizumab.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors. ATC code: L01FF05.

Mechanism of action

Programmed death-ligand 1 (PD-L1) may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.

Clinical efficacy and safety

Urothelial carcinoma

IMvigor211 (GO29294): Randomised trial in locally advanced or metastatic UC patients previously treated with chemotherapy

A phase III, open-label, multi-centre, international, randomised study, (IMvigor211), was conducted to evaluate the efficacy and safety of atezolizumab compared with chemotherapy (investigator's choice of vinflunine, docetaxel, or paclitaxel) in patients with locally advanced or metastatic UC who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrolment; and administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 9 weeks for the first 54 weeks, and every 12 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 931 patients were enrolled. Patients were randomised (1:1) to receive either atezolizumab or chemotherapy. Randomisation was stratified by chemotherapy (vinflunine vs. taxane), PD-L1 expression status on IC (< 5% vs. ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no). Prognostic risk factors included time from prior chemotherapy of < 3 months, ECOG performance status > 0 and haemoglobin < 10 g/dL.

Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks. No dose reduction of atezolizumab was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. Vinflunine was administered 320 mg/m^2 by

intravenous infusion on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. Paclitaxel was administered 175 mg/m^2 by intravenous infusion over 3 hours on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. Docetaxel was administered 75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. For all treated patients, the median duration of treatment was 2.8 months for the atezolizumab arm, 2.1 months for the vinflunine and paclitaxel arms and 1.6 months for the docetaxel arm.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 67 years (range: 31 to 88), and 77.1% of patients were male. The majority of patients were white (72.1%), 53.9% of patients within the chemotherapy arm received vinflunine, 71.4% of patients had at least one poor prognostic risk factor and 28.8% had liver metastases at baseline. Baseline ECOG performance status was 0 (45.6%) or 1 (54.4%). Bladder was the primary tumour site for 71.1% of patients and 25.4% of patients had upper tract UC. There were 24.2% of patients who received only prior platinum-containing adjuvant or neoadjuvant therapy and progressed within 12 months.

The primary efficacy endpoint for IMvigor211 is overall survival (OS). Secondary efficacy endpoints evaluated per investigator-assessed Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 are objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR). Comparisons with respect to OS between the treatment arm and control arm within the IC2/3, IC1/2/3, and ITT (Intention-to-treat, i.e. all comers) populations were tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% as follows: step 1) IC2/3 population; step 2) IC1/2/3 population; step 3) all comers population. OS results for each of steps 2 and 3 could be formally tested for statistical significance only if the result in the preceding step was statistically significant.

The median survival follow-up is 17 months. The primary analysis of study IMvigor211 did not meet its primary endpoint of OS. Atezolizumab did not demonstrate a statistically significant survival benefit compared to chemotherapy in patients with previously treated, locally advanced or metastatic UC. Per the pre-specified hierarchical testing order, the IC2/3 population was tested first, with an OS HR of 0.87 (95% CI: 0.63, 1.21; median OS of 11.1 vs. 10.6 months for atezolizumab and chemotherapy respectively). The stratified log-rank p-value was 0.41 and therefore the results are considered not statistically significant in this population. As a consequence, no formal tests of statistical significance could be performed for OS in the IC1/2/3 or all comer populations, and results of those analyses would be considered exploratory. The key results in the all comer population are summarised in Table 4. The Kaplan-Meier curve for OS in the all comer population is presented in Figure 1.

An exploratory updated survival analysis was performed with a median duration of survival follow up of 34 months in the ITT population. The median OS was 8.6 months (95% CI: 7.8, 9.6) in the atezolizumab arm and 8.0 months (95% CI: 7.2, 8.6) in the chemotherapy arm with a hazard ratio of 0.82 (95% CI: 0.71, 0.94). Consistent with the trend observed at primary analysis for 12-month OS rates, numerically higher 24-month and 30-month OS rates were observed for patients in the atezolizumab arm compared with the chemotherapy arm in the ITT population. The percentage of patients alive at 24 months (KM estimate) was 12.7% in the chemotherapy arm and 22.5% in the atezolizumab arm; and at 30 months (KM estimate) was 9.8% in the chemotherapy arm and 18.1% in the atezolizumab arm.

Table 4: Summary of efficacy in all comers (IMvigor211)

Efficacy endpoint	Atezolizumab (n = 467)	Chemotherapy (n = 464)
Primary efficacy endpoint		
OS*		
No. of deaths (%)	324 (69.4%)	350 (75.4%)
Median time to events (months)	8.6	8.0
95% CI	7.8, 9.6	7.2, 8.6
Stratified‡ hazard ratio (95% CI)	0.85 (0.73, 0.99)	
12-month OS (%)**	39.2%	32.4%
Secondary and exploratory endpoints		
Investigator-assessed PFS (RECIST v1.1)		
No. of events (%)	407 (87.2%)	410 (88.4%)
Median duration of PFS (months)	2.1	4.0
95% CI	2.1, 2.2	3.4, 4.2
Stratified hazard ratio (95% CI)	1.10 (0.95, 1.26)	
Investigator-assessed ORR (RECIST v1.1)	n = 462	n = 461
No. of confirmed responders (%)	62 (13.4%)	62 (13.4%)
95% CI	10.45, 16.87	10.47, 16.91
No. of complete response (%)	16 (3.5%)	16 (3.5%)
No. of partial response (%)	46 (10.0%)	46 (10.0%)
No. of stable disease (%)	92 (19.9%)	162 (35.1%)
Investigator-assessed DOR (RECIST v1.1)	n = 62	n = 62
Median in months ***	21.7	7.4
95% CI	13.0, 21.7	6.1, 10.3

CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

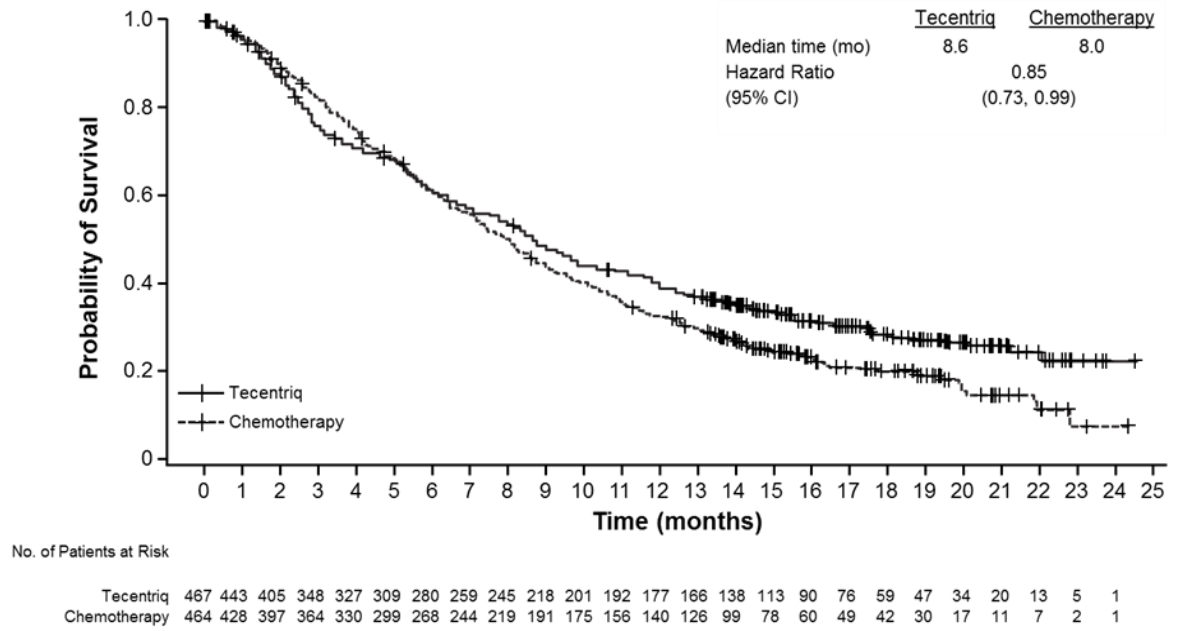
* An analysis of OS in the all comer population was performed based on the stratified log-rank test and the result is provided for descriptive purposes only (p = 0.0378); according to the pre-specified analysis hierarchy, the p-value for the OS analysis in the all comer population cannot be considered statistically significant.

‡ Stratified by chemotherapy (vinflunine vs. taxane), status on IC (< 5% vs. ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no).

** Based on Kaplan-Meier estimate

*** Responses were ongoing in 63% of responders in the atezolizumab arm and in 21% of responders in the chemotherapy arm.

Figure 1: Kaplan-Meier curve for overall survival (IMvigor211)



IMvigor210 (GO29293): Single-arm trial in previously untreated urothelial carcinoma patients who are ineligible for cisplatin therapy and in urothelial carcinoma patients previously treated with chemotherapy

A phase II, multi-centre, international, two-cohort, single-arm clinical trial, IMvigor210, was conducted in patients with locally advanced or metastatic UC (also known as urothelial bladder cancer).

The study enrolled a total of 438 patients and had two patient cohorts. Cohort 1 included previously untreated patients with locally advanced or metastatic UC who were ineligible or unfit for cisplatin-based chemotherapy or had disease progression at least 12 months after treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Cohort 2 included patients who received at least one platinum-based chemotherapy regimen for locally advanced or metastatic UC or had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen.

In Cohort 1, 119 patients were treated with atezolizumab 1 200 mg by intravenous infusion every 3 weeks until disease progression. The median age was 73 years. Most patients were male (81%), and the majority of patients were White (91%).

Cohort 1 included 45 patients (38%) with ECOG performance status of 0, 50 patients (42%) with ECOG performance status of 1 and 24 patients (20%) with ECOG performance status of 2, 35 patients (29%) with no Bajorin risk factors (ECOG performance status ≥ 2 and visceral metastasis), 66 patients (56%) with one Bajorin risk factor and 18 patients (15 %) with two Bajorin risk factors, 84 patients (71%) with impaired renal function (glomerular filtration rate [GFR] < 60 mL/min), and 25 patients (21%) with liver metastasis.

The primary efficacy endpoint for Cohort 1 was confirmed objective response rate (ORR) as assessed by an independent review facility (IRF) using RECIST v1.1.

The primary analysis was performed when all patients had at least 24 weeks of follow-up. Median duration of treatment was 15.0 weeks and median duration of survival follow-up was 8.5 months in all comers. Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a pre-specified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The confirmed ORRs per IRF-RECIST v1.1 were 21.9% (95% CI:

9.3, 40.0) in patients with PD-L1 expression ≥ 5%, 18.8% (95% CI: 10.9, 29.0) in patients with PD-L1 expression ≥ 1%, and 19.3% (95% CI: 12.7, 27.6) in all comers. The median duration of response (DOR) was not reached in any PD-L1 expression subgroup or in all comers. OS was not mature with an event patient ratio of approximately 40%. Median OS for all patient subgroups (PD-L1 expression ≥ 5 % and ≥ 1 %) and in all comers was 10.6 months.

An updated analysis was performed with a median duration of survival follow-up of 17.2 months for Cohort 1 and is summarised in Table 5. The median DOR was not reached in any PD-L1 expression subgroup or in all comers.

Table 5: Summary of updated efficacy (IMvigor210 Cohort 1)

Efficacy endpoint	**PD-L1 expression of ≥ 5% in IC**	**PD-L1 expression of ≥ 1% in IC**	**All Comers**
ORR (IRF-assessed; RECIST v1.1)	n = 32	n = 80	n = 119
No. of Responders (%)	9 (28.1%)	19 (23.8%)	27 (22.7%)
95% CI	13.8, 46.8	15.0, 34.6	15.5, 31.3
No. of complete response (%)	4 (12.5%)	8 (10.0%)	11 (9.2%)
95% CI	(3.5, 29.0)	(4.4, 18.8)	(4.7, 15.9)
No. of partial response (%)	5 (15.6%)	11 (13.8%)	16 (13.4%)
95% CI	(5.3, 32.8)	(7.1, 23.3)	(7.9, 20.9)
DOR (IRF-assessed; RECIST v1.1)	n = 9	n = 19	n = 27
Patients with event (%)	3 (33.3%)	5 (26.3%)	8 (29.6%)
Median (months) (95% CI)	NE (11.1, NE)	NE (NE)	NE (14.1, NE)
PFS (IRF-assessed; RECIST v1.1)	n = 32	n = 80	n = 119
Patients with event (%)	24 (75.0%)	59 (73.8%)	88 (73.9%)
Median (months) (95% CI)	4.1 (2.3, 11.8)	2.9 (2.1, 5.4)	2.7 (2.1, 4.2)
OS	n = 32	n = 80	n = 119
Patients with event (%)	18 (56.3%)	42 (52.5%)	59 (49.6%)
Median (months) (95% CI)	12.3 (6.0, NE)	14.1 (9.2, NE)	15.9 (10.4, NE)
1-year OS rate (%)	52.4%	54.8%	57.2%

CI = confidence interval; DOR=duration of response; IC = tumour-infiltrating immune cells; IRF = independent review facility; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

At the time of the final analysis for Cohort 1, patients had a median survival follow-up time of 96.4 months. Median OS was 12.3 months (95% CI: 6.0, 49.8) in patients with PD-L1 expression ≥ 5% (patients who are included in the therapeutic indication).

In Cohort 2, the co-primary efficacy endpoints were confirmed ORR as assessed by an IRF using RECIST v1.1 and investigator-assessed ORR according to Modified RECIST (mRECIST) criteria. There were 310 patients treated with atezolizumab 1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit. The primary analysis of Cohort 2 was performed when all patients had at least 24 weeks of follow-up. The study met its co-primary endpoints in Cohort 2, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST compared to a pre-specified historical control response rate of 10%.

An analysis was also performed with a median duration of survival follow-up of 21.1 months for Cohort 2. The confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI: 19.5, 37.9) in patients with PD-L1 expression ≥ 5%, 19.3% (95% CI: 14.2, 25.4) in patients with PD-L1 expression ≥ 1%, and 15.8% (95% CI: 11.9, 20.4) in all comers. The confirmed ORR per investigator-assessed mRECIST was 29.0% (95% CI: 20.4, 38.9) in patients with PD-L1 expression ≥ 5%, 23.7% (95% CI: 18.1, 30.1) in patients with PD-L1 expression ≥ 1%, and 19.7% (95% CI: 15.4, 24.6) in all comers. The rate of complete response per IRF-RECIST v1.1 in the all comer population was 6.1% (95% CI: 3.7, 9.4). For Cohort 2, median DOR was not reached in any PD-L1 expression subgroup or in all comers, however was reached in patients with PD-L1 expression < 1% (13.3 months; 95% CI 4.2, NE). The OS rate at 12 months was 37% in all comers.

At the time of the final analysis for Cohort 2, patients had a median survival follow-up time of 46.2 months. Median OS was 11.9 months (95% CI: 9.0, 22.8) in patients with PD-L1 expression ≥ 5%, 9.0 months (95% CI: 7.1, 11.1) in patients with PD-L1 expression ≥ 1%, and 7.9 months (95% CI: 6.7, 9.3) in all comers.

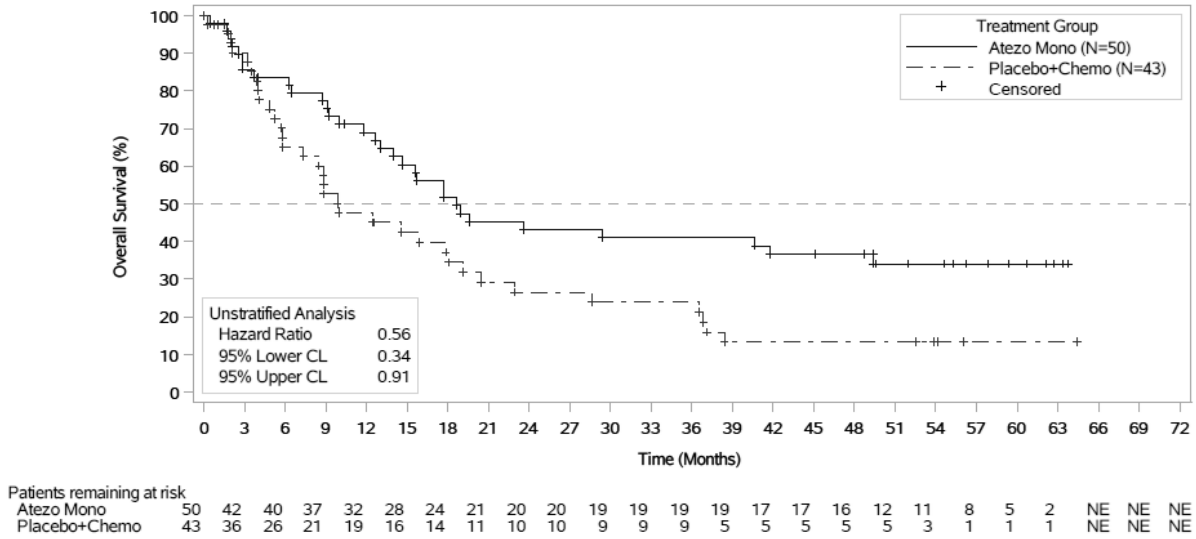
IMvigor130 (WO30070): Phase III study of atezolizumab monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma

A phase III, multi-centre, randomised, placebo-controlled, partially blinded (Arms A and C only) study, IMvigor130, was conducted to evaluate the efficacy and safety of atezolizumab + platinum-based combination chemotherapy (i.e., either cisplatin or carboplatin with gemcitabine), Arm A, or atezolizumab monotherapy (Arm B, open-label arm) versus placebo + platinum-based combination chemotherapy (Arm C) in patients with locally advanced or metastatic UC who had not received prior systemic therapy in the metastatic setting. The co-primary efficacy outcomes were investigator-assessed progression-free survival (PFS) in Arm A versus Arm C and overall survival (OS) in Arm A versus C and then Arm B versus C, analyzed in a hierarchical fashion. Overall survival was not statistically significant for the comparison of Arm A versus Arm C, and thus no further formal testing could be conducted per the pre-defined hierarchical testing order.

Based on an independent Data Monitoring Committee (iDMC) recommendation following an early review of survival data, accrual of patients on the atezolizumab monotherapy treatment arm whose tumours had a low PD-L1 expression (less than 5% of immune cells staining positive for PD-L1 by immunohistochemistry using VENTANA PD-L1 [SP142] assay) was stopped after observing decreased overall survival for this subgroup at an unplanned early analysis, however, this occurred after the vast majority of patients had already been enrolled.

Out of 719 patients enrolled in the atezolizumab monotherapy (n=360) and chemotherapy alone (n=359) arms, 50 and 43 patients, respectively, were cisplatin-ineligible by Galsky criteria and had tumours with high PD-L1 expression (≥ 5% of immune cells staining positive for PD-L1 by immunohistochemistry using VENTANA PD-L1 [SP142] assay). In an exploratory analysis in this subgroup of patients, the unstratified HR for OS was 0.56 (95% CI: 0.34, 0.91). The median OS was 18.6 months (95% CI: 14.0, 49.4) in the atezolizumab monotherapy arm vs. 10.0 months (95% CI: 7.4, 18.1) in the chemotherapy alone arm (see Figure 2).

Figure 2 Kaplan-Meier Plot of Overall Survival in Cisplatin-ineligible patients whose tumours are PD-L1 high (Arm B vs. Arm C)



<u>*Non-small cell lung cancer*</u>

Adjuvant treatment of early-stage NSCLC

IMpower010 (GO29527): Randomised phase III trial in patients with resected NSCLC after cisplatin-based chemotherapy

A phase III, open label, multi-centre, randomised study, GO29527 (IMpower010), was conducted to evaluate the efficacy and safety of atezolizumab for the adjuvant treatment of patients with stage IB (tumours ≥ 4 cm) – IIIA NSCLC (per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition).

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with stage II – IIIA according to the 7th edition staging system:

Tumour size ≥ 5 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

The study did not include patients who had N2 status with tumours invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

A total of 1 280 enrolled patients had complete tumour resection and were eligible to receive up to 4 cycles of cisplatin-based chemotherapy. The cisplatin-based chemotherapy regimens are described in Table 6.

Table 6: Adjuvant chemotherapy regimens (IMpower010)

Adjuvant cisplatin-based chemotherapy: Cisplatin 75 mg/m^2 intravenous on Day 1 of each 21 day cycle with one of the following treatment regimens	Vinorelbine 30 mg/m^2 intravenous, Days 1 and 8
	Docetaxel 75 mg/m^2 intravenous, Day 1
	Gemcitabine 1 250 mg/m^2 intravenous, Days 1 and 8
	Pemetrexed 500 mg/m^2 intravenous, Day 1(non-squamous)

After completion of cisplatin-based chemotherapy (up to four cycles), a total of 1 005 patients were randomised in a 1:1 ratio to receive atezolizumab (Arm A) or best supportive care (BSC) (Arm B). Atezolizumab was administered as a fixed dose of 1 200 mg by IV infusion every 3 weeks for 16 cycles unless there was disease recurrence or unacceptable toxicity. Randomisation was stratified by sex, stage of disease, histology, and PD-L1 expression.

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomisation; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomisation. Tumour assessments were conducted at baseline of the randomisation phase and every 4 months for the first year following Cycle 1, Day 1 and then every 6 months until year five, then annually thereafter.

The demographics and baseline disease characteristics in the ITT population were well balanced between the treatment arms. The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%), and 24% were Asian. Most patients were current or previous smokers (78%) and baseline ECOG performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had stage IB, 47% had stage II and 41% had stage IIIA disease. The percentage of patients who had tumours with PD-L1 expression ≥ 1% and ≥ 50% on TC as measured by the VENTANA PD-L1 (SP263) Assay was 55% and 26%, respectively.

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. DFS was defined as the time from the date of randomisation to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. The primary efficacy objective was to evaluate DFS in the PD-L1 ≥ 1% TC stage II – IIIA patient population. Key secondary efficacy objectives were to evaluate DFS in the PD-L1 ≥ 50% TC stage II – IIIA patient population and overall survival (OS) in the ITT population.

At the time of the interim DFS analysis, the study met its primary endpoint. In the analysis of patients with PD-L1 ≥ 50% TC stage II – IIIA without EGFR mutations or ALK rearrangements (n = 209), an improvement in DFS in the atezolizumab arm was observed compared to the BSC arm. Results were consistent at the time of the final DFS analysis, with median follow up time of 65 months.

The key efficacy results for DFS and OS in the PD-L1 ≥ 50% TC stage II – IIIA patient population, without EGFR mutations and ALK rearrangements, are summarised in Table 7. The Kaplan-Meier curve for DFS is presented in Figure 3.

Table 7: Summary of efficacy in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010)

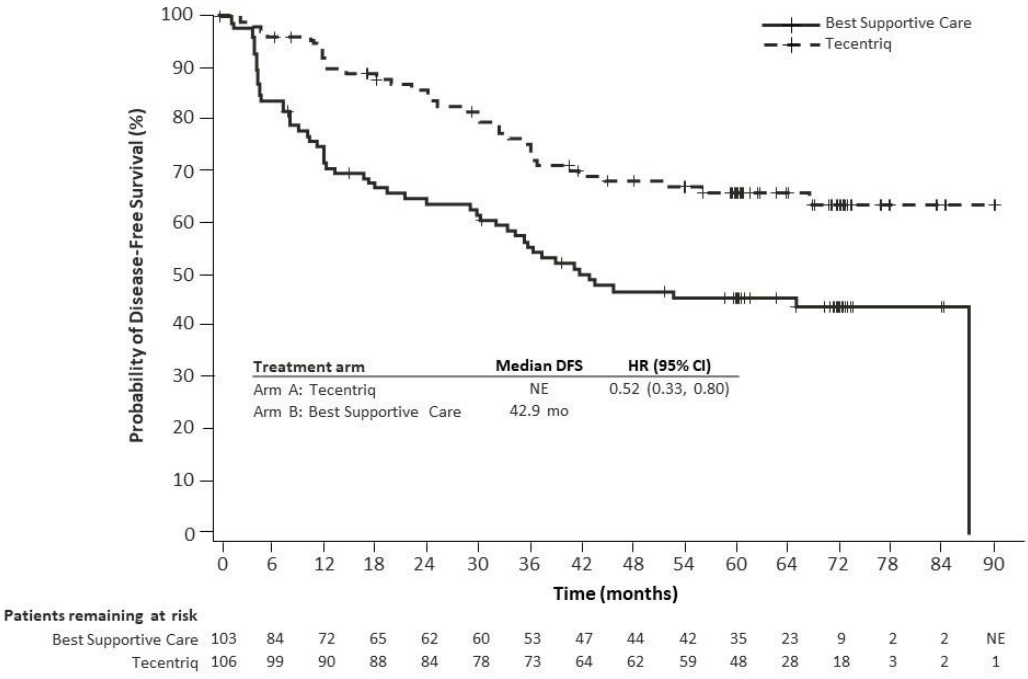
Efficacy endpoint	**Arm A** (Atezolizumab)	**Arm B** (Best supportive care)
Investigator-assessed DFS*	n = 106	n = 103
No. of events (%)	34 (32.1%)	55 (53.4%)
Median duration of DFS (months)	NE	42.9
95% CI	(NE)	(32.0, NE)
Stratified‡ hazard ratio (95% CI)	0.52 (0.33, 0.80)	
OS*	n=106	n=103
No. of events (%)	22 (20.8%)	41 (39.8%)
Median OS (months)	NE	87.1
95% CI	(NE)	(72.0, NE)
Stratified‡ hazard ratio (95% CI)	0.47 (0.28, 0.80)	

DFS = Disease-free survival; CI = confidence interval; NE = not estimable

***** Updated DFS and OS analysis at clinical cut-off 26 January 2024

‡ Stratified by stage, sex, and histology.

Figure 3: Kaplan-Meier curve for disease-free survival in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010)



The observed DFS improvement in the atezolizumab arm compared with the BSC arm was consistently shown across the majority of pre-specified subgroups in the PD-L1 ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements, including both non-squamous NSCLC patients (unstratified HR of 0.40, 95% CI: 0.23, 0.70; median DFS NE vs. 36.8 months) and squamous NSCLC patients (unstratified HR of 0.67, 95% CI: 0.34, 1.32; median DFS could not be estimated).

First-line treatment of advanced NSCLC

IMpower150 (GO29436): Randomised phase III trial in chemotherapy-naïve patients with metastatic non-squamous NSCLC, in combination with paclitaxel and carboplatin with or without bevacizumab

A phase III, open-label, multi-centre, international, randomised study, IMpower150, was conducted to evaluate the efficacy and safety of atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, in chemotherapy-naïve patients with metastatic non-squamous NSCLC.

Patients were excluded if they had history of autoimmune disease, administration of a live, attenuated vaccine within 28 days prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to randomisation, active or untreated CNS metastases, clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumour specimens were evaluated for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 1 202 patients were enrolled and were randomised (1:1:1) to receive one of the treatment regimens described in Table 8. Randomisation was stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC.

Table 8: Intravenous treatment regimens (IMpower150)

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
A	Atezolizumab[a] (1 200 mg) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Atezolizumab[a] (1 200 mg)
B	Atezolizumab[a] (1 200 mg) + bevacizumab[d] (15 mg/kg bw) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Atezolizumab[a] (1 200 mg) + bevacizumab[d] (15 mg/kg bw)
C	Bevacizumab[d] (15 mg/kg bw) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Bevacizumab[d] (15 mg/kg bw)

[a] Atezolizumab is administered until loss of clinical benefit as assessed by the investigator
[b] The paclitaxel starting dose for patients of Asian race/ethnicity was 175 mg/m^2 due to higher overall level of haematologic toxicities in patients from Asian countries compared with those from non-Asian countries
[c] Paclitaxel and carboplatin are administered until completion of 4 or 6 cycles, or progressive disease, or unacceptable toxicity whichever occurs first
[d.] Bevacizumab is administered until progressive disease or unacceptable toxicity

The demographics and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were white (82%). Approximately 10% of patients had known EGFR mutation, 4% had known ALK rearrangements, 14% had liver metastasis at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). 51% of patients' tumours had PD-L1 expression of ≥ 1% TC or ≥ 1% IC and 49% of patients' tumours had PD-L1 expression of < 1% TC and < 1% IC.

At the time of the final analysis for PFS, patients had a median follow up time of 15.3 months. The ITT population, including patients with EGFR mutations or ALK rearrangements who should have been previously treated with tyrosine kinase inhibitors, demonstrated clinically meaningful PFS improvement in Arm B as compared to Arm C (HR of 0.61, 95% CI: 0.52, 0.72; median PFS 8.3 vs. 6.8 months).

At the time of the interim OS analysis, patients had a median follow-up of 19.7 months. The key results from this analysis as well as from the updated PFS analysis in the ITT population are summarised in Tables 9 and 10. The Kaplan-Meier curve for OS in the ITT population is presented in Figure 4. Figure 5 summarises the results of OS in the ITT and PD-L1 subgroups. Updated PFS results are also presented in Figures 6 and 7.

Table 9: Summary of updated efficacy in the ITT population (IMpower150)

Efficacy endpoint	**Arm A (Atezolizumab + Paclitaxel + Carboplatin)**	**Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)**	**Arm C (Bevacizumab + Paclitaxel + Carboplatin)**
Secondary Endpoints[#]			
Investigator-assessed PFS (RECIST v1.1)*	n = 402	n = 400	n = 400
No. of events (%)	330 (82.1%)	291 (72.8%)	355 (88.8%)
Median duration of PFS (months)	6.7	8.4	6.8
95% CI	(5.7, 6.9)	(8.0, 9.9)	(6.0, 7.0)
Stratified hazard ratio[‡^] (95% CI)	0.91 (0.78, 1.06)	0.59 (0.50, 0.69)	---
p-value[1,2]	0.2194	< 0.0001	
12-month PFS (%)	24	38	20
OS interim analysis*	n = 402	n = 400	n = 400
No. of deaths (%)	206 (51.2%)	192 (48.0%)	230 (57.5%)
Median time to events (months)	19.5	19.8	14.9
95% CI	(16.3, 21.3)	(17.4, 24.2)	(13.4, 17.1)
Stratified hazard ratio[‡^] (95% CI)	0.85 (0.71, 1.03)	0.76 (0.63, 0.93)	---
p-value[1,2]	0.0983	0.006	
6-month OS (%)	84	85	81
12-month OS (%)	66	68	61
Investigator-assessed Overall Best Response[3]* (RECIST 1.1)	n = 401	n = 397	n = 393
No. of responders (%)	163 (40.6%)	224 (56.4%)	158 (40.2%)
95% CI	(35.8, 45.6)	(51.4, 61.4)	(35.3, 45.2)
No. of complete response (%)	8 (2.0%)	11 (2.8%)	3 (0.8%)
No. of partial response (%)	155 (38.7%)	213 (53.7%)	155 (39.4%)
Investigator-assessed DOR* (RECIST v1.1)	n = 163	n = 224	n = 158
Median in months	8.3	11.5	6.0
95% CI	(7.1, 11.8)	(8.9, 15.7)	(5.5, 6.9)

[#] Primary efficacy endpoints were PFS and OS and they were analysed in the ITT-wild-type (WT) population, i.e. excluding patients with EGFR mutations or ALK rearrangements.
[1] Based on the stratified log-rank test
[2] For informational purposes; in the ITT population, comparisons between Arm B and Arm C as well as between Arm A and Arm C were not formally tested yet as per the pre-specified analysis hierarchy
[3] Overall best response for complete response and partial response
[‡] Stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC
^ The Arm C is the comparison group for all hazard ratios
***** Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018

PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1. CI = confidence interval; DOR = duration of response; OS = overall survival.

Table 10: Summary of updated efficacy for Arm A vs. Arm B in the ITT population (IMpower150)

Efficacy endpoint	Arm A (Atezolizumab + Paclitaxel + Carboplatin)	Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)
Investigator-assessed PFS (RECIST v1.1)*	n = 402	n = 400
No. of events (%)	330 (82.1%)	291 (72.8%)
Median duration of PFS (months)	6.7	8.4
95% CI	(5.7, 6.9)	(8.0, 9.9)
Stratified hazard ratio‡^ (95% CI)	0.67 (0.57, 0.79)	
p-value[1,2]	< 0.0001	
OS interim analysis*	n = 402	n = 400
No. of deaths (%)	206 (51.2%)	192 (48.0%)
Median time to events (months)	19.5	19.8
95% CI	(16.3, 21.3)	(17.4, 24.2)
Stratified hazard ratio‡^ (95% CI)	0.90 (0.74, 1.10)	
p-value[1,2]	0.3000	

[1] Based on the stratified log-rank test
[2] For informational purposes; in the ITT population, comparisons between Arm A and Arm B were not included in the pre-specified analysis hierarchy
‡ Stratified by sex, presence of liver metastases and PD-L1 expression on TC and IC
* Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018
^ The Arm A is the comparison group for all hazard ratios

Figure 4: Kaplan-Meier curve for overall survival in the ITT population (IMpower150)

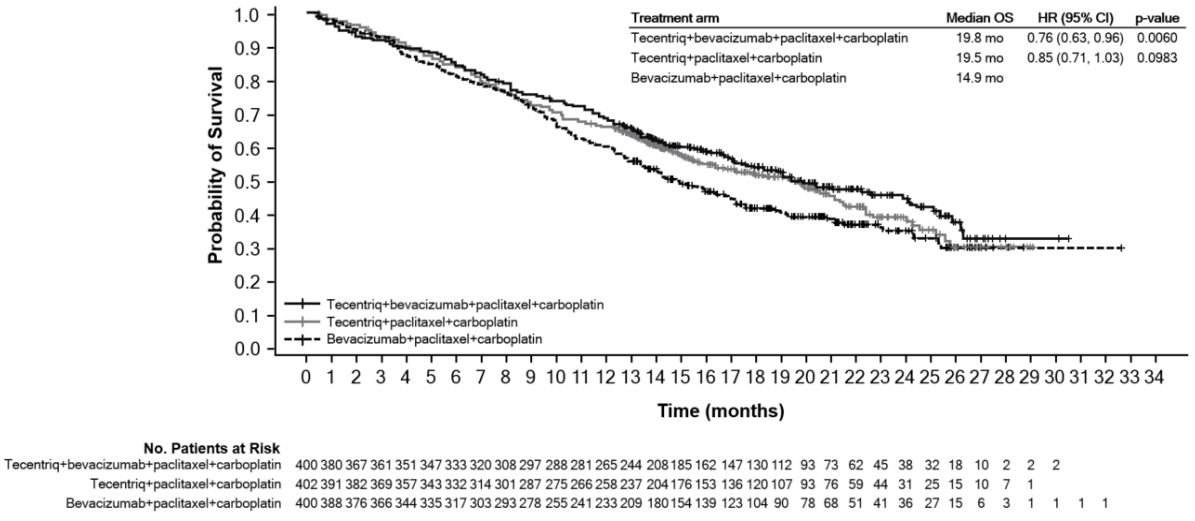


Figure 5: Forest plot of overall survival by PD-L1 expression in the ITT population, Arm B vs. C (IMpower150)

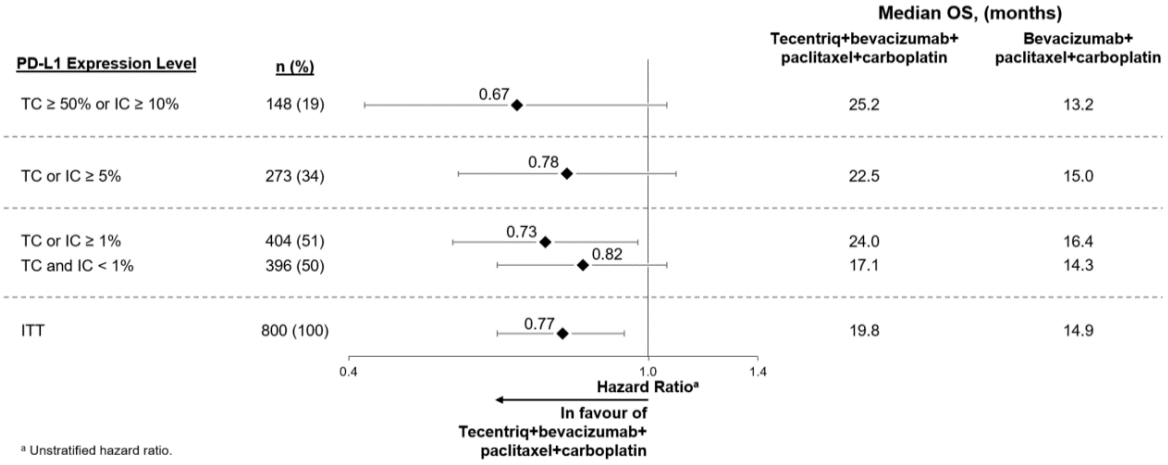


Figure 6: Kaplan-Meier curve for PFS in the ITT population (IMpower150)

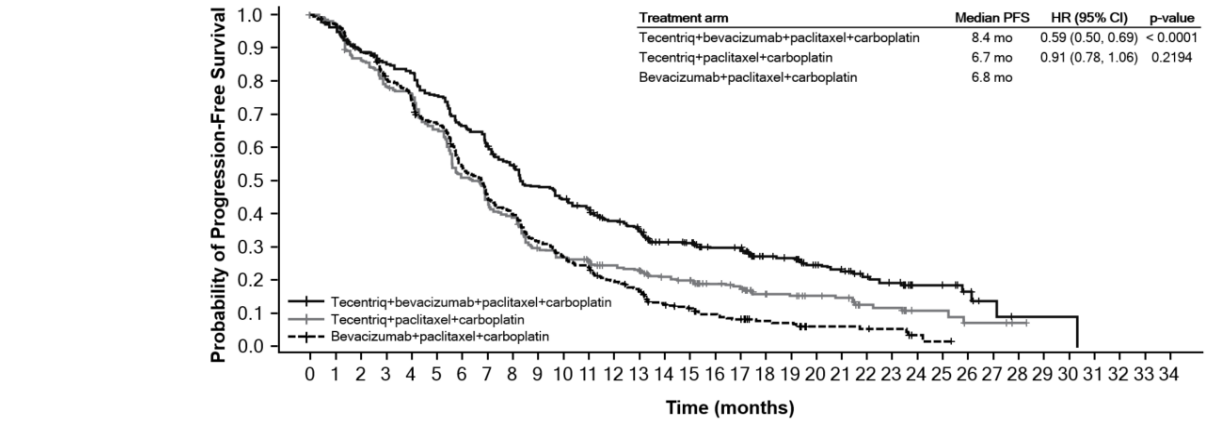
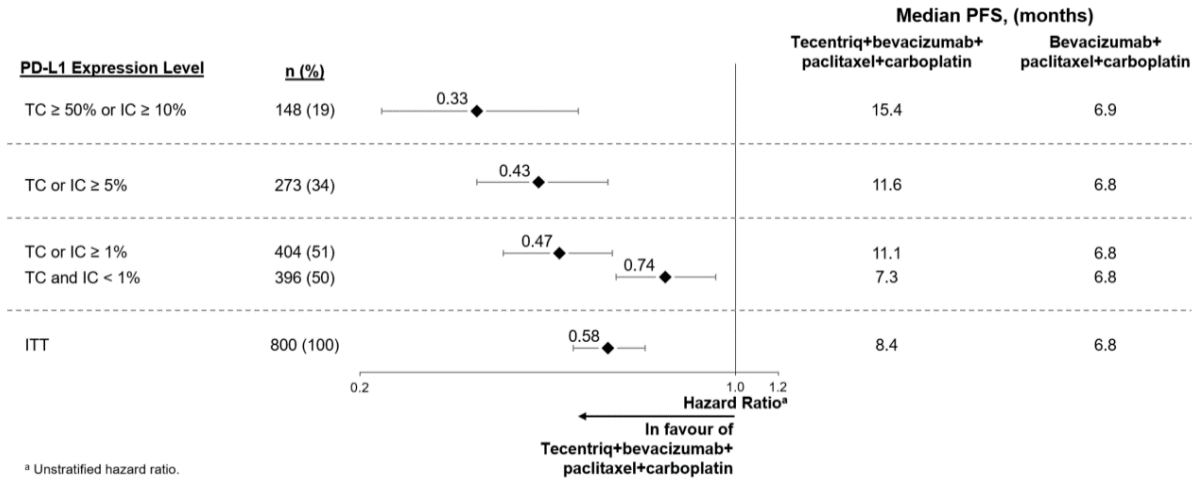


Figure 7: Forest plot of progression free survival by PD-L1 expression in the ITT population, Arm B vs. C (IMpower150)



In Arm B as compared to Arm C, pre-specified subgroup analyses from the interim OS analysis showed an OS improvement for patients with EGFR mutations or ALK rearrangements (hazard ratio [HR] of 0.54, 95% CI: 0.29, 1.03; median OS not reached vs. 17.5 months), and liver metastases (HR of 0.52, 95% CI: 0.33, 0.82; median OS 13.3 vs. 9.4 months). PFS improvements were also shown in patients with EGFR mutations or ALK rearrangements (HR of 0.55, 95% CI: 0.35, 0.87; median PFS 10.0 vs. 6.1 months) and liver metastases (HR of 0.41, 95% CI: 0.26, 0.62; median PFS 8.2 vs. 5.4 months). OS results were similar for patients aged < 65 and ≥ 65 subgroups, respectively. Data for patients ≥ 75 years of age are too limited to draw conclusions on this population. For all subgroup analyses, formal statistical testing was not planned.

IMpower130 (GO29537): Randomised phase III trial in chemotherapy-naïve patients with metastatic non-squamous NSCLC, in combination with nab-paclitaxel and carboplatin

A phase III, open-label, randomised study, GO29537 (IMpower130), was conducted to evaluate the efficacy and safety of atezolizumab in combination with nab-paclitaxel and carboplatin, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. Patients with EGFR mutations or ALK rearrangements should have been previously treated with tyrosine kinase inhibitors.

Patients were staged according to the American Joint Committee on Cancer (AJCC) 7th edition. Patients were excluded if they had a history of autoimmune disease, administration of live, attenuated vaccine within 28 days prior to randomisation, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation, and active or untreated CNS metastases. Patients who had prior treatment with CD137 agonists or immune checkpoint blockade therapies (anti-PD-1, and anti-PD-L1 therapeutic antibodies) were not eligible. However, patients who had prior anti-CTLA-4 treatment could be enrolled, as long as the last dose was received at least 6 weeks prior to randomisation, and there was no history of severe immune-mediated adverse events from anti-CTLA-4 (NCI CTCAE Grades 3 and 4). Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, then every 9 weeks thereafter. Tumour specimens were evaluated for PD-L1 expression on tumour cells (TC) and tumour infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

Patients, including those with EGFR mutations or ALK rearrangements, were enrolled and were randomised in a 2:1 ratio to receive one of the treatment regimens described in Table 11. Randomisation was stratified by sex, presence of liver metastases and PD-L1 expression on TC and IC. Patients receiving treatment regimen B were able to crossover and receive atezolizumab monotherapy following disease progression.

Table 11: Intravenous treatment regimens (IMpower130)

Treatment Regimen	**Induction (Four or six 21-day cycles)**	**Maintenance (21-day cycles)**
A	Atezolizumab (1 200 mg)[a] + nab-paclitaxel (100 mg/m^2)[b,c] + carboplatin (AUC 6)[c]	Atezolizumab (1 200 mg)[a]
B	Nab-paclitaxel (100 mg/m^2)[b,c] + carboplatin (AUC 6)[c]	Best supportive care or pemetrexed

[a] Atezolizumab is administered until loss of clinical benefit as assessed by investigator
[b] Nab-paclitaxel is administered on days 1, 8, and 15 of each cycle
[c] Nab-paclitaxel and carboplatin are administered until completion of 4-6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

The demographics and baseline disease characteristics of the study population defined as ITT-WT (n=679) were well balanced between the treatment arms. The median age was 64 years (range: 18 to 86 years). The majority of the patients were male (59%) and white (90%). Fourteen point seven percent of patients had liver metastases at baseline, and most patients were current or previous smokers (90%). The majority of patients had a baseline ECOG performance status of 1 (59%) and PD-L1 expression < 1% (approximately 52%). Among 107 Arm B patients who had a response status of stable disease, partial response, or complete response after induction therapy, 40 received pemetrexed switch maintenance therapy.

The primary analysis was conducted in all patients, excluding those with EGFR mutations or ALK rearrangements, defined as ITT-WT population (n=679). Patients had a median survival follow up time of 18.6 months and showed improved OS and PFS with atezolizumab, nab-paclitaxel and carboplatin as compared to the control. The key results are summarised in Table 12 and Kaplan-Meier curves for OS and PFS are presented in Figures 8 and 10, respectively. The exploratory results of OS and PFS by PD-L1 expression are summarised in Figures 9 and 11, respectively. Patients with liver metastases did not show improved PFS or OS with atezolizumab, nab-paclitaxel and carboplatin, compared to nab-paclitaxel and carboplatin (HR of 0.93, 95% CI: 0.59, 1.47 for PFS and HR of 1.04, 95% CI: 0.63, 1.72 for OS, respectively).

Fifty-nine percent of patients in the nab-paclitaxel and carboplatin arm received any cancer immunotherapy after disease progression, which includes atezolizumab as crossover treatment (41% of all patients), compared to 7.3% of patients in the atezolizumab, nab paclitaxel and carboplatin arm.

In an exploratory analysis with longer follow up (median: 24.1 months), the median OS for both arms was unchanged relative to the primary analysis, with HR = 0.82 (95% CI: 0.67, 1.01).

Table 12: Summary of efficacy from IMpower130 in the primary analysis (ITT-WT population)

Efficacy endpoints	**Arm A** **Atezolizumab + nab-paclitaxel + carboplatin**	**Arm B** **Nab-paclitaxel + carboplatin**
Co-primary endpoints		
OS	n=451	n=228
No. of deaths (%)	226 (50.1%)	131 (57.5%)
Median time to events (months)	18.6	13.9
95% CI	(16.0, 21.2)	(12.0, 18.7)
Stratified hazard ratio‡ (95% CI)	0.79 (0.64, 0.98)	
p-value	0.033	
12-month OS (%)	63	56
Investigator-assessed PFS (RECIST v1.1)	n=451	n=228
No. of events (%)	347 (76.9%)	198 (86.8%)
Median duration of PFS (months)	7.0	5.5
95% CI	(6.2, 7.3)	(4.4, 5.9)
Stratified hazard ratio‡ (95% CI)	0.64 (0.54, 0.77)	
p-value	< 0.0001	
12-month PFS (%)	29%	14%

Efficacy endpoints	Arm A Atezolizumab + nab-paclitaxel + carboplatin	Arm B Nab-paclitaxel + carboplatin
Other endpoints		
Investigator-assessed ORR (RECIST v1.1)^	n=447	n=226
No. of confirmed responders (%)	220 (49.2%)	72 (31.9%)
95% CI	(44.5, 54.0)	(25.8, 38.4)
No. of complete response (%)	11 (2.5%)	3 (1.3%)
No. of partial response (%)	209 (46.8%)	69 (30.5%)
Investigator-assessed confirmed DOR (RECIST 1.1)^	n=220	n=72
Median in months	8.4	6.1
95% CI	(6.9, 11.8)	(5.5, 7.9)

‡ Stratified by sex and PD-L1 expression on TC and IC
^ Confirmed ORR and DoR are exploratory endpoints
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival

Figure 8: Kaplan-Meier curves for overall survival (IMpower130)

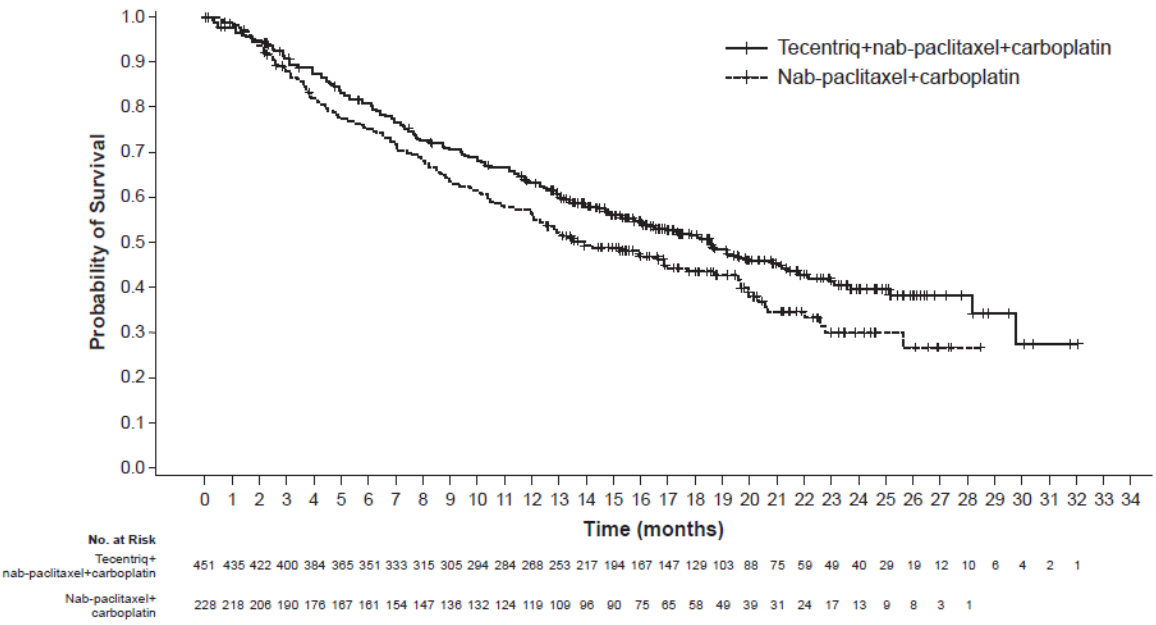


Figure 9: Forest plot of overall survival by PD-L1 expression (IMpower130)

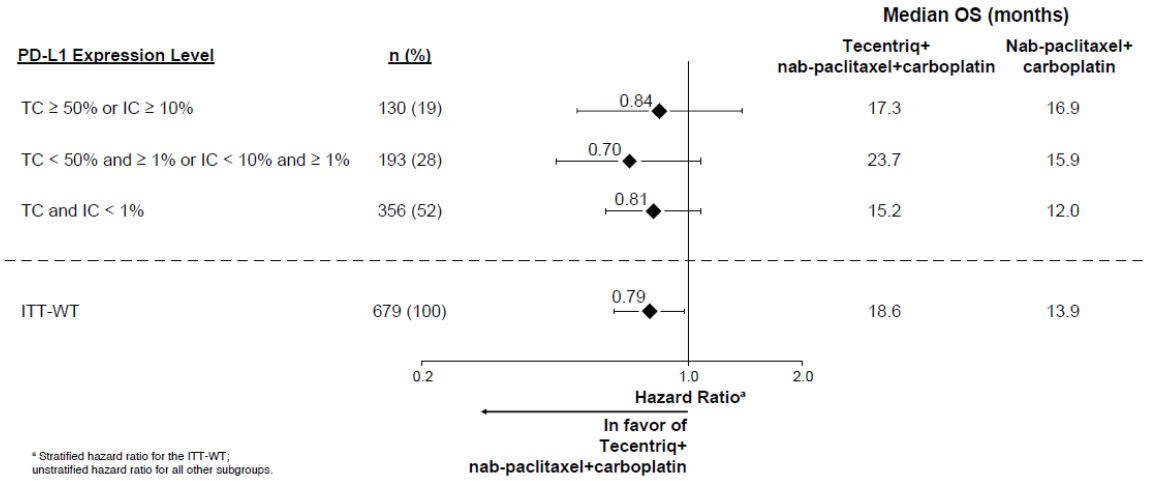


Figure 10: Kaplan-Meier curves for progression free survival (IMpower130)

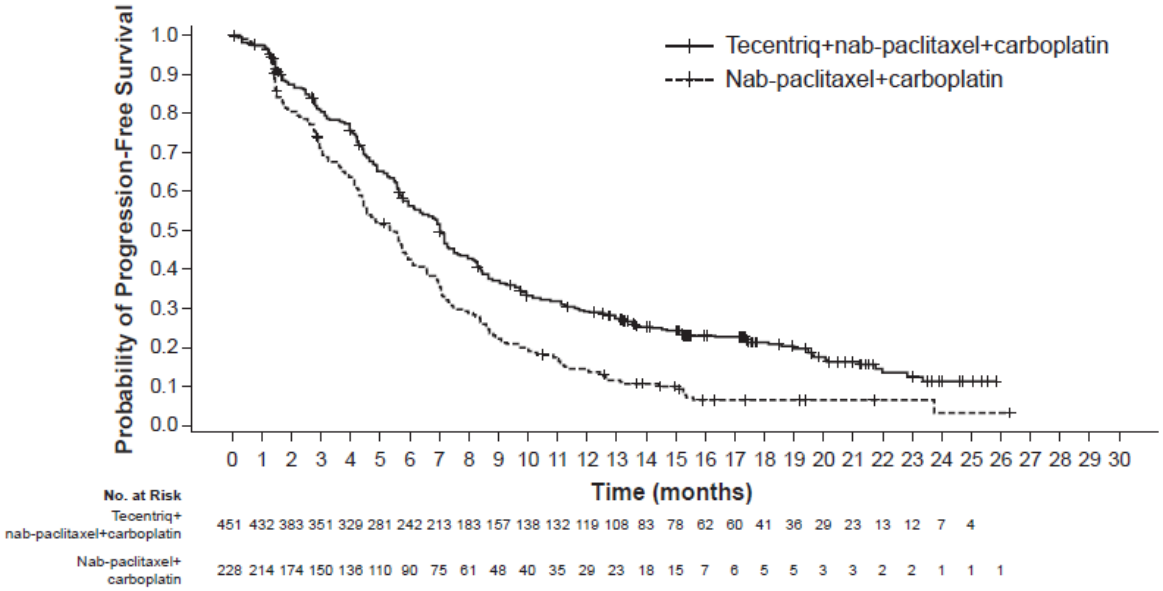
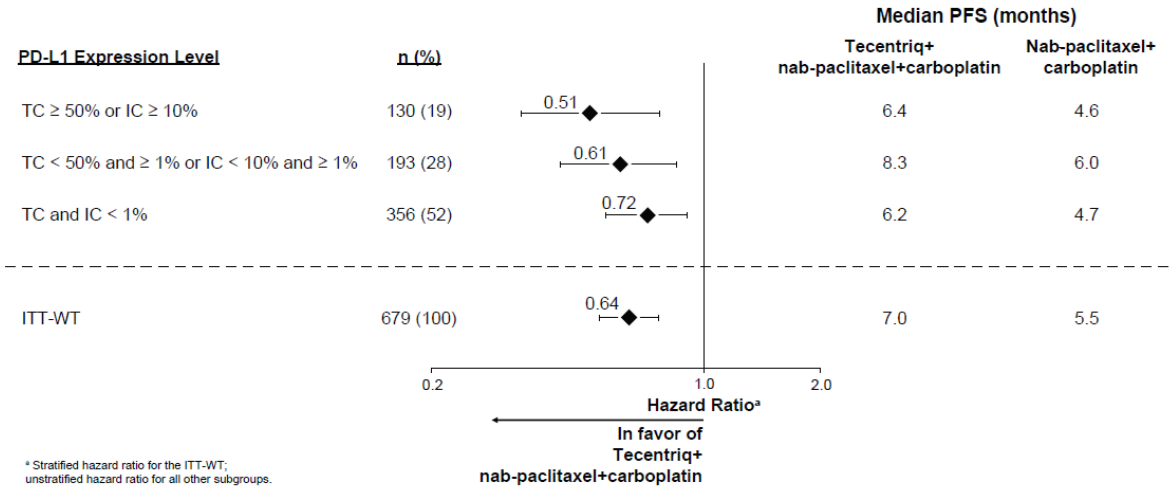


Figure 11: Forest plot of progression free survival by PD-L1 expression (IMpower130)



IMpower110 (GO29431): Randomised phase III trial in chemotherapy-naïve patients with metastatic NSCLC

A phase III, open-label, multi-centre, randomised study, IMpower110, was conducted to evaluate the efficacy and safety of atezolizumab in chemotherapy-naïve patients with metastatic NSCLC. Patients had PD-L1 expression ≥ 1% TC (PD-L1 stained ≥ 1% of tumour cells) or ≥ 1% IC (PD-L1 stained tumour-infiltrating immune cells covering ≥ 1% of the tumour area) based on the VENTANA PD-L1 (SP142) Assay.

A total of 572 patients were randomised in a 1:1 ratio to receive atezolizumab (Arm A) or chemotherapy (Arm B). Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. The chemotherapy regimens are described in Table 13. Randomisation was stratified by sex, ECOG performance status, histology, and PD-L1 tumour expression on TC and IC.

Table 13: Chemotherapy intravenous treatment regimens (IMpower110)

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
B (Non-squamous)	Cisplatin[a] (75 mg/m²) + pemetrexed[a] (500 mg/m²) OR carboplatin[a](AUC 6) + pemetrexed[a] (500 mg/m²)	Pemetrexed[b,d] (500 mg/m²)
B (Squamous)	Cisplatin[a] (75 mg/m²) + gemcitabine[a,c] (1 250 mg/m²) OR carboplatin[a] (AUC 5) + gemcitabine[a,c] (1 000 mg/m²)	Best supportive care[d]

[a] Cisplatin, carboplatin, pemetrexed and gemcitabine are administered until completion of 4 or 6 cycles, or progressive disease, or unacceptable toxicity
[b] Pemetrexed is administered as maintenance regimen every 21 days until progressive disease or unacceptable toxicity
[c] Gemcitabine is administered on days 1 and 8 of each cycle
[d] No crossover was allowed from the control arm (platinum-based chemotherapy) to the atezolizumab arm (Arm A)

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation, active or untreated CNS metastases. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

The demographics and baseline disease characteristics in patients with PD-L1 expression ≥ 1% TC or ≥ 1% IC who do not have EGFR mutations or ALK rearrangements (n=554) were well balanced between the treatment arms. The median age was 64.5 years (range: 30 to 87), and 70% of patients were male. The majority of patients were white (84%) and Asian (14%). Most patients were current or previous smokers (87%) and baseline ECOG performance status in patients was 0 (36%) or 1 (64%). Overall, 69% of patients had non-squamous disease and 31% of patients had squamous disease. The demographics and baseline disease characteristics in patients with high PD-L1 expression (PD-L1 ≥ 50% TC or ≥ 10% IC) who do not have with EGFR mutations or ALK rearrangements (n=205) were generally representative of the broader study population and were balanced between the treatment arms.

The primary endpoint was overall survival (OS). At the time of the interim OS analysis, patients with high PD-L1 expression excluding those with EGFR mutations or ALK rearrangements (n=205) showed statistically significant improvement in OS for the patients randomised to atezolizumab (Arm A) as compared with chemotherapy (Arm B) (HR of 0.59, 95% CI: 0.40, 0.89; median OS of 20.2 months vs 13.1 months) with a two-sided p-value of 0.0106. The median survival follow-up time in patients with high PD-L1 expression was 15.7 months.

In an exploratory OS analysis with longer follow up (median: 31.3 months) for these patients, the median OS for the atezolizumab arm was unchanged relative to the primary OS interim analysis (20.2 months) and was 14.7 months for the chemotherapy arm (HR of 0.76, 95% CI: 0.54, 1.09). The key results at the exploratory analysis are summarised in Table 14. The Kaplan-Meier curves for OS and PFS in patients with high PD-L1 expression are presented in Figures 12 and 13. A higher proportion of patients experienced death within the first 2.5 months in the atezolizumab arm (16/107, 15.0%) as compared to the chemotherapy arm (10/98, 10.2%). No specific factor(s) associated with early deaths could be identified.

Table 14: Summary of efficacy in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)

Efficacy endpoints	**Arm A** (Atezolizumab)	**Arm B** (Chemotherapy)
Primary endpoint		
Overall survival	n = 107	n = 98
No. of deaths (%)	64 (59.8%)	64 (65.3%)
Median time to events (months)	20.2	14.7
95% CI	(17.2, 27.9)	(7.4, 17.7)
Stratified hazard ratio‡ (95% CI)	0.76 (0.54, 1.09)	
12-month OS (%)	66.1	52.3
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n = 107	n = 98
No. of events (%)	82 (76.6%)	87 (88.8%)
Median duration of PFS (months)	8.2	5.0
95% CI	(6.8, 11.4)	(4.2, 5.7)
Stratified hazard ratio‡ (95% CI)	0.59 (0.43, 0.81)	
12-month PFS (%)	39.2	19.2
Investigator-assessed ORR (RECIST 1.1)	n = 107	n = 98
No. of responders (%)	43 (40.2%)	28 (28.6%)
95% CI	(30.8, 50.1)	(19.9, 38.6)
No. of complete response (%)	1 (0.9%)	2 (2.0%)
No. of partial response (%)	42 (39.3%)	26 (26.5%)
Investigator-assessed DOR (RECIST 1.1)	n = 43	n = 28
Median in months	38.9	8.3
95% CI	(16.1, NE)	(5.6, 11.0)

‡ Stratified by sex and ECOG performance status (0 vs. 1)
PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1; CI = confidence interval; ORR = objective response rate; DOR = duration of response; OS = overall survival; NE = not estimable.

Figure 12: Kaplan-Meier curve for overall survival in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)

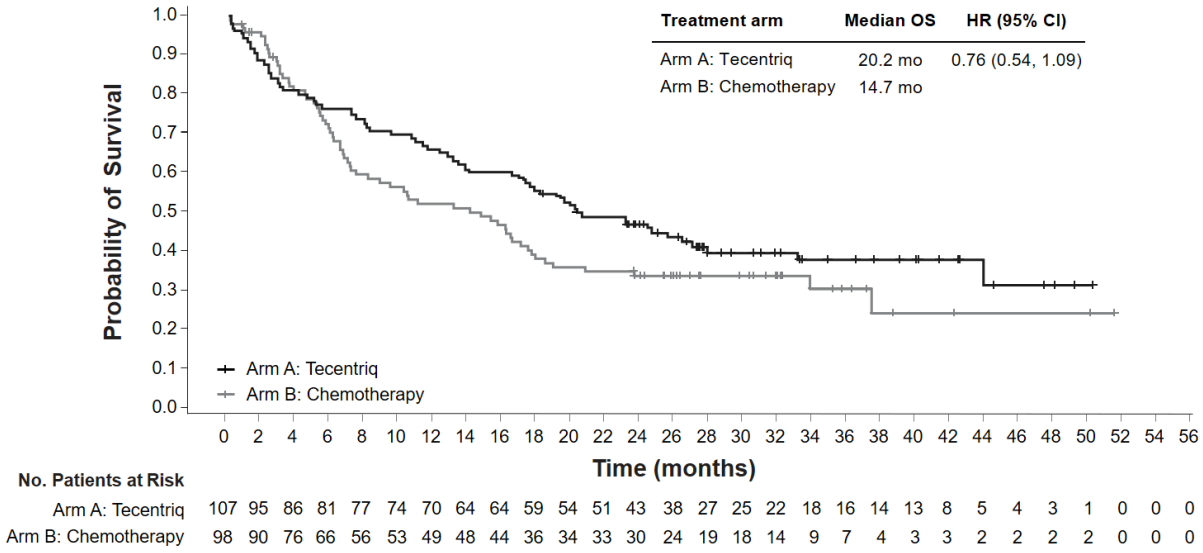
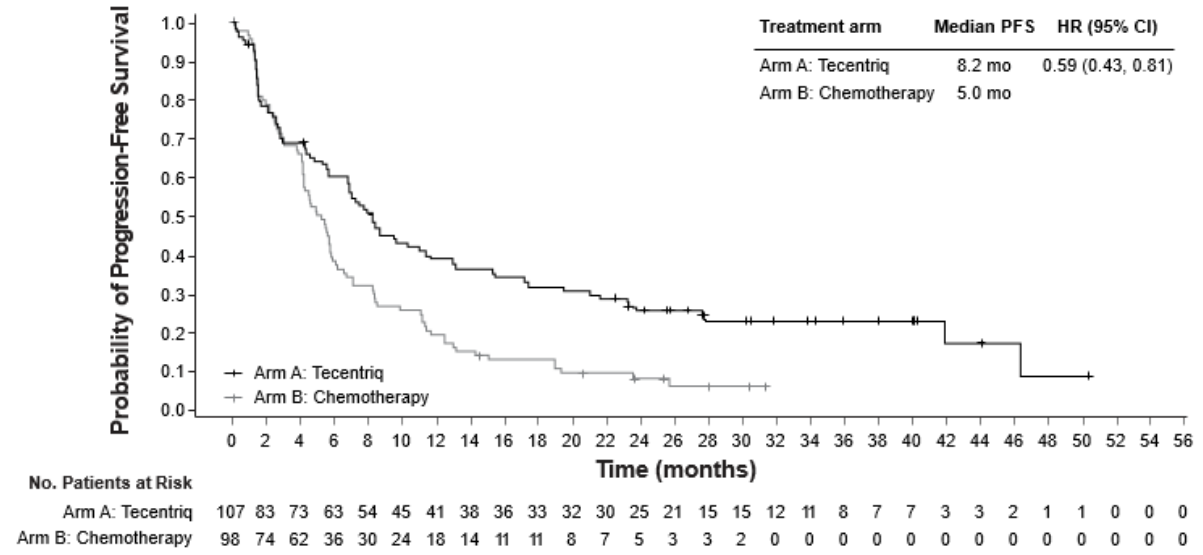


Figure 13: Kaplan-Meier curve for progression free survival in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)



The observed OS improvement in the atezolizumab arm compared with the chemotherapy arm was consistently shown across subgroups in patients with high PD-L1 expression including both non-squamous NSCLC patients (hazard ratio [HR] of 0.62, 95% CI: 0.40, 0.96; median OS 20.2 vs. 10.5 months) and squamous NSCLC patients (HR of 0.56, 95% CI: 0.23, 1.37; median OS not reached vs. 15.3 months). Data for patients ≥ 75 years of age and patients who were never smokers are too limited to draw conclusions in these subgroups.

IPSOS study (MO29872): Randomised phase III trial in patients with treatment-naïve locally advanced unresectable or metastatic NSCLC who are ineligible for platinum-based chemotherapy

A phase III, open label, randomised, controlled study, MO29872 (IPSOS), was conducted to evaluate the efficacy and safety of atezolizumab compared with a single-agent chemotherapy regimen (vinorelbine or gemcitabine by investigator choice) in treatment-naïve patients with advanced or recurrent (Stage IIIB [according to the AJCC 7th edition] not amenable to multimodality treatment) or metastatic (Stage IV) NSCLC who were considered ineligible for platinum-based chemotherapy.

The following selection criteria define patients ineligible for platinum-based chemotherapy who are included in the therapeutic indication: Patients > 80 years of age, or with an ECOG performance status (PS) of 3, or patients with an ECOG PS 2 in combination with relevant comorbidities, or of older age (≥ 70 years) in combination with relevant comorbidities. Relevant comorbidities are related to cardiac disorders, nervous system disorders, psychiatric disorders, vascular disorders, renal disorders, metabolism and nutrition disorders, or pulmonary disorders contraindicating treatment with platinum-based therapy, as assessed by the treating physician.

The study excluded patients younger than 70 years who had an ECOG PS of 0 or 1; patients with active or untreated CNS metastases; administration of live, attenuated vaccine within 4 weeks prior to randomisation; administration of systemic immunostimulatory or systemic immunosuppressive medicinal products within 4 weeks prior to randomisation. Patients with EGFR mutations or ALK rearrangements were also excluded from the study. Patients were eligible regardless of their tumour PD-L1 status.

Patients were randomised in a 2:1 ratio to receive atezolizumab (Arm A) or chemotherapy (Arm B). Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks. The chemotherapy regimens are described in Table 15. Treatment was administered until disease progression per RECIST v1.1 or unacceptable toxicity. Randomisation was stratified by histology (squamous/non-squamous), PD-L1 expression (PD-L1 IHC status as measured by the VENTANA PD-L1 (SP142) assay: TC3 or IC3 vs TC0/1/2 and IC0/1/2 vs unknown) and brain metastases (yes/no).

Table 15: Treatment regimens (IPSOS)

Treatment Regimen	
A	Atezolizumab 1 200 mg by IV infusion on Day 1 of every 21-day cycle.
B	Vinorelbine: IV infusion at 25-30 mg/m^2 or oral administration at 60-80 mg/m^2 on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle or weekly administration or Gemcitabine: IV infusion at 1 000-1 250 mg/m^2 on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle.

A total of 453 patients were enrolled in the study (ITT population). The population predominantly comprised White (65.8%) and male (72.4%) patients. The median age of patients was 75 years and 72.8% of patients were aged 70 years or older. The proportion of patients with ECOG PS of 0, 1, 2 and 3 was 1.5%, 15.0%, 75.9%, and 7.5%, respectively. Overall, 13.7% of patients had stage IIIB disease not amenable to multimodality treatment and 86.3% had stage IV disease. The percentage of patients who had tumours with PD-L1 expression TC< 1%, 1-49% and ≥ 50% as measured by the VENTANA PD-L1 (SP263) assay was 46.8%, 28.7% and 16.6%, respectively, while 7.9% of patients had an unknown PD-L1 expression status.

