テセントリク点滴静注 840mg
テセントリク点滴静注 1200mg
に関する資料

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1.5 起原又は発見の経緯及び開発の経緯 2

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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

アテゾリズマブ（遺伝子組換え）（以下，アテゾリズマブ）は，programmed death-ligand 1（PD-L1）を標的とするヒト化免疫グロブリン G1モノクローナル抗体である。テセントリク点滴静注1200 mg 及び同840 mg（以下，本剤）は，アテゾリズマブを有効成分として含有する点滴静脈内注射剤であり，本邦で非小細胞肺癌，小細胞肺癌，乳癌，肝細胞癌の適応で製造販売承認され，複数の悪性腫瘍を対象として開発を行っている。

2歳以上の，測定可能病変を有する治癒切除不能な胞巣状軟部肉腫（ASPS）患者に対し本剤を投与する海外第 II 相非盲検単群試験（NCI 試験）を実施した結果，本剤の有効性に関して，臨床的意義のある結果が得られ，忍容性も良好であった。

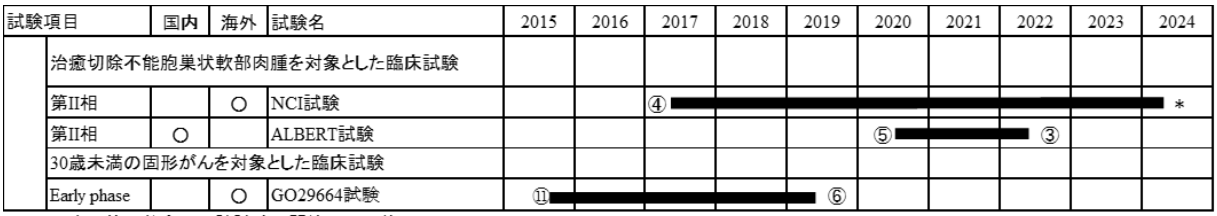
また，16歳以上の，測定可能病変を有する治癒切除不能な ASPS 患者を対象に，本剤の有効性及び安全性を評価する国内第 II 相非盲検単群試験（ALBERT 試験）を実施した結果，日本人での本剤の有効性が期待される結果が得られ，忍容性も良好であった。

加えて，既治療固形がんの小児及び若年成人患者（30歳未満）での本剤の安全性及び薬物動態を評価する海外多施設共同非盲検早期相試験（GO29664試験）の結果から，18歳未満の患者に本剤15 mg/kg（最大1200 mg）を3週間に1回投与した場合の薬物動態プロファイル及び安全性プロファイルは，成人での既知の薬物動態プロファイル及び安全性プロファイルと概ね一致していることが示唆され，新たな安全性シグナルは確認されなかった。

そこで，これらの結果に基づき，「切除不能な胞巣状軟部肉腫」を効能・効果とする製造販売承認事項一部変更承認申請を行うこととした。

起源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



図中の算用数字は当該試験の開始月又は終了月

*試験継続中

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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

2023年5月時点で，テセントリク点滴静注1200mg 及び840mg は非小細胞肺癌，尿路上皮癌，乳癌，小細胞肺癌，肝細胞癌，胞巣状軟部肉腫のいずれかに対して，欧米を含む世界120カ国で承認を取得している。また，2024年10月時点で，テセントリク皮下注1875mg は，欧州で非小細胞肺癌，尿路上皮癌，乳癌，小細胞肺癌，肝細胞癌に対して，米国で非小細胞肺癌，小細胞肺癌，肝細胞癌，悪性黒色腫，胞巣状軟部肉腫に対して承認を取得している。

2024年10月時点での米国及び欧州における承認状況を表 1.6.1-1に示す。胞巣状軟部肉腫に対しては，2024年10月時点で，米国及びイスラエルで承認を取得している。

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。

表 1.6.1-1 米国及び欧州における承認状況（2024年10月時点）

国・地域	効能・効果（要約）	承認年月*
米国 点滴静注 ・1200mg ・840mg 皮下注 ・1875mg	化学療法の治療歴がある転移性非小細胞肺癌	2016年10月
	化学療法未治療の転移性非扁平上皮非小細胞肺癌におけるベバシズマブ，パクリタキセル及びカルボプラチンとの併用療法	2018年12月
	進展型小細胞肺癌におけるカルボプラチン及びエトポシドとの併用療法	2019年3月
	化学療法未治療の転移性非扁平上皮非小細胞肺癌における nab-パクリタキセル及びカルボプラチンとの併用療法	2019年12月
	PD-L1陽性の未治療の進行・再発非小細胞肺癌	2020年5月
	全身化学療法未治療の局所進行又は転移性肝細胞癌におけるベバシズマブとの併用療法	2020年5月
	BRAF V600変異陽性の切除不能又は転移性悪性黒色腫におけるコビメチニブ及びベムラフェニブとの併用療法	2020年7月
	切除及びプラチナベース化学療法施行後の PD-L1発現（TC≥1%）を認める II 期～IIIA 期の非小細胞肺癌における術後補助療法	2021年10月
	2歳以上の小児及び成人における切除不能又は転移性胞巣状軟部肉腫（皮下注は成人のみ）	2022年12月
欧州 点滴静注 ・1200mg ・840mg 皮下注 ・1875mg	化学療法の治療歴がある転移性非小細胞肺癌	2017年9月
	白金製剤を含む化学療法の治療歴のある局所進行又は転移性尿路上皮癌	2017年9月
	シスプラチン化学療法が不適格かつ, PD-L1発現を認める局所進行又は転移性尿路上皮癌	2018年7月
	化学療法未治療の転移性非扁平上皮非小細胞肺癌におけるベバシズマブ，パクリタキセル及びカルボプラチンとの併用療法	2019年3月
	PD-L1陽性の局所進行又は転移性乳癌における nab-パクリタキセルとの併用療法	2019年8月
	進展型小細胞肺癌におけるカルボプラチン及びエトポシドとの併用療法	2019年9月
	化学療法未治療の転移性非扁平上皮非小細胞肺癌における nab-パクリタキセル及びカルボプラチンとの併用療法	2019年9月
	全身化学療法未治療の進行又は切除不能な肝細胞癌におけるベバシズマブとの併用療法	2020年10月
	PD-L1陽性の未治療の進行・再発非小細胞肺癌	2021年5月
	切除及びプラチナベース化学療法施行後の PD-L1発現（TC≥50%）を認める非小細胞肺癌における術後補助療法	2022年6月
	プラチナ製剤による治療が適応とならない未治療の進行性非小	2024年8月

	細胞肺癌に対する単剤療法	

* 効能・効果に変更を生じた場合には，直近の承認年月を示した

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（2024年4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。

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/CompanionDiagnostics 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。	

適応症	テセントリクの推奨投与量*	治療継続期間
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
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

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（2024年10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 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。	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 ES-SCLC，カルボプラ	導入及び維持期：	病勢進行，又は管理できない毒

適応症	推奨投与量とスケジュール	治療継続期間
チンとエトポシドとの併用	• 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。	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。

免疫関連副作用	重症度	投与の調節
	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	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 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

免疫関連副作用	重症度	投与の調節
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（TEN）[1]の疑い	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

免疫関連副作用	重症度	投与の調節
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
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

免疫関連副作用	重症度	投与の調節
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

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。

テセントリクの初回投与は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

Dosage and Administration (2.3)	04/2023
Warnings and Precautions (5.1)	04/2024

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)

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. When administering with carboplatin and etoposide, 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: 04/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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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).

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/CompanionDiagnostics.

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 administered intravenously as a single agent are presented in Table 1.

Table 1: Recommended Dosage of TECENTRIQ as a Single Agent

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	

* 60-minute intravenous infusion. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

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.	

* 60-minute intravenous infusion. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

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
Myocarditis or Pericarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[b]

Adverse Reaction	Severity[a]	Dosage Modification
	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. 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 aminotranferase (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 atezolizumab 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

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 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)

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.

Hepatocellular Carcinoma (HCC)

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 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ and bevacizumab in IMbrave150.

Table 16: 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 17: 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				

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] (%)
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

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 18 and 19 summarize the incidence of adverse reactions and laboratory abnormalities in Study IMspire150.

Table 18: 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 erythrodysaesthesia syndrome, dermatitis, dermatitis contact, erythema multiforme, rash pruritic, drug eruption, nodular rash, dermatitis allergic, exfoliative rash, dermatitis exfoliative generalised and rash morbilliform

[2] Includes fatigue, asthenia and malaise

[3] Includes pyrexia and hyperpyrexia

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

[5] Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, transaminases increased, hepatitis, hepatic enzyme increased, hepatotoxicity, hypertransaminasaemia, bilirubin conjugated increased, hepatocellular injury, hyperbilirubinaemia, 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 19: 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)

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 20 and 21 summarize adverse reactions and laboratory abnormalities in Study ML39345.

Table 20: 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 disoders		
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 21: 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

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.

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.

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 × ULN and any AST), moderate hepatic impairment (bilirubin >1.5 to 3x 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, 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, 4.3% to 27.5% of neutralizing antibody (NAb)-evaluable patients had a positive NAb status at any timepoint post-treatment. 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 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 22 and Figure 1.

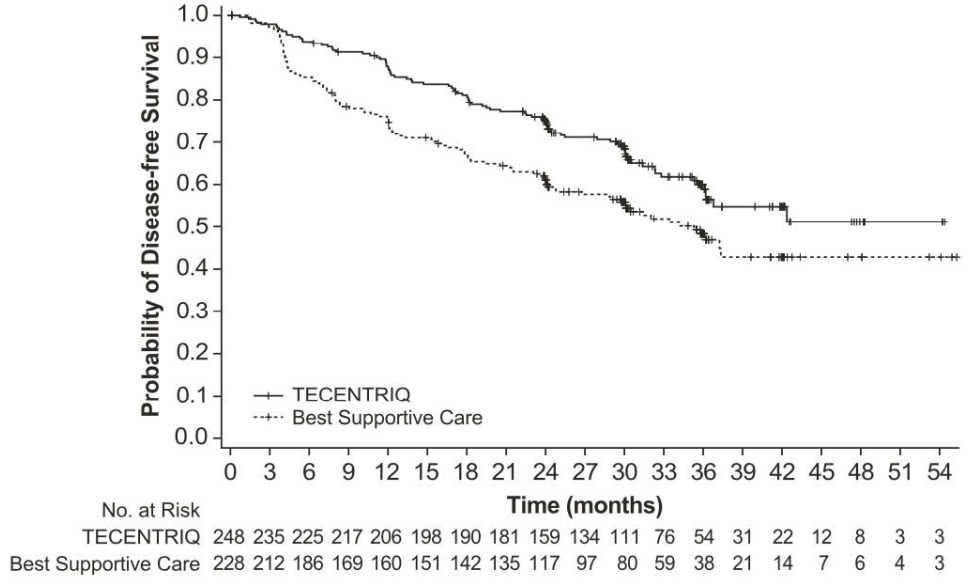
Table 22 Efficacy Results from IMpower010 in Patients with Stage II - IIIA NSCLC with PD-L1 expression ≥ 1% TC

	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.

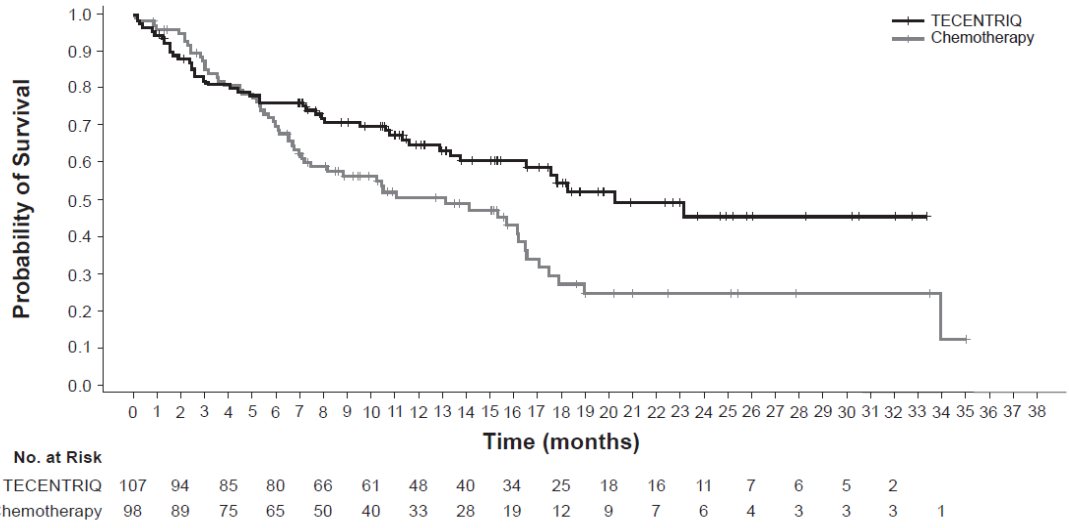
The trial demonstrated a statistically significant improvement in OS for patients with high PD-L1 expression (TC ≥50% or IC ≥10%) at the time of the OS interim analysis. There was no statistically significant difference in OS for the other two PD-L1 subgroups (TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%) at the interim or final analyses. Efficacy results for patients with NSCLC with high PD-L1 expression are presented in Table 23 and Figure 2.

Table 23: 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.

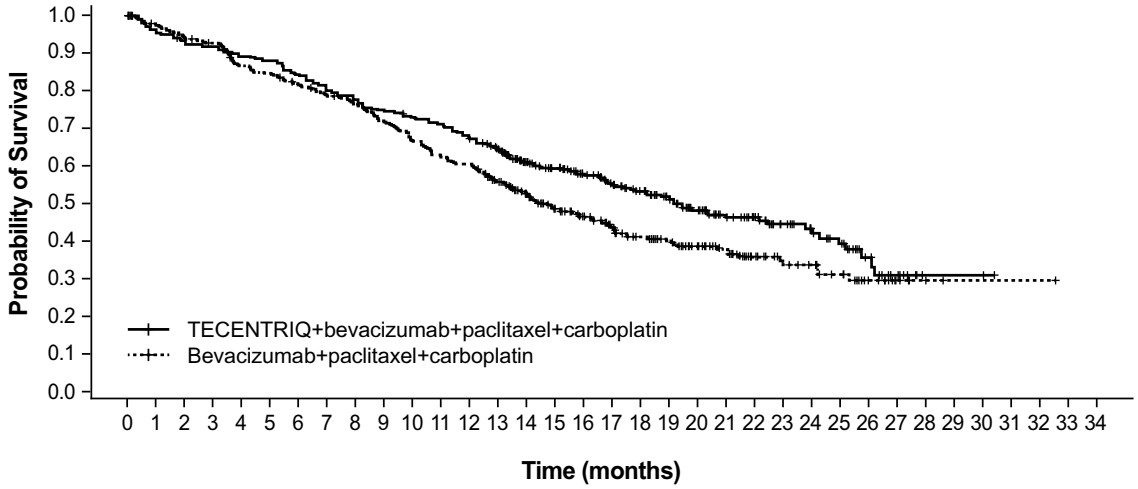
The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically 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 24 and Figure 3.

Table 24: 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



No. at Risk																													
TECENTRIQ+bevacizumab+ paclitaxel+carboplatin	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
Bevacizumab+ paclitaxel+carboplatin	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

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 25 and Figure 4.

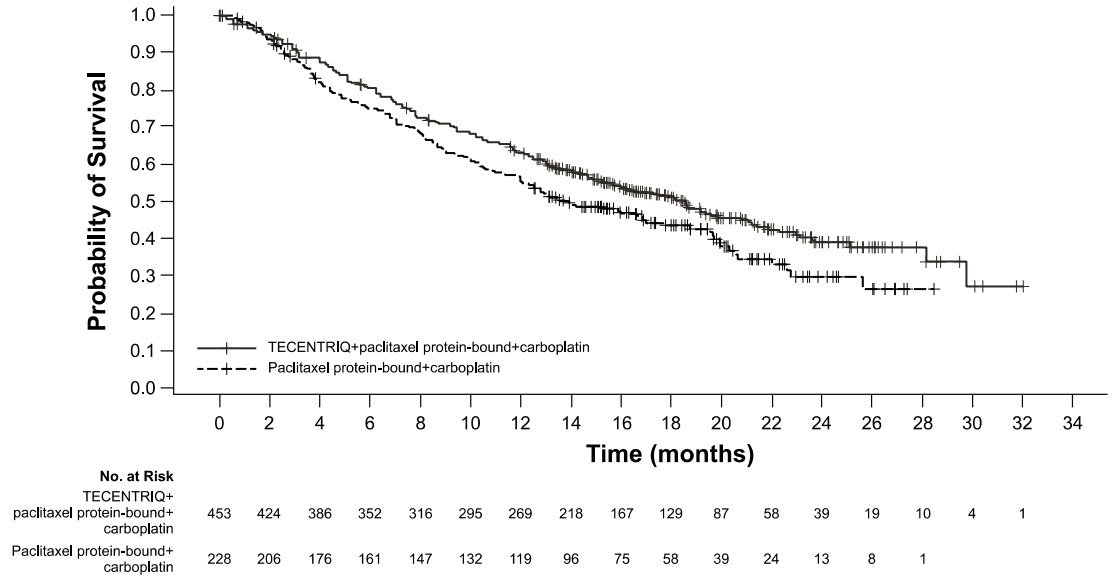
Table 25: Efficacy Results from IMpower130

	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

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 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 26 and Figure 5.