The primary endpoint of the study was overall survival (OS). At the time of the final OS analysis, the median follow-up was 41.0 months. Efficacy results are presented in Table 16 and Figure 14.

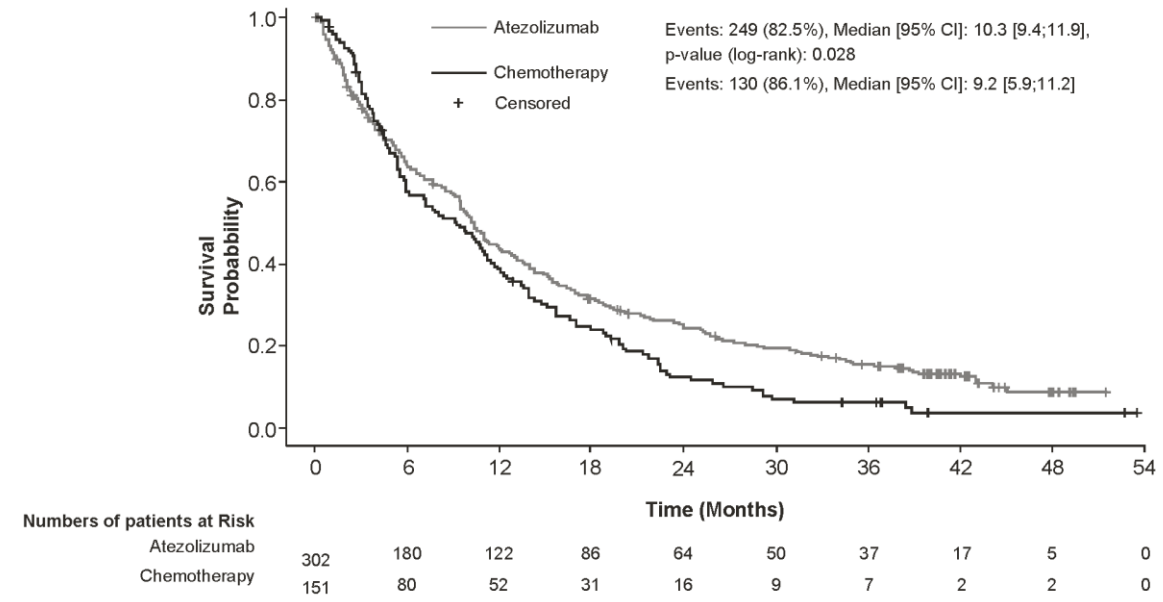
Table 16: Summary of efficacy for NSCLC patients ineligible for platinum-based chemotherapy (IPSOS)

Efficacy endpoint	Atezolizumab (n = 302)	Chemotherapy (n = 151)
Primary endpoint		
OS		
No. of events (%)	249 (82.5%)	130 (86.1%)
Median time to events (months) (95% CI)	10.3 (9.4, 11.9)	9.2 (5.9, 11.2)
Stratified hazard ratio (95% CI) ǂ	0.78 (0.63, 0.97)	
p-value (Stratified Log-rank)	p = 0.028	
Secondary endpoints		
Investigator-assessed PFS (RECIST 1.1)		
No. of events (%)	276 (91.4%)	138 (91.4%)
Median duration of PFS (months) (95% CI)	4.2 (3.7, 5.5)	4.0 (2.9, 5.4)
Stratified hazard ratio (95% CI) ǂ	0.87 (0.70, 1.07)	
ORR (RECIST 1.1)		
No. of confirmed responders (%)	51 (16.9%)	12 (7.9%)
DOR (RECIST 1.1)		
Median in months (95% CI)	14.0 (8.1, 20.3)	7.8 (4.8, 9.7)

CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

ǂ Estimated hazard ratio and 95% CI obtained from Cox model with treatment group as covariate. For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (yes/no) were added as stratification factors.

Figure 14: Kaplan-Meier curves for overall survival for NSCLC patients ineligible for platinum-based chemotherapy (IPSOS)



Second-line treatment of NSCLC

OAK (GO28915): Randomised phase III trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy

A phase III, open-label, multi-centre, international, randomised study, OAK, was conducted to evaluate the efficacy and safety of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrolment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC).

A total of 1 225 patients were enrolled and per the analysis plan the first 850 randomised patients were included in the primary efficacy analysis. Randomisation was stratified by PD-L1 expression status on IC, by the number of prior chemotherapy regimens, and by histology. Patients were randomised (1:1) to receive either atezolizumab or docetaxel.

Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator. Docetaxel was administered 75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression. For all treated patients, the median duration of treatment was 2.1 months for the docetaxel arm and 3.4 months for the atezolizumab arm.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-quarters of patients had non-squamous histology (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had CNS metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy-five percent of patients received only one prior platinum-based therapeutic regimen.

The primary efficacy endpoint was OS. The key results of this study with a median survival follow-up of 21 months are summarised in Table 17. Kaplan-Meier curves for OS in the ITT population are presented in Figure 15. Figure 16 summarises the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with atezolizumab in all subgroups, including those with PD-L1 expression < 1% in TC and IC.

Table 17: Summary of efficacy in the primary analysis population (all comers)* (OAK)

Efficacy endpoint	**Atezolizumab (n = 425)**	**Docetaxel (n = 425)**
Primary efficacy endpoint		
OS		
No. of deaths (%)	271 (64%)	298 (70%)
Median time to events (months)	13.8	9.6
95% CI	(11.8, 15.7)	(8.6, 11.2)
Stratified‡ hazard ratio (95% CI)	0.73 (0.62, 0.87)	
p-value**	0.0003	
12-month OS (%)***	218 (55%)	151 (41%)
18-month OS (%)***	157 (40%)	98 (27%)
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)		
No. of events (%)	380 (89%)	375 (88%)
Median duration of PFS (months)	2.8	4.0
95% CI	(2.6, 3.0)	(3.3, 4.2)
Stratified hazard ratio (95% CI)	0.95 (0.82, 1.10)	
Investigator-assessed ORR (RECIST v1.1)		
No. of responders (%)	58 (14%)	57 (13%)
95% CI	(10.5, 17.3)	(10.3, 17.0)
Investigator-assessed DOR (RECIST v1.1)	n = 58	n = 57
Median in months	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

* The primary analysis population consists of the first 850 randomised patients

‡ Stratified by PD-L1 expression in tumour infiltrating immune cells, the number of prior chemotherapy regimens, and histology

** Based on the stratified log-rank test

*** Based on Kaplan-Meier estimates

Figure 15: Kaplan-Meier curve for overall survival in the primary analysis population (all comers) (OAK)

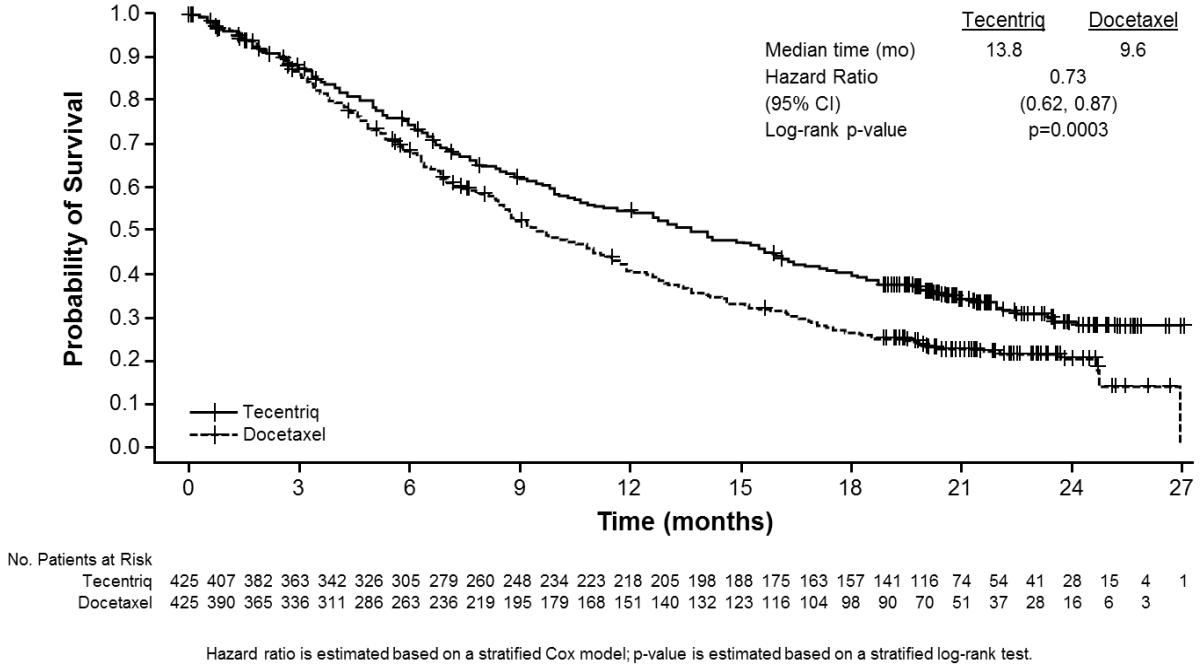
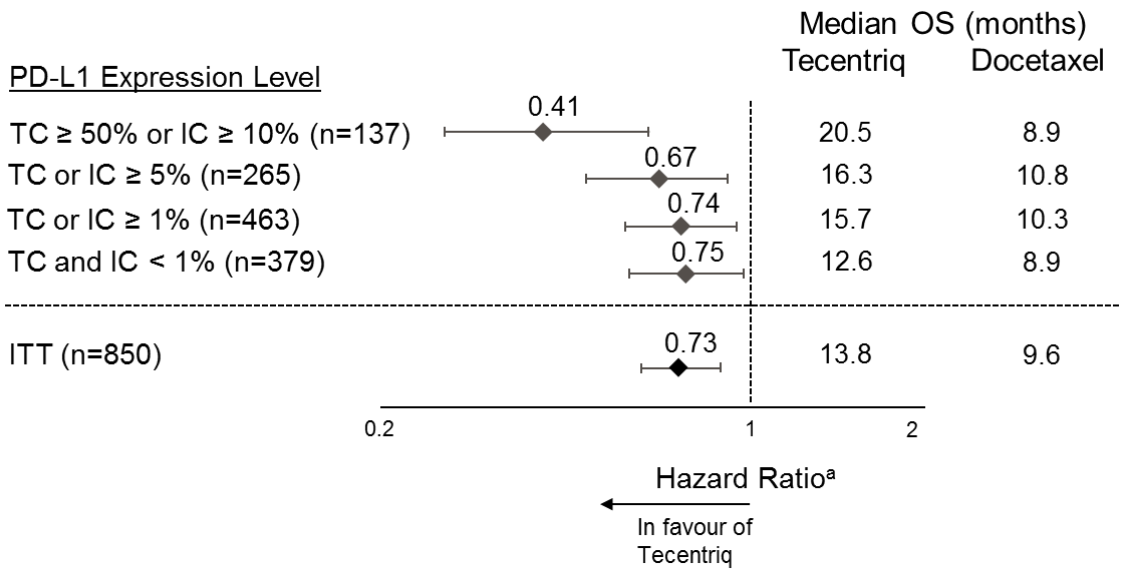


Figure 16: Forest plot of overall survival by PD-L1 expression in the primary analysis population (OAK)



[a] Stratified HR for ITT and TC or IC ≥ 1%. Unstratified HR for other exploratory subgroups.

An improvement in OS was observed with atezolizumab compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for atezolizumab and docetaxel, respectively) and squamous NSCLC patients (HR of 0.73, 95% CI: 0.54, 0.98; median OS of 8.9 vs. 7.7 months for atezolizumab and docetaxel, respectively). The observed OS improvement was consistently demonstrated across subgroups of patients including those with brain metastases at baseline (HR of 0.54, 95% CI: 0.31, 0.94; median OS of 20.1 vs. 11.9 months for atezolizumab and docetaxel respectively) and patients who were never smokers (HR of 0.71, 95% CI: 0.47, 1.08; median OS of 16.3 vs. 12.6 months for atezolizumab and docetaxel, respectively). However, patients with EGFR mutations did not show improved OS with atezolizumab

compared to docetaxel (HR of 1.24, 95% CI: 0.71, 2.18; median OS of 10.5 vs. 16.2 months for atezolizumab and docetaxel, respectively).

Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with atezolizumab compared to docetaxel (HR of 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ-LC13 was similar between atezolizumab and docetaxel. These results should be interpreted with caution due to the open-label design of the study.

POPLAR (GO28753): Randomised phase II trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy

A phase II, multi-centre, international, randomised, open-label, controlled study, POPLAR, was conducted in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression. The primary efficacy outcome was overall survival. A total of 287 patients were randomised 1:1 to receive either atezolizumab (1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit) or docetaxel (75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression). Randomisation was stratified by PD-L1 expression status on IC, by the number of prior chemotherapy regimens and by histology. An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with atezolizumab, vs. 9.7 months in patients treated with docetaxel (HR of 0.69, 95% CI: 0.52, 0.92). ORR was 15.3% vs. 14.7% and median DOR was 18.6 months vs. 7.2 months for atezolizumab vs. docetaxel, respectively.

Small cell lung cancer

IMpower133 (GO30081): Randomised phase I/III trial in patients with chemotherapy-naïve extensive-stage SCLC, in combination with carboplatin and etoposide

A Phase I/III, randomised, multicentre, double-blind, placebo-controlled study, IMpower133, was conducted to evaluate the efficacy and safety of atezolizumab in combination with carboplatin and etoposide in patients with chemotherapy-naïve ES-SCLC.

Patients were excluded if they had active or untreated CNS metastases; history of autoimmune disease; administration of live, attenuated vaccine within 4 weeks prior to randomisation; administration of systemic immunosuppressive medicinal products within 1 week prior to randomisation. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients who met established criteria and who agreed to be treated beyond disease progression had tumour assessments conducted every 6 weeks until treatment discontinuation.

A total of 403 patients were enrolled and randomised (1:1) to receive one of the treatment regimens described in Table 18. Randomisation was stratified by sex, ECOG performance status, and presence of brain metastases.

Table 18: Intravenous treatment regimens (IMpower133)

Treatment regimen	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	atezolizumab (1 200 mg)[a] + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	atezolizumab (1 200 mg) [a]
B	placebo + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	placebo

[a] Atezolizumab was administered until loss of clinical benefit as assessed by investigator
[b] Carboplatin and etoposide were administered until completion of 4 cycles, or progressive disease or unacceptable toxicity, whichever occurs first
[c] Etoposide was administered on day 1, 2 and 3 of each cycle

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 64 years (range: 26 to 90 years) with 10% of patients ≥ 75 years of age. The majority of patients were male (65%), white (80%), and 9% had brain metastases and most patients were current or previous smokers (97%). Baseline ECOG performance status was 0 (35%) or 1 (65%).

At the time of the primary analysis, patients had a median survival follow up time of 13.9 months. A statistically significant improvement in OS was observed with atezolizumab in combination with carboplatin and etoposide compared to the control arm (HR of 0.70, 95% CI: 0.54, 0.91; median OS of 12.3 months vs. 10.3 months). In the exploratory OS final analysis with longer follow up (median: 22.9 months), the median OS for both arms was unchanged relative to the primary OS interim analysis. The PFS, ORR and DOR results from the primary analysis as well as the exploratory OS final analysis results are summarised in Table 19. Kaplan-Meier curves for OS and PFS are presented in Figures 17 and 18. Data for patients with brain metastases are too limited to draw conclusions on this population.

Table 19: Summary of efficacy (IMpower133)

Key efficacy endpoints	Arm A (Atezolizumab + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)
Co-primary endpoints		
OS analysis*	n=201	n=202
No. of deaths (%)	142 (70.6%)	160 (79.2%)
Median time to events (months)	12.3	10.3
95% CI	(10.8, 15.8)	(9.3, 11.3)
Stratified hazard ratio‡ (95% CI)	0.76 (0.60, 0.95)	
p-value	0.0154***	
12-month OS (%)	51.9	39.0
Investigator-assessed PFS (RECIST v1.1) **	n=201	n=202
No. of events (%)	171 (85.1%)	189 (93.6%)
Median duration of PFS (months)	5.2	4.3
95% CI	(4.4, 5.6)	(4.2, 4.5)
Stratified hazard ratio‡ (95% CI)	0.77 (0.62, 0.96)	
p-value	0.0170	
6-month PFS (%)	30.9	22.4
12-month PFS (%)	12.6	5.4

Key efficacy endpoints	Arm A (Atezolizumab + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)
Co-primary endpoints		
Other endpoints		
Investigator-assessed ORR (RECIST 1.1)* ^	n=201	n=202
No. of responders (%)	121 (60.2%)	130 (64.4%)
95% CI	(53.1, 67.0)	(57.3, 71.0)
No. of complete response (%)	5 (2.5%)	2 (1.0%)
No. of partial response (%)	116 (57.7%)	128 (63.4%)
Investigator-assessed DOR (RECIST 1.1)* ^	n =121	n = 130
Median in months	4.2	3.9
95% CI	(4.1, 4.5)	(3.1, 4.2)

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival

‡ Stratified by sex and ECOG performance status

* Exploratory OS final analysis at clinical cut-off 24 January 2019

** PFS, ORR and DOR analyses at clinical cut-off 24 April 2018

*** For descriptive purposes only

^ Confirmed ORR and DoR are exploratory endpoints

Figure 17: Kaplan-Meier curve for overall survival (IMpower133)

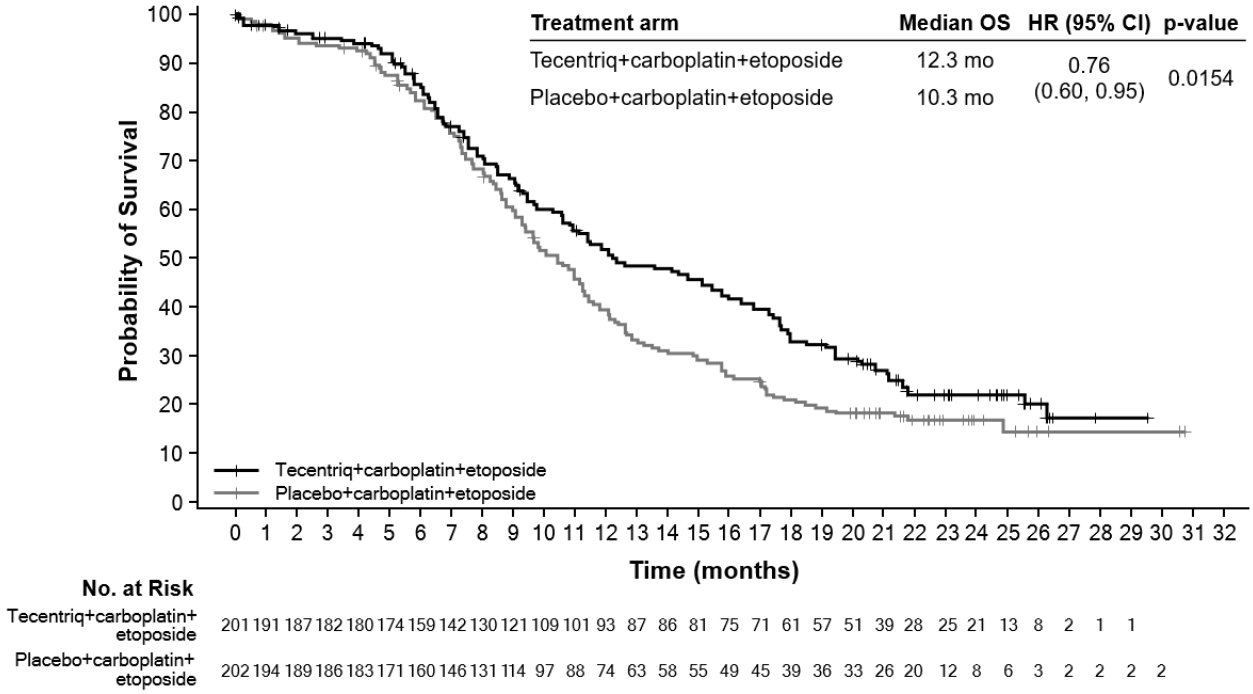
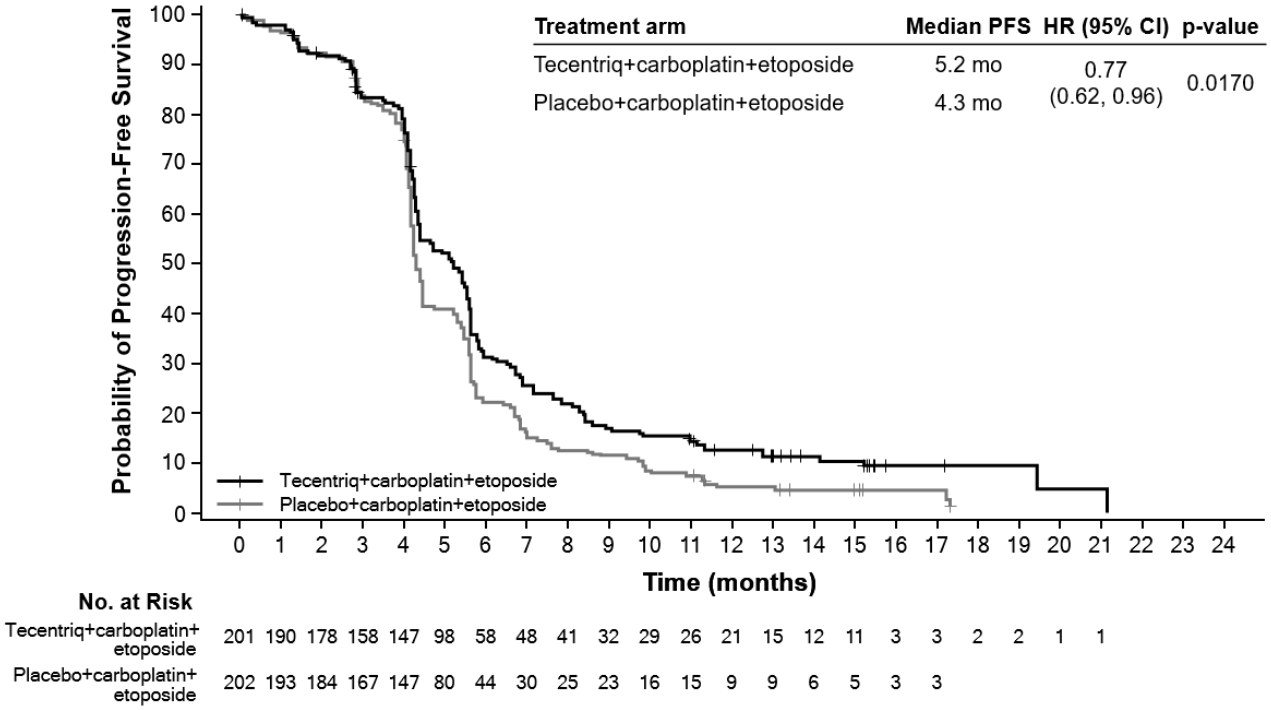


Figure 18: Kaplan-Meier curve for progression-free survival (IMpower133)



<u>*Triple-negative breast cancer*</u>

IMpassion130 (WO29522): Randomised phase III trial in locally advanced or metastatic TNBC patients previously untreated for metastatic disease

A phase III, double-blind, two-arm, multi-centre, international, randomised, placebo-controlled study, IMpassion130, was conducted to evaluate the efficacy and safety of atezolizumab in combination with nab-paclitaxel, in patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. Patients had to be eligible for taxane monotherapy (i.e. absence of rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control) and were excluded if they had received prior chemotherapy in the neoadjuvant or adjuvant setting within the last 12 months, a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation; untreated, symptomatic or corticosteroid-dependent brain metastases. Tumour assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter.

A total of 902 patients were enrolled and stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumour-infiltrating immune cells (IC) (PD-L1 stained tumour-infiltrating immune cells [IC] < 1% of tumour area vs. ≥ 1% of the tumour area) assessed by the VENTANA PD-L1 (SP142) Assay.

Patients were randomised to receive atezolizumab 840 mg or placebo by intravenous infusions on days 1 and 15 of every 28-day cycle, plus nab-paclitaxel (100 mg/m^2) administered via intravenous infusion on days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. Treatment with atezolizumab could be continued when nab-paclitaxel was stopped due to unacceptable toxicity. The median number of treatment cycles was 7 for atezolizumab and 6 for nab-paclitaxel in each treatment arm.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Most patients were women (99.6%), 67.5% were white and 17.8% Asian. The median age was 55 years (range: 20-86). Baseline ECOG performance status was 0 (58.4%) or 1 (41.3%). Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% asymptomatic brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumour disease in patients with PD-L1 expression ≥ 1% were generally representative of the broader study population.

The co-primary efficacy endpoints included investigator-assessed progression free survival (PFS) in the ITT population and in patients with PD-L1 expression ≥ 1% per RECIST v1.1 as well as overall survival (OS) in the ITT population and in patients with PD-L1 expression ≥ 1%. Secondary efficacy endpoints included objective response rate (ORR) and duration of response (DOR) per RECIST v1.1.

PFS, ORR and DOR results of IMpassion130 for patients with PD-L1 expression ≥ 1% at the time of the final analysis for PFS with a median survival follow up of 13 months are summarised in Table 20 with Kaplan-Meier curves for PFS in Figure 19. Patients with PD-L1 expression < 1% did not show improved PFS when atezolizumab was added to nab-paclitaxel (HR of 0.94, 95% CI 0.78, 1.13).

The final OS analysis was performed in patients with PD-L1 expression ≥ 1% with a median follow up of 19.12 months. OS results are presented in Table 20 and Kaplan-Meier curves in Figure 20. Patients with PD-L1 expression < 1% did not show improved OS when atezolizumab was added to nab-paclitaxel (HR of 1.02, 95% CI 0.84, 1.24).

Exploratory subgroup analyses were performed in patients with PD-L1 expression ≥ 1%, exploring prior (neo)adjuvant treatment, BRCA1/2 mutation and asymptomatic brain metastases at baseline.

In patients who had received prior (neo) adjuvant treatment (n=242), the hazard ratio for primary (final) PFS was 0.79 and 0.77 for final OS while in patients who had not received prior (neo)adjuvant treatment (n=127), the hazard ratio for primary (final) PFS was 0.44 and 0.54 for final OS.

In the IMpassion130 study, of the 614 patients tested, 89 (15%) carried pathogenic BRCA1/2 mutations. From the PD-L1+/BRCA1/2 mutant subgroup, 19 patients received atezolizumab plus nab-paclitaxel and 26 placebo plus nab-paclitaxel. Based on exploratory analysis and acknowledging the small sample size, the presence of BRCA1/2 mutation does not seem to impact the PFS clinical benefit of atezolizumab and nab-paclitaxel.

There was no evidence of efficacy in patients with asymptomatic brain metastases at baseline, although the number of patients treated was small; the median PFS was 2.2 months in the atezolizumab plus nab-paclitaxel arm (n=15) compared to 5.6 months in the placebo plus nab-paclitaxel arm (n=11) (HR 1.40; 95% CI 0.57, 3.44).

Table 20: Summary of efficacy in patients with PD-L1 expression ≥ 1% (IMpassion130)

Key efficacy endpoints	**Atezolizumab + nab-paclitaxel**	**Placebo + nab-paclitaxel**
Primary efficacy endpoints	n=185	n=184
Investigator-assessed PFS (RECIST v1.1) – Primary analysis[3]		
No. of events (%)	138 (74.6%)	157 (85.3%)
Median duration of PFS (months)	7.5	5.0
95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.62 (0.49, 0.78)	
p-value[1]	<0.0001	
12-month PFS (%)	29.1	16.4

Key efficacy endpoints	Atezolizumab + nab-paclitaxel	Placebo + nab-paclitaxel
Investigator-assessed PFS (RECIST v1.1) – Updated exploratory analysis[4]		
No. of events (%)	149 (80.5%)	163 (88.6%)
Median duration of PFS (months)	7.5	5.3
95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.63 (0.50-0.80)	
p-value[1]	<0.0001	
12-month PFS (%)	30.3	17.3
OS [1,2,5]		
No. of deaths (%)	120 (64.9%)	139 (75.5%)
Median time to events (months)	25.4	17.9
95% CI	(19.6, 30.7)	(13.6, 20.3)
Stratified hazard ratio‡ (95% CI)	0.67 (0.53, 0.86)	
Secondary and exploratory endpoints		
Investigator-assessed ORR (RECIST 1.1)[3]	n=185	n=183
No. of responders (%)	109 (58.9%)	78 (42.6%)
95% CI	(51.5, 66.1)	(35.4, 50.1)
No. of complete response (%)	19 (10.3%)	2 (1.1%)
No. of partial response (%)	90 (48.6%)	76 (41.5%)
No. of stable disease	38 (20.5%)	49 (26.8%)
Investigator-assessed DOR[3]	n=109	n=78
Median in months	8.5	5.5
95% CI	(7.3, 9.7)	(3.7, 7.1)

1. Based on the stratified log-rank test.
2. OS comparisons between treatment arms in patients with PD-L1 expression ≥1% were not formally tested, as per the pre-specified analysis hierarchy.
3. Per final analysis for PFS, ORR, DOR and first interim analysis for OS at clinical cut off 17th April 2018
4. Per exploratory PFS analysis at clinical cut off January 2nd 2019
5. Per final analysis for OS at clinical cut off April 14th 2020

‡ Stratified by presence of liver metastases, and by prior taxane treatment.

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival, NE=not estimable

Figure 19: Kaplan-Meier curve for progression free survival in patients with PD-L1 expression ≥ 1% (IMpassion130)

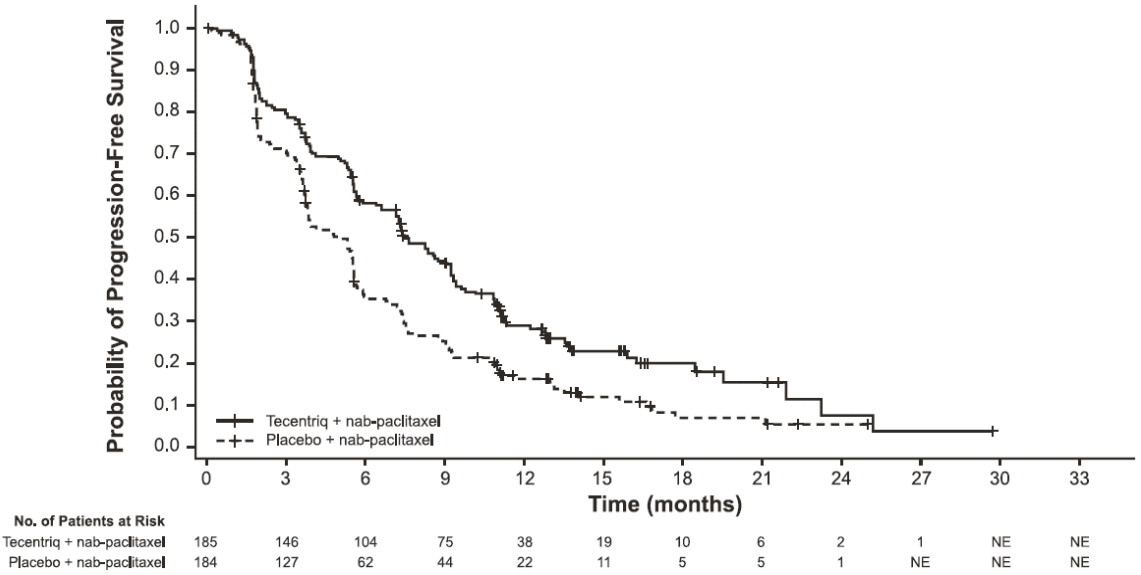
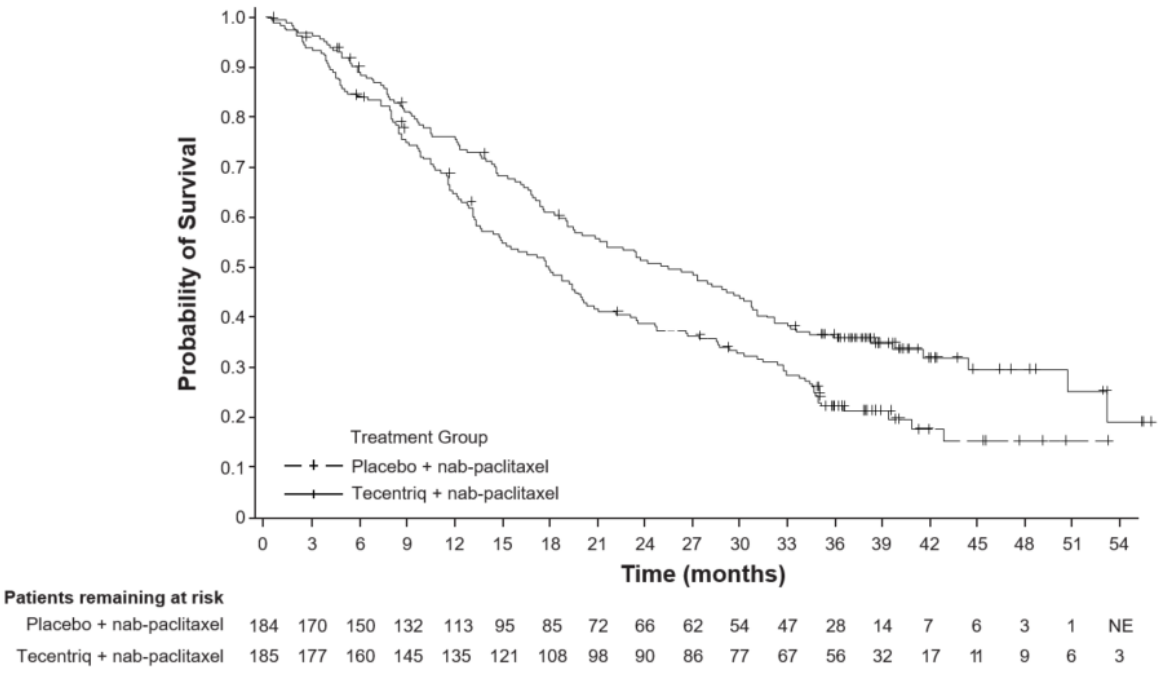


Figure 20: Kaplan-Meier curve for overall survival in patients with PD-L1 expression ≥ 1% (IMpassion130)



The time to deterioration (a sustained ≥ 10-point decline from baseline score) of patient-reported global health status/health-related quality of life as measured by the EORTC QLQ-C30 was similar in each treatment group indicating that all patients maintained their baseline HRQoL for a comparable duration of time.

Hepatocellular carcinoma

IMbrave150 (YO40245): Randomised phase III trial in patients with unresectable HCC who have not received prior systemic therapy, in combination with bevacizumab

A phase III, randomised, multi-centre, international, open-label study, IMbrave150, was conducted to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab, in patients with locally advanced or metastatic and/or unresectable HCC, who have not received prior systemic treatment. A total of 501 patients were randomised (2:1) to receive either atezolizumab (1 200 mg) and 15 mg/kg bw of bevacizumab every 3 weeks administered by intravenous infusion, or sorafenib 400 mg orally twice per day. Randomisation was stratified by geographic region, macrovascular invasion and/or extrahepatic spread, baseline α-fetoprotein (AFP) and ECOG performance status. Patients in both arms received treatment until loss of clinical benefit, or unacceptable toxicity. Patients could discontinue either atezolizumab or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until loss of clinical benefit or unacceptable toxicity associated with the single-agent.

The study enrolled adults whose disease was not amenable to or progressed after surgical and/or locoregional therapies, were Child-Pugh A, ECOG 0/1, and who had not received prior systemic treatment. Bleeding (including fatal events) is a known adverse reaction with bevacizumab and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC. Hence, patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding or high risk of bleeding. For patients with active hepatitis B, HBV DNA < 500 IU/mL was required within 28 days prior to initiation of study treatment, and standard anti-HBV treatment for a minimum of 14 days prior to study entry and for the length of study.

Patients were also excluded if they had moderate or severe ascites; history of hepatic encephalopathy; known fibrolamellar HCC; sarcomatoid HCC, mixed cholangiocarcinoma and HCC; active co-infection of HBV and HCV; history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomization; untreated or corticosteroid-dependent brain metastases. Tumour assessments were performed every 6 weeks for the first 54 weeks following Cycle 1, Day 1, then every 9 weeks thereafter.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 65 years (range: 26 to 88 years) and 83% were male. The majority of patients were Asian (57%) and white (35%). 40% were from Asia (excluding Japan), while 60% were from rest of world. Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥ 400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). The primary risk factors for the development of HCC were Hepatitis B virus infection in 48% of patients, Hepatitis C virus infection in 22% of patients, and non-viral disease in 31% of patients. HCC was categorized as Barcelona Clinic Liver Cancer (BCLC) stage C in 82% of patients, stage B in 16% of patients, and stage A in 3% of patients.

The co-primary efficacy endpoints were OS and IRF-assessed PFS according to RECIST v1.1. At the time of the primary analysis, patients had a median survival follow up time of 8.6 months. The data demonstrated a statistically significant improvement in OS and PFS as assessed by IRF per RECIST v1.1 with atezolizumab + bevacizumab compared to sorafenib. A statistically significant improvement was also observed in confirmed objective response rate (ORR) by IRF per RECIST v1.1 and HCC modified RECIST (mRECIST). The key efficacy results from the primary analysis are summarized in Table 21.

A descriptive updated efficacy analysis was performed with a median survival follow up time of 15.6 months. The median OS was 19.2 months (95% CI: 17.0, 23.7) in the atezolizumab + bevacizumab

arm versus 13.4 months (95% CI: 11.4, 16.9) in the sorafenib arm with a HR of 0.66 (95% CI: 0.52, 0.85). The median PFS by IRF-assessment per RECIST v1.1 was 6.9 months (95% CI: 5.8, 8.6) in the atezolizumab + bevacizumab arm versus 4.3 months (95% CI: 4.0, 5.6) in the sorafenib arm with a HR of 0.65 (95% CI: 0.53, 0.81).

The IRF-assessed ORR per RECIST v1.1 was 29.8% (95% CI: 24.8, 35.0) in the atezolizumab + bevacizumab arm and 11.3% (95% CI: 6.9, 17.3) in the sorafenib arm. The median duration of response (DOR) by IRF-assessment per RECIST v1.1 in confirmed responders was 18.1 months (95% CI: 14.6, NE) in the atezolizumab + bevacizumab arm compared to 14.9 months (95% CI: 4.9, 17.0) in the sorafenib arm.

Kaplan-Meier curves for OS (updated analysis) and PFS (primary analysis) are presented in Figures 21 and 22, respectively.

Table 21: Summary of efficacy (IMbrave150 primary analysis)

Key efficacy endpoints	Atezolizumab + Bevacizumab		Sorafenib
OS	n=336		n=165
No. of deaths (%)	96 (28.6%)		65 (39.4%)
Median time to event (months)	NE		13.2
95% CI	(NE, NE)		(10.4, NE)
Stratified hazard ratio‡ (95% CI)		0.58 (0.42, 0.79)	
p-value[1]		0.0006	
6-month OS (%)	84.8%		72.3%
IRF-assessed PFS, RECIST 1.1	n=336		n=165
No. of events (%)	197 (58.6%)		109 (66.1%)
Median duration of PFS (months)	6.8		4.3
95% CI	(5.8, 8.3)		(4.0, 5.6)
Stratified hazard ratio‡ (95% CI)		0.59 (0.47, 0.76)	
p-value[1]		<0.0001	
6-month PFS	54.5%		37.2%
IRF-assessed ORR, RECIST 1.1	n=326		n=159
No. of confirmed responders (%)	89 (27.3%)		19 (11.9%)
95% CI	(22.5, 32.5)		(7.4, 18.0)
p-value[2]		<0.0001	
No. of complete responses (%)	18 (5.5%)		0
No. of partial responses (%)	71 (21.8%)		19 (11.9%)
No. of stable disease (%)	151 (46.3%)		69 (43.4%)
IRF-assessed DOR, RECIST 1.1	n=89		n=19
Median in months	NE		6.3
95% CI	(NE, NE)		(4.7, NE)
Range (months)	(1.3+, 13.4+)		(1.4+, 9.1+)

Key efficacy endpoints	Atezolizumab + Bevacizumab		Sorafenib
IRF-assessed ORR, HCC mRECIST	n=325		n=158
No. of confirmed responders (%)	108 (33.2%)		21 (13.3%)
95% CI	(28.1, 38.6)		(8.4, 19.6)
p-value[2]		<0.0001	
No. of complete responses (%)	33 (10.2%)		3 (1.9%)
No. of partial responses (%)	75 (23.1%)		18 (11.4%)
No. of stable disease (%)	127 (39.1%)		66 (41.8%)
IRF-assessed DOR, HCC mRECIST	n=108		n=21
Median in months	NE		6.3
95% CI	(NE, NE)		(4.9, NE)
Range (months)	(1.3+, 13.4+)		(1.4+, 9.1+)

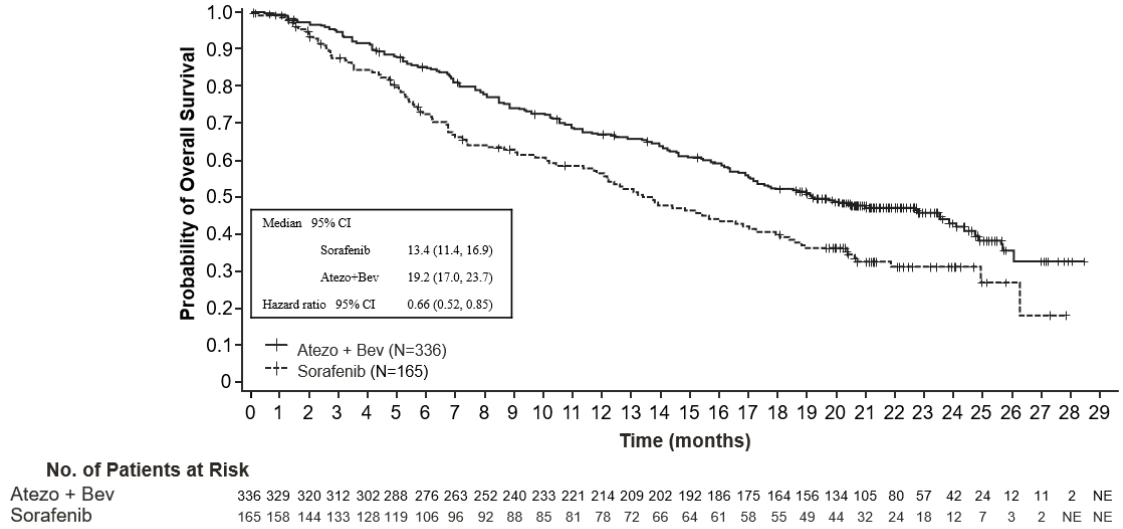
‡ Stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)

1. Based on two-sided stratified log-rank test
2. Nominal p-values based on two-sided Cochran-Mantel-Haenszel test

\+ Denotes a censored value

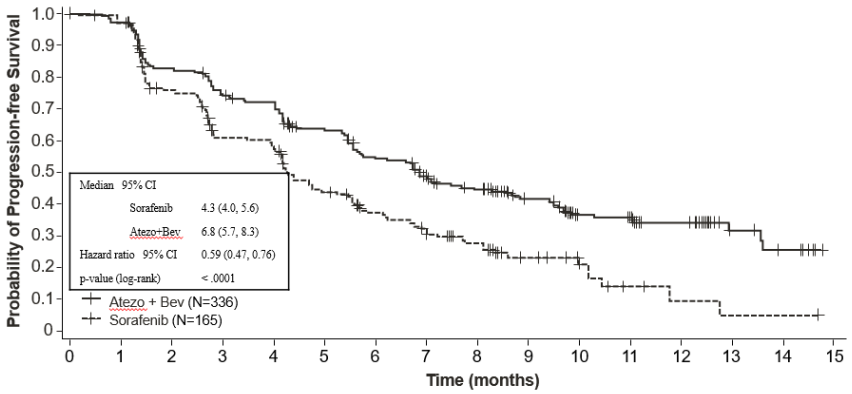
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; HCC mRECIST = Modified RECIST Assessment for Hepatocellular Carcinoma; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival; NE=not estimable

Figure 21: Kaplan-Meier curve for OS in the ITT population (IMbrave150 updated analysis)



Hazard ratio is from stratified analysis. Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs absence) and AFP (<400 vs >=400 ng/ml) at screening per IxRS.

Figure 22: Kaplan-Meier curve for IRF-PFS per RECIST v1.1 in the ITT population (IMbrave150 primary analysis)



No. of Patients at Risk															
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE

Hazard ratio and p-value are from stratified analysis.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs absence) and AFP (<400 vs >=400 ng/ml) at screening per IxRS.

Efficacy in elderly

No overall differences in efficacy were observed between patients ≥ 65 years of age and younger patients receiving atezolizumab monotherapy. In study IMpower150, age ≥ 65 was associated with a diminished effect of atezolizumab in patients receiving atezolizumab in combination with carboplatin and paclitaxel.

In studies IMpower150, IMpower133 and IMpower110, data for patients ≥ 75 years of age are too limited to draw conclusions on this population.

Paediatric population

An early phase, multi-centre open-label study was conducted in paediatric (< 18 years, n=69) and young adult patients (18-30 years, n=18) with relapsed or progressive solid tumours as well as with Hodgkin's and non-Hodgkin's lymphoma, to evaluate the safety and pharmacokinetics of atezolizumab. Patients were treated with 15 mg/kg bw atezolizumab intravenously every 3 weeks (see section 5.2).

5.2 Pharmacokinetic properties

Exposure to atezolizumab increased dose proportionally over the dose range 1 mg/kg bw to 20 mg/kg bw including the fixed dose 1 200 mg administered every 3 weeks. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range: 1 to 20 mg/kg bw with a linear two-compartment disposition model with first-order elimination. The pharmacokinetic properties of 840 mg intravenous atezolizumab administered every 2 weeks, 1 200 mg administered every 3 weeks, and 1 680 mg administered every 4 weeks are the same; comparable total exposures are expected to be achieved with these three dosing regimens. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks of multiple dosing. The systemic accumulation in area under the curve, maximum concentration and trough concentration was 1.91, 1.46 and 2.75-fold, respectively.

Absorption

Atezolizumab is administered as an intravenous infusion.

Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution is 3.28 L and volume at steady-state is 6.91 L in the typical patient.

Biotransformation

The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism.

Elimination

A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life is 27 days.

Special populations

Based on population PK and exposure-response analyses age (21-89 years), region, ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG performance status have no effect on atezolizumab pharmacokinetics. Body weight, gender, positive ADA status, albumin levels and tumour burden have a statistically significant, but not clinically relevant effect on atezolizumab pharmacokinetics. No dose adjustments are recommended.

Elderly

No dedicated studies of atezolizumab have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing atezolizumab pharmacokinetics based on patients of age range of 21-89 years (n=472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of atezolizumab among patients < 65 years (n=274), patients between 65−75 years (n=152) and patients > 75 years (n=46) (see section 4.2).

Paediatric population

The pharmacokinetic results from one early-phase, multi-centre open-label study that was conducted in paediatric (< 18 years, n=69) and young adult patients (18-30 years, n=18), show that the clearance and volume of distribution of atezolizumab were comparable between paediatric patients receiving 15 mg/kg bw and young adult patients receiving 1 200 mg of atezolizumab every 3 weeks when normalized by body weight, with exposure trending lower in paediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure. Data for children < 2 years is limited thus no definitive conclusions can be made.

Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2; n=208) or, moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n=140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n=8) (see section 4.2). The effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.

Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab observed in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 × to 1.5 × ULN and any AST) or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST) in comparison to patients with normal hepatic function (bilirubin ≤ ULN and AST ≤ ULN). No data are available in patients with severe hepatic impairment (bilirubin > 3 X ULN and any AST). Hepatic impairment was defined by the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria of hepatic dysfunction (see section 4.2). The effect of severe hepatic impairment (bilirubin > 3 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been performed to establish the carcinogenic potential of atezolizumab.

Mutagenicity

Mutagenicity studies have not been performed to establish the mutagenic potential of atezolizumab. However, monoclonal antibodies are not expected to alter DNA or chromosomes.

Fertility

No fertility studies have been conducted with atezolizumab; however, assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Weekly administration of atezolizumab to female monkeys at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries which were reversible. There was no effect on the male reproductive organs.

Teratogenicity

No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to immune-mediated rejection of the developing foetus resulting in foetal death. Administration of atezolizumab could cause foetal harm, including embryo-foetal lethality.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
Glacial acetic acid
Sucrose
Polysorbate 20 (E 432)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

Diluted solution

Chemical and physical in-use stability has been demonstrated for up to 24 hours at ≤ 30 °C and for up to 30 days at 2 °C to 8 °C from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C) unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass-vial with a butyl rubber stopper and an aluminium seal with a plastic grey or aqua flip-off cap containing 14 mL or 20 mL of concentrate solution for infusion.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Tecentriq does not contain any antimicrobial preservative or bacteriostatic agents and should be prepared by a healthcare professional using aseptic technique to ensure the sterility of prepared solutions. Use a sterile needle and syringe to prepare Tecentriq.

Aseptic preparation, handling and storage

Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions.

Do not shake.

Instructions for dilution

For the recommended dose of 840 mg: fourteen mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

For the recommended dose of 1 200 mg: twenty mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE) or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

For the recommended dose of 1 680 mg: twenty-eight mL of Tecentriq concentrate should be withdrawn from two vials of Tecentriq 840 mg and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL.

The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately (see section 6.3).

Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration. If particulates or discoloration are observed, the solution should not be used.

No incompatibilities have been observed between Tecentriq and intravenous bags with product-contacting surfaces of PVC, PO, PE, or PP. In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane. The use of in-line filter membranes is optional.

Do not co-administer other medicinal products through the same infusion line.

Disposal

The release of Tecentriq in the environment should be minimised. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1220/001
EU/1/17/1220/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2017
Date of latest renewal: 25 April 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Tecentriq 1 875 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 15 mL solution for injection contains 1 875 mg of atezolizumab.
Each mL of solution contains 125 mg of atezolizumab.

Atezolizumab is an Fc-engineered, humanised IgG1 anti-programmed death-ligand 1 (PD-L1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient with known effect
Each 1 875 mg vial of Tecentriq contains 9 mg of polysorbate 20.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to slightly yellowish liquid. The solution has a pH of 5.5 - 6.1 and an osmolality of 359 - 459 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Urothelial carcinoma (UC)

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC:

- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% (see section 5.1).

Early-stage non-small cell lung cancer (NSCLC)

Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR-mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).

Advanced NSCLC

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR-mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1).

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR-mutant or ALK-positive NSCLC (see section 5.1).

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR-mutant or ALK-positive NSCLC (see section 5.1).

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy (see section 5.1 for selection criteria).

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq (see section 5.1).

Small cell lung cancer (SCLC)

Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (see section 5.1).

Triple-negative breast cancer (TNBC)

Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

Hepatocellular carcinoma (HCC)

Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy (see section 5.1).

4.2 Posology and method of administration

Tecentriq must be initiated and supervised by physicians experienced in the treatment of cancer.

Patients currently receiving intravenous atezolizumab can switch to Tecentriq solution for injection and vice versa.

PD-L1 testing for patients with UC or TNBC or NSCLC

Tecentriq monotherapy

If specified in the indication, patient selection for treatment with Tecentriq based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1 and 5.1).

Tecentriq in combination therapy

Patients with previously untreated TNBC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology

The recommended dose of Tecentriq solution for injection is 1 875 mg administered every three weeks, as presented in Table 1.

When Tecentriq is administered in combination therapy please also refer to the full prescribing information for the combination products (see also section 5.1).

Table 1: Recommended dose for Tecentriq by subcutaneous administration

Indication	Recommended dose and schedule	Duration of treatment
Tecentriq monotherapy		
1L UC	1 875 mg every 3 weeks	Until disease progression or unmanageable toxicity.
1L metastatic NSCLC		
1L platinum-ineligible NSCLC		
Early-stage NSCLC	1 875 mg every 3 weeks	For 1 year unless disease recurrence or unacceptable toxicity. Treatment duration for more than 1 year was not studied.
2L UC	1 875 mg every 3 weeks	Until loss of clinical benefit or unmanageable toxicity.
2L NSCLC		
Tecentriq combination therapy		
1L non-squamous NSCLC with bevacizumab, paclitaxel, and carboplatin	Induction and maintenance phases: 1 875 mg every 3 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four or six cycles): Bevacizumab, paclitaxel, and then carboplatin are administered every three weeks. Maintenance phase (without chemotherapy): Bevacizumab every 3 weeks.	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be considered at the discretion of the physician.
1L non-squamous NSCLC with nab-paclitaxel and carboplatin	Induction and maintenance phases: 1 875 mg every 3 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four or six cycles): Nab-paclitaxel, and carboplatin are administered on day 1; in addition, nab-paclitaxel is administered on days 8 and 15 of each 3-weekly cycle.	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be considered at the discretion of the physician.

Indication	Recommended dose and schedule	Duration of treatment
1L ES-SCLC with carboplatin and etoposide	Induction and maintenance phases: 1 875 mg every 3 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four cycles): Carboplatin, and then etoposide are administered on day 1; etoposide is also administered on days 2 and 3 of each 3-weekly cycle.	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be considered at the discretion of the physician.
1L unresectable locally advanced or metastatic TNBC with nab-paclitaxel	1 875 mg every 3 weeks Tecentriq should be administered prior to nab-paclitaxel when given on the same day. Nab-paclitaxel should be administered at 100 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.	Until disease progression or unmanageable toxicity.
Advanced or unresectable HCC with bevacizumab	1 875 mg every 3 weeks Tecentriq should be administered prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg body weight (bw) every 3 weeks.	Until loss of clinical benefit or unmanageable toxicity.

Delayed or missed doses

If a planned dose of Tecentriq is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses.

Dose modifications during treatment

Dose reductions of Tecentriq are not recommended.

Dose delay or discontinuation (see also sections 4.4 and 4.8)

Table 2: Dose modification advice for Tecentriq

Immune-mediated adverse reaction	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue Tecentriq
Hepatitis in patients without HCC	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN]	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or

Immune-mediated adverse reaction	Severity	Treatment modification
	or blood bilirubin > 1.5 to 3 x ULN)	Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x ULN)	Permanently discontinue Tecentriq
Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3 x to ≤ 10x ULN *or* If AST/ALT is > 1 to ≤ 3 x ULN at baseline and increases to > 5x to ≤ 10x ULN *or* If AST/ALT is > 3 x to ≤ 5 x ULN at baseline and increases to >8 x to ≤ 10x ULN	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	If AST/ALT increases to > 10 x ULN or total bilirubin increases to > 3 x ULN	Permanently discontinue Tecentriq
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic Colitis	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue Tecentriq

Immune-mediated adverse reaction	Severity	Treatment modification
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold Tecentriq *Hypothyroidism:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism:* Treatment may be resumed when symptoms are controlled by anti-thyroid medicinal product and thyroid function is improving
Adrenal insufficiency	Symptomatic	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue Tecentriq
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold Tecentriq Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Permanently discontinue Tecentriq
Myasthenic syndrome/myasthenia	Facial paresis Grade 1 or 2	Withhold Tecentriq

Immune-mediated adverse reaction	Severity	Treatment modification
gravis, Guillain-Barré syndrome, Meningoencephalitis, and Facial paresis		Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding Tecentriq, permanently discontinue Tecentriq
	All Grades Myasthenic syndrome/myasthenia gravis, Guillain Barré syndrome and Meningoencephalitis or Facial paresis Grade 3 or 4	Permanently discontinue Tecentriq
Myelitis	Grade 2, 3, or 4	Permanently discontinue Tecentriq
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold Tecentriq Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue Tecentriq
Myocarditis	Grade 2 or above	Permanently discontinue Tecentriq
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue Tecentriq
Myositis	Grade 2 or 3	Withhold Tecentriq
	Grade 4 or Grade 3 recurrent myositis	Permanently discontinue Tecentriq

Immune-mediated adverse reaction	Severity	Treatment modification
Pericardial disorders	Grade 1 pericarditis	Withhold Tecentriq[2]
	Grade 2 or above	Permanently discontinue Tecentriq
Haemophagocytic lymphohistiocytosis	Suspected haemophagocytic lymphohistiocytosis[1]	Permanently discontinue Tecentriq
Other immune-mediated adverse reactions	Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or recurrent Grade 3	Permanently discontinue Tecentriq (except endocrinopathies controlled with replacement hormones)
Other adverse reactions	**Severity**	**Treatment modification**
Infusion-related reactions	Grade 1 or 2	Reduce injection rate or pause the injection. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue Tecentriq

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
Note: Toxicity should be graded with the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).
[1] Regardless of severity
[2] Conduct a detailed cardiac evaluation to determine the aetiology and manage appropriately

Special populations

Paediatric population

The safety and efficacy of Tecentriq in children and adolescents aged below 18 years have not been established. Currently available data for intravenous atezolizumab are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections 4.8 and 5.1).

Asian patients

Due to increased haematologic toxicities observed in Asian patients in IMpower150, it is recommended that the starting dose of paclitaxel should be 175 mg/m^2 every three weeks.

Renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild or moderate hepatic impairment. Tecentriq has not been studied in patients with severe hepatic impairment (see section 5.2).

Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2

Patients with ECOG performance status ≥ 2 were excluded from the clinical trials in TNBC, ES-SCLC, 2nd line UC and HCC (see sections 4.4 and 5.1).

Method of administration

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed.

Tecentriq solution for injection is not intended for intravenous administration and must be given by subcutaneous injection only.

Prior to administration, remove Tecentriq solution for injection from refrigeration and allow the solution to reach room temperature. For instructions on the use and handling of Tecentriq solution for injection prior to administration, refer to section 6.6.

Administer 15 mL of Tecentriq solution for injection subcutaneously in the thigh in approximately 7 minutes. Use of a subcutaneous infusion set (e.g. winged/butterfly) is recommended. DO NOT administer the remaining residual hold-up volume in the tubing to the patient.

The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Tecentriq solution for injection other medicinal products for subcutaneous administration should preferably be injected at different sites.

4.3 Contraindications

Hypersensitivity to atezolizumab or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immune-mediated adverse reactions

Most immune-mediated adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system have been observed. Immune-mediated adverse reactions with atezolizumab may occur after the last dose of atezolizumab.

For suspected immune-mediated adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical trials in patients whose immune-mediated adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Immune-mediated pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-mediated pneumonitis should be ruled out.

Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg body weight (bw)/day prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

Immune-mediated hepatitis

Cases of hepatitis, some leading to fatal outcomes have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be monitored prior to initiation of treatment, periodically during treatment with atezolizumab and as indicated based on clinical evaluation.

For patients without HCC, treatment with atezolizumab should be withheld if Grade 2 event (ALT or AST > 3 to 5 x ULN or blood bilirubin > 1.5 to 3 x ULN) persists for more than 5 to 7 days, and 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month.

Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 3 x ULN).

For patients with HCC, treatment with atezolizumab should be withheld if ALT or AST increases to > 3 to ≤ 10 x ULN from normal limits at baseline, or > 5 to ≤ 10 x ULN from > 1 ULN to ≤ 3 x ULN at baseline, or > 8 to ≤ 10 x ULN from > 3 ULN to ≤ 5 x ULN at baseline, and persists for more than 5 to 7 days, and 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month.

Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued if ALT or AST increases to > 10 x ULN or total bilirubin increases > 3 x ULN).

Immune-mediated colitis

Cases of diarrhoea or colitis have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis.

Treatment with atezolizumab should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, treatment with 1 to 2 mg/kg bw/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis. The potential complication of gastrointestinal perforation associated with colitis should be taken into consideration.

Immune-mediated endocrinopathies

Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, including diabetic ketoacidosis have been observed in clinical trials with atezolizumab (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies. Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered.

Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab. For symptomatic hypothyroidism, atezolizumab should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, atezolizumab should be withheld and an anti-thyroid medicinal product should be initiated as needed. Treatment with atezolizumab may be resumed when symptoms are controlled and thyroid function is improving.

For symptomatic adrenal insufficiency, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).

For Grade 2 or Grade 3 hypophysitis, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started, and hormone replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required). Treatment with atezolizumab should be permanently discontinued for Grade 4 hypophysitis.

Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

Immune-mediated meningoencephalitis

Meningoencephalitis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis.

Treatment with atezolizumab must be permanently discontinued for any grade of meningitis or encephalitis. Treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or

equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow.

Immune-mediated neuropathies

Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, and facial paresis were observed in patients receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy.

Myelitis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of myelitis.

Treatment with atezolizumab must be permanently discontinued for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Initiation of systemic corticosteroids (at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent) should be considered.

Treatment with atezolizumab should be withheld for Grade 1 or 2 facial paresis, and treatment with systemic corticosteroids (1 to 2 mg/kg bw/day prednisone or equivalent) should be considered. Treatment may be resumed only if the event fully resolves. Treatment with atezolizumab should be permanently discontinued for Grade 3 or Grade 4 facial paresis, or any other neuropathy that does not fully resolve while withholding atezolizumab.

Treatment with atezolizumab must be permanently discontinued for Grade 2, 3 or 4 myelitis.

Immune-mediated pancreatitis

Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.

Treatment with atezolizumab should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Immune-mediated myocarditis

Cases of myocarditis, including fatal cases, have been observed with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.

Patients with cardiac or cardiopulmonary symptoms should be assessed for potential myocarditis, to ensure the initiation of appropriate measures at an early stage. If myocarditis is suspected, treatment with atezolizumab should be withheld, prompt initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started, and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, treatment with atezolizumab must be permanently discontinued for Grade ≥ 2 myocarditis (see section 4.2).

Immune-mediated nephritis

Nephritis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for changes in renal function.

Treatment with atezolizumab should be withheld for Grade 2 nephritis, and treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 nephritis.

Immune-mediated myositis

Cases of myositis, including fatal cases, have been observed with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myositis. Patients with possible myositis should be monitored for signs of myocarditis.

If a patient develops signs and symptoms of myositis, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Treatment with atezolizumab should be withheld for Grade 2 or 3 myositis and corticosteroid therapy (1 to 2 mg/kg bw/day prednisone or equivalent) should be initiated. If symptoms improve to ≤ Grade 1, taper corticosteroids as clinically indicated. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4 or Grade 3 recurrent myositis, or when unable to reduce the corticosteroid dose to the equivalent of ≤ 10 mg prednisone per day within 12 weeks after onset.

Immune-mediated severe cutaneous adverse reactions

Immune-mediated severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. For suspected SCARs, patients should be referred to a specialist for further diagnosis and management.

Based on the severity of the adverse reaction, atezolizumab should be withheld for Grade 3 skin reactions and treatment with systemic corticosteroids at a dose of 1 to2 mg/kg bw/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered.

Atezolizumab should be withheld for patients with suspected SJS or TEN. For confirmed SJS or TEN, atezolizumab should be permanently discontinued.

Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Immune-mediated pericardial disorders

Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some leading to fatal outcomes, have been observed with atezolizumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of pericardial disorders.

For suspected Grade 1 pericarditis, treatment with atezolizumab should be withheld and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be

initiated. For suspected Grade ≥ 2 pericardial disorders, treatment with atezolizumab should be withheld, prompt treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of a pericardial disorder event is established, treatment with atezolizumab must be permanently discontinued for Grade ≥ 2 pericardial disorders (see section 4.2).

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has been reported in patients receiving atezolizumab (see section 4.8). HLH should be considered when the presentation of cytokine release syndrome is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH. For suspected HLH, atezolizumab must be permanently discontinued and patients should be referred to a specialist for further diagnosis and management.

Other immune-mediated adverse reactions

Given the mechanism of action of atezolizumab, other potential immune-mediated adverse reactions may occur, including noninfective cystitis.

Evaluate all suspected immune-mediated adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and, based on the severity of the reaction, managed with treatment modifications and corticosteroids as clinically indicated (see section 4.2 and section 4.8).

Infusion-related reactions

Infusion-related reactions have been observed with atezolizumab, including anaphylaxis (see section 4.8). The rate of injection should be reduced or paused in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion-related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

Disease-specific precautions

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in metastatic non-squamous NSCLC

Physicians should carefully consider the combined risks of the four-drug regimen of atezolizumab bevacizumab, paclitaxel, and carboplatin before initiating treatment (see section 4.8).

Use of atezolizumab in combination with nab-paclitaxel in metastatic TNBC

Neutropenia and peripheral neuropathies occurring during treatment with atezolizumab and nab-paclitaxel may be reversible with interruptions of nab-paclitaxel. Physicians should consult the nab-paclitaxel summary of product characteristics (SmPC) for specific precautions and contraindications of this medicine.

Use of atezolizumab in UC for previously untreated patients who are considered cisplatin ineligible

The baseline and prognostic disease characteristics of the IMvigor210 Cohort 1 study population were overall comparable to patients in the clinic who would be considered cisplatin ineligible but would be eligible for a carboplatin-based combination chemotherapy. There are insufficient data for the subgroup of patients that would be unfit for any chemotherapy; therefore, atezolizumab should be used

with caution in these patients, after careful consideration of the potential balance of risks and benefits on an individual basis.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

Patients with NSCLC that had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were excluded from the pivotal clinical trial IMpower150 after several cases of fatal pulmonary haemorrhage were observed, which is a known risk factor of treatment with bevacizumab.

In the absence of data, atezolizumab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients with NSCLC who have progressed on erlotinib+bevacizumab

In study IMpower150, there are no data on the efficacy of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients who have progressed previously on erlotinib+bevacizumab.

Use of atezolizumab in combination with bevacizumab in HCC

Data in HCC patients with Child-Pugh B liver disease treated with atezolizumab in combination with bevacizumab are very limited and there are currently no data available in HCC patients with Child-Pugh C liver disease.

Patients treated with bevacizumab have an increased risk of haemorrhage, and cases of severe gastrointestinal haemorrhage, including fatal events, were reported in patients with HCC treated with atezolizumab in combination with bevacizumab. In patients with HCC, screening for and subsequent treatment of oesophageal varices should be performed as per clinical practice prior to starting treatment with the combination of atezolizumab and bevacizumab. Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding with the combination treatment. Please refer to the bevacizumab Summary of Product Characteristics.

Diabetes mellitus can occur during treatment with atezolizumab in combination with bevacizumab. Physicians should monitor blood glucose levels prior to and periodically during treatment with atezolizumab in combination with bevacizumab as clinically indicated.

Use of atezolizumab as monotherapy for first-line treatment in metastatic NSCLC

Physicians should consider the delayed onset of atezolizumab effect before initiating first-line treatment as monotherapy in patients with NSCLC. A higher number of deaths within 2.5 months after randomisation followed by a long-term survival benefit was observed with atezolizumab compared with chemotherapy. No specific factor(s) associated with early deaths could be identified (see section 5.1).

Patients excluded from clinical trials

Patients with the following conditions were excluded from clinical trials: a history of autoimmune disease, history of pneumonitis, active brain metastasis, ECOG PS ≥ 2 (except for patients with advanced NSCLC ineligible for a platinum-based therapy), HIV, hepatitis B or hepatitis C infection (for non-HCC patients), significant cardiovascular disease and patients with inadequate hematologic and end-organ function. Patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry; therapeutic oral or

intravenous antibiotics within 2 weeks prior to initiation of study treatment were excluded from clinical trials.

Excipients with known effect

This medicinal product contains polysorbate 20. Each vial of Tecentriq 1 875 mg solution for injection contains 9 mg of polysorbate 20, which is equivalent to 0.6 mg/ml. Polysorbate 20 may cause allergic reactions.

Patient card

The prescriber must discuss the risks of Tecentriq therapy with the patient. The patient will be provided with the patient card and instructed to carry the card at all times.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-mediated adverse reactions after starting atezolizumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab.

Pregnancy

There are no data from the use of atezolizumab in pregnant women. No developmental and reproductive studies were conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway in murine pregnancy models can lead to immune-mediated rejection of the developing foetus resulting in foetal death (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of atezolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

Human immunoglobulins G1 (IgG1) are known to cross the placental barrier and atezolizumab is an IgG1; therefore, atezolizumab has the potential to be transmitted from the mother to the developing foetus.

Atezolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with atezolizumab.

Breast-feeding

It is unknown whether atezolizumab is excreted in human milk. Atezolizumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Tecentriq therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data are available on the possible effects of atezolizumab on fertility. No reproductive and development toxicity studies have been conducted with atezolizumab; however, based on the 26-week repeat dose toxicity study, atezolizumab had an effect on menstrual cycles at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible (see section 5.3). There were no effects on the male reproductive organs.

4.7 Effects on ability to drive and use machines

Tecentriq has minor influence on the ability to drive and use machines. Patients experiencing fatigue should be advised not to drive and use machines until symptoms abate (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of atezolizumab as monotherapy is based on pooled data in 5 039 patients with various tumour types that were administered atezolizumab intravenously and 247 patients with NSCLC that were administered atezolizumab subcutaneously. The most common adverse reactions (> 10%) were fatigue (29.3%), decreased appetite (20.1%), rash (19.7%), nausea (18.8%), cough (18.2%), diarrhoea (18.1%), pyrexia (17.9%), dyspnoea (16.6%), , arthralgia (16.2%), pruritus (13.3%), asthenia (13%), back pain (12.2%), vomiting (11.7%), urinary tract infection (11%) and headache (10.2%).

The safety of intravenous atezolizumab given in combination with other medicinal products, has been evaluated in 4 535 patients across multiple tumour types. The most common adverse reactions (≥ 20%) were anaemia (36.8%), neutropenia (36.6%), nausea (35.5%), fatigue (33.1%), alopecia (28.1%), rash (27.8%), diarrhoea (27.6%), thrombocytopenia (27.1%), constipation (25.8%), decreased appetite (24.7%) and peripheral neuropathy (24.4%).

The safety profile of Tecentriq solution for injection was overall similar to the known safety profile of the intravenous formulation, with an additional adverse reaction of injection site reaction (4.5% in the subcutaneous Tecentriq arm vs 0% in the intravenous atezolizumab arm).

Use of atezolizumab in the adjuvant NSCLC setting

The safety profile of atezolizumab in the adjuvant setting in the non-small cell lung cancer (NSCLC) patient population (IMpower010) was generally consistent with the overall pooled monotherapy safety profile in the advanced setting. Nevertheless, the incidence of immune-mediated adverse reactions of atezolizumab in IMpower010 was 51.7% compared to 38.4% in the pooled monotherapy population with advanced disease. No new immune-mediated adverse reactions were identified in the adjuvant setting.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

In the first-line NSCLC study (IMpower150), an overall higher frequency of adverse events was observed in the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin compared to atezolizumab, paclitaxel and carboplatin, including Grade 3 and 4 events (63.6% compared to 57.5%), Grade 5 events (6.1% compared to 2.5%), adverse events of special interest to atezolizumab (52.4% compared to 48.0%), as well as adverse events leading to withdrawal of any study treatment (33.8% compared to 13.3%). Nausea, diarrhoea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria were reported higher (≥5% difference) in patients receiving atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, haemoptysis, cerebrovascular accident, including fatal events.

Further details on serious adverse reactions are provided in section 4.4.

Tabulated list of adverse reactions

The adverse reactions (ARs) are listed by MedDRA system organ class (SOC) and categories of frequency in Table 3 for atezolizumab (intravenous and subcutaneous) given as monotherapy or as combination therapy. Adverse reactions known to occur with atezolizumab or chemotherapies given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy. The following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Summary of adverse reactions occurring in patients treated with atezolizumab

Atezolizumab monotherapy		Atezolizumab in combination therapy
Infections and infestations		
Very common	urinary tract infection[a]	lung infection[b]
Common		sepsis[aj]
Blood and lymphatic system disorders		
Very common		anaemia, thrombocytopenia[d], neutropenia[e], leukopenia[f]
Common	thrombocytopenia[d]	lymphopenia[g]
Rare	haemophagocytic lymphohistiocytosis	haemophagocytic lymphohistiocytosis
Immune system disorders		
Common	infusion-related reaction[h]	infusion-related reaction[h]
Endocrine disorders		
Very common		hypothyroidism[i]
Common	hypothyroidism[i], hyperthyroidism[j]	hyperthyroidism[j]
Uncommon	diabetes mellitus[k], adrenal insufficiency[l], hypophysitis[m]	hypophysitis[m]
Metabolism and nutrition disorders		
Very common	decreased appetite	decreased appetite
Common	hypokalaemia[ae], hyponatraemia[af], hyperglycaemia	hypokalaemia[ae], hyponatraemia[af], hypomagnesaemia[n]
Nervous system disorders		
Very common	headache	peripheral neuropathy[o], headache
Common	peripheral neuropathy[o]	syncope, dizziness
Uncommon	Guillain-Barré syndrome[p], meningoencephalitis[q]	
Rare	myasthenic syndrome[r], facial paresis, myelitis	facial paresis
Eye disorders		
Rare	uveitis	
Cardiac disorders		
Common	pericardial disorders[ao]	
Uncommon		pericardial disorders[ao]
Rare	myocarditis[s]	
Vascular disorders		
Very common		hypertension[ai]
Common	hypotension	
Respiratory, thoracic, and mediastinal disorders		
Very common	dyspnoea, cough	dyspnoea, cough, nasopharyngitis[am]
Common	pneumonitis[t], hypoxia[ag], nasopharyngitis[am]	dysphonia

Atezolizumab monotherapy		Atezolizumab in combination therapy
Gastrointestinal disorders		
Very common	nausea, vomiting, diarrhoea[u]	nausea, vomiting, diarrhoea[u], constipation
Common	colitis[v], abdominal pain, dysphagia, oropharyngeal pain[w], dry mouth	stomatitis, dysgeusia, colitis[v]
Uncommon	pancreatitis[x]	
Rare	coeliac disease	coeliac disease
Hepatobiliary disorders		
Common	AST increased, ALT increased, hepatitis[y]	AST increased, ALT increased
Skin and subcutaneous tissue disorders		
Very common	rash[z], pruritus	rash[z], pruritus, alopecia[ah]
Common	dry skin[aq]	
Uncommon	severe cutaneous adverse reactions[ak], psoriasis[an], lichen disorders[ar]	severe cutaneous adverse reactions[ak], psoriasis[an]
Rare	pemphigoid	pemphigoid, lichen disorders[ar]
Musculoskeletal and connective tissue disorders		
Very common	arthralgia, back pain	arthralgia, musculoskeletal pain[aa], back pain
Common	musculoskeletal pain[aa]	
Uncommon	myositis[ab]	
Renal and urinary disorders		
Common	blood creatinine increased[c]	proteinuria[ac], blood creatinine increased[c]
Uncommon	nephritis[ad]	
Not known	cystitis noninfective[al]	
General disorders and administration site conditions		
Very common	pyrexia, fatigue, asthenia	pyrexia, fatigue, asthenia, oedema peripheral
Common	influenza like illness, chills, injection site reaction[ap]	
Investigations		
Common		blood alkaline phosphatase increased
Uncommon	blood creatine phosphokinase increased	

[a] Includes reports of urinary tract infection, cystitis, pyelonephritis, escherichia urinary tract infection, urinary tract infection bacterial, kidney infection, pyelonephritis acute, pyelonephritis chronic, pyelitis, renal abscess, streptococcal urinary tract infection, urethritis, urinary tract infection fungal, urinary tract infection pseudomonal.

[b] Includes reports of pneumonia, bronchitis, lower respiratory tract infection, infectious pleural effusion, tracheobronchitis, atypical pneumonia, lung abscess, infective exacerbation of chronic obstructive airways disease, paracancerous pneumonia, pyopneumothorax, pleural infection, post procedural pneumonia.

[c] Includes reports of blood creatinine increased, hypercreatininaemia.
[d] Includes reports of immune thrombocytopenia, thrombocytopenia, platelet count decreased.
[e] Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis, granulocytopenia.
[f] Includes reports of white blood cell count decreased, leukopenia.
[g] Includes reports of lymphopenia, lymphocyte count decreased.
[h] Includes reports of infusion-related reaction, cytokine release syndrome, hypersensitivity, anaphylaxis.
[i] Includes reports of anti-thyroid antibody positive, autoimmune hypothyroidism, autoimmune thyroiditis, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, euthyroid sick syndrome, goitre, hypothyroidism, immune-mediated hypothyroidism, immune-mediated thyroiditis, myxoedema, primary hypothyroidism, thyroid disorder, thyroid hormones decreased, thyroid function test abnormal, thyroiditis, thyroiditis acute, thyroxine decreased, thyroxine free decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine decreased, tri-iodothyronine increased, tri-iodothyronine free abnormal, tri-iodothyronine free decreased, tri-iodothyronine free increased, silent thyroiditis.
[j] Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos.
[k] Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis, ketoacidosis.
[l] Includes reports of adrenal insufficiency, blood corticotropin decreased, glucocorticoid deficiency, primary adrenal insufficiency, secondary adrenocortical insufficiency.
[m] Includes reports of hypophysitis, hypopituitarism, secondary adrenocortical insufficiency, temperature regulation disorder.
[n] Includes reports of hypomagnesaemia, blood magnesium decreased.
[o] Includes reports of neuropathy peripheral, autoimmune neuropathy, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy, axonal neuropathy, lumbosacral plexopathy, neuropathic arthropathy, peripheral nerve infection, neuritis, immune-mediated neuropathy.
[p] Includes reports of Guillain-Barré syndrome, ascending flaccid paralysis, demyelinating polyneuropathy.
[q] Includes reports of encephalitis, encephalitis autoimmune, meningitis, meningitis aseptic, photophobia.
[r] Includes reports of myasthenia gravis.
[s] Includes reports of myocarditis, autoimmune myocarditis, and immune-mediated myocarditis.
[t] Includes reports of pneumonitis, lung infiltration, bronchiolitis, immune-mediated lung disease, immune-mediated pneumonitis, interstitial lung disease, alveolitis, lung opacity, pulmonary fibrosis, pulmonary toxicity, radiation pneumonitis.
[u] Includes reports of diarrhoea, defaecation urgency, frequent bowel movements, gastrointestinal hypermotility.
[v] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative, diversion colitis, eosinophilic colitis, immune-mediated enterocolitis.
[w] Includes reports of oropharyngeal pain, oropharyngeal discomfort, throat irritation.
[x] Includes reports of autoimmune pancreatitis, pancreatitis, pancreatitis acute, lipase increased, amylase increased.
[y] Includes reports of ascites, autoimmune hepatitis, hepatic cytolysis, hepatitis, hepatitis acute, hepatitis toxic, hepatotoxicity, immune-mediated hepatitis, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, liver injury, oesophageal varices haemorrhage, varices oesophageal, spontaneous bacterial peritonitis.
[z] Includes reports of acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, eczema infected, erythema, erythema of eyelid, eyelid rash, fixed eruption, folliculitis, furuncle, hand dermatitis, immune-mediated dermatitis, lip blister, oral blood blister, palmar-plantar erythrodysaesthesia syndrome, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash vesicular, scrotal dermatitis, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, vascular access site rash.
[aa] Includes reports of musculoskeletal pain, myalgia, bone pain.
[ab] Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present, myopathy, polymyositis.

[ac] Includes reports of proteinuria, protein urine present, haemoglobinurea, urine abnormality, nephrotic syndrome, albuminuria.
[ad] Includes reports of nephritis, autoimmune nephritis, Henoch-Schonlein purpura nephritis, paraneoplastic glomerulonephritis, tubulointerstitial nephritis.
[ae] Includes reports of hypokalaemia, blood potassium decreased.
[af] Includes reports of hyponatraemia, blood sodium decreased.
[ag] Includes reports of hypoxia, oxygen saturation decreased, pO2 decreased.
[ah] Includes reports of alopecia, madarosis, alopecia areata, alopecia totalis, hypotrichosis.
[ai] Includes reports of hypertension, blood pressure increased, hypertensive crisis, blood pressure systolic increased, diastolic hypertension, blood pressure inadequately controlled, retinopathy hypertensive, hypertensive nephropathy, essential hypertension, orthostatic hypertension.
[aj] Includes reports of sepsis, septic shock, urosepsis, neutropenic sepsis, pulmonary sepsis, bacterial sepsis, klebsiella sepsis, abdominal sepsis, candida sepsis, escherichia sepsis, pseudomonal sepsis, staphylococcal sepsis.
[ak] Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative, dermatitis exfoliative generalised, toxic skin eruption, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, cutaneous vasculitis.
[al] Includes reports of cystitis noninfective and immune-mediated cystitis.
[am] Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea.
[an] Includes reports of psoriasis, dermatitis psoriasiform.
[ao] Includes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive
[ap] Reported in a study outside the pooled dataset (subcutaneous administration related). The frequency is based on exposure to Tecentriq solution for injection in IMscin001 and IMscin002 and includes reports of injection site reaction, injection site pain, injection site erythema, and injection site rash.
[aq] Includes reports of dry skin, xerosis.
[ar] Includes reports of lichenoid keratosis, lichen sclerosus and lichen planus.

Description of selected adverse reactions

The data below reflect information for significant adverse reactions for atezolizumab as monotherapy in clinical trials (see section 5.1). Details for the significant adverse reactions for atezolizumab when given in combination are presented if clinically relevant differences were noted in comparison to atezolizumab monotherapy. The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Immune-mediated pneumonitis

Pneumonitis occurred in 3.0% (151/5 039) of patients who received atezolizumab monotherapy. Of these patients, three experienced fatal events. The median time to onset was 3.7 months (range: 3 days to 29.8 months). The median duration was 1.7 months (range: 0 days to 27.8+ months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 41 (0.8%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.8% (92/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated hepatitis

Hepatitis occurred in 1.7% (88/5 039) of patients who received atezolizumab monotherapy. Of the 88 patients, three experienced fatal events. The median time to onset was 1.4 months (range: 0 days to 26.3 months). The median duration was 1 months (range: 0 day to 52.1+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 46 (0.9%) patients. Hepatitis requiring the use of corticosteroids occurred in 2.6% (130/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated colitis

Colitis occurred in 1.2% (62/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 4.5 months (range: 15 days to 36.4 months). The median duration was 1.4 months (range: 3 days to 50.2+ months; + denotes a censored value). Colitis led to discontinuation of

atezolizumab in 24 (0.5%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (30/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated endocrinopathies

Thyroid disorders

Hypothyroidism occurred in 8.5% (427/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 4.2 months (range: 0 days to 38.5 months). Hypothyroidism occurred in 17.4% (86/495) of patients who received atezolizumab monotherapy in the adjuvant NSCLC setting. The median time to onset was 4.0 months (range: 22 days to 11.8 months).

Hyperthyroidism occurred in 2.4% (121/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 2.7 months (range: 0 days to 24.3 months). Hyperthyroidism occurred in 6.5% (32/495) of patients who received atezolizumab monotherapy in the adjuvant NSCLC setting. The median time to onset was 2.8 months (range: 1 day to 9.9 months).

Adrenal insufficiency

Adrenal insufficiency occurred in 0.5% (25/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 6.2 months (range: 3 days to 21.4 months). Adrenal insufficiency led to discontinuation of atezolizumab in 5 (0.1%) patients. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.4% (20/5 039) of patients receiving atezolizumab monotherapy.

Hypophysitis

Hypophysitis occurred in 0.2% (9/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 5.3 months (range: 21 days to 13.7 months). Six (0.1%) patients required the use of corticosteroids and treatment with atezolizumab was discontinued in 1 (< 0.1%) patient.

Hypophysitis occurred in 1.4% (15/1 093) of patients who received atezolizumab in combination with paclitaxel followed by atezolizumab, dose-dense doxorubicin or epirubicin, and cyclophosphamide. The median time to onset was 3.8 months (range: 2.4 to 10.7 months). Eleven patients (1.0%) required the use of corticosteroids. Treatment with atezolizumab was discontinued in 7 (0.6%) patients.

Hypophysitis occurred in 0.8% (3/393) of patients who received atezolizumab with bevacizumab, paclitaxel, and carboplatin. The median time to onset was 7.7 months (range: 5.0 to 8.8 months). Two patients required the use of corticosteroids.

Hypophysitis occurred in 0.4% (2/473) of patients who received atezolizumab in combination with nab-paclitaxel and carboplatin. The median time to onset was 5.2 months (range: 5.1 to 5.3 months). Both patients required the use of corticosteroids.

Diabetes mellitus

Diabetes mellitus occurred in 0.6% (30/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 5.5 months (range: 3 days to 29.0 months). Diabetes mellitus led to the discontinuation of atezolizumab in < 0.1% (3/5 039) patients. Four (< 0.1%) patients required the use of corticosteroids.

Diabetes mellitus occurred in 2.0% (10/493) of HCC patients who received atezolizumab in combination with bevacizumab. The median time to onset was 4.4 months (range: 1.2 months to 8.3 months). No events of diabetes mellitus led to atezolizumab withdrawal.

Immune-mediated meningoencephalitis

Meningoencephalitis occurred in 0.4% (22/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 15 days (range: 0 days to 12.5 months). The median duration was 24 days (range: 6 days to 14.5+ months; + denotes a censored value).

Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (12/5 039) of patients receiving atezolizumab and eight patients (0.2%) discontinued atezolizumab.

Immune-mediated neuropathies

Guillain-Barré syndrome and demyelinating polyneuropathy

Guillain-Barré syndrome and demyelinating polyneuropathy occurred in 0.1% (6/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 4.1 months (range: 18 days to 8.1 months). The median duration was 8.0 months (range: 18 days to 24.5+ months; + denotes a censored value). Guillain-Barré syndrome led to discontinuation of atezolizumab in 1 patient (< 0.1%). Guillain-Barré syndrome requiring the use of corticosteroids occurred in < 0.1% (3/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated facial paresis

Facial paresis occurred in < 0.1% (1/5 039) of patients who received atezolizumab monotherapy. The time to onset was 29 days. The duration was 1.1 months. The event did not require the use of corticosteroids and the event did not lead to discontinuation of atezolizumab.

Immune-mediated myelitis

Myelitis occurred in < 0.1% (1/5 039) of patients who received atezolizumab monotherapy. The time to onset was 3 days. The event required the use of corticosteroids but did not lead to discontinuation of atezolizumab.

Myasthenic syndrome

Myasthenia gravis occurred in < 0.1% (2/5 039) of patients (including 1 fatal case) who received atezolizumab monotherapy. The median time to onset was 2.6 months (range: 1.2 months to 4 months).

Immune-mediated pancreatitis

Pancreatitis, including amylase increased and lipase increased, occurred in 0.8% (40/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 5 months (range: 0 days to 24.8 months). The median duration was 24 days (range: 3 days to 40.4+ months; + denotes a censored value). Pancreatitis led to the discontinuation of atezolizumab in 3 (< 0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in 0.2% (8/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated myocarditis

Myocarditis occurred in < 0.1% (5/5 039) of patients who received atezolizumab monotherapy. Of the 5 patients, one experienced a fatal event in the adjuvant NSCLC setting. The median time to onset was 3.7 months (range: 1.5 to 4.9 months). The median duration was 14 days (range: 12 days to

2.8 months). Myocarditis led to the discontinuation of atezolizumab in 3 (< 0.1%) patients. Three (<0.1%) patients required the use of corticosteroids.

Immune-mediated nephritis

Nephritis occurred in 0.2% (11/5 039) of patients who received atezolizumab. The median time to onset was 5.1 months (range: 3 days to 17.5 months). Nephritis led to discontinuation of atezolizumab in 5 (≤ 0.1%) patients. Five (0.1%) patients required the use of corticosteroids.

Immune-mediated myositis

Myositis occurred in 0.6% (32/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 3.5 months (range: 12 days to 11.5 months). The median duration was 3.2 months (range: 9 days to 51.1+ months; + denotes a censored value). Myositis led to discontinuation of atezolizumab in 6 (0.1%) patients. Ten (0.2%) patients required the use of corticosteroids.

Immune-mediated severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) occurred in 0.6% (30/5 039) of patients who received atezolizumab monotherapy. Of the 30 patients, one experienced a fatal event. The median time to onset was 4.8 months (range: 3 days to 15.5 months). The median duration was 2.4 months (range: 1 day to 37.5+ months; + denotes a censored value). SCARs led to discontinuation of atezolizumab in 3 (< 0.1%) patients. SCARs requiring the use of systemic corticosteroids occurred in 0.2% (9/5 039) of patients receiving atezolizumab monotherapy.

Immune-mediated pericardial disorders

Pericardial disorders occurred in 1% (49/5 039) of patients who received atezolizumab monotherapy. The median time to onset was 1.4 months (range: 6 days to 17.5 months). The median duration was 2.5 months (range: 0 to 51.5+ months; + denotes a censored value). Pericardial disorders led to discontinuation of Tecentriq in 3 (< 0.1%) patients. Pericardial disorders requiring the use of corticosteroids occurred in 0.2% (7/5 039) of patients.

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reaction(s) reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with atezolizumab: pancreatic exocrine insufficiency.

Immunogenicity

Subcutaneous formulation

In IMscin001, the incidence of treatment-emergent anti-atezolizumab antibodies in patients treated with subcutaneous and intravenous Tecentriq was comparable (19.5% [43/221] and 13.9% [15/108], respectively), following a median of 2.8 months of treatment. The incidence of treatment-emergent anti-rHuPH20 antibodies in patients treated with subcutaneous Tecentriq was 5.4% (12/224). The clinical relevance of the development of anti-rHuPH20 antibodies after treatment with Tecentriq solution for injection is unknown.

Intravenous formulation

Across multiple phase II and III studies, 13.1% to 54.1% of patients developed treatment-emergent anti-drug antibodies (ADAs). Patients who developed treatment-emergent ADAs tended to have overall poorer health and disease characteristics at baseline. Those imbalances in health and disease characteristics at baseline can confound the interpretation of PK, efficacy and safety analyses.

Exploratory analyses adjusting for imbalances in baseline health and disease characteristics were conducted to assess the effect of ADA on efficacy. These analyses did not exclude possible attenuation of efficacy benefit in patients who developed ADA compared to patients who did not develop ADA. The median time to ADA onset ranged from 3 weeks to 5 weeks.

Across pooled datasets for patients treated with atezolizumab monotherapy (N=3 460) and with combination therapies (N= 2 285), the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: Grade 3-4 AEs 46.2% vs. 39.4%, Serious Adverse Events (SAEs) 39.6% vs. 33.3%, AEs leading to treatment withdrawal 8.5% vs 7.8% (for monotherapy); Grade 3-4 AEs 63.9% vs. 60.9%, SAEs 43.9% vs. 35.6%, AEs leading to treatment withdrawal 22.8% vs 18.4% (for combination therapy). However, available data do not allow firm conclusions to be drawn on possible patterns of adverse reactions.

Paediatric population

The safety of atezolizumab in children and adolescents has not been established. No new safety signals were observed in a clinical trial with 69 paediatric patients (< 18 years) and the safety profile was comparable to adults.

Elderly

No overall differences in safety were observed between patients < 65, 65-74, and 75-84 years of age receiving atezolizumab monotherapy. The data for patients ≥ 85 years of age are too limited to draw meaningful conclusions about this population.

In study IMpower150, age ≥ 65 was associated with an increased risk of developing adverse events in patients receiving atezolizumab in combination with bevacizumab, carboplatin and paclitaxel. In studies IMpower150, IMpower133, IMpower110 and IMscin001 data for patients ≥ 75 years of age were too limited to draw conclusions. In the IPSOS study in 1L platinum-ineligible NSCLC patients, there were no overall differences in the safety profile for 1L atezolizumab monotherapy between the patient age subgroups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with atezolizumab.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors. ATC code: L01FF05.

Tecentriq solution for injection contains the active substance atezolizumab which provides the therapeutic effect of this medicinal product and recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated substances when administered subcutaneously.

Mechanism of action

Programmed death-ligand 1 (PD-L1) may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.

Clinical efficacy and safety

Urothelial carcinoma

Intravenous formulation

IMvigor211 (GO29294): Randomised trial in locally advanced or metastatic UC patients previously treated with chemotherapy

A phase III, open-label, multi-centre, international, randomised study, (IMvigor211), was conducted to evaluate the efficacy and safety of atezolizumab compared with chemotherapy (investigator's choice of vinflunine, docetaxel, or paclitaxel) in patients with locally advanced or metastatic UC who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrolment; and administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 9 weeks for the first 54 weeks, and every 12 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 931 patients were enrolled. Patients were randomised (1:1) to receive either atezolizumab or chemotherapy. Randomisation was stratified by chemotherapy (vinflunine vs. taxane), PD-L1 expression status on IC (< 5% vs. ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no). Prognostic risk factors included time from prior chemotherapy of < 3 months, ECOG performance status > 0 and haemoglobin < 10 g/dL.

Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks. No dose reduction of atezolizumab was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. Vinflunine was administered 320 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression or unacceptable toxicity.

Paclitaxel was administered 175 mg/m^2 by intravenous infusion over 3 hours on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. Docetaxel was administered 75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. For all treated patients, the median duration of treatment was 2.8 months for the atezolizumab arm, 2.1 months for the vinflunine and paclitaxel arms and 1.6 months for the docetaxel arm.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 67 years (range: 31 to 88), and 77.1% of patients were male. The majority of patients were white (72.1%), 53.9% of patients within the chemotherapy arm received vinflunine, 71.4% of patients had at least one poor prognostic risk factor and 28.8% had liver metastases at baseline. Baseline ECOG performance status was 0 (45.6%) or 1 (54.4%). Bladder was the primary tumour site for 71.1% of patients and 25.4% of patients had upper tract UC. There were 24.2% of patients who received only prior platinum-containing adjuvant or neoadjuvant therapy and progressed within 12 months.

The primary efficacy endpoint for IMvigor211 is overall survival (OS). Secondary efficacy endpoints evaluated per investigator-assessed Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 are objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR). Comparisons with respect to OS between the treatment arm and control arm within the IC2/3, IC1/2/3, and ITT (Intention-to-treat, i.e. all comers) populations were tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% as follows: step 1) IC2/3 population; step 2) IC1/2/3 population; step 3) all comers population. OS results for each of steps 2 and 3 could be formally tested for statistical significance only if the result in the preceding step was statistically significant.

The median survival follow-up is 17 months. The primary analysis of study IMvigor211 did not meet its primary endpoint of OS. Atezolizumab did not demonstrate a statistically significant survival benefit compared to chemotherapy in patients with previously treated, locally advanced or metastatic UC. Per the pre-specified hierarchical testing order, the IC2/3 population was tested first, with an OS hazard ratio (HR) of 0.87 (95% CI: 0.63, 1.21; median OS of 11.1 vs. 10.6 months for atezolizumab and chemotherapy respectively). The stratified log-rank p-value was 0.41 and therefore the results are considered not statistically significant in this population. As a consequence, no formal tests of statistical significance could be performed for OS in the IC1/2/3 or all comer populations, and results of those analyses would be considered exploratory. The key results in the all comer population are summarised in Table 4. The Kaplan-Meier curve for OS in the all comer population is presented in Figure 1.

An exploratory updated survival analysis was performed with a median duration of survival follow up of 34 months in the ITT population. The median OS was 8.6 months (95% CI: 7.8, 9.6) in the atezolizumab arm and 8.0 months (95% CI: 7.2, 8.6) in the chemotherapy arm with a hazard ratio of 0.82 (95% CI: 0.71, 0.94). Consistent with the trend observed at primary analysis for 12-month OS rates, numerically higher 24-month and 30-month OS rates were observed for patients in the atezolizumab arm compared with the chemotherapy arm in the ITT population. The percentage of patients alive at 24 months (KM estimate) was 12.7% in the chemotherapy arm and 22.5% in the atezolizumab arm; and at 30 months (KM estimate) was 9.8% in the chemotherapy arm and 18.1% in the atezolizumab arm.

Table 4: Summary of efficacy in all comers (IMvigor211)

Efficacy endpoint	Atezolizumab (n = 467)	Chemotherapy (n = 464)
Primary efficacy endpoint		
OS*		
No. of deaths (%)	324 (69.4%)	350 (75.4%)
Median time to events (months)	8.6	8.0
95% CI	7.8, 9.6	7.2, 8.6
Stratified‡ hazard ratio (95% CI)	0.85 (0.73, 0.99)	
12-month OS (%)**	39.2%	32.4%
Secondary and exploratory endpoints		
Investigator-assessed PFS (RECIST v1.1)		
No. of events (%)	407 (87.2%)	410 (88.4%)
Median duration of PFS (months)	2.1	4.0
95% CI	2.1, 2.2	3.4, 4.2
Stratified hazard ratio (95% CI)	1.10 (0.95, 1.26)	
Investigator-assessed ORR (RECIST v1.1)	n = 462	n = 461
No. of confirmed responders (%)	62 (13.4%)	62 (13.4%)
95% CI	10.45, 16.87	10.47, 16.91
No. of complete response (%)	16 (3.5%)	16 (3.5%)
No. of partial response (%)	46 (10.0%)	46 (10.0%)
No. of stable disease (%)	92 (19.9%)	162 (35.1%)
Investigator-assessed DOR (RECIST v1.1)	n = 62	n = 62
Median in months ***	21.7	7.4
95% CI	13.0, 21.7	6.1, 10.3

CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

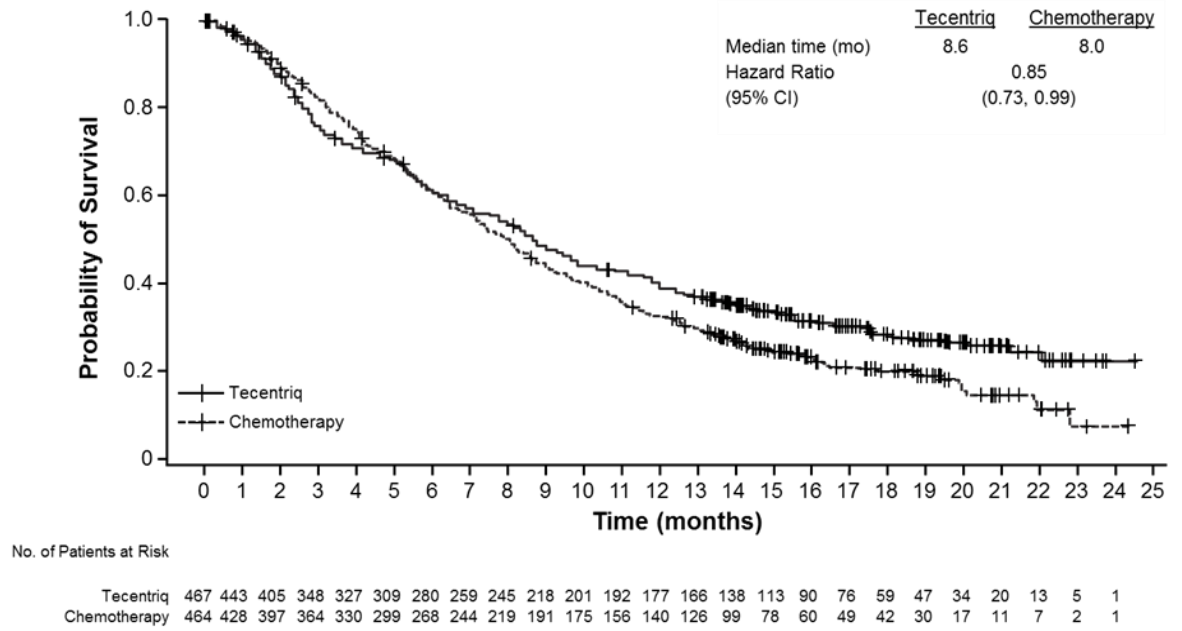
* An analysis of OS in the all comer population was performed based on the stratified log-rank test and the result is provided for descriptive purposes only (p = 0.0378); according to the pre-specified analysis hierarchy, the p-value for the OS analysis in the all comer population cannot be considered statistically significant.

‡ Stratified by chemotherapy (vinflunine vs. taxane), status on IC (< 5% vs. ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no).

** Based on Kaplan-Meier estimate

*** Responses were ongoing in 63% of responders in the atezolizumab arm and in 21% of responders in the chemotherapy arm.

Figure 1: Kaplan-Meier curve for overall survival (IMvigor211)



IMvigor210 (GO29293): Single-arm trial in previously untreated urothelial carcinoma patients who are ineligible for cisplatin therapy and in urothelial carcinoma patients previously treated with chemotherapy

A phase II, multi-centre, international, two-cohort, single-arm clinical trial, IMvigor210, was conducted in patients with locally advanced or metastatic UC (also known as urothelial bladder cancer).

The study enrolled a total of 438 patients and had two patient cohorts. Cohort 1 included previously untreated patients with locally advanced or metastatic UC who were ineligible or unfit for cisplatin-based chemotherapy or had disease progression at least 12 months after treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Cohort 2 included patients who received at least one platinum-based chemotherapy regimen for locally advanced or metastatic UC or had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen.

In Cohort 1, 119 patients were treated with atezolizumab 1 200 mg by intravenous infusion every 3 weeks until disease progression. The median age was 73 years. Most patients were male (81%), and the majority of patients were White (91%).

Cohort 1 included 45 patients (38%) with ECOG performance status of 0, 50 patients (42%) with ECOG performance status of 1 and 24 patients (20%) with ECOG performance status of 2, 35 patients (29%) with no Bajorin risk factors (ECOG performance status ≥ 2 and visceral metastasis), 66 patients (56%) with one Bajorin risk factor and 18 patients (15 %) with two Bajorin risk factors, 84 patients (71%) with impaired renal function (glomerular filtration rate [GFR] < 60 mL/min), and 25 patients (21%) with liver metastasis.

The primary efficacy endpoint for Cohort 1 was confirmed objective response rate (ORR) as assessed by an independent review facility (IRF) using RECIST v1.1.

The primary analysis was performed when all patients had at least 24 weeks of follow-up. Median duration of treatment was 15.0 weeks and median duration of survival follow-up was 8.5 months in all comers. Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a pre-specified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The confirmed ORRs per IRF-RECIST v1.1 were 21.9% (95% CI:

9.3, 40.0) in patients with PD-L1 expression ≥ 5%, 18.8% (95% CI: 10.9, 29.0) in patients with PD-L1 expression ≥ 1%, and 19.3% (95% CI: 12.7, 27.6) in all comers. The median duration of response (DOR) was not reached in any PD-L1 expression subgroup or in all comers. OS was not mature with an event patient ratio of approximately 40%. Median OS for all patient subgroups (PD-L1 expression ≥ 5 % and ≥ 1 %) and in all comers was 10.6 months.

An updated analysis was performed with a median duration of survival follow-up of 17.2 months for Cohort 1 and is summarised in Table 5. The median DOR was not reached in any PD-L1 expression subgroup or in all comers.

Table 5: Summary of updated efficacy (IMvigor210 Cohort 1)

Efficacy endpoint	**PD-L1 expression of ≥ 5% in IC**	**PD-L1 expression of ≥ 1% in IC**	**All Comers**
ORR (IRF-assessed; RECIST v1.1)	n = 32	n = 80	n = 119
No. of Responders (%)	9 (28.1%)	19 (23.8%)	27 (22.7%)
95% CI	13.8, 46.8	15.0, 34.6	15.5, 31.3
No. of complete response (%)	4 (12.5%)	8 (10.0%)	11 (9.2%)
95% CI	(3.5, 29.0)	(4.4, 18.8)	(4.7, 15.9)
No. of partial response (%)	5 (15.6%)	11 (13.8%)	16 (13.4%)
95% CI	(5.3, 32.8)	(7.1, 23.3)	(7.9, 20.9)
DOR (IRF-assessed; RECIST v1.1)	n = 9	n = 19	n = 27
Patients with event (%)	3 (33.3%)	5 (26.3%)	8 (29.6%)
Median (months) (95% CI)	NE (11.1, NE)	NE (NE)	NE (14.1, NE)
PFS (IRF-assessed; RECIST v1.1)	n = 32	n = 80	n = 119
Patients with event (%)	24 (75.0%)	59 (73.8%)	88 (73.9%)
Median (months) (95% CI)	4.1 (2.3, 11.8)	2.9 (2.1, 5.4)	2.7 (2.1, 4.2)
OS	n = 32	n = 80	n = 119
Patients with event (%)	18 (56.3%)	42 (52.5%)	59 (49.6%)
Median (months) (95% CI)	12.3 (6.0, NE)	14.1 (9.2, NE)	15.9 (10.4, NE)
1-year OS rate (%)	52.4%	54.8%	57.2%

CI = confidence interval; DOR=duration of response; IC = tumour-infiltrating immune cells; IRF = independent review facility; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

At the time of the final analysis for Cohort 1, patients had a median survival follow-up time of 96.4 months. Median OS was 12.3 months (95% CI: 6.0, 49.8) in patients with PD-L1 expression ≥ 5% (patients who are included in the therapeutic indication).

In Cohort 2, the co-primary efficacy endpoints were confirmed ORR as assessed by an IRF using RECIST v1.1 and investigator-assessed ORR according to Modified RECIST (mRECIST) criteria. There were 310 patients treated with atezolizumab 1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit. The primary analysis of Cohort 2 was performed when all patients had at least 24 weeks of follow-up. The study met its co-primary endpoints in Cohort 2, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST compared to a pre-specified historical control response rate of 10%.

An analysis was also performed with a median duration of survival follow-up of 21.1 months for Cohort 2. The confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI: 19.5, 37.9) in patients with PD-L1 expression ≥ 5%, 19.3% (95% CI: 14.2, 25.4) in patients with PD-L1 expression ≥ 1%, and 15.8% (95% CI: 11.9, 20.4) in all comers. The confirmed ORR per investigator-assessed mRECIST was 29.0% (95% CI: 20.4, 38.9) in patients with PD-L1 expression ≥ 5%, 23.7% (95% CI: 18.1, 30.1) in patients with PD-L1 expression ≥ 1%, and 19.7% (95% CI: 15.4, 24.6) in all comers. The rate of complete response per IRF-RECIST v1.1 in the all comer population was 6.1% (95% CI: 3.7, 9.4). For Cohort 2, median DOR was not reached in any PD-L1 expression subgroup or in all comers, however was reached in patients with PD-L1 expression < 1% (13.3 months; 95% CI 4.2, NE). The OS rate at 12 months was 37% in all comers.

At the time of the final analysis for Cohort 2, patients had a median survival follow-up time of 46.2 months. Median OS was 11.9 months (95% CI: 9.0, 22.8) in patients with PD-L1 expression ≥ 5%, 9.0 months (95% CI: 7.1, 11.1) in patients with PD-L1 expression ≥ 1%, and 7.9 months (95% CI: 6.7, 9.3) in all comers.

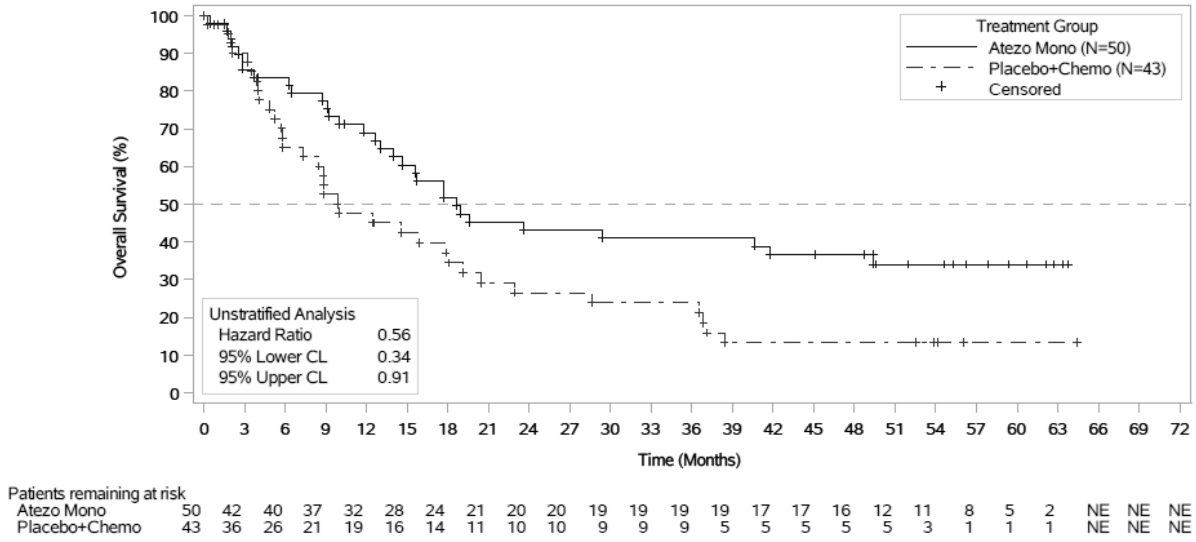
IMvigor130 (WO30070): Phase III study of atezolizumab monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma

A phase III, multi-centre, randomised, placebo-controlled, partially blinded (Arms A and C only) study, IMvigor130, was conducted to evaluate the efficacy and safety of atezolizumab + platinum-based combination chemotherapy (i.e., either cisplatin or carboplatin with gemcitabine), Arm A, or atezolizumab monotherapy (Arm B, open-label arm) versus placebo + platinum-based combination chemotherapy (Arm C) in patients with locally advanced or metastatic UC who had not received prior systemic therapy in the metastatic setting. The co-primary efficacy outcomes were investigator-assessed progression-free survival (PFS) in Arm A versus Arm C and overall survival (OS) in Arm A versus C and then Arm B versus C, analyzed in a hierarchical fashion. Overall survival was not statistically significant for the comparison of Arm A versus Arm C, and thus no further formal testing could be conducted per the pre-defined hierarchical testing order.

Based on an independent Data Monitoring Committee (iDMC) recommendation following an early review of survival data, accrual of patients on the atezolizumab monotherapy treatment arm whose tumours had a low PD-L1 expression (less than 5% of immune cells staining positive for PD-L1 by immunohistochemistry using VENTANA PD-L1 [SP142] assay) was stopped after observing decreased overall survival for this subgroup at an unplanned early analysis, however, this occurred after the vast majority of patients had already been enrolled.

Out of 719 patients enrolled in the atezolizumab monotherapy (n=360) and chemotherapy alone (n=359) arms, 50 and 43 patients, respectively, were cisplatin-ineligible by Galsky criteria and had tumours with high PD-L1 expression (≥ 5% of immune cells staining positive for PD-L1 by immunohistochemistry using VENTANA PD-L1 [SP142] assay). In an exploratory analysis in this subgroup of patients, the unstratified HR for OS was 0.56 (95% CI: 0.34, 0.91). The median OS was 18.6 months (95% CI: 14.0, 49.4) in the atezolizumab monotherapy arm vs. 10.0 months (95% CI: 7.4, 18.1) in the chemotherapy alone arm (see Figure 2).

Figure 2 Kaplan-Meier Plot of Overall Survival in Cisplatin-ineligible patients whose tumours are PD-L1 high (Arm B vs. Arm C)



<u>*Non-small cell lung cancer*</u>

Adjuvant treatment of early-stage NSCLC

Intravenous formulation

IMpower010 (GO29527): Randomised phase III trial in patients with resected NSCLC after cisplatin-based chemotherapy

A phase III, open label, multi-centre, randomised study, GO29527 (IMpower010), was conducted to evaluate the efficacy and safety of atezolizumab for the adjuvant treatment of patients with stage IB (tumours ≥ 4 cm) – IIIA NSCLC (per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition).

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with stage II – IIIA according to the 7th edition staging system:

Tumour size ≥ 5 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

The study did not include patients who had N2 status with tumours invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

A total of 1 280 enrolled patients had complete tumour resection and were eligible to receive up to 4 cycles of cisplatin-based chemotherapy. The cisplatin-based chemotherapy regimens are described in Table 6.

Table 6: Adjuvant chemotherapy regimens (IMpower010)

Adjuvant cisplatin-based chemotherapy: Cisplatin 75 mg/m^2 intravenous on Day 1 of each 21 day cycle with one of the following treatment regimens	Vinorelbine 30 mg/m^2 intravenous, Days 1 and 8
	Docetaxel 75 mg/m^2 intravenous, Day 1
	Gemcitabine 1 250 mg/m^2 intravenous, Days 1 and 8
	Pemetrexed 500 mg/m^2 intravenous, Day 1(non-squamous)

After completion of cisplatin-based chemotherapy (up to four cycles), a total of 1 005 patients were randomised in a 1:1 ratio to receive atezolizumab (Arm A) or best supportive care (BSC) (Arm B). Atezolizumab was administered as a fixed dose of 1 200 mg by IV infusion every 3 weeks for 16 cycles unless there was disease recurrence or unacceptable toxicity. Randomisation was stratified by sex, stage of disease, histology, and PD-L1 expression.

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomisation; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomisation. Tumour assessments were conducted at baseline of the randomisation phase and every 4 months for the first year following Cycle 1, Day 1 and then every 6 months until year five, then annually thereafter.

The demographics and baseline disease characteristics in the ITT population were well balanced between the treatment arms. The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%), and 24% were Asian. Most patients were current or previous smokers (78%) and baseline ECOG performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had stage IB, 47% had stage II and 41% had stage IIIA disease. The percentage of patients who had tumours with PD-L1 expression ≥ 1% and ≥ 50% on TC as measured by the VENTANA PD-L1 (SP263) Assay was 55% and 26%, respectively.

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. DFS was defined as the time from the date of randomisation to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. The primary efficacy objective was to evaluate DFS in the PD-L1 ≥ 1% TC stage II – IIIA patient population. Key secondary efficacy objectives were to evaluate DFS in the PD-L1 ≥ 50% TC stage II – IIIA patient population and overall survival (OS) in the ITT population.

At the time of the interim DFS analysis, the study met its primary endpoint. In the analysis of patients with PD-L1 ≥ 50% TC stage II – IIIA without EGFR mutations or ALK rearrangements (n = 209), an improvement in DFS in the atezolizumab arm was observed compared to the BSC arm. Results were consistent at the time of the final DFS analysis, with median follow up time of 65 months.

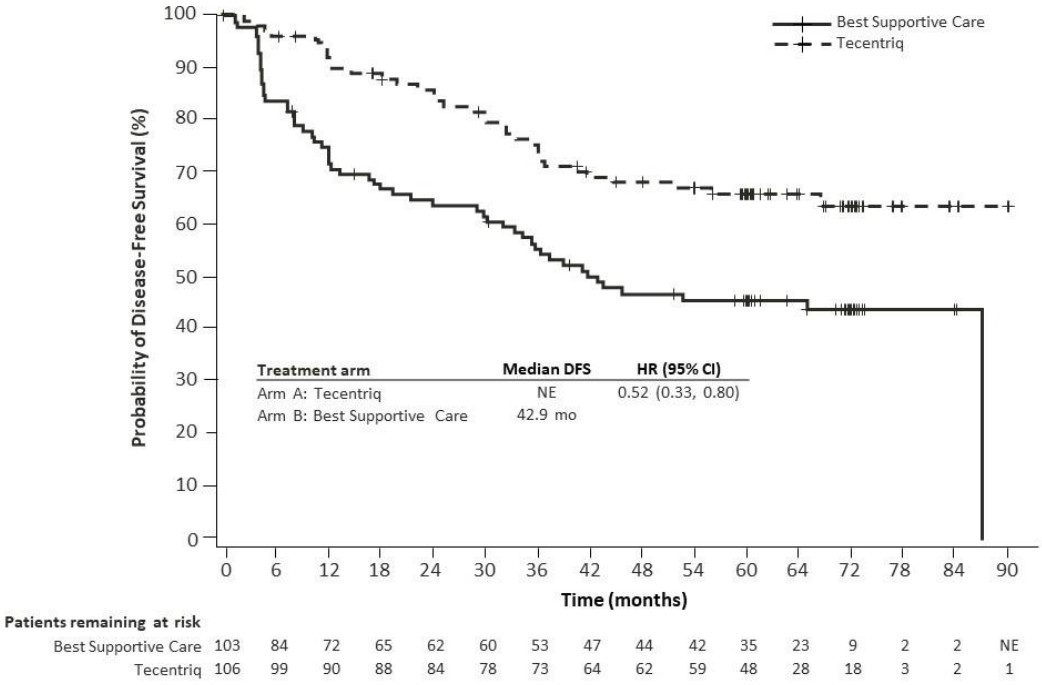
The key efficacy results for DFS and OS in the PD-L1 ≥ 50% TC stage II – IIIA patient population, without EGFR mutations and ALK rearrangements, are summarised in Table 7. The Kaplan-Meier curve for DFS is presented in Figure 3.

Table 7: Summary of efficacy in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010)

Efficacy endpoint	Arm A (Atezolizumab)	Arm B (Best supportive care)
Investigator-assessed DFS*	n = 106	n = 103
No. of events (%)	34 (32.1%)	55 (53.4%)
Median duration of DFS (months)	NE	42.9
95% CI	(NE)	(32.0, NE)
Stratified‡ hazard ratio (95% CI)	0.52 (0.33, 0.80)	
OS*	n=106	n=103
No. of events (%)	22 (20.8%)	41 (39.8%)
Median OS (months)	NE	87.1
95% CI	(NE)	(72.0, NE)
Stratified‡ hazard ratio (95% CI)	0.47 (0.28, 0.80)	

DFS = Disease-free survival; CI = confidence interval; NE = not estimable
* Updated DFS and OS analysis at clinical cut-off 26 January 2024
‡ Stratified by stage, sex, and histology.

Figure 3: Kaplan-Meier curve for disease-free survival in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010)



The observed DFS improvement in the atezolizumab arm compared with the BSC arm was consistently shown across the majority of pre-specified subgroups in the PD-L1 ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements, including both non-squamous NSCLC patients (unstratified HR of 0.40, 95% CI: 0.23, 0.70; median DFS NE vs. 36.8 months) and squamous NSCLC patients (unstratified HR of 0.67, 95% CI: 0.34, 1.32; median DFS could not be estimated).

First-line treatment of advanced NSCLC

Intravenous formulation

IMpower150 (GO29436): Randomised phase III trial in chemotherapy-naïve patients with metastatic non-squamous NSCLC, in combination with paclitaxel and carboplatin with or without bevacizumab

A phase III, open-label, multi-centre, international, randomised study, IMpower150, was conducted to evaluate the efficacy and safety of atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, in chemotherapy-naïve patients with metastatic non-squamous NSCLC.

Patients were excluded if they had history of autoimmune disease, administration of a live, attenuated vaccine within 28 days prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to randomisation, active or untreated CNS metastases, clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumour specimens were evaluated for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 1 202 patients were enrolled and were randomised (1:1:1) to receive one of the treatment regimens described in Table 8. Randomisation was stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC.

Table 8: Intravenous treatment regimens (IMpower150)

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
A	Atezolizumab[a] (1 200 mg) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Atezolizumab[a] (1 200 mg)
B	Atezolizumab[a] (1 200 mg) + bevacizumab[d] (15 mg/kg bw) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Atezolizumab[a] (1 200 mg) + bevacizumab[d] (15 mg/kg bw)
C	Bevacizumab[d] (15 mg/kg bw) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Bevacizumab[d] (15 mg/kg bw)

[a] Atezolizumab is administered until loss of clinical benefit as assessed by the investigator
[b] The paclitaxel starting dose for patients of Asian race/ethnicity was 175 mg/m^2 due to higher overall level of haematologic toxicities in patients from Asian countries compared with those from non-Asian countries
[c] Paclitaxel and carboplatin are administered until completion of 4 or 6 cycles, or progressive disease, or unacceptable toxicity whichever occurs first
[d.] Bevacizumab is administered until progressive disease or unacceptable toxicity

The demographics and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were white (82%). Approximately 10% of patients had known EGFR mutation, 4% had known ALK rearrangements, 14% had liver metastasis at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). 51% of patients' tumours had PD-L1 expression of ≥ 1% TC or ≥ 1% IC and 49% of patients' tumours had PD-L1 expression of < 1% TC and < 1% IC.

At the time of the final analysis for PFS, patients had a median follow up time of 15.3 months. The ITT population, including patients with EGFR mutations or ALK rearrangements who should have been previously treated with tyrosine kinase inhibitors, demonstrated clinically meaningful PFS

improvement in Arm B as compared to Arm C (HR of 0.61, 95% CI: 0.52, 0.72; median PFS 8.3 vs. 6.8 months).

At the time of the interim OS analysis, patients had a median follow-up of 19.7 months. The key results from this analysis as well as from the updated PFS analysis in the ITT population are summarised in Tables 9 and 10. The Kaplan-Meier curve for OS in the ITT population is presented in Figure 4. Figure 5 summarises the results of OS in the ITT and PD-L1 subgroups. Updated PFS results are also presented in Figures 6 and 7.

Table 9: Summary of updated efficacy in the ITT population (IMpower150)

Efficacy endpoint	**Arm A (Atezolizumab + Paclitaxel + Carboplatin)**	**Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)**	**Arm C (Bevacizumab + Paclitaxel + Carboplatin)**
Secondary Endpoints[#]			
Investigator-assessed PFS (RECIST v1.1)*	n = 402	n = 400	n = 400
No. of events (%)	330 (82.1%)	291 (72.8%)	355 (88.8%)
Median duration of PFS (months)	6.7	8.4	6.8
95% CI	(5.7, 6.9)	(8.0, 9.9)	(6.0, 7.0)
Stratified hazard ratio[‡^] (95% CI)	0.91 (0.78, 1.06)	0.59 (0.50, 0.69)	---
p-value[1,2]	0.2194	< 0.0001	
12-month PFS (%)	24	38	20
OS interim analysis*	n = 402	n = 400	n = 400
No. of deaths (%)	206 (51.2%)	192 (48.0%)	230 (57.5%)
Median time to events (months)	19.5	19.8	14.9
95% CI	(16.3, 21.3)	(17.4, 24.2)	(13.4, 17.1)
Stratified hazard ratio[‡^] (95% CI)	0.85 (0.71, 1.03)	0.76 (0.63, 0.93)	---
p-value[1,2]	0.0983	0.006	
6-month OS (%)	84	85	81
12-month OS (%)	66	68	61
Investigator-assessed Overall Best Response[3]* (RECIST 1.1)	n = 401	n = 397	n = 393
No. of responders (%)	163 (40.6%)	224 (56.4%)	158 (40.2%)
95% CI	(35.8, 45.6)	(51.4, 61.4)	(35.3, 45.2)
No. of complete response (%)	8 (2.0%)	11 (2.8%)	3 (0.8%)
No. of partial response (%)	155 (38.7%)	213 (53.7%)	155 (39.4%)
Investigator-assessed DOR* (RECIST v1.1)	n = 163	n = 224	n = 158
Median in months	8.3	11.5	6.0
95% CI	(7.1, 11.8)	(8.9, 15.7)	(5.5, 6.9)

[#] Primary efficacy endpoints were PFS and OS and they were analysed in the ITT-wild-type (WT) population, i.e. excluding patients with EGFR mutations or ALK rearrangements.
[1] Based on the stratified log-rank test
[2] For informational purposes; in the ITT population, comparisons between Arm B and Arm C as well as between Arm A and Arm C were not formally tested yet as per the pre-specified analysis hierarchy
[3] Overall best response for complete response and partial response
[‡] Stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC
^ The Arm C is the comparison group for all hazard ratios
***** Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018
PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.
CI = confidence interval; DOR = duration of response; OS = overall survival.

Table 10: Summary of updated efficacy for Arm A vs. Arm B in the ITT population (IMpower150)

Efficacy endpoint	Arm A (Atezolizumab + Paclitaxel + Carboplatin)	Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)
Investigator-assessed PFS (RECIST v1.1)*	n = 402	n = 400
No. of events (%)	330 (82.1%)	291 (72.8%)
Median duration of PFS (months)	6.7	8.4
95% CI	(5.7, 6.9)	(8.0, 9.9)
Stratified hazard ratio‡^ (95% CI)	0.67 (0.57, 0.79)	
p-value[1,2]	< 0.0001	
OS interim analysis*	n = 402	n = 400
No. of deaths (%)	206 (51.2%)	192 (48.0%)
Median time to events (months)	19.5	19.8
95% CI	(16.3, 21.3)	(17.4, 24.2)
Stratified hazard ratio‡^ (95% CI)	0.90 (0.74, 1.10)	
p-value[1,2]	0.3000	

[1] Based on the stratified log-rank test

[2] For informational purposes; in the ITT population, comparisons between Arm A and Arm B were not included in the pre-specified analysis hierarchy

‡ Stratified by sex, presence of liver metastases and PD-L1 expression on TC and IC

* Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018

^ The Arm A is the comparison group for all hazard ratios

Figure 4: Kaplan-Meier curve for overall survival in the ITT population (IMpower150)

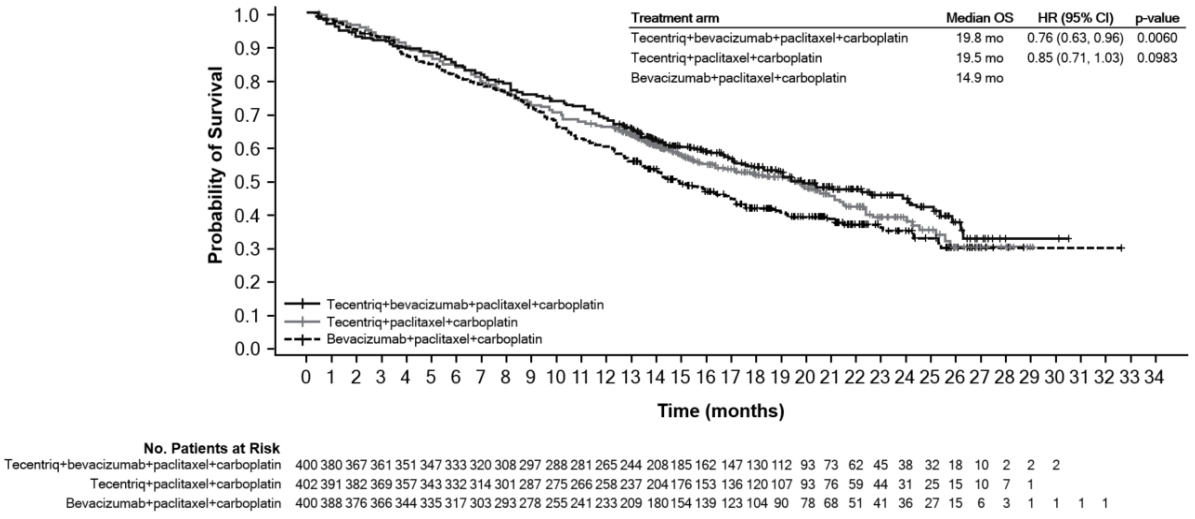


Figure 5: Forest plot of overall survival by PD-L1 expression in the ITT population, Arm B vs. C (IMpower150)

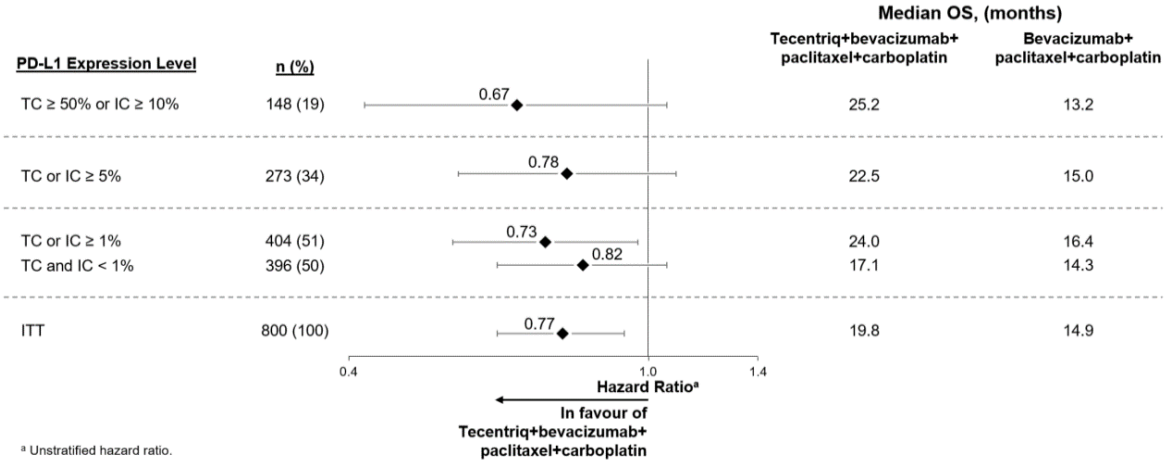
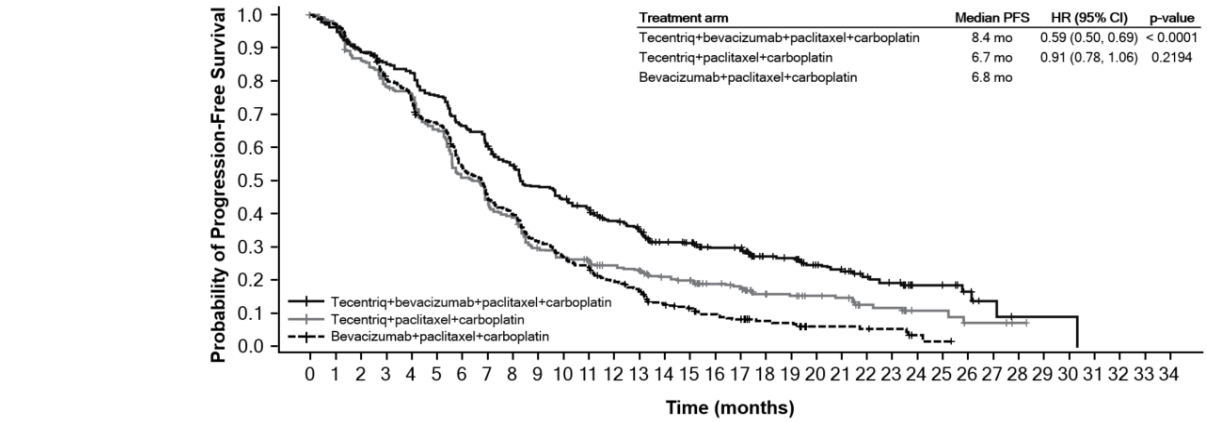


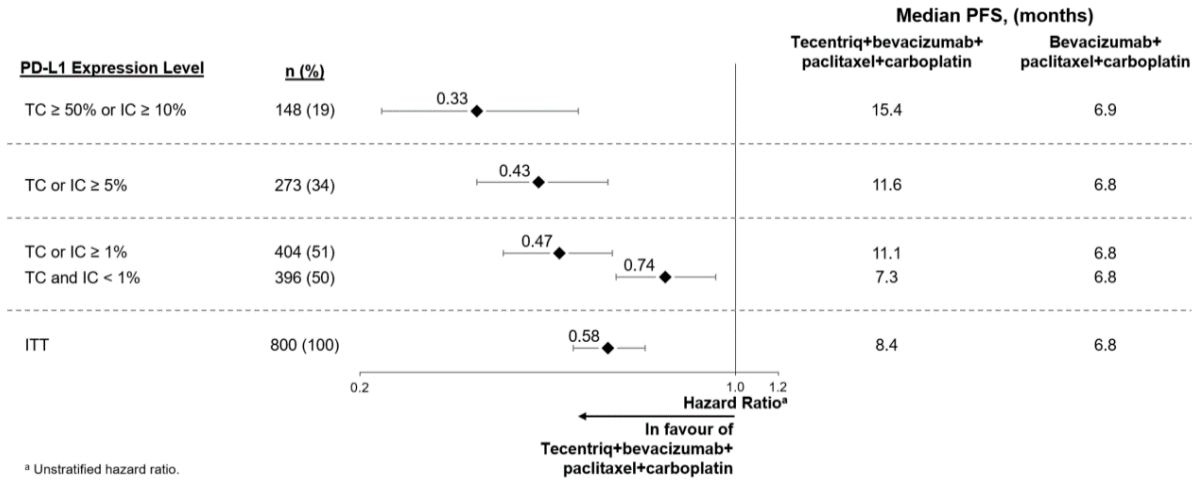
Figure 6: Kaplan-Meier curve for PFS in the ITT population (IMpower150)



No. Patients at Risk

Tecentriq+bevacizumab+paclitaxel+carboplatin	400	376	352	336	326	297	262	240	215	189	174	163	141	127	96	91	76	75	58	55	40	35	26	22	13	12	7	3	1	1	1
Tecentriq+paclitaxel+carboplatin	402	387	343	313	302	258	204	171	154	116	105	100	87	83	66	62	48	43	31	29	25	23	14	13	6	6	3	3	1		
Bevacizumab+paclitaxel+carboplatin	400	385	353	318	297	261	213	176	154	122	104	93	74	62	43	35	26	22	16	15	8	8	7	6	2	1					

Figure 7: Forest plot of progression free survival by PD-L1 expression in the ITT population, Arm B vs. C (IMpower150)



In Arm B as compared to Arm C, pre-specified subgroup analyses from the interim OS analysis showed an OS improvement for patients with EGFR mutations or ALK rearrangements (hazard ratio [HR] of 0.54, 95% CI: 0.29, 1.03; median OS not reached vs. 17.5 months), and liver metastases (HR of 0.52, 95% CI: 0.33, 0.82; median OS 13.3 vs. 9.4 months). PFS improvements were also shown in patients with EGFR mutations or ALK rearrangements (HR of 0.55, 95% CI: 0.35, 0.87; median PFS 10.0 vs. 6.1 months) and liver metastases (HR of 0.41, 95% CI: 0.26, 0.62; median PFS 8.2 vs. 5.4 months). OS results were similar for patients aged < 65 and ≥ 65 subgroups, respectively. Data for patients ≥ 75 years of age are too limited to draw conclusions on this population. For all subgroup analyses, formal statistical testing was not planned.

IMpower130 (GO29537): Randomised phase III trial in chemotherapy-naïve patients with metastatic non-squamous NSCLC, in combination with nab-paclitaxel and carboplatin

A phase III, open-label, randomised study, GO29537 (IMpower130), was conducted to evaluate the efficacy and safety of atezolizumab in combination with nab-paclitaxel and carboplatin, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. Patients with EGFR mutations or ALK rearrangements should have been previously treated with tyrosine kinase inhibitors.

Patients were staged according to the American Joint Committee on Cancer (AJCC) 7th edition. Patients were excluded if they had a history of autoimmune disease, administration of live, attenuated vaccine within 28 days prior to randomisation, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation, and active or untreated CNS metastases. Patients who had prior treatment with CD137 agonists or immune checkpoint blockade therapies (anti-PD-1, and anti-PD-L1 therapeutic antibodies) were not eligible. However, patients who had prior anti-CTLA-4 treatment could be enrolled, as long as the last dose was received at least 6 weeks prior to randomisation, and there was no history of severe immune-mediated adverse events from anti-CTLA-4 (NCI CTCAE Grades 3 and 4). Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, then every 9 weeks thereafter. Tumour specimens were evaluated for PD-L1 expression on tumour cells (TC) and tumour infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

Patients, including those with EGFR mutations or ALK rearrangements, were enrolled and were randomised in a 2:1 ratio to receive one of the treatment regimens described in Table 11. Randomisation was stratified by sex, presence of liver metastases and PD-L1 expression on TC and IC. Patients receiving treatment regimen B were able to crossover and receive atezolizumab monotherapy following disease progression.

Table 11: Intravenous treatment regimens (IMpower130)

Treatment Regimen	**Induction (Four or six 21-day cycles)**	**Maintenance (21-day cycles)**
A	Atezolizumab (1 200 mg)[a] + nab-paclitaxel (100 mg/m^2)[b,c] + carboplatin (AUC 6)[c]	Atezolizumab (1 200 mg)[a]
B	Nab-paclitaxel (100 mg/m^2)[b,c] + carboplatin (AUC 6)[c]	Best supportive care or pemetrexed

[a] Atezolizumab is administered until loss of clinical benefit as assessed by investigator
[b] Nab-paclitaxel is administered on days 1, 8, and 15 of each cycle
[c] Nab-paclitaxel and carboplatin are administered until completion of 4-6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

The demographics and baseline disease characteristics of the study population defined as ITT-WT (n=679) were well balanced between the treatment arms. The median age was 64 years (range: 18 to 86 years). The majority of the patients were male (59%) and white (90%). Fourteen point seven percent of patients had liver metastases at baseline, and most patients were current or previous smokers (90%). The majority of patients had a baseline ECOG performance status of 1 (59%) and PD-L1 expression < 1% (approximately 52%). Among 107 Arm B patients who had a response status of stable disease, partial response, or complete response after induction therapy, 40 received pemetrexed switch maintenance therapy.

The primary analysis was conducted in all patients, excluding those with EGFR mutations or ALK rearrangements, defined as ITT-WT population (n=679). Patients had a median survival follow up time of 18.6 months and showed improved OS and PFS with atezolizumab, nab-paclitaxel and carboplatin as compared to the control. The key results are summarised in Table 12 and Kaplan-Meier curves for OS and PFS are presented in Figures 8 and 10, respectively. The exploratory results of OS and PFS by PD-L1 expression are summarised in Figures 9 and 11, respectively. Patients with liver metastases did not show improved PFS or OS with atezolizumab, nab-paclitaxel and carboplatin, compared to nab-paclitaxel and carboplatin (HR of 0.93, 95% CI: 0.59, 1.47 for PFS and HR of 1.04, 95% CI: 0.63, 1.72 for OS, respectively).