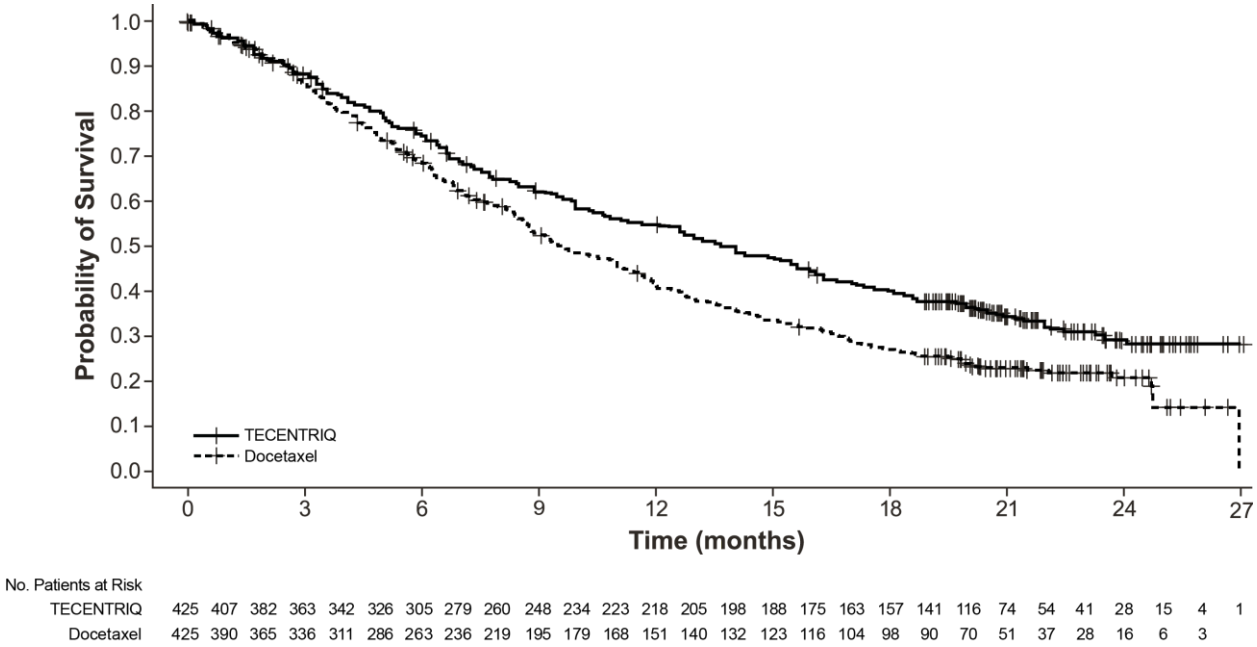
Table 26: Efficacy Results in OAK

	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



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 atezolizumab arm with a matched population in the docetaxel arm and ADA negative patients in the atezolizumab 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

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.

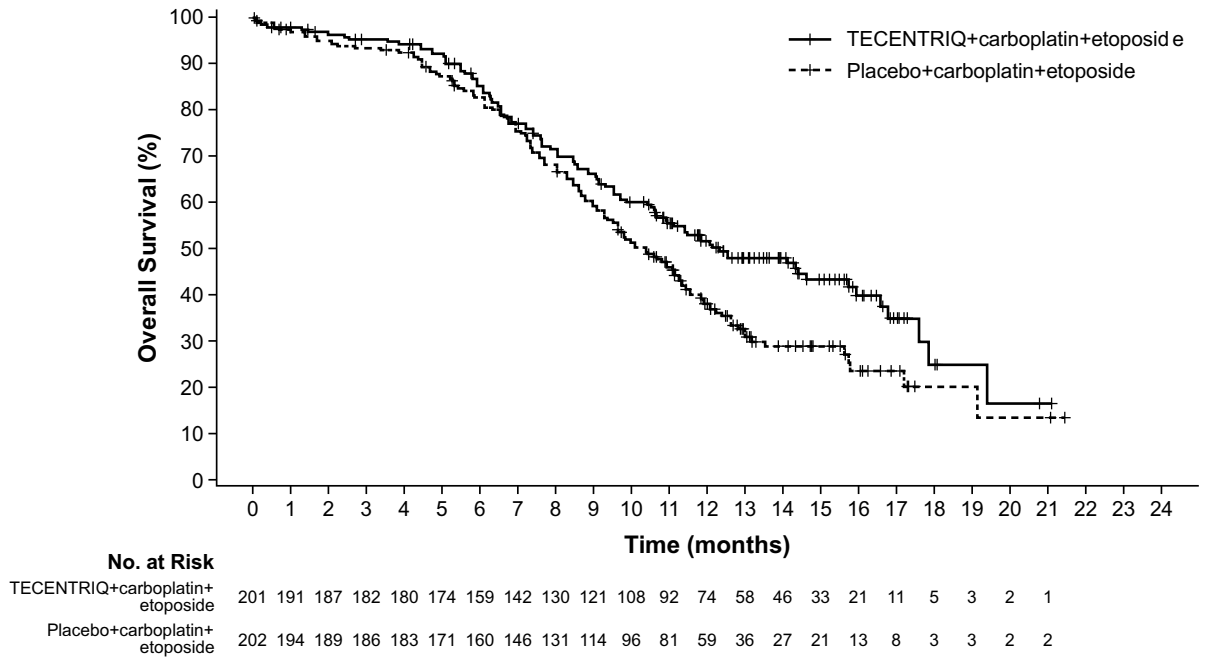
Efficacy results are presented in Table 27 and Figure 6.

Table 27: 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



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 28 and Figure 7.

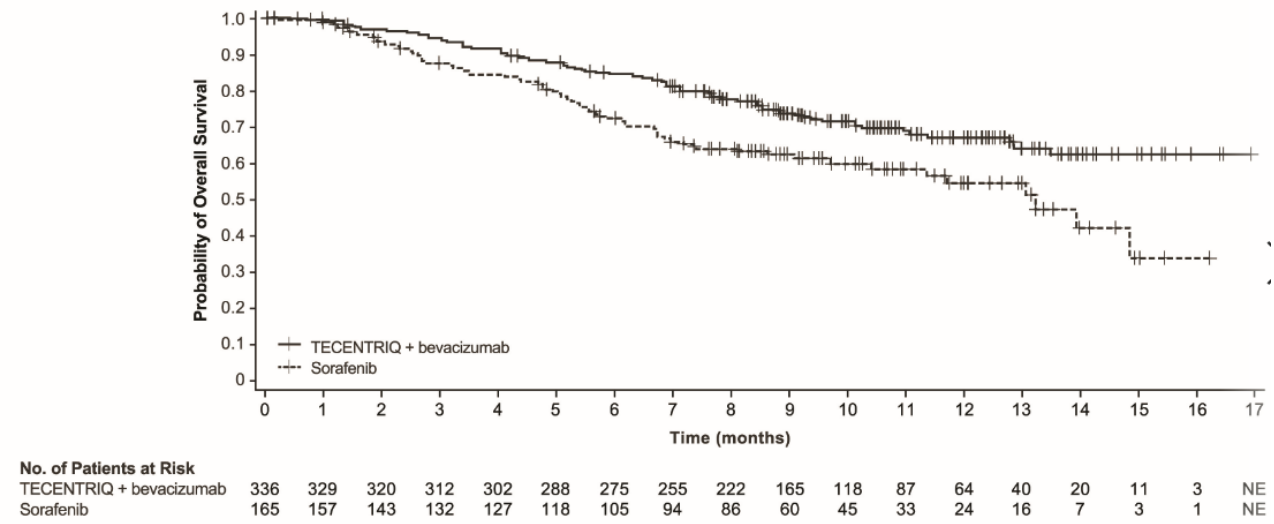
Table 28: Efficacy Results from IMbrave150

	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 7: 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.

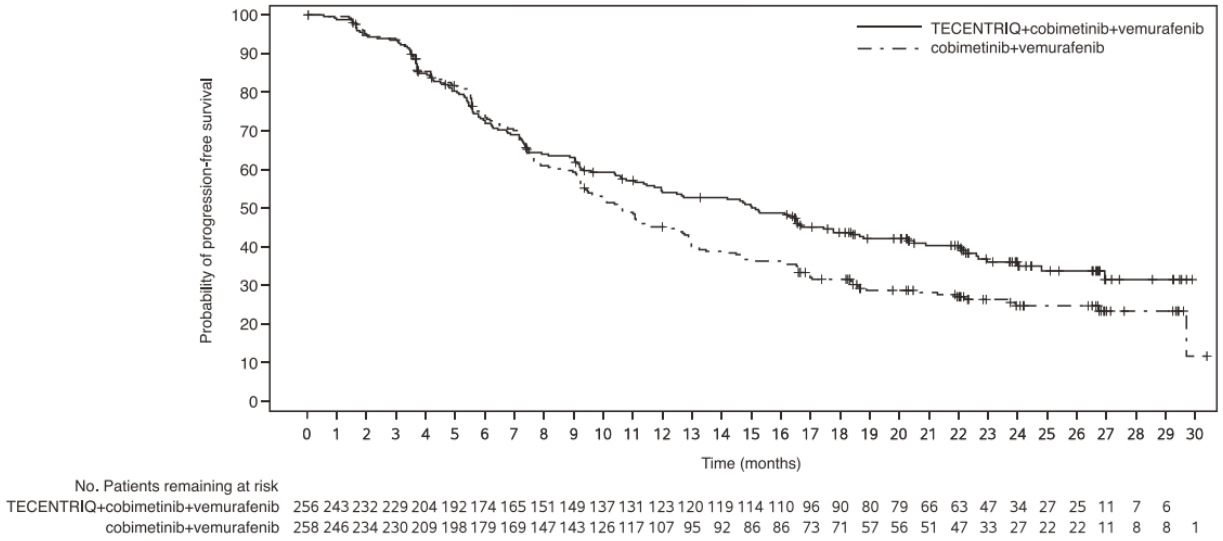
Efficacy results are summarized in Table 29 and Figure 8. Patients had a median survival follow up time of 18.9 months.

Table 29 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 8: 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 30.

Table 30: 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 eye sight
- 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 small cell lung cancer (SCLC). TECENTRIQ may be used with the chemotherapy medicines carboplatin and etoposide as your first treatment when your lung cancer**
  - is a type called “extensive-stage SCLC,” which means that it has spread or grown.
- **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:12/2022

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.

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, 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: • 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.

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.

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 (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.

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]
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		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
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]	severe cutaneous adverse reactions[ak], psoriasis[an]
Rare	pemphigoid	pemphigoid
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 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.

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.

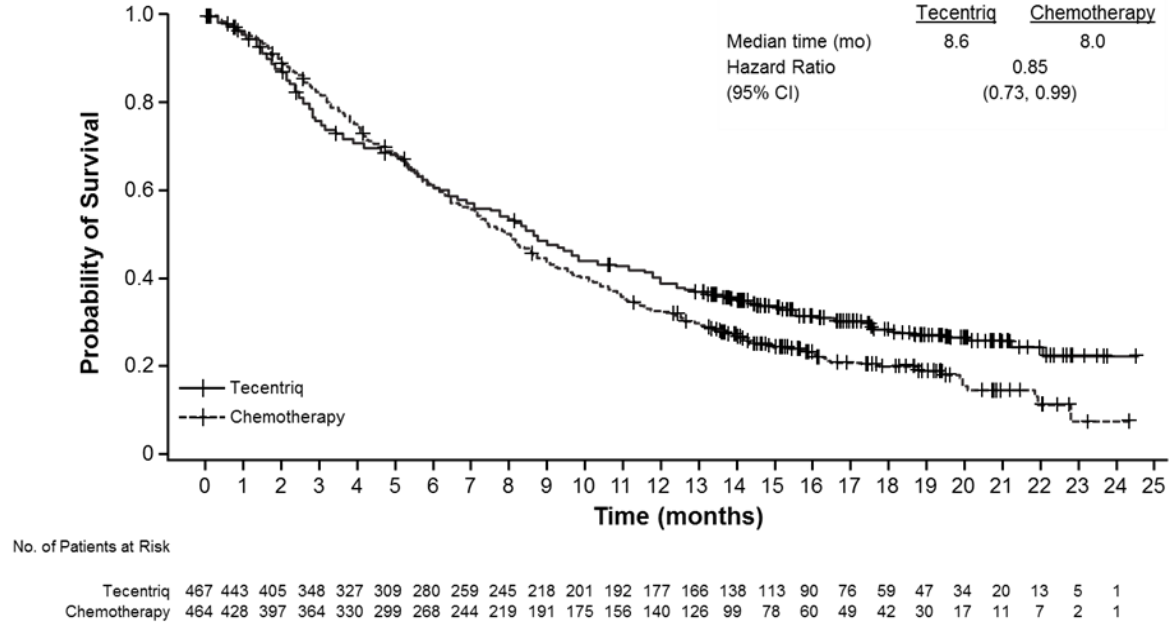
* An analysis of OS in the all comer population was performed based on the stratified log-rank test and the result is provided for descriptive purposes only (p = 0.0378); according to the pre-specified analysis hierarchy, the p-value for the OS analysis in the all comer population cannot be considered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

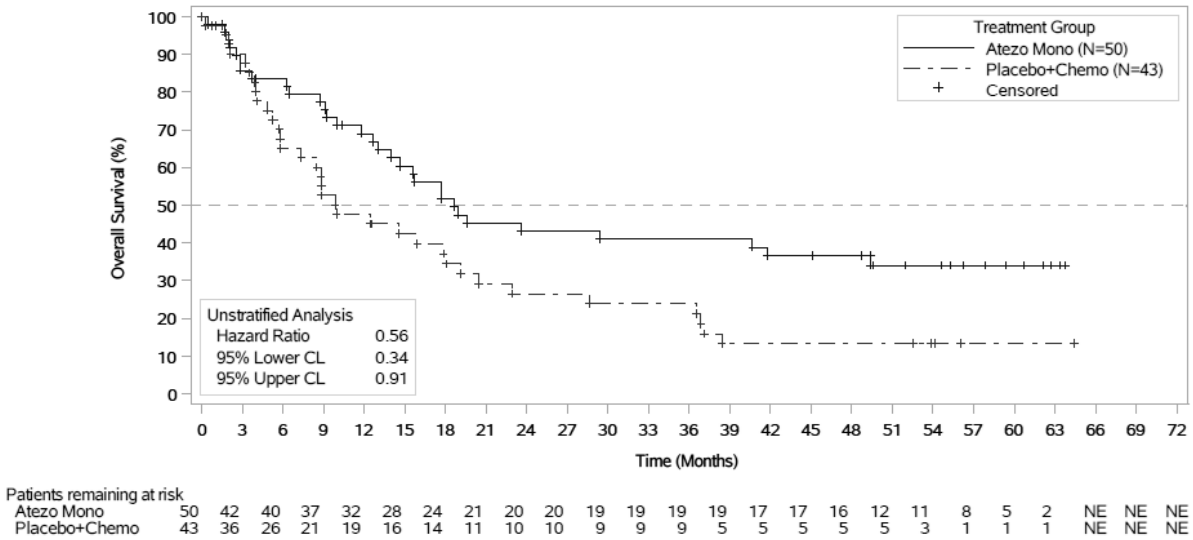
IMvigor130 (WO30070): Phase III study of atezolizumab monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma

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)



Non-small cell lung cancer

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.

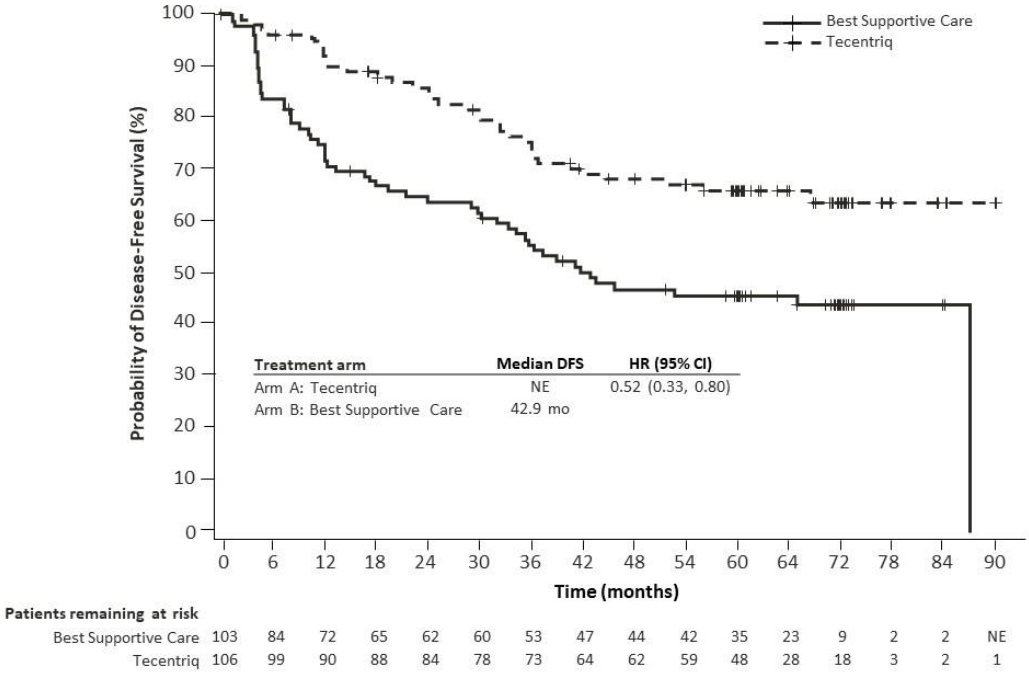
The key efficacy results for DFS and OS in the PD-L1 ≥ 50% TC stage II – IIIA patient population, without EGFR mutations and ALK rearrangements, are summarised in Table 7. The Kaplan-Meier curve for DFS is presented in Figure 3.