Fifty-nine percent of patients in the nab-paclitaxel and carboplatin arm received any cancer immunotherapy after disease progression, which includes atezolizumab as crossover treatment (41% of all patients), compared to 7.3% of patients in the atezolizumab, nab paclitaxel and carboplatin arm.

In an exploratory analysis with longer follow up (median: 24.1 months), the median OS for both arms was unchanged relative to the primary analysis, with HR = 0.82 (95% CI: 0.67, 1.01).

Table 12: Summary of efficacy from IMpower130 in the primary analysis (ITT-WT population)

Efficacy endpoints	**Arm A** **Atezolizumab + nab-paclitaxel + carboplatin**	**Arm B** **Nab-paclitaxel + carboplatin**
Co-primary endpoints		
OS	n=451	n=228
No. of deaths (%)	226 (50.1%)	131 (57.5%)
Median time to events (months)	18.6	13.9
95% CI	(16.0, 21.2)	(12.0, 18.7)
Stratified hazard ratio‡ (95% CI)	0.79 (0.64, 0.98)	
p-value	0.033	
12-month OS (%)	63	56
Investigator-assessed PFS (RECIST v1.1)	n=451	n=228
No. of events (%)	347 (76.9%)	198 (86.8%)
Median duration of PFS (months)	7.0	5.5
95% CI	(6.2, 7.3)	(4.4, 5.9)
Stratified hazard ratio‡ (95% CI)	0.64 (0.54, 0.77)	
p-value	< 0.0001	
12-month PFS (%)	29%	14%

Efficacy endpoints	Arm A Atezolizumab + nab-paclitaxel + carboplatin	Arm B Nab-paclitaxel + carboplatin
Other endpoints		
Investigator-assessed ORR (RECIST v1.1)^	n=447	n=226
No. of confirmed responders (%)	220 (49.2%)	72 (31.9%)
95% CI	(44.5, 54.0)	(25.8, 38.4)
No. of complete response (%)	11 (2.5%)	3 (1.3%)
No. of partial response (%)	209 (46.8%)	69 (30.5%)
Investigator-assessed confirmed DOR (RECIST 1.1)^	n=220	n=72
Median in months	8.4	6.1
95% CI	(6.9, 11.8)	(5.5, 7.9)

‡ Stratified by sex and PD-L1 expression on TC and IC
^ Confirmed ORR and DoR are exploratory endpoints
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival

Figure 8: Kaplan-Meier curves for overall survival (IMpower130)

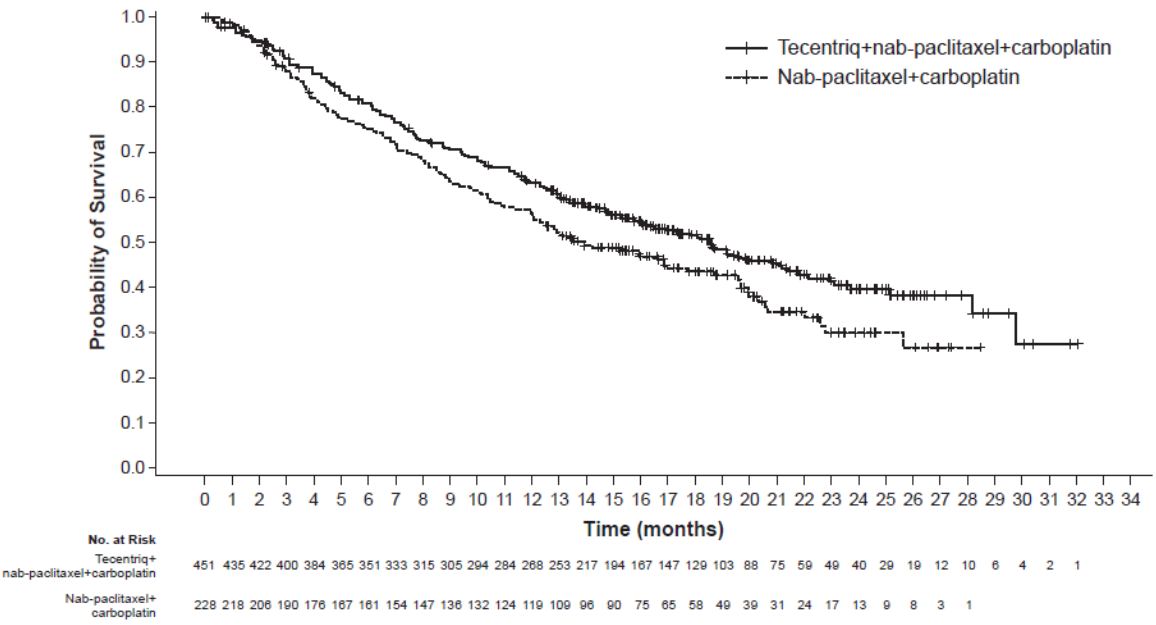


Figure 9: Forest plot of overall survival by PD-L1 expression (IMpower130)

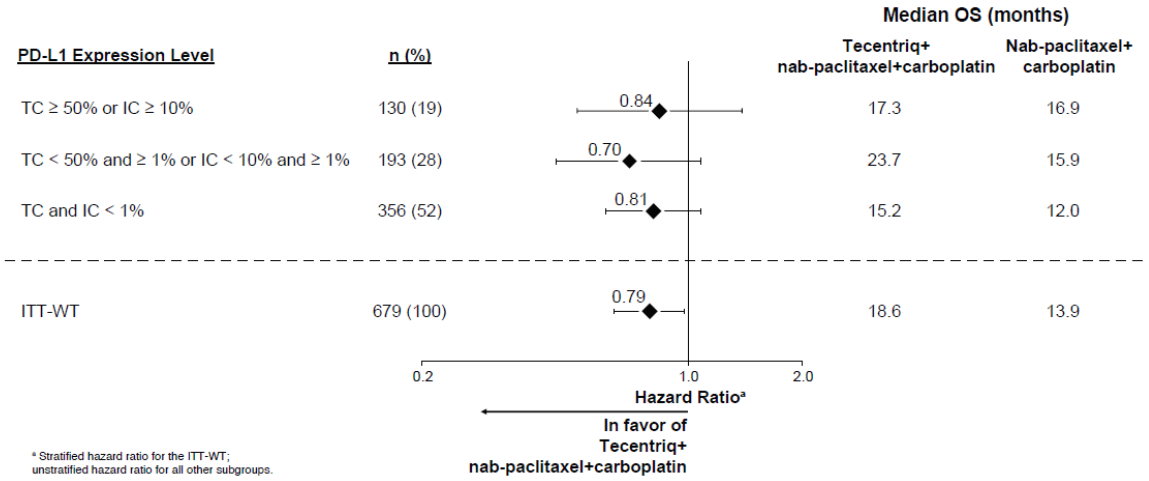


Figure 10: Kaplan-Meier curves for progression free survival (IMpower130)

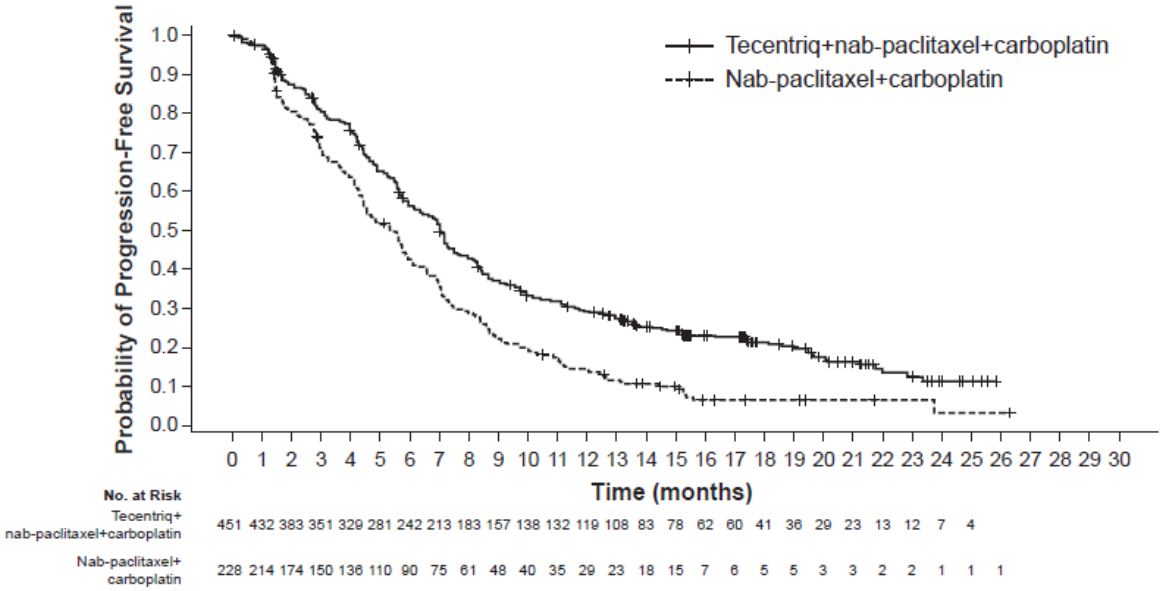
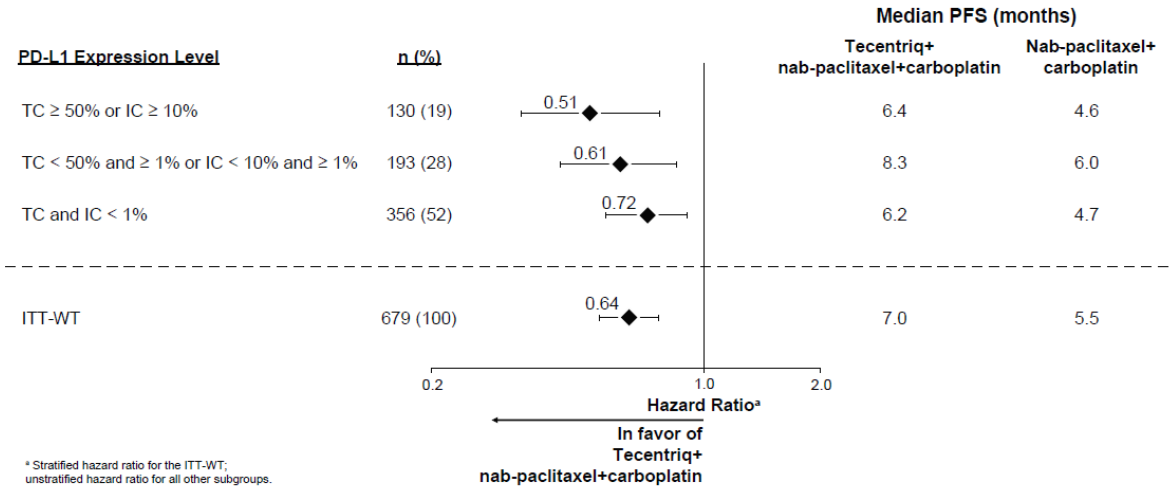


Figure 11: Forest plot of progression free survival by PD-L1 expression (IMpower130)



IMpower110 (GO29431): Randomised phase III trial in chemotherapy-naïve patients with metastatic NSCLC

A phase III, open-label, multi-centre, randomised study, IMpower110, was conducted to evaluate the efficacy and safety of atezolizumab in chemotherapy-naïve patients with metastatic NSCLC. Patients had PD-L1 expression ≥ 1% TC (PD-L1 stained ≥ 1% of tumour cells) or ≥ 1% IC (PD-L1 stained tumour-infiltrating immune cells covering ≥ 1% of the tumour area) based on the VENTANA PD-L1 (SP142) Assay.

A total of 572 patients were randomised in a 1:1 ratio to receive atezolizumab (Arm A) or chemotherapy (Arm B). Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. The chemotherapy regimens are described in Table 13. Randomisation was stratified by sex, ECOG performance status, histology, and PD-L1 tumour expression on TC and IC.

Table 13: Chemotherapy intravenous treatment regimens (IMpower110)

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
B (Non-squamous)	Cisplatin[a] (75 mg/m²) + pemetrexed[a] (500 mg/m²) OR carboplatin[a](AUC 6) + pemetrexed[a] (500 mg/m²)	Pemetrexed[b,d] (500 mg/m²)
B (Squamous)	Cisplatin[a] (75 mg/m²) + gemcitabine[a,c] (1 250 mg/m²) OR carboplatin[a] (AUC 5) + gemcitabine[a,c] (1 000 mg/m²)	Best supportive care[d]

[a] Cisplatin, carboplatin, pemetrexed and gemcitabine are administered until completion of 4 or 6 cycles, or progressive disease, or unacceptable toxicity
[b] Pemetrexed is administered as maintenance regimen every 21 days until progressive disease or unacceptable toxicity
[c] Gemcitabine is administered on days 1 and 8 of each cycle
[d] No crossover was allowed from the control arm (platinum-based chemotherapy) to the atezolizumab arm (Arm A)

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation, active or untreated CNS metastases. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

The demographics and baseline disease characteristics in patients with PD-L1 expression ≥ 1% TC or ≥ 1% IC who do not have EGFR mutations or ALK rearrangements (n=554) were well balanced between the treatment arms. The median age was 64.5 years (range: 30 to 87), and 70% of patients were male. The majority of patients were white (84%) and Asian (14%). Most patients were current or previous smokers (87%) and baseline ECOG performance status in patients was 0 (36%) or 1 (64%). Overall, 69% of patients had non-squamous disease and 31% of patients had squamous disease. The demographics and baseline disease characteristics in patients with high PD-L1 expression (PD-L1 ≥ 50% TC or ≥ 10% IC) who do not have with EGFR mutations or ALK rearrangements (n=205) were generally representative of the broader study population and were balanced between the treatment arms.

The primary endpoint was OS. At the time of the interim OS analysis, patients with high PD-L1 expression excluding those with EGFR mutations or ALK rearrangements (n=205) showed statistically significant improvement in OS for the patients randomised to atezolizumab (Arm A) as compared with chemotherapy (Arm B) (HR of 0.59, 95% CI: 0.40, 0.89; median OS of 20.2 months vs 13.1 months) with a two-sided p-value of 0.0106. The median survival follow-up time in patients with high PD-L1 expression was 15.7 months.

In an exploratory OS analysis with longer follow up (median: 31.3 months) for these patients, the median OS for the atezolizumab arm was unchanged relative to the primary OS interim analysis (20.2 months) and was 14.7 months for the chemotherapy arm (HR of 0.76, 95% CI: 0.54, 1.09). The key results at the exploratory analysis are summarised in Table 14. The Kaplan-Meier curves for OS and PFS in patients with high PD-L1 expression are presented in Figures 12 and 13. A higher proportion of patients experienced death within the first 2.5 months in the atezolizumab arm (16/107, 15.0%) as compared to the chemotherapy arm (10/98, 10.2%). No specific factor(s) associated with early deaths could be identified.

Table 14: Summary of efficacy in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)

Efficacy endpoints	**Arm A** (Atezolizumab)	**Arm B** (Chemotherapy)
Primary endpoint		
Overall survival	n = 107	n = 98
No. of deaths (%)	64 (59.8%)	64 (65.3%)
Median time to events (months)	20.2	14.7
95% CI	(17.2, 27.9)	(7.4, 17.7)
Stratified hazard ratio‡ (95% CI)	0.76 (0.54, 1.09)	
12-month OS (%)	66.1	52.3
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n = 107	n = 98
No. of events (%)	82 (76.6%)	87 (88.8%)
Median duration of PFS (months)	8.2	5.0
95% CI	(6.8, 11.4)	(4.2, 5.7)
Stratified hazard ratio‡ (95% CI)	0.59 (0.43, 0.81)	
12-month PFS (%)	39.2	19.2
Investigator-assessed ORR (RECIST 1.1)	n = 107	n = 98
No. of responders (%)	43 (40.2%)	28 (28.6%)
95% CI	(30.8, 50.1)	(19.9, 38.6)
No. of complete response (%)	1 (0.9%)	2 (2.0%)
No. of partial response (%)	42 (39.3%)	26 (26.5%)
Investigator-assessed DOR (RECIST 1.1)	n = 43	n = 28
Median in months	38.9	8.3
95% CI	(16.1, NE)	(5.6, 11.0)

‡ Stratified by sex and ECOG performance status (0 vs. 1)
PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1; CI = confidence interval; ORR = objective response rate; DOR = duration of response; OS = overall survival; NE = not estimable.

Figure 12: Kaplan-Meier curve for overall survival in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)

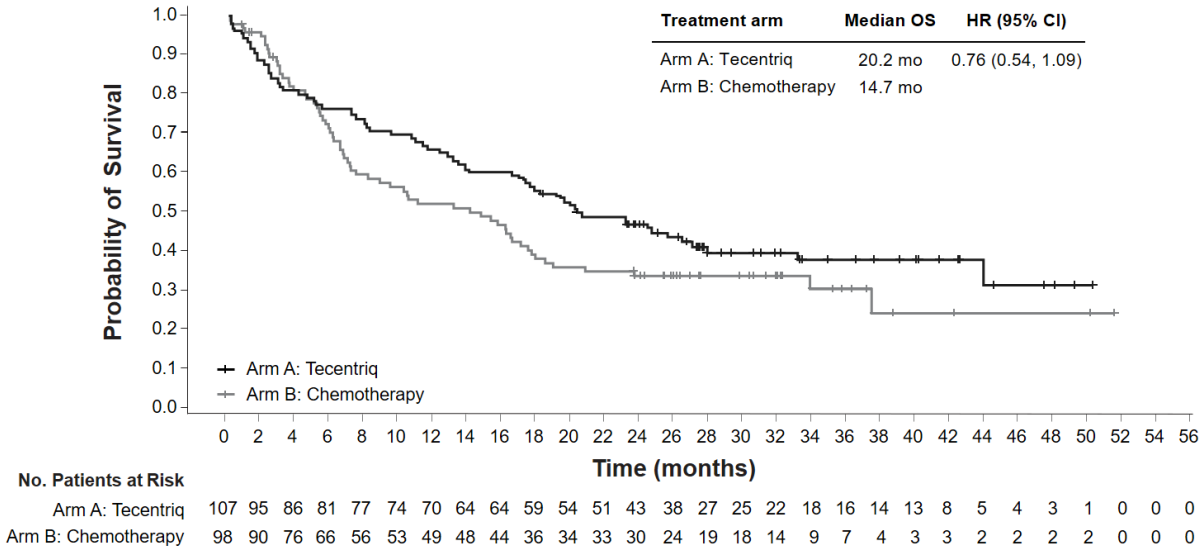
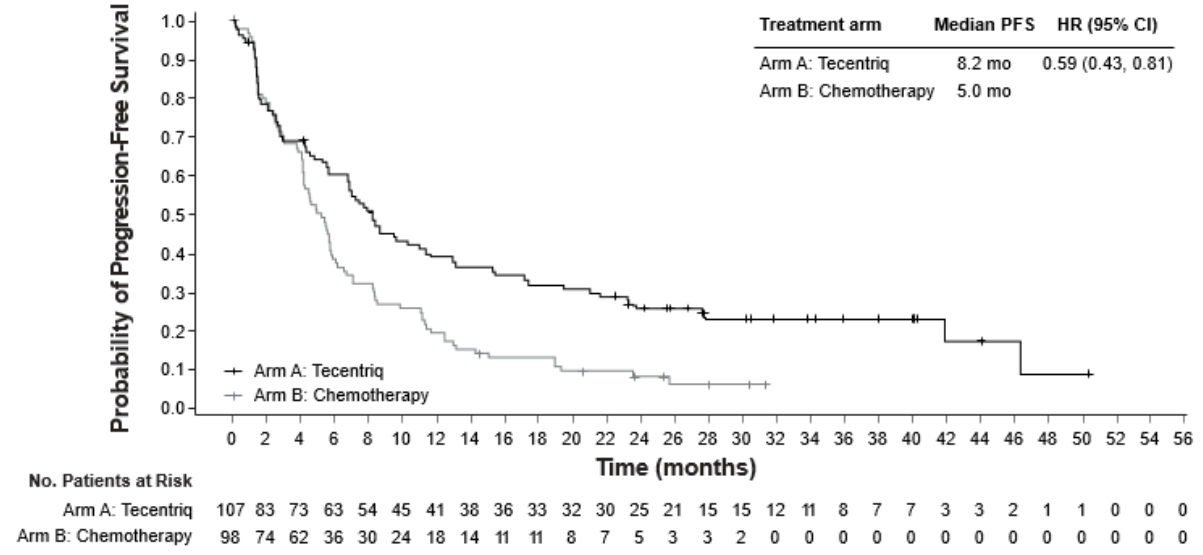


Figure 13: Kaplan-Meier curve for progression free survival in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)



The observed OS improvement in the atezolizumab arm compared with the chemotherapy arm was consistently shown across subgroups in patients with high PD-L1 expression including both non-squamous NSCLC patients (hazard ratio [HR] of 0.62, 95% CI: 0.40, 0.96; median OS 20.2 vs. 10.5 months) and squamous NSCLC patients (HR of 0.56, 95% CI: 0.23, 1.37; median OS not reached vs. 15.3 months). Data for patients ≥ 75 years of age and patients who were never smokers are too limited to draw conclusions in these subgroups.

IPSOS study (MO29872): Randomised phase III trial in patients with treatment-naïve locally advanced unresectable or metastatic NSCLC who are ineligible for platinum-based chemotherapy

A phase III, open label, randomised, controlled study, MO29872 (IPSOS), was conducted to evaluate the efficacy and safety of atezolizumab compared with a single-agent chemotherapy regimen (vinorelbine or gemcitabine by investigator choice) in treatment-naïve patients with advanced or recurrent (Stage IIIB [according to the AJCC 7th edition] not amenable to multimodality treatment) or metastatic (Stage IV) NSCLC who were considered ineligible for platinum-based chemotherapy.

The following selection criteria define patients ineligible for platinum-based chemotherapy who are included in the therapeutic indication: Patients > 80 years of age, or with an ECOG performance status (PS) of 3, or patients with an ECOG PS 2 in combination with relevant comorbidities, or of older age (≥ 70 years) in combination with relevant comorbidities. Relevant comorbidities are related to cardiac disorders, nervous system disorders, psychiatric disorders, vascular disorders, renal disorders, metabolism and nutrition disorders, or pulmonary disorders contraindicating treatment with platinum-based therapy, as assessed by the treating physician.

The study excluded patients younger than 70 years who had an ECOG PS of 0 or 1; patients with active or untreated CNS metastases; administration of live, attenuated vaccine within 4 weeks prior to randomisation; administration of systemic immunostimulatory or systemic immunosuppressive medicinal products within 4 weeks prior to randomisation. Patients with EGFR mutations or ALK rearrangements were also excluded from the study. Patients were eligible regardless of their tumour PD-L1 status.

Patients were randomised in a 2:1 ratio to receive atezolizumab (Arm A) or chemotherapy (Arm B). Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks. The chemotherapy regimens are described in Table 15. Treatment was administered until disease progression per RECIST v1.1 or unacceptable toxicity. Randomisation was stratified by histology (squamous/non-squamous), PD-L1 expression (PD-L1 IHC status as measured by the VENTANA PD-L1 (SP142) assay: TC3 or IC3 vs TC0/1/2 and IC0/1/2 vs unknown) and brain metastases (yes/no).

Table 15: Treatment regimens (IPSOS)

Treatment Regimen	
A	Atezolizumab 1 200 mg by IV infusion on Day 1 of every 21-day cycle.
B	Vinorelbine: IV infusion at 25-30 mg/m^2 or oral administration at 60-80 mg/m^2 on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle or weekly administration or Gemcitabine: IV infusion at 1 000-1 250 mg/m^2 on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle.

A total of 453 patients were enrolled in the study (ITT population). The population predominantly comprised White (65.8%) and male (72.4%) patients. The median age of patients was 75 years and 72.8% of patients were aged 70 years or older. The proportion of patients with ECOG PS of 0, 1, 2 and 3 was 1.5%, 15.0%, 75.9%, and 7.5%, respectively. Overall, 13.7% of patients had stage IIIB disease not amenable to multimodality treatment and 86.3% had stage IV disease. The percentage of patients who had tumours with PD-L1 expression TC< 1%, 1-49% and ≥ 50% as measured by the VENTANA PD-L1 (SP263) assay was 46.8%, 28.7% and 16.6%, respectively, while 7.9% of patients had an unknown PD-L1 expression status.

The primary endpoint of the study was overall survival (OS). At the time of the final OS analysis, the median follow-up was 41.0 months. Efficacy results are presented in Table 16 and Figure 14.

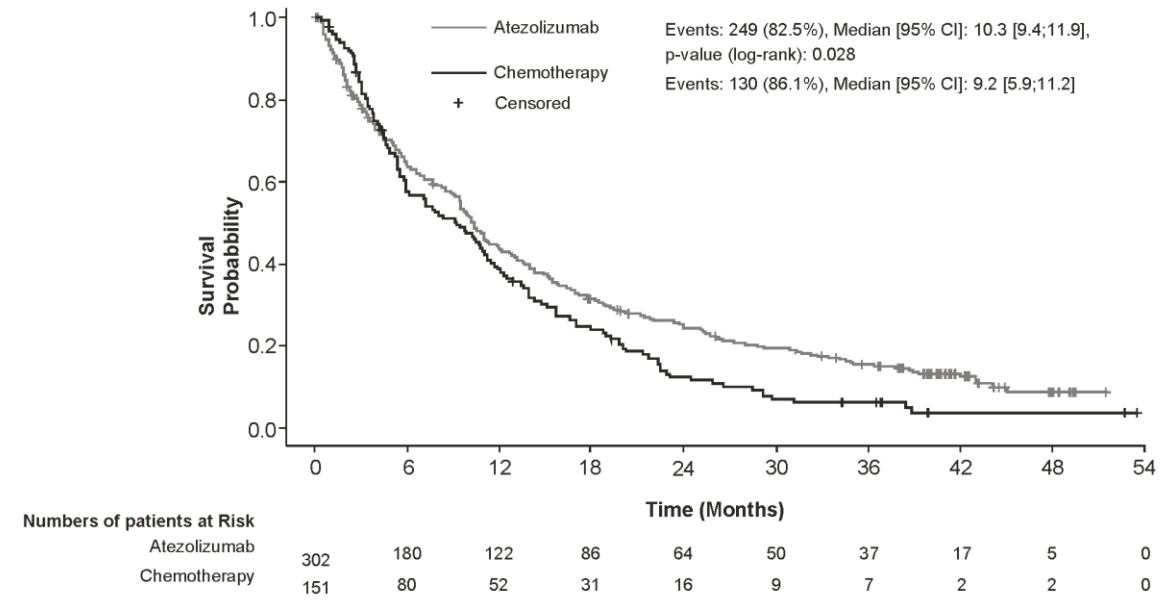
Table 16: Summary of efficacy for NSCLC patients ineligible for platinum-based chemotherapy (IPSOS)

Efficacy endpoint	Atezolizumab (n = 302)	Chemotherapy (n = 151)
Primary endpoint		
OS		
No. of events (%)	249 (82.5%)	130 (86.1%)
Median time to events (months) (95% CI)	10.3 (9.4, 11.9)	9.2 (5.9, 11.2)
Stratified hazard ratio (95% CI) ǂ	0.78 (0.63, 0.97)	
p-value (Stratified Log-rank)	p = 0.028	
Secondary endpoints		
Investigator-assessed PFS (RECIST 1.1)		
No. of events (%)	276 (91.4%)	138 (91.4%)
Median duration of PFS (months) (95% CI)	4.2 (3.7, 5.5)	4.0 (2.9, 5.4)
Stratified hazard ratio (95% CI) ǂ	0.87 (0.70, 1.07)	
ORR (RECIST 1.1)		
No. of confirmed responders (%)	51 (16.9%)	12 (7.9%)
DOR (RECIST 1.1)		
Median in months (95% CI)	14.0 (8.1, 20.3)	7.8 (4.8, 9.7)

CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

ǂ Estimated hazard ratio and 95% CI obtained from Cox model with treatment group as covariate. For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (yes/no) were added as stratification factors.

Figure 14: Kaplan-Meier curves for overall survival for NSCLC patients ineligible for platinum-based chemotherapy (IPSOS)



Second-line treatment of NSCLC

Subcutaneous formulation

IMscin001 (BP40657): Randomised phase Ib/III trial in locally advanced or metastatic NSCLC patients previously treated with platinum-containing chemotherapy

A phase Ib/III, open-label, multi-centre, international, randomised study, BP40657 (IMscin001), was conducted to evaluate the pharmacokinetics, efficacy and safety of subcutaneous Tecentriq compared with intravenous atezolizumab in patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy (CIT) and for whom prior platinum-based therapy has failed. IMscin001 was designed to demonstrate non-inferiority of the atezolizumab cycle 1 (pre-dose Cycle 2) serum C_{trough} and model-predicted AUC from 0 to 21 days at cycle 1 of subcutaneous atezolizumab compared with intravenous atezolizumab (co-primary endpoint). Secondary endpoints included efficacy [PFS, ORR, OS, DOR], and safety.

In Part 2 (Phase III), a total of 371 patients were enrolled and randomised 2:1 to receive either 1 875 mg of subcutaneous Tecentriq Q3W or 1 200 mg of intravenous atezolizumab Q3W. No dose reduction was allowed.

Patients were excluded if they had a history of autoimmune disease; active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 4 weeks prior to randomisation; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomisation.

The median age was 64 years (range: 27 to 85), and 69% of patients were male. The majority of patients were white (67%). Approximately two-third of patients (65%) had non-squamous disease, 5% had known EGFR mutation, 2% had known ALK rearrangements, 40% were PD-L1 positive (TC≥1% and/or IC≥1%), 16% had non-active CNS metastases at baseline, 26% had an ECOG PS of 0, 74% had an ECOG PS of 1, and most patients were current or previous smokers (70%). 80% received one prior therapeutic regimen.

At the time of primary analysis, the median survival follow-up was 4.7 months and OS results were immature. There were 86 (35%) deaths in the subcutaneous Tecentriq arm and 37 (30%) deaths in the

intravenous atezolizumab arm. A post hoc updated analysis was performed 9 months after the primary analysis with a median survival duration of follow-up of 9.5 months. The efficacy results of the updated analyses are summarized in Table 17 below.

Table 17: Summary of updated efficacy analyses (IMscin001)

Efficacy endpoint	**Subcutaneous Tecentriq**	**Intravenous Tecentriq**
Investigator-assessed ORR (RECIST v1.1)*	n = 245	n = 124
No. of confirmed responders (%)	27 (11.0%)	13 (10.5%)
95% CI	(7.39, 15.63)	(5.70, 17.26)
Investigator-assessed PFS (RECIST v1.1)*	n = 247	n = 124
No. of events (%)	219 (88.7%)	107 (86.3%)
Median (months) (95% CI)	2.8 (2.7, 4.1)	2.9 (1.8, 4.2)
OS*	n = 247	n = 124
No. of events (%)	144 (58.3%)	79 (63.7%)
Median (months) (95% CI)	10.7 (8.5, 13.8)	10.1 (7.5, 12.1)

CI = confidence interval; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors v1.1
* descriptive analyses

Intravenous formulation

OAK (GO28915): Randomised phase III trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy

A phase III, open-label, multi-centre, international, randomised study, OAK, was conducted to evaluate the efficacy and safety of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrolment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC).

A total of 1 225 patients were enrolled and per the analysis plan the first 850 randomised patients were included in the primary efficacy analysis. Randomisation was stratified by PD-L1 expression status on IC, by the number of prior chemotherapy regimens, and by histology. Patients were randomised (1:1) to receive either atezolizumab or docetaxel.

Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator. Docetaxel was administered 75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression. For all treated patients, the median duration of treatment was 2.1 months for the docetaxel arm and 3.4 months for the atezolizumab arm.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-quarters of patients had non-squamous histology (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had CNS metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy-five percent of patients received only one prior platinum-based therapeutic regimen.

The primary efficacy endpoint was OS. The key results of this study with a median survival follow-up of 21 months are summarised in Table 18. Kaplan-Meier curves for OS in the ITT population are presented in Figure 15. Figure 16 summarises the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with atezolizumab in all subgroups, including those with PD-L1 expression < 1% in TC and IC.

Table 18: Summary of efficacy in the primary analysis population (all comers)* (OAK)

Efficacy endpoint	**Atezolizumab (n = 425)**	**Docetaxel (n = 425)**
Primary efficacy endpoint		
OS		
No. of deaths (%)	271 (64%)	298 (70%)
Median time to events (months)	13.8	9.6
95% CI	(11.8, 15.7)	(8.6, 11.2)
Stratified‡ hazard ratio (95% CI)	0.73 (0.62, 0.87)	
p-value**	0.0003	
12-month OS (%)***	218 (55%)	151 (41%)
18-month OS (%)***	157 (40%)	98 (27%)
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)		
No. of events (%)	380 (89%)	375 (88%)
Median duration of PFS (months)	2.8	4.0
95% CI	(2.6, 3.0)	(3.3, 4.2)
Stratified hazard ratio (95% CI)	0.95 (0.82, 1.10)	
Investigator-assessed ORR (RECIST v1.1)		
No. of responders (%)	58 (14%)	57 (13%)
95% CI	(10.5, 17.3)	(10.3, 17.0)
Investigator-assessed DOR (RECIST v1.1)	n = 58	n = 57
Median in months	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

* The primary analysis population consists of the first 850 randomised patients

‡ Stratified by PD-L1 expression in tumour infiltrating immune cells, the number of prior chemotherapy regimens, and histology

** Based on the stratified log-rank test

*** Based on Kaplan-Meier estimates

Figure 15: Kaplan-Meier curve for overall survival in the primary analysis population (all comers) (OAK)

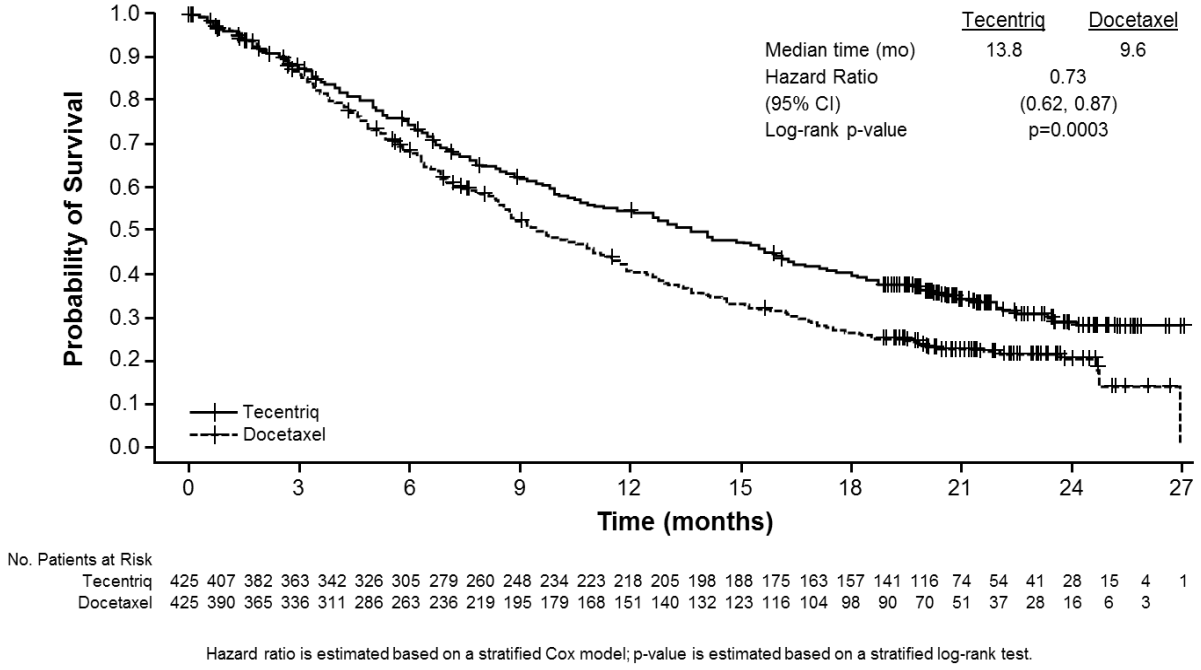
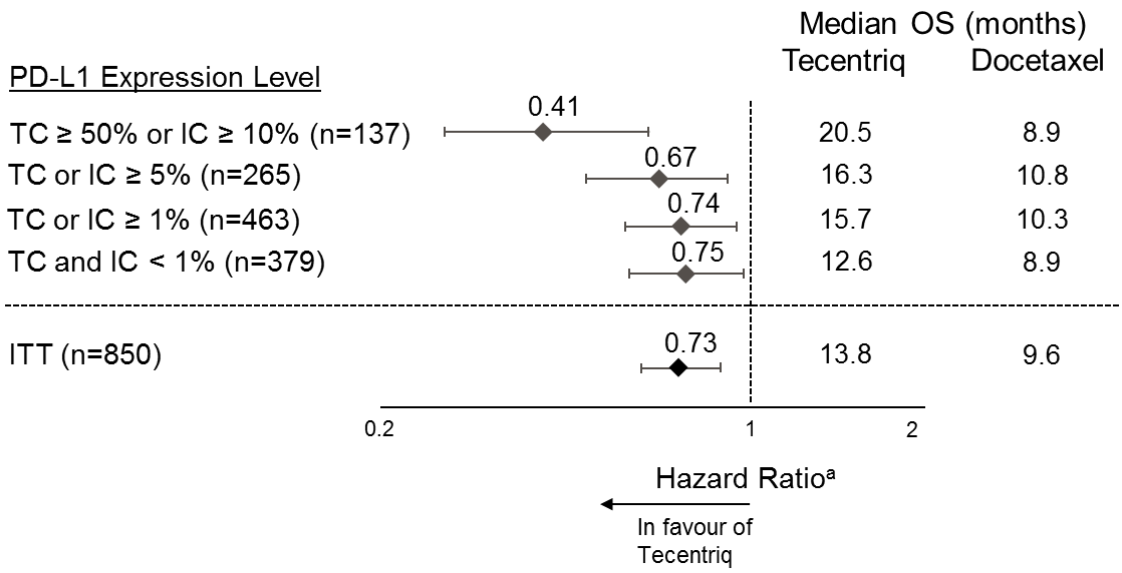


Figure 16: Forest plot of overall survival by PD-L1 expression in the primary analysis population (OAK)



[a] Stratified HR for ITT and TC or IC ≥ 1%. Unstratified HR for other exploratory subgroups.

An improvement in OS was observed with atezolizumab compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for atezolizumab and docetaxel, respectively) and squamous NSCLC patients (HR of 0.73, 95% CI: 0.54, 0.98; median OS of 8.9 vs. 7.7 months for atezolizumab and docetaxel, respectively). The observed OS improvement was consistently demonstrated across subgroups of patients including those with brain metastases at baseline (HR of 0.54, 95% CI: 0.31, 0.94; median OS of 20.1 vs. 11.9 months for atezolizumab and docetaxel respectively) and patients who were never smokers (HR of 0.71, 95% CI: 0.47, 1.08; median OS of 16.3 vs. 12.6 months for atezolizumab and docetaxel, respectively). However, patients with EGFR mutations did not show improved OS with atezolizumab

compared to docetaxel (HR of 1.24, 95% CI: 0.71, 2.18; median OS of 10.5 vs. 16.2 months for atezolizumab and docetaxel, respectively).

Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with atezolizumab compared to docetaxel (HR of 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ-LC13 was similar between atezolizumab and docetaxel. These results should be interpreted with caution due to the open-label design of the study.

POPLAR (GO28753): Randomised phase II trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy

A phase II, multi-centre, international, randomised, open-label, controlled study, POPLAR, was conducted in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression. The primary efficacy outcome was overall survival. A total of 287 patients were randomised 1:1 to receive either atezolizumab (1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit) or docetaxel (75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression). Randomisation was stratified by PD-L1 expression status on IC, by the number of prior chemotherapy regimens and by histology. An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with atezolizumab, vs. 9.7 months in patients treated with docetaxel (HR of 0.69, 95% CI: 0.52, 0.92). ORR was 15.3% vs. 14.7% and median DOR was 18.6 months vs. 7.2 months for atezolizumab vs. docetaxel, respectively.

Small cell lung cancer

Intravenous formulation

IMpower133 (GO30081): Randomised phase I/III trial in patients with chemotherapy-naïve extensive-stage SCLC, in combination with carboplatin and etoposide

A Phase I/III, randomised, multicentre, double-blind, placebo-controlled study, IMpower133, was conducted to evaluate the efficacy and safety of atezolizumab in combination with carboplatin and etoposide in patients with chemotherapy-naïve ES-SCLC.

Patients were excluded if they had active or untreated CNS metastases; history of autoimmune disease; administration of live, attenuated vaccine within 4 weeks prior to randomisation; administration of systemic immunosuppressive medicinal products within 1 week prior to randomisation. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients who met established criteria and who agreed to be treated beyond disease progression had tumour assessments conducted every 6 weeks until treatment discontinuation.

A total of 403 patients were enrolled and randomised (1:1) to receive one of the treatment regimens described in Table 19. Randomisation was stratified by sex, ECOG performance status, and presence of brain metastases.

Table 19: Intravenous treatment regimens (IMpower133)

Treatment regimen	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	atezolizumab (1 200 mg)[a] + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	atezolizumab (1 200 mg) [a]
B	placebo + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	placebo

[a] Atezolizumab was administered until loss of clinical benefit as assessed by investigator
[b] Carboplatin and etoposide were administered until completion of 4 cycles, or progressive disease or unacceptable toxicity, whichever occurs first
[c] Etoposide was administered on day 1, 2 and 3 of each cycle

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 64 years (range: 26 to 90 years) with 10% of patients ≥ 75 years of age. The majority of patients were male (65%), white (80%), and 9% had brain metastases and most patients were current or previous smokers (97%). Baseline ECOG performance status was 0 (35%) or 1 (65%).

At the time of the primary analysis, patients had a median survival follow up time of 13.9 months. A statistically significant improvement in OS was observed with atezolizumab in combination with carboplatin and etoposide compared to the control arm (HR of 0.70, 95% CI: 0.54, 0.91; median OS of 12.3 months vs. 10.3 months). In the exploratory OS final analysis with longer follow up (median: 22.9 months), the median OS for both arms was unchanged relative to the primary OS interim analysis. The PFS, ORR and DOR results from the primary analysis as well as the exploratory OS final analysis results are summarised in Table 20. Kaplan-Meier curves for OS and PFS are presented in Figures 17 and 18. Data for patients with brain metastases are too limited to draw conclusions on this population.

Table 20: Summary of efficacy (IMpower133)

Key efficacy endpoints	Arm A (Atezolizumab + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)
Co-primary endpoints		
OS analysis*	n = 201	n = 202
No. of deaths (%)	142 (70.6%)	160 (79.2%)
Median time to events (months)	12.3	10.3
95% CI	(10.8, 15.8)	(9.3, 11.3)
Stratified hazard ratio‡ (95% CI)	0.76 (0.60, 0.95)	
p-value	0.0154***	
12-month OS (%)	51.9	39.0
Investigator-assessed PFS (RECIST v1.1) **	n = 201	n = 202
No. of events (%)	171 (85.1%)	189 (93.6%)
Median duration of PFS (months)	5.2	4.3
95% CI	(4.4, 5.6)	(4.2, 4.5)
Stratified hazard ratio‡ (95% CI)	0.77 (0.62, 0.96)	
p-value	0.0170	
6-month PFS (%)	30.9	22.4
12-month PFS (%)	12.6	5.4

Key efficacy endpoints	Arm A (Atezolizumab + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)
Co-primary endpoints		
Other endpoints		
Investigator-assessed ORR (RECIST 1.1)* ^	n = 201	n = 202
No. of responders (%)	121 (60.2%)	130 (64.4%)
95% CI	(53.1, 67.0)	(57.3, 71.0)
No. of complete response (%)	5 (2.5%)	2 (1.0%)
No. of partial response (%)	116 (57.7%)	128 (63.4%)
Investigator-assessed DOR (RECIST 1.1)* ^	n =121	n = 130
Median in months	4.2	3.9
95% CI	(4.1, 4.5)	(3.1, 4.2)

PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.; CI = confidence interval; ORR = objective response rate; DOR = duration of response; OS = overall survival

‡ Stratified by sex and ECOG performance status

* Exploratory OS final analysis at clinical cut-off 24 January 2019

** PFS, ORR and DOR analyses at clinical cut-off 24 April 2018

*** For descriptive purposes only

^ Confirmed ORR and DoR are exploratory endpoints

Figure 17: Kaplan-Meier curve for overall survival (IMpower133)

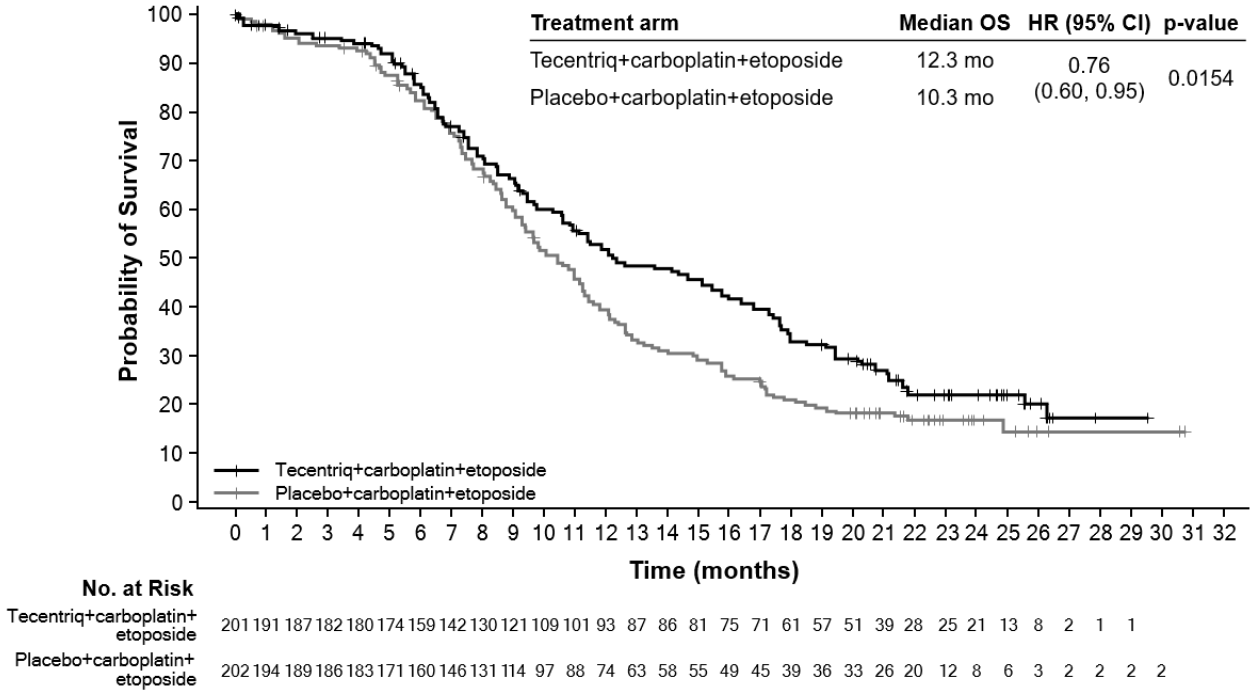
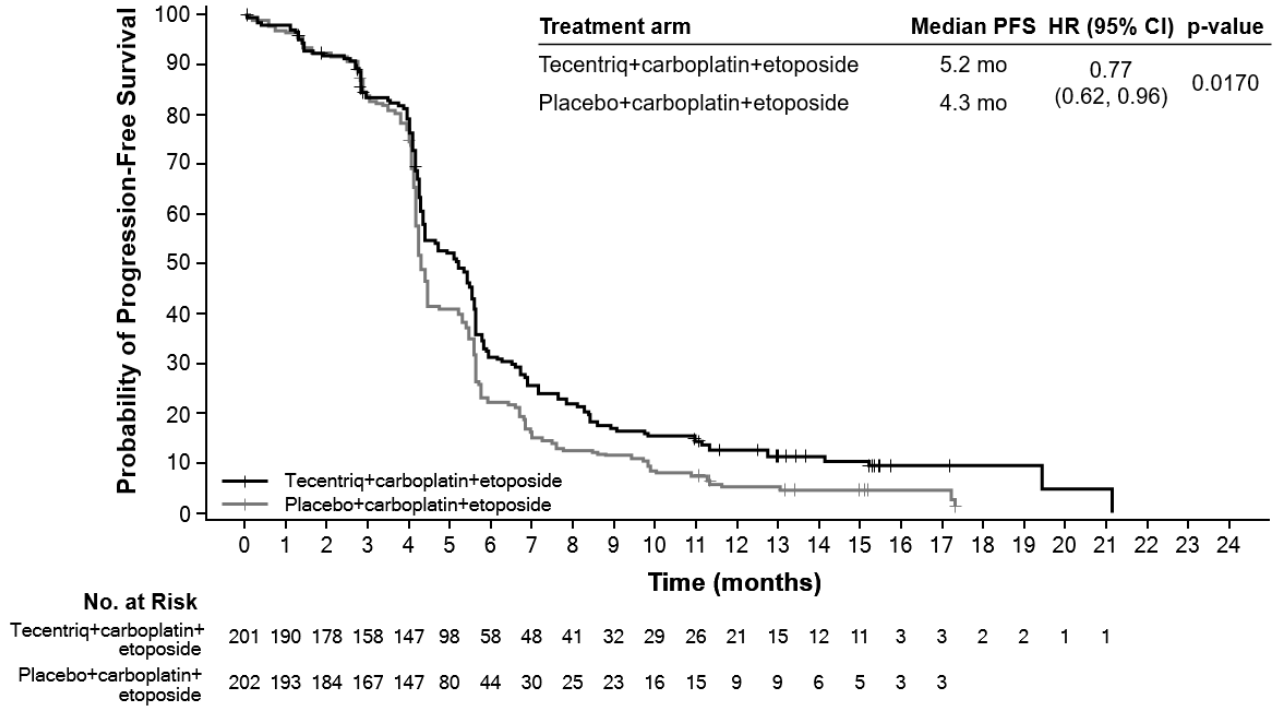


Figure 18: Kaplan-Meier curve for progression-free survival (IMpower133)



Triple-negative breast cancer

Intravenous formulation

IMpassion130 (WO29522): Randomised phase III trial in locally advanced or metastatic TNBC patients previously untreated for metastatic disease

A phase III, double-blind, two-arm, multi-centre, international, randomised, placebo-controlled study, IMpassion130, was conducted to evaluate the efficacy and safety of atezolizumab in combination with nab-paclitaxel, in patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. Patients had to be eligible for taxane monotherapy (i.e. absence of rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control) and were excluded if they had received prior chemotherapy in the neoadjuvant or adjuvant setting within the last 12 months, a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation; untreated, symptomatic or corticosteroid-dependent brain metastases. Tumour assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter.

A total of 902 patients were enrolled and stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumour-infiltrating immune cells (IC) (PD-L1 stained tumour-infiltrating immune cells [IC] < 1% of tumour area vs. ≥ 1% of the tumour area) assessed by the VENTANA PD-L1 (SP142) Assay.

Patients were randomised to receive atezolizumab 840 mg or placebo by intravenous infusions on days 1 and 15 of every 28-day cycle, plus nab-paclitaxel (100 mg/m^2) administered via intravenous infusion on days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. Treatment with atezolizumab could be continued when nab-paclitaxel was stopped due to unacceptable toxicity. The median number of treatment cycles was 7 for atezolizumab and 6 for nab-paclitaxel in each treatment arm.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Most patients were women (99.6%), 67.5% were white and 17.8% Asian. The median age was 55 years (range: 20-86). Baseline ECOG performance status was 0 (58.4%) or 1 (41.3%). Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% asymptomatic brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumour disease in patients with PD-L1 expression ≥ 1% were generally representative of the broader study population.

The co-primary efficacy endpoints included investigator-assessed progression free survival (PFS) in the ITT population and in patients with PD-L1 expression ≥ 1% per RECIST v1.1 as well as overall survival (OS) in the ITT population and in patients with PD-L1 expression ≥ 1%. Secondary efficacy endpoints included objective response rate (ORR) and duration of response (DOR) per RECIST v1.1.

PFS, ORR and DOR results of IMpassion130 for patients with PD-L1 expression ≥ 1% at the time of the final analysis for PFS with a median survival follow up of 13 months are summarised in Table 21with Kaplan-Meier curves for PFS in Figure 19. Patients with PD-L1 expression < 1% did not show improved PFS when atezolizumab was added to nab-paclitaxel (HR of 0.94, 95% CI 0.78, 1.13).

The final OS analysis was performed in patients with PD-L1 expression ≥ 1% with a median follow up of 19.12 months. OS results are presented in Table 21 and Kaplan-Meier curves in Figure 20. Patients with PD-L1 expression < 1% did not show improved OS when atezolizumab was added to nab-paclitaxel (HR of 1.02, 95% CI 0.84, 1.24).

Exploratory subgroup analyses were performed in patients with PD-L1 expression ≥ 1%, exploring prior (neo)adjuvant treatment, BRCA1/2 mutation and asymptomatic brain metastases at baseline.

In patients who had received prior (neo) adjuvant treatment (n = 242), the hazard ratio for primary (final) PFS was 0.79 and 0.77 for final OS while in patients who had not received prior (neo)adjuvant treatment (n = 127), the hazard ratio for primary (final) PFS was 0.44 and 0.54 for final OS.

In the IMpassion130 study, of the 614 patients tested, 89 (15%) carried pathogenic BRCA1/2 mutations. From the PD-L1+/BRCA1/2 mutant subgroup, 19 patients received atezolizumab plus nab-paclitaxel and 26 placebo plus nab-paclitaxel. Based on exploratory analysis and acknowledging the small sample size, the presence of BRCA1/2 mutation does not seem to impact the PFS clinical benefit of atezolizumab and nab-paclitaxel.

There was no evidence of efficacy in patients with asymptomatic brain metastases at baseline, although the number of patients treated was small; the median PFS was 2.2 months in the atezolizumab plus nab-paclitaxel arm (n = 15) compared to 5.6 months in the placebo plus nab-paclitaxel arm (n = 11) (HR 1.40; 95% CI 0.57, 3.44).

Table 21: Summary of efficacy in patients with PD-L1 expression ≥ 1% (IMpassion130)

Key efficacy endpoints	**Atezolizumab + nab-paclitaxel**	**Placebo + nab-paclitaxel**
Primary efficacy endpoints	n = 185	n = 184
Investigator-assessed PFS (RECIST v1.1) – Primary analysis[3]		
No. of events (%)	138 (74.6%)	157 (85.3%)
Median duration of PFS (months)	7.5	5.0
95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.62 (0.49, 0.78)	
p-value[1]	<0.0001	

Key efficacy endpoints	Atezolizumab + nab-paclitaxel	Placebo + nab-paclitaxel
12-month PFS (%)	29.1	16.4
Investigator-assessed PFS (RECIST v1.1) – Updated exploratory analysis[4]		
No. of events (%)	149 (80.5%)	163 (88.6%)
Median duration of PFS (months)	7.5	5.3
95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.63 (0.50-0.80)	
p-value[1]	<0.0001	
12-month PFS (%)	30.3	17.3
OS [1,2,5]		
No. of deaths (%)	120 (64.9%)	139 (75.5%)
Median time to events (months)	25.4	17.9
95% CI	(19.6, 30.7)	(13.6, 20.3)
Stratified hazard ratio‡ (95% CI)	0.67 (0.53, 0.86)	
Secondary and exploratory endpoints		
Investigator-assessed ORR (RECIST 1.1)[3]	n=185	n=183
No. of responders (%)	109 (58.9%)	78 (42.6%)
95% CI	(51.5, 66.1)	(35.4, 50.1)
No. of complete response (%)	19 (10.3%)	2 (1.1%)
No. of partial response (%)	90 (48.6%)	76 (41.5%)
No. of stable disease	38 (20.5%)	49 (26.8%)
Investigator-assessed DOR[3]	n=109	n=78
Median in months	8.5	5.5
95% CI	(7.3, 9.7)	(3.7, 7.1)

1. Based on the stratified log-rank test.
2. OS comparisons between treatment arms in patients with PD-L1 expression ≥1% were not formally tested, as per the pre-specified analysis hierarchy.
3. Per final analysis for PFS, ORR, DOR and first interim analysis for OS at clinical cut off 17th April 2018
4. Per exploratory PFS analysis at clinical cut off January 2nd 2019
5. Per final analysis for OS at clinical cut off April 14th 2020

‡ Stratified by presence of liver metastases, and by prior taxane treatment.

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival, NE=not estimable

Figure 19: Kaplan-Meier curve for progression free survival in patients with PD-L1 expression ≥ 1% (IMpassion130)

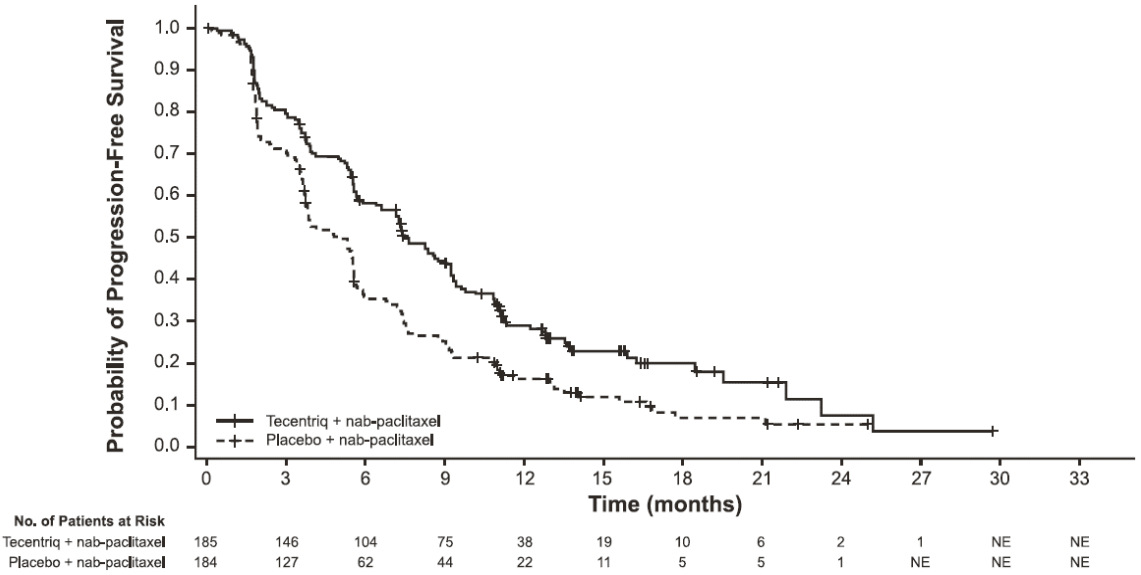
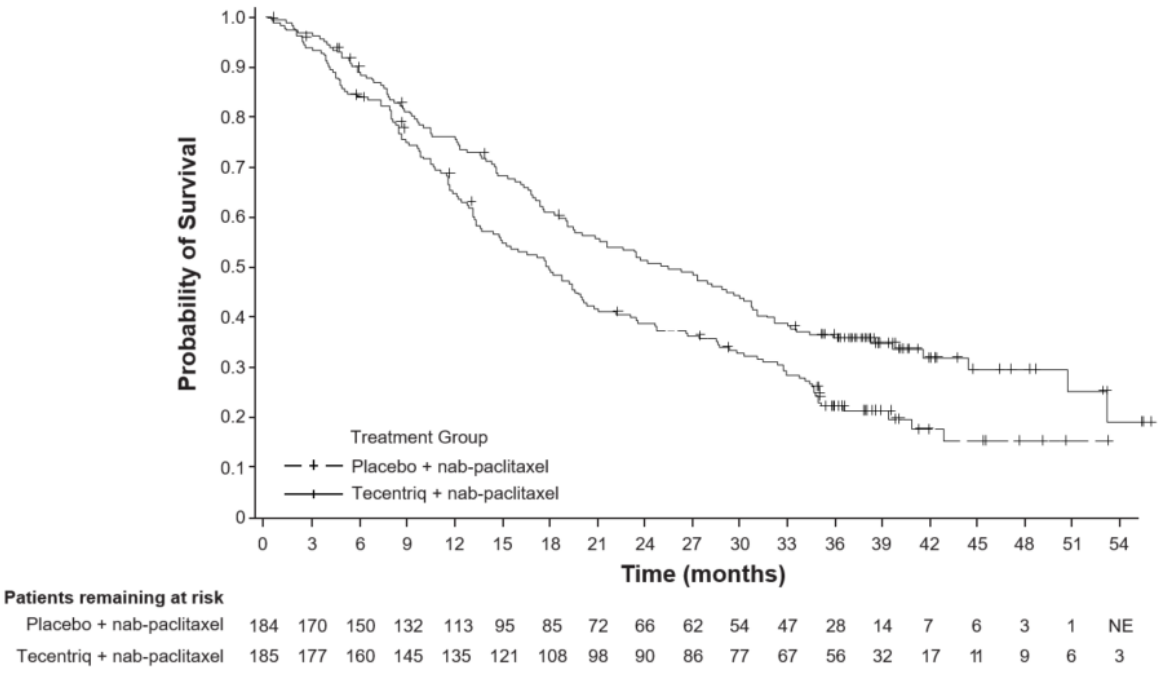


Figure 20: Kaplan-Meier curve for overall survival in patients with PD-L1 expression ≥ 1% (IMpassion130)



The time to deterioration (a sustained ≥ 10-point decline from baseline score) of patient-reported global health status/health-related quality of life as measured by the EORTC QLQ-C30 was similar in each treatment group indicating that all patients maintained their baseline HRQoL for a comparable duration of time.

Hepatocellular carcinoma

Intravenous formulation

IMbrave150 (YO40245): Randomised phase III trial in patients with unresectable HCC who have not received prior systemic therapy, in combination with bevacizumab

A phase III, randomised, multi-centre, international, open-label study, IMbrave150, was conducted to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab, in patients with locally advanced or metastatic and/or unresectable HCC, who have not received prior systemic treatment. A total of 501 patients were randomised (2:1) to receive either atezolizumab (1 200 mg) and 15 mg/kg bw of bevacizumab every 3 weeks administered by intravenous infusion, or sorafenib 400 mg orally twice per day. Randomisation was stratified by geographic region, macrovascular invasion and/or extrahepatic spread, baseline α-fetoprotein (AFP) and ECOG performance status. Patients in both arms received treatment until loss of clinical benefit, or unacceptable toxicity. Patients could discontinue either atezolizumab or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until loss of clinical benefit or unacceptable toxicity associated with the single-agent.

The study enrolled adults whose disease was not amenable to or progressed after surgical and/or locoregional therapies, were Child-Pugh A, ECOG 0/1, and who had not received prior systemic treatment. Bleeding (including fatal events) is a known adverse reaction with bevacizumab and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC. Hence, patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding or high risk of bleeding. For patients with active hepatitis B, HBV DNA < 500 IU/mL was required within 28 days prior to initiation of study treatment, and standard anti-HBV treatment for a minimum of 14 days prior to study entry and for the length of study.

Patients were also excluded if they had moderate or severe ascites; history of hepatic encephalopathy; known fibrolamellar HCC; sarcomatoid HCC, mixed cholangiocarcinoma and HCC; active co-infection of HBV and HCV; history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomisation; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation; untreated or corticosteroid-dependent brain metastases. Tumour assessments were performed every 6 weeks for the first 54 weeks following Cycle 1, Day 1, then every 9 weeks thereafter.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 65 years (range: 26 to 88 years) and 83% were male. The majority of patients were Asian (57%) and white (35%). 40% were from Asia (excluding Japan), while 60% were from rest of world. Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥ 400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). The primary risk factors for the development of HCC were Hepatitis B virus infection in 48% of patients, Hepatitis C virus infection in 22% of patients, and non-viral disease in 31% of patients. HCC was categorized as Barcelona Clinic Liver Cancer (BCLC) stage C in 82% of patients, stage B in 16% of patients, and stage A in 3% of patients.

The co-primary efficacy endpoints were OS and IRF-assessed PFS according to RECIST v1.1. At the time of the primary analysis, patients had a median survival follow up time of 8.6 months. The data demonstrated a statistically significant improvement in OS and PFS as assessed by IRF per RECIST v1.1 with atezolizumab + bevacizumab compared to sorafenib. A statistically significant improvement was also observed in confirmed objective response rate (ORR) by IRF per RECIST v1.1 and HCC modified RECIST (mRECIST). The key efficacy results from the primary analysis are summarized in Table 22.

A descriptive updated efficacy analysis was performed with a median survival follow up time of 15.6 months. The median OS was 19.2 months (95% CI: 17.0, 23.7) in the atezolizumab + bevacizumab arm versus 13.4 months (95% CI: 11.4, 16.9) in the sorafenib arm with a HR of 0.66 (95% CI: 0.52, 0.85). The median PFS by IRF-assessment per RECIST v1.1 was 6.9 months (95% CI: 5.8, 8.6) in the atezolizumab + bevacizumab arm versus 4.3 months (95% CI: 4.0, 5.6) in the sorafenib arm with a HR of 0.65 (95% CI: 0.53, 0.81).

The IRF-assessed ORR per RECIST v1.1 was 29.8% (95% CI: 24.8, 35.0) in the atezolizumab + bevacizumab arm and 11.3% (95% CI: 6.9, 17.3) in the sorafenib arm. The median duration of response (DOR) by IRF-assessment per RECIST v1.1 in confirmed responders was 18.1 months (95% CI: 14.6, NE) in the atezolizumab + bevacizumab arm compared to 14.9 months (95% CI: 4.9, 17.0) in the sorafenib arm.

Kaplan-Meier curves for OS (updated analysis) and PFS (primary analysis) are presented in Figures 21 and 22, respectively.