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)

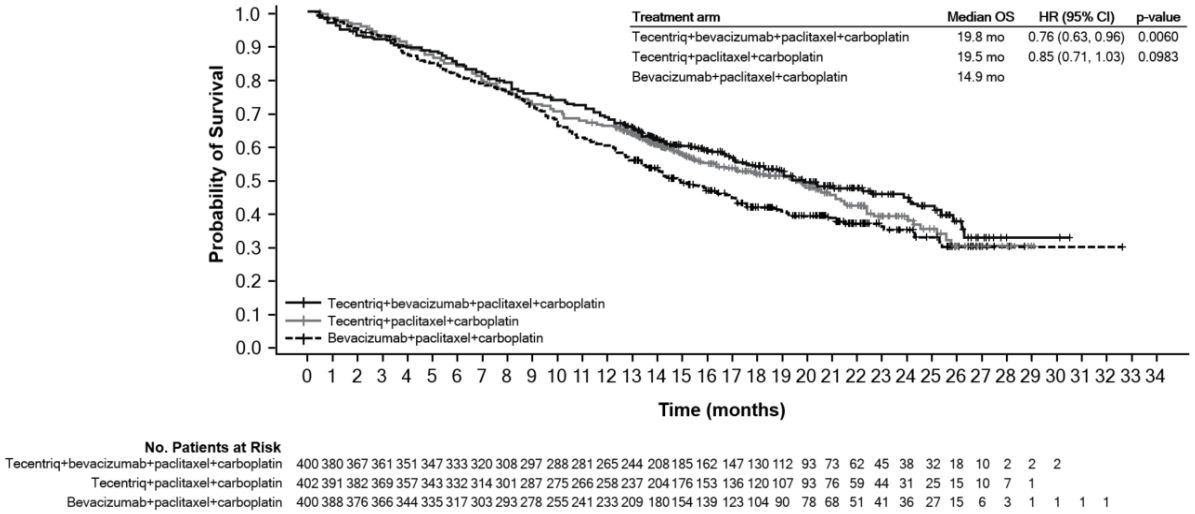


Figure 5: Forest plot of overall survival by PD-L1 expression in the ITT population, Arm B vs. C (IMpower150)

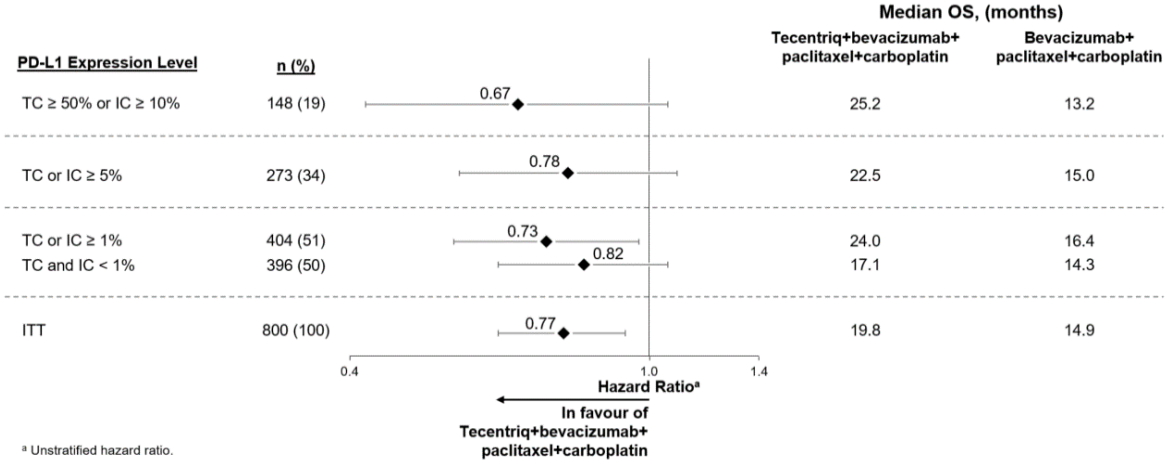
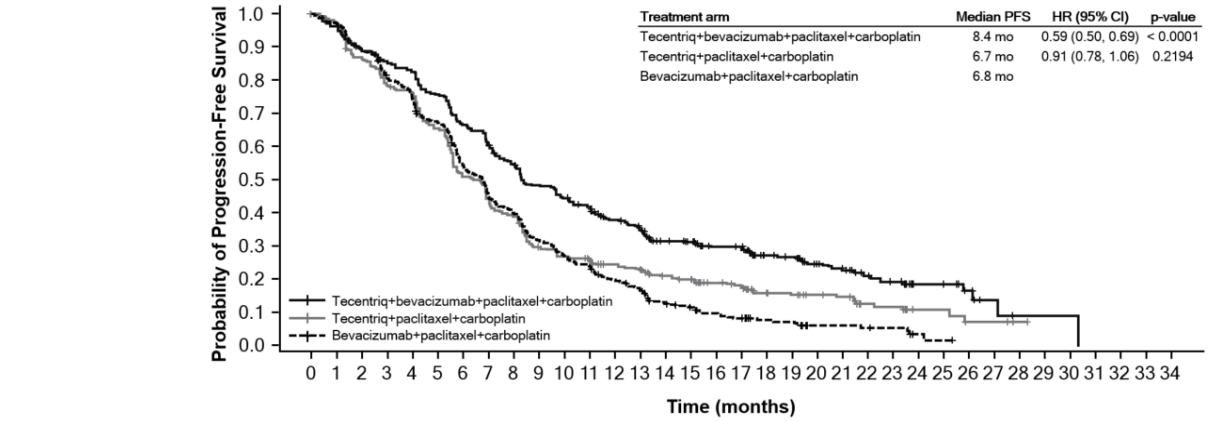


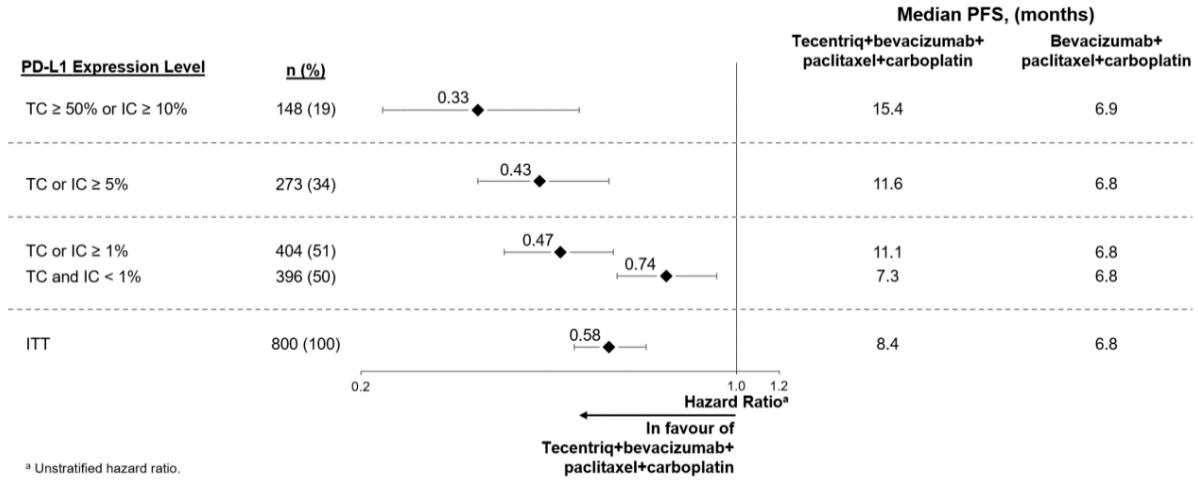
Figure 6: Kaplan-Meier curve for PFS in the ITT population (IMpower150)



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%
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)

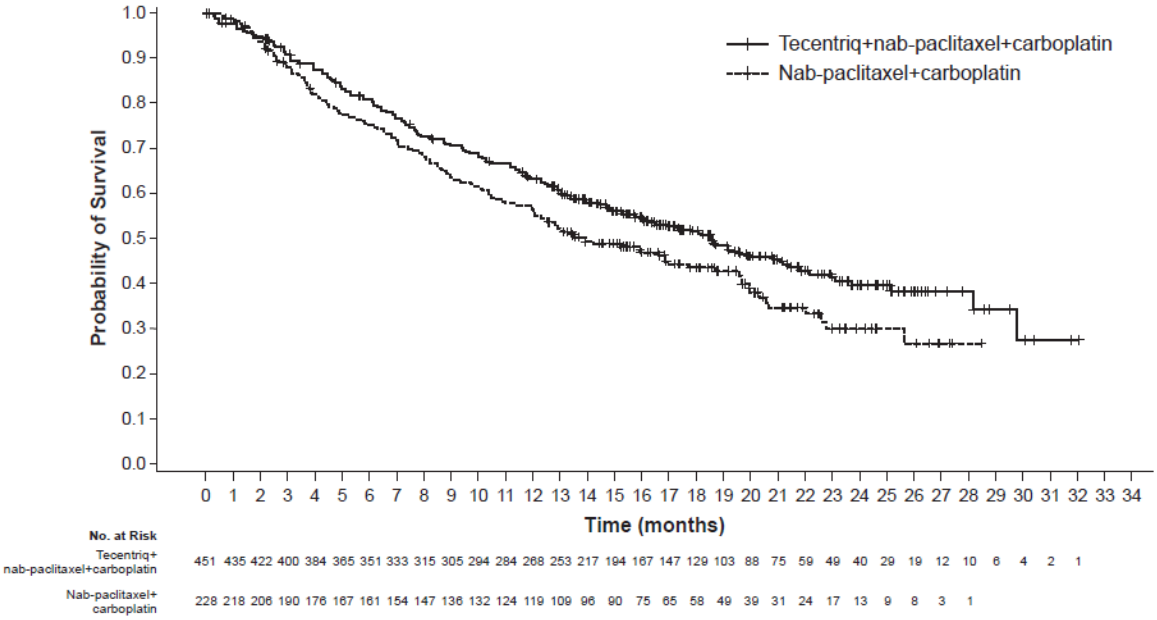


Figure 9: Forest plot of overall survival by PD-L1 expression (IMpower130)

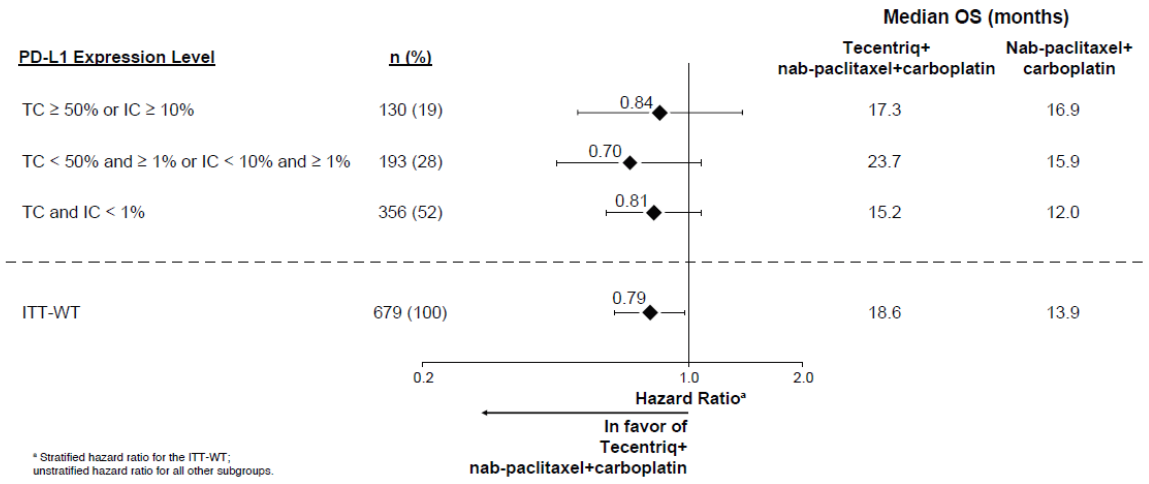


Figure 10: Kaplan-Meier curves for progression free survival (IMpower130)

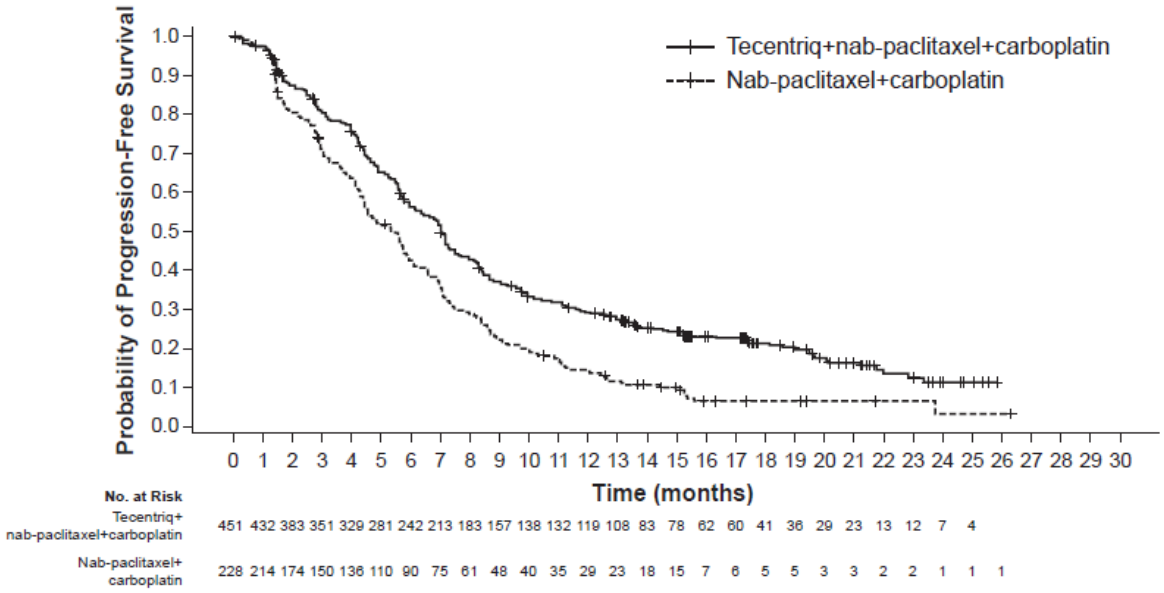
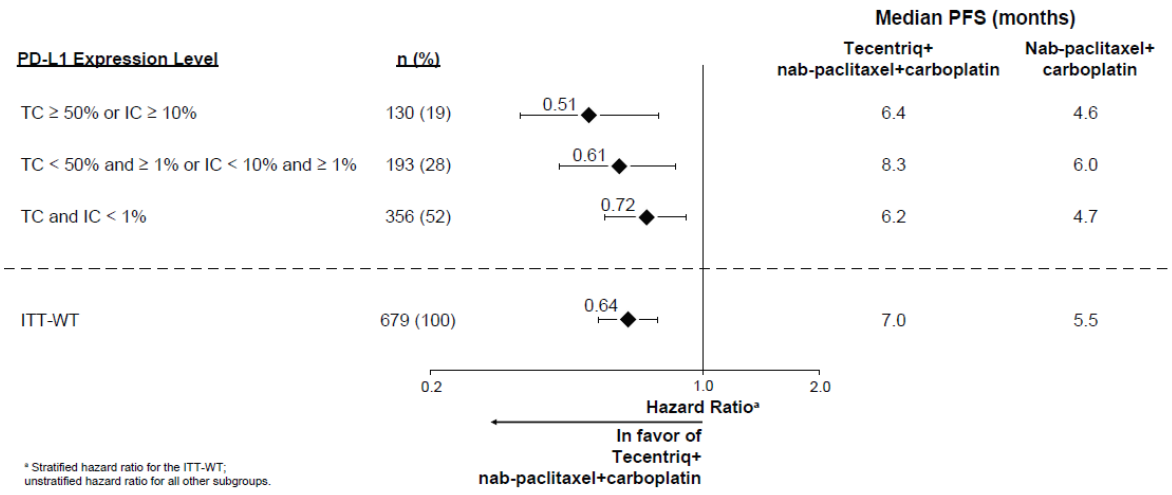


Figure 11: Forest plot of progression free survival by PD-L1 expression (IMpower130)



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/m^2) OR carboplatin[a] (AUC 5) + gemcitabine[a,c] (1 000 mg/m^2)	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)

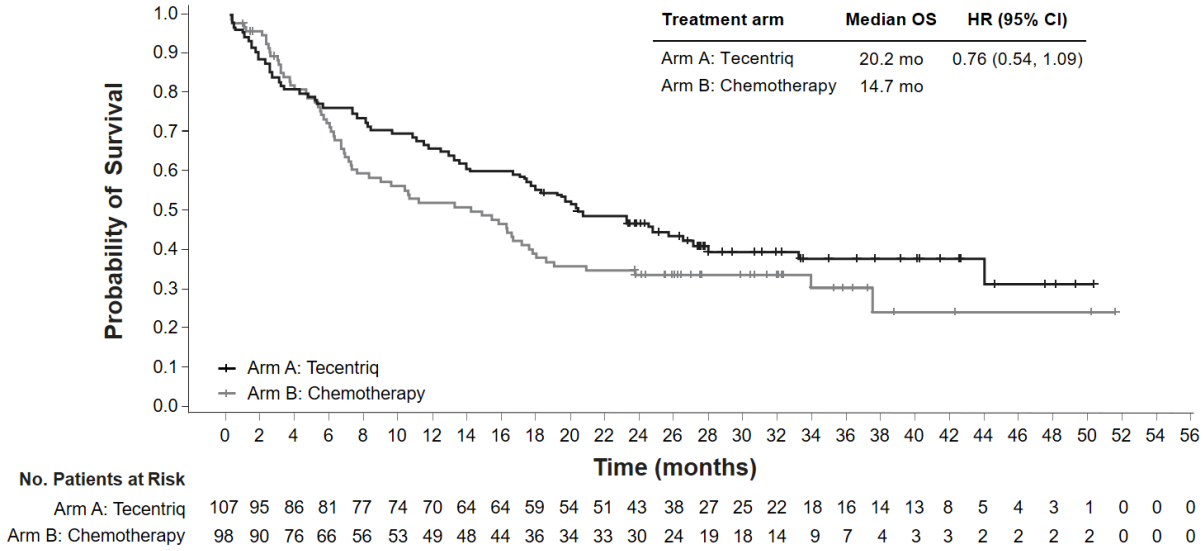
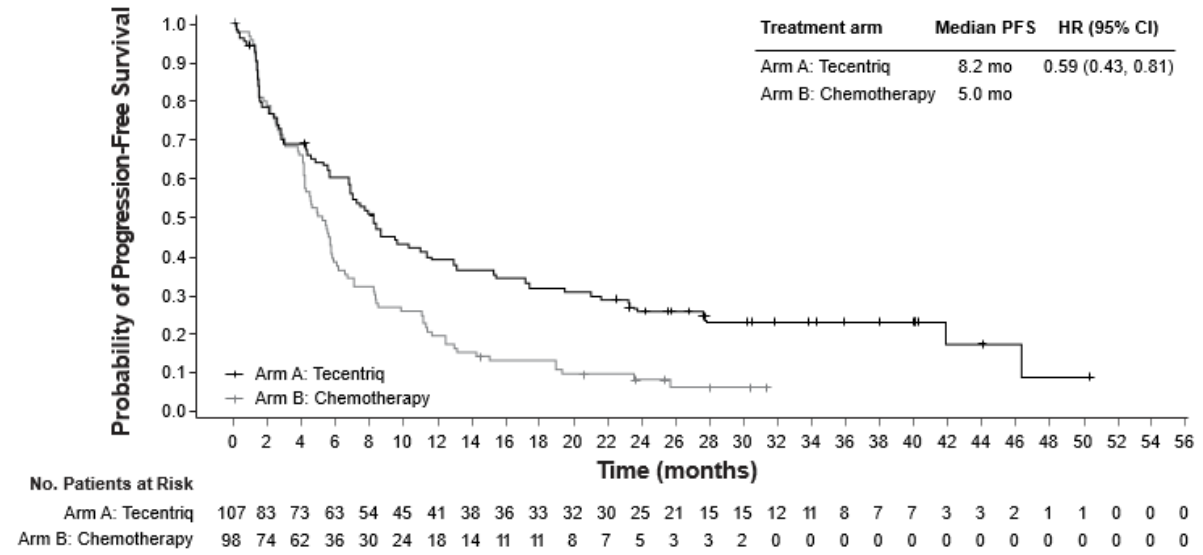


Figure 13: Kaplan-Meier curve for progression free survival in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)



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.