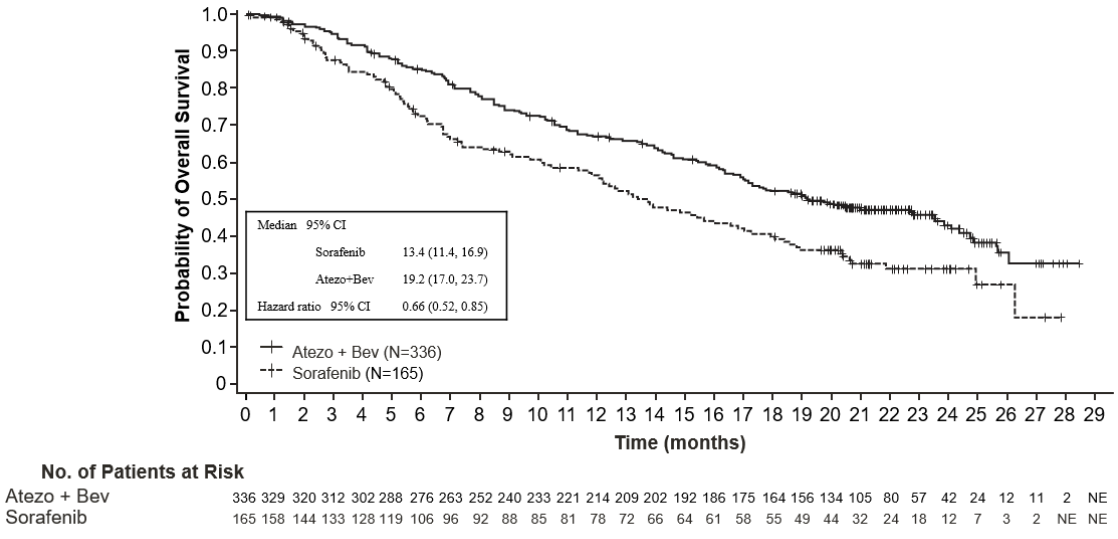
Table 22: Summary of efficacy (IMbrave150 primary analysis)

Key efficacy endpoints	**Atezolizumab + Bevacizumab**		**Sorafenib**
OS	n = 336		n = 165
No. of deaths (%)	96 (28.6%)		65 (39.4%)
Median time to event (months)	NE		13.2
95% CI	(NE, NE)		(10.4, NE)
Stratified hazard ratio‡ (95% CI)		0.58 (0.42, 0.79)	
p-value[1]		0.0006	
6-month OS (%)	84.8%		72.3%
IRF-assessed PFS, RECIST 1.1	n = 336		n = 165
No. of events (%)	197 (58.6%)		109 (66.1%)
Median duration of PFS (months)	6.8		4.3
95% CI	(5.8, 8.3)		(4.0, 5.6)
Stratified hazard ratio‡ (95% CI)		0.59 (0.47, 0.76)	
p-value[1]		<0.0001	
6-month PFS	54.5%		37.2%
IRF-assessed ORR, RECIST 1.1	n = 326		n = 159
No. of confirmed responders (%)	89 (27.3%)		19 (11.9%)
95% CI	(22.5, 32.5)		(7.4, 18.0)
p-value[2]		<0.0001	
No. of complete responses (%)	18 (5.5%)		0
No. of partial responses (%)	71 (21.8%)		19 (11.9%)
No. of stable disease (%)	151 (46.3%)		69 (43.4%)
IRF-assessed DOR, RECIST 1.1	n = 89		n = 19
Median in months	NE		6.3
95% CI	(NE, NE)		(4.7, NE)
Range (months)	(1.3+, 13.4+)		(1.4+, 9.1+)

Key efficacy endpoints	Atezolizumab + Bevacizumab		Sorafenib
IRF-assessed ORR, HCC mRECIST	n = 325		n = 158
No. of confirmed responders (%)	108 (33.2%)		21 (13.3%)
95% CI	(28.1, 38.6)		(8.4, 19.6)
p-value[2]		<0.0001	
No. of complete responses (%)	33 (10.2%)		3 (1.9%)
No. of partial responses (%)	75 (23.1%)		18 (11.4%)
No. of stable disease (%)	127 (39.1%)		66 (41.8%)
IRF-assessed DOR, HCC mRECIST	n = 108		n = 21
Median in months	NE		6.3
95% CI	(NE, NE)		(4.9, NE)
Range (months)	(1.3+, 13.4+)		(1.4+, 9.1+)

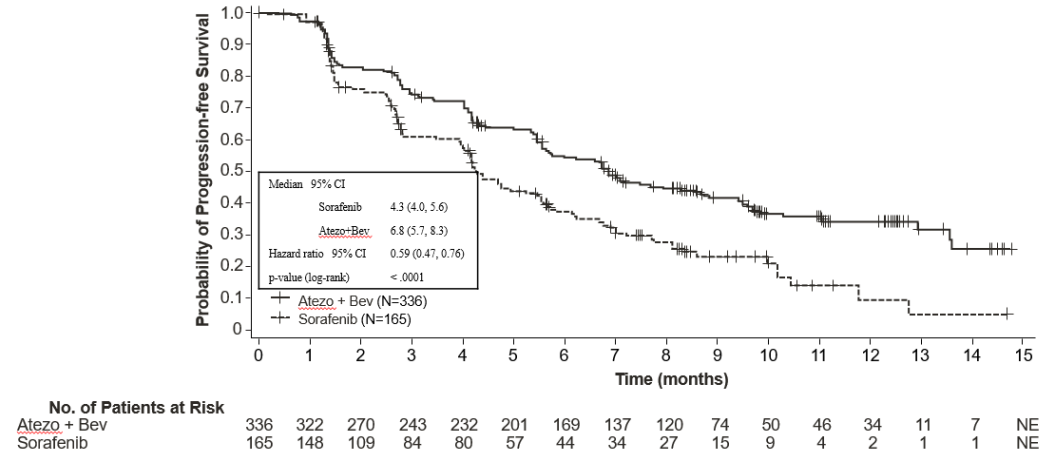
‡ Stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)
1. Based on two-sided stratified log-rank test
2. Nominal p-values based on two-sided Cochran-Mantel-Haenszel test
+ Denotes a censored value
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; HCC mRECIST = Modified RECIST Assessment for Hepatocellular Carcinoma; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival; NE=not estimable

Figure 21: Kaplan-Meier curve for OS in the ITT population (IMbrave150 updated analysis)



Hazard ratio is from stratified analysis. Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs absence) and AFP (<400 vs >=400 ng/ml) at screening per IxRS.

Figure 22: Kaplan-Meier curve for IRF-PFS per RECIST v1.1 in the ITT population (IMbrave150 primary analysis)



Hazard ratio and p-value are from stratified analysis.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs absence) and AFP (<400 vs >=400 ng/ml) at screening per IxRS.

Efficacy in elderly

No overall differences in efficacy were observed between patients ≥ 65 years of age and younger patients receiving atezolizumab monotherapy. In study IMpower150, age ≥ 65 was associated with a diminished effect of atezolizumab in patients receiving atezolizumab in combination with carboplatin and paclitaxel.

In studies IMpower150, IMpower133, IMpower110 and IMscin001 data for patients ≥ 75 years of age are too limited to draw conclusions on this population.

Paediatric population

Intravenous formulation

An early phase, multi-centre open-label study was conducted in paediatric (< 18 years, n = 69) and young adult patients (18-30 years, n = 18) with relapsed or progressive solid tumours as well as with Hodgkin's and non-Hodgkin's lymphoma, to evaluate the safety and pharmacokinetics of atezolizumab. Patients were treated with 15 mg/kg bw atezolizumab intravenously every 3 weeks (see section 5.2).

Subcutaneous Formulation

No dedicated studies of Tecentriq solution for injection have been conducted in paediatric patients.

5.2 Pharmacokinetic properties

Atezolizumab model-predicted exposure metrics following 1 875 mg Q3W subcutaneous Tecentriq and intravenous atezolizumab (1 200 mg Q3W) administration in the IMscin001 study are shown in Table 23.

Atezolizumab cycle 1 C_{trough} (i.e., pre-dose cycle 2) showed non-inferiority of atezolizumab within Tecentriq solution for injection to intravenous atezolizumab, with a geometric mean ratio (GMR) of 1.05 (90% CI: 0.88–1.24).

The GMR for cycle 1 model-predicted for AUC from 0 to 21 days ($AUC_{0\text{-}21d}$) was 0.87 (90% CI: 0.83–0.92).

The maximum systemic accumulation ratio following 1 875 mg Q3W of Tecentriq solution for injection is 2.2.

The model-predicted C_{trough} and AUC at steady state were comparable for subcutaneous Tecentriq and intravenous atezolizumab (see Table 23). A pharmacokinetic analysis suggests that steady state is obtained after 6 to 9 weeks of multiple dosing.

Table 23: Atezolizumab model-predicted exposure (geometric mean with 5th-95th percentiles) following subcutaneous or intravenous administration of atezolizumab

Parameter	Subcutaneous Tecentriq	Intravenous Atezolizumab
C_{trough} at steady state[a] (mcg/mL)	205 (70.3 – 427)	179 (98.4 – 313)
AUC at steady state[a] (mcg/mL•day)	6163 (2561 – 11340)	6107 (3890 – 9334)

[a] Model-predicted exposure based on population pharmacokinetics analysis

Absorption

Tecentriq solution for injection is administered as a subcutaneous injection.

Based on population PK analysis of Cycle 1 data from the randomised portion of IMscin001 study, the absolute bioavailability was 61% and the first-order absorption rate (K_a) is 0.37 (1/day).

The atezolizumab geometric mean maximum serum concentration (C_{max}) was 189 mcg/mL and median time to maximum serum concentration (T_{max}) was 4.5 days.

Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution is 3.28 L and volume at steady-state is 6.91 L in the typical patient.

Biotransformation

The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism.

Elimination

A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life is 27 days.

Special populations

Based on population PK and exposure-response analyses age (21-89 years), region, ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG performance status have no effect on atezolizumab pharmacokinetics. Body weight, gender, positive ADA status, albumin levels and tumour burden have a statistically significant, but not clinically relevant effect on atezolizumab pharmacokinetics. No dose adjustments are recommended.

Elderly

No dedicated studies of atezolizumab have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population PK analysis. Age was not identified as a significant covariate influencing the PK of intravenous atezolizumab based on patients of age range of 21 − 89 years (n=472), and median of 62 years of age. No clinically important difference was

observed in the pharmacokinetics of atezolizumab among patients < 65 years (n = 274), patients between 65 – 75 years (n=152) and patients > 75 years (n = 46) (see section 4.2).

No clinically relevant difference was observed in the PK of subcutaneous atezolizumab among patients < 65 years (n = 138), patients between 65 - 75 years (n = 89), and patients > 75 years of age (n = 19).

Paediatric population

The pharmacokinetic results from one early-phase, multi-centre open-label study that was conducted in paediatric (< 18 years, n = 69) and young adult patients (18 - 30 years, n = 18), show that the clearance and volume of distribution of intravenous atezolizumab were comparable between paediatric patients receiving 15 mg/kg bw and young adult patients receiving 1 200 mg of intravenous atezolizumab every 3 weeks when normalized by body weight, with exposure trending lower in paediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure. Data for children < 2 years is limited thus no definitive conclusions can be made.

No dedicated studies of Tecentriq solution for injection have been conducted in paediatric patients.

Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of intravenous atezolizumab were found in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2; n=208) or, moderate (eGFR 30 to 59 mL/min/1.73 m^2; n = 116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n = 140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n = 8) (see section 4.2). The effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.

No clinically relevant differences in the clearance of subcutaneous atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n = 111) or moderate (eGFR 30 to 59 mL/min/1.73 m^2; n = 32) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n = 103) renal function.

Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of intravenous or subcutaneously administered atezolizumab observed in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 × to 1.5 × ULN and any AST) or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST) in comparison to patients with normal hepatic function (bilirubin ≤ ULN and AST ≤ ULN). No data are available in patients with severe hepatic impairment (bilirubin > 3 X ULN and any AST). Hepatic impairment was defined by the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria of hepatic dysfunction (see section 4.2). The effect of severe hepatic impairment (bilirubin > 3 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been performed to establish the carcinogenic potential of atezolizumab.

Mutagenicity

Mutagenicity studies have not been performed to establish the mutagenic potential of atezolizumab. However, monoclonal antibodies are not expected to alter DNA or chromosomes.

Fertility

No fertility studies have been conducted with atezolizumab; however, assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Weekly administration of intravenous atezolizumab to female monkeys at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries which were reversible. There was no effect on the male reproductive organs.

Teratogenicity

No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to immune-mediated rejection of the developing foetus resulting in foetal death. Administration of atezolizumab could cause foetal harm, including embryo-foetal lethality.

Subcutaneous formulation

Hyaluronidase is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. Reproductive toxicology studies with rHuPH20 revealed embryofetal toxicity in mice at high systemic exposure but did not show teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
L-histidine
Acetic acid
L-methionine
Polysorbate 20 (E 432)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

3 years.

Prepared syringe

Once transferred from the vial into the syringe, Tecentriq solution for injection is physically and chemically stable for up to 30 days at 2 °C to 8 °C and for up to 8 hours at ≤ 30 °C in diffuse daylight and from the time of preparation.

From a microbiological point of view, the solution should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative or bacteriostatic agents. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after preparation of the syringe, see section 6.3.

6.5 Nature and contents of container

Type I glass-vial with a butyl rubber stopper and an aluminium seal with a plastic violet flip-off cap containing15 mL of solution for injection.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Preparation of the syringe

Tecentriq solution for injection should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Tecentriq solution for injection is a ready to use solution which should NOT be diluted or mixed with other medicinal products. Do not shake.

Tecentriq solution for injection is for single use only and should be prepared by a healthcare professional.

No incompatibilities have been observed between Tecentriq solution for injection and polypropylene (PP), polycarbonate (PC), stainless steel (SS), polyvinyl chloride (PVC), and polyurethanes (PU).

Tecentriq solution for injection does not contain any antimicrobial preservative or bacteriostatic agents.

- Remove the vial from refrigerated storage and allow the solution to come to room temperature.
- Withdraw the entire contents of Tecentriq solution for injection from the vial with a sterile syringe and transfer needle (18G recommended).
- Remove the transfer needle and attach a subcutaneous infusion set (e.g. winged/butterfly) containing a 23-25G stainless steel needle for injection. Use a SC infusion set with residual hold-up volume NOT exceeding 0.5 mL for administration.
- Prime the subcutaneous infusion line with the medicinal product solution to eliminate the air in the infusion line and stop before the fluid reaches the needle.

- Ensure the syringe contains exactly 15 mL of the solution after priming and expelling any excess volume from the syringe.
- Administer immediately to avoid needle clogging. DO NOT store the prepared syringe that has been attached to the already-primed SC infusion set.

If the dose is not administered immediately, refer to “Storage of the syringe” below.

Storage of the syringe

- If the dose is not to be administered immediately, use aseptic technique to withdraw the entire contents of Tecentriq solution for injection from the vial into the syringe to account for the dose volume (15 mL) and priming volume for the subcutaneous infusion set. Replace the transfer needle with a syringe closing cap. DO NOT attach a subcutaneous infusion set for storage.
- If the syringe is stored in a refrigerator, allow the syringe to reach room temperature prior to administration.

Disposal

The release of Tecentriq in the environment should be minimised. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/17/1220/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2017
Date of latest renewal: 25 April 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

F. Hoffmann-La Roche AG
Grenzacherstrasse 124
4058 Basel
SWITZERLAND

and

Roche Diagnostics GmbH
Nonnenwald 2
82377 Penzberg
GERMANY

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Tecentriq in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of important identified risks of atezolizumab, including certain immune-mediated adverse reactions, and infusion-related reactions, and how to manage them.

The MAH shall ensure that in each Member State where Tecentriq is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Tecentriq have access to/are provided with the following educational package:

- Patient Card

The patient card shall contain the following key messages:

- Brief introduction to atezolizumab (indication and purpose of this tool)
- Information that atezolizumab can cause serious side effects during or after treatment, that need to be treated right away
- Description of the main signs and symptoms of the following safety concerns and reminder of the importance of notifying their treating physician immediately if symptoms occur, persist or worsen:
  - Immune-Mediated Hepatitis
  - Immune-Mediated Pneumonitis
  - Immune-Mediated Colitis
  - Immune-Mediated Pancreatitis
  - Immune-Mediated Endocrinopathies (Type 1 Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency and Hypophysitis)
  - Immune-Mediated Neuropathies (Guillain-Barre Syndrome, Myasthenic Syndrome / Myasthenia Gravis, Facial Paresis)
  - Immune-Mediated Myelitis
  - Immune-Mediated Meningoencephalitis
  - Immune-Mediated Myocarditis
  - Immune-Mediated Nephritis
  - Immune-Mediated Myositis
  - Immune-Mediated Pericardial Disorders
  - Haemophagocytic lymphohistiocytosis
  - Infusion-Related Reactions

- Warning message for patients on the importance of consulting their doctor immediately in case they develop any of the listed signs and symptoms and on the important not attempting to treat themselves.
- Reminder to carry the Patient Card at all times and to show it to all healthcare professionals that may treat them.
- The card should also prompt to enter contact details of the physician and include a warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tecentriq.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tecentriq 840 mg concentrate for solution for infusion
atezolizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 14 mL vial of concentrate contains 840 mg atezolizumab
After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, glacial acetic acid, sucrose, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
840 mg/14 mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake the vial

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1220/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tecentriq 840 mg concentrate for solution for infusion
atezolizumab
Intravenous use

2. METHOD OF ADMINISTRATION

For intravenous use after dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

840 mg/14 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tecentriq 1 200 mg concentrate for solution for infusion
atezolizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each 20 mL vial of concentrate contains 1 200 mg atezolizumab
After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, glacial acetic acid, sucrose, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 200 mg/20 mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake the vial

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1220/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tecentriq 1 200 mg concentrate for solution for infusion
atezolizumab
Intravenous use

2. METHOD OF ADMINISTRATION

For intravenous use after dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 200 mg/20 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tecentriq 1 875 mg solution for injection
atezolizumab

2. STATEMENT OF ACTIVE SUBSTANCE

One vial contains 1 875 mg atezolizumab in 15 mL solution.

3. LIST OF EXCIPIENTS

Excipients: recombinant human hyaluronidase (rHuPH20), L-histidine, acetic acid, L-methionine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 875 mg/15 mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
For subcutaneous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake the vial

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1220/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tecentriq 1 875 mg solution for injection
atezolizumab
For subcutaneous use only

2. METHOD OF ADMINISTRATION

For subcutaneous use only

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 875 mg/15 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tecentriq 840 mg concentrate for solution for infusion
Tecentriq 1 200 mg concentrate for solution for infusion
atezolizumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- It is important that you keep the Patient Card with you during treatment.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecentriq is and what it is used for
2. What you need to know before you are given Tecentriq
3. How Tecentriq is given
4. Possible side effects
5. How to store Tecentriq
6. Contents of the pack and other information

1. What Tecentriq is and what it is used for

What Tecentriq is

Tecentriq is an anti-cancer medicine that contains the active substance atezolizumab.
- It belongs to a group of medicines called monoclonal antibodies.
- A monoclonal antibody is a type of protein designed to recognise and attach to a specific target in the body.
- This antibody can help your immune system fight your cancer.

What Tecentriq is used for

Tecentriq is used in adults to treat:
- A kind of bladder cancer, called urothelial carcinoma
- A kind of lung cancer, called non-small cell lung cancer
- A kind of lung cancer, called small cell lung cancer
- A kind of breast cancer, called triple negative breast cancer
- A kind of liver cancer, called hepatocellular carcinoma

Patients may get Tecentriq when their cancer has spread to other parts of the body or has come back after previous treatment.

Patients may get Tecentriq when their lung cancer has not spread to other parts of the body and treatment will be given after surgery and chemotherapy. Treatment after surgery is called adjuvant therapy.

Tecentriq may be given in combination with other anticancer medicines. It is important that you also read the package leaflets for the other anticancer medicines you may be receiving. If you have any questions about these medicines, ask your doctor.

How Tecentriq works

Tecentriq works by attaching to a specific protein in your body called programmed death-ligand 1 (PD-L1). This protein suppresses the body's immune (defence) system, thereby protecting cancer cells from being attacked by the immune cells. By attaching to the protein, Tecentriq helps your immune system to fight your cancer.

2. What you need to know before you are given Tecentriq

You must not be given Tecentriq

- if you are allergic to atezolizumab or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor or nurse before you are given Tecentriq.

Warnings and precautions

Talk to your doctor or nurse before you are given Tecentriq if you:
- have an auto-immune disease (a condition where the body attacks its own cells)
- have been told that your cancer has spread to your brain
- have any history of inflammation of your lungs (called pneumonitis)
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have a significant cardiovascular (heart) disease or blood disorders or organ damage due to inadequate blood flow
- have had serious side effects because of other antibody therapies that help your immune system to fight cancer
- have been given medicines to stimulate your immune system
- have been given medicines to suppress your immune system
- have been given a live, attenuated vaccine
- have been given medicines to treat infections (antibiotics) in the past two weeks

Tecentriq acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

If any of the above applies to you (or you are not sure), talk to your doctor or nurse before you are given Tecentriq.

Tecentriq may cause some side effects that you must tell your doctor about straight away. They may happen weeks or months after your last dose. Tell your doctor straight away if you notice any of the symptoms below:
- inflammation of the lung (pneumonitis): symptoms may include new or worsening cough, shortness of breath, and chest pain
- inflammation of the liver (hepatitis): symptoms may include yellowing of skin or eyes, nausea, vomiting, bleeding or bruising, dark urine, and stomach pain
- inflammation of the intestines (colitis): symptoms may include diarrhoea (watery, loose or soft stools), blood in stools, and stomach pain

- inflammation of the thyroid, adrenal glands and the pituitary gland (hypothyroidism, hyperthyroidism, adrenal insufficiency or hypophysitis): symptoms may include tiredness, weight loss, weight gain, change in mood, hair loss, constipation, dizziness, headaches, increased thirst, increased urination and changes in vision
- type 1 diabetes, including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis): symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, nausea or vomiting, stomach pain, and deep or fast breathing
- inflammation of the brain (encephalitis) or inflammation of the membrane around the spinal cord and brain (meningitis): symptoms may include neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness
- inflammation or problems of the nerves (neuropathy): symptoms may include weakness in the arm and leg muscles, or face muscles, double vision, difficulties with speech and chewing, numbness, and tingling in hands and feet
- inflammation of the spinal cord (myelitis): symptoms may include pain, abnormal sensations such as numbness, tingling, coldness or burning, weakness in the arms or legs, and bladder and bowel problems
- inflammation of the pancreas (pancreatitis): symptoms may include abdominal pain, nausea and vomiting
- inflammation of the heart muscle (myocarditis): symptoms may include shortness of breath, decreased exercise tolerance, feeling tired, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
- inflammation of the kidneys (nephritis); symptoms may include changes in urine output and colour, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
- inflammation of the muscles (myositis); symptoms may include muscle weakness, fatigue after walking or standing, tripping or falling, and trouble swallowing or breathing
- severe reactions associated with infusion, including serious allergic reactions (events occurring during the infusion or within one day of the infusion): may include fever, chills, shortness of breath and flushing
- severe skin reactions (SCARs); which may include rash, itching, skin blistering, peeling or sores, and/or ulcers in the mouth or in lining of the nose, throat or genital area
- inflammation of the heart sac with build-up of fluid in the sac (in some cases) (pericardial disorders): symptoms are similar to those of myocarditis and may include chest pain (usually over the front of the chest, sharp, and worsened by deep breathing and better when you sit up and lean forward in case of inflammation of the heart sac), cough, irregular heartbeat, swelling of the ankles, legs or abdomen, shortness of breath, fatigue, and fainting
- a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (haemophagocytic lymphohistiocytosis): symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems

If you notice any of the symptoms above, tell your doctor straight away.

Do not try to treat yourself with other medicines. Your doctor may:
- Give you other medicines to prevent complications and reduce symptoms.
- Delay giving your next dose of Tecentriq.
- Stop your treatment with Tecentriq.

Tests and checks

Before your treatment, your doctor will check your general health. You will also have blood tests during your treatment.

Children and adolescents

This medicine should not be given to children or adolescents below 18 years of age. This is because the safety and efficacy of Tecentriq have not been established in this age group.

Other medicines and Tecentriq

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

Pregnancy and contraception

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- You will not be given Tecentriq if you are pregnant unless your doctor considers it necessary. This is because the effect of Tecentriq in pregnant women is not known - it is possible that it could harm your unborn baby.
- If you could become pregnant, you must use effective contraception:
  - while you are being treated with Tecentriq and
  - for 5 months after the last dose.
- If you become pregnant while you are being treated with Tecentriq tell your doctor.

Breast-feeding

It is not known if Tecentriq gets into breast milk. Ask your doctor if you should stop breast-feeding or if you should stop treatment with Tecentriq.

Driving and using machines

Tecentriq has minor influence on your ability to drive and use machines. If you feel tired, do not drive or use machines until you feel better.

Tecentriq contains Polysorbate (E 432)

Tecentriq 840 mg contains 5.6 mg of polysorbate 20 in each 14 ml dose, which is equivalent to 0.4 mg/mL. Tecentriq 1 200 mg contains 8.0 mg of polysorbate 20 in each 20 ml dose, which is equivalent to 0.4 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Patient Card

Important information from this package leaflet can be found in the Patient Card you have been given by your doctor. It is important that you keep this Patient Card and show it to your partner or caregivers.

3. How Tecentriq is given

You will be given Tecentriq by a doctor experienced in cancer treatment in a hospital or clinic.

Two different types (formulations) of Tecentriq exist:
• one is given as an infusion into a vein (intravenous infusion)
• the other is given as an injection under the skin (subcutaneous injection).

Your doctor may consider switching your intravenous Tecentriq treatment to subcutaneous Tecentriq treatment (and vice versa) if considered appropriate for you.

How much intravenous Tecentriq is given

The recommended dose is either:
- 840 milligrams (mg) every two weeks, or
- 1 200 milligrams (mg) every three weeks, or
- 1 680 milligrams (mg) every four weeks.

How intravenous Tecentriq is given

Tecentriq is given as a drip into a vein (an intravenous infusion).

Your first infusion will be given over 60 minutes.
- Your doctor will monitor you carefully during the first infusion.
- If you do not have an infusion reaction during the first infusion, the next infusions will be given to you over a period of 30 minutes.

How long treatment lasts

Your doctor will keep giving you Tecentriq until you no longer benefit from it. However, it may be stopped if the side effects become too much of a problem.

If you miss a dose of Tecentriq

If you miss an appointment, make another one straight away. For the treatment to be fully effective, it is very important to keep having the infusions.

If you stop receiving Tecentriq

Do not stop treatment with Tecentriq unless you have discussed this with your doctor. This is because stopping treatment may stop the effect of the medicine.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the side effects below or if they get worse. They may happen weeks or months after your last dose. Do not try to treat yourself with other medicines.

Tecentriq used alone

The following side effects have been reported in clinical trials with Tecentriq used alone:

Very common: may affect more than 1 in 10 people
- fever
- nausea
- vomiting
- feeling very tired with no energy (fatigue)
- lack of energy
- itching of the skin
- diarrhoea
- joint pain
- rash
- loss of appetite

- shortness of breath
- urinary tract infection
- back pain
- cough
- headache

Common: may affect up to 1 in 10 people
- inflammation of the lungs (pneumonitis)
- low oxygen levels, which may cause shortness of breath as a consequence of inflamed lungs (hypoxia)
- stomach pain
- pain in the muscles and bones
- inflammation of the liver
- elevated liver enzymes (shown in tests), which may be a sign of an inflamed liver
- difficulty swallowing
- blood tests showing low levels of potassium (hypokalaemia) or sodium (hyponatremia)
- low blood pressure (hypotension)
- underactive thyroid gland (hypothyroidism)
- reactions related to the infusion of the medicine (infusion-related reaction, hypersensitivity, cytokine release syndrome or anaphylaxis)
- flu-like illness
- chills
- inflammation of the intestines
- low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia)
- high blood sugar
- common cold (nasopharyngitis)
- mouth and throat pain, or dry mouth
- dry skin
- abnormal kidney test (possible kidney damage)
- overactive thyroid gland (hyperthyroidism)
- inflammation of the heart sac with build-up of fluid in the sac (in some cases) (pericardial disorders)
- nerve damage resulting in possible numbness, pain, and/or loss of motor function (peripheral neuropathy)

Uncommon: may affect up to 1 in 100 people
- inflammation of the pancreas
- numbness or paralysis, which may be signs of Guillain-Barré syndrome
- inflammation of the membrane around the spinal cord and brain
- low levels of adrenal hormones
- type 1 diabetes (including diabetic ketoacidosis)
- inflammation of muscles (myositis)
- red, dry, scaly patches of thickened skin (psoriasis)
- inflammation of the kidneys
- itching, skin blistering, peeling or sores, and/or ulcers in the mouth or in lining of nose, throat, or genital area which can be severe (severe skin reactions)
- inflammation of the pituitary gland situated at the base of the brain
- elevated creatine phosphokinase in the blood (shown in test), which may be a sign of muscle or heart inflammation
- changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen disorders)

Rare: may affect up to 1 in 1,000 people
- inflammation of the heart muscle

- myasthenia gravis, an illness that can cause muscle weakness
- inflammation of the eye (uveitis)
- haemophagocytic lymphohistiocytosis, a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms
- inflammation of the spinal cord (myelitis)
- weakness of facial nerves and muscles (facial paresis)
- coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- inflammation of the bladder; signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Tecentriq used in combination with anticancer medicines

The following side effects have been reported in clinical trials when Tecentriq is given in combination with anticancer medicines:

Very common: may affect more than 1 in 10 people
- low number of red blood cells, which can cause tiredness and shortness of breath
- low white blood cell count with and without fever, which can increase the risk of infection (neutropenia, leukopenia)
- low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia)
- constipation
- nerve damage resulting in possible numbness, pain, and/or loss of motor function (peripheral neuropathy)
- underactive thyroid gland (hypothyroidism)
- loss of appetite
- shortness of breath
- diarrhoea
- nausea
- itching of the skin
- rash
- joint pain
- feeling very tired (fatigue)
- fever
- headache
- cough
- pain in the muscles and bones
- vomiting
- back pain
- lack of energy
- infection of the lung
- common cold (nasopharyngitis)
- hair loss
- high blood pressure (hypertension)
- swelling in arms or legs

Common: may affect up to 1 in 10 people
- blood tests showing low levels of potassium (hypokalaemia) or sodium (hyponatremia)
- inflammation of the mouth or lips
- hoarse voice (dysphonia)

- low levels of magnesium (hypomagnesaemia), which can cause weakness and muscle cramping, numbness and pain in the arms and legs
- protein in urine (proteinuria)
- inflammation of the intestines
- fainting
- elevated liver enzymes (shown in tests), which may be a sign of an inflamed liver
- changes to sense of taste (dysgeusia)
- decreased number of lymphocyte (a type of white blood cells), which is associated with an increased risk of infection
- abnormal kidney test (possible kidney damage)
- overactive thyroid gland (hyperthyroidism)
- dizziness
- reactions related to the infusion of the medicine (infusion-related reaction, hypersensitivity, cytokine release syndrome or anaphylaxis)
- severe infection in the blood (sepsis)

Uncommon: may affect up to 1 in 100 people
- red, dry, scaly patches of thickened skin (psoriasis)
- itching, skin blistering, peeling or sores, and/or ulcers in the mouth or in lining of nose, throat, or genital area which can be severe (severe skin reactions)
- inflammation of the heart sac with build-up of fluid in the sac (in some cases) (pericardial disorders)
- inflammation of the pituitary gland situated at the base of the brain

Rare: may affect up to 1 in 1,000 people
- haemophagocytic lymphohistiocytosis, a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms
- weakness of facial nerves and muscles (facial paresis)
- coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)
- changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen disorders)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

If you notice any of the side effects above or if they get worse, tell your doctor straight away.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tecentriq

Tecentriq will be stored by the healthcare professionals at the hospital or clinic. The storage details are as follows:
- Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C - 8 °C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.

- The diluted solution should not be kept more than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C), unless dilution has taken place in controlled and validated aseptic conditions.
- Do not use if this medicine is cloudy, discoloured or contains particles.

Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help to protect the environment.

6. Contents of the pack and other information

What Tecentriq contains

- The active substance is atezolizumab. Each mL contains 60 mg of atezolizumab.
  Each 14 mL vial contains 840 mg of atezolizumab.
  Each 20 mL vial contains 1 200 mg of atezolizumab.
- After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL.
- The other ingredients are L-histidine, glacial acetic acid, sucrose, polysorbate 20 (E 432) (see section 2 “Tecentriq contains Polysorbate”) and water for injections.

What Tecentriq looks like and contents of the pack

Tecentriq is a concentrate for solution for infusion. It is a clear, colourless to slightly yellowish liquid.

Tecentriq is available in a pack containing 1 glass vial.

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Manufacturer

Roche Pharma AG
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Germany

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Instructions for dilution

For the recommended dose of 840 mg: fourteen mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

For the recommended dose of 1 200 mg: twenty mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

For the recommended dose of 1 680 mg: twenty-eight mL of Tecentriq concentrate should be withdrawn from two vials of Tecentriq 840 mg and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL. The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately.

Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration. If particulates or discoloration are observed, the solution should not be used.

No incompatibilities have been observed between Tecentriq and intravenous bags with product-contacting surfaces of PVC, PO, PE, or PP. In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane. The use of in-line filter membranes is optional.

Diluted solution

Chemical and physical in-use stability has been demonstrated for up to 24 hours at ≤ 30 °C and for up to 30 days at 2 °C to 8 °C from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C), unless dilution has taken place in controlled and validated aseptic conditions.

Method of administration

Tecentriq is for intravenous use. The infusions must not be administered as an intravenous push or bolus.

The initial dose of Tecentriq must be administered over 60 minutes. If the first infusion is well tolerated all subsequent infusions may be administered over 30 minutes.

Do not co-administer other medicinal products through the same infusion line.

Disposal

The release of Tecentriq in the environment should be minimised. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the patient

Tecentriq 1 875 mg solution for injection
atezolizumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- It is important that you keep the Patient Card with you during treatment.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecentriq is and what it is used for
2. What you need to know before you are given Tecentriq
3. How Tecentriq is given
4. Possible side effects
5. How to store Tecentriq
6. Contents of the pack and other information

1. What Tecentriq is and what it is used for

What Tecentriq is

Tecentriq is an anti-cancer medicine that contains the active substance atezolizumab.
- It belongs to a group of medicines called monoclonal antibodies.
- A monoclonal antibody is a type of protein designed to recognise and attach to a specific target in the body.
- This antibody can help your immune system fight your cancer.

What Tecentriq is used for

Tecentriq is used in adults to treat:
- A kind of bladder cancer, called urothelial carcinoma
- A kind of lung cancer, called non-small cell lung cancer
- A kind of lung cancer, called small cell lung cancer
- A kind of breast cancer, called triple negative breast cancer
- A kind of liver cancer, called hepatocellular carcinoma

Patients may get Tecentriq when their cancer has spread to other parts of the body or has come back after previous treatment.

Patients may get Tecentriq when their lung cancer has not spread to other parts of the body and treatment will be given after surgery and chemotherapy. Treatment after surgery is called adjuvant therapy.

Tecentriq may be given in combination with other anticancer medicines. It is important that you also read the package leaflets for the other anticancer medicines you may be receiving. If you have any questions about these medicines, ask your doctor.

How Tecentriq works

Tecentriq works by attaching to a specific protein in your body called programmed death-ligand 1 (PD-L1). This protein suppresses the body's immune (defence) system, thereby protecting cancer cells from being attacked by the immune cells. By attaching to the protein, Tecentriq helps your immune system to fight your cancer.

2. What you need to know before you are given Tecentriq

You must not be given Tecentriq

- if you are allergic to atezolizumab or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor or nurse before you are given Tecentriq.

Warnings and precautions

Talk to your doctor or nurse before you are given Tecentriq if you:
- have an auto-immune disease (a condition where the body attacks its own cells)
- have been told that your cancer has spread to your brain
- have any history of inflammation of your lungs (called pneumonitis)
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have a significant cardiovascular (heart) disease or blood disorders or organ damage due to inadequate blood flow
- have had serious side effects because of other antibody therapies that help your immune system to fight cancer
- have been given medicines to stimulate your immune system
- have been given medicines to suppress your immune system
- have been given a live, attenuated vaccine
- have been given medicines to treat infections (antibiotics) in the past two weeks

Tecentriq acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

If any of the above applies to you (or you are not sure), talk to your doctor or nurse before you are given Tecentriq.

Tecentriq may cause some side effects that you must tell your doctor about straight away. They may happen weeks or months after your last dose. Tell your doctor straight away if you notice any of the symptoms below:
- inflammation of the lung (pneumonitis): symptoms may include new or worsening cough, shortness of breath, and chest pain
- inflammation of the liver (hepatitis): symptoms may include yellowing of skin or eyes, nausea, vomiting, bleeding or bruising, dark urine, and stomach pain
- inflammation of the intestines (colitis): symptoms may include diarrhoea (watery, loose or soft stools), blood in stools, and stomach pain

- inflammation of the thyroid, adrenal glands and the pituitary gland (hypothyroidism, hyperthyroidism, adrenal insufficiency or hypophysitis): symptoms may include tiredness, weight loss, weight gain, change in mood, hair loss, constipation, dizziness, headaches, increased thirst, increased urination and changes in vision
- type 1 diabetes, including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis): symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, nausea or vomiting, stomach pain, and deep or fast breathing
- inflammation of the brain (encephalitis) or inflammation of the membrane around the spinal cord and brain (meningitis): symptoms may include neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness
- inflammation or problems of the nerves (neuropathy): symptoms may include weakness in the arm and leg muscles, or face muscles, double vision, difficulties with speech and chewing, numbness, and tingling in hands and feet
- inflammation of the spinal cord (myelitis): symptoms may include pain, abnormal sensations such as numbness, tingling, coldness or burning**,** weakness in the arms or legs, and bladder and bowel problems
- inflammation of the pancreas (pancreatitis): symptoms may include abdominal pain, nausea and vomiting
- inflammation of the heart muscle (myocarditis): symptoms may include shortness of breath, decreased exercise tolerance, feeling tired, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
- inflammation of the kidneys (nephritis); symptoms may include changes in urine output and colour, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
- inflammation of the muscles (myositis); symptoms may include muscle weakness, fatigue after walking or standing, tripping or falling, and trouble swallowing or breathing
- severe reactions associated with injection, including serious allergic reactions (events occurring during the injection or within one day of the injection): may include fever, chills, shortness of breath and flushing
- severe skin reactions (SCARs); which may include rash, itching, skin blistering, peeling or sores, and/or ulcers in the mouth or in lining of the nose, throat or genital area
- inflammation of the heart sac with build-up of fluid in the sac (in some cases) (pericardial disorders): symptoms are similar to those of myocarditis and may include chest pain (usually over the front of the chest, sharp, and worsened by deep breathing and better when you sit up and lean forward in case of inflammation of the heart sac), cough, irregular heartbeat, swelling of the ankles, legs or abdomen, shortness of breath, fatigue, and fainting
- a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (haemophagocytic lymphohistiocytosis): symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems

If you notice any of the symptoms above, tell your doctor straight away.

Do not try to treat yourself with other medicines. Your doctor may:
- Give you other medicines to prevent complications and reduce symptoms.
- Delay giving your next dose of Tecentriq.
- Stop your treatment with Tecentriq.

Tests and checks

Before your treatment, your doctor will check your general health. You will also have blood tests during your treatment.

Children and adolescents

This medicine should not be given to children or adolescents below 18 years of age. This is because the safety and efficacy of Tecentriq have not been established in this age group.

Other medicines and Tecentriq

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

Pregnancy and contraception

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- You will not be given Tecentriq if you are pregnant unless your doctor considers it necessary. This is because the effect of Tecentriq in pregnant women is not known - it is possible that it could harm your unborn baby.
- If you could become pregnant, you must use effective contraception:
  - while you are being treated with Tecentriq and
  - for 5 months after the last dose.
- If you become pregnant while you are being treated with Tecentriq tell your doctor.

Breast-feeding

It is not known if Tecentriq gets into breast milk. Ask your doctor if you should stop breast-feeding or if you should stop treatment with Tecentriq.

Driving and using machines

Tecentriq has minor influence on your ability to drive and use machines. If you feel tired, do not drive or use machines until you feel better.

Tecentriq contains Polysorbate (E 432)

This medicine contains 9 mg of polysorbate 20 in each 15 ml dose, which is equivalent to 0.6 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Patient Card

Important information from this package leaflet can be found in the Patient Card you have been given by your doctor. It is important that you keep this Patient Card and show it to your partner or caregivers.

3. How Tecentriq is given

You will be given Tecentriq by a doctor experienced in cancer treatment.

Two different types (formulations) of Tecentriq exist:
• one is given as an infusion into a vein (intravenous infusion)
• the other is given as an injection under the skin (subcutaneous injection).

Your doctor may consider switching your subcutaneous Tecentriq treatment to intravenous Tecentriq treatment (and vice versa) if considered appropriate for you.

How much subcutaneous Tecentriq is given

The recommended dose of Tecentriq solution for injection is 1 875 mg every three weeks.

How subcutaneous Tecentriq is given

Tecentriq is given as injection under your skin (subcutaneous injection).
- Injections will be given in the thigh in approximately 7 minutes
- The injection site will be alternated between the left and right thigh
- Your doctor or nurse will make sure each injection is given in a new place (at least 2.5 cm away from any previous place of injection), and where the skin is not red, bruised, tender or hard
- Different places for injection should be used for other medicines

How long treatment lasts

Your doctor will keep giving you Tecentriq until you no longer benefit from it. However, it may be stopped if the side effects become too much of a problem.

If you miss a dose of Tecentriq

If you miss an appointment, make another one straight away. For the treatment to be fully effective, it is very important to keep having the injections.

If you stop receiving Tecentriq

Do not stop treatment with Tecentriq unless you have discussed this with your doctor. This is because stopping treatment may stop the effect of the medicine.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the side effects below or if they get worse. They may happen weeks or months after your last dose. Do not try to treat yourself with other medicines.

Tecentriq used alone

The following side effects have been reported in clinical trials with Tecentriq used alone:

Very common (may affect more than 1 in 10 people):
- fever
- nausea
- vomiting
- feeling very tired with no energy (fatigue)
- lack of energy
- itching of the skin
- diarrhoea
- joint pain
- rash
- loss of appetite
- shortness of breath
- urinary tract infection
- back pain

- cough
- headache

Common (may affect up to 1 in 10 people):
- inflammation of the lungs (pneumonitis)
- low oxygen levels, which may cause shortness of breath as a consequence of inflamed lungs (hypoxia)
- stomach pain
- pain in the muscles and bones
- inflammation of the liver
- elevated liver enzymes (shown in tests), which may be a sign of an inflamed liver
- difficulty swallowing
- blood tests showing low levels of potassium (hypokalaemia) or sodium (hyponatremia)
- low blood pressure (hypotension)
- underactive thyroid gland (hypothyroidism)
- reactions related to the infusion of the medicine (infusion-related reaction, hypersensitivity, cytokine release syndrome or anaphylaxis)
- flu-like illness
- chills
- inflammation of the intestines
- low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia)
- high blood sugar
- common cold (nasopharyngitis)
- mouth and throat pain, or dry mouth
- dry skin
- abnormal kidney test (possible kidney damage)
- overactive thyroid gland (hyperthyroidism)
- inflammation of the heart sac with build-up of fluid in the sac (in some cases) (pericardial disorders)
- local reaction at injection site
- nerve damage resulting in possible numbness, pain, and/or loss of motor function (peripheral neuropathy)

Uncommon (may affect up to 1 in 100 people):
- inflammation of the pancreas
- numbness or paralysis, which may be signs of Guillain-Barré syndrome
- inflammation of the membrane around the spinal cord and brain
- low levels of adrenal hormones
- type 1 diabetes (including diabetic ketoacidosis)
- inflammation of muscles (myositis)
- red, dry, scaly patches of thickened skin (psoriasis)
- inflammation of the kidneys
- itching, skin blistering, peeling or sores, and/or ulcers in the mouth or in lining of nose, throat, or genital area which can be severe (severe skin reactions)
- inflammation of the pituitary gland situated at the base of the brain
- elevated creatine phosphokinase in the blood (shown in test), which may be a sign of muscle or heart inflammation
- changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen disorders)

Rare (may affect up to 1 in 1,000 people):
- inflammation of the heart muscle
- myasthenia gravis, an illness that can cause muscle weakness
- inflammation of the eye (uveitis)

- haemophagocytic lymphohistiocytosis, a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms
- inflammation of the spinal cord (myelitis)
- weakness of facial nerves and muscles (facial paresis)
- coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- inflammation of the bladder; signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

Tecentriq used in combination with anticancer medicines

The following side effects have been reported in clinical trials when Tecentriq is given in combination with anticancer medicines:

Very common (may affect more than 1 in 10 people):
- low number of red blood cells, which can cause tiredness and shortness of breath
- low white blood cell count with and without fever, which can increase the risk of infection (neutropenia, leukopenia)
- low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia)
- constipation
- nerve damage resulting in possible numbness, pain, and/or loss of motor function (peripheral neuropathy)
- underactive thyroid gland (hypothyroidism)
- loss of appetite
- shortness of breath
- diarrhoea
- nausea
- itching of the skin
- rash
- joint pain
- feeling very tired (fatigue)
- fever
- headache
- cough
- pain in the muscles and bones
- vomiting
- back pain
- lack of energy
- infection of the lung
- common cold (nasopharyngitis)
- hair loss
- high blood pressure (hypertension)
- swelling in arms or legs

Common (may affect up to 1 in 10 people):
- blood tests showing low levels of potassium (hypokalaemia) or sodium (hyponatremia)
- inflammation of the mouth or lips
- hoarse voice (dysphonia)
- low levels of magnesium (hypomagnesaemia), which can cause weakness and muscle cramping, numbness and pain in the arms and legs
- protein in urine (proteinuria)

- inflammation of the intestines
- fainting
- elevated liver enzymes (shown in tests), which may be a sign of an inflamed liver
- changes to sense of taste (dysgeusia)
- decreased number of lymphocyte (a type of white blood cells), which is associated with an increased risk of infection
- abnormal kidney test (possible kidney damage)
- overactive thyroid gland (hyperthyroidism)
- dizziness
- reactions related to the infusion of the medicine (infusion-related reaction, hypersensitivity, cytokine release syndrome or anaphylaxis)
- severe infection in the blood (sepsis)

Uncommon (may affect up to 1 in 100 people):
- red, dry, scaly patches of thickened skin (psoriasis)
- itching, skin blistering, peeling or sores, and/or ulcers in the mouth or in lining of nose, throat, or genital area which can be severe (severe skin reactions)
- inflammation of the heart sac with build-up of fluid in the sac (in some cases) (pericardial disorders)
- inflammation of the pituitary gland situated at the base of the brain

Rare (may affect up to 1 in 1,000 people):
- haemophagocytic lymphohistiocytosis, a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms
- weakness of facial nerves and muscles (facial paresis)
- coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)
- changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen disorders)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

If you notice any of the side effects above or if they get worse, tell your doctor straight away.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tecentriq

Tecentriq will be stored by the healthcare professionals at the hospital or clinic. The storage details are as follows:
- Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C - 8 °C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not use if this medicine is cloudy, discoloured or contains particles.

Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help to protect the environment.

6. Contents of the pack and other information

What Tecentriq contains

- The active substance is atezolizumab. Each mL contains 125 mg of atezolizumab.
  One vial of 15 mL solution contains 1 875 mg of atezolizumab.
- The other ingredients are L-histidine, L-methionine, acetic acid, sucrose, polysorbate 20 (E 432) (see section 2 “Tecentriq contains Polysorbate”), recombinant human hyaluronidase (rHuPH20), and water for injections.

What Tecentriq looks like and contents of the pack

Tecentriq is a solution for injection. It is a clear, colourless to slightly yellowish liquid.

Tecentriq is available in a pack containing 1 glass vial.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

Manufacturer

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tel: +48 - 22 345 18 88

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Tel: +351 - 21 425 70 00

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Tel: +40 21 206 47 01

Slovenija
Roche farmacevtska družba d.o.o.
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Roche Slovensko, s.r.o.
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Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
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Tel: +46 (0) 8 726 1200

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

To prevent medication errors, it is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient as prescribed.

Tecentriq solution for injection should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Tecentriq solution for injection is a ready to use solution which should NOT be diluted or mixed with other medicinal products.

Tecentriq solution for injection is for single use only and should be prepared by a healthcare professional.

No incompatibilities have been observed between Tecentriq solution for injection and polypropylene (PP), polycarbonate (PC), stainless steel (SS), polyvinyl chloride (PVC), and polyurethanes (PU).

Preparation of the syringe

From a microbiological point of view, Tecentriq solution for injection should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative or bacteriostatic agents.

- Remove the vial from refrigerated storage and allow the solution to come to room temperature.
- Withdraw the entire contents of Tecentriq solution for injection from the vial with a sterile syringe and transfer needle (18G recommended).
- Remove the transfer needle and attach a subcutaneous infusion set (e.g. winged/butterfly) containing a 23-25G stainless steel needle for injection. Use a subcutaneous infusion set with residual hold-up volume NOT exceeding 0.5 mL for administration.
- Prime the subcutaneous infusion line with the drug product solution to eliminate the air in the infusion line and stop before the fluid reaches the needle.
- Ensure the syringe contains exactly 15 mL of the solution after priming and expelling any excess volume from the syringe.
- Administer immediately to avoid needle clogging. DO NOT store the prepared syringe that has been attached to the already-primed subcutaneous infusion set.

If the dose is not administered immediately, refer to “Storage of the syringe” below.

Storage of syringe

- If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2°C to 8°C, unless preparation has taken place under controlled and validated aseptic conditions.
- If the dose is not to be administered immediately, use aseptic technique to withdraw the entire contents of Tecentriq solution for injection from the vial into the syringe to account for the dose volume (15 mL) and priming volume for the subcutaneous infusion set. Replace the transfer needle with a syringe closing cap. DO NOT attach a subcutaneous infusion set for storage.
- The prepared syringe can be stored for up to 30 days at 2 °C to 8 °C and for up to 8 hours at ≤30°C in diffuse daylight from the time of preparation.
- If the syringe is stored in a refrigerator, allow the syringe to reach room temperature prior to administration.

Method of Administration

Tecentriq solution for injection is not intended for intravenous administration and must be given by subcutaneous injection only.

Prior to administration, remove Tecentriq solution for injection from refrigeration and allow the solution to reach room temperature. For instructions on the use and handling of Tecentriq solution for injection prior to administration, refer to Section 6.6 of the SmPC.

Administer 15 mL of Tecentriq solution for injection subcutaneously in the thigh in approximately 7 minutes. Use of a subcutaneous infusion set (e.g. winged/butterfly) is recommended. DO NOT administer the remaining residual hold-up volume in the tubing to the patient.

The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Tecentriq subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.

Disposal

The release of Tecentriq in the environment should be minimised. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

次頁以降は非公表のため削除

Core Data Sheet [redacted]

[redacted]

TECENTRIQ®

atezolizumab

[redacted]

目次

1.7 同種同効品一覧表 2

表一覧

表 1.7-1 同種同効品一覧表 2

各製品の最新の添付文書を参照すること。

1.7 同種同効品一覧表

表 1.7-1 同種同効品一覧表

販売名	テセントリク点滴静注840mg テセントリク点滴静注1200mg	パラプラチン注射液50mg パラプラチン注射液150mg パラプラチン注射液450mg	タキソール注射液30mg タキソール注射液100mg	レンビマカプセル4mg レンビマカプセル10mg
一般名	アテゾリズマブ（遺伝子組換え）	カルボプラチン	パクリタキセル	レンバチニブメシル酸塩
会社名	中外製薬株式会社	チェプラファーム株式会社	チェプラファーム株式会社	エーザイ株式会社
効能又は効果	〈製剤共通〉 ○ 切除不能な進行・再発の非小細胞肺癌 ○ PD-L1陽性の非小細胞肺癌における術後補助療法 ○ 進展型小細胞肺癌 ○ 切除不能な胞巣状軟部肉腫 ○ 再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型 〈テセントリク点滴静注1200mg〉 ○切除不能な肝細胞癌 ○切除不能な胸腺癌 〈テセントリク点滴静注840mg〉 ○PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌	○頭頸部癌、肺小細胞癌、睾丸腫瘍、卵巣癌、子宮頸癌、悪性リンパ腫、非小細胞肺癌、乳癌、子宮体癌 ○以下の悪性腫瘍に対する他の抗悪性腫瘍剤との併用療法 小児悪性固形腫瘍（神経芽腫・網膜芽腫・肝芽腫・中枢神経系胚細胞腫瘍、再発又は難治性のユーイング肉腫ファミリー腫瘍・腎芽腫）	○卵巣癌 ○非小細胞肺癌 ○乳癌 ○胃癌 ○子宮体癌 ○再発又は遠隔転移を有する頭頸部癌 ○再発又は遠隔転移を有する食道癌 ○血管肉腫 ○進行又は再発の子宮頸癌 ○再発又は難治性の胚細胞腫瘍（精巣腫瘍、卵巣腫瘍、性腺外腫瘍）	〈レンビマカプセル4mg〉 根治切除不能な甲状腺癌、切除不能な肝細胞癌、切除不能な胸腺癌、がん化学療法後に増悪した切除不能な進行・再発の子宮体癌、根治切除不能又は転移性の腎細胞癌 〈レンビマカプセル10mg〉 根治切除不能な甲状腺癌、切除不能な胸腺癌、がん化学療法後に増悪した切除不能な進行・再発の子宮体癌、根治切除不能又は転移性の腎細胞癌
添付文書改訂日	－	2025年6月改訂（第6版）	2024年7月改訂（第4版）	2025年6月改訂（第6版）
備考欄	－	併用薬	併用薬	－

＊＊2025年6月改訂（第6版）
＊2024年7月改訂

貯　　法：室温保存
有効期間：24箇月

日本標準商品分類番号
874291

	注射液50 mg	注射液150 mg	注射液450 mg
承認番号	21800AMX10584	21800AMX10583	21800AMX10588
販売開始	1990年5月	1990年5月	1990年5月

抗悪性腫瘍剤
日本薬局方　カルボプラチン注射液
毒薬、処方箋医薬品[注)]

パラプラチン®注射液50mg
パラプラチン®注射液150mg
パラプラチン®注射液450mg

PARAPLATIN® INJECTION

CHEPLA PHARM

注）注意－医師等の処方箋により使用すること

1. 警告

1.1 本剤を含むがん化学療法は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本療法が適切と判断される症例についてのみ実施すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

1.2 本剤を含む小児悪性固形腫瘍に対するがん化学療法は、小児のがん化学療法に十分な知識・経験を持つ医師のもとで実施すること。

2. 禁忌（次の患者には投与しないこと）

2.1 重篤な骨髄抑制のある患者［骨髄抑制は用量規制因子であり、感染症又は出血を伴い、重篤化する可能性がある。］

2.2 本剤又は他の白金を含む薬剤に対し、重篤な過敏症の既往歴のある患者

2.3 妊婦又は妊娠している可能性のある女性［9.5 参照］

3. 組成・性状

3.1 組成

販　売　名		パラプラチン注射液50 mg	パラプラチン注射液150 mg	パラプラチン注射液450 mg
成　　分		1バイアル中の分量		
		5 mL	15 mL	45 mL
有効成分	カルボプラチン	50 mg	150 mg	450 mg

3.2 製剤の性状

販　売　名	パラプラチン注射液50 mg	パラプラチン注射液150 mg	パラプラチン注射液450 mg
色・剤形	無色～微黄色澄明の注射液		
pH	5.0～7.0		
浸透圧比	約0.1（日局生理食塩液に対する比）		

4. 効能又は効果

○頭頸部癌、肺小細胞癌、睾丸腫瘍、卵巣癌、子宮頸癌、悪性リンパ腫、非小細胞肺癌、乳癌、子宮体癌

○以下の悪性腫瘍に対する他の抗悪性腫瘍剤との併用療法
小児悪性固形腫瘍（神経芽腫・網膜芽腫・肝芽腫・中枢神経系胚細胞腫瘍、再発又は難治性のユーイング肉腫ファミリー腫瘍・腎芽腫）

＊＊5. 効能又は効果に関連する注意

〈切除不能な進行・再発の悪性胸膜中皮腫〉
ペムブロリズマブ（遺伝子組換え）及びペメトレキセドナトリウムと併用する際の用法及び用量は、ペムブロリズマブ（遺伝子組換え）の電子添文を参照すること。

6. 用法及び用量

〈頭頸部癌、肺小細胞癌、睾丸腫瘍、卵巣癌、子宮頸癌、悪性リンパ腫、非小細胞肺癌〉
通常、成人にはカルボプラチンとして、1日1回300～400 mg/m^2（体表面積）を投与し、少なくとも4週間休薬する。これを1クールとし、投与を繰り返す。なお、投与量は、年齢、疾患、症状により適宜増減する。

〈乳癌〉
トラスツズマブ（遺伝子組換え）及びタキサン系抗悪性腫瘍剤との併用において、通常、成人にはカルボプラチンとして、1日1回300～400 mg/m^2（体表面積）を投与し、少なくとも3週間休薬する。これを1クールとし、投与を繰り返す。なお、投与量は、患者の状態により適宜減ずる。

〈小児悪性固形腫瘍（神経芽腫・網膜芽腫・肝芽腫・中枢神経系胚細胞腫瘍、再発又は難治性のユーイング肉腫ファミリー腫瘍・腎芽腫）に対する他の抗悪性腫瘍剤との併用療法〉

(1) 神経芽腫・肝芽腫・中枢神経系胚細胞腫瘍、再発又は難治性のユーイング肉腫ファミリー腫瘍・腎芽腫に対する他の抗悪性腫瘍剤との併用療法
イホスファミドとエトポシドとの併用療法において、カルボプラチンの投与量及び投与方法は、カルボプラチンとして635 mg/m^2（体表面積）を1日間点滴静注又は400 mg/m^2（体表面積）を2日間点滴静注し、少なくとも3～4週間休薬する。これを1クールとし、投与を繰り返す。
なお、投与量及び投与日数は疾患、症状、併用する他の抗悪性腫瘍剤により適宜減ずる。
また、1歳未満もしくは体重10 kg未満の小児に対して、投与量には十分配慮すること。

(2) 網膜芽腫に対する他の抗悪性腫瘍剤との併用療法
ビンクリスチン硫酸塩とエトポシドとの併用療法において、カルボプラチンの投与量及び投与方法は、カルボプラチンとして560 mg/m^2（体表面積）を1日間点滴静注し、少なくとも3～4週間休薬する。これを1クールとし、投与を繰り返す。

ただし、36ヵ月齢以下の患児にはカルボプラチンを18.6 mg/kgとする。
なお、投与量及び投与日数は疾患、症状、併用する他の抗悪性腫瘍剤により適宜減ずる。

〈子宮体癌〉
他の抗悪性腫瘍剤との併用において、通常、成人にはカルボプラチンとして、1日1回AUC5～6 mg・min/mL相当量を投与し、少なくとも3週間休薬する。これを1クールとし、投与を繰り返す。なお、投与量は、患者の状態により適宜減ずる。

〈効能共通〉
本剤投与時、投与量に応じて250 mL以上のブドウ糖注射液又は生理食塩液に混和し、30分以上かけて点滴静注する。

7. 用法及び用量に関連する注意

〈子宮体癌〉
AUC目標値及び腎機能に基づく本剤の投与量については、関連する学会の最新のガイドライン等を参考に設定すること。

8. 重要な基本的注意

〈効能共通〉
8.1 骨髄抑制等の重篤な副作用が起こることがあるので、適宜臨床検査（血液検査、肝機能検査、腎機能検査等）を行うなど、患者の状態を十分に観察すること。また、使用が長期間にわたると副作用が強くあらわれ、遷延性に推移することがあるので、投与は慎重に行うこと。[9.1.1-9.1.2、11.1.1、11.1.4-11.1.5、11.1.12 参照]
8.2 腫瘍崩壊症候群があらわれることがあるので、血清中電解質濃度及び腎機能検査を行うなど、患者の状態を十分に観察すること。[11.1.18 参照]
8.3 本剤の投与にあたってはG-CSF製剤等の適切な使用に関しても考慮すること。
8.4 悪心・嘔吐、食欲不振等の消化器症状が起こることがあるので、患者の状態を十分に観察し、適切な処置を行うこと。
8.5 感染症、出血傾向の発現又は増悪に十分注意すること。

〈小児悪性固形腫瘍（神経芽腫・網膜芽腫・肝芽腫・中枢神経系胚細胞腫瘍、再発又は難治性のユーイング肉腫ファミリー腫瘍・腎芽腫）に対する他の抗悪性腫瘍剤との併用療法〉
8.6 関連文献（「抗がん剤報告書：カルボプラチン（小児）」等）を熟読すること。

〈乳癌〉
8.7 関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議　公知申請への該当性に係る報告書：カルボプラチン（乳癌）」等）を熟読すること。

〈子宮体癌〉
8.8 関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議　公知申請への該当性に係る報告書：カルボプラチン（子宮体癌）」等）を熟読すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 骨髄抑制のある患者
骨髄抑制を増悪させることがある。[8.1、11.1.1 参照]

9.1.2 感染症を合併している患者
骨髄抑制により、感染症を増悪させることがある。[8.1、11.1.1 参照]

9.1.3 水痘患者
致命的な全身障害があらわれるおそれがある。

9.2 腎機能障害患者
腎機能が低下しているので、副作用が強くあらわれることがある。

9.2.1 前治療、特にシスプラチンの投与を受け腎機能が低下している患者
初回投与量を適宜減量し、血液検査値に十分注意すること。骨髄抑制が強くあらわれることがある。

9.2.2 小児悪性固形腫瘍（神経芽腫・網膜芽腫・肝芽腫・中枢神経系胚細胞腫瘍、再発又は難治性のユーイング肉腫ファミリー腫瘍・腎芽腫）に対する他の抗悪性腫瘍剤との併用療法において、腎機能が低下している患者
骨髄抑制、聴器障害、腎障害の発現に特に注意し、用量並びに投与間隔に留意するなど患者の状態を観察しながら慎重に投与すること。なお、腎機能の指標としてGFR（Glomerular filtration rate：糸球体ろ過値）等を考慮して、投与量を選択することが望ましい。

9.3 肝機能障害患者
代謝機能等が低下しているので、副作用が強くあらわれることがある。

9.4 生殖能を有する者

9.4.1 小児及び生殖可能な年齢の患者に投与する必要がある場合には、性腺に対する影響を考慮すること。

9.4.2 妊娠する可能性のある女性には、本剤投与中及び投与終了後一定期間は適切な避妊をするよう指導すること。[9.5 参照]

9.4.3 パートナーが妊娠する可能性のある男性には、本剤投与中及び投与終了後一定期間は適切な避妊をするよう指導すること。細菌を用いた復帰突然変異試験、哺乳類培養細胞を用いた染色体異常試験及びマウスを用いた小核試験において、遺伝毒性が報告されている。

9.5 妊婦
妊婦又は妊娠している可能性のある女性には投与しないこと。動物実験（ラット）において催奇形性作用、胎児致死作用が報告されている。[2.3、9.4.2 参照]

9.6 授乳婦
授乳しないことが望ましい。動物実験（ラット）で乳汁中への移行が報告されている。

9.7 小児等

9.7.1 小児悪性固形腫瘍（神経芽腫・網膜芽腫・肝芽腫・中枢神経系胚細胞腫瘍、再発又は難治性のユーイング肉腫ファミリー腫瘍・腎芽腫）に対する他の抗悪性腫瘍剤との併用療法においては、骨髄抑制、聴器障害、ファンコニー症候群等の腎障害の発現に特に注意し、用量並びに投与間隔に留意するなど患者の状態を観察しながら慎重に投与すること。

9.7.2 外国で、本剤を高用量で他の聴器毒性を有する薬剤と併用した場合、臨床上有意な聴力低下が小児患者に発現するとの報告がある。

9.8 高齢者
用量並びに投与間隔に留意するなど患者の状態を観察しながら慎重に投与すること。一般に生理機能（骨髄機能、肝機能、腎機能等）が低下している。

10. 相互作用

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
放射線照射	骨髄抑制等の副作用が増強することがあるので、併用療法を行う場合には、患者の状態を観察しながら、減量するなど用量に注意すること。	ともに骨髄抑制等の副作用を有する。
	胸部への放射線照射を併用した場合に、重篤な食道炎又は肺臓炎が発現したとの報告がある。併用する場合には、患者の状態に注意し、食道炎や肺陰影等が出現した場合には、本剤の投与及び放射線照射を直ちに中止し、適切な処置を行うこと。	機序は不明であるが、動物試験（マウス）で本剤による放射線感受性増加が認められている。
	本剤と放射線照射の併用により、肝中心静脈閉塞症（VOD）が発症したとの報告があるので、十分注意すること[1)]。	機序不明
抗悪性腫瘍剤	骨髄抑制等の副作用が増強することがあるので、併用療法を行う場合には、患者の状態を観察しながら、減量するなど用量に注意すること。	ともに骨髄抑制等の副作用を有する。
	本剤と他の抗悪性腫瘍剤の併用により､肝中心静脈閉塞症(VOD)が発症したとの報告があるので、十分注意すること[1)]。	機序不明
腎毒性及び聴器毒性を有する薬剤 アミノグリコシド系抗生物質等	腎障害及び聴器障害が増強することがあるので、併用療法を行う場合には、慎重に投与すること。	ともに腎障害及び聴器障害を有する。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 骨髄抑制

汎血球減少（0.1%未満)､貧血（ヘモグロビン減少（40.1%)、赤血球減少（36.1%)、ヘマトクリット値減少（31.7%))、白血球減少（56.4%)、好中球減少（7.4%)、血小板減少（42.7%)､出血（0.1%未満）等があらわれることがある。[8.1、9.1.1-9.1.2 参照]

11.1.2 ショック、アナフィラキシー（0.1%未満）

チアノーゼ、呼吸困難、胸内苦悶、血圧低下、気管支痙攣等があらわれた場合には投与を中止し、適切な処置を行うこと。なお、本剤の投与回数を重ねると、ショック、アナフィラキシーの発現頻度が高くなる傾向もみられる。[15.1.3 参照]

11.1.3 間質性肺炎（0.1%）

発熱、咳嗽、呼吸困難、胸部X線異常等を伴う間質性肺炎があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。

11.1.4 急性腎障害（0.1%未満)、**ファンコニー症候群**（頻度不明）

急性腎障害、ファンコニー症候群等があらわれることがあるので、観察を十分に行い、BUN、血清クレアチニン、クレアチニン・クリアランス値等に異常が認められた場合には投与を中止し､適切な処置を行うこと。[8.1 参照]

11.1.5 肝不全、肝機能障害、黄疸（いずれも頻度不明）

[8.1 参照]

11.1.6 消化管壊死、消化管穿孔、消化管出血、消化管潰瘍（いずれも頻度不明）

11.1.7 出血性腸炎、偽膜性大腸炎（頻度不明）

出血性腸炎、偽膜性大腸炎等があらわれることがあるので、観察を十分に行い、激しい腹痛・下痢等があらわれた場合には投与を中止し、適切な処置を行うこと。

11.1.8 麻痺性イレウス（0.1%未満）

腸管麻痺（食欲不振、悪心・嘔吐、著しい便秘、腹痛、腹部の膨満あるいは弛緩及び腸内容物のうっ滞等）を来し、麻痺性イレウスに移行することがあるので、腸管麻痺があらわれた場合には投与を中止し、腸管減圧法等の適切な処置を行うこと。

11.1.9 脳梗塞（0.1%未満)、**肺梗塞**（頻度不明）

11.1.10 血栓・塞栓症（頻度不明）

血栓・塞栓症（肺塞栓、脳血栓、その他の動脈又は静脈血栓症等）があらわれることがある。

11.1.11 心筋梗塞、うっ血性心不全（頻度不明）

11.1.12 溶血性尿毒症症候群（頻度不明）

血小板減少、溶血性貧血、腎不全を主徴とする溶血性尿毒症症候群があらわれることがある。[8.1 参照]

11.1.13 急性呼吸窮迫症候群（頻度不明）

急速に進行する呼吸困難、低酸素症、両側性びまん性肺浸潤影等の胸部X線異常等が認められた場合には投与を中止し、適切な処置を行うこと。

11.1.14 播種性血管内凝固症候群（DIC）（頻度不明）

血小板数、血清FDP値、血漿フィブリノゲン濃度等の血液検査に異常が認められた場合には投与を中止し、適切な処置を行うこと。

11.1.15 急性膵炎（頻度不明）

血清アミラーゼ値、血清リパーゼ値等に異常が認められた場合には投与を中止すること。

11.1.16 難聴（0.1%未満）

難聴、耳鳴等があらわれることがある。

11.1.17 白質脳症（可逆性後白質脳症症候群を含む）（頻度不明）

歩行時のふらつき、舌のもつれ、痙攣、頭痛、錯乱、視覚障害等が認められた場合には投与を中止し、適切な処置を行うこと。

11.1.18 腫瘍崩壊症候群（頻度不明）

異常が認められた場合には投与を中止し､適切な処置（生理食塩液、高尿酸血症治療剤等の投与、透析等）を行うとともに、症状が回復するまで患者の状態を十分に観察すること。[8.2 参照]

11.1.19 うっ血乳頭、球後視神経炎、皮質盲（頻度不明）

うっ血乳頭、球後視神経炎、皮質盲等の視覚障害があらわれることがある。

11.1.20 溶血性貧血（頻度不明）

クームス陽性の溶血性貧血があらわれることがある。

11.2 その他の副作用

	10%以上	1%～10%未満	1%未満	頻度不明
消化器	悪心･嘔吐[注1)]（50.5%)、食欲不振（45.4%）	下痢、口内炎、腹痛、便秘	口渇	
腎臓		血尿、蛋白尿	乏尿	
過敏症[注2)]		発疹	瘙痒感	蕁麻疹
精神神経系		末梢神経障害（しびれ等)、頭痛	耳鳴､聴力低下、視力障害､眩暈、痙攣､異常感覚、味覚異常、神経過敏、不安、不眠	
肝臓	ALT上昇（10.2%）	AST上昇、Al-P上昇、ビリルビン上昇、LDH上昇、γ-GTP上昇		

	10%以上	1%～10%未満	1%未満	頻度不明
循環器			心電図異常（期外収縮）、心悸亢進、血圧上昇、血圧低下、不整脈（頻脈、徐脈、心房細動、心房粗動、房室ブロック）	
電解質		血清ナトリウム、カリウム、クロール、カルシウム、リン、マグネシウム等の異常	抗利尿ホルモン分泌異常症候群	
皮膚	脱毛(18.3%)		色素沈着、爪の変色、皮膚疾患	
その他	全身倦怠感(18.6%)	発熱、浮腫	疼痛、潮紅、ほてり、胸部不快感、吃逆、注射部位反応(発赤、腫脹、疼痛、壊死、硬結等)、低蛋白血症	無力症、尿酸上昇、悪寒、脱水、体重減少、アルブミン低下、呼吸困難

注1）処置として制吐剤等の投与を行う。
注2）このような症状があらわれた場合には投与を中止すること。
「重大な副作用」及び「その他の副作用」の発現頻度は、承認時までの国内臨床試験620例に製造販売後の使用成績調査5,598例を含めた総症例6,218例による