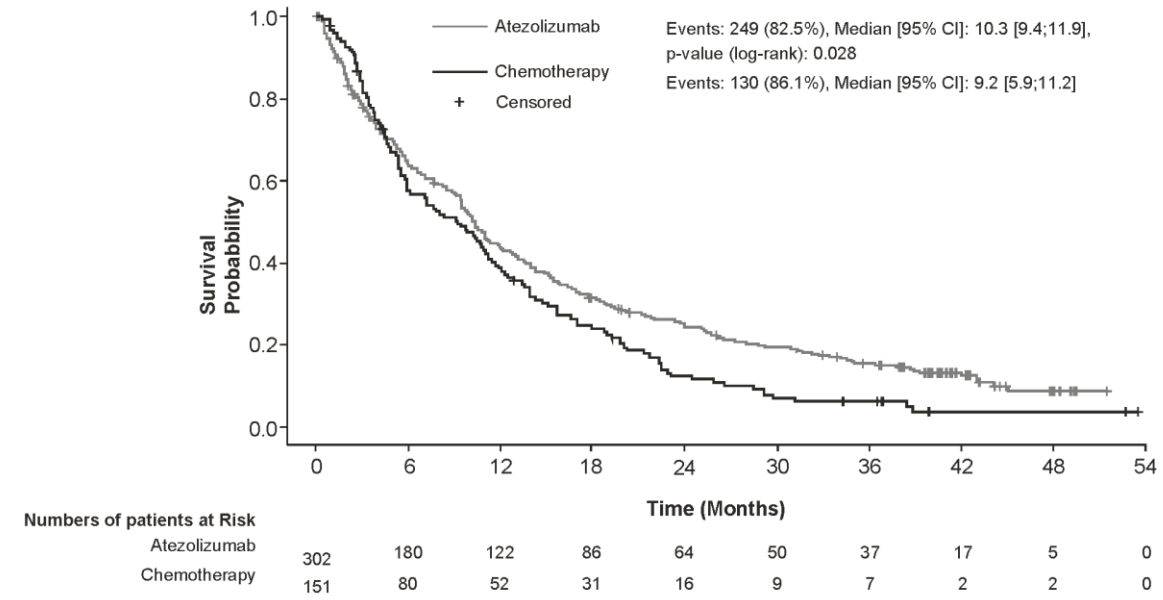
Table 16: Summary of efficacy for NSCLC patients ineligible for platinum-based chemotherapy (IPSOS)

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)

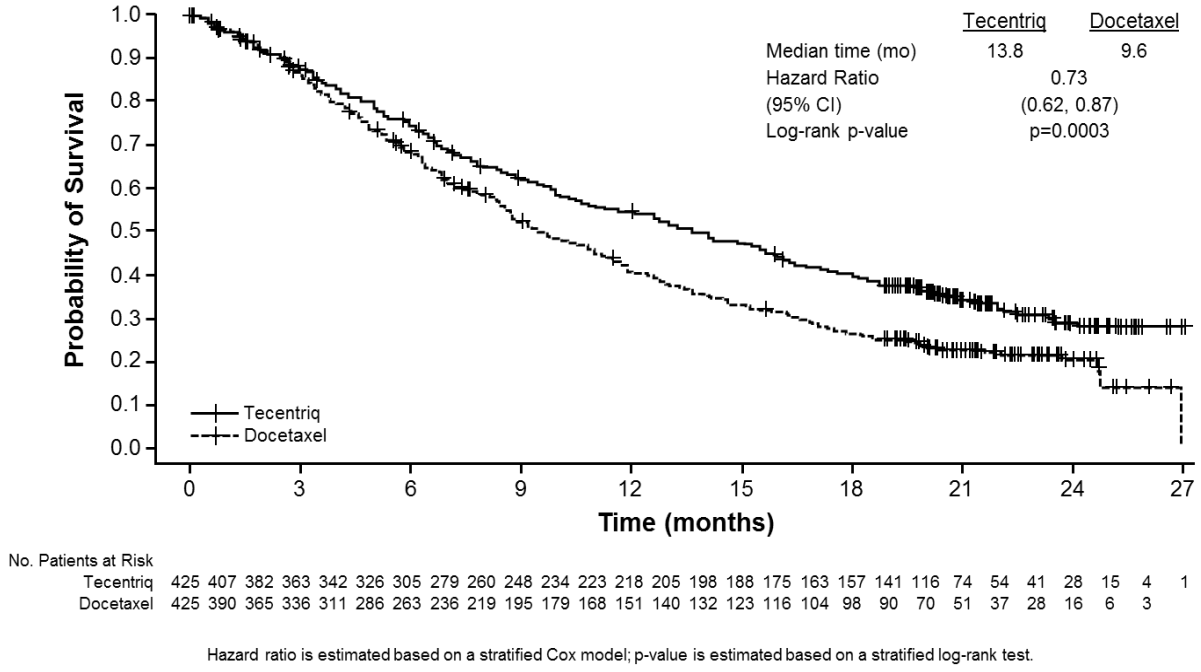
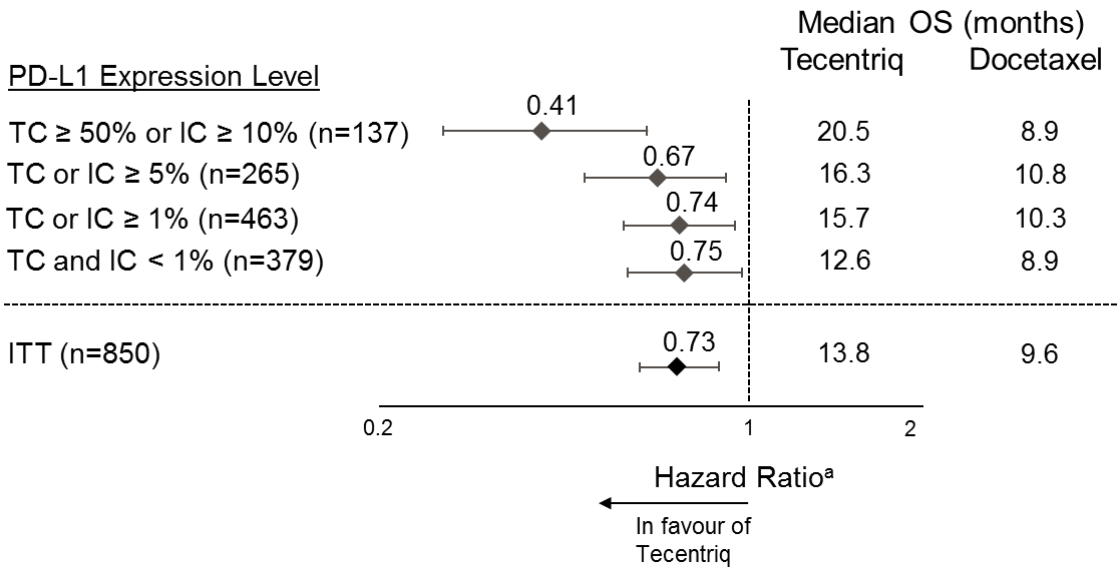


Figure 16: Forest plot of overall survival by PD-L1 expression in the primary analysis population (OAK)



[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
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)

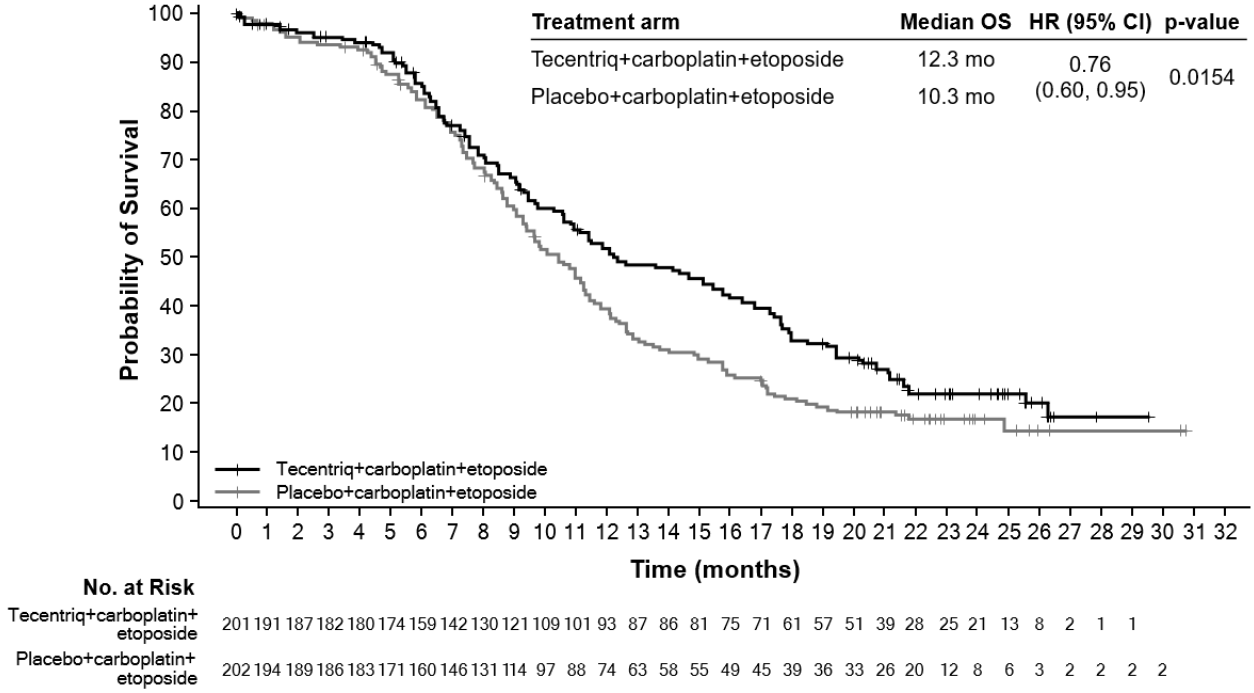
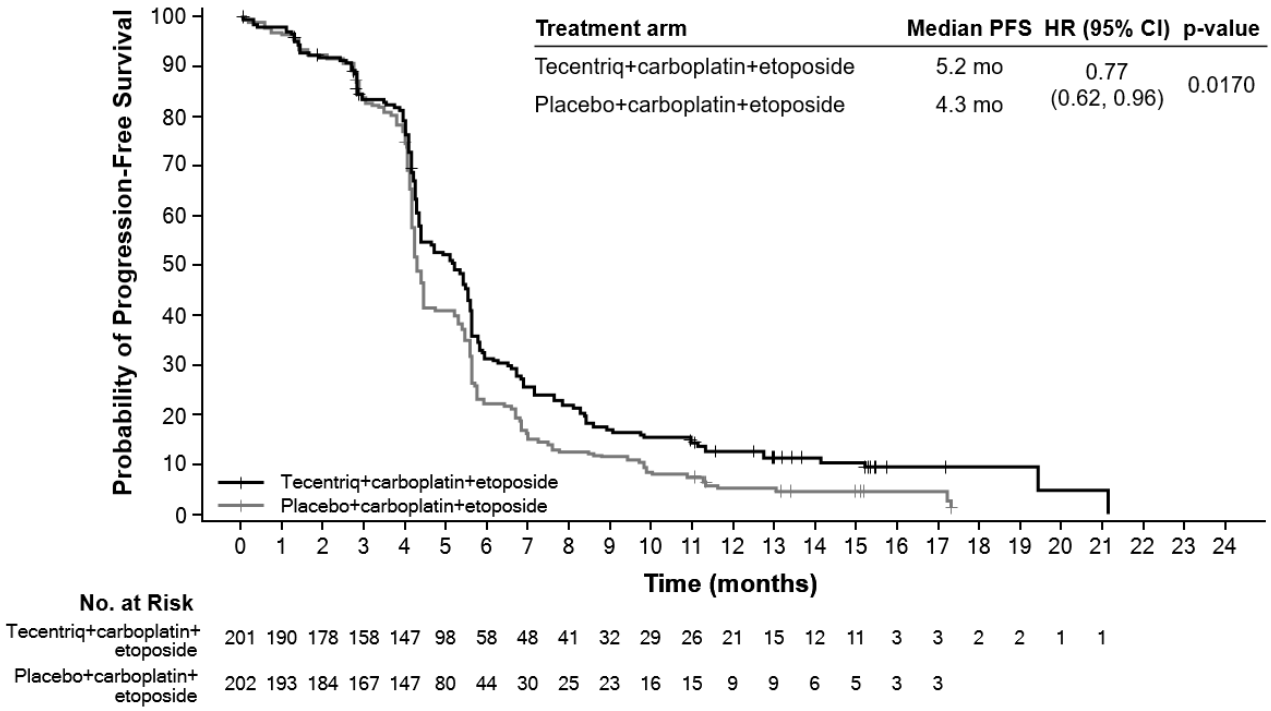


Figure 18: Kaplan-Meier curve for progression-free survival (IMpower133)



Triple-negative breast cancer

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
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)	

Key efficacy endpoints	Atezolizumab + nab-paclitaxel	Placebo + nab-paclitaxel
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)

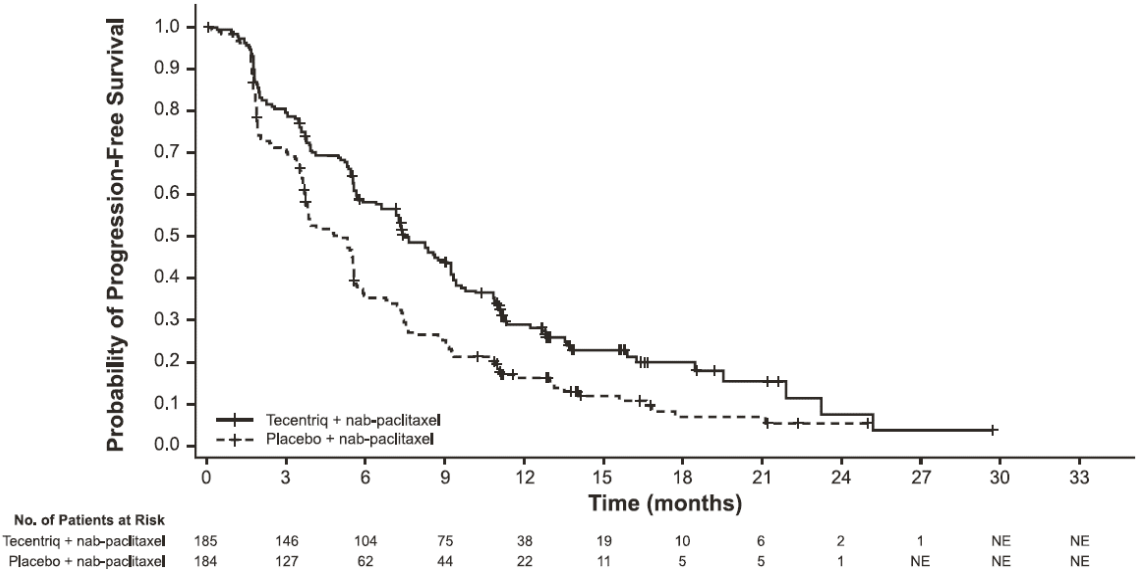
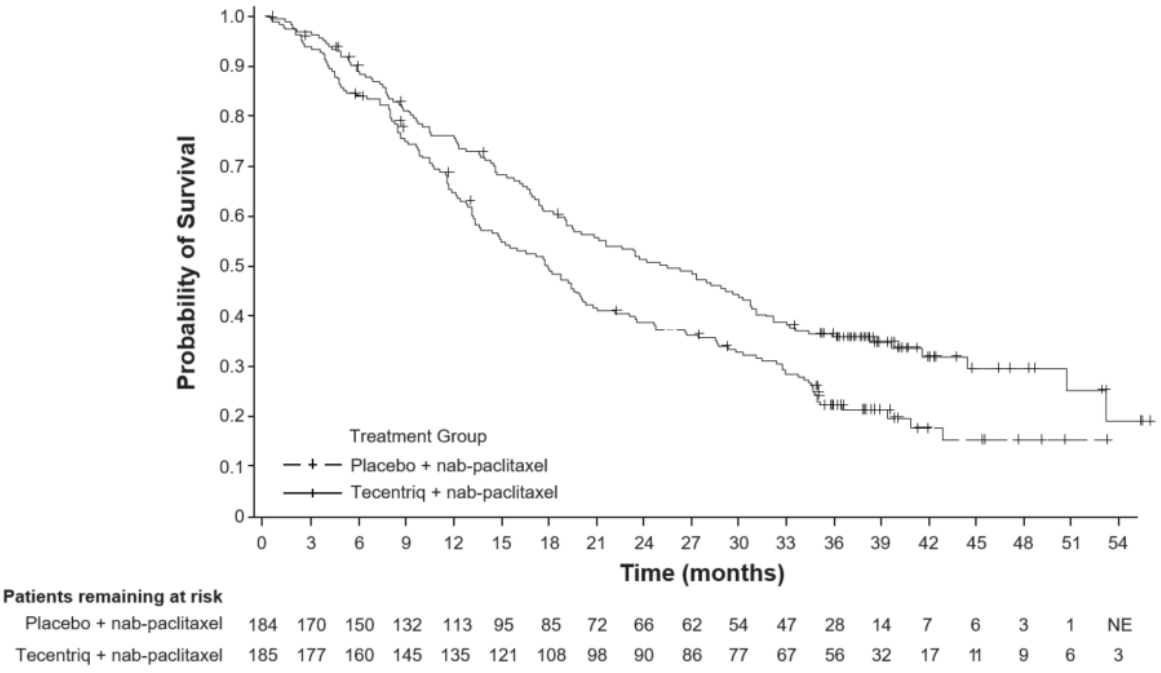


Figure 20: Kaplan-Meier curve for overall survival in patients with PD-L1 expression ≥ 1% (IMpassion130)



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+)

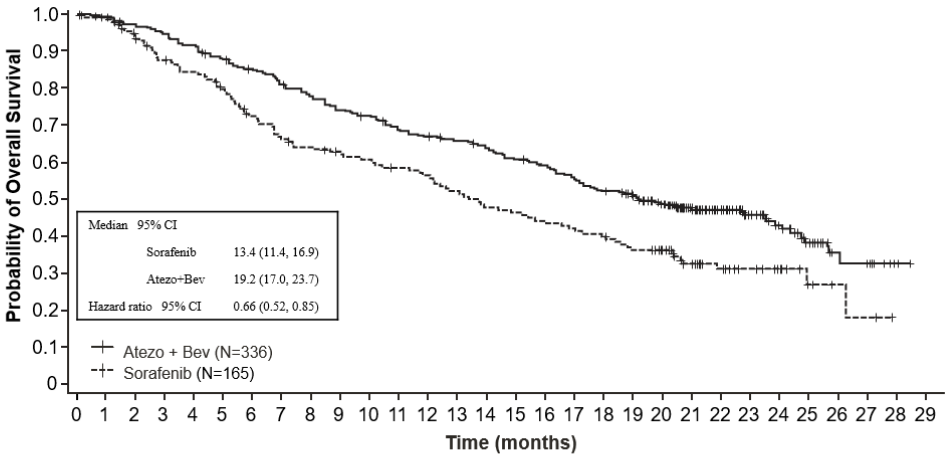
‡ Stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)

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)

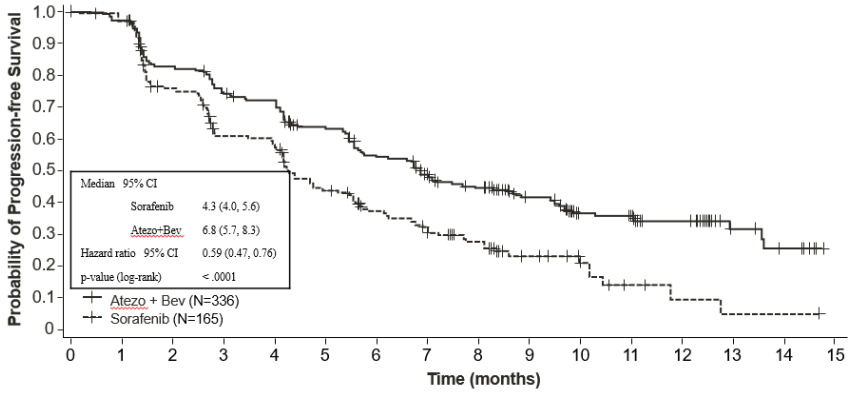


No. of Patients at Risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

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
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.

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 may transition to Tecentriq solution for injection.

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] *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
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	Withhold Tecentriq Treatment may be resumed when the symptoms improve to

Immune-mediated adverse reaction	Severity	Treatment modification
	or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	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 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 (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.

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		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
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]	severe cutaneous adverse reactions[ak], psoriasis[an]
Rare	pemphigoid	pemphigoid
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 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 includes reports of injection site reaction, injection site pain, injection site erythema, and injection site rash.
[aq] Includes reports of dry skin, xerosis.

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.

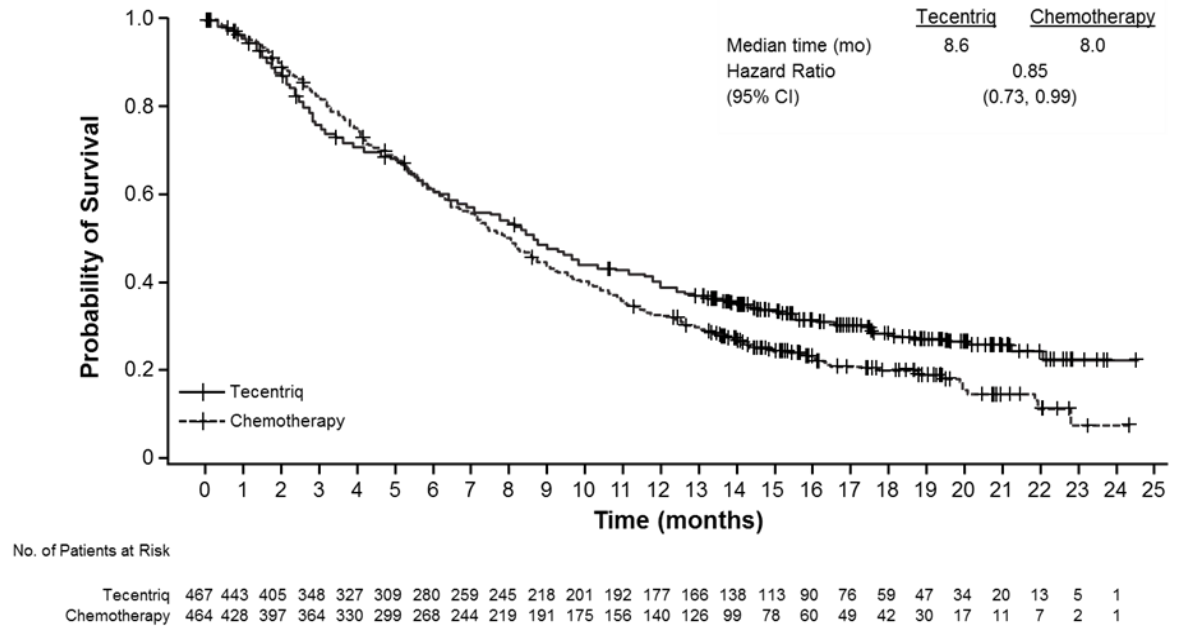
* An analysis of OS in the all comer population was performed based on the stratified log-rank test and the result is provided for descriptive purposes only (p = 0.0378); according to the pre-specified analysis hierarchy, the p-value for the OS analysis in the all comer population cannot be considered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

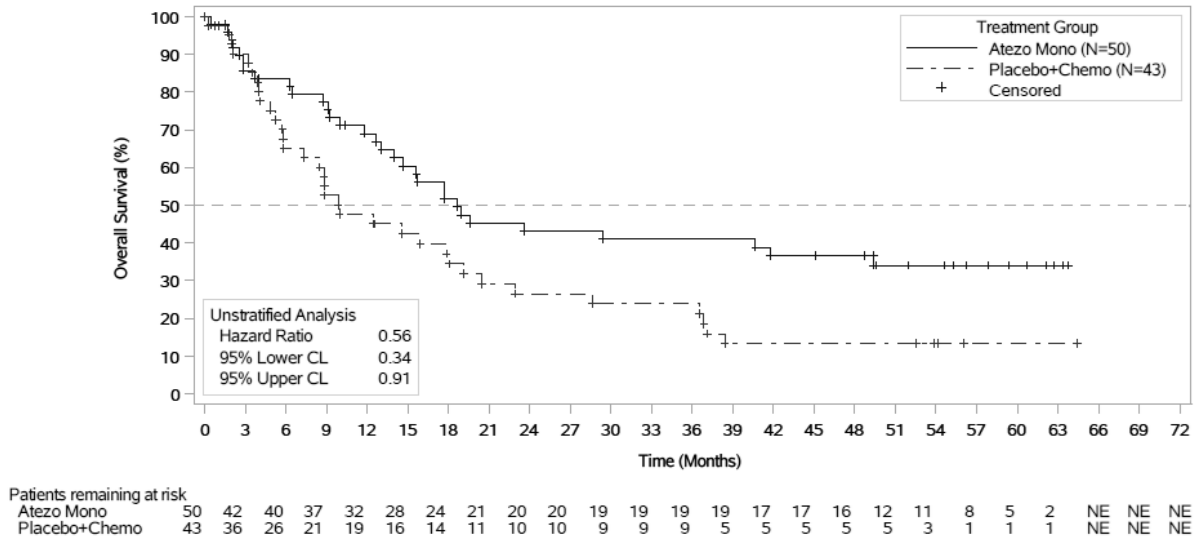
IMvigor130 (WO30070): Phase III study of atezolizumab monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma

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)



Non-small cell lung cancer

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.

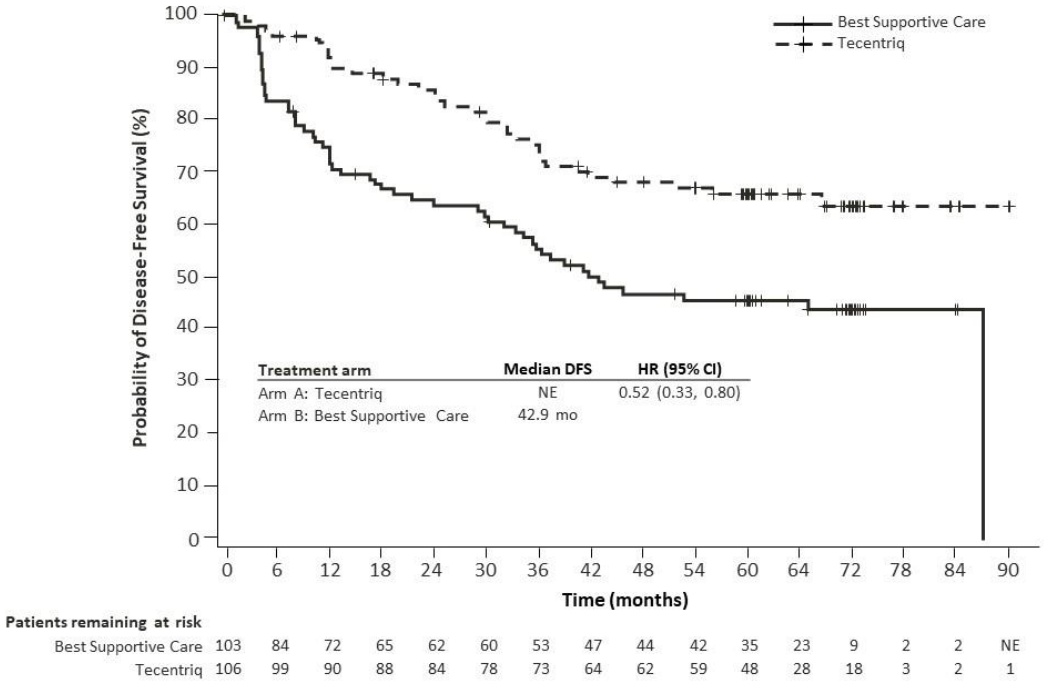
The key efficacy results for DFS and OS in the PD-L1 ≥ 50% TC stage II – IIIA patient population, without EGFR mutations and ALK rearrangements, are summarised in Table 7. The Kaplan-Meier curve for DFS is presented in Figure 3.

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)

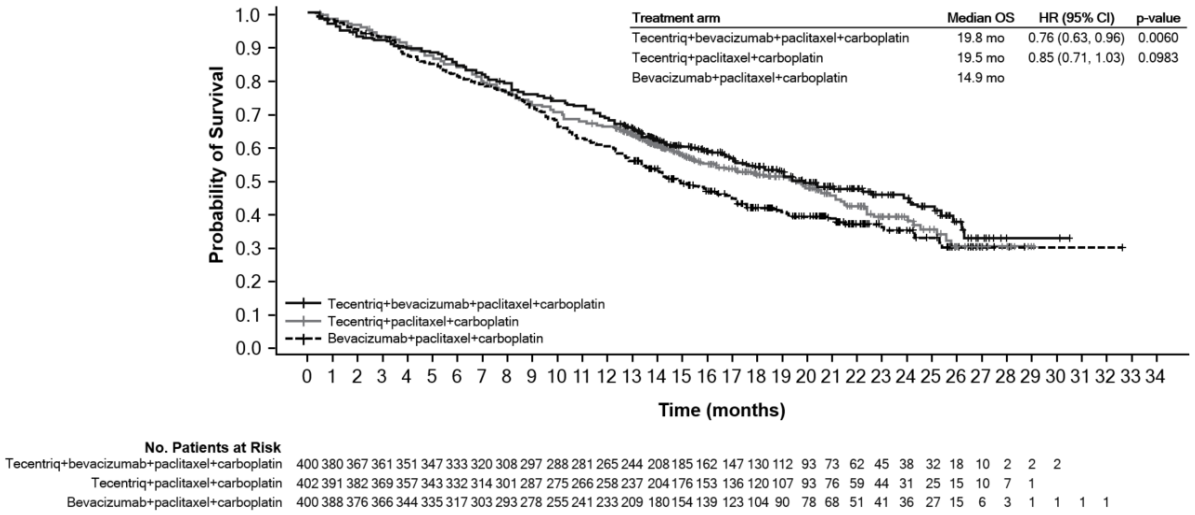


Figure 5: Forest plot of overall survival by PD-L1 expression in the ITT population, Arm B vs. C (IMpower150)

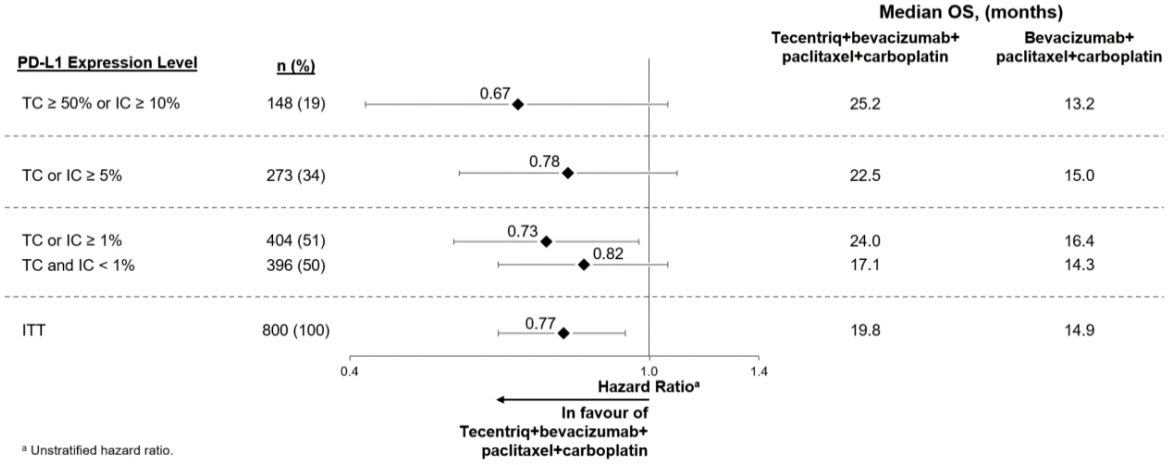
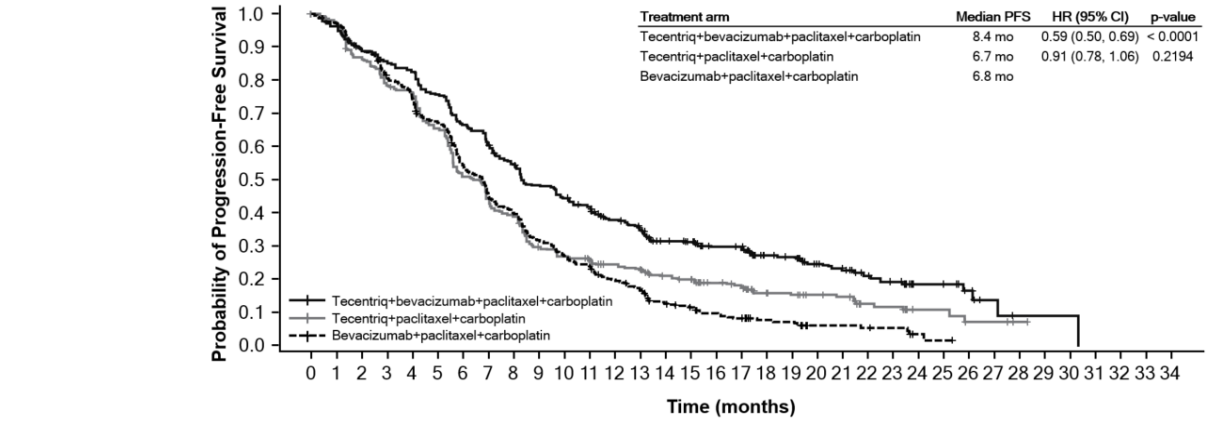


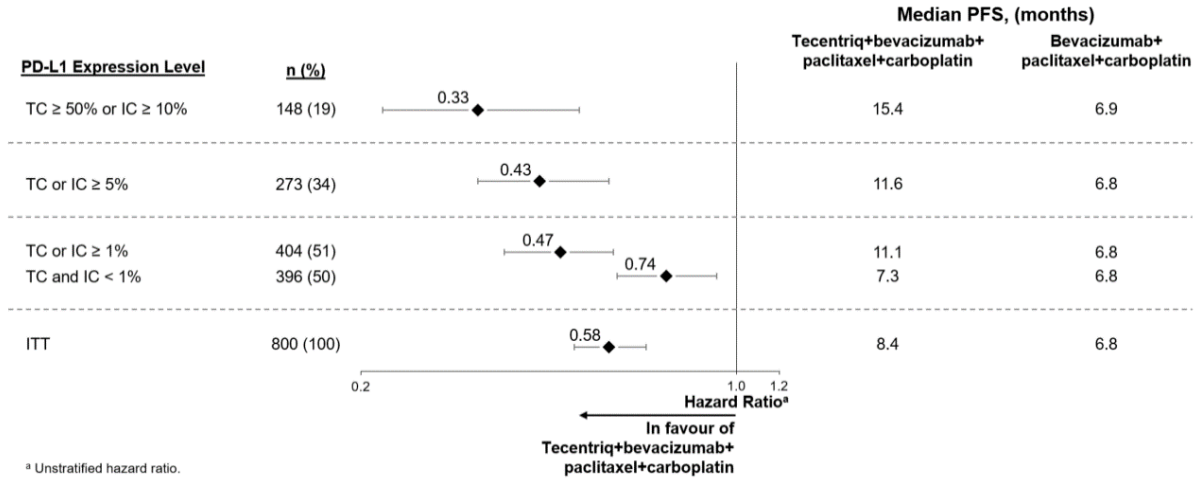
Figure 6: Kaplan-Meier curve for PFS in the ITT population (IMpower150)



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%
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)

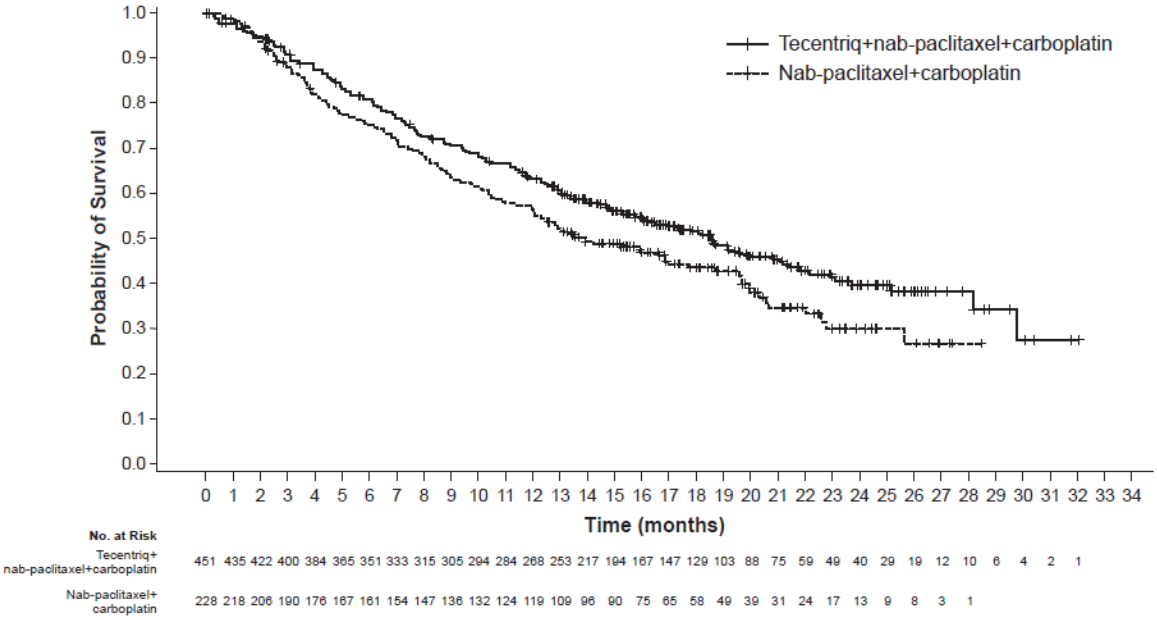


Figure 9: Forest plot of overall survival by PD-L1 expression (IMpower130)