13. 過量投与

13.1 症状

本剤を高用量で投与した際に、失明を含む視覚障害があらわれたとの報告がある。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 本剤は、イオウを含むアミノ酸（メチオニン及びシスチン）輸液中で分解が起こるため、これらのアミノ酸輸液との配合を避けること。

14.1.2 本剤は、アルミニウムと反応して沈殿物を形成し、活性が低下するので、使用にあたってはアルミニウムを含む医療器具を用いないこと。[14.2.1 参照]

14.1.3 本剤は、錯化合物であるので、他の抗悪性腫瘍剤とは混注しないこと。

14.1.4 本剤は細胞毒性を有するため、調製時には手袋を着用することが望ましい。皮膚に薬液が付着した場合は、直ちに多量の流水でよく洗い流すこと。

14.1.5 本剤は輸液と混和した後、できるだけ速やかに使用すること。

14.2 薬剤投与時の注意

14.2.1 使用にあたってはアルミニウムを含む医療器具を用いないこと。[14.1.2 参照]

14.2.2 本剤は、生理食塩液等の無機塩類（NaCl、KCl、$CaCl_2$等）を含有する輸液に混和するときは、8時間以内に投与を終了すること。

14.2.3 静脈内投与に際し、薬液が血管外に漏れると、注射部位に硬結・壊死等を起こすことがあるので、薬液が血管外に漏れないように慎重に投与すること。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 本剤は、シスプラチン投与で効果が認められなかった症例に対しては、有効性が認められていない。

15.1.2 本剤と他の抗悪性腫瘍剤の併用により、急性白血病（前白血病相を伴う場合もある）、骨髄異形成症候群（MDS）が発生したとの報告がある。

15.1.3 本剤の投与回数を重ねると、ショック、アナフィラキシーの発現頻度が高くなる傾向がみられ、特に白金製剤の投与回数が8回を超えるとその傾向は顕著となるとの報告がある。[11.1.2 参照]

15.2 非臨床試験に基づく情報

15.2.1 本剤は、細菌及びヒトリンパ芽球細胞に対し変異原性が認められており、また、ハムスターに対する染色体異常誘起性が認められている。

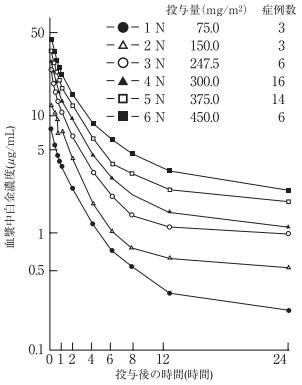
15.2.2 ラットの慢性毒性試験（静脈内投与）により耳下腺及び乳腺の腺癌、前立腺の前癌病変が発生したとの報告がある。

16. 薬物動態

16.1 血中濃度

癌患者にパラプラチンをカルボプラチンとして75～450 mg/m^{2}注)を1回点滴静注したときの血中濃度の推移は3相性の減衰曲線を示し、α相の半減期は0.16～0.32時間、β相は1.29～1.69時間、γ相は22～32時間であり、大部分のカルボプラチンは投与後速やかに、また、時間の経過とともに緩慢に血中より消失した[2)～4)]。

注）本剤の承認された用量は300～400 mg/m^{2}である。



カルボプラチン投与後の血漿中白金濃度

16.5 排泄

本剤の癌患者における尿中排泄は、投与後比較的速く、投与後24時間に57～82%が排泄された[2),3)]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国内臨床試験成績

臨床第Ⅱ相試験（本剤単独療法）による疾患別奏効率（寛解率）は次のとおりである。

疾患名	解析対象症例数	著効(CR)	有効(PR)	不変(NC)	進行(PD)	奏効率%(CR+PR)
頭頸部癌[5)]	67	1	13	35	18	20.9
肺小細胞癌[6)～9)]	116	1	30	56	29	26.7
睾丸腫瘍[10)]	21	1	9	7	4	47.6
卵巣癌[11)]	50	5	14	22	9	38.0
子宮頸癌[12)]	32	2	5	16	9	21.9
悪性リンパ腫[13)]	33	2	11	20		39.4

*）著効=完全寛解、有効=不完全寛解、不変・進行=無寛解

また、頭頸部癌及び卵巣癌を対象とした本剤を含む併用化学療法とシスプラチンを含む併用化学療法との臨床第Ⅲ相比較試験でも本剤の有用性が認められている[14),15)]。

臨床第Ⅱ相試験及び臨床第Ⅲ相試験の安全性評価症例620例（承認外の「効能・効果」に対する臨床試験の223例を含む）において報告された副作用及び臨床検査値異常の発現率は88.7%であり、主なものは悪心・嘔吐49.2%、食欲不振40.0%、全身倦怠感19.7%、発熱4.2%、血小板減少49.7%、白血球減少49.5%、ヘモグロビン減少37.4%、赤血球減少20.7%、ヘマトクリット値減少14.5%、AST上昇9.7%、ALT上昇9.5%、BUN上昇4.0%、クレアチニン・クリアランス低下2.7%、血中クレアチニン上昇2.3%等であった。

なお、パラプラチンはシスプラチンの臨床第Ⅱ相試験成績と比べ奏効率において統計学的に有意差は認められなかったが、シスプラチンの治療に耐えられない患者（腎機能が低下している患者、大量の水分負荷により心・循環器に障害を及ぼす患者、腎、尿路、膀胱の排尿経路に閉塞性障害を有する患者、悪心・嘔吐等の消化器症状が強くあらわれ治療に支障をきたす患者）に選択投与が可能であり、また、末梢神経障害、聴器毒性の発現率はシスプラチンより低かった。

17.1.2 海外臨床試験成績

海外における非小細胞肺癌を対象とした本剤単独療法による奏効率及び生存期間は次のとおりである。

研究者	解析対象症例数	奏効例（CR＋PR）	奏効率（%）	生存期間（中央値）
Kreisman et al.[16]	70	11	16	6.5カ月
Kramer et al.[17]	50	6	12	−
Bonomi et al.[18]	88	8	9	31.7週

また、近年、非小細胞肺癌に対して本剤を含む併用化学療法が汎用されており、これら併用化学療法における奏効率及び生存期間は次のとおりである。

併用療法	解析対象症例数	奏効例（CR＋PR）	奏効率（%）	生存期間（中央値）
カルボプラチン＋エトポシド[19]	102	16	16	27週
カルボプラチン＋パクリタキセル[20]	190	43	23	233日

18. 薬効薬理

18.1 作用機序

癌細胞内のDNA鎖と結合し、DNA合成及びそれに引き続く癌細胞の分裂を阻害するものと考えられている[21)〜23)]。

18.2 抗腫瘍作用

マウスのL1210白血病、P388白血病、B16メラノーマ、colon26結腸癌、M5076卵巣癌、Lewis肺癌に対して抗腫瘍作用が認められた。シスプラチン耐性卵巣癌細胞株KFr及びTYK-nu(R)細胞に対しカルボプラチンは交叉耐性を示したが、その程度はシスプラチンの1/2又は1/4であった[24)〜30)]。

19. 有効成分に関する理化学的知見

一般的名称：カルボプラチン（Carboplatin）

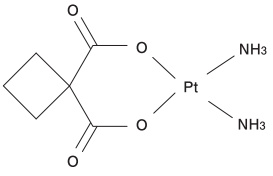
化学名：(*SP*-4-2)-Diammine[cyclobutan-1, 1-dicarboxylato(2-)-*O*, *O'*]platinum

分子式：$C_6H_{12}N_2O_4Pt$

分子量：371.25

性状：カルボプラチンは白色の結晶又は結晶性の粉末である。
水にやや溶けにくく、エタノール（99.5）に極めて溶けにくい。

化学構造式：



20. 取扱い上の注意

20.1 本剤は、光及び熱により分解するので、直射日光や高温を避け、外箱開封後は遮光して保存すること。

20.2 冷蔵庫保存では、結晶が析出することがある。

22. 包装

〈パラプラチン注射液50 mg〉
5 mL［1バイアル］

〈パラプラチン注射液150 mg〉
15 mL［1バイアル］

〈パラプラチン注射液450 mg〉
45 mL［1バイアル］

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*26. 製造販売業者等

26.1 製造販売元

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注）注意－医師等の処方箋により使用すること

1. 警告

1.1 本剤を含むがん化学療法は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本療法が適切と判断される症例についてのみ実施すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

1.2 本剤の骨髄抑制に起因したと考えられる死亡例（敗血症、脳出血）あるいは高度の過敏反応に起因したと考えられる死亡例が認められている。骨髄抑制等の重篤な副作用が起こることがあるので、頻回に臨床検査（血液検査、肝機能検査、腎機能検査等）を行うなど、患者の状態を十分に観察すること。本剤による重篤な過敏症状の発現を防止するため、本剤投与前に必ず前投薬を行うこと。［7.1.1、7.1.2 参照］また、前投薬を実施した患者においても死亡例が報告されているので、患者の状態に十分に注意し、重篤な過敏症状が発現した場合は、本剤の投与を直ちに中止し、適切な処置を行うこと。なお、重篤な過敏症状が発現した症例には、本剤を再投与しないこと。

2. 禁忌（次の患者には投与しないこと）

2.1 重篤な骨髄抑制のある患者［骨髄抑制は用量規制因子であり、感染症を伴い、重篤化する可能性がある。］
2.2 感染症を合併している患者［骨髄抑制により、感染症を増悪させるおそれがある。］
2.3 本剤又はポリオキシエチレンヒマシ油含有製剤（例えばシクロスポリン注射液等）に対し過敏症の既往歴のある患者
2.4 妊婦又は妊娠している可能性のある女性［9.5 参照］
2.5 次の薬剤を投与中の患者：ジスルフィラム、シアナミド、プロカルバジン塩酸塩［10.1 参照］

3. 組成・性状

3.1 組成

販　売　名		タキソール注射液30 mg	タキソール注射液100 mg
成　　分		1バイアル中の分量	
		5 mL	16.7 mL
有効成分	パクリタキセル	30 mg	100 mg
添加剤	ポリオキシエチレンヒマシ油	2.5 mL	8.35 mL
	無水エタノール	適量	適量

3.2 製剤の性状

外　　観	無色～微黄色澄明の粘稠性の油液
pH	4.3～6.3（10v/v%水溶液）
浸透圧比（生理食塩液に対する比）	約4（本剤50 mLを生理食塩液又は5%ブドウ糖液500 mLで希釈時）
	約3（本剤33.3 mLを生理食塩液又は5%ブドウ糖液500 mLで希釈時）

4. 効能又は効果

○卵巣癌
○非小細胞肺癌
○乳癌
○胃癌
○子宮体癌
○再発又は遠隔転移を有する頭頸部癌
○再発又は遠隔転移を有する食道癌
○血管肉腫
○進行又は再発の子宮頸癌
○再発又は難治性の胚細胞腫瘍（精巣腫瘍、卵巣腫瘍、性腺外腫瘍）

6. 用法及び用量

非小細胞肺癌及び子宮体癌にはA法を使用する。
乳癌にはA法又はB法を使用する。
卵巣癌にはA法又はカルボプラチンとの併用でC法を使用する。
胃癌にはA法又はE法を使用する。
再発又は難治性の胚細胞腫瘍には他の抗悪性腫瘍剤と併用でA法を使用する。
再発又は遠隔転移を有する頭頸部癌、再発又は遠隔転移を有する食道癌、血管肉腫にはB法を使用する。
進行又は再発の子宮頸癌にはシスプラチンとの併用において、D法を使用する。

A法：通常、成人にはパクリタキセルとして、1日1回210 mg/m^2（体表面積）を3時間かけて点滴静注し、少なくとも3週間休薬する。これを1クールとして、投与を繰り返す。
B法：通常、成人にはパクリタキセルとして、1日1回100 mg/m^2（体表面積）を1時間かけて点滴静注し、週1回投与を6週連続し、少なくとも2週間休薬する。これを1クールとして、投与を繰り返す。
C法：通常、成人にはパクリタキセルとして、1日1回80 mg/m^2（体表面積）を1時間かけて点滴静注し、週1回投与を3週連続する。これを1クールとして、投与を繰り返す。
D法：通常、成人にはパクリタキセルとして、1日1回135 mg/m^2（体表面積）を24時間かけて点滴静注し、少なくとも3週間休薬する。これを1クールとして、投与を繰り返す。

E法：通常、成人にはパクリタキセルとして、1日1回80 mg/m^2（体表面積）を1時間かけて点滴静注し、週1回投与を3週連続し、少なくとも2週間休薬する。これを1クールとして、投与を繰り返す。
なお、投与量は、患者の状態により適宜減量する。

7. 用法及び用量に関連する注意

7.1 本剤投与による重篤な過敏症状の発現を防止するため、本剤投与前に必ず前投薬を行うこと。

7.1.1 A法

本剤投与約12～14時間前及び約6～7時間前の2回、もしくは本剤投与約30分前までに投与を終了するように、1回デキサメタゾンリン酸エステルナトリウム注射液（デキサメタゾンとして20 mg）を静脈内投与、本剤投与約30分前までに投与を終了するように、ジフェンヒドラミン塩酸塩錠（ジフェンヒドラミン塩酸塩として50 mg）を経口投与、本剤投与約30分前までに投与を終了するように、ラニチジン塩酸塩注射液（ラニチジンとして50 mg）又は注射用ファモチジン（ファモチジンとして20 mg）を静脈内投与すること。

7.1.2 B法、C法、D法及びE法

(1) 本剤投与約30分前までに投与を終了するように、デキサメタゾンリン酸エステルナトリウム注射液（デキサメタゾンとして8 mg）及びラニチジン塩酸塩注射液（ラニチジンとして50 mg）又は注射用ファモチジン（ファモチジンとして20 mg）を静脈内投与、ジフェンヒドラミン塩酸塩錠（ジフェンヒドラミン塩酸塩として50 mg）を経口投与すること。

(2) デキサメタゾンは初回投与時8 mgとし、次回投与時までに過敏症状の発現がみられなかった場合又は臨床上特に問題のない過敏症状の場合は、2週目の投与より半量（4 mg）に減量し投与してもよい。以降の投与週においても同様の場合、半量ずつ最低1 mgまで減量し投与してもよい。

7.2 本剤の投与にあたっては、投与法毎に下記に留意し、必要に応じ休薬、減量を実施すること。また、重篤な末梢神経障害が発現した場合には、次回の投与量を骨髄抑制の減量の目安に従い、減量して投与することを考慮する。

・A法

白血球及び好中球の変動に十分留意し、投与前の臨床検査で白血球数が4,000/mm^{3}未満又は好中球数が2,000/mm^{3}未満であれば、骨髄機能が回復するまでは投与を延期すること。投与後、白血球数が1,000/mm^{3}未満となった場合には次回の投与量を減量すること。

・B法

各クールを開始する際（初回クールを含む）、投与前の臨床検査で白血球数が3,000/mm^{3}未満又は好中球数が1,500/mm^{3}未満であれば、骨髄機能が回復するまでは投与を延期すること。同一クール内での本剤の投与にあたっては、投与前の臨床検査で白血球数が2,000/mm^{3}未満又は好中球数が1,000/mm^{3}未満であれば、骨髄機能が回復するまでは投与を延期すること。投与後、白血球数が1,000/mm^{3}未満となった場合には次回の投与量を減量すること。

〈減量の目安〉

投与方法	減量段階	投与量
A法	通常投与量	210 mg/m^2
	1段階減量	180 mg/m^2
	2段階減量	150 mg/m^2
	3段階減量	135 mg/m^2
B法	通常投与量	100 mg/m^2
	1段階減量	80 mg/m^2
	2段階減量	60 mg/m^2

8. 重要な基本的注意

8.1 骨髄抑制等の重篤な副作用が起こることがあるので、頻回に臨床検査（血液検査、肝機能検査、腎機能検査等）を行うなど、患者の状態を十分に観察すること。また、使用が長期間にわたると副作用が強くあらわれ、遷延性に推移することがあるので、投与は慎重に行うこと。なお、白血球減少が軽度であっても著明な好中球減少を発現する症例を認めていることから、血液検査の際には、白血球分画の測定を実施すること。また、本剤の投与にあたってはG-CSF製剤の適切な使用に関しても考慮すること。

8.2 重篤な過敏反応が起こることがあるので、観察を十分に行い、重篤な過敏症状（呼吸困難、胸痛、低血圧、頻脈、徐脈、潮紅、血管浮腫、発汗等）があらわれた場合には、直ちに投与を中止し、適切な処置を行うこと。本剤投与開始後1時間は頻回にバイタルサイン（血圧、脈拍数）のモニタリングを行うなど、患者の状態を十分に観察すること。

8.3 低血圧、高血圧、徐脈等が起こることがあるので、本剤投与開始後1時間は頻回にバイタルサイン（血圧、脈拍数）のモニタリングを行うなど、患者の状態を十分に観察すること。重篤な刺激伝導障害があらわれた場合には、適切な処置を行い、その後の本剤投与に際しては継続的に心電図のモニタリングを行うなど、患者の状態を十分に観察すること。

8.4 関節痛及び筋肉痛が高頻度に起こるので、観察を十分に行い、症状があらわれた場合には鎮痛剤投与等の適切な処置を行うこと。症状は一般に、投与開始後2、3日後にあらわれ、また、早期のクール（1～3クール目）より発現する傾向にあるので、十分注意すること。

8.5 発熱が高頻度に起こるので、観察を十分に行い、症状があらわれた場合には感染に対する管理を十分に行い、解熱剤投与等の適切な処置を行うこと。発熱は一般に、投与開始後約6～10日後にあらわれ、また、1クール目の発現頻度が高い傾向にあるので、十分注意すること。

8.6 末梢神経障害が高頻度に起こるので、観察を十分に行うこと。症状は一般に、投与開始後約3～5日後にあらわれ、また、使用が長期間にわたると発現頻度が高くなる傾向にあるので、投与は慎重に行うこと。

8.7 投与初期又は比較的低用量の投与でも副作用があらわれることがあるので、使用上の注意に十分注意すること。

8.8 本剤は無水エタノールを含有するため、前投薬で投与されるジフェンヒドラミン塩酸塩錠とアルコールの相互作用による中枢神経抑制作用の増強の可能性があるので、本剤投与後の患者の経過を観察し、アルコール等の影響が疑われる場合には、自動車の運転等危険を伴う機械の操作に従事させないよう注意すること。

8.9 頭頸部癌、食道癌、血管肉腫、子宮頸癌、卵巣癌（C法）、胚細胞腫瘍、胃癌（E法）に本剤を使用する際には、関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議公知申請への該当性に係る報告書」[1)~7)]等）を熟読すること。

8.10 腫瘍崩壊症候群があらわれることがあるので、血清中電解質濃度及び腎機能検査を行うなど、患者の状態を十分に観察すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 骨髄抑制のある患者

骨髄抑制を増悪させるおそれがある。

9.1.2 アルコールに過敏な患者

本剤を投与する場合には問診により適切かどうか判断すること。本剤は溶剤として無水エタノールを含有するため、アルコールの中枢神経系への影響が強くあらわれるおそれがある。

9.1.3 間質性肺炎又は肺線維症のある患者

症状を増悪させるおそれがある。

9.2 腎機能障害患者
腎機能が低下しているので、副作用が強くあらわれるおそれがある。

9.3 肝機能障害患者
代謝機能等が低下しているので、副作用が強くあらわれるおそれがある。

9.4 生殖能を有する者
9.4.1 妊娠する可能性のある女性には、本剤投与中及び投与終了後一定期間は適切な避妊をするよう指導すること。［9.5 参照］

9.4.2 パートナーが妊娠する可能性のある男性には、本剤投与中及び投与終了後一定期間は適切な避妊をするよう指導すること。哺乳類培養細胞を用いた染色体異常試験及びマウス骨髄細胞を用いた小核試験において、遺伝毒性が報告されている。

9.4.3 小児及び生殖可能な年齢の患者に投与する必要がある場合には、性腺に対する影響を考慮すること。

9.5 妊婦
妊婦又は妊娠している可能性のある女性には投与しないこと。動物実験（ラット、ウサギ）において催奇形作用、胚・胎児死亡が報告されている。［2.4、9.4.1 参照］

9.6 授乳婦
授乳しないことが望ましい。動物実験（ラット）で乳汁中への移行が報告されている。

9.7 小児等
小児等を対象とした臨床試験は実施していない。

9.8 高齢者
用量並びに投与間隔に留意し、頻回に臨床検査（血液検査、肝機能検査、腎機能検査等）を行うなどして注意すること。一般に生理機能が低下していることが多く骨髄抑制等があらわれやすい。

10. 相互作用
10.1 併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
ジスルフィラム（ノックビン） シアナミド（シアナマイド） プロカルバジン塩酸塩（塩酸プロカルバジン）	アルコール反応（顔面潮紅、血圧降下、悪心、頻脈、めまい、呼吸困難、視力低下等）を起こすおそれがある。	本剤はエタノールを含有しているため。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
放射線照射	胸部への放射線照射を併用した場合に、重篤な食道炎又は肺臓炎が発現したとの報告がある。併用する場合には、患者の状態に注意し、食道炎や肺陰影等が出現した場合には、本剤の投与及び放射線照射を直ちに中止し、適切な処置を行うこと。	機序は不明であるが、動物試験（マウス）で本剤による放射線感受性増加が認められている。
	骨髄抑制等を増強することがあるので、併用する場合には、患者の状態を観察しながら、本剤を減量するか又は投与間隔を延長すること。	骨髄抑制等の予想される副作用項目が重複している。
抗悪性腫瘍剤	骨髄抑制等の副作用が増強するおそれがある。併用療法を行う場合には、患者の状態を観察しながら、減量するか又は投与間隔を延長すること。	骨髄抑制等の予想される副作用が重複している。
シスプラチン	本剤をシスプラチンの後に投与した場合、逆の順序で投与した場合より骨髄抑制が増強するおそれがある。併用療法を行う場合には、本剤をシスプラチンの前に投与すること。	本剤をシスプラチンの後に投与した場合、パクリタキセルのクリアランスが低下し、パクリタキセルの血中濃度が上昇する。
	末梢神経障害が増強するおそれがある。併用療法を行う場合には、患者の状態を観察しながら、減量するか又は投与間隔を延長すること。	末梢神経障害が予想される副作用として重複している。
ドキソルビシン塩酸塩	本剤をドキソルビシンの前に投与した場合、逆の順序で投与した場合より骨髄抑制が増強するおそれがある。併用療法を行う場合には、本剤をドキソルビシンの後に投与すること。	本剤をドキソルビシンの前に投与した場合、ドキソルビシンのクリアランスが低下し、ドキソルビシンの血中濃度が上昇する。
	心毒性が増強するおそれがある。併用療法を行う場合には、患者の状態を観察しながら、減量するか又は投与間隔を延長すること。	胆汁排泄の競合により、ドキソルビシン及びその代謝物であるドキソルビシノールの血中濃度が上昇する。
ビタミンA、 アゾール系抗真菌剤（ミコナゾール等）、 マクロライド系抗生剤（エリスロマイシン等）、 ステロイド系ホルモン剤（エチニルエストラジオール等）、 ジヒドロピリジン系カルシウムチャンネルブロッカー（ニフェジピン等）、 シクロスポリン、ベラパミル塩酸塩、キニジン硫酸塩水和物、ミダゾラム、フェナセチン、ラバチニブトシル酸塩水和物	骨髄抑制等の副作用が増強するおそれがある。併用療法を行う場合には、患者の状態を観察しながら、減量するか又は投与間隔を延長すること。	併用薬剤がP450-CYP2C8、CYP3A4等を阻害し、パクリタキセルの代謝が阻害され、パクリタキセルの血中濃度が上昇する。
N-メチルテトラゾールチオメチル基を有するセフェム系抗生物質 セフメノキシム塩酸塩、セフォペラゾンナトリウム、セフブペラゾンナトリウム、セフミノクスナトリウム水和物、セフメタゾールナトリウム、ラタモキセフナトリウム メトロニダゾール	アルコール反応（顔面潮紅、悪心、頻脈、多汗、頭痛等）を起こすおそれがある。	本剤はエタノールを含有しているため。

11. 副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用
11.1.1 ショック（0.2%）、**アナフィラキシー**（0.3%）
呼吸困難、胸痛、低血圧、頻脈、徐脈、潮紅、血管浮腫、発汗等の異常が認められた場合には投与を中止し、適切な処置を行うこと。

11.1.2 白血球減少等の骨髄抑制
白血球減少（61.4%）、好中球減少（55.5%）、貧血［ヘモグロビン減少（30.7%）、ヘマトクリット値減少（5.0%）、赤血球減少（11.2%）等］、血小板減少（11.7%）、汎血球減少等があらわれることがある。また、骨髄抑制の持続により、感染症［尿路感染（2.3%）、上気道感染（4.8%）、敗血症（0.9%）、帯状疱疹（1.0%）、肺炎（1.1%）等］の

併発が報告されている。感染症、出血傾向の発現又は増悪に十分注意すること。A法では、白血球及び好中球減少の最低値までの期間（中央値）はそれぞれ投与開始後11日後、13日後にあらわれ、最低値発現日から白血球、好中球ともに7日間（中央値）で回復した。また、B法では、白血球及び好中球減少の最低値までの期間（中央値）はともに投与開始後22日後にあらわれ、最低値発現日から白血球、好中球はそれぞれ14日間（中央値）、13日間（中央値）で回復した。

11.1.3 末梢神経障害、麻痺

しびれ等の末梢神経障害（43.8%）、麻痺（0.1%）、片麻痺（0.1%未満）、不全麻痺（頻度不明）があらわれることがある。

11.1.4 間質性肺炎（0.5%）、**肺線維症**（頻度不明）

発熱、咳嗽、呼吸困難及び胸部X線検査異常等が認められた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。

11.1.5 急性呼吸窮迫症候群（0.1%未満）

急速に進行する呼吸困難、低酸素症、両側性びまん性肺浸潤影等の胸部X線異常等が認められた場合には投与を中止し、適切な処置を行うこと。

11.1.6 心筋梗塞（0.1%未満）、**うっ血性心不全**（0.1%未満）、**心伝導障害**（頻度不明）、**肺塞栓**（0.1%）、**血栓性静脈炎**（0.4%）、**脳卒中**（0.1%未満）、**肺水腫**（0.1%未満）

11.1.7 難聴（0.2%）、**耳鳴**（0.5%）

11.1.8 消化管壊死（頻度不明）、**消化管穿孔**（0.1%未満）、**消化管出血**（0.1%未満）、**消化管潰瘍**（0.1%）

11.1.9 重篤な腸炎

出血性大腸炎（0.1%未満）、偽膜性大腸炎（頻度不明）、虚血性大腸炎（頻度不明）等があらわれることがあるので、激しい腹痛・下痢等があらわれた場合には投与を中止し、適切な処置を行うこと。

11.1.10 腸管閉塞、腸管麻痺

腸管閉塞（1.6%）、腸管麻痺（0.1%）（食欲不振、悪心・嘔吐、著しい便秘、腹痛、腹部膨満あるいは腹部弛緩及び腸内容物のうっ滞等）を来し、麻痺性イレウスに移行することがあるので、腸管閉塞、腸管麻痺があらわれた場合には投与を中止し、腸管減圧法等の適切な処置を行うこと。

11.1.11 肝機能障害（4.0%）、**黄疸**（0.1%未満）

11.1.12 膵炎（0.1%未満）

血清アミラーゼ値等に異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1.13 急性腎障害（0.2%）

BUN、血清クレアチニン、クレアチニン・クリアランス値等に異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1.14 中毒性表皮壊死融解症（Toxic Epidermal Necrolysis：TEN）（頻度不明）、**皮膚粘膜眼症候群（Stevens-Johnson症候群）**（頻度不明）

11.1.15 播種性血管内凝固症候群（DIC）（0.1%）

血小板数、血清FDP値、血漿フィブリノゲン濃度等の血液検査に異常が認められた場合には投与を中止し、適切な処置を行うこと。

11.1.16 腫瘍崩壊症候群（頻度不明）

異常が認められた場合には投与を中止し、適切な処置（生理食塩液、高尿酸血症治療剤等の投与、透析等）を行うとともに、症状が回復するまで患者の状態を十分に観察すること。

11.1.17 白質脳症（可逆性後白質脳症症候群を含む）（頻度不明）

歩行時のふらつき、痙攣、頭痛、視覚障害、高血圧、意識障害等が認められた場合には投与を中止し、適切な処置を行うこと。

＊11.2 その他の副作用

	20%以上	5%～20%未満	5%未満	頻度不明
過敏症[注1)]		発疹	発赤	
循環器		低血圧	不整脈、頻脈、徐脈、期外収縮、高血圧、心悸亢進、心電図異常、心房細動、心室細動、心肥大、狭心症	
消化器	悪心・嘔吐(35.1%)	下痢、食欲不振、口内炎、便秘	消化不良、鼓腸放屁、胃炎、腹部膨満感、直腸疼痛、嚥下障害、歯肉炎、直腸障害、口唇炎、舌苔、歯肉痛	食道炎、粘膜炎、腹水、腸間膜血栓症
肝臓		AST上昇、Al-P上昇、LDH上昇、ALT上昇	ビリルビン上昇	
泌尿器		電解質異常、BUN上昇	クレアチニン上昇、蛋白尿、排尿困難、血尿、尿失禁、尿閉、出血性膀胱炎	
＊皮膚	脱毛(45.3%)		そう痒、皮膚疾患、爪の障害、皮膚潰瘍、蕁麻疹、皮膚炎、色素沈着、皮膚乾燥、表皮剥離、皮膚腫脹、爪変色	斑状丘疹性皮疹、強皮症様変化、亜急性皮膚エリテマトーデス、手足症候群
精神神経系			めまい、不眠、不安、うつ病、傾眠、思考異常、振戦、失神、激越、神経学的疾患、痙攣、運動失調、健忘症、緊張低下、意識障害、寡動、言語障害、緊張亢進、精神症状、譫妄、眼振、不随意運動、嗄声、気分変動	
感覚器			味覚倒錯、味覚喪失、視力異常、眼疾患、結膜炎、耳痛、眼痛、霧視、流涙増加、眼精疲労、飛蚊症、眼乾燥、角膜炎、舌異常感、結膜出血、光視症	暗点、黄斑浮腫
呼吸器		呼吸困難	低酸素症、咳増加、喀痰増加、咽頭不快感	
全身症状		無力症、腹痛、倦怠感、頭痛	浮腫、疼痛、インフルエンザ様症候群、腹部腫脹、さむけ、体重増加、体重減少	
筋骨格	関節痛(32.3%)、筋肉痛(28.8%)	骨痛、背部痛	頸部痛、腰痛	筋力低下
その他		発熱、潮紅	胸痛、出血、注射部反応、末梢性浮腫、総蛋白減少、アルブミン減少、骨盤痛、発汗、吃逆、口渇、不正出血、無月経、注射部痛、酩酊感、高血糖、低血糖、脱水	血栓症

注1）投与を中止すること

注2）発現頻度は、卵巣癌、非小細胞肺癌、乳癌、胃癌、子宮体癌患者を対象とした国内第Ⅱ相試験及び卵巣癌、乳癌患者を対象とした海外第Ⅱ相試験、使用成績調査並びに市販後臨床試験の結果に基づき記載した。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 本剤は5%ブドウ糖注射液及び生理食塩液を除く他の薬剤とは混注しないこと。

14.1.2 本剤は細胞毒性を有するため、調製時には手袋を着用することが望ましい。皮膚に薬液が付着した場合は、直ちに多量の流水でよく洗い流すこと。

14.1.3 調製時に、注射針に塗布されているシリコーン油により不溶物を生じることがある。調製後に薬液中に不溶物がないか目視で確認すること。不溶物が認められた場合は使用しないこと。

14.2 薬剤投与時の注意

14.2.1 静脈内投与に際し、薬液が血管外に漏れると、注射部位に硬結・壊死を起こすことがあるので、薬液が血管外に漏れないように投与すること。また、以前に同反応を発現した注射部位とは異なる部位に本剤を再投与した場合、以前の注射部位に同反応を再発するといった、いわゆる「Recall現象」が認められたとの報告がある。

14.2.2 本剤は、輸液に混和後、できるだけ速やかに投与すること。

14.2.3 本剤投与時、A法では500 mLの5%ブドウ糖注射液又は生理食塩液に混和し、3時間かけて点滴静注すること。B法、C法及びE法では250 mLの5%ブドウ糖注射液又は生理食塩液に混和し、1時間かけて点滴静注すること。D法では12時間毎の2回に分けて調製及び投与すること。本剤投与量の半量を250 mLの5%ブドウ糖注射液又は生理食塩液に混和し、12時間かけて点滴静注する。これを1回分として、2回連続して投与する。

14.2.4 本剤の希釈液は、過飽和状態にあるためパクリタキセルが結晶として析出する可能性があるので、本剤投与時には、0.22ミクロン以下のメンブランフィルターを用いたインラインフィルターを通して投与すること。

14.2.5 点滴用セット等で本剤の溶解液が接触する部分に、可塑剤としてDEHP〔di-(2-ethylhexyl)phthalate：フタル酸ジ-(2-エチルヘキシル)〕を含有しているものの使用を避けること。

14.2.6 輸液ポンプを使用して本剤を投与する場合は、チューブ内にろ過網（面積の小さなフィルター）が組み込まれた輸液セットを使用すると、まれにポンプの物理的刺激により析出するパクリタキセルの結晶がろ過網を詰まらせ、ポンプの停止が起こることがあるので、ろ過網が組み込まれた輸液セットは使用しないこと。

14.2.7 本剤は非水性注射液であり、輸液で希釈された薬液は表面張力が低下し、1滴の大きさが生理食塩液などに比べ小さくなるため、輸液セットあるいは輸液ポンプを用いる場合は以下の点に十分注意すること。

・自然落下方式で投与する場合、輸液セットに表示されている滴数で投与速度を設定すると、目標に比べ投与速度が低下するので、滴数を増加させて設定する等の調整が必要である。

・滴下制御型輸液ポンプを用いる場合は、流量を増加させて設定する等の調整が必要である。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 使用成績調査において、重篤な間質性肺炎等の肺障害の発現率は、休薬期間が承認用法の3週間以上の症例では0.27%（5例/1,862例）であったが、3週間より短かった症例では1.41%（12例/852例）であった。

15.1.2 放射線療法に関連した照射部位の皮膚異常を発現した既往のある患者に本剤を投与した場合、同部位に同様の皮膚異常を再発するといった、いわゆる「Radiation recall現象」が認められたとの報告がある。

15.1.3 本剤と他の抗悪性腫瘍剤や放射線療法を併用した患者で、急性白血病、骨髄異形成症候群（MDS）が発生したとの報告がある。

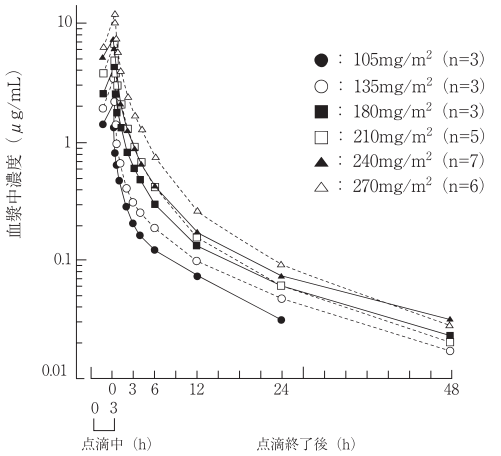
16. 薬物動態

16.1 血中濃度

16.1.1 単回投与

各種悪性腫瘍患者に本剤105～270 mg/m^{2}を3時間かけて点滴静注したときの血漿中濃度は2相性の消失を示し、半減期は9.9～16.0時間であった。AUC及びC_{max}は用量依存的な増加傾向を示した。血中動態は非線形性を示し、AUC及びC_{max}は投与量の増加に比例する以上の増加傾向を示した[8),9)]。

（注）本剤の承認されたA法の用量は210 mg/m^{2}である。

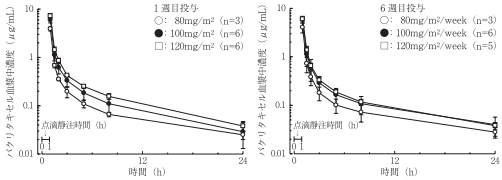


パクリタキセル3時間点滴静注時の血漿中濃度

16.1.2 反復投与

非小細胞肺癌患者に本剤80～120 mg/m^{2}を1時間かけて点滴静注したとき、半減期は8.5～11.6時間であった。AUC及びC_{max}は用量依存的な増加傾向を示した。血中動態は非線形性を示し、AUC及びC_{max}は投与量の増加に比例する以上の増加傾向を示した。また、6週間投与においても蓄積はなく、薬物動態に変化はみられなかった[8),9)]。

(注)本剤のB法の承認は、乳癌に100 mg/m^{2}の用量である。



パクリタキセル1時間点滴静注時の血漿中濃度

血漿中濃度パラメータ（100 mg/m^{2}投与時の平均値）

	C_{max}	AUC	$t_{1/2}$	CLT	V_{SS}
1週目投与時	5.9 μg/mL	8.1 μg·h/mL	8.5h	211.5 mL/min/m^2	50.0 L/m^2
6週目投与時	5.9 μg/mL	8.5 μg·h/mL	12.0h	208.1 mL/min/m^2	71.0 L/m^2

16.3 分布

ラットに^{14}C標識体を単回静注した後の組織内放射能濃度は、脳、中枢神経系を除く各臓器・組織に速やかに移行し、特に、肝臓、消化管、胸腺、腎臓、唾液腺、膵臓、肺、脾臓で高値を示した。投与後120時間後においても胸腺では比較的高濃度の放射能が検出されたが、この時点での放射能の体内残存率は1%未満であった。ヒト血清を用いて*in vitro*で蛋白結合率を測定した結果、0.1～50 μg/mLの濃度範囲で88.4～90.6%であった[10),11)]。

16.4 代謝

動物（ラット、イヌ）において本剤は主として肝臓で代謝され胆汁中へ排泄された。代謝反応としては水酸化、脱アセチル化、エピ化、加水分解が確認又は推定されたが、未

変化体及び代謝物の抱合体は検出されなかった。ヒトにおける主代謝物はタキサン環6位の水酸化及び3'位フェニル基の水酸化体で、これらの代謝にはP450-CYP2C8、CYP3A4等の分子種が関与していることが知られている[12)～16)]。

16.5 排泄

各種悪性腫瘍患者に本剤105～270 mg/m^{2}を3時間かけて点滴静注したときの未変化体の尿中排泄率は、投与後75時間までで6～12%であった[8)]。

（注）本剤の承認されたA法の用量は210 mg/m^{2}である。

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国内臨床試験

(1) A法

日本国内における本剤単独3時間点滴静注のA法による第Ⅱ相試験は、卵巣癌患者66例、非小細胞肺癌患者122例、乳癌患者65例、胃癌患者107例、子宮体癌23例を対象として実施された。適格例に対する奏効率は、卵巣癌26.6%（17/64）、非小細胞肺癌35.0%（42/120）、乳癌33.9%（21/62）、胃癌23.4%（25/107）、子宮体癌30.4%（7/23）であった[17)～24)]。

総症例3,817例（承認時500例、使用成績調査3,169例及び市販後臨床試験148例）における副作用及び臨床検査値異常の発現率は83.3%（3,181例/3,817例）であり、主な副作用は末梢神経障害（37.6%）、関節痛（23.5%）、筋肉痛（18.7%）及び悪心（21.3%）、嘔吐（15.0%）等の消化器症状であり、その他脱毛(30.5%)、発熱(11.0%)等が認められた。臨床検査値異常は白血球数減少（48.5%)、好中球数減少（43.8%）、ヘモグロビン減少（16.6%）、血小板数減少（10.6%）等の骨髄抑制が主であり、AST上昇（8.0%)、ALT上昇（9.4%）等の肝機能検査値異常、BUN上昇（4.0%）等の腎機能検査値異常が認められた。また、臨床試験における間質性肺炎の発現率は、1.6%（6例/373例）であった。

(2) B法

本剤単独1時間点滴静注のB法による第Ⅱ相試験は、乳癌患者69例を対象として実施された。有効性評価対象例に対する奏効率は、乳癌44.9%（31/69）であった[25), 26)]。安全性評価対象181例（承認外の「効能・効果」に対する臨床試験の112例を含む）において報告された主な副作用及び臨床検査値異常変動は下表のとおりである。また、臨床試験における間質性肺炎の発現率は、2.2%（4例/181例）であった。

主な副作用発現率（10%以上の副作用）

総投与量（中央値）	1,100 mg/m^2	
副作用	全体	Grade3以上
脱毛症	92.3%	–[a]
発疹	37.6%	1.1%
爪の障害	20.4%	–[a]
感覚減退[b]	76.8%	5.0%
味覚異常	12.7%	–[a]
浮動性めまい	11.0%	0.6%
疲労	70.2%	2.8%
浮腫	17.1%	0.6%
発熱	12.2%	0%
悪心	39.2%	2.2%
嘔吐	18.2%	1.7%
下痢	29.8%	1.1%
便秘	22.1%	3.9%
食欲不振	21.0%	1.7%
口内炎	17.7%	0%
筋痛	43.1%	0%
関節痛	39.8%	0%
鼻咽頭炎	18.2%	0%
体重減少	12.7%	0.6%
体重増加	10.5%	0%
総投与量（中央値）	1,100 mg/m^2	
副作用	全体	Grade3以上
高血圧	12.7%	1.1%

判定基準：「NCI-CTC version 2」
a NCI-CTCではGrade3～4の評価基準がない
b しびれ等の末梢神経障害

主な臨床検査値異常（10%以上の臨床検査値異常）

総投与量（中央値）	1,100 mg/m^2	
臨床検査値異常変動項目	全体	Grade3以上
白血球数減少	77.9%（141/181）	24.3%（44/181）
好中球数減少	75.1%（136/181）	31.5%（57/181）
ヘモグロビン減少	74.0%（134/181）	4.4%（ 8/181）
赤血球数減少	62.4%（113/181）	–
血小板数増加	16.0%（ 29/181）	–
ALT上昇	38.1%（ 69/181）	1.1%（ 2/181）
AST上昇	28.7%（ 52/181）	1.1%（ 2/181）
LDH上昇	26.5%（ 48/181）	–
Al-P上昇	10.6%（ 19/180）	0.6%（ 1/180）
CRP増加	52.6%（ 90/171）	–
血中アルブミン減少	27.6%（ 50/181）	1.1%（ 2/181）
総蛋白減少	22.2%（ 40/180）	–
血中ナトリウム減少	16.7%（ 30/180）	3.9%（ 7/180）
血中カリウム増加	15.6%（ 28/180）	1.1%（ 2/180）
尿中蛋白陽性	12.7%（ 22/173）	0.6%（ 1/173）
BUN上昇	11.6%（ 21/181）	–

判定基準：「NCI-CTC version 2」

17.1.2 海外臨床試験

海外における本剤単独3時間点滴静注の3週間隔投与（用量175 mg/m^{2}又は135 mg/m^2 注)）による第Ⅱ相試験は、卵巣癌患者195例、乳癌患者471例を対象として実施された。全症例に対する奏効率は、卵巣癌14.9%（29/195）、乳癌24.6%（116/471）であった[27), 28)]。

本剤投与による安全性評価症例1,106例中（本剤単独3時間点滴静注の3週間隔投与(用量175 mg/m^{2}又は135 mg/m^2 注)）による臨床試験の651例を含む)、主な副作用は筋肉痛・関節痛（61.4%)、末梢神経障害（59.3%）及び悪心・嘔吐(50.8%)、腹痛（39.8%)、下痢（35.7%）等の消化器症状であり、その他脱毛（88.7%)、無力症（64.0%)、発熱(33.5%）等が認められた。主な臨床検査値異常は白血球減少（90.3%)、好中球減少（88.7%)、ヘモグロビン減少(72.3%)、血小板減少（15.6%）等の骨髄抑制であり、AST(29.7%)、ALT（37.6%）の上昇等の肝機能検査値異常、BUN上昇（32.2%）等の腎機能検査値異常が認められた。

注）本剤の承認されたA法の用量は210 mg/m^{2}である。

18. 薬効薬理

18.1 作用機序

微小管蛋白重合を促進することにより微小管の安定化・過剰形成を引き起こし、紡錘体の機能を障害することにより細胞分裂を阻害して抗腫瘍活性を発揮する。

また、パクリタキセル処理培養癌細胞（HeLa細胞）を用いて染色体の動態を検討したところ、経時的にG2＋M期細胞の増加とG1期細胞の減少が認められ、薬剤添加18及び27時間後にはほとんどの細胞がG2＋M期であり、4倍体の染色体を示した。この結果より、パクリタキセルは細胞周期をG2＋M期でブロックすると考えられた[29)～33)]。

18.2 抗腫瘍作用

マウス可移植性ヒト卵巣癌(A2780)、非小細胞肺癌(LX-1、L2987、H2981)、乳癌（MCF-7、MX-1)、胃癌（MKN-1、MKN-45、MKN-74、St-4)、子宮体癌（EC-1-JCK）に対し、腫瘍退縮効果あるいは腫瘍増殖抑制効果が認められている。*in vitro*の試験で、シスプラチン（CDDP）感受性ヒト卵巣癌培養細胞KF1とそのCDDP耐性株KFrbに対し、腫瘍増殖抑制効果が認められている。

また、CDDP耐性株（A2780卵巣癌）での検討において、パクリタキセルは交叉耐性を示さなかった[34)～42)]。

19. 有効成分に関する理化学的知見

一般的名称：パクリタキセル（Paclitaxel）

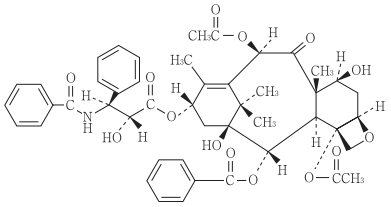
化　学　名：(−)-(1*S*,2*S*,3*R*,4*S*,5*R*,7*S*,8*S*,10*R*,13*S*)-4,10-Diacetoxy-2-benzoyloxy-5,20-epoxy-1,7-dihydroxy-9-oxotax-11-en-13-yl(2*R*,3*S*)-3-benzoylamino-2-hydroxy-3-phenylpropionate

分　子　式：$C_{47}H_{51}NO_{14}$

分　子　量：853.91

性　　状：パクリタキセルは白色～微黄白色の粉末である。ベンジルアルコールに溶けやすく、アセトニトリル又はメタノールにやや溶けやすく、エタノール（99.5）に溶けにくく、水にほとんど溶けない。

化学構造式：



融　　点：220～223℃

20. 取扱い上の注意

20.1 包装開封後もバイアルを箱に入れて保存すること。

22. 包装

〈タキソール注射液30 mg〉

5 mL（パクリタキセル30 mg含有）［1バイアル］

〈タキソール注射液100 mg〉

16.7 mL（パクリタキセル100 mg含有）［1バイアル］

23. 主要文献

1)医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：パクリタキセル（頭頸部癌）
2)医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：パクリタキセル（食道癌）
3)医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：パクリタキセル（血管肉腫）
4)医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：パクリタキセル（子宮頸癌）
5)医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：パクリタキセル（卵巣癌の週1回投与の用法・用量の追加）
6)医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：パクリタキセル（再発又は難治性の胚細胞腫瘍）
7)医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書：パクリタキセル（胃癌に対する週1回投与の用法・用量追加）
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**24. 文献請求先及び問い合わせ先

チェプラファーム株式会社　メディカルインフォメーションセンター
〒101-0021　東京都千代田区外神田4丁目14-1
TEL：0120-772-073
https://www.cheplapharm.jp/

**26. 製造販売業者等

26.1 製造販売元

チェプラファーム株式会社
東京都千代田区外神田４丁目１４-１

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＊2024年2月改訂（第5版）

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販売開始	2015年5月	2015年5月

抗悪性腫瘍剤
レンバチニブメシル酸塩製剤

劇薬、処方箋医薬品[注)]

レンビマ®カプセル4mg
レンビマ®カプセル10mg
Lenvima® capsules

注）注意－医師等の処方箋により使用すること

1. 警告

本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の使用が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に本剤の有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

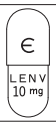
2.1 本剤の成分に対し過敏症の既往歴のある患者
2.2 妊婦又は妊娠している可能性のある女性［9.5参照］

3. 組成・性状

3.1 組成

販売名	レンビマカプセル4mg	レンビマカプセル10mg
有効成分	1カプセル中 レンバチニブメシル酸塩4.90mg（レンバチニブとして4mg）	1カプセル中 レンバチニブメシル酸塩12.25mg（レンバチニブとして10mg）
添加剤	結晶セルロース、タルク、沈降炭酸カルシウム、低置換度ヒドロキシプロピルセルロース、ヒドロキシプロピルセルロース、ヒプロメロース、D-マンニトール、ラウリル硫酸ナトリウム	結晶セルロース、タルク、沈降炭酸カルシウム、低置換度ヒドロキシプロピルセルロース、ヒドロキシプロピルセルロース、ヒプロメロース、D-マンニトール、ラウリル硫酸ナトリウム

3.2 製剤の性状

販売名	レンビマカプセル4mg	レンビマカプセル10mg
剤形	硬カプセル	硬カプセル
識別コード	ЄLENV 4mg	ЄLENV 10mg
外形		
全長（mm）	14.3	14.3
質量（mg）	137	137
号数	4	4
色	カプセル 上半分：黄赤色不透明 下半分：黄赤色不透明 内容物 白色の顆粒	カプセル 上半分：黄赤色不透明 下半分：黄色不透明 内容物 白色の顆粒

4. 効能又は効果

〈レンビマカプセル4mg〉
根治切除不能な甲状腺癌、切除不能な肝細胞癌、切除不能な胸腺癌、がん化学療法後に増悪した切除不能な進行・再発の子宮体癌、根治切除不能又は転移性の腎細胞癌
〈レンビマカプセル10mg〉
根治切除不能な甲状腺癌、切除不能な胸腺癌、がん化学療法後に増悪した切除不能な進行・再発の子宮体癌、根治切除不能又は転移性の腎細胞癌

5. 効能又は効果に関連する注意

〈根治切除不能な甲状腺癌〉
5.1 放射性ヨウ素による治療歴のない分化型甲状腺癌患者に対する本剤の有効性及び安全性は確立していない。
5.2 臨床試験に組み入れられた患者の病理組織型等について、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。［17.1.1、17.1.2参照］
〈切除不能な肝細胞癌〉
5.3 局所療法（経皮的エタノール注入療法、ラジオ波焼灼療法、マイクロ波凝固療法、肝動脈塞栓療法／肝動脈化学塞栓療法、放射線療法等）の適応となる肝細胞癌患者に対する本剤の有効性及び安全性は確立していない。
5.4 臨床試験に組み入れられた患者の肝機能障害の程度等について、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。［17.1.3参照］
〈切除不能な胸腺癌〉
5.5 本剤の術前補助療法としての有効性及び安全性は確立していない。
5.6「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。［17.1.4参照］
〈がん化学療法後に増悪した切除不能な進行・再発の子宮体癌〉
5.7 本剤の一次治療における有効性及び安全性は確立していない。
5.8 本剤の術後補助療法における有効性及び安全性は確立していない。
5.9「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。［17.1.5参照］
〈根治切除不能又は転移性の腎細胞癌〉
5.10 本剤の術後補助療法における有効性及び安全性は確立していない。

6. 用法及び用量

	効能又は効果	用法及び用量
レンビマカプセル4mg レンビマカプセル10mg	根治切除不能な甲状腺癌 切除不能な胸腺癌	通常、成人にはレンバチニブとして1日1回24mgを経口投与する。なお、患者の状態により適宜減量する。
	がん化学療法後に増悪した切除不能な進行・再発の子宮体癌 根治切除不能又は転移性の腎細胞癌	ペムブロリズマブ（遺伝子組換え）との併用において、通常、成人にはレンバチニブとして1日1回20mgを経口投与する。なお、患者の状態により適宜減量する。

	効能又は効果	用法及び用量
レンビマカプセル4mg	切除不能な肝細胞癌	通常、成人には体重にあわせてレンバチニブとして体重60kg以上の場合は12mg、体重60kg未満の場合は8mgを1日1回、経口投与する。なお、患者の状態により適宜減量する。

7. 用法及び用量に関連する注意

〈根治切除不能な甲状腺癌、切除不能な胸腺癌〉

7.1 本剤と他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。

7.2 副作用があらわれた場合は、症状、重症度等に応じて以下の基準を考慮して、本剤を減量、休薬又は中止すること。減量して投与を継続する場合には、1日1回20mg、14mg、10mg、8mg又は4mgに減量すること。

減量、休薬及び中止基準

副作用	程度*	処置
高血圧[8.1、9.1.1、11.1.1参照]	収縮期血圧140mmHg以上又は拡張期血圧90mmHg以上のとき	本剤の投与を継続し、降圧剤の投与を行う。
	降圧治療にも係らず、収縮期血圧160mmHg以上又は拡張期血圧100mmHg以上のとき	収縮期血圧150mmHg以下及び拡張期血圧95mmHg以下になるまで本剤を休薬し、降圧剤による治療を行う。 本剤の投与を再開する場合、1段階減量する。
	Grade 4の副作用が発現した場合	本剤の投与を中止する。
上記以外の副作用	忍容性がないGrade 2又はGrade 3の副作用が発現した場合	本剤の投与開始前の状態又はGrade 1以下に回復するまで休薬する(悪心・嘔吐・下痢に対しては休薬の前に適切な処置を行い、コントロールできない場合に本剤を休薬すること)。 本剤の投与を再開する場合、1段階減量する。
	Grade 4の副作用が発現した場合 (生命を脅かさない臨床検査値異常の場合は、Grade 3の副作用と同じ処置とする)	本剤の投与を中止する。

*：GradeはCTCAE（Common Terminology Criteria for Adverse Events）version 4.0に準じる。

〈切除不能な肝細胞癌〉

7.3 本剤と他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。

7.4 臨床試験において、中等度（Child-Pughスコア7～8）の肝機能障害を有する肝細胞癌患者に対する最大耐用量は1日1回8mgであることが確認されている。[9.3.2参照]

7.5 副作用があらわれた場合は、症状、重症度等に応じて以下の基準を考慮して、本剤を減量、休薬又は中止すること。

減量段階基準

開始用量	1段階減量	2段階減量	3段階減量
12mgを1日1回投与	8mgを1日1回投与	4mgを1日1回投与	4mgを隔日投与
8mgを1日1回投与	4mgを1日1回投与	4mgを隔日投与	投与を中止する

減量、休薬及び中止基準

副作用	程度*	処置
高血圧[8.1、9.1.1、11.1.1参照]	収縮期血圧140mmHg以上又は拡張期血圧90mmHg以上のとき	本剤の投与を継続し、降圧剤の投与を行う。
	降圧治療にも係らず、収縮期血圧160mmHg以上又は拡張期血圧100mmHg以上のとき	収縮期血圧150mmHg以下及び拡張期血圧95mmHg以下になるまで本剤を休薬し、降圧剤による治療を行う。 本剤の投与を再開する場合、1段階減量する。
	Grade 4の副作用が発現した場合	本剤の投与を中止する。
血液毒性及び蛋白尿[8.2、8.3、11.1.8、11.1.14参照]	Grade 3の副作用が発現した場合(臨床的に意義がない臨床検査値異常の場合を除く)	本剤の投与開始前の状態又はGrade 2以下に回復するまで休薬する。 本剤の投与を再開する場合、初回の副作用発現時は減量せず、2回目以降の副作用発現時は1段階減量する。
	Grade 4の副作用が発現した場合	本剤の投与開始前の状態又はGrade 2以下に回復するまで休薬する。 本剤の投与を再開する場合、1段階減量する。
上記以外の副作用	忍容性がないGrade 2の副作用が発現した場合	本剤の投与開始前の状態若しくはGrade 1以下に回復するまで休薬する、又は本剤の投与量を1段階減量して投与を継続する（悪心・嘔吐・下痢・甲状腺機能低下に対しては休薬又は減量の前に適切な処置を行い、コントロールできない場合に本剤を休薬又は減量すること)。 本剤の投与を再開する場合、1段階減量する。
	Grade 3の副作用が発現した場合(臨床的に意義がない臨床検査値異常の場合を除く)	本剤の投与開始前の状態又はGrade 1以下に回復するまで休薬する(悪心・嘔吐・下痢・甲状腺機能低下に対しては休薬の前に適切な処置を行い、コントロールできない場合に本剤を休薬すること)。 本剤の投与を再開する場合、1段階減量する。
	Grade 4の副作用が発現した場合 (生命を脅かさない臨床検査値異常の場合は、Grade 3の副作用と同じ処置とする)	本剤の投与を中止する。

*：GradeはCTCAE version 4.0に準じる。

〈がん化学療法後に増悪した切除不能な進行・再発の子宮体癌、根治切除不能又は転移性の腎細胞癌〉

7.6 副作用があらわれた場合は、症状、重症度等に応じて以下の基準を考慮して、本剤を減量、休薬又は中止すること。減量して投与を継続する場合には、1日1回14mg、10mg、8mg又は4mgに減量すること。

減量、休薬及び中止基準

副作用	程度*	処置
高血圧 [8.1、9.1.1、11.1.1参照]	収縮期血圧140mmHg以上又は拡張期血圧90mmHg以上のとき	本剤の投与を継続し、降圧剤の投与を行う。
	降圧治療にも係らず、収縮期血圧160mmHg以上又は拡張期血圧100mmHg以上のとき	収縮期血圧150mmHg以下及び拡張期血圧95mmHg以下になるまで本剤を休薬し、降圧剤による治療を行う。 本剤の投与を再開する場合、1段階減量する。
	Grade 4の副作用が発現した場合	本剤の投与を中止する。
上記以外の副作用	忍容性がないGrade 2又はGrade 3の副作用が発現した場合	本剤の投与開始前の状態又は忍容性のあるGrade 2以下に回復するまで休薬する（悪心・嘔吐・下痢・甲状腺機能低下に対しては休薬又は減量の前に適切な処置を行い、コントロールできない場合に本剤を休薬又は減量すること）。 本剤の投与を再開する場合、1段階減量する。
	Grade 4の副作用が発現した場合 （生命を脅かさない臨床検査値異常の場合は、Grade 3の副作用と同じ処置とする）	本剤の投与を中止する。

*：GradeはCTCAE version 4.0に準じる。

8. 重要な基本的注意

〈効能共通〉

8.1 血圧の上昇が認められることがあるので、本剤の投与開始前及び投与期間中は定期的に血圧測定を行うこと。[7.2、7.5、7.6、9.1.1、11.1.1参照]

8.2 蛋白尿があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に尿蛋白を観察すること。[7.5、11.1.8参照]

8.3 骨髄抑制があらわれることがあるので、定期的に血液学的検査を行うなど、患者の状態を十分に観察すること。[7.5、11.1.14参照]

8.4 肝障害があらわれることがあるので、本剤の投与期間中は定期的に肝機能検査、血中アンモニア値の測定を行うなど、患者の状態を十分に観察すること。[11.1.6参照]

8.5 心機能不全があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に心エコー、十二誘導心電図検査等の心機能検査を行うなど、患者の状態を十分に観察すること。[11.1.11参照]

8.6 創傷治癒を遅らせる可能性があるので、外科的処置が予定されている場合には、外科的処置の前に本剤の投与を中断すること。外科的処置後の投与再開は、患者の状態に応じて判断すること。[9.1.4、11.1.16参照]

8.7 疲労、無力症、めまい、筋痙縮等があらわれることがあるので、自動車の運転等、危険を伴う機械の操作に従事する際には注意するよう患者に十分に説明すること。

8.8 定期的に血清カルシウム濃度を測定すること。[11.1.15参照]

8.9 甲状腺機能低下があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に甲状腺機能検査を行うなど、患者の状態を十分に観察すること。[11.1.18参照]

〈根治切除不能な甲状腺癌〉

8.10 本剤投与前には頸動脈・静脈等への腫瘍浸潤を十分確認するとともに、本剤の投与期間中は患者の状態の観察や瘻孔形成の有無の確認を十分に行うこと。[9.1.5、11.1.3参照]

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 高血圧症の患者

高血圧が悪化するおそれがある。[7.2、7.5、7.6、8.1、11.1.1参照]

9.1.2 脳転移のある患者

転移部位からの出血があらわれるおそれがある。[11.1.3参照]

9.1.3 血栓塞栓症又はその既往歴のある患者

血栓塞栓症が悪化又は再発するおそれがある。[11.1.4、11.1.5参照]

9.1.4 外科的処置後、創傷が治癒していない患者

創傷治癒遅延があらわれることがある。[8.6、11.1.16参照]

9.1.5 頸動脈・静脈等への腫瘍浸潤のある患者

腫瘍縮小・壊死に伴う頸動脈露出、頸動脈出血、腫瘍出血があらわれることがある。なお、甲状腺未分化癌患者では、頸動脈・静脈への腫瘍浸潤例が多いので、特に注意すること。[8.10、11.1.3参照]

9.1.6 肺転移を有する患者

気胸が発現するおそれがある。[11.1.9参照]

9.3 肝機能障害患者

9.3.1 重度の肝機能障害のある患者

減量を考慮するとともに、患者の状態をより慎重に観察し、有害事象の発現に十分注意すること。本剤の血中濃度が上昇するとの報告がある。なお、重度の肝機能障害を有する肝細胞癌患者に対する臨床試験は実施していない。[16.6.2参照]

9.3.2 中等度の肝機能障害のある肝細胞癌患者

減量を考慮するとともに、患者の状態を慎重に観察し、有害事象の発現に十分注意すること。なお、中等度（Child-Pughスコア9）の肝機能障害を有する肝細胞癌患者に対する臨床試験は実施していない。[7.4参照]

＊＊9.4 生殖能を有する者

妊娠する可能性のある女性には、本剤投与中及び最終投与後30日間において避妊する必要性及び適切な避妊法について説明すること。[9.5参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、投与しないこと。外国臨床試験において、本剤の投与終了後に妊娠が判明し、自然流産となったことが報告されている。ラット及びウサギにおいて胚毒性・催奇形性が報告されている。なお、ラットでは臨床曝露量以下で認められた。[2.2、9.4参照]

9.6 授乳婦

授乳しないことが望ましい。ラットにおいて乳汁中へ移行することが報告されている。

9.7 小児等

小児等を対象とした臨床試験は実施していない。幼若ラットを用いた反復投与毒性試験において、切歯の異形成及び骨の短小など成長を阻害する影響が認められ、成熟ラットに比較し、致死量での死亡がより早期にみられた。[15.2.2参照]

9.8 高齢者

患者の状態を十分に観察し、慎重に投与すること。一般に高齢者では生理機能が低下していることが多く、副作用があらわれやすい。

10. 相互作用

本剤はP糖蛋白（P-gp）及びCYP3Aの基質となる。[16.4参照]

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
P-gp阻害剤 ケトコナゾール イトラコナゾール リファンピシン アミオダロン クラリスロマイシン シクロスポリン キニジン ベラパミル等 [16.7.1参照]	本剤の血中濃度が上昇する可能性がある。	これらの薬剤が消化管のP-gp活性を阻害することによる。
CYP3A／P-gp誘導剤 リファンピシン フェニトイン カルバマゼピン セイヨウオトギリソウ（St. John's Wort、セント・ジョーンズ・ワート）含有食品等 [16.7.2参照]	本剤の血中濃度が低下する可能性がある。	これらの薬剤がCYP3A及びP-gp等を誘導することによる。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 高血圧

高血圧（56.8%）、高血圧クリーゼ（0.2%）等があらわれることがある。必要に応じて降圧剤の投与を行うなど適切な処置を行うこと。重症、持続性あるいは通常の降圧治療でコントロールできない高血圧があらわれた場合には、減量、休薬又は投与を中止すること。また、高血圧クリーゼがあらわれた場合には投与を中止し、適切な処置を行うこと。[7.2、7.5、7.6、8.1、9.1.1参照]

＊**11.1.2 動脈解離**（頻度不明）

大動脈解離を含む動脈解離があらわれることがある[1)]。

11.1.3 出血（14.9%）

鼻出血、血尿、消化管出血、喀血、脳出血、肺出血、腫瘍出血等の出血があらわれることがある。また、甲状腺癌患者において、腫瘍縮小・壊死に伴う頸動脈露出、頸動脈出血、腫瘍出血があらわれることがある。頸動脈露出部位や皮膚瘻形成部位より大量出血した例が認められており、気管瘻や食道瘻を形成している場合には、喀血や吐血のおそれがある。重篤な出血があらわれた場合には、投与を中止し、適切な処置を行うこと。[8.10、9.1.2、9.1.5参照]

＊＊**11.1.4 動脈血栓塞栓症**（1.8%）

心筋梗塞、脳卒中、脾臓梗塞等の動脈血栓塞栓症があらわれることがある。[9.1.3参照]

11.1.5 静脈血栓塞栓症（2.4%）

肺塞栓症、深部静脈血栓症、門脈血栓症、網膜静脈血栓症等の静脈血栓塞栓症があらわれることがある。[9.1.3参照]

11.1.6 肝障害

AST、ALT等の上昇を伴う肝障害（20.1%）、アルブミン低下（3.8%）、肝性脳症（1.1%）、肝不全（0.4%）等があらわれることがある。[8.4参照]

11.1.7 急性胆嚢炎（0.6%）

無石胆嚢炎を含む急性胆嚢炎があらわれることがあり、胆嚢穿孔に至った例も報告されている。

11.1.8 腎障害

蛋白尿（29.7%）、腎機能障害（1.8%）、腎不全（0.7%）、ネフローゼ症候群（0.2%）等があらわれることがある。[7.5、8.2参照]

11.1.9 消化管穿孔、瘻孔形成、気胸

腸管穿孔（0.4%）、気胸（0.2%）、痔瘻（0.1%）、腸膀胱瘻（0.1%）等があらわれることがある。[9.1.6参照]

11.1.10 可逆性後白質脳症症候群（0.3%）

痙攣、頭痛、錯乱、視覚障害、皮質盲等が認められた場合には投与を中止し、血圧のコントロールを含め、適切な処置を行うこと。

11.1.11 心障害

心電図QT延長（4.1%）、駆出率減少（0.9%）、心不全（0.6%）、心房細動・粗動（0.4%）等があらわれることがある。[8.5参照]

11.1.12 手足症候群（29.1%）

11.1.13 感染症

気道感染（1.4%）、肺炎（1.3%）、敗血症（0.4%）等があらわれることがある。

11.1.14 骨髄抑制

血小板減少（17.2%）、好中球減少（8.2%）、白血球減少（7.8%）、貧血（7.2%）、リンパ球減少（4.2%）等があらわれることがある。感染症、出血傾向等の発現に留意すること。[7.5、8.3参照]

11.1.15 低カルシウム血症（2.5%）

副甲状腺機能低下症の既往歴がある患者で高発現したことが報告されている。観察を十分に行い、異常が認められた場合には、血清カルシウム濃度を確認し、カルシウム剤やビタミンD製剤の投与等の適切な処置を行うこと。[8.8参照]

11.1.16 創傷治癒遅延

治癒不良（0.3%）、創離開（0.2%）等があらわれることがある。創傷治癒遅延があらわれた場合には、創傷が治癒するまで本剤の投与を中止すること。[8.6、9.1.4参照]

11.1.17 間質性肺疾患（1.8%）

11.1.18 甲状腺機能低下（37.5%）[8.9参照]

11.2 その他の副作用

	30%以上	10～30%未満	5～10%未満	5%未満	頻度不明
消化器	下痢(45.1%)	悪心、口内炎、嘔吐、腹痛	口腔内乾燥、便秘、血中リパーゼの上昇、口腔咽頭痛、消化不良、血中アミラーゼの上昇	嚥下障害、舌痛、膵炎	
全身症状	疲労(30.6%)	無力症	浮腫、発熱	疼痛、創傷	
精神神経系		発声障害、頭痛、味覚異常	めまい	睡眠障害	
代謝	食欲減退(36.9%)		血中コレステロールの上昇、血中トリグリセリドの上昇	血中カリウムの低下、脱水	
筋骨格系		関節痛、筋肉痛		四肢痛、筋痙縮、背部痛	
呼吸器				咳嗽、呼吸困難	
皮膚		発疹	瘙痒症、皮膚乾燥、皮膚病変	脱毛症、皮膚炎	
その他		体重減少		CRPの上昇	甲状腺炎

14. 適用上の注意

14.1 薬剤交付時の注意

14.1.1 PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

14.1.2 本剤は湿気に不安定なため、服用直前にPTPシートから取り出すよう指導すること。

15. その他の注意

15.2 非臨床試験に基づく情報

15.2.1 反復投与毒性試験（ラット、イヌ及びサル）の病理組織学的検査において、精巣（精上皮細胞の減少）及び卵巣（卵胞閉鎖）の変化が認められており、生殖機能に障害を及ぼす可能性が示唆されている。

15.2.2 反復投与毒性試験において、ラット及びサル（成長板が残存する場合）に骨端軟骨成長板の肥厚が認められた。[9.7参照]