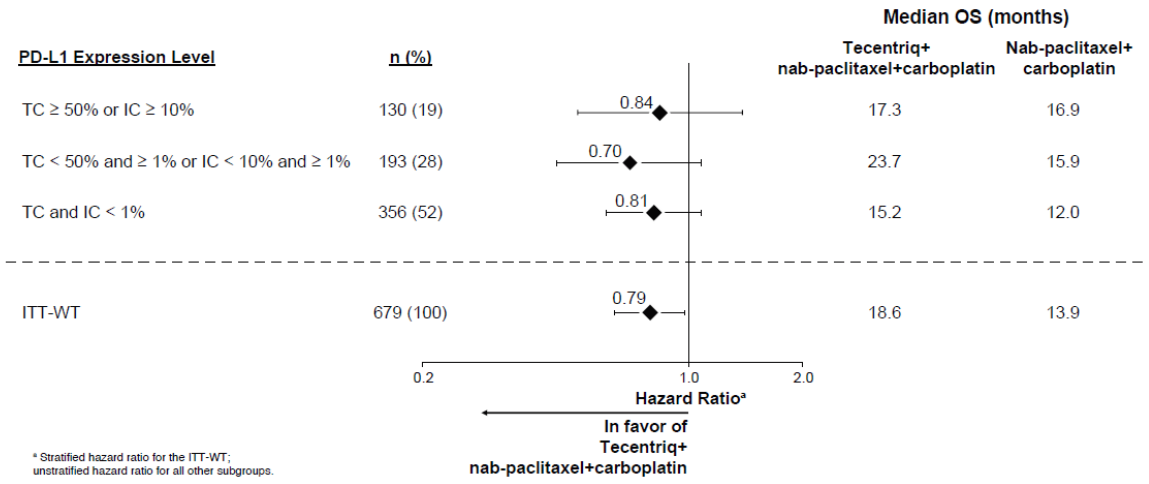


Figure 10: Kaplan-Meier curves for progression free survival (IMpower130)

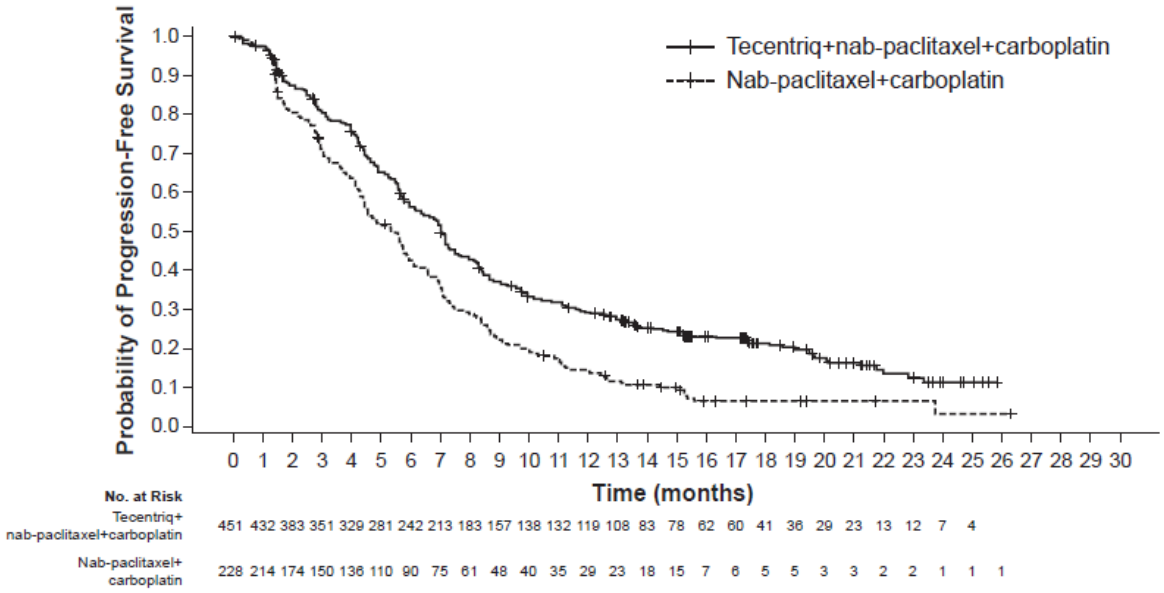
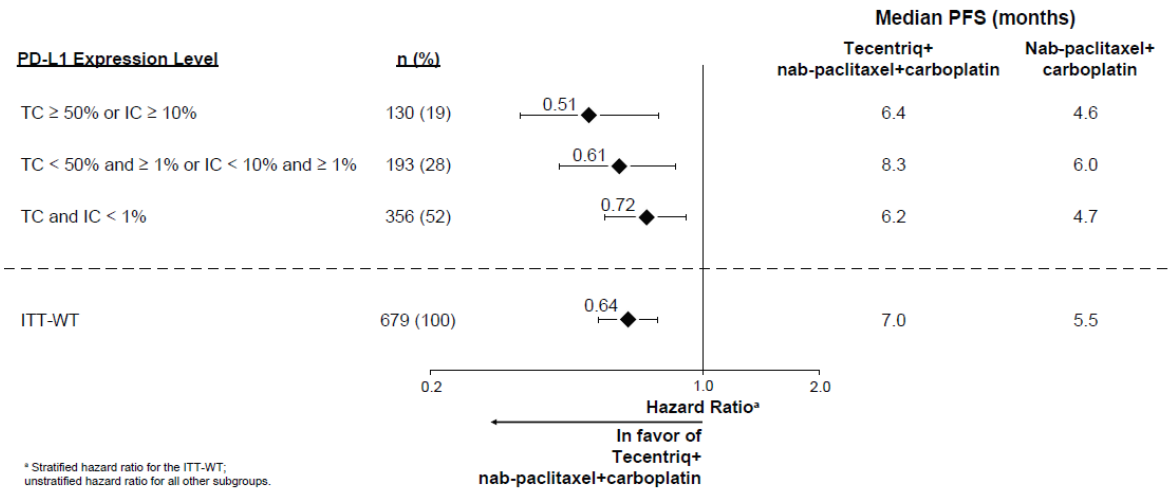


Figure 11: Forest plot of progression free survival by PD-L1 expression (IMpower130)



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/m^2) OR carboplatin[a] (AUC 5) + gemcitabine[a,c] (1 000 mg/m^2)	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)

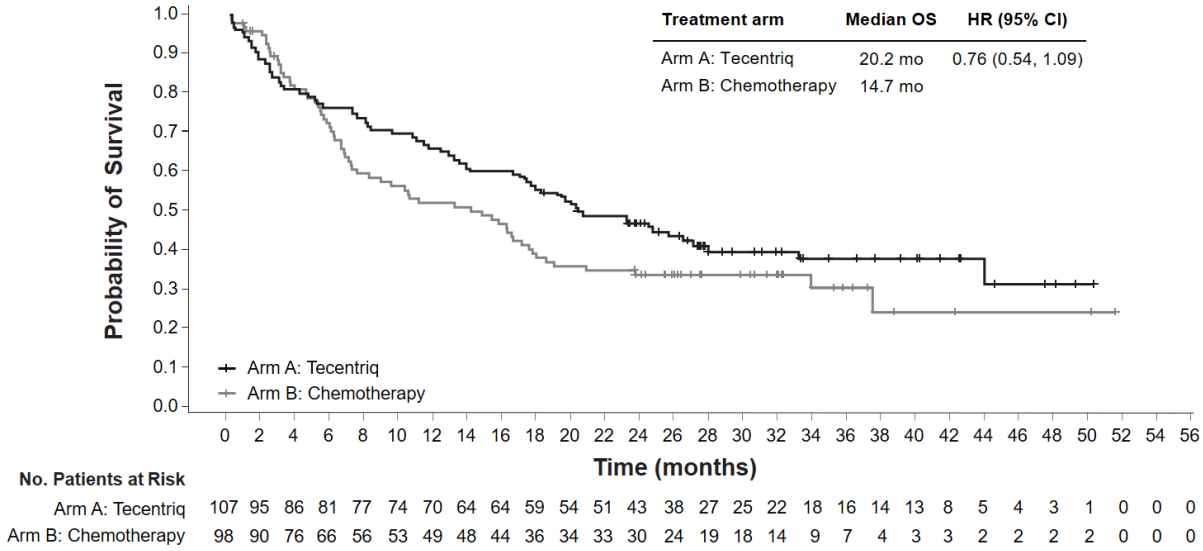
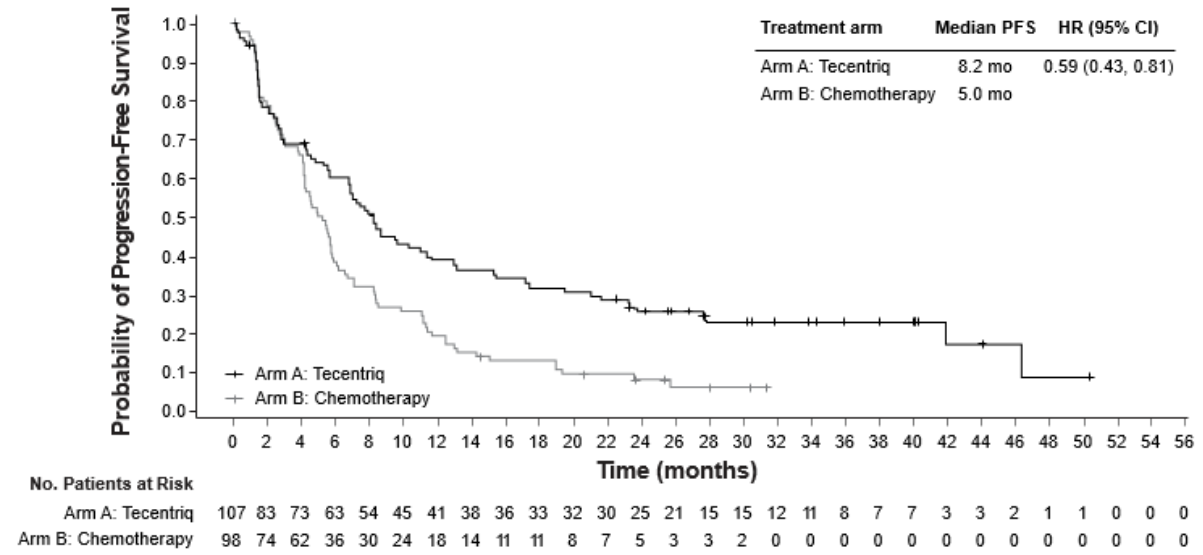


Figure 13: Kaplan-Meier curve for progression free survival in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)



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.

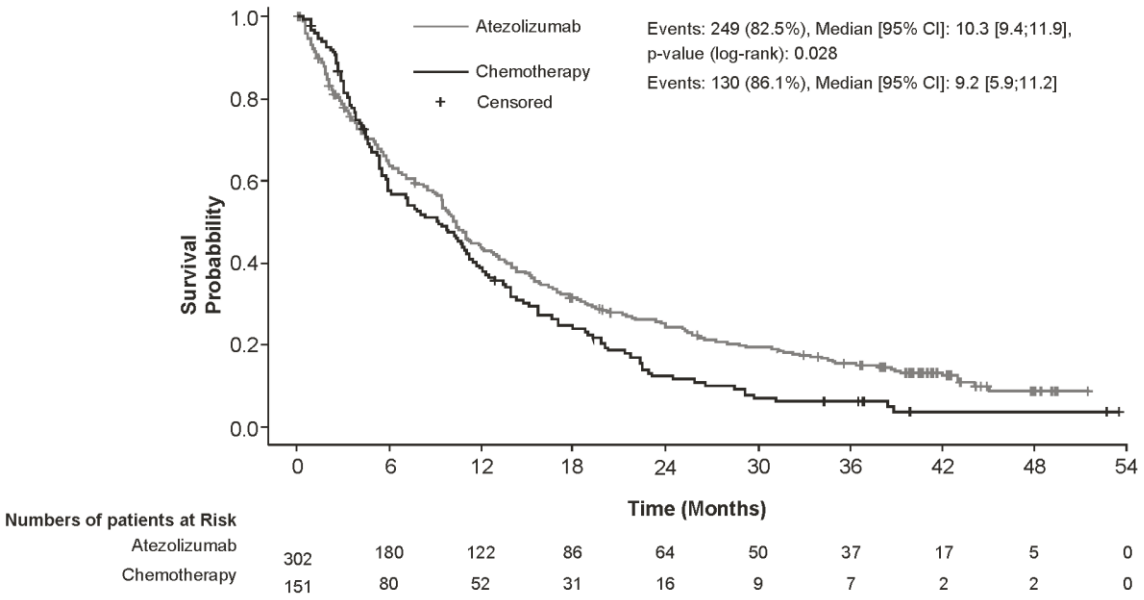
Table 16: Summary of efficacy for NSCLC patients ineligible for platinum-based chemotherapy (IPSOS)

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)



<u>*Second-line treatment of NSCLC*</u>

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)

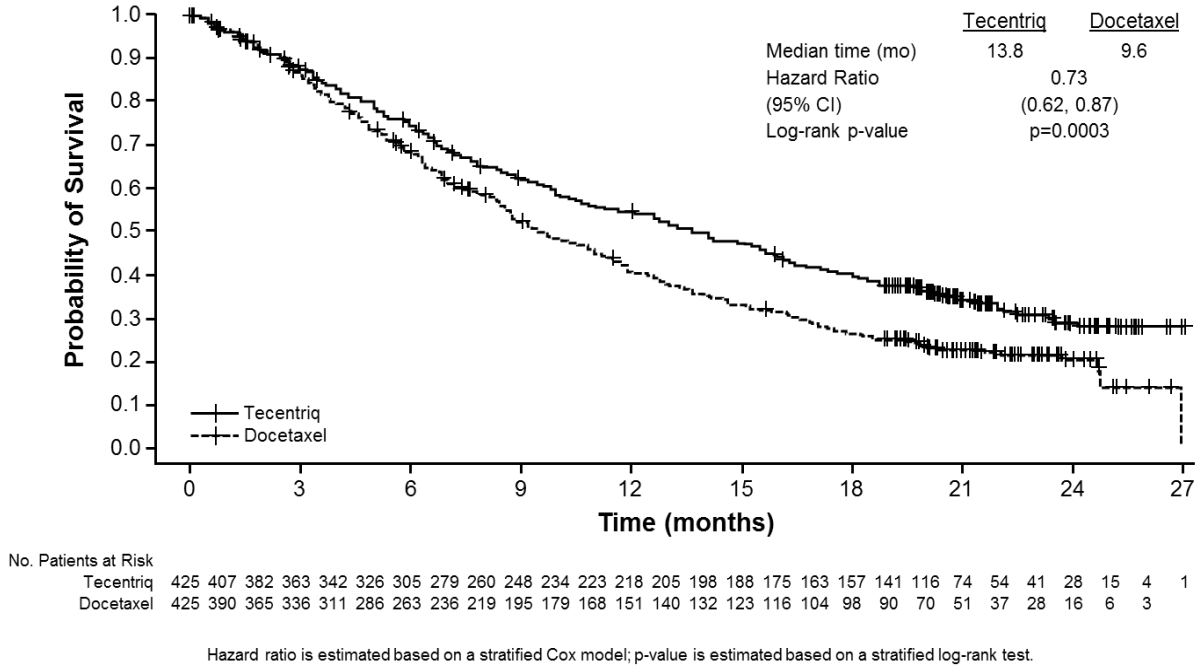
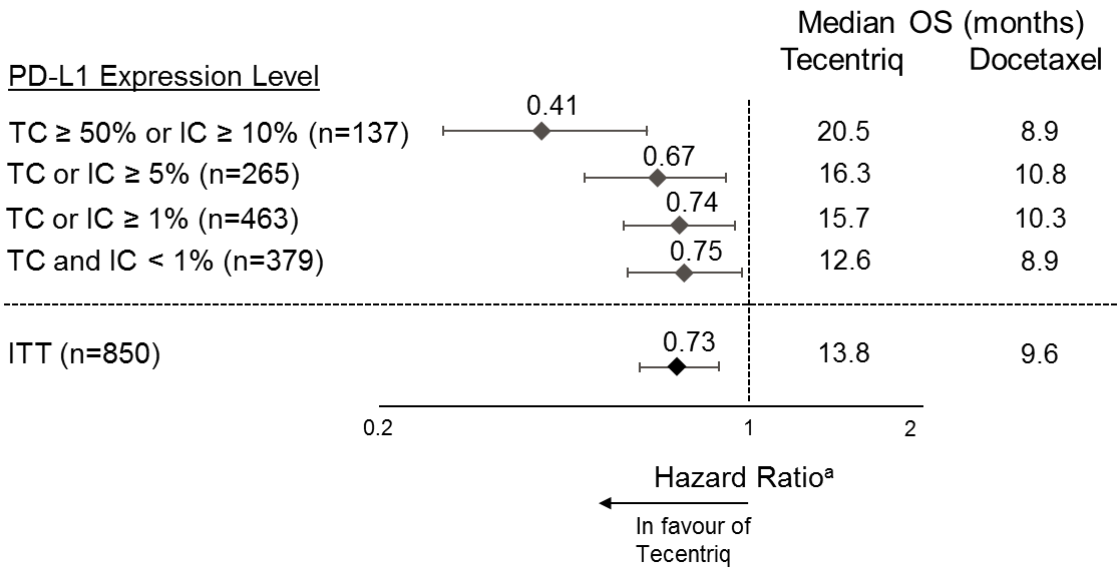


Figure 16: Forest plot of overall survival by PD-L1 expression in the primary analysis population (OAK)



[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 Table19. 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
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)

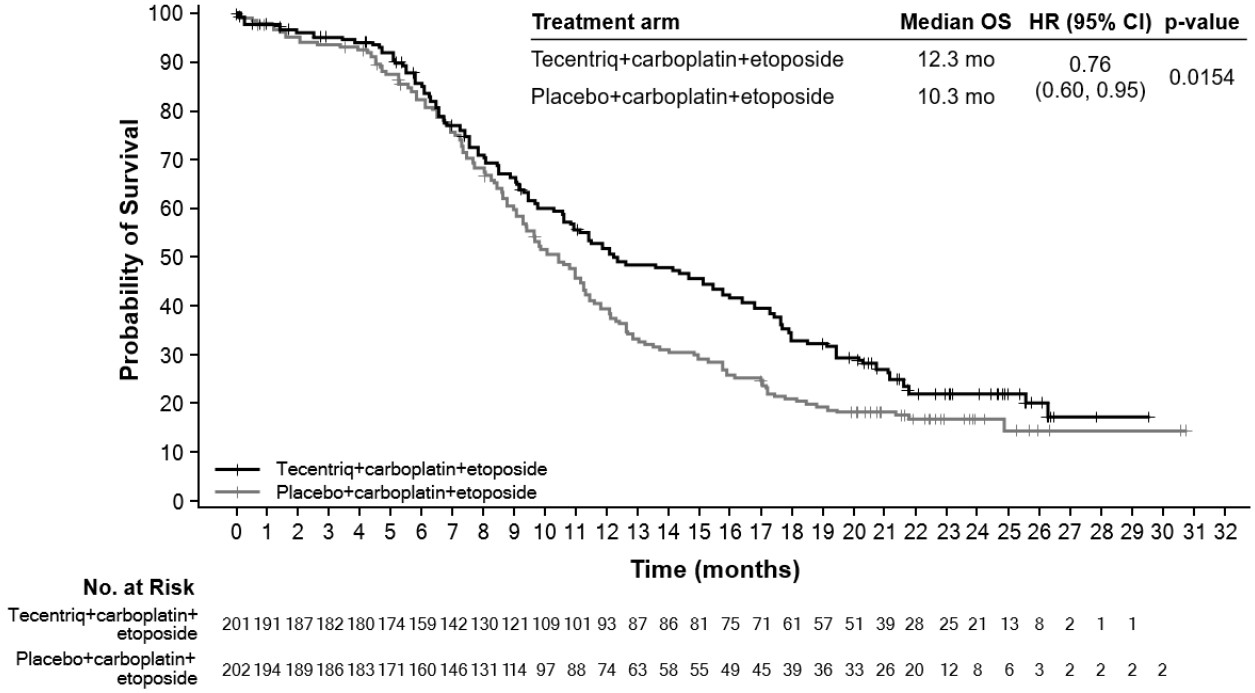
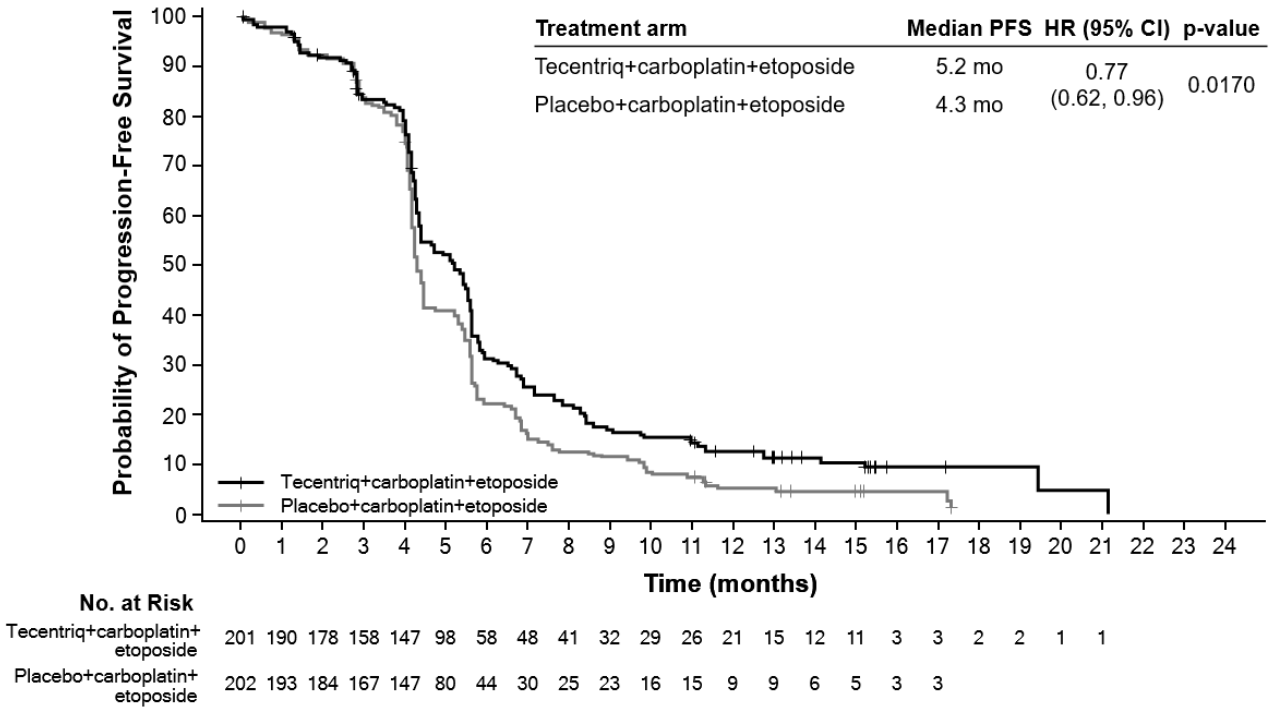


Figure 18: Kaplan-Meier curve for progression-free survival (IMpower133)



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 21 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 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	
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)	

Key efficacy endpoints	Atezolizumab + nab-paclitaxel	Placebo + nab-paclitaxel
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)

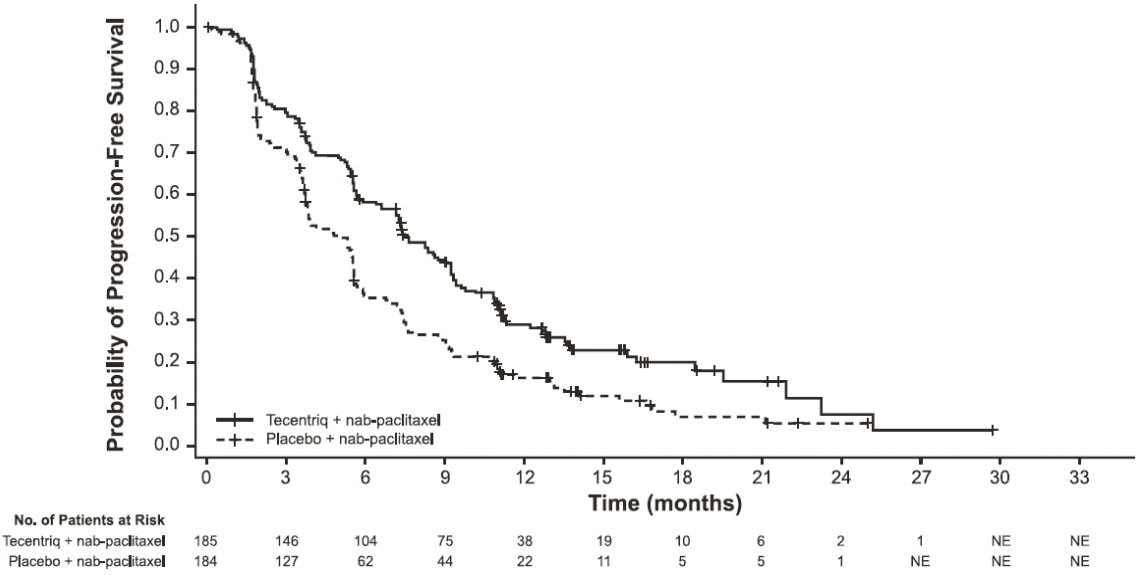
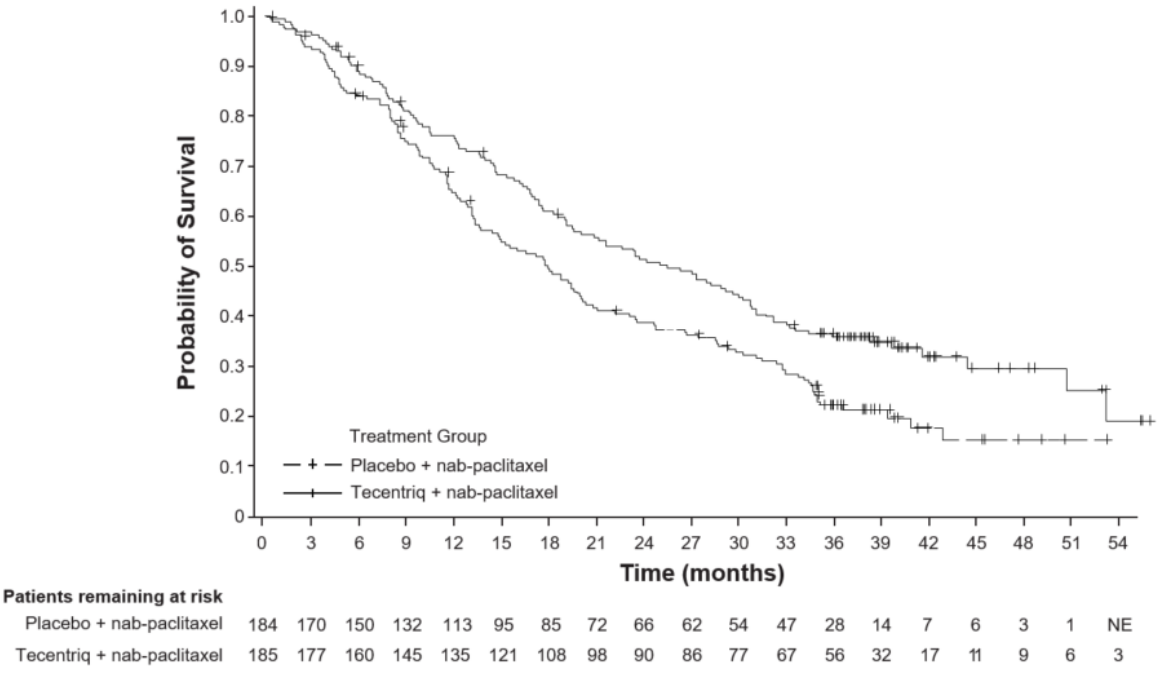


Figure 20: Kaplan-Meier curve for overall survival in patients with PD-L1 expression ≥ 1% (IMpassion130)



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+)

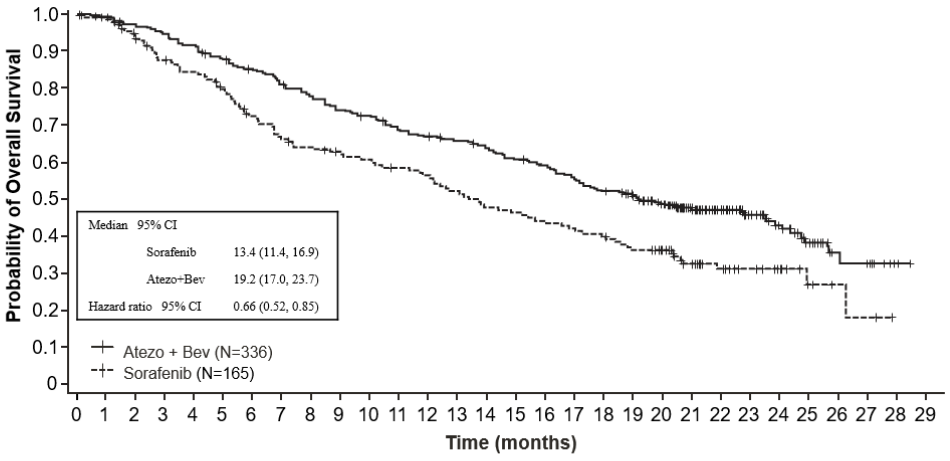
‡ Stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)

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)

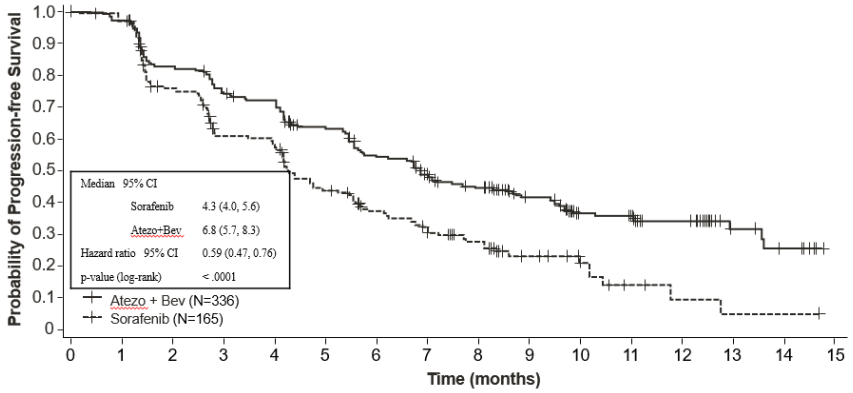


No. of Patients at Risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

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, 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
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

2 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 (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

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.

How much 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 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)
- allergic reaction (infusion-related reaction, hypersensitivity or anaphylaxis)
- flu-like illness
- chills
- inflammation of the intestines
- low platelet count, which may make you more likely to bruise or bleed
- 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)

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

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)
- 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
- infusion-related reactions
- 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)

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 (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.

Marketing Authorisation Holder

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Germany

Manufacturer

Roche Pharma AG
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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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 (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

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.

How much Tecentriq is given

The recommended dose of Tecentriq solution for injection is 1 875 mg every three weeks.

How 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)
- allergic reaction (infusion-related reaction, hypersensitivity or anaphylaxis)
- flu-like illness
- chills
- inflammation of the intestines
- low platelet count, which may make you more likely to bruise or bleed
- 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

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

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)
- 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
- infusion-related reactions
- 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)

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 (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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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.

次項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	ハラヴェン静注1mg	ヨンデリス点滴静注用0.25mg ヨンデリス点滴静注用1mg	ヴォトリエント錠200mg
一般名	アテゾリズマブ（遺伝子組換え）	エリブリンメシル酸塩	トラベクテジン	パゾパニブ塩酸塩
会社名	中外製薬株式会社	エーザイ株式会社	大鵬薬品工業株式会社	ノバルティスファーマ株式会社
効能 又は 効果	〈テセントリク点滴静注1200mg〉 ○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 〈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 〈製剤共通〉 ○切除不能な胞巣状軟部肉腫	手術不能又は再発乳癌，悪性軟部腫瘍	悪性軟部腫瘍	○悪性軟部腫瘍 ○根治切除不能又は転移性の腎細胞癌
添付文書 改訂年月	－	2022年1月改訂（第1版）	2024年6月改訂（第2版）	2024年2月改訂（第2版）

＊2024年2月改訂（第2版）
2020年12月改訂（第1版）

貯法：室温保存

有効期間：3年

日本標準商品分類番号
874291

承認番号	22400AMX01405000
販売開始	2012年11月

抗悪性腫瘍剤／キナーゼ阻害剤
パゾパニブ塩酸塩錠

ヴォトリエント®錠200mg
Votrient® Tablets 200mg

劇薬、処方箋医薬品
（注意－医師等の処方箋により使用すること）

NOVARTIS

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、本剤の投与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。

1.2 重篤な肝機能障害があらわれることがあり、肝不全により死亡に至った例も報告されているので、本剤投与開始前及び投与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。[8.1、11.1.1参照]

1.3 中等度以上の肝機能障害を有する患者では、本剤の最大耐用量が低いことから、これらの患者への投与の可否を慎重に判断するとともに、本剤を投与する場合には減量すること。[7.4、9.3.1、16.6.2、17.3.1参照]

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

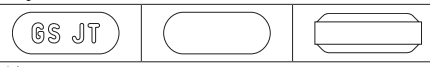
2.2 妊婦又は妊娠している可能性のある女性［9.5参照］

3. 組成・性状

3.1 組成

販売名	ヴォトリエント錠200mg
有効成分	1錠中パゾパニブ塩酸塩216.7mg（パゾパニブとして200mg）
添加剤	結晶セルロース、ポビドン、デンプングリコール酸ナトリウム、ステアリン酸マグネシウム、ヒプロメロース、酸化チタン、マクロゴール400、ポリソルベート80、三二酸化鉄

3.2 製剤の性状

販売名	ヴォトリエント錠200mg
性状	淡紅色カプセル形のフィルムコーティング錠
識別コード	GS JT
外形	
大きさ（約）	長径：14.3mm 短径：5.6mm 厚さ：5.3mm 質量：330mg

4. 効能又は効果

○悪性軟部腫瘍

○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

〈悪性軟部腫瘍〉

5.1 本剤の化学療法未治療例における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］

〈根治切除不能又は転移性の腎細胞癌〉

5.3 本剤の術後補助化学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

通常、成人にはパゾパニブとして1日1回800mgを食事の1時間以上前又は食後2時間以降に経口投与する。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

7.1 他の抗悪性腫瘍剤（サイトカイン製剤を含む）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 食後に本剤を投与した場合、Cmax及びAUCが上昇するとの報告がある。食事の影響を避けるため、用法及び用量を遵守して服用すること。［16.2.1参照］

7.3 副作用の発現により用量を減量して投与を継続する場合は、症状、重症度等に応じて、200mgずつ減量すること。また、本剤を減量後に増量する場合は、200mgずつ増量すること。ただし、800mgを超えないこと。

7.4 臨床試験において、中等度の肝機能障害を有する患者に対する最大耐用量は200mgであることが確認されており、中等度以上の肝機能障害を有する患者に対して本剤200mgを超える用量の投与は、最大耐用量を超えるため推奨されない。［1.3、9.3.1、16.6.2、17.3.1参照］

7.5 本剤を服用中に肝機能検査値異常が発現した場合は、以下の基準を考慮して、休薬、減量又は中止すること。［8.1、11.1.1参照］

肝機能検査値異常に対する休薬、減量及び中止基準

肝機能検査値	処置
3.0×ULN≦ALT≦8.0×ULN	投与継続（Grade 1以下あるいは投与前値に回復するまで1週間毎に肝機能検査を実施）
ALT＞8.0×ULN	Grade 1以下あるいは投与前値に回復するまで投与を中断し、投与を再開する場合は、400mgの投与とする。再開後、肝機能検査値異常（ALT＞3.0×ULN）が再発した場合は、投与を中止する。
ALT＞3.0×ULN、かつ総ビリルビン＞2.0×ULN （直接ビリルビン＞35%）	投与中止（Grade 1以下あるいは投与前値に回復するまで経過を観察）