15.2.3 ラット及びイヌを用いた反復投与毒性試験において、副腎の出血（イヌ）及び副腎皮質壊死（ラット）が認められた。

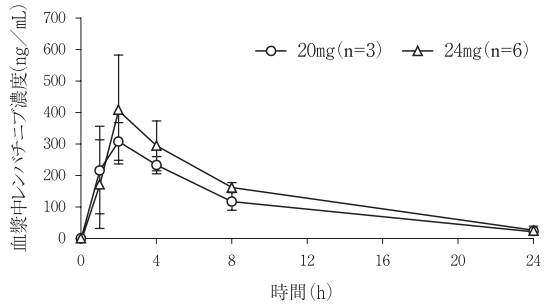
16. 薬物動態

16.1 血中濃度

16.1.1 反復投与

(1) 固形がん患者

日本人固形がん患者9例に本剤20mg[注)]又は24mg[注)]を1日1回経口投与したときの、初回投与時の血漿中レンバチニブ濃度推移を以下の図に示した。初回投与時及び1日1回反復投与した15日目の薬物動態パラメータを表に示した。レンバチニブのC_{max}及びAUC $_{(0\text{-}24h)}$ には用量比例性が認められた。反復投与15日後の薬物動態は、初回投与の結果から推測可能であり、C_{max}及びAUC $_{(0\text{-}24h)}$ の累積係数の平均値は、20mg投与群で1.27及び1.44、24mg投与群で1.42及び1.32であった[2)]。



日本人固形がん患者に本剤を経口投与したときの血漿中レンバチニブ濃度（1日目）　（平均値±標準偏差）

日本人固形がん患者に本剤を反復経口投与したときの血漿中レンバチニブの薬物動態パラメータ

		C_{max} (ng／mL)	AUC $_{(0\text{-}24h)}$ (ng・h／mL)	t_{max}^{c} (h)
20mg／日[注)]	1日目 (n=3)	309±60.1	2500±647	2（2–2）
	15日目 (n=3)	415±267	3690±1790	2（2–2）
24mg／日[注)]	1日目 (n=6)	418±167	3150±352[a]	2（2–4）
	15日目 (n=6)	518±209	4140±1350[b]	2（2–4）

平均値±標準偏差

a:n=4、b:n=5、c:中央値（最小値–最大値）

注）本剤の承認された用法及び用量は、「根治切除不能な甲状腺癌」、「切除不能な胸腺癌」は24mg／日、「がん化学療法後に増悪した切除不能な進行・再発の子宮体癌」、「根治切除不能又は転移性の腎細胞癌」はペムブロリズマブ（遺伝子組換え）との併用において20mg／日、「切除不能な肝細胞癌」は体重60kg以上の場合は12mg／日、体重60kg未満の場合は8mg／日である。

(2) 肝細胞癌患者

国際共同第Ⅲ相試験において、日本人及び外国人肝細胞癌患者に開始用量として本剤8mg（体重60kg未満）又は12mg（体重60kg以上）を1日1回反復経口投与したときのレンバチニブの血漿中トラフ濃度を開始用量ごとに表に示した。開始用量8mgとした場合と12mgとした場合との間でレンバチニブの血漿中トラフ濃度に明確な差異は認められなかった。

国際共同第Ⅲ相試験におけるレンバチニブの血漿中トラフ濃度

測定時点	開始用量			
	8mg		12mg	
	N	C_{trough} (ng/mL)	N	C_{trough} (ng/mL)
第1サイクル第15日目	136	37.70±25.58	299	40.83±34.97
第2サイクル第1日目	128	36.80±33.01	275	37.30±28.19
第3サイクル第1日目	62	32.46±33.83	139	40.95±40.39
第4サイクル第1日目	65	29.74±28.01	136	38.25±36.82
第5サイクル第1日目	65	36.07±40.59	129	34.02±27.09
第6サイクル第1日目	59	38.73±50.49	128	32.94±25.89

平均値±標準偏差

16.2 吸収

16.2.1 食事の影響

外国人健康成人16例に本剤10mg[注)]をクロスオーバー法により、空腹時又は食後（高脂肪食）に単回経口投与した。空腹時と比較して、食後投与のC_{max}及びAUC $_{(0\text{-}inf)}$ の臨床的に意味のある変化は認められなかった[3)]。

注）本剤の承認された用法及び用量は、「根治切除不能な甲状腺癌」、「切除不能な胸腺癌」は24mg／日、「がん化学療法後に増悪した切除不能な進行・再発の子宮体癌」、「根治切除不能又は転移性の腎細胞癌」はペムブロリズマブ（遺伝子組換え）との併用において20mg／日、「切除不能な肝細胞癌」は体重60kg以上の場合は12mg／日、体重60kg未満の場合は8mg／日である。

16.3 分布

レンバチニブの蛋白結合率は97.9～98.6%（*in vitro*試験）、96.6～98.2%（日本人固形がん患者）であった。主な結合蛋白はアルブミンであった[4)、5)]。

16.4 代謝

本剤は主にアルデヒドオキシダーゼ、CYP3Aにより代謝され、グルタチオンが非酵素的に結合する[6)]（*in vitro*試験）。

外国人固形がん患者6例に^{14}C標識–レンバチニブ24mgを単回経口投与した結果、血漿中の放射能の大部分は未変化体であった[7)]。[10.参照]

16.5 排泄

外国人固形がん患者6例に^{14}C標識–レンバチニブ24mgを単回経口投与したとき、投与10日後までに投与した総放射能の25%が尿中に、64%が糞中に回収された。また、尿及び糞中に排泄された未変化体は投与量のそれぞれ0.38%及び2.5%であった。未変化体の血漿中消失半減期は、約35.4時間であった[7)]。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

レンバチニブ24mgを外国人の腎機能が正常な被験者（クレアチニンクリアランス［CL_{cr}］：≥90mL／min、n＝8）、軽度（CL_{cr}：60～89mL／min）、中等度（CL_{cr}：30～59mL／min）及び重度（CL_{cr}：15～29mL／min）の腎機能障害を有する被験者（各6例）に単回投与した。

軽度、中等度及び重度の腎機能障害を有する被験者におけるC_{max}は健康被験者のそれぞれ1.0、0.61及び0.87倍であり、AUC $_{(0\text{-}inf)}$ は、健康被験者のそれぞれ1.0、0.90及び1.2倍であった[8)]。

16.6.2 肝機能障害患者

本剤10mgを外国人の肝機能が正常な被験者（n＝8）、軽度（Child-Pugh分類A）及び中等度（Child-Pugh分類B）の肝機能障害を有する被験者（各6例）に単回投与した。また、本剤5mgを外国人の重度（Child-Pugh分類C）の肝機能障害を有する被験者（6例）に単回投与した。

軽度、中等度及び重度の肝機能障害を有する被験者における投与量補正したC_{max}は健康被験者のそれぞれ0.97、0.79及び1.1倍であり、投与量補正したAUC $_{(0\text{-}inf)}$ は健康被験者のそれぞれ1.2、1.1及び1.8倍であった[9)]。[9.3.1参照]

16.7 薬物相互作用

16.7.1 ケトコナゾール

外国人健康成人16例に、レンバチニブをケトコナゾールと併用投与した際のC_{max}及び$AUC_{(0\text{-}inf)}$は、レンバチニブをプラセボと併用した場合と比べてそれぞれ19%及び15%上昇した[10)]。[10.2参照]

16.7.2 リファンピシン

外国人健康成人15例に、レンバチニブをリファンピシンと単回同時併用投与した際のC_{max}及び$AUC_{(0\text{-}inf)}$は、レンバチニブを単独投与した場合と比べてそれぞれ33%及び31%上昇した。リファンピシンの反復投与後に、レンバチニブをリファンピシンと同時併用投与した際のC_{max}及び$AUC_{(0\text{-}inf)}$は、レンバチニブをリファンピシンと単回同時併用投与した場合と比べてそれぞれ24%及び37%減少した[11)]。[10.2参照]

16.7.3 その他

レンバチニブは、乳癌耐性蛋白（BCRP）の基質となること、及びUGT1A1を阻害すること（IC_{50}値：10.6μmol／L）が示されている[6)、12)]（*in vitro*）。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈根治切除不能な甲状腺癌〉

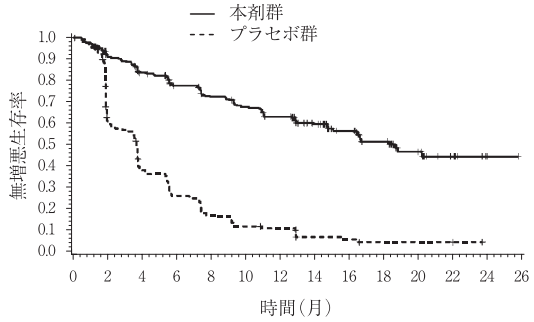
17.1.1 国際共同第Ⅲ相試験

放射性ヨウ素治療抵抗性・難治性（ヨウ素の取込みが認められない、放射性ヨウ素治療後12ヵ月以内に病勢の進行が認められた、又は累積線量が600mCi［22GBq］を超える放射性ヨウ素治療を受けている）の分化型甲状腺癌患者（乳頭癌、濾胞癌、Hürthle細胞癌、及び低分化癌）392例（本剤群261例［日本人患者30例］、プラセボ群131例［日本人患者10例］）において、プラセボを比較対照として本剤24mgを1日1回投与した場合の有効性と安全性を評価した。

なお、心不全の既往、心血管系疾患の既往、不整脈、出血性疾患、血栓性疾患又は活動性の喀血がある患者、抗凝固剤を投与されている患者、3週間以内に大手術を受けた患者、及びQTc間隔が480ms超の患者は除外された。主要評価項目である無増悪生存期間（PFS）の中央値は本剤投与群で18.3ヵ月、プラセボ群で3.6ヵ月であり、本剤はプラセボ群に対してPFSを有意に延長した（P<0.0001；層別Log Rank検定、ハザード比：0.21、99%信頼区間：0.14、0.31）[13)]。

無作為化期において、本剤が投与された261例（日本人30例を含む）中254例（97.3%）に副作用が認められた。主な副作用は、高血圧177例（67.8%）、下痢159例（60.9%）、食欲減退135例（51.7%）、体重減少123例（47.1%）、悪心107例（41.0%）、疲労104例（39.8%）、口内炎96例（36.8%）、蛋白尿85例（32.6%）、手掌・足底発赤知覚不全症候群83例（31.8%）等であった。[5.2参照]

無増悪生存期間のKaplan-Meier曲線



at risk数

本剤群：	261	225	198	176	159	148	136	92	66	44	24	11	3	0
プラセボ群：	131	71	43	29	19	13	11	5	4	2	2	2	0	0

17.1.2 国内第Ⅱ相試験

甲状腺癌（放射性ヨウ素治療抵抗性・難治性の分化型甲状腺癌［ヨウ素の取込みが認められない、放射性ヨウ素治療後12ヵ月以内に病勢の進行が認められた、又は累積線量が600mCi［22GBq］を超える放射性ヨウ素治療を受けている］、切除不能の甲状腺髄様癌及び切除不能の甲状腺未分化癌）43例に対し、本剤24mgを1日1回投与した場合の安全性と有効性を評価した。主要評価項目を安全性とし、副次評価項目として有効性を評価した。有効性解析対象例はそれぞれ23例、8例及び11例であった[14)]。

43例中全例（100%）に副作用が認められた。主な副作用は、高血圧37例（86.0%）、手掌・足底発赤知覚不全症候群34例（79.1%）、食欲減退33例（76.7%）、疲労31例（72.1%）、蛋白尿25例（58.1%）、口内炎24例（55.8%）及び下痢22例（51.2%）であった。[5.2参照]

n（%）	分化型甲状腺癌（N=23）	甲状腺髄様癌（N=8）	甲状腺未分化癌（N=11）
完全奏効（CR）	0	0	0
部分奏効（PR）	16（69.6）	1（12.5）	3（27.3）
安定（SD）	7（30.4）	7（87.5）	7（63.6）
病勢進行（PD）	0	0	1（9.1）

〈切除不能な肝細胞癌〉

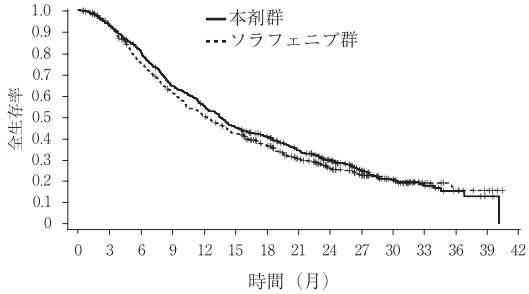
17.1.3 国際共同第Ⅲ相試験

全身化学療法歴のないChild-Pugh分類Aの切除不能な肝細胞癌患者954例（本剤群478例［日本人患者81例］、ソラフェニブ群476例［日本人患者87例］）において、ソラフェニブを比較対照として本剤の有効性と安全性を評価した。本剤群では体重60kg以上の患者には本剤12mgを1日1回、体重60kg未満の患者には本剤8mgを1日1回投与した。

なお、局所療法（経皮的エタノール注入療法、ラジオ波焼灼療法、マイクロ波凝固療法、肝動脈塞栓療法／肝動脈化学塞栓療法、放射線療法等）の適応となる患者は除外された。主要評価項目である全生存期間（OS）において、ハザード比（95%信頼区間）は0.92（0.79、1.06）であり、95%信頼区間の上限が事前に規定した非劣性マージンの1.08を下回ったことから、本剤群のソラフェニブ群に対する非劣性が統計学的に検証された（OSの中央値：本剤群13.6ヵ月、ソラフェニブ群12.3ヵ月）[15)]。

本剤が投与された476例（日本人81例を含む）中447例（93.9%）に副作用が認められた。主な副作用は、高血圧189例（39.7%）、下痢143例（30.0%）、手掌・足底発赤知覚不全症候群126例（26.5%）、食欲減退122例（25.6%）、蛋白尿114例（23.9%）、疲労111例（23.3%）、発声障害104例（21.8%）等であった。[5.4参照]

全生存期間のKaplan-Meier曲線



at risk数

本剤群：	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
ソラフェニブ群：	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

〈切除不能な胸腺癌〉

17.1.4 国内第Ⅱ相試験

プラチナ製剤を含む化学（放射線）療法歴を有する切除不能な胸腺癌患者[注)]42例に対し、本剤24mgを1日1回投与した場合の安全性と有効性を評価した。主要評価項目である奏効率（RECISTガイドライン1.1版に基づく中央判定によるCR又はPR）は38.1%（90%信頼区間：25.6、52.0）であった[16)]。また安全性評価対象42例中全例（100%）に副作用が認められた。主な副作用は、高血圧37例（88.1%）、蛋白尿30例（71.4%）、手掌・足底発赤知覚不全症候群29例（69.0%）、甲

状腺機能低下症27例（64.3%）、血小板数減少22例（52.4%）及び下痢21例（50.0%）であった。[5.6参照]

注）正岡-古賀分類Ⅲa～Ⅳb 又は術後再発の患者が臨床試験に組入れられた。

n（%）	切除不能な胸腺癌 （N=42）
完全奏効（CR）	0
部分奏効（PR）	16（38.1）
安定（SD）	24（57.1）
病勢進行（PD）	2（4.8）

〈がん化学療法後に増悪した切除不能な進行・再発の子宮体癌〉

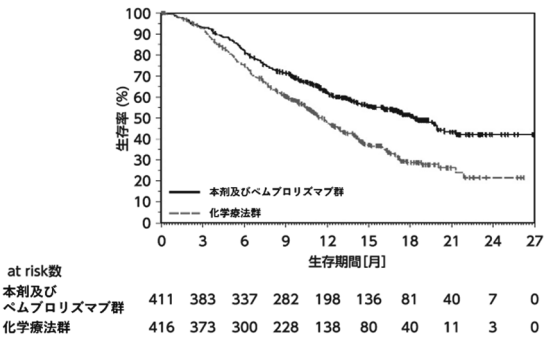
17.1.5 国際共同第Ⅲ相試験

プラチナ製剤を含む化学療法歴のある切除不能な進行・再発の子宮体癌患者827例（日本人104例を含む）を対象に、本剤20mg1日1回投与とペムブロリズマブ200mg3週間間隔投与の併用療法の有効性及び安全性が、化学療法（ドキソルビシン又はパクリタキセル）[注)]を対照として検討された。化学療法は担当医師が患者ごとに選択した。なお、画像評価で疾患進行が認められた場合に、疾患進行を示す症状が認められない等の臨床的に安定している患者では、次回以降の画像評価で疾患進行が認められるまで投与を継続することが可能とされた。主要評価項目は全生存期間（OS）及び無増悪生存期間（PFS）とされ、OSの中央値は本剤とペムブロリズマブの併用群では18.3ヵ月、化学療法群では11.4ヵ月（P＜0.0001；層別Log Rank検定、ハザード比：0.62、95%信頼区間：0.51、0.75）、PFSの中央値は本剤とペムブロリズマブの併用群では7.2ヵ月、化学療法群では3.8ヵ月（P＜0.0001；層別Log Rank検定、ハザード比：0.56、95%信頼区間：0.47、0.66）であり、本剤とペムブロリズマブの併用群は化学療法と比較してOS及びPFSを有意に延長した[17)]。また、無作為化前に選択された化学療法群の薬剤（①ドキソルビシン（605例）又は②パクリタキセル（222例））別の部分集団解析を事後的に実施した結果、化学療法群に対する本剤とペムブロリズマブの併用群のPFSのハザード比［95%信頼区間］は、それぞれ①0.47［0.39、0.58］及び②0.85［0.61、1.20］であった。また、OSのハザード比［95%信頼区間］は、それぞれ①0.49［0.39、0.61］及び②1.40［0.93、2.12］であった（2020年10月26日カットオフ）。

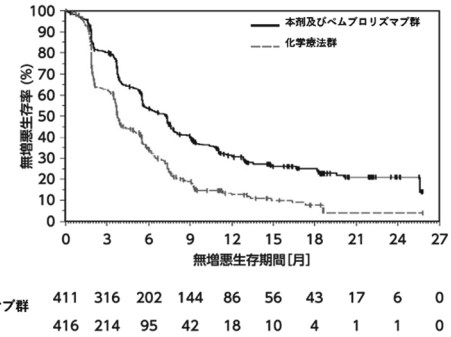
安全性解析対象例406例中395例（97.3%）（日本人52例中51例を含む）に副作用が認められた。主な副作用は、高血圧249例（61.3%）、甲状腺機能低下症222例（54.7%）、下痢171例（42.1%）、悪心158例（38.9%）、食欲減退151例（37.2%）、疲労113例（27.8%）、蛋白尿105例（25.9%）、嘔吐98例（24.1%）、体重減少91例（22.4%）、関節痛87例（21.4%）、手掌・足底発赤知覚不全症候群84例（20.7%）であった（2021年2月8日カットオフ）。[5.9参照]

注）ドキソルビシン塩酸塩60mg/m^{2}を3週間隔投与、又はパクリタキセル80mg/m^{2}を各コース（1コース28日間）の1、8、15日目に投与した。

全生存期間のKaplan-Meier曲線



無増悪生存期間のKaplan-Meier曲線



〈根治切除不能又は転移性の腎細胞癌〉

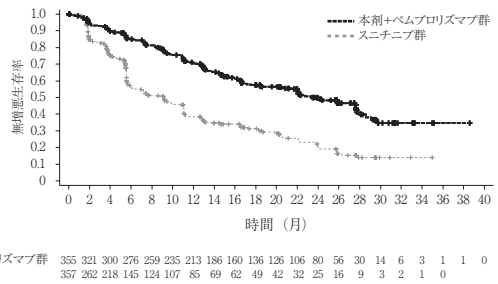
17.1.6 国際共同第Ⅲ相試験

化学療法歴のない根治切除不能又は転移性の淡明細胞型腎細胞癌患者[注)]712例（日本人73例を含む）を対象に、本剤20mg1日1回投与とペムブロリズマブ200mg3週間間隔投与の併用療法の有効性及び安全性が、スニチニブを対照として検討された。なお、画像評価で疾患進行が認められた場合に、疾患進行を示す症状が認められない等の臨床的に安定している患者では、次回以降の画像評価で疾患進行が認められるまで投与を継続することが可能とされた。主要評価項目である無増悪生存期間（PFS）の中央値は、本剤とペムブロリズマブ併用群では23.9ヵ月、スニチニブ群では9.2ヵ月（P＜0.0001；層別Log Rank検定、ハザード比：0.39、95%信頼区間：0.32、0.49）であり、本剤とペムブロリズマブの併用群はスニチニブ群と比較して有意に延長した[18)]。

安全性解析対象例352例中341例（96.9%）（日本人42例中42例を含む）に副作用が認められた。主な副作用は、下痢192例（54.5%）、高血圧184例（52.3%）、甲状腺機能低下症150例（42.6%）、食欲減退123例（34.9%）、疲労113例（32.1%）、口内炎113例（32.1%）、手掌・足底発赤知覚不全症候群99例（28.1%）、蛋白尿97例（27.6%）、悪心94例（26.7%）、発声障害87例（24.7%）、発疹77例（21.9%）、無力症71例（20.2%）等であった。

注）腫瘍組織において組織学的又は細胞学的に淡明細胞が確認された患者が対象とされた。

無増悪生存期間のKaplan-Meier曲線



18. 薬効薬理

18.1 作用機序

レンバチニブは、腫瘍血管新生及び腫瘍増殖等に関与する、血管内皮増殖因子（VEGF）受容体（VEGFR1-3）、線維芽細胞増殖因子（FGF）受容体（FGFR1-4）、血小板由来増殖因子受容体（PDGFR）α、幹細胞因子受容体（KIT）、Rearranged During Transfectionがん原遺伝子（RET）等の受容体チロシンキナーゼを阻害した。また、レンバチニブは、VEGF及びFGFによって誘導される血管内皮細胞の血管様管腔構造の形成を阻害した[19)、20)]。

18.2 抗腫瘍効果

レンバチニブは、ヒト甲状腺乳頭癌由来細胞株（K1）、ヒト甲状腺濾胞癌由来細胞株（RO82-W-1）、ヒト甲状腺髄様癌由来細胞株（TT）、ヒト甲状腺未分化癌由来細胞株（8305C）、ヒト甲状腺由来扁平上皮癌由来細胞株（SW579）、ヒト肝

細胞癌由来細胞株（Hep 3B2.1-7、LIXC-012及びPLC/PRF/5）、肝細胞癌患者由来腫瘍組織片（LI0050及びLI0334）、ヒト胸腺癌由来細胞株（Ty-82）及びマウス腎細胞癌由来細胞株（RAG）を移植したマウスにおいて、腫瘍増殖抑制作用を示した[21)~24)]。

19．有効成分に関する理化学的知見

一般名：レンバチニブメシル酸塩（Lenvatinib Mesilate）

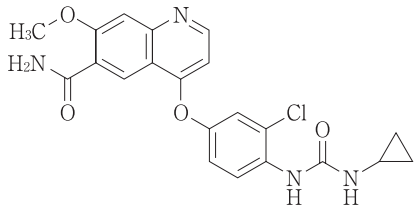
化学名：4-{3-Chloro-4-[(cyclopropylcarbamoyl)amino]phenoxy}-7-methoxyquinoline-6-carboxamide monomethanesulfonate

分子式：$C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$

分子量：522.96

性　状：レンバチニブメシル酸塩は白色～うすい帯赤黄色の粉末である。
本品は水、メタノール又はN-メチルピロリドンに溶けにくく、エタノール（99.5）にほとんど溶けない。

構造式：



・ H_3C-SO_3H

融　点：221～224℃（分解）

分配係数：log P＝3.30（1-オクタノール／水系）

21．承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22．包装

〈レンビマカプセル4mg〉

20カプセル［10カプセル（PTP）×2］

〈レンビマカプセル10mg〉

20カプセル［10カプセル（PTP）×2］

23．主要文献

＊1）NDBを用いた調査結果の概要（VEGF/VEGFR阻害作用を有する薬剤の動脈解離に関するリスク評価）：https://www.pmda.go.jp/files/000266521.pdf

2）社内資料：固形がん患者を対象とした臨床第Ⅰ相試験（国内試験）（2015年3月26日承認、CTD 2.7.6.6）［LEN-0001］

3）Shumaker R. et al.：Int. J. Clin. Pharmacol. Ther.,2014；52（4）：284-291［LEN-0002］

4）社内資料：血漿蛋白結合率（*in vitro*）（2015年3月26日承認、CTD 2.6.4.4.2）［LEN-0005］

5）Yamada K. et al.：Clin. Cancer Res.,2011；17（8）：2528-2537［LEN-0006］

6）社内資料：代謝（*in vitro*及び*in vivo*）（2015年3月26日承認、CTD 2.7.2.3.2.3）［LEN-0003］

7）社内資料：がん患者を対象としたマスバランス試験（外国試験）（2015年3月26日承認、CTD 2.7.2.2.2.2.1,2.7.6.9）［LEN-0004］

8）社内資料：腎機能障害患者を対象とした臨床薬理試験（外国試験）（2015年3月26日承認、CTD 2.7.2.2.2.3.2）［LEN-0009］

9）社内資料：肝機能障害患者を対象とした臨床薬理試験（外国試験）（2015年3月26日承認、CTD 2.7.2.2.2.3.1）［LEN-0008］

10）社内資料：ケトコナゾールとの薬物相互作用試験（外国試験）（2015年3月26日承認、CTD 2.7.2.2.2.3.3.1）［LEN-0010］

11）社内資料：リファンピシンとの薬物相互作用試験（外国試験）（2015年3月26日承認、CTD 2.7.2.2.2.3.3.2）［LEN-0011］

12）社内資料：トランスポーター（*in vitro*）（2015年3月26日承認、CTD 2.6.4.8.1）［LEN-0018］

13）社内資料：^{131}Ⅰ難治性の甲状腺分化癌患者を対象とした臨床第Ⅲ相試験（国際共同試験）（2015年3月26日承認、CTD 2.7.6.17）［LEN-0012］

14）社内資料：進行性甲状腺癌患者を対象とした臨床第Ⅱ相試験（国内試験）（2015年3月26日承認、CTD 2.7.6.16）［LEN-0014］

15）社内資料：切除不能な肝細胞癌患者を対象とした臨床第Ⅲ相試験（国際共同試験）（2018年3月23日承認、CTD 2.7.6.1）［LEN-0168］

16）社内資料：NCCH1508試験（2021年3月23日承認、CTD 2.7.6.1）［LEN-0470］

17）社内資料：進行子宮体癌患者を対象とした臨床第Ⅲ相試験（国際共同試験）（2021年12月24日承認、CTD 2.7.6）［LEN-0653］

18）社内資料：根治切除不能又は転移性の腎細胞癌患者を対象とした臨床第Ⅲ相試験（国際共同試験）（2022年2月25日承認、CTD 2.7.6.1.3）［LEN-0720］

19）社内資料：*In vitro*薬理試験（1）（2015年3月26日承認、CTD 2.6.2.2.1）［LEN-0015］

20）社内資料：*In vitro*薬理試験（2）（2018年3月23日承認、CTD 2.6.2.2.1）［LEN-0169］

21）社内資料：*In vivo*薬理試験（1）（2015年3月26日承認、CTD 2.6.2.2.2）［LEN-0016］

22）社内資料：*In vivo*薬理試験（2）（2018年3月23日承認、CTD 2.6.2.2.2）［LEN-0170］

23）社内資料：効力を裏付ける試験（2021年3月23日承認、CTD 2.6.2.2）［LEN-0508］

24）社内資料：*In vivo*薬理試験（3）（2022年2月25日承認、CTD 2.6.2.2）［LEN-0721］

24．文献請求先及び問い合わせ先

エーザイ株式会社　hhcホットライン

〒112-8088　東京都文京区小石川4-6-10

フリーダイヤル　0120-419-497

26．製造販売業者等

26.1 製造販売元

エーザイ株式会社

東京都文京区小石川4-6-10

26.2 販売提携

MSD株式会社

東京都千代田区九段北1-13-12

目次

1.8 添付文書（案） 2
1.8.1 効能・効果，用法・用量の設定の根拠 2
1.8.1.1 効能・効果及びその設定理由 2
1.8.1.1.1 効能又は効果の設定根拠 2
1.8.1.1.2 効能又は効果に関連する注意の設定根拠 3
1.8.1.2 用法・用量及びその設定理由 5
1.8.1.2.1 用法及び用量の設定根拠 6
1.8.1.2.2 用法及び用量に関連する注意の設定根拠 6
1.8.2 使用上の注意の設定の根拠 7
1.8.3 添付文書（案） 12

表一覧

表 1.8.1.1-1 比較的よくみられる有害事象（発現割合20%以上） 3

最新の添付文書を参照すること。

1.8 添付文書（案）

1.8.1 効能・効果，用法・用量の設定の根拠

1.8.1.1 効能・効果及びその設定理由

4. 効能又は効果
〈製剤共通〉
○ 切除不能な進行・再発の非小細胞肺癌
○ PD-L1陽性の非小細胞肺癌における術後補助療法
○ 進展型小細胞肺癌
○ 切除不能な胞巣状軟部肉腫
○ 再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型
〈テセントリク点滴静注1200mg〉
○ 切除不能な肝細胞癌
○ 切除不能な胸腺癌
〈テセントリク点滴静注840mg〉
○ PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌

5. 効能又は効果に関する注意
〈切除不能な胸腺癌〉
5.12 本剤の術前補助療法としての有効性及び安全性は確立していない。

注）追加，変更箇所に下線を付した。

1.8.1.1.1 効能又は効果の設定根拠

本剤は2016年5月18日にプラチナ製剤既治療の進行尿路上皮癌に対して米国で最初に承認され，現在では本邦においても種々の効能又は効果にて製造販売承認されている。

以下に示すように，切除不能進行・再発の化学療法未治療胸腺癌患者を対象とした医師主導治験である JTD2101試験（Marble 試験，以下，本試験）で，本剤とカルボプラチン，パクリタキセルとの併用療法での有効性及び安全性が確認されたことから，「切除不能な胸腺癌」の効能又は効果を追加するために承認事項一部変更承認申請を行う。

Marble 試験の試験概要

切除不能進行・再発の化学療法未治療胸腺癌患者を対象とした，本剤とカルボプラチン，パクリタキセルとの併用療法での有効性及び安全性を検討する第 II 相単群非盲検非対照試験である。導入療法は，カルボプラチン（AUC 6 mg・min/mL, day 1） + パクリタキセル（200 mg/m^2, day 1） + アテゾリズマブ（1200 mg, day 1）を3週（21日）1サイクルとして4～6サイクル繰り返した（導入療法の投与サイクル数は治験責任医師又は分担医師の判断で行った）。導入療法後の画像評価で，固形がんの治療効果判定のための新ガイドライン（RECIST）上病勢増悪を認めない［増悪（PD）以外］症例に対し，維持療法としてアテゾリズマブ（1200 mg, day 1）を3週（21日）1サイクルとして投与した。維持療法は，PD が認められるまで，もしくは許容されない有害事象が出現するまで，（導入療法開始時を起算日として）最長で2年間継続した。

Marble 試験の結果概要

本試験では，画像中央判定による奏効割合（ORR）を主要評価項目とした。

画像中央判定による ORR は56.3%（95%信頼区間［CI］：41.2～70.5%）であり，95%CI の下限値は事前に設定された閾値 ORR 30%を上回った。その内訳は，治験実施計画適合集団48例中 PR が27例，SD が20例，PD が1例であった。

本試験の安全性解析対象集団48例で，有害事象は48例（100.0%）に認められた。

発現割合が20%以上の事象は表 1.8.1.1-1に示す。本試験で認められた有害事象の内，多くは休薬や適切な治療によって管理可能であった。

表 1.8.1.1-1 比較的よくみられる有害事象（発現割合20%以上）

System Organ Class Preferred Term	N (%)
血液およびリンパ系障害	
貧血	26 (54.2%)
発熱性好中球減少症	11 (22.9%)
好中球減少症	19 (39.6%)
胃腸障害	
便秘	33 (68.8%)
下痢	13 (27.1%)
悪心	20 (41.7%)
口内炎	13 (27.1%)
一般・全身障害および投与部位の状態	
倦怠感	15 (31.3%)
発熱	11 (22.9%)
臨床検査	
アラニンアミノトランスフェラーゼ増加	14 (29.2%)
アスパラギン酸アミノトランスフェラーゼ増加	13 (27.1%)
好中球数減少	18 (37.5%)
血小板数減少	12 (25.0%)
白血球数減少	22 (45.8%)
代謝および栄養障害	
食欲減退	18 (37.5%)
筋骨格系および結合組織障害	
関節痛	15 (31.3%)
神経系障害	
末梢性感覚ニューロパチー	42 (87.5%)
呼吸器，胸郭および縦郭障害	
しゃっくり	11 (22.9%)
皮膚および皮下組織障害	
脱毛症	41 (85.4%)
斑状丘疹状皮疹	20 (41.7%)

本剤の作用機序を考慮し，本剤の注目すべき有害事象を検討した。注目すべき有害事象の発現割合は，本剤の安全性プロファイルから予測可能な範囲であり，多くは軽度で休薬や適切な治療によって管理可能であった。

以上，本試験で得られた有効性及び安全性の結果から，切除不能進行・再発の化学療法未治療胸腺癌患者に対して本剤の高い有効性及び忍容性が示されたことから，効能又は効果に「切除不能な胸腺癌」を設定した。

1.8.1.1.2 効能又は効果に関連する注意の設定根拠

胸腺癌に係る国内診療ガイドラインにおいて，術前補助療法が治療選択肢として推奨されているため，本剤の術前補助療法としての有効性及び安全性は確立していない旨を注意喚起として設定した。なお，術後補助療法はガイドラインに記載されておらず，推奨されている治療ではないことを踏まえると，本薬が術後補助療法として投与される可能性は低いことから，注意喚起は不要と判断した。

1.8.1.2 用法・用量及びその設定理由

6. 用法及び用量
〈効能共通〉
アテゾリズマブ（遺伝子組換え）の初回投与時は60分かけて点滴静注し、初回投与の忍容性が良好であれば、2回目以降の投与時間は30分間まで短縮できる。

効能又は効果	用法及び用量
切除不能な進行・再発の非小細胞肺癌	化学療法未治療の扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌 他の抗悪性腫瘍剤との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。その後、単独投与する場合には、アテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。 化学療法未治療の PD-L1陽性の切除不能な進行・再発の非小細胞肺癌 通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。 化学療法既治療の切除不能な進行・再発の非小細胞肺癌 通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。
PD-L1陽性の非小細胞肺癌における術後補助療法	通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。投与期間は12カ月間までとする。
進展型小細胞肺癌	カルボプラチン及びエトポシドとの併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で4回点滴静注する。その後、アテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。
切除不能な肝細胞癌	ベバシズマブ（遺伝子組換え）との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。
PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌	パクリタキセル（アルブミン懸濁型）との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回840mg を2週間間隔又は1回1680mg を4週間間隔で点滴静注する。
切除不能な胞巣状軟部肉腫	通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。通常、2歳以上の小児にはアテゾリズマブ（遺伝子組換え）として1回15mg/kg（体重）（最大1200mg）を3週間間隔で点滴静注する。
再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型	通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。通常、12歳以上の小児にはアテゾリズマブ（遺伝子組換え）として1回15mg/kg（体重）（最大1200mg）を3週間間隔で点滴静注する。
切除不能な胸腺癌	カルボプラチン及びパクリタキセルとの併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。

7. 用法及び用量に関連する注意
〈切除不能な胸腺癌〉
7.6 カルボプラチン及びパクリタキセルとの併用に際しては、通常、成人には、3週間間隔で、カルボプラチンは1回 AUC 6mg・min/mL 相当量を30分以上かけて点滴静注し、パクリタキセルは1回200mg/m^{2}を3時間かけて点滴静注すること。なお、患者の状態により適宜減量すること。

1.8.1.2.1 用法及び用量の設定根拠

切除不能な胸腺癌において，1200 mg/body 3週間間隔投与の用法及び用量は妥当であると考えた。以下に詳細を示す。

本試験では，3週（21日）を1サイクルとし，カルボプラチン及びパクリタキセルとの併用にて，各サイクルの Day 1に本剤1200 mg/body を静脈内投与した。

本設定において有効性が示されたことより，本剤1200 mg/body 3週間間隔投与と設定することが妥当であると判断した。また，1.8.1.1.1項に記載したとおり，本剤の主な有害事象の種類，重症度，重篤度及び発現頻度は，使用経験から予測されうるものであり，特異的な有害事象が発現する可能性は低いと考えられ，本剤1200 mg/body 3週間間隔投与の設定は忍容性があると判断した。

以上より，切除不能な胸腺癌患者に対する用法及び用量として，「カルボプラチン及びパクリタキセルとの併用において，通常，成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。なお，アテゾリズマブ（遺伝子組換え）の初回投与時は60分かけて点滴静注し，初回投与の忍容性が良好であれば，2回目以降の投与時間は30分間まで短縮できる。」とすることが適切と判断した。

1.8.1.2.2 用法及び用量に関連する注意の設定根拠

切除不能な胸腺癌に対し，本剤はカルボプラチン及びパクリタキセルとの併用にて投与されることから，カルボプラチン及びパクリタキセルとの併用療法に関する注意が必要と考え，7.6項に「切除不能な胸腺癌」を追加した。

1.8.2 使用上の注意の設定の根拠

使用上の注意（案）	設定根拠
1. 警告 1.1 本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の使用が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。 1.2 間質性肺疾患があらわれ、死亡に至った症例も報告されているので、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部 X 線検査の実施等、患者の状態を十分に観察すること。異常が認められた場合には本剤の投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。[8.2、9.1.2、11.1.1参照]	変更なし
2. 禁忌（次の患者には投与しないこと） 本剤の成分に対し過敏症の既往歴のある患者	変更なし
8. 重要な基本的注意 ＜効能共通＞ 8.1 本剤の T 細胞活性化作用により、過度の免疫反応に起因すると考えられる様々な疾患や病態があらわれることがある。患者の状態を十分に観察し、異常が認められた場合には、過度の免疫反応による副作用の発現を考慮し、適切な鑑別診断を行うこと。過度の免疫反応による副作用が疑われた場合には、副腎皮質ホルモン剤の投与等を考慮すること。また、本剤投与終了後に重篤な副作用があらわれることがあるので、本剤投与終了後も患者の状態を十分に観察すること。 8.2 間質性肺疾患があらわれることがあるので、本剤の投与にあたっては、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部 X 線検査の実施等、患者の状態を十分に観察すること。また、必要に応じて、胸部 CT、血清マーカー等の検査を実施すること。[1.2、9.1.2、11.1.1参照] 8.3 肝機能障害、肝炎、硬化性胆管炎があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に肝機能検査を行い、患者の状態を十分に観察すること。[11.1.2参照] 8.4 1型糖尿病があらわれることがあるので、口渇、悪心、嘔吐等の症状の発現や血糖値の上昇に十分注意すること。[11.1.5参照] 8.5 甲状腺機能障害、副腎機能障害及び下垂体機能障害があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に内分泌機能検査（TSH、遊離 T3、遊離 T4、ACTH、血中コルチゾール等の測定）等を行うこと。また、必要に応じて、画像検査等の実施も考慮すること。[11.1.6-11.1.8参照] 8.6 重症筋無力症があらわれることがあるので、筋力低下、眼瞼下垂、呼吸困難、嚥下障害等の観察を十分に行うこと。[11.1.11参照] 8.7 腎機能障害があらわれることがあるので、定期的に腎機能検査を行い、患者の状態を十分に観察すること。[11.1.13参照] 8.8 筋炎、横紋筋融解症があらわれることがあるので、筋力低下、筋肉痛、CK 上昇、血中及び尿中ミオグロビン上昇等の観察を十分に行うこと。[11.1.14参照] 8.9 心筋炎があらわれることがあるので、胸痛、CK 上昇、心電図異常等の観察を十分に行うこと。[11.1.15参照] ＜化学療法未治療の扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌＞ 8.10 本剤とカルボプラチン及びパクリタキセルを併用投与、並びに本剤とカルボプラチン、パクリタキセル及びベバシズマブ（遺伝子組換え）を併用投与する際には、発熱性好中球減少症があらわれ	専門協議後照会の内容を踏まえて修正した

ることがあるので、投与中は定期的に血液検査を行う等、患者の状態を十分に観察すること。[11.1.19参照]	
9. 特定の背景を有する患者に関する注意 9.1 合併症・既往歴等のある患者 9.1.1 自己免疫疾患の合併又は慢性的若しくは再発性の自己免疫疾患の既往歴のある患者 免疫関連の副作用が発現又は増悪するおそれがある。 9.1.2 間質性肺疾患のある患者又はその既往歴のある患者 間質性肺疾患が発現又は増悪するおそれがある。[1.2、8.2、11.1.1参照] 9.4 生殖能を有する者 妊娠する可能性のある女性には、本剤投与中及び最終投与後、5カ月間において避妊する必要性及び適切な避妊法について説明すること。[9.5参照] 9.5 妊婦 妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤を用いた生殖発生毒性試験は実施されていない。本剤を投与すると、胎児に対する免疫寛容が妨害され、流産率又は死産率が増加する可能性がある。また、ヒト IgG は胎盤を通過することが知られており、本剤は母体から胎児へ移行する可能性がある。[9.4参照] 9.6 授乳婦 治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行性については不明であるが、ヒト IgG はヒト乳汁中に排出されることが知られている。 9.7 小児等 <切除不能な進行・再発の非小細胞肺癌、PD-L1陽性の非小細胞肺癌における術後補助療法、進展型小細胞肺癌、切除不能な肝細胞癌、PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌、切除不能な胸腺癌> 小児等を対象とした臨床試験は実施していない。 <切除不能な胞巣状軟部肉腫> 低出生体重児、新生児、乳児又は2歳未満の幼児を対象とした臨床試験は実施していない。［16.6.1参照］ 9.8 高齢者 患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下していることが多い。	Marble 試験（2024年7月6日データカットオフ）に基づき変更した。
11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1 重大な副作用 11.1.1 間質性肺疾患（3.0%） [1.2、8.2、9.1.2参照] 11.1.2 肝機能障害、肝炎、硬化性胆管炎 AST 増加（6.3%）、ALT 増加（6.3%）、Al-P 増加（2.1%）、ビリルビン増加（1.5%）、γ-GTP 増加（1.0%）等を伴う肝機能障害、肝炎（0.8%）、硬化性胆管炎（頻度不明）があらわれることがある。[8.3参照] 11.1.3 大腸炎（1.1%）、重度の下痢（1.2%） 持続する下痢、腹痛、血便等の症状があらわれた場合には本剤の投与を中止する等の適切な処置を行うこと。 11.1.4 膵炎（0.1%） 11.1.5 1型糖尿病（0.1%） 糖尿病性ケトアシドーシスに至るおそれがある。1型糖尿病が疑われた場合には本剤の投与を中止し、インスリン製剤を投与する等の適切な処置を行うこと。[8.4参照] 11.1.6 甲状腺機能障害	Marble 試験（2024年7月6日データカットオフ）に基づき変更した。また、専門協議後照会の内容を踏まえて修正した。

甲状腺機能低下症(8.0%)、甲状腺機能亢進症(3.5%)、甲状腺炎(0.6%)等の甲状腺機能障害があらわれることがある。[8.5参照] 11.1.7 副腎機能障害 副腎機能不全(0.6%)、急性副腎皮質機能不全(0.1%未満)等の副腎機能障害があらわれることがある。[8.5参照] 11.1.8 下垂体機能障害 下垂体炎(0.2%)、下垂体機能低下症(0.1%)等の下垂体機能障害があらわれることがある。[8.5参照] 11.1.9 脳炎(0.1%)、髄膜炎(0.1%)、脊髄炎(頻度不明) 11.1.10 神経障害 末梢性ニューロパチー(4.4%)、多発ニューロパチー(0.3%)、ギラン・バレー症候群(0.1%)等の神経障害があらわれることがある。 11.1.11 重症筋無力症(頻度不明) 重症筋無力症によるクリーゼのため急速に呼吸不全が進行することがあるので、呼吸状態の悪化に十分注意すること。[8.6参照] 11.1.12 重度の皮膚障害 中毒性表皮壊死融解症(Toxic Epidermal Necrolysis:TEN)(頻度不明)、皮膚粘膜眼症候群(Stevens-Johnson 症候群)(頻度不明)、多形紅斑(0.3%)等の重度の皮膚障害があらわれることがある。 11.1.13 腎機能障害 急性腎障害(0.4%)、腎不全(0.4%)、尿細管間質性腎炎(0.2%)、腎炎(0.2%)等の腎機能障害があらわれることがある。[8.7参照] 11.1.14 筋炎(0.2%)、横紋筋融解症(0.1%) [8.8参照] 11.1.15 心筋炎(0.1%) [8.9参照] 11.1.16 血球貪食症候群(0.1%未満) 11.1.17 免疫性血小板減少症(頻度不明) 11.1.18 Infusion reaction(2.6%) アナフィラキシーを含む Infusion reaction があらわれることがある。重度の Infusion reaction があらわれた場合には本剤の投与を直ちに中止し、適切な処置を行うとともに、症状が回復するまで患者の状態を十分に観察すること。 11.1.19 発熱性好中球減少症(5.0%注1)) 本剤とカルボプラチン及びパクリタキセルとの併用、並びに本剤とカルボプラチン、パクリタキセル及びベバシズマブ(遺伝子組換え)との併用において、発熱性好中球減少症があらわれることがある。[8.10参照] 注1)発現頻度は、IMpower150試験及び Marble 試験から集計した。	

11.2 その他の副作用

	5%以上	1%以上～5%未満	1%未満	頻度不明
精神神経系		頭痛、味覚異常、浮動性めまい、錯感覚、不眠症	意識レベルの低下、回転性めまい、感覚鈍麻、失神	顔面不全麻痺
眼			結膜炎、霧視、眼乾燥、流涙増加	
消化器	下痢（11.2%）、悪心（10.7%）、食欲減退、便秘	嘔吐、口内炎、腹痛、口内乾燥	腹部膨満、消化不良、嚥下障害、アミラーゼ増加、リパーゼ増加	
循環器		高血圧	低血圧、頻脈、ほてり、潮紅	
呼吸器		呼吸困難、咳嗽、気道感染、肺炎、鼻出血	発声障害、鼻炎、しゃっくり、口腔咽頭痛、胸水、喀血、低酸素症、鼻閉	
皮膚	発疹、そう痒症	脱毛症、斑状丘疹上皮疹、皮膚乾燥、ざ瘡様皮膚炎、紅斑	蕁麻疹、皮膚炎、そう痒性皮疹、乾癬、紅斑性皮疹、寝汗	
筋骨格系	関節痛	筋肉痛、筋骨格痛	筋力低下、筋痙縮、関節炎、血中CK増加	
泌尿器		高クレアチニン血症、蛋白尿	尿路感染	
血液	貧血、好中球減少、血小板減少	白血球減少、リンパ球減少		
代謝		低マグネシウム血症、低ナトリウム血症、低カリウム血症、低アルブミン血症、血中甲状腺刺激ホルモン増加、高血糖、	血中甲状腺刺激ホルモン減少、高カリウム血症、低カルシウム血症低リン血症	

Marble 試験（2024年7月6日データカットオフ）に基づき変更した。また、専門協議後照会の内容を踏まえて修正した。

		脱水			
その他	疲労（14.7%）、無力症、発熱	浮腫、体重減少、倦怠感、悪寒、粘膜の炎症、インフルエンザ様疾患	腫脹、過敏症、胸痛、血中乳酸脱水素酵素増加、疼痛		

注2）Marble 試験においては、本剤、カルボプラチン又はパクリタキセルのいずれかにより発現した副作用について集計した。

14. 適用上の注意 14.1 薬剤調製時の注意 14.1.1 調製時には、日局生理食塩液以外は使用しないこと。 14.1.2 調製時は静かに転倒混和すること。 14.1.3 用時調製し、調製後は速やかに使用すること。また、残液は廃棄すること。 14.1.4 投与時には本剤を注射筒で抜き取り、日局生理食塩液に添加し、最終濃度を3.2～12.0mg/mL とした上で点滴静注する。 14.2 薬剤投与時の注意 14.2.1 0.2又は0.22μm のインラインフィルターを使用すること。 14.2.2 他剤との混注をしないこと。	変更なし
15. その他の注意 15.1 臨床使用に基づく情報 国内外の臨床試験において、本剤に対する抗体の産生が報告されている。 15.2 非臨床試験に基づく情報 カニクイザルに本剤50mg/kg を週1回、26週間反復投与した毒性試験において、雌動物に月経周期異常が認められたとの報告がある。	変更なし

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20XX 年 X 月改訂（第 XX 版、効能変更、用法及び用量変更）
2025 年 9 月改訂（第 10 版　効能変更、用法及び用量変更）

日本標準商品分類番号
874291

貯　　法：2～8℃保存
有効期間：36 箇月

抗悪性腫瘍剤／抗 PD-L1 注1) ヒト化モノクローナル抗体
アテゾリズマブ（遺伝子組換え）注
生物由来製品、劇薬、処方箋医薬品 注2)

テセントリク®点滴静注 840mg
テセントリク®点滴静注 1200mg

TECENTRIQ® for Intravenous Infusion

	点滴静注 840mg	点滴静注 1200mg
承認番号	30100AMX00261	23000AMX00014
販売開始	2019 年 11 月	2018 年 4 月

注 1）PD-L1：Programmed Death-Ligand 1
注 2）注意―医師等の処方箋により使用すること

最適使用推進ガイドライン対象品目

1. 警告

1.1 本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の使用が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

1.2 間質性肺疾患があらわれ、死亡に至った症例も報告されているので、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部 X 線検査の実施等、患者の状態を十分に観察すること。異常が認められた場合には本剤の投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。[8.2、9.1.2、11.1.1 参照]

2. 禁忌（次の患者には投与しないこと）

本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	テセントリク点滴静注 840mg	テセントリク点滴静注 1200mg
有効成分	1 バイアル（14.0mL）中 アテゾリズマブ（遺伝子組換え）注) 840mg	1 バイアル（20.0mL）中 アテゾリズマブ（遺伝子組換え）注) 1200mg
添加剤	1 バイアル（14.0mL）中 L-ヒスチジン 43.4mg 氷酢酸 11.5mg 精製白糖 575.1mg ポリソルベート 20 5.6mg	1 バイアル（20.0mL）中 L-ヒスチジン 62.0mg 氷酢酸 16.5mg 精製白糖 821.6mg ポリソルベート 20 8.0mg

注）本剤は、チャイニーズハムスター卵巣細胞を用いて製造される。

3.2 製剤の性状

販売名	テセントリク点滴静注 840mg	テセントリク点滴静注 1200mg
剤形	注射剤（バイアル）	
性状	澄明～乳白光を呈する無色～帯褐黄色の液	
pH	5.5～6.1	
浸透圧比	0.45～0.80	

4. 効能又は効果

〈製剤共通〉
○ 切除不能な進行・再発の非小細胞肺癌
○ PD-L1 陽性の非小細胞肺癌における術後補助療法
○ 進展型小細胞肺癌
○ 切除不能な胞巣状軟部肉腫
○ 再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型
〈テセントリク点滴静注 1200mg〉
○ 切除不能な肝細胞癌
○ 切除不能な胸腺癌
〈テセントリク点滴静注 840mg〉
○ PD-L1 陽性のホルモン受容体陰性かつ HER2 陰性の手術不能又は再発乳癌

5. 効能又は効果に関連する注意

〈切除不能な進行・再発の非小細胞肺癌〉

5.1 化学療法未治療の PD-L1 陰性の扁平上皮癌患者における本剤の有効性及び安全性は確立していない。

5.2 化学療法未治療の切除不能な進行・再発の非小細胞肺癌に対して本剤を単独で投与する場合には、腫瘍細胞及び腫瘍浸潤免疫細胞における PD-L1 発現率について、「17.臨床成績」の項の内容を熟知し、十分な経験を有する病理医又は検査施設における検査により、PD-L1 の発現が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html
［17.1.2 参照］

5.3 臨床試験に組み入れられた患者の前治療歴、*EGFR* 遺伝子変異又は *ALK* 融合遺伝子の有無等について、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。［17.1.1-17.1.5 参照］

〈PD-L1 陽性の非小細胞肺癌における術後補助療法〉

5.4 腫瘍細胞における PD-L1 発現率について、「17.臨床成績」の項の内容を熟知し、十分な経験を有する病理医又は検査施設における検査により、PD-L1 の発現が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html
［17.1.6 参照］

5.5 臨床試験に組み入れられた患者の前治療歴、病期等について、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。また、本剤の延命効果は、PD-L1 発現率（TC）により異なる傾向が示唆されていることから、本剤の有効性及

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び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.6 参照]

〈進展型小細胞肺癌〉

5.6 臨床試験に組み入れられた患者の進展型の基準等について、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.7 参照]

〈切除不能な肝細胞癌〉

5.7 局所療法（経皮的エタノール注入療法、ラジオ波焼灼療法、マイクロ波凝固療法、肝動脈塞栓療法/肝動脈化学塞栓療法、放射線療法等）の適応となる肝細胞癌患者に対する本剤の有効性及び安全性は確立していない。

5.8 臨床試験に組み入れられた患者の肝機能障害の程度等について、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.8 参照]

〈PD-L1 陽性のホルモン受容体陰性かつ HER2 陰性の手術不能又は再発乳癌〉

5.9 本剤の術前・術後薬物療法としての有効性及び安全性は確立していない。

5.10 PD-L1 を発現した腫瘍浸潤免疫細胞の占める割合について、十分な経験を有する病理医又は検査施設における検査により、PD-L1 の発現が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html

HER2：Human Epidermal Growth Factor Receptor Type 2（ヒト上皮増殖因子受容体 2 型、別称：*c-erb*B-2）

〈再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型〉

5.11 臨床試験に組み入れられた患者の前治療歴等について、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.12 参照]

〈切除不能な胸腺癌〉

5.12 本剤の術前補助療法としての有効性及び安全性は確立していない。

6. 用法及び用量

〈効能共通〉

アテゾリズマブ（遺伝子組換え）の初回投与時は 60 分かけて点滴静注し、初回投与の忍容性が良好であれば、2 回目以降の投与時間は 30 分間まで短縮できる。

効能又は効果	用法及び用量
切除不能な進行・再発の非小細胞肺癌	化学療法未治療の扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌 他の抗悪性腫瘍剤との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔で点滴静注する。その後、単独投与する場合には、アテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔又は 1 回 1680mg を 4 週間間隔で点滴静注する。 化学療法未治療の PD-L1 陽性の切除不能な進行・再発の非小細胞肺癌 通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔又は 1 回 1680mg を 4 週間間隔で点滴静注する。 化学療法既治療の切除不能な進行・再発の非小細胞肺癌 通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔又は 1 回 1680mg を 4 週間間隔で点滴静注する。
PD-L1 陽性の非小細胞肺癌における術後補助療法	通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔又は 1 回 1680mg を 4 週間間隔で点滴静注する。投与期間は 12 カ月間までとする。
進展型小細胞肺癌	カルボプラチン及びエトポシドとの併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔で 4 回点滴静注する。その後、アテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔又は 1 回 1680mg を 4 週間間隔で点滴静注する。
切除不能な肝細胞癌	ベバシズマブ（遺伝子組換え）との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔で点滴静注する。
PD-L1 陽性のホルモン受容体陰性かつ HER2 陰性の手術不能又は再発乳癌	パクリタキセル（アルブミン懸濁型）との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 840mg を 2 週間間隔又は 1 回 1680mg を 4 週間間隔で点滴静注する。
切除不能な胞巣状軟部肉腫	通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔で点滴静注する。通常、2 歳以上の小児にはアテゾリズマブ（遺伝子組換え）として 1 回 15mg/kg（体重）（最大 1200mg）を 3 週間間隔で点滴静注する。
再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型	通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔で点滴静注する。通常、12 歳以上の小児にはアテゾリズマブ（遺伝子組換え）として 1 回 15mg/kg（体重）（最大 1200mg）を 3 週間間隔で点滴静注する。
切除不能な胸腺癌	カルボプラチン及びパクリタキセルとの併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として 1 回 1200mg を 3 週間間隔で点滴静注する。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤投与により副作用が発現した場合には、以下の基準を目安に、本剤の休薬等を考慮すること。

副作用	程度	処置
間質性肺疾患等の呼吸器障害	Grade 2 の場合	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	Grade 3 以上又は再発性の場合	本剤を中止する。

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副作用	程度	処置
肝機能障害（切除不能な肝細胞癌を除く）	Grade 2（AST 若しくは ALT が基準値上限の 3 倍超かつ 5 倍以下又は総ビリルビンが基準値上限の 1.5 倍超かつ 3 倍以下の増加）が 5 日を超えて継続する場合	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	Grade 3 以上（AST 若しくは ALT が基準値上限の 5 倍超又は総ビリルビンが基準値上限の 3 倍超に増加）の場合	本剤を中止する。
肝機能障害（切除不能な肝細胞癌の場合）	・ ベースラインの AST 又は ALT が基準値内の患者では、AST 又は ALT が基準値上限の 3 倍超かつ 10 倍以下に増加した場合 ・ ベースラインの AST 又は ALT が基準値上限の 1 倍超かつ 3 倍以下の患者では、AST 又は ALT が基準値上限の 5 倍超かつ 10 倍以下に増加した場合 ・ ベースラインの AST 又は ALT が基準値上限の 3 倍超かつ 5 倍以下の患者では、AST 又は ALT が基準値上限の 8 倍超かつ 10 倍以下に増加した場合	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	AST 若しくは ALT が基準値上限の 10 倍超又は総ビリルビンが基準値上限の 3 倍超に増加した場合	本剤を中止する。
大腸炎/下痢	Grade 2 又は 3 の場合	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	Grade 4 の場合	本剤を中止する。
膵炎	・ アミラーゼ又はリパーゼが基準値上限の 2 倍超に増加した場合 ・ Grade 2 又は 3 の膵炎	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	Grade 4 又は再発性の膵炎	本剤を中止する。
内分泌障害	空腹時血糖値が 250mg/dL 超	血糖値が安定するまで、本剤を休薬する。
	・ 症候性の甲状腺機能低下症 ・ 症候性の甲状腺機能亢進症、又は甲状腺刺激ホルモン値 0.1mU/L 未満の無症候性の甲状腺機能亢進症	左記の状態が回復するまで、本剤を休薬する。
	Grade 2 以上の副腎機能不全	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	・ Grade 2 又は 3 の下垂体炎 ・ Grade 2 又は 3 の下垂体機能低下症	Grade 1 以下に回復するまで、本剤を休薬する。12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	・ Grade 4 又は再発性の下垂体炎 ・ Grade 4 又は再発性の下垂体機能低下症	本剤を中止する。
脳炎、髄膜炎	全 Grade	本剤を中止する。
神経障害	Grade 2 の場合	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	Grade 3 以上の場合	本剤を中止する。
	全 Grade のギラン・バレー症候群	本剤を中止する。
重症筋無力症	全 Grade	本剤を中止する。
皮膚障害	Grade 3 の場合	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	Grade 4 の場合	本剤を中止する。
腎炎	血清クレアチニンが基準値上限又はベースラインの 1.5 倍超かつ 3 倍以下に増加した場合	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	血清クレアチニンが基準値上限又はベースラインの 3 倍超に増加した場合	本剤を中止する。
筋炎	Grade 2 又は 3 の場合	Grade 1 以下に回復するまで、本剤を休薬する。 12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	Grade 3 の再発又は Grade 4 の場合	本剤を中止する。
心筋炎	Grade 2 以上の場合	本剤を中止する。
血球貪食症候群	全 Grade	本剤を中止する。

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副作用	程度	処置
眼障害	Grade 2 の場合	Grade 1 以下に回復するまで、本剤を休薬する。12 週間を超える休薬後も Grade 1 以下まで回復しない場合は、本剤を中止する。
	Grade 3 以上の場合	本剤を中止する。
Infusion reaction	Grade 1 の場合	投与速度を 50%に減速する。なお、軽快した後 30 分間経過観察し、再発しない場合には投与速度を元に戻すことができる。
	Grade 2 の場合	投与を中断し、軽快後に投与速度を 50%に減速し再開する。
	Grade 3 以上の場合	本剤を直ちに中止する。

Grade は NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events) v5.0 に準じる。

〈化学療法未治療の扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌〉

7.2 併用する他の抗悪性腫瘍剤は「17. 臨床成績」の項の内容を熟知し選択すること。[17.1.3-17.1.5 参照]

〈化学療法未治療の PD-L1 陽性の切除不能な進行・再発の非小細胞肺癌〉

7.3 扁平上皮癌の場合、他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。

〈化学療法既治療の切除不能な進行・再発の非小細胞肺癌、PD-L1 陽性の非小細胞肺癌における術後補助療法、切除不能な胞巣状軟部肉腫、再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型〉

7.4 他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。

〈進展型小細胞肺癌〉

7.5 カルボプラチン及びエトポシドとの併用に際しては「17. 臨床成績」の項の内容、特に、併用する抗悪性腫瘍剤の用法及び用量を十分に理解した上で投与すること。[17.1.7 参照]

〈切除不能な胸腺癌〉

7.6 カルボプラチン及びパクリタキセルとの併用に際しては、通常、成人には、3 週間間隔で、カルボプラチンは 1 回 AUC 6mg・min/mL 相当量を 30 分以上かけて点滴静注し、パクリタキセルは 1 回 200mg/m^2 を 3 時間かけて点滴静注すること。なお、患者の状態により適宜減量すること。

8. 重要な基本的注意

〈効能共通〉

8.1 本剤の T 細胞活性化作用により、過度の免疫反応に起因すると考えられる様々な疾患や病態があらわれることがある。患者の状態を十分に観察し、異常が認められた場合には、過度の免疫反応による副作用の発現を考慮し、適切な鑑別診断を行うこと。過度の免疫反応による副作用が疑われた場合には、副腎皮質ホルモン剤の投与等を考慮すること。また、本剤投与終了後に重篤な副作用があらわれることがあるので、本剤投与終了後も患者の状態を十分に観察すること。

8.2 間質性肺疾患があらわれることがあるので、本剤の投与にあたっては、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部 X 線検査の実施等、患者の状態を十分に観察すること。また、必要に応じて、胸部 CT、血清マーカー等の検査を実施すること。[1.2、9.1.2、11.1.1 参照]

8.3 肝機能障害、肝炎、硬化性胆管炎があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に肝機能検査を行い、患者の状態を十分に観察すること。[11.1.2 参照]

8.4 1 型糖尿病があらわれることがあるので、口渇、悪心、嘔吐等の症状の発現や血糖値の上昇に十分注意すること。[11.1.5 参照]

8.5 甲状腺機能障害、副腎機能障害及び下垂体機能障害があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に内分泌機能検査（TSH、遊離 T3、遊離 T4、ACTH、血中コルチゾール等の測定）等を行うこと。また、必要に応じて、画像検査等の実施も考慮すること。[11.1.6-11.1.8 参照]

8.6 重症筋無力症があらわれることがあるので、筋力低下、眼瞼下垂、呼吸困難、嚥下障害等の観察を十分に行うこと。[11.1.11 参照]

8.7 腎機能障害があらわれることがあるので、定期的に腎機能検査を行い、患者の状態を十分に観察すること。[11.1.13 参照]

8.8 筋炎、横紋筋融解症があらわれることがあるので、筋力低下、筋肉痛、CK 上昇、血中及び尿中ミオグロビン上昇等の観察を十分に行うこと。[11.1.14 参照]

8.9 心筋炎があらわれることがあるので、胸痛、CK 上昇、心電図異常等の観察を十分に行うこと。[11.1.15 参照]

〈化学療法未治療の扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌、切除不能な胸腺癌〉

8.10 本剤とカルボプラチン及びパクリタキセルを併用投与、並びに本剤とカルボプラチン、パクリタキセル及びベバシズマブ（遺伝子組換え）を併用投与する際には、発熱性好中球減少症があらわれることがあるので、投与中は定期的に血液検査を行う等、患者の状態を十分に観察すること。[11.1.19 参照]

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 自己免疫疾患の合併又は慢性的若しくは再発性の自己免疫疾患の既往歴のある患者

免疫関連の副作用が発現又は増悪するおそれがある。

9.1.2 間質性肺疾患のある患者又はその既往歴のある患者

間質性肺疾患が発現又は増悪するおそれがある。[1.2、8.2、11.1.1 参照]

9.4 生殖能を有する者

妊娠する可能性のある女性には、本剤投与中及び最終投与後 5 カ月間において避妊する必要性及び適切な避妊法について説明すること。[9.5 参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤を用いた生殖発生毒性試験は実施されていない。本剤を投与すると、胎児に対する免疫寛容が妨害され、流産率又は死産率が増加する可能性がある。また、ヒト IgG は胎盤を通過することが知られており、本剤は母体から胎児へ移行する可能性がある。[9.4 参照]

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9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行性については不明であるが、ヒト IgG はヒト乳汁中に排出されることが知られている。

9.7 小児等

〈切除不能な進行・再発の非小細胞肺癌、PD-L1 陽性の非小細胞肺癌における術後補助療法、進展型小細胞肺癌、切除不能な肝細胞癌、PD-L1 陽性のホルモン受容体陰性かつ HER2 陰性の手術不能又は再発乳癌、切除不能な胸腺癌〉

9.7.1 小児等を対象とした臨床試験は実施していない。

〈切除不能な胞巣状軟部肉腫〉

9.7.2 低出生体重児、新生児、乳児又は 2 歳未満の幼児を対象とした臨床試験は実施していない。[16.6.1 参照]

〈再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型〉

9.7.3 低出生体重児、新生児、乳児、幼児又は 12 歳未満の小児を対象とした臨床試験は実施していない。ATTACK 試験は 12 歳以上を対象として実施されたが、18 歳未満の患者は組み入れられなかった。[16.6.1、17.1.12 参照]

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下していることが多い。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 間質性肺疾患（3.0%）

[1.2、8.2、9.1.2 参照]

11.1.2 肝機能障害、肝炎、硬化性胆管炎

AST 増加（6.3%）、ALT 増加（6.3%）、Al-P 増加（2.1%）、ビリルビン増加（1.5%）、γ-GTP 増加（1.0%）等を伴う肝機能障害、肝炎（0.8%）、硬化性胆管炎（頻度不明）があらわれることがある。[8.3 参照]

11.1.3 大腸炎（1.1%）**、重度の下痢**（1.2%）

持続する下痢、腹痛、血便等の症状があらわれた場合には本剤の投与を中止する等の適切な処置を行うこと。

11.1.4 膵炎（0.1%）

11.1.5 1 型糖尿病（0.1%）

1 型糖尿病（劇症 1 型糖尿病を含む）があらわれ、糖尿病性ケトアシドーシスに至るおそれがある。1 型糖尿病が疑われた場合には本剤の投与を中止し、インスリン製剤を投与する等の適切な処置を行うこと。[8.4 参照]

11.1.6 甲状腺機能障害

甲状腺機能低下症（8.0%）、甲状腺機能亢進症（3.5%）、甲状腺炎（0.6%）等の甲状腺機能障害があらわれることがある。[8.5 参照]

11.1.7 副腎機能障害

副腎機能不全（0.6%）、急性副腎皮質機能不全（0.1%未満）等の副腎機能障害があらわれることがある。[8.5 参照]

11.1.8 下垂体機能障害

下垂体炎（0.2%）、下垂体機能低下症（0.1%）等の下垂体機能障害があらわれることがある。[8.5 参照]

11.1.9 脳炎（0.1%）**、髄膜炎**（0.1%）**、脊髄炎**（頻度不明）

11.1.10 神経障害

末梢性ニューロパチー（4.4%）、多発ニューロパチー（0.3%）、ギラン・バレー症候群（0.1%）等の神経障害があらわれることがある。

11.1.11 重症筋無力症（頻度不明）

重症筋無力症によるクリーゼのため急速に呼吸不全が進行することがあるので、呼吸状態の悪化に十分注意すること。[8.6 参照]

11.1.12 重度の皮膚障害

中毒性表皮壊死融解症（Toxic Epidermal Necrolysis：TEN）（頻度不明）、皮膚粘膜眼症候群（Stevens-Johnson 症候群）（頻度不明）、多形紅斑（0.3%）等の重度の皮膚障害があらわれることがある。

11.1.13 腎機能障害

急性腎障害（0.4%）、腎不全（0.4%）、尿細管間質性腎炎（0.2%）、腎炎（0.2%）等の腎機能障害があらわれることがある。[8.7 参照]

11.1.14 筋炎（0.2%）**、横紋筋融解症**（0.1%）

[8.8 参照]

11.1.15 心筋炎（0.1%）

[8.9 参照]

11.1.16 血球貪食症候群（0.1%未満）

11.1.17 免疫性血小板減少症（頻度不明）

11.1.18 Infusion reaction（2.6%）

アナフィラキシーを含む Infusion reaction があらわれることがある。重度の Infusion reaction があらわれた場合には本剤の投与を直ちに中止し、適切な処置を行うとともに、症状が回復するまで患者の状態を十分に観察すること。

11.1.19 発熱性好中球減少症（5.0%[注1)]）

本剤とカルボプラチン及びパクリタキセルとの併用、並びに本剤とカルボプラチン、パクリタキセル及びベバシズマブ（遺伝子組換え）との併用において、発熱性好中球減少症があらわれることがある。[8.10 参照]

注 1）発現頻度は、IMpower150 試験及び Marble 試験から集計した。

11.2 その他の副作用

	5%以上	1%以上～5%未満	1%未満	頻度不明
精神神経系		頭痛、味覚異常、浮動性めまい、錯感覚、不眠症	意識レベルの低下、回転性めまい、感覚鈍麻、失神	顔面不全麻痺
眼			結膜炎、霧視、眼乾燥、流涙増加	
消化器	下痢（11.2%）、悪心（10.7%）、食欲減退、便秘	嘔吐、口内炎、腹痛、口内乾燥	腹部膨満、消化不良、嚥下障害、アミラーゼ増加、リパーゼ増加	
循環器		高血圧	低血圧、頻脈、ほてり、潮紅	
呼吸器		呼吸困難、咳嗽、気道感染、肺炎、鼻出血	発声障害、鼻炎、しゃっくり、口腔咽頭痛、胸水、喀	

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	5%以上	1%以上～5%未満	1%未満	頻度不明
			血、低酸素症、鼻閉	
皮膚	発疹、そう痒症	脱毛症、斑状丘疹状皮疹、皮膚乾燥、ざ瘡様皮膚炎、紅斑	蕁麻疹、皮膚炎、そう痒性皮疹、乾癬、紅斑性皮疹、寝汗	
筋骨格系	関節痛	筋肉痛、筋骨格痛	筋力低下、筋痙縮、関節炎、血中CK増加	
泌尿器		高クレアチニン血症、蛋白尿	尿路感染	
血液	貧血、好中球減少、血小板減少	白血球減少、リンパ球減少		
代謝		低マグネシウム血症、低ナトリウム血症、低カリウム血症、低アルブミン血症、血中甲状腺刺激ホルモン増加、高血糖、脱水	血中甲状腺刺激ホルモン減少、高カリウム血症、低カルシウム血症、低リン血症	
その他	疲労（14.7%）、無力症、発熱	浮腫、体重減少、倦怠感、悪寒、粘膜の炎症、インフルエンザ様疾患	腫脹、過敏症、胸痛、血中乳酸脱水素酵素増加、疼痛	

注2）Marble試験においては、本剤、カルボプラチン又はパクリタキセルのいずれかにより発現した副作用について集計した。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 調製時には、日局生理食塩液以外は使用しないこと。

14.1.2 調製時は静かに転倒混和すること。

14.1.3 用時調製し、調製後は速やかに使用すること。また、残液は廃棄すること。

14.1.4 投与時には本剤を注射筒で抜き取り、日局生理食塩液に添加し、最終濃度を3.2～16.8mg/mLとした上で点滴静注する。

14.2 薬剤投与時の注意

14.2.1 0.2又は0.22μmのインラインフィルターを使用すること。

14.2.2 他剤との混注をしないこと。

15. その他の注意

15.1 臨床使用に基づく情報

国内外の臨床試験において、本剤に対する抗体の産生が報告されている。

15.2 非臨床試験に基づく情報

カニクイザルに本剤50mg/kgを週1回、26週間反復投与した毒性試験において、雌動物に月経周期異常が認められたとの報告がある。

16. 薬物動態

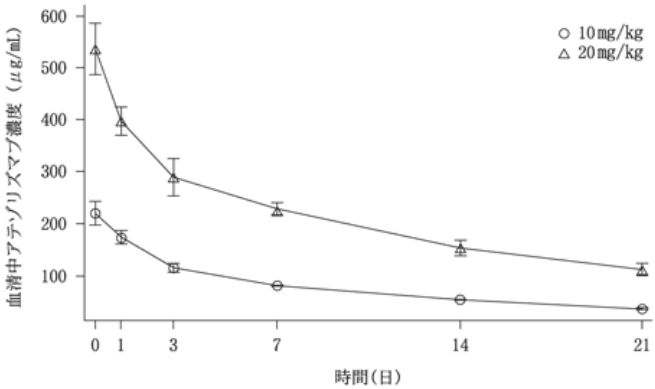
16.1 血中濃度

16.1.1 単回投与

(1) 日本人の進行固形癌患者3例ずつに本剤10又は20mg/kg[注1)]を90分（±15分）間点滴静注したときの血清中アテゾリズマブ濃度推移は以下のとおりであった。両用量群の全身クリアランスは同程度の値を示し、分布容積はほぼ血漿容量に相当した[1)]。

注1）承認された用法及び用量：1200mg若しくは15mg/kgを3週間間隔、840mgを2週間間隔又は1680mgを4週間間隔で60分かけて点滴静注

単回投与時の血清中濃度推移（各用量N=3、平均値±標準偏差）



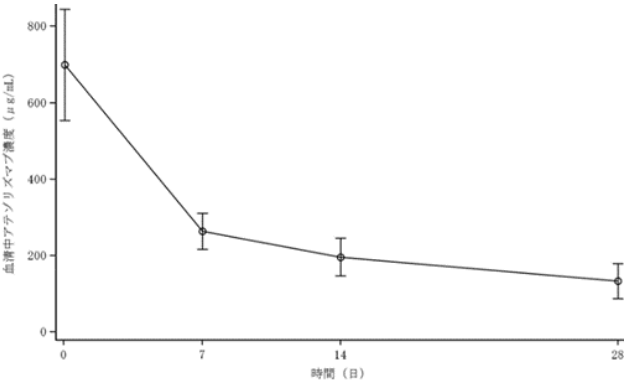
単回投与時の薬物動態パラメータ（各用量N=3、平均値±標準偏差）

投与量 (mg/kg)	C_{max}* (μg/mL)	AUC_{inf} (μg・day/mL)	$V_{d,ss}$ (L)	CL (L/day)	$t_{1/2}$ (day)
10	220±21.9	2290±101	3.72±1.14	0.236±0.0572	11.7±0.969
20	536±49.4	6630±668	3.82±0.718	0.213±0.0609	13.0±1.32

*C_{max}：初回投与時（Cycle 1 Day 1）の投与後30分の採血

(2) 日本人の進行固形癌患者21例に本剤1680mgを60分（±15分）間点滴静注したときの血清中アテゾリズマブ濃度推移は以下のとおりであった[2)]。

単回投与時の血清中濃度推移（平均値±標準偏差）



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単回投与時の薬物動態パラメータ
（平均値±標準偏差(例数)）

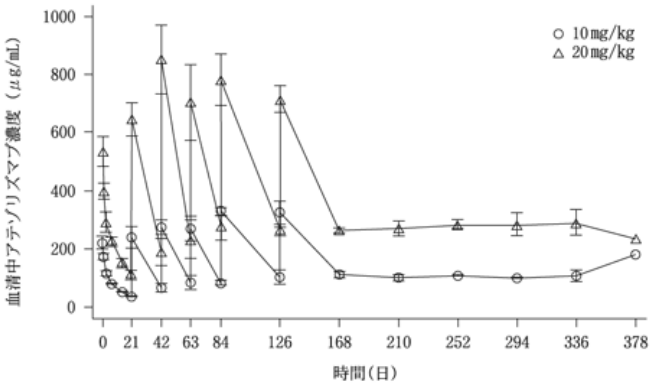
投与量 (mg/body)	C_{max}* (μg/mL)	AUC_{last} (μg・day/mL)	$t_{1/2}$ (day)
1680	699±146 (N=21)	7180±1340 (N=18)	24.4±11.5 (N=18)

*C_{max}：初回投与時（Cycle 1 Day 1）の投与後 30 分の採血

16.1.2 反復投与

(1) 日本人の進行固形癌患者 3 例ずつに本剤 10 又は 20mg/kg を 3 週間間隔で 90 分[注1)]（±15 分、初回投与における忍容性が確認された場合、2 回目以降 30 分（±10 分）に短縮可能）間点滴静注したときの血清中アテゾリズマブ濃度推移は以下のとおりであった。蓄積係数の平均値は 1.25～3.06 であった [1)]。

反復投与時の血清中濃度推移（各用量 N=1～3、平均値±標準偏差）



(2) 非小細胞肺癌患者 613 例（日本人患者 56 例）を対象に本剤 1200mg を 3 週間間隔で 60 分（±15 分、初回投与における忍容性が確認された場合、2 回目以降 30 分（±10 分）に短縮可能）間点滴静注したときの日本人における血清中アテゾリズマブ濃度は以下のとおりであった。(1 サイクル：21 日) [3)]

反復投与時の日本人における血清中アテゾリズマブ濃度（平均値±標準偏差（例数））

サイクル	採血時点	血清中濃度 (μg/mL)
Cycle1 Day1	投与 30 分後	452±107 (N=56)
Cycle2 Day1	投与前	98.2±32.4 (N=46)
Cycle3 Day1	投与前	162±40.8 (N=40)
Cycle4 Day1	投与前	188±55.6 (N=35)
Cycle8 Day1	投与前	224±99.1 (N=18)

(3) 乳癌患者 451 例（日本人患者 34 例）を対象に本剤 840mg を 2 週間間隔で 60 分（±15 分、初回投与における忍容性が確認された場合、2 回目以降 30 分（±10 分）に短縮可能）間点滴静注したときの日本人における血清中アテゾリズマブ濃度は以下のとおりであった。(1 サイクル：28 日) [4)]

反復投与時の日本人における血清中アテゾリズマブ濃度（平均値±標準偏差（例数））

サイクル	採血時点	血清中濃度 (μg/mL)
Cycle1 Day1	投与 30 分後	411±98.9 (N=34)
Cycle2 Day1	投与前	178±67.5 (N=32)
Cycle3 Day1	投与前	264±95.0 (N=32)
Cycle4 Day1	投与前	293±116 (N=29)
Cycle8 Day1	投与前	316±162 (N=17)

(4) 日本人の進行固形癌患者 21 例に本剤 1680mg を 4 週間間隔で 60 分（±15 分、初回投与における忍容性が確認された場合、2 回目以降 30 分（±10 分）に短縮可能）間点滴静注したときの血清中アテゾリズマブ濃度推移は以下の通りであった。(1 サイクル：28 日) [2)]

反復投与時の血清中アテゾリズマブ濃度（平均値±標準偏差（例数））

サイクル	採血時点	血清中濃度 (μg/mL)
Cycle1 Day1	投与 30 分後	699±146 (N=21)
Cycle2 Day1	投与前	133±46.0 (N=19)
Cycle4 Day1	投与前	252±68.7 (N=5)
Cycle7 Day1	投与前	300* (N=1)
Cycle7 Day1	投与 30 分後	1120* (N=1)

*個別値

16.1.3 母集団薬物動態解析

〈切除不能な進行・再発の非小細胞肺癌、PD-L1 陽性の非小細胞肺癌における術後補助療法、進展型小細胞肺癌、及び PD-L1 陽性のホルモン受容体陰性かつ HER2 陰性の手術不能又は再発乳癌〉

母集団薬物動態解析において、国際共同第Ⅲ相試験 6 試験の各試験（OAK 試験、IMpower132 試験、IMpower110 試験、IMpower010 試験、IMpower133 試験、及び IMpassion130 試験）に組み入れられた全体集団及び日本人集団の患者背景の分布に基づき、1000 例の仮想患者集団をそれぞれ生成し、当該仮想患者集団に本剤 840mg を 2 週間間隔投与、1200mg を 3 週間間隔投与、1680mg を 4 週間間隔投与した時のサイクル 1 及び定常状態におけるアテゾリズマブの曝露量を推定した結果（OAK 試験、IMpower133 試験、IMpassion130 試験）は、以下のとおりであった。なお、IMpower132 試験、IMpower110 試験及び IMpower010 試験におけるアテゾリズマブの曝露量の推定結果については、OAK 試験におけるアテゾリズマブの曝露量の推定結果と同様であった [5)]。

OAK 試験（非小細胞肺癌）におけるアテゾリズマブの曝露量（推定値）

用法・用量	集団	C_{max} (μg/mL)		C_{trough} (μg/mL)	
		Cycle1	定常状態	Cycle1	定常状態
1200mg 3 週間間隔	全体	392 [271, 577]	574 [380, 889]	77.6 [42.3, 128]	165 [60.9, 389]
	日本人	432 [296, 629]	665 [435, 1020]	92.9 [57.7, 146]	216 [87.6, 476]
1680mg 4 週間間隔	全体	545 [381, 798]	719 [501, 1100]	82.9 [41.8, 151]	151 [54.8, 402]
	日本人	600 [416, 865]	826 [576, 1250]	102 [55.9, 175]	202 [77.4, 481]

幾何平均値［5%点, 95%点］

IMpower133 試験（小細胞肺癌）におけるアテゾリズマブの曝露量（推定値）

用法・用量	集団	C_{max} (μg/mL)		C_{trough} (μg/mL)	
		Cycle1	定常状態	Cycle1	定常状態

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1200mg 3 週間間隔	全体	403 [308, 551]	587 [414, 881]	82.1 [51.0, 132]	176 [86.5, 353]
	日本人	446 [366, 564]	682 [513, 934]	94.4 [64.2, 140]	228 [124, 410]
1680mg 4 週間間隔	全体	563 [434, 762]	735 [530, 1080]	88.3 [51.6, 149]	162 [75.6, 353]
	日本人	624 [511, 780]	849 [653, 1130]	105 [68.2, 160]	215 [112, 399]

幾何平均値［5%点，95%点］

IMpassion130 試験（乳癌）におけるアテゾリズマブの曝露量（推定値）

用法・用量	集団	C_{max}（μg/mL）		C_{trough}（μg/mL）	
		Cycle1	定常状態	Cycle1	定常状態
840mg 2 週間間隔	全体	325 [229, 465]	599 [388, 928]	86.5 [59.4, 127]	263 [132, 503]
	日本人	370 [264, 520]	682 [447, 1040]	93.8 [63.7, 136]	299 [156, 548]
1680mg 4 週間間隔	全体	653 [465, 915]	880 [603, 1300]	112 [67.3, 178]	206 [88.3, 432]
	日本人	742 [536, 1030]	1010 [704, 1470]	124 [78.8, 190]	239 [108, 487]

幾何平均値［5%点，95%点］

16.6 特定の背景を有する患者

16.6.1 小児等

小児を含む進行悪性腫瘍患者を対象に、本剤 15mg/kg（最大 1200mg）を 3 週間間隔で 60 分（±15 分、初回投与における忍容性が確認された場合、2 回目以降 30 分（±10 分）に短縮可能）間点滴静注したときの血清中アテゾリズマブ濃度は以下のとおりであった（外国人データ）。（1 サイクル：21 日）[6]［9.7 参照］

反復投与時の血清中アテゾリズマブ濃度（幾何平均値（幾何変動係数%）（例数））

サイクル	採血時点	血清中濃度（μg/mL）	
		2 歳以上 12 歳未満	12 歳以上 18 歳未満
Cycle1 Day1	投与 30 分後	312（28.7） (N=26)	337（26.8） (N=34)
Cycle2 Day1	投与前	59.3（31.4） (N=25)	56.5（50.4） (N=32)
Cycle3 Day1	投与前	58.9（234.4） (N=13)	85.0（47.4） (N=19)
Cycle4 Day1	投与前	99.2（36.4） (N=11)	113（41.1） (N=16)
Cycle4 Day1	投与 30 分後	382（16.4） (N=11)	373（78.9） (N=16)
Cycle8 Day1	投与前	166（19.8） (N=4)	145（21.9） (N=4)

16.8 その他

〈切除不能な進行・再発の非小細胞肺癌、PD-L1 陽性の非小細胞肺癌における術後補助療法、進展型小細胞肺癌、PD-L1 陽性のホルモン受容体陰性かつ HER2 陰性の手術不能又は再発乳癌〉

本剤の安全性に対する曝露-反応解析の結果、本剤の曝露量（C_{max} 及び C_{trough}）と安全性との間に明確な関連は認められなかったことから、本剤 840mg を 2 週間間隔投与、1200mg を 3 週間間隔投与、1680mg を 4 週間間隔投与した際の安全性に明確な差異はないと予測された[2]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈切除不能な進行・再発の非小細胞肺癌〉

17.1.1 国際共同第Ⅲ相臨床試験（OAK 試験）

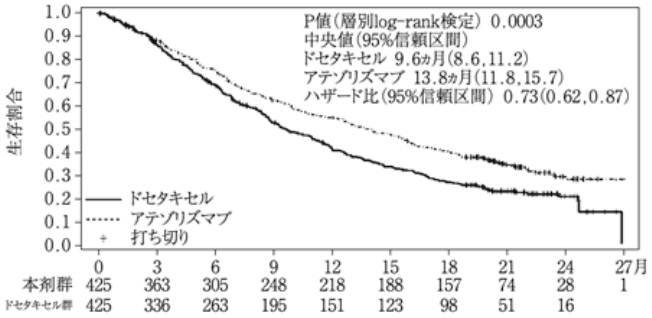
プラチナ製剤を含む化学療法歴[注1)]のある切除不能な進行・再発の非小細胞肺癌患者 1225 例（本剤群 613 例、ドセタキセル群 612 例）を対象に、本剤とドセタキセルとの有効性及び安全性を比較する第Ⅲ相試験を実施した。

本剤 1200mg 又はドセタキセル 75mg/m^2 を 3 週間間隔で点滴静注した。最初にランダム化された 850 例（日本人 64 例を含む）の全患者集団において、本剤群でドセタキセル群と比較して主要評価項目である全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］：0.73［0.62，0.87］、P=0.0003［層別 log-rank 検定］）、中央値［95%信頼区間］は本剤群で 13.8［11.8，15.7］カ月、ドセタキセル群で 9.6［8.6，11.2］カ月であった[7]。

本剤が投与された 609 例（日本人 56 例を含む）において 390 例（64.0%）に副作用が認められた。主な副作用（5%以上）は、疲労 87 例（14.3%）、悪心 53 例（8.7%）、食欲減退 52 例（8.5%）、無力症 51 例（8.4%）、発熱 49 例（8.0%）、下痢 47 例（7.7%）、発疹 42 例（6.9%）、そう痒症 38 例（6.2%）等であった[8]。

注 1）*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者では、プラチナ製剤を含む化学療法に加え、それぞれ EGFR 阻害作用又は ALK 阻害作用を有する抗悪性腫瘍剤による治療歴がある患者が組み入れられた。

OAK 試験の全生存期間の Kaplan-Meier 曲線（全患者集団）



17.1.2 国際共同第Ⅲ相臨床試験（IMpower110 試験）

化学療法歴のない[注2)]、PD-L1 陽性（腫瘍細胞又は腫瘍浸潤免疫細胞における PD-L1 発現率が 1%以上）の切除不能な進行・再発の非小細胞肺癌患者 572 例（日本人 51 例を含む）を対象に、本剤 1200 mg（本剤群）の有効性及び安全性を、プラチナ製剤（シスプラチン又はカルボプラチン）及びペメトレキセド又はゲムシタビンの併用投与（化学療法群）と比較する第Ⅲ相試験を実施した。中間解析の結

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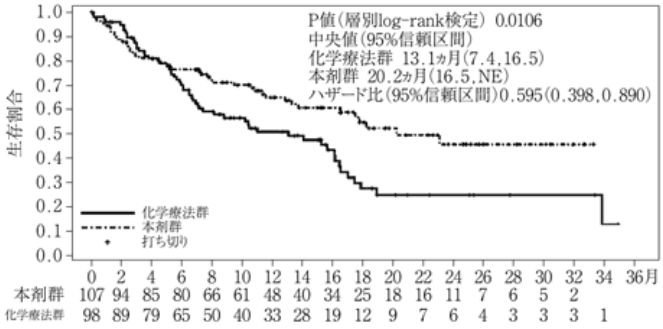
果、*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者を除く 554 例の ITT-WT 集団のうち TC3/IC3-WT [注3)] 集団 205 例（日本人 24 例を含む）において、本剤群（107 例）で化学療法群（98 例）と比較して主要評価項目である全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］0.595［0.398，0.890］、P = 0.0106［層別 log-rank 検定］、有意水準両側 0.0413）、中央値［95%信頼区間］は本剤群で 20.2［16.5，推定不能］カ月、化学療法群で 13.1［7.4，16.5］カ月であった [9]。

本剤が投与された 286 例（日本人 28 例を含む）において 173 例（60.5%）に副作用が認められた。主な副作用（5%以上）は、疲労 22 例（7.7%）、無力症 21 例（7.3%）、悪心 20 例（7.0%）、食欲減退 20 例（7.0%）、甲状腺機能低下症 19 例（6.6%）、発疹 19 例（6.6%）、ALT 増加 18 例（6.3%）、下痢 17 例（5.9%）等であった [10]。

注 2）*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者では、それぞれ EGFR 阻害作用又は ALK 阻害作用を有する抗悪性腫瘍剤による治療歴がある患者が組み入れられた。

注 3）腫瘍細胞又は腫瘍浸潤免疫細胞における PD-L1 発現率がそれぞれ 50%以上又は 10%以上と判定された患者。

IMpower110 試験の全生存期間の Kaplan-Meier 曲線（TC3/IC3-WT 集団）



17.1.3 国際共同第Ⅲ相臨床試験（IMpower150 試験）

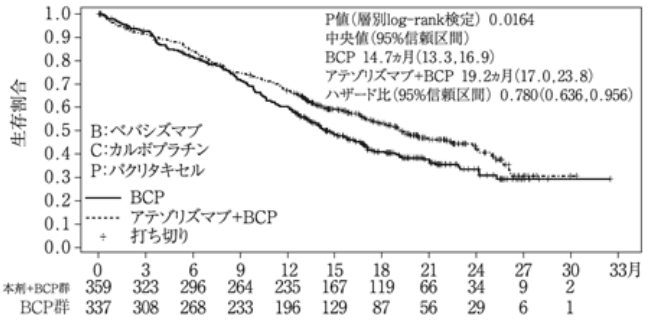
化学療法歴のない[注4)]、扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌患者 1202 例（日本人 93 例を含む）を対象に、本剤 1200mg と他の抗悪性腫瘍剤（カルボプラチン＋パクリタキセル［A 群、402 例］、又はカルボプラチン＋パクリタキセル＋ベバシズマブ（遺伝子組換え）［B 群、400 例］）の併用投与の有効性及び安全性を、併用化学療法（カルボプラチン＋パクリタキセル＋ベバシズマブ（遺伝子組換え）［C 群、400 例］）と比較する第Ⅲ相試験を実施した[注5)]。2018 年 1 月 22 日の中間解析の結果、*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者を除く 1045 例（日本人 67 例を含む）の ITT-WT 集団において、本剤併用群（B 群 359 例）で対照群（C 群 337 例）と比較して主要評価項目である全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］：0.780［0.636，0.956］、P=0.0164［層別 log-rank 検定］、有意水準両側 0.0184）、中央値［95%信頼区間］は本剤併用群 B 群で 19.2［17.0，23.8］カ月、対照群 C 群で 14.7［13.3，16.9］カ月であった。なお、本剤併用群（A 群 349 例）は対照群 C 群と比較して全生存期間において有意な延長は認められなかった [11]。また、日本人患者における ITT-WT 集団の全生存期間の中央値［95%信頼区間］は、本剤併用群（B 群 32 例）で 19.8［14.1，24.2］カ月、対照群（C 群 14 例）で推定不能［13.2，推定不能］であった（ハザード比［95%信頼区間］：1.311［0.498，3.446］）[12]。

本剤と抗悪性腫瘍剤（カルボプラチン＋パクリタキセル＋ベバシズマブ（遺伝子組換え））が投与された B 群 393 例（日本人 36 例を含む）において 370 例（94.1%）に副作用が認められた。主な副作用（20%以上）は、脱毛症 185 例（47.1%）、悪心 135 例（34.4%）、疲労 104 例（26.5%）、貧血 97 例（24.7%）、食欲減退 89 例（22.6%）、末梢性ニューロパチー88 例（22.4%）、下痢 84 例（21.4%）等であった。また、B 群の日本人 36 例において 7 例（19.4%）に発熱性好中球減少症が認められた [12]。

注 4）*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者では、それぞれ EGFR 阻害作用又は ALK 阻害作用を有する抗悪性腫瘍剤による治療歴がある患者が組み入れられた。

注 5）本剤 1200mg、カルボプラチン AUC6、パクリタキセル 200mg/m^2、ベバシズマブ（遺伝子組換え）15mg/kg を 3 週間間隔で 4 又は 6 サイクル投与後、本剤及びベバシズマブ（遺伝子組換え）を 3 週間間隔で投与した。

IMpower150 試験の全生存期間の Kaplan-Meier 曲線（ITT-WT 集団）



17.1.4 国際共同第Ⅲ相臨床試験（IMpower132 試験）

化学療法歴のない、扁平上皮癌を除く、*EGFR* 遺伝子変異陰性及び *ALK* 融合遺伝子陰性の切除不能な進行・再発の非小細胞肺癌患者 578 例（日本人 101 例を含む）を対象に、本剤 1200mg と他の抗悪性腫瘍剤（カルボプラチン又はシスプラチン＋ペメトレキセド［本剤併用群 292 例］）の併用投与の有効性及び安全性を、併用化学療法（カルボプラチン又はシスプラチン＋ペメトレキセド［対照群 286 例］）と比較する第Ⅲ相試験を実施した[注6)]。全患者集団において、本剤併用群で対照群と比較して主要評価項目である無増悪生存期間の有意な延長が認められ（ハザード比［95%信頼区間］：0.596［0.494，0.719］、P<0.0001［層別 log-rank 検定］、有意水準両側 0.004）、中央値［95%信頼区間］は本剤併用群で 7.6［6.6，8.5］カ月、対照群で 5.2［4.3，5.6］カ月であった。

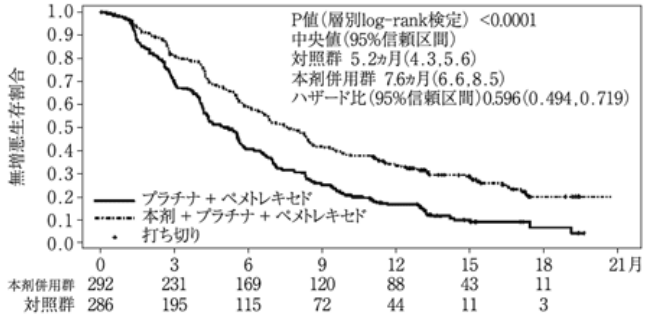
本剤と抗悪性腫瘍剤（カルボプラチン又はシスプラチン＋ペメトレキセド）が投与された 291 例（日本人 48 例を含む）において 267 例（91.8%）に副作用が認められた。主な副作用（20%以上）は、貧血 113 例（38.8%）、悪心 96 例（33.0%）、無力症 59 例（20.3%）等であった [13]。

注 6）本剤 1200mg、カルボプラチン AUC6 又はシスプラチン 75mg/m^2、ペメトレキセド 500mg/m^2 を 3 週間間隔で 4 又は 6 サイクル投与後、本剤及びペメトレキセドを 3 週間間隔で投与した。

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IMpower132 試験の無増悪生存期間の Kaplan-Meier 曲線（全患者集団）



17.1.5 海外第Ⅲ相臨床試験（IMpower130 試験）

化学療法歴のない[注7]、扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌患者 724 例を対象に、本剤 1200mg と他の抗悪性腫瘍剤（カルボプラチン＋パクリタキセル（アルブミン懸濁型）（以下、nab-パクリタキセル）［本剤併用群 484 例］）の併用投与の有効性及び安全性を、併用化学療法（カルボプラチン＋nab-パクリタキセル［対照群 240 例］）と比較する第Ⅲ相試験を実施した[注8]。

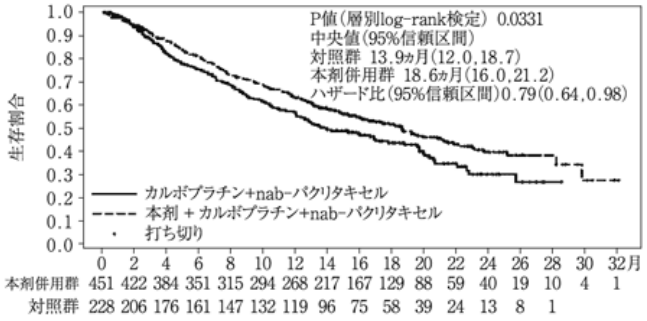
中間解析の結果、*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者を除く 679 例の ITT-WT 集団において、本剤併用群（451 例）で対照群（228 例）と比較して主要評価項目である全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］0.791［0.637，0.982］、P=0.0331［層別 log-rank 検定］、有意水準両側 0.0425）、中央値［95%信頼区間］は本剤併用群で 18.6［16.0，21.2］カ月、対照群で 13.9［12.0，18.7］カ月であった[14]。

本剤と抗悪性腫瘍剤（カルボプラチン＋nab-パクリタキセル）が投与された 473 例において 455 例（96.2%）に副作用が認められた。主な副作用（20%以上）は、貧血 248 例（52.4%）、好中球減少症 218 例（46.1%）、悪心 207 例（43.8%）、疲労 185 例（39.1%）、下痢 150 例（31.7%）、脱毛症 145 例（30.7%）、血小板減少症 127 例（26.8%）、食欲減退 107 例（22.6%）、血小板数減少 105 例（22.2%）、嘔吐 99 例（20.9%）等であった[15]。

注 7）*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者では、それぞれ EGFR 阻害作用又は ALK 阻害作用を有する抗悪性腫瘍剤による治療歴がある患者が組み入れられた。

注 8）本剤 1200mg 及びカルボプラチン AUC6 を各サイクルの 1 日目に、nab-パクリタキセル 100mg/m^2 を各サイクルの 1、8、15 日目に 3 週間間隔で 4 又は 6 サイクル投与後、本剤を 3 週間間隔で投与した。

IMpower130 試験の全生存期間の Kaplan-Meier 曲線（ITT-WT 集団）



〈PD-L1 陽性の非小細胞肺癌における術後補助療法〉

17.1.6 国際共同第Ⅲ相臨床試験（IMpower010 試験）

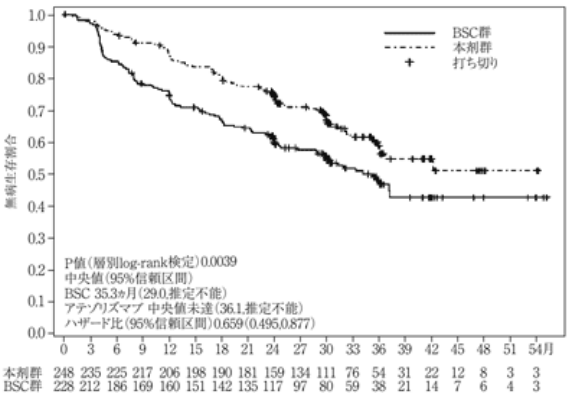
プラチナ製剤を含む術後補助療法後の術後病理病期 IB（腫瘍径≥4cm）～ⅢA（UICC/AJCC 病期分類第 7 版）の非小細胞肺癌患者 1005 例（日本人 117 例を含む）を対象に、本剤 1200mg の有効性及び安全性を支持療法（BSC）[注9]と比較する第Ⅲ相試験を実施した[注10]。中間解析の結果、PD-L1 陽性（腫瘍細胞における PD-L1 発現率（TC）が 1%以上）のⅡ又はⅢA 期集団において、本剤群（248 例）で BSC 群（228 例）と比較して主要評価項目である無病生存期間の有意な延長が認められ（ハザード比［95%信頼区間］0.659［0.495，0.877］、P=0.0039［層別 log-rank 検定］、有意水準両側 0.0370）、中央値［95%信頼区間］は本剤群で中央値未達［36.1，推定不能］、BSC 群で 35.3［29.0，推定不能］カ月であった[16]。

本剤が投与された 495 例（日本人 56 例を含む）において 335 例（67.7%）に副作用が認められた。主な副作用（5%以上）は、甲状腺機能低下症 53 例（10.7%）、そう痒症 43 例（8.7%）、発疹 40 例（8.1%）、AST 増加 37 例（7.5%）、ALT 増加 36 例（7.3%）、甲状腺機能亢進症 29 例（5.9%）、発熱 27 例（5.5%）、関節痛 26 例（5.3%）等であった[17]。

注 9）プラチナ製剤を含む術後補助療法後に治験薬の投与はされず、観察のみ行った。

注 10）本剤 1200mg を 3 週間間隔で最大 16 回投与した。

IMpower010 試験の無病生存期間の Kaplan-Meier 曲線（PD-L1 陽性（TC≧1%）のⅡ又はⅢA 期集団）



なお、副次的又は探索的解析の PD-L1 発現状況別の無病生存期間及び全生存期間の結果は以下のとおりであった[17]。

IMpower010 試験の PD-L1 発現状況別の無病生存期間[*1]（Ⅱ又はⅢA 期集団）

PD-L1 発現	投与群	例数	中央値［95%CI］（月）	ハザード比［95%CI］
1≦TC＜50%	本剤	133	32.8［29.4，NE］	0.868[*2]［0.600，1.256］
	BSC	114	31.4［24.0，NE］	
TC≧50%	本剤	115	NE［42.3，NE］	0.432[*2]［0.272，0.684］
	BSC	114	35.7［29.7，NE］	

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＊1：中間解析時のデータ：2021 年 1 月 21 日カットオフ
＊2：非層別 Cox 比例ハザードモデル
CI：信頼区間、NE：未達又は推定不能

IMpower010 試験の PD-L1 発現状況別の全生存期間*1（Ⅱ又はⅢA 期集団）

PD-L1 発現	投与群	例数	中央値［95%CI］（月）	ハザード比［95%CI］
TC≧1%	本剤 BSC	248 228	NE［NE, NE］ NE［NE, NE］	0.772*2 ［0.509, 1.170］
1≦TC＜50%	本剤 BSC	133 114	NE［NE, NE］ NE［NE, NE］	1.218*3 ［0.705, 2.104］
TC≧50%	本剤 BSC	115 114	NE［NE, NE］ NE［NE, NE］	0.366*3 ［0.181, 0.742］

＊1：中間解析時のデータ：2021 年 1 月 21 日カットオフ
＊2：層別 Cox 比例ハザードモデル
＊3：非層別 Cox 比例ハザードモデル
CI：信頼区間、NE：未達又は推定不能

〈進展型小細胞肺癌〉

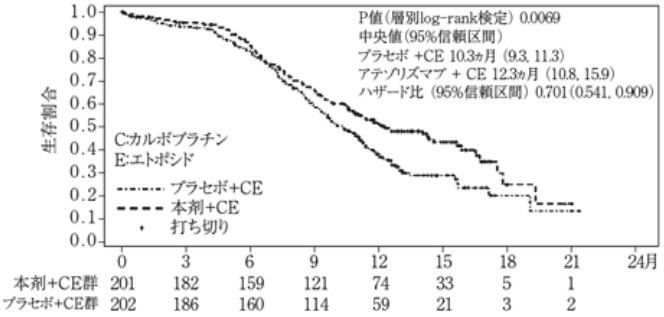
17.1.7 国際共同第Ⅰ/Ⅲ相臨床試験（IMpower133 試験）

化学療法歴のない進展型小細胞肺癌患者[注11] 403 例（日本人 42 例を含む）を対象に、本剤 1200mg とカルボプラチン＋エトポシドの併用療法（本剤群、201 例）の 3 週間間隔投与の有効性及び安全性をプラセボとカルボプラチン＋エトポシドの併用療法（プラセボ群、202 例）と比較する第Ⅰ/Ⅲ相ランダム化試験を実施した[注12]。中間解析の結果、全患者集団において、本剤群でプラセボ群と比較して主要評価項目である全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］：0.701［0.541，0.909］、P=0.0069［層別 log-rank 検定］、有意水準両側 0.0193）、中央値［95%信頼区間］は本剤群で 12.3［10.8，15.9］カ月、プラセボ群で 10.3［9.3，11.3］カ月であった[18]。
本剤とカルボプラチン＋エトポシドが投与された 198 例（日本人 20 例を含む）において 188 例（94.9%）に副作用が認められた。主な副作用（20%以上）は、貧血 77 例（38.9%）、好中球減少症 72 例（36.4%）、脱毛症 69 例（34.8%）、悪心 63 例（31.8%）、疲労 42 例（21.2%）、食欲減退 41 例（20.7%）等であった[19]。

注 11）進展型の基準は Veterans Administration Lung Study Group（VALG）staging system for SCLC に基づいて判断された。また、限局型小細胞肺癌に対する根治的化学放射線療法（CRT）を施行し、かつ直近の化学療法、放射線療法又は CRT から 6 カ月以上経過した後に進展型小細胞肺癌と診断された患者も組み入れられた。

注 12）本剤 1200mg（又はプラセボ）及びカルボプラチン AUC5 を各サイクルの 1 日目に、エトポシド 100mg/m^2 を各サイクルの 1、2、3 日目に 3 週間間隔で 4 サイクル投与後、本剤 1200mg（又はプラセボ）を 3 週間間隔で投与した。

IMpower133 試験の全生存期間の Kaplan-Meier 曲線（全患者集団）



〈切除不能な肝細胞癌〉

17.1.8 国際共同第Ⅲ相臨床試験（IMbrave150 試験）

全身化学療法歴のない Child-Pugh 分類 A の切除不能な肝細胞癌患者[注13] 501 例（日本人 61 例を含む）を対象に、本剤 1200mg とベバシズマブ（遺伝子組換え）（本剤併用群、336 例）の併用投与の有効性及び安全性を、ソラフェニブ（対照群、165 例）と比較する第Ⅲ相ランダム化試験を実施した[注14]。中間解析の結果、501 例（日本人 61 例を含む）の ITT 集団において、本剤併用群で対照群と比較して、主要評価項目の一つである全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］0.58［0.42，0.79］、P=0.0006［層別 log-rank 検定］、有意水準両側 0.0033）、中央値［95%信頼区間］は本剤併用群で中央値未達［推定不能］、対照群で 13.2［10.4，推定不能］カ月であった。もう一つの主要評価項目である無増悪生存期間の有意な延長が認められ（ハザード比［95%信頼区間］0.59［0.47，0.76］、P<0.0001［層別 log-rank 検定］、有意水準両側 0.002）、中央値［95%信頼区間］は本剤併用群で 6.8［5.7，8.3］カ月、対照群で 4.3［4.0，5.6］カ月であった[21]。また、日本人患者（本剤併用群 35 例、対照群 26 例）における ITT 集団の全生存期間の中央値［95%信頼区間］は、本剤併用群で中央値未達［推定不能］、対照群で 14.9［推定不能］カ月であり（ハザード比［95%信頼区間］：1.71［0.50，5.84］）、無増悪生存期間の中央値［95%信頼区間］は、本剤併用群で中央値未達［6.4，推定不能］カ月、対照群で 7.7［4.2，12.7］カ月であった（ハザード比［95%信頼区間］：0.85［0.39，1.86］）。
本剤とベバシズマブ（遺伝子組換え）が投与された 329 例（日本人 35 例を含む）において 276 例（83.9%）に副作用が認められた。主な副作用（10%以上）は、高血圧 78 例（23.7%）、蛋白尿 62 例（18.8%）、疲労 50 例（15.2%）、AST 増加 46 例（14.0%）、そう痒症 43 例（13.1%）、注入に伴う反応 36 例（10.9%）、下痢 34 例（10.3%）、ALT 増加 34 例（10.3%）、食欲減退 33 例（10.0%）等であった[20]。

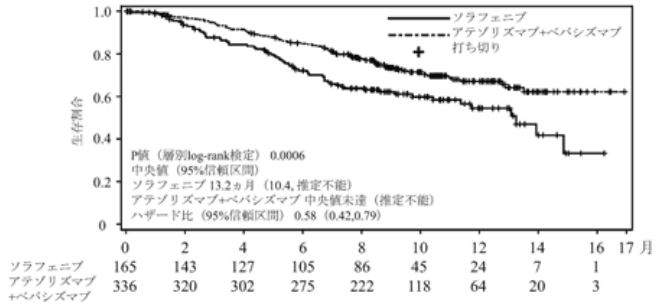
注 13）局所療法（経皮的エタノール注入療法、ラジオ波焼灼療法、マイクロ波凝固療法、肝動脈塞栓療法/肝動脈化学塞栓療法、放射線療法等）の適応となる患者は除外された。

注 14）本剤併用群では本剤 1200mg 及びベバシズマブ（遺伝子組換え）15mg/kg を 3 週間間隔で投与し、対照群ではソラフェニブ 400mg を 1 日 2 回投与した。

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IMbrave150 試験の全生存期間の Kaplan-Meier 曲線（ITT 集団）



〈PD-L1 陽性のホルモン受容体陰性かつ HER2 陰性の手術不能又は再発乳癌〉

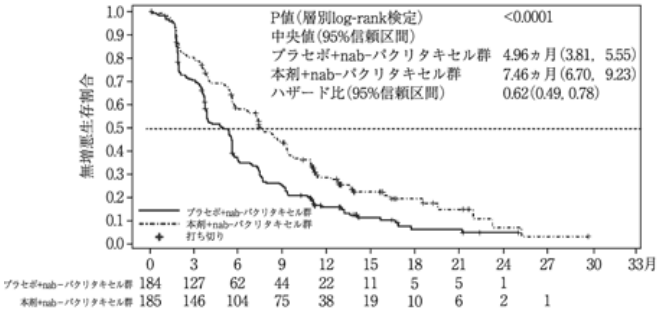
17.1.9 国際共同第Ⅲ相臨床試験（IMpassion130 試験）

転移・再発乳癌に対する全身性の前治療歴のない転移・再発又は局所進行性のホルモン受容体陰性かつ HER2 陰性の乳癌患者 902 例（日本人 65 例を含む）を対象に、本剤＋nab-パクリタキセル併用療法（本剤群 451 例）とプラセボ＋nab-パクリタキセル併用療法（プラセボ群 451 例）の有効性及び安全性を比較する第Ⅲ相試験を実施した。本剤 840mg は 2 週間間隔、nab-パクリタキセル 100mg/m^2 は週 1 回（28 日を 1 サイクルとし、第 1、8、15 日目に投与）で点滴静注した。なお、本剤群では、有害事象又はその他の理由によりどちらかの薬剤を中止した後は、本剤又は nab-パクリタキセルを同一の用法及び用量で病勢進行まで投与継続した。ランダム化された患者のうち、PD-L1 陽性患者集団 369 例（日本人 25 例を含む）において、本剤群（185 例）でプラセボ群（184 例）と比較して主要評価項目[注 15)]の一つである無増悪生存期間の有意な延長が認められ（ハザード比［95%信頼区間］：0.62［0.49, 0.78］、P<0.0001［層別 log-rank 検定］）、中央値［95%信頼区間］は本剤群で 7.46［6.70, 9.23］カ月、プラセボ群で 4.96［3.81, 5.55］カ月であった[21)]。

PD-L1 陽性患者集団のうち、本剤と nab-パクリタキセルが投与された 185 例（日本人 12 例を含む）において 180 例（97.3%）に副作用が認められた。主な副作用（20%以上）は、脱毛症 109 例（58.9%）、疲労 85 例（45.9%）、悪心 83 例（44.9%）、貧血 49 例（26.5%）、下痢 41 例（22.2%）、好中球減少症 41 例（22.2%）、末梢性ニューロパチー39 例（21.1%）等であった[22)]。

注 15）主要評価項目はランダム化されたすべての患者集団及び PD-L1 陽性患者集団における無増悪生存期間及び全生存期間とした。

IMpassion130 試験の無増悪生存期間の Kaplan-Meier 曲線（PD-L1 陽性患者集団）



〈切除不能な胞巣状軟部肉腫〉

17.1.10 海外第Ⅱ相臨床試験（ML39345 試験）

2 歳以上の切除不能な胞巣状軟部肉腫患者 49 例を対象に、18 歳以上の患者には本剤 1200mg を 3 週間間隔投与、2 歳以上 18 歳未満の患者には本剤 15mg/kg（最大 1200mg）を 3 週間間隔投与したときの有効性及び安全性を評価する第Ⅱ相試験を実施した。独立評価機関判定による奏効率は 24.5%［95%信頼区間：13.3～38.9%］であった。本剤が投与された 49 例において副作用は 47 例（95.9%）に認められた。主な副作用（15%以上）は、疲労 18 例（36.7%）、リンパ球数減少 10 例（20.4%）、発疹 10 例（20.4%）、白血球数減少 9 例（18.4%）、血中アルカリホスファターゼ増加 9 例（18.4%）、悪心 8 例（16.3%）、貧血 8 例（16.3%）等であった[23)]。

17.1.11 国内第Ⅱ相臨床試験（ALBERT 試験）

16 歳以上の切除不能な胞巣状軟部肉腫患者 20 例を対象に、18 歳以上の患者には本剤 1200mg を 3 週間間隔投与、16 歳以上 18 歳未満の患者には本剤 15mg/kg（最大 1200mg）を 3 週間間隔投与したときの有効性及び安全性を評価する第Ⅱ相試験を実施した。主要評価項目である独立評価機関判定による奏効率は 10.0%［95%信頼区間：1.2～31.7%］であり、95%信頼区間の下限は事前に設定した閾値奏効率（5%）を下回った。

本剤が投与された 20 例において副作用は 16 例（80.0%）に認められた。主な副作用（10%以上）は、AST 増加 5 例（25.0%）、ALT 増加 4 例（20.0%）、リンパ球数減少 4 例（20.0%）、好中球数減少 4 例（20.0%）、血小板数減少 3 例（15.0%）、白血球数減少 3 例（15.0%）、貧血 3 例（15.0%）、発熱 3 例（15.0%）、筋肉痛 2 例（10.0%）等であった[24)]。

〈再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型〉

17.1.12 国内第Ⅱ相臨床試験（ATTACK 試験）

12 歳以上の再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型患者[注 16)] 14 例を対象に、18 歳以上の患者には本剤 1200mg を 3 週間間隔投与、12 歳以上 18 歳未満の患者には本剤 15mg/kg（最大 1200mg）を 3 週間間隔で投与したときの有効性及び安全性を評価する第Ⅱ相試験を実施した。主要評価項目である中央判定による奏効率は 53.8%［95%信頼区間：25.1～80.8%］（7/13 例）であり、事前に設定した閾値奏効率（5%）を超える事後確率は＞99.99%であった。

本剤が投与された 14 例において副作用は 11 例（78.6%）に認められた。主な副作用（20%以上）は、発熱 8 例（57.1%）、好中球数減少 5 例（35.7%）、AST 増加 4 例（28.6%）、白血球数減少 4 例（28.6%）、発疹 3 例（21.4%）等であった[25)]。

注 16）節外性 NK/T 細胞リンパ腫・鼻型に対する 1 レジメン以上の治療歴があり、かつ、SMILE 療法（デキサメタゾン、メソトレキセート、イホスファミド、L-アスパラギナーゼ及びエトポシド）による治療歴がある又は適応とならない患者が対象とされた。なお、次の①～⑧のいずれかに該当した場合に、SMILE 療法に適応とならない患者と判断された：①ECOG Performance Status2、②70 歳以上、③組入れ前に実施された化学療法により、支持療法として週 1 回以上の輸血を必要とする状態、④末梢血リンパ球数 500/mm^3 未満、⑤造血幹細胞移植歴がある、⑥虚血性変化、心房細動若しくは治療を要する

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心室性不整脈が1つ以上認められる、⑦左室駆出率50%未満、又は⑧SMILE療法以外のがん薬物療法に対して不耐容である。

〈切除不能な胸腺癌〉

17.1.13 国内第Ⅱ相臨床試験（Marble試験）

化学療法歴のない切除不能な進行・再発の胸腺癌患者[注17)]48例を対象に、本剤1200mgとカルボプラチン＋パクリタキセルの併用療法を3週間間隔投与したときの有効性及び安全性を評価する第Ⅱ相試験を実施した[注18)]。主要評価項目である独立評価機関判定による奏効率は56.3%［95%信頼区間：41.2～70.5%］であった。

本剤が投与された48例において副作用は48例（100%）に認められた。主な副作用（30%以上）は、末梢性感覚ニューロパチー42例（87.5%）、脱毛症40例（83.3%）、貧血26例（54.2%）、便秘26例（54.2%）、白血球数減少22例（45.8%）、悪心20例（41.7%）、好中球減少症19例（39.6%）、斑状丘疹状皮疹19例（39.6%）、好中球数減少18例（37.5%）、食欲減退18例（37.5%）、倦怠感15例（31.3%）等であった[注19),26)]。

注17）根治的手術・放射線療法が不能な正岡分類III、IVa又はIVb期と診断された患者、及び根治的手術・放射線療法後の再発の患者が組み入れられた。

注18）本剤1200mg、カルボプラチンAUC6及びパクリタキセル200mg/m^{2}を各サイクルの1日目に3週間間隔で4～6サイクル投与後、本剤1200mgを3週間間隔で投与した。

注19）Marble試験においては、本剤、カルボプラチン又はパクリタキセルのいずれかにより発現した副作用について集計した。

18. 薬効薬理

18.1 作用機序

アテゾリズマブは、ヒトPD-L1に対するヒト化モノクローナル抗体であり、PD-L1とその受容体であるPD-1との結合を阻害すること等により、がん抗原特異的なT細胞の細胞傷害活性を増強し、腫瘍の増殖を抑制すると考えられる[27)]。

19. 有効成分に関する理化学的知見

一般的名称：アテゾリズマブ（遺伝子組換え）
(Atezolizumab (Genetical Recombination))
(JAN)

分子式：H鎖（$C_{2191}H_{3362}N_{580}O_{665}S_{15}$）
L鎖（$C_{1032}H_{1593}N_{273}O_{334}S_6$）

分子量：144,610.56

構造式：アミノ酸214個のL鎖2本とアミノ酸448個のH鎖2本からなるタンパク質

20. 取扱い上の注意

外箱開封後は遮光して保存すること。

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

〈再発又は難治性の節外性NK/T細胞リンパ腫・鼻型〉

21.2 製造販売後、一定数の症例に係るデータが集積されるまでの間は、小児の再発又は難治性の節外性NK/T細胞リンパ腫・鼻型患者については全症例を対象に使用成績調査を実施すること。

22. 包装

〈テセントリク点滴静注840mg〉
14mL×1バイアル

〈テセントリク点滴静注1200mg〉
20mL×1バイアル

23. 主要文献

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2) 社内資料：国内第Ⅰ/Ⅱ相臨床試験（JO44110試験）
3) 国際共同第Ⅲ相臨床試験（OAK試験）（2018年1月19日承認、申請資料概要 2.7.2.2.3.4）
4) 社内資料：薬物動態解析報告書（IMpassion130試験）
5) 社内資料：母集団薬物動態解析（再推定及び再推定後のシミュレーション）
6) 社内資料：海外第Ⅰ/Ⅱ相試験（GO29664試験）
7) Rittmeyer A, et al. Lancet. 2017;389 (10066) :255-265
8) 国際共同第Ⅲ相臨床試験（OAK試験）（2018年1月19日承認、申請資料概要 2.7.6.2.1.3）
9) Herbst R, et al. N Engl J Med. 2020;383 (14) :1328-1339
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12) 社内資料：国際共同第Ⅲ相臨床試験（IMpower150試験）
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18) Horn L, et al. N Engl J Med. 2018;379 (23) :2220-2229
19) 国際共同第Ⅰ/Ⅲ相臨床試験（IMpower133試験）（2019年8月22日承認、申請資料概要 2.7.4.2.1.1）
20) 社内資料：国際共同第Ⅲ相臨床試験（IMbrave150試験）
21) Schmid P, et al. N Engl J Med. 2018;379 (22) :2108-2121
22) 社内資料：国際共同第Ⅲ相臨床試験（IMpassion130試験）
23) 海外第Ⅱ相臨床試験（ML39345試験）（2025年2月20日承認、申請資料概要 2.7.6.1.2）
24) 国内第Ⅱ相臨床試験（ALBERT試験）（2025年2月20日承認、申請資料概要 2.7.6.1.1）
25) 国内第Ⅱ相臨床試験（ATTACK試験）（2025年9月19日承認、申請資料概要 2.7.6.1.1）

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26）社内資料：国内第Ⅱ相臨床試験（Marble 試験）
27）効力を裏付ける試験（2018 年 1 月 19 日承認、申請資料概要 2.6.2.2）

24. 文献請求先及び問い合わせ先

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26. 製造販売業者等

26.1 製造販売元

中外製薬株式会社
東京都中央区日本橋室町 2-1-1

Ⓡ F.ホフマン・ラ・ロシュ社（スイス） 登録商標

Confidential - 秘

目次

1.10 毒薬・劇薬等の指定審査資料のまとめ 2

1.10　毒薬・劇薬等の指定審査資料のまとめ

（現行）

<table>
<tr><td>化学名・別名</td><td>アテゾリズマブは，ヒトプログラム細胞死リガンド1（PD-L1）に対する遺伝子組換えヒト化モノクローナル抗体であり，ヒト及びマウス抗体由来の相補性決定部，並びにヒト IgG1のフレームワーク部及び定常部からなり，H 鎖の298番目のアミノ酸残基が Ala に置換されている。アテゾリズマブは，チャイニーズハムスター卵巣細胞により産生される。アテゾリズマブは，448個のアミノ酸残基からなる H 鎖（γ1鎖）2本及び214個のアミノ酸残基からなる L 鎖（κ鎖）2本で構成されるタンパク質である。
別名 アテゾリズマブ（遺伝子組換え）及びその製剤</td></tr>
<tr><td>構　造　式</td><td>別紙のとおり</td></tr>
<tr><td>効能・効果</td><td>〈製剤共通〉
○切除不能な進行・再発の非小細胞肺癌
○PD-L1陽性の非小細胞肺癌における術後補助療法
○進展型小細胞肺癌
○切除不能な胞巣状軟部肉腫
○再発又は難治性の節外性 NK/T 細胞リンパ腫・鼻型
〈テセントリク点滴静注1200mg〉
○切除不能な肝細胞癌
〈テセントリク点滴静注840mg〉
○PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌</td></tr>
<tr><td>用法・用量</td><td>〈効能共通〉
アテゾリズマブ（遺伝子組換え）の初回投与時は60分かけて点滴静注し、初回投与の忍容性が良好であれば、2回目以降の投与時間は30分間まで短縮できる。
<table>
<tr><th>効能又は効果</th><th>用法及び用量</th></tr>
<tr><td>切除不能な進行・再発の非小細胞肺癌</td><td>化学療法未治療の扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌
他の抗悪性腫瘍剤との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。その後、単独投与する場合には、アテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。

化学療法未治療の PD-L1陽性の切除不能な進行・再発の非小細胞肺癌
通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。

化学療法既治療の切除不能な進行・再発の非小細胞肺癌
通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。</td></tr>
<tr><td>PD-L1 陽性の非小細胞肺癌における術後補助</td><td>通常、成人にはアテゾリズマブ（遺伝子組換え）として 1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。投与期間は12カ月間までとする。</td></tr>
</table>
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</table>

	療法	
	進展型小細胞肺癌	カルボプラチン及びエトポシドとの併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で4回点滴静注する。その後、アテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔又は1回1680mg を4週間間隔で点滴静注する。
	切除不能な肝細胞癌	ベバシズマブ（遺伝子組換え）との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。
	PD-L1 陽性のホルモン受容体陰性かつHER2陰性の手術不能又は再発乳癌	パクリタキセル（アルブミン懸濁型）との併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回840mg を2週間間隔又は1回1680mg を4週間間隔で点滴静注する。
	切除不能な胞巣状軟部肉腫	通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。通常、2歳以上の小児にはアテゾリズマブ（遺伝子組換え）として1回15mg/kg（体重）（最大1200mg）を3週間間隔で点滴静注する。
	再発又は難治性の節外性NK/T細胞リンパ腫・鼻型	通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。通常、12歳以上の小児にはアテゾリズマブ（遺伝子組換え）として1回15mg/kg（体重）（最大1200mg）を3週間間隔で点滴静注する。
劇薬等の指定	生物由来製品，劇薬，処方箋医薬品	
市販名及び有効成分・分量	原体：アテゾリズマブ（遺伝子組換え） 製剤：テセントリク点滴静注1200 mg（1バイアル（20.0mL）中アテゾリズマブ（遺伝子組換え）1200mg 含有） テセントリク点滴静注840 mg（1バイアル（14.0mL）中アテゾリズマブ（遺伝子組換え）840mg 含有）	

毒性

【急性】

	動物種	静脈内
概略の致死量（mg/kg）	マウス♀	>50[a)]
	カニクイザル♂・♀	>50[a)]

[a)] 急性毒性は，マウス及びカニクイザルを用いた亜急性毒性試験の初回投与時の成績により評価した。

【亜急性】

動物種	投与期間	投与経路	投与量（mg/kg/週）	無毒性量（mg/kg/週）	主な所見
マウス	2週間	静脈内	10,50（C57BL/6） 50（CD-1）	－	・C57BL/6マウスの10及び50 mg/kg/週で坐骨神経病変（ニューロパチー），CD-1マウスの50 mg/kg/週で異常なし。
カニクイザル	8週間	静脈内，皮下	5, 15, 50（静脈内） 15, 50（皮下）	5（静脈内）	・15及び50 mg/kg/週で全身諸器官の動脈炎/動脈周囲炎。12週間の休薬期間終了時に動脈炎/動脈周囲炎は認められなかった。

－：非 GLP 試験の参考資料であり，無毒性量は求めていない。

【慢性】

動物種	投与期間	投与経路	投与量（mg/kg/週）	無毒性量（mg/kg/週）	主な所見
カニクイザル	26週間	静脈内	5, 15, 50	5	・15及び50 mg/kg/週で全身諸器官の動脈炎/動脈周囲炎，50 mg/kg/週の雌で月経周期異常及び卵巣での新生黄体欠如。13週間の休薬期間終了時に動脈炎/動脈周囲炎は認められず，月経周期及び卵巣の異常は回復した。

<table>
<tr><td>副　作　用</td><td>非小細胞肺癌患者を対象としたOAK試験，IMpower110試験，IMpower010試験，IMpower150試験（そのうち本剤とカルボプラチン，パクリタキセル及びベバシズマブ（遺伝子組換え）が併用投与された被験者），IMpower132試験，IMpower130試験，進展型小細胞肺癌患者を対象としたIMpower133試験，肝細胞癌患者を対象としたIMbrave150試験，乳癌患者を対象としたIMpassion130試験（そのうちPD-L1陽性の被験者）及び胞巣状軟部肉腫患者を対象としたNCI試験，ALBERT試験及び再発又は難治性の節外性NK/T細胞リンパ腫・鼻型患者を対象としたATTACK試験のうち本剤が投与された被験者の3342例中2353例（70.4%）に副作用が発現した。

<table>
<tr><th>試験全体
副作用</th><th>例数</th><th></th><th>試験全体
臨床検査値異常</th><th>例数</th><th></th></tr>
<tr><td>疲労</td><td>491</td><td></td><td>血小板減少</td><td>218</td><td></td></tr>
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<tr><td>食欲減退</td><td>274</td><td>等</td><td>白血球減少</td><td>118</td><td>等</td></tr>
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（変　更）

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		3週間間隔で点滴静注する。
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	切除不能な胸腺癌	カルボプラチン及びパクリタキセルとの併用において、通常、成人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を3週間間隔で点滴静注する。
劇薬等の指定		
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会社		

（下線部：変更箇所）

別紙
アミノ酸配列及びジスルフィド結合：



H 鎖 E1：部分的ピログルタミン酸；H 鎖 K448：部分的プロセシング
L 鎖 C214‐H 鎖 C221，H 鎖 C227‐H 鎖 C227，H 鎖 C230‐H 鎖 C230：ジスルフィド結合

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.2 全臨床試験一覧表

CTD No	表題
5.2	全臨床試験一覧表

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.3 臨床試験報告書

CTD No	著者	表題	実施期間	実施場所	掲載誌・その他	評価/参考の別	申請電子データの提出
5.3.1　生物薬剤学試験報告書							
5.3.1.1　バイオアベイラビリティ（BA）試験報告書							
該当資料なし							
5.3.1.2　比較BA試験及び生物学的同等性（BE）試験報告書							
該当資料なし							
5.3.1.3　In Vitro-In Vivoの関連を検討した試験報告書							
該当資料なし							
5.3.1.4　生物学的及び理化学的分析法検討報告書							
該当資料なし							
5.3.2　ヒト生体試料を用いた薬物動態関連の試験報告書							
5.3.2.1　血漿蛋白結合試験報告書							
該当資料なし							
5.3.2.2　肝代謝及び薬物相互作用試験報告書							
該当資料なし							
5.3.2.3　他のヒト生体試料を用いた試験報告書							
該当資料なし							

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.3 臨床試験報告書

CTD No	著者	表題	実施期間	実施場所	掲載誌・その他	評価/参考の別	申請電子データの提出
5.3.3　臨床薬物動態（PK）試験報告書							
5.3.3.1　健康被験者におけるPK及び初期忍容性試験報告書							
該当資料なし							
5.3.3.2　患者におけるPK及び初期忍容性試験報告書							
該当資料なし							
5.3.3.3　内因性要因を検討したPK試験報告書							
該当資料なし							
5.3.3.4　外因性要因を検討したPK試験報告書							
該当資料なし							
5.3.3.5　ポピュレーションPK試験報告書							
該当資料なし							

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.3 臨床試験報告書

CTD No	著者	表題	実施期間	実施場所	掲載誌・その他	評価/参考の別	申請電子データの提出
5.3.4　臨床薬力学（PD）試験報告書							
5.3.4.1　健康被験者におけるPD試験及びPK/PD試験報告書							
該当資料なし							
5.3.4.2　患者におけるPD試験及びPK/PD試験報告書							
該当資料なし							
5.3.5　有効性及び安全性試験報告書							
5.3.5.1　申請する適応症に関する比較対照試験報告書							
該当資料なし							
5.3.5.2　非対照試験報告書							
5.3.5.2-1	[redacted]	進行・再発胸腺癌に対するカルボプラチン＋パクリタキセル＋アテゾリズマブ（MPDL3280A）の第II相試験 治験総括報告書	2022年6月14日～2024年7月6日	国内	ー	評価	あり
5.3.5.2-1	[redacted]	進行・再発胸腺癌に対するカルボプラチン＋パクリタキセル＋アテゾリズマブ（MPDL3280A）の第II相試験 治験総括報告書	2022年6月14日～2024年7月6日	国内	ー	評価	あり
5.3.5.2-1	[redacted]	進行・再発胸腺癌に対するカルボプラチン＋パクリタキセル＋アテゾリズマブ（MPDL3280A）の第II相試験 治験総括報告書	2022年6月14日～2024年7月6日	国内	ー	評価	あり
5.3.5.3　複数の試験成績を併せて解析した報告書							
該当資料なし							
5.3.5.4　その他の試験報告書							
該当資料なし							

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.3 臨床試験報告書

CTD No	著者	表題	実施期間	実施場所	掲載誌・その他	評価/参考の別	申請電子データの提出
5.3.6　市販後の使用経験に関する報告書							
5.3.6-1	—	Periodic Benefit-Risk Evaluation Report/ Periodic Safety Update Report 1130553	—	国内/海外	—	参考	なし
5.3.7　患者データ一覧表及び症例記録							
5.3.7.1　症例一覧表							
5.3.7.1-1	—	症例一覧表	—	国内	—	評価	なし
5.3.7.2　副作用一覧表							
5.3.7.2-1	—	有害事象一覧表（Marble試験）	—	国内	—	評価	なし
5.3.7.3　重篤な有害事象一覧表							
5.3.7.3-1	—	重篤な有害事象一覧表（Marble試験）	—	国内	—	評価	なし
5.3.7.4　臨床検査値異常一覧表							
5.3.7.4-1	—	臨床検査値異常一覧表（Marble試験）	—	国内	—	評価	なし
5.3.7.5　臨床検査値変動図							
5.3.7.5-1	—	臨床検査値変動図	—	国内	—	評価	なし

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.4　参考文献

CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-1	Koizumi T, et al.	National incidence and initial therapy for thymic carcinoma in Japan: based on analysis of hospital-based cancer registry data, 2009-2015	Jpn J Clin Oncol 2020;50(4):434-9	2.5-02
5.4-2	Hishida T, et al.	Long-term outcome and prognostic factors of surgically treated thymic carcinoma: results of 306 cases from a Japanese Nationwide Database Study	Eur J Cardiothorac Surg 2016;49(3):835-41	2.5-03
5.4-3	Kondo K, et al.	Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan	Ann Thorac Surg. 2003;76(3):878-85	2.5-04
5.4-4	National Comprehensive Cancer Network	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®) Thymomas and Thymic Carcinomas	Version 1. 2025	2.5-05
5.4-5	Girard N, et al.	Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Ann Oncol 2015;26 Suppl 5:v40-v55	2.5-06
5.4-6	Igawa S, et al.	Efficacy of chemotherapy with carboplatin and paclitaxel for unresectable thymic carcinoma	Lung Cancer 2010;67(2):194-7	2.5-07
5.4-7	Lemma GL, et al.	Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma	J Clin Oncol 2011;29(15):2060-5	2.5-08
5.4-8	Furugen M, et al.	Combination chemotherapy with carboplatin and paclitaxel for advanced thymic cancer	Jpn J Clin Oncol 2011;41(8):1013-6	2.5-09

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.4　参考文献

CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-9	Hirai F, et al.	A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L	Ann Oncol 2015;26(2):363-8	2.5-10
5.4-10	Inoue A, et al.	Phase II study of Amrubicin combined with carboplatin for thymic carcinoma and invasive thymoma: North Japan Lung Cancer group study 0803	J Thorac Oncol 2014;9(12):1805-9	2.5-11
5.4-11	Sato J, et al.	Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial	Lancet Oncol 2020;21(6):843-50	2.5-12
5.4-12	Giaccone G, et al.	Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study	Lancet Oncol. 2018;19(3):347-55	2.5-13
5.4-13	Cho J, et al.	Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial	J Clin Oncol 2019;37(24):2162-70	2.5-14
5.4-14	Katsuya Y, et al.	Single-arm, multicentre, phase II trial of nivolumab for unresectable or recurrent thymic carcinoma: PRIMER study	Eur J Cancer 2019;113:78-86	2.5-15
5.4-15	Socinski MA, et al.	Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC	N Engl J Med 2018;378(24):2288-301	2.5-16
5.4-16	Nishio M, et al.	Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results From the Randomized Phase 3 IMpower132 Trial	J Thorac Oncol 2021;16(4):653-64	2.5-17

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.4　参考文献

CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-17	Gandhi L, et al.	Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer	N Engl J Med 2018;378(22):2078-92	2.5-18
5.4-18	Mimori T, et al.	Efficacy and safety of atezolizumab plus carboplatin and paclitaxel in patients with advanced or recurrent thymic carcinoma: MARBLE phase II study (JTD2101)	ESMO-ASIA Congress 2024. LBA8	2.5-19
5.4-19	Tanaka H, et al.	The long-term survival of a thymic carcinoma patient treated with S-1: a case report and literature review.	Onco Targets Ther 2013;7:87-90	2.5-20
5.4-20	Bolzacchini E, et al.	Response of Malignant Thymoma to Sorafenib	J Thorac Oncol 2016;11(10):e125-6	2.5-21

提出すべき資料がない項目リスト

セクション	項目	表題
第3部	品質に関する文書	
第4部	非臨床試験報告書	
第5部	臨床試験報告書	
	5.3.1.1	バイオアベイラビリティ（BA）試験報告書
	5.3.1.2	比較BA試験及び生物学的同等性（BE）試験報告書
	5.3.1.3	In Vitro-In Vivoの関連を検討した試験報告書
	5.3.1.4	生物学的及び理化学的分析法検討報告書
	5.3.2.1	血漿蛋白結合試験報告書
	5.3.2.2	肝代謝及び薬物相互作用試験報告書
	5.3.2.3	他のヒト生体試料を用いた試験報告書
	5.3.3.1	健康被験者におけるPK及び初期忍容性試験報告書
	5.3.3.2	患者におけるPK及び初期忍容性試験報告書
	5.3.3.3	内因性要因を検討したPK試験報告書
	5.3.3.4	外因性要因を検討したPK試験報告書
	5.3.3.5	ポピュレーションPK試験報告書
	5.3.4.1	健康被験者におけるPD試験及びPK　PD試験報告書
	5.3.4.2	患者におけるPD試験及びPK　PD試験報告書
	5.3.5.1	申請する適応症に関する比較対照試験報告書
	5.3.5.3	複数の試験成績を併せて解析した報告書
	5.3.5.4	その他の試験報告書