GradeはNCI CTCAEによる。
ULN：基準値上限

8. 重要な基本的注意

8.1 肝不全、肝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中は定期的に肝機能検査を行うこと。［1.2、7.5、11.1.1参照］

8.2 高血圧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血圧測定を行い、血圧を十分観察すること。また、高血圧クリーゼがあらわれることがあるので、血圧の推移等に十分注意して投与すること。［9.1.1、11.1.2参照］

8.3 心機能不全が発現することから、本剤の投与開始前及び投与中は定期的に心エコー等の心機能検査を行うこと。［9.1.2、11.1.3参照］

8.4 QT間隔延長、心室性不整脈（Torsade de pointesを含む）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中は定期的に心電図検査及び電解質測定を行い、必要に応じて、電解質（カルシウム、マグネシウム、カリウム）を補正すること。［9.1.3、11.1.4参照］

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8.5 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。[9.1.7、11.1.13参照]

8.6 甲状腺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甲状腺機能の検査を実施すること。[11.1.10参照]

8.7 ネフローゼ症候群、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。[11.1.11参照]

8.8 毛髪変色又は皮膚の色素脱失があらわれることがあるので、本剤を投与する場合にはその内容を適切に患者に説明すること。また、剥脱性皮膚炎、手足症候群等の皮膚障害があらわれることがあるので、十分に観察を行い、異常が認められた場合には適切な処置を行うこと。必要に応じて患者に皮膚科受診等を指導すること。

8.9 血栓性微小血管症があらわれることがあるので、定期的に検査を行うなど観察を十分に行うこと。[11.1.15参照]

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 高血圧の患者

高血圧や心機能障害が悪化するおそれがある。[8.2、11.1.2参照]

9.1.2 心機能障害のリスク因子を有する患者（特に、アントラサイクリン系薬剤等の心毒性を有する薬剤、及び放射線治療による治療歴のある患者）

症状が悪化するおそれがある。[8.3、11.1.3参照]

9.1.3 QT間隔延長の既往のある患者

QT間隔延長や心室性不整脈をおこすおそれがある。[8.4、11.1.4参照]

9.1.4 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。[11.1.5、11.1.6参照]

9.1.5 脳転移を有する患者

臨床試験において、転移部位からの出血が報告されている。[11.1.8参照]

9.1.6 肺転移を有する患者

気胸が悪化又は発現するおそれがある。また、臨床試験において、転移部位からの出血が報告されている。[11.1.8参照]

9.1.7 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。[8.5、11.1.13参照]

9.2 腎機能障害患者

9.2.1 重度の腎機能障害患者

臨床試験では除外されている。

9.3 肝機能障害患者

9.3.1 中等度以上の肝機能障害患者

本剤を減量するとともに、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。[1.3、7.4、16.6.2、17.3.1参照]

9.4 生殖能を有する者

妊娠可能な女性に対しては、本剤投与中及び投与終了後一定期間は避妊を行うよう指導すること。[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。動物実験では、ラットで母体毒性及び催奇形性（心血管奇形及び骨化遅延）（3mg/kg/日以上）、胎児体重の低値及び胚致死作用（10mg/kg/日以上）、雌受胎率の低値（300mg/kg/日）、ウサギで母体毒性、流産（30mg/kg/日以上）及び胎児体重の低値（3mg/kg/日以上）が報告されている。[2.2、9.4参照]

9.6 授乳婦

授乳しないことが望ましい。ヒトで乳汁移行に関するデータはないが、BCRPの基質であるため、乳汁移行の可能性がある。

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。本剤の作用機序より、出生後早期の発達において臓器の成長や成熟に重大な影響を与えるおそれがある。

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。

10. 相互作用

*In vitro*試験で、本剤の代謝には主にチトクロームP450（CYP）3A4が、一部CYP1A2及び2C8が関与することから、CYP3A4阻害剤及び誘導剤は本剤の薬物動態に影響を及ぼす可能性がある。また、本剤はCYP（2B6、2C8、2E1及び3A4）、UGT1A1及びOATP1B1を阻害し、P-糖蛋白質（Pgp）及びBCRPの基質であった。[16.4、16.7参照]

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
プロトンポンプ阻害剤 エソメプラゾール等	エソメプラゾールとの併用により、本剤のAUC及びCmaxがそれぞれ約40%及び42%低下したとの報告があるので、プロトンポンプ阻害剤との併用は可能な限り避けること。	プロトンポンプ阻害剤が胃内の酸分泌を抑制することで、本剤の溶解度が低下し吸収が低下する可能性がある。
CYP3A4阻害剤 ケトコナゾール等	ケトコナゾールとの併用により、本剤のAUC及びCmaxは、それぞれ約66%及び45%増加した。 CYP3A4阻害作用のない又は弱い薬剤への代替を考慮すること。併用が避けられない場合には、副作用の発現・増強に注意し、減量等を考慮すること。	これらの薬剤がCYP3A4活性を阻害することにより、本剤の代謝が阻害され、血中濃度が上昇する可能性がある。
グレープフルーツ（ジュース）	本剤投与時はグレープフルーツ（ジュース）を摂取しないよう注意すること。	
CYP3A4誘導剤 カルバマゼピン フェニトイン等	カルバマゼピン、フェニトイン等との併用により、本剤のAUC及びCmaxは、それぞれ約54%及び35%低下した。 CYP3A4誘導作用のない又は弱い薬剤への代替を考慮すること。併用に際しては、本剤の有効性が減弱する可能性があることを考慮すること。	これらの薬剤がCYP3A4活性を誘導することにより、本剤の代謝が誘導され、血中濃度が低下する可能性がある。
パクリタキセル	本剤は血漿中パクリタキセルのAUC及びCmaxをそれぞれ約26%及び31%増加させた。	本剤がCYP3A4及びCYP2C8活性を阻害することにより、パクリタキセルの代謝が阻害され、血中濃度が上昇する可能性がある。
ラパチニブ	ラパチニブとの併用により本剤のAUC及びCmaxは、それぞれ約59%及び51%増加した。	ラパチニブはCYP3A4、Pgp及びBCRPの基質であり阻害作用を有することによる。
シンバスタチン	併用によりALTが上昇するおそれがある。	機序は不明である。
抗不整脈薬 キニジン プロカインアミド ジソピラミド等 QT間隔を延長させる可能性のある薬剤 クラリスロマイシン イミプラミン ピモジド等	QT間隔延長や心室性不整脈をおこすおそれがある。	本剤及びこれらの薬剤はいずれもQT間隔を延長させるおそれがあり、併用により作用が増強する可能性がある。

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 肝不全（頻度不明）、肝機能障害（28.4%）

肝不全、AST、ALT、ビリルビン及びγ-GTP上昇等を伴う肝機能障害があらわれることがあり、死亡に至る例が報告されている。[1.2、7.5、8.1参照]

11.1.2 高血圧（42.0%）、**高血圧クリーゼ**（0.6%）
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。管理できない重症の高血圧が認められた場合には休薬すること。[8.2、9.1.1参照]

11.1.3 心機能障害（2.8%）
うっ血性心不全及び左室駆出率低下等の心機能障害があらわれることがある。[8.3、9.1.2参照]

11.1.4 QT間隔延長（0.6%）、**心室性不整脈（Torsade de pointesを含む）**（0.1%）
[8.4、9.1.3参照]

11.1.5 動脈血栓性事象（1.8%）
心筋梗塞、狭心症、虚血性脳卒中、一過性脳虚血発作、心筋虚血等の動脈血栓性事象があらわれることがある。[9.1.4参照]

11.1.6 静脈血栓性事象（1.1%）
静脈血栓症及び肺塞栓症があらわれることがある。[9.1.4参照]

＊**11.1.7 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)]。

11.1.8 出血（13.2%）
腫瘍関連出血を含む、脳出血（0.5%）、喀血（1.3%）、消化管出血（4.1%）、血尿（1.8%）、肺出血（0.1%）、鼻出血（4.9%）等の出血があらわれることがある。[9.1.5、9.1.6参照]

11.1.9 消化管穿孔（頻度不明）、**消化管瘻**（0.5%）

11.1.10 甲状腺機能障害（12.6%）
[8.6参照]

11.1.11 ネフローゼ症候群（0.1%）、**蛋白尿**（12.5%）
[8.7参照]

11.1.12 感染症（8.6%）
好中球減少の有無にかかわらず重篤な感染症があらわれることがある。

11.1.13 創傷治癒遅延（0.4%）
創傷が治癒するまで本剤の投与を中止すること。[8.5、9.1.7参照]

11.1.14 間質性肺炎（0.1%）

11.1.15 血栓性微小血管症（0.1%）
血栓性血小板減少性紫斑病、溶血性尿毒症症候群等の血栓性微小血管症があらわれることがある。破砕赤血球を伴う貧血、血小板減少、腎機能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。[8.9参照]

11.1.16 可逆性後白質脳症症候群（頻度不明）
可逆性後白質脳症症候群に一致する徴候や症状（高血圧（伴わない例もある）、頭痛、覚醒低下、精神機能変化、及び皮質盲を含めた視力消失など）が認められた場合は、本剤の投与を中止し、高血圧管理を含め、適切な処置を行うこと。

11.1.17 膵炎（3.8%）
膵炎を示唆する症状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。

11.1.18 網膜剥離（0.1%）
飛蚊症、光視症、視野欠損、視力低下等が認められた場合には、眼科検査を実施し、投与を中止するなど適切な処置を行うこと。

11.2 その他の副作用

	30%以上	5～30%未満	5%未満
代謝	食欲減退	体重減少	高カリウム血症、高血糖
神経系	—	味覚異常、頭痛	浮動性めまい、末梢性ニューロパチー、不眠症、傾眠
循環器	—	—	徐脈（無症候性）
呼吸器	—	発声障害	呼吸困難、咳嗽、気胸
消化器	下痢、悪心	嘔吐、腹痛、消化不良、口内炎、便秘	口内乾燥、腹部膨満、口腔咽頭痛、胃炎、しゃっくり、痔核、嚥下障害、鼓腸
皮膚	毛髪変色	手掌・足底発赤知覚不全症候群、発疹、脱毛症、皮膚色素減少、皮膚乾燥	剥脱性発疹、そう痒症、皮膚障害、爪の障害、ざ瘡、皮膚潰瘍、毛髪成長異常
筋骨格	—	筋骨格痛	筋肉痛、関節痛、筋痙縮
血液	—	血小板減少症、好中球減少症、白血球減少症、貧血	リンパ球減少症、赤血球増加症
臨床検査	—	—	血中クレアチニン増加、リパーゼ増加、血中アルカリホスファターゼ増加、LDH異常、血中ナトリウム減少、血中カルシウム減少、血中マグネシウム減少、血中尿素増加、血中リン減少、血中ブドウ糖減少、血中アルブミン減少
その他	疲労	粘膜炎、無力症	末梢性浮腫、顔面浮腫、胸痛、霧視、ほてり、発熱、多汗症、脱水、腫瘍疼痛、浮腫、悪寒、挫傷、不規則月経

注）副作用の頻度については、悪性軟部腫瘍患者を対象とした国際共同第Ⅲ相臨床試験並びに腎細胞癌患者を対象とした国際共同第Ⅲ相臨床試験及び外国第Ⅲ相臨床試験に基づき記載した。

14. 適用上の注意

14.1 薬剤交付時の注意
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。

15. その他の注意

15.1 臨床使用に基づく情報
本剤とペメトレキセド及びラパチニブを併用した固形癌患者を対象とした臨床試験において、毒性の増大、死亡率の増加が懸念されたため早期に中止されている。

15.2 非臨床試験に基づく情報
15.2.1 マウスを用いた反復投与毒性試験において、1000mg/kg/日の雌で増殖性変化（好酸性変異肝細胞巣及び肝細胞腺腫がそれぞれ2及び1例）が認められた。

15.2.2 幼若ラットの生後9～21日まで投与した試験において、30mg/kg/日以上で体重増加抑制及び早期死亡が認められ、生後21～62日まで投与した試験においては、10mg/kg/日以上で大腿骨の短小が認められた（これらの用量はいずれも成熟ラットにおいて同様の影響がみられた用量よりも低用量）。

16. 薬物動態

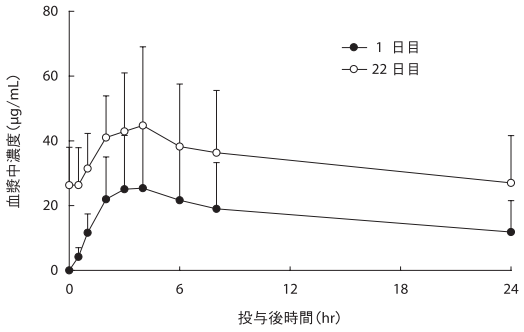
16.1 血中濃度

16.1.1 経口投与
固形癌患者13例に本剤を1日1回反復経口投与したときの薬物動態パラメータは下表のとおりであった。本剤の投与量と1日目のCmax及び$AUC_{0\text{-}24}$との間に、用量比例性は認められなかった。また、本剤の血漿中からの消失は緩やかであり、反復投与で蓄積性を示すと考えられた[2)]。

日本人固形癌患者に本剤を単回及び反復経口投与したときの
血漿中パゾパニブの薬物動態パラメータ

パラメータ	400/800mg[注1),注2)] (N=3)		800mg (N=7)		1000mg[注2)] (N=3)	
	1日目	22日目	1日目	22日目	1日目	22日目
Cmax (μg/mL)	25.1 (34.0%)	55.8 (35.2%)	22.9 (69.5%)	40.6 (47.7%)	21.3 (118.1%)	53.9 (55.4%)
tmax (hr)	4.00 (3.00-23.72)	2.50 (2.00-3.00)	2.98 (1.97-5.95)	2.52 (1.92-3.97)	3.00 (2.97-3.00)	4.00 (3.00-4.05)
$AUC_{0\text{-}24}$ (μg·hr/mL)	402 (17.7%)	962 (46.3%)	325 (76.7%)	677 (45.5%)	305 (128.6%)	759 (63.8%)
$t_{1/2}$ (hr)	28.4 (35.9%)	40.1 (67.2%)	42.5 (31.6%)	37.8 (47.2%)	33.0 (23.8%)	21.4 (60.7%)
C_{24} (μg/mL)	14.8 (12.7%)	34.6 (47.2%)	9.1 (90.1%)	22.0 (48.4%)	8.5 (139.6%)	21.1 (80.5%)

幾何平均値（CVb%）、tmax：中央値（範囲）
注1）1日目に400mgを投与し、2日目以降は800mgを投与
注2）本剤の承認された用法及び用量は、1日1回800mgである。



日本人固形癌患者に本剤800mgを単回及び反復経口投与したときの血漿中パゾパニブ濃度推移（平均値＋標準偏差、n＝7）

16.1.2 静脈内投与

外国人固形癌患者3例に承認用法・用量（1日1回経口800mg）とは異なる5mgを静脈内投与後のクリアランスは0.206～0.347L/hr、Vssは9.2～13.1Lであった[3]。

16.2 吸収

16.2.1 食事の影響

外国人固形癌患者35例を対象に本剤800mgを単回経口投与したときのAUC及びCmaxは絶食下に比べて、高脂肪食摂食後のAUCは絶食下の約2.3倍に、低脂肪食摂食後では約1.9倍に増加し、高脂肪食及び低脂肪食摂食後のCmaxはいずれも約2.1倍に増加した[4]。［7.2参照］

16.3 分布

本剤（10～100μg/mL）のヒト血漿蛋白結合率は*in vitro*で99%超であった[5]。また、本剤は主に血清アルブミン（99%超）及びα_1-酸性糖蛋白質（96%超）に結合すると考えられた[6]。

外国人固形癌患者3例に^{14}C-標識体400mgを単回経口投与したときの放射能の血液/血漿比は0.59～0.93と血球移行性は低かった[3]。

*In vitro*試験で、本剤はPgp及びBCRPの基質であった[7,8]。

16.4 代謝

*In vitro*試験で、本剤の一部は酸化的に代謝され、この代謝には主にCYP3A4が、一部CYP1A2及び2C8が関与する[9]。

固形癌患者13例に本剤800mg並びに、承認用法・用量（1日1回800mg）とは異なる400及び1000mgを経口投与後の血漿中には、おもに未変化体が検出された。代謝物である脱メチル体及び一酸化体なども検出されたが、個体間のばらつきが大きく、未変化体に対する割合はいずれも5%未満であった[2]。［10.参照］

16.5 排泄

外国人固形癌患者3例に^{14}C-標識体を単回経口投与したときの放射能の主排泄経路は糞中であり、投与後168時間までの排泄率は糞で約82.2%、尿で約2.6%であった。糞中の主成分は未変化体であり、投与量の平均67%であった[3]。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

腎機能低下者における本剤の特別な薬物動態は検討していない。クレアチニンクリアランス30～150mL/minの外国人健康被験者及び癌患者408例で母集団薬物動態を解析した結果、腎機能による本剤のクリアランスに有意な影響はみられていない[10]。

16.6.2 肝機能障害患者

外国人肝機能障害患者98例（肝機能正常者23例、軽度肝機能低下者23例、中等度肝機能低下者20例、重度肝機能低下者32例）に本剤を1日1回反復経口投与したときの安全性及び薬物動態について評価した（薬物動態解析対象例69例）。軽度の肝機能低下患者12例に本剤800mgを1日1回反復経口投与したときのCmax及び$AUC_{0\text{-}24}$は肝機能正常者18例と同程度であった。肝機能低下患者（中等度11例及び重度14例）に200mgを1日1回反復経口投与したときのCmax及び$AUC_{0\text{-}24}$の中央値は、肝機能正常者に800mgを1日1回反復経口投与したときのCmax及び$AUC_{0\text{-}24}$のそれぞれ約43%及び29%、約18%及び15%であった[11]。［1.3、7.4、9.3.1、17.3.1参照］

外国人の肝機能低下患者に本剤を反復経口投与したときの血漿中パゾパニブの薬物動態パラメータ

群（N）	投与量（mg）	Cmax（μg/mL）	tmax（hr）	C_{24}（μg/mL）	$AUC_{0\text{-}24}$（μg・hr/mL）
A（18）	800	52.0（17.1-85.7）	2.8（1.0-24.2）	29.8（10.3-750）	888.2（345.5-1482）
B（12）	800	33.5（11.3-104.2）	3.0（0.5-24.4）	24.0（8.3-74.6）	774.2（214.7-2034.4）
C（11）	200	22.2（4.2-32.9）	2.0（0.0-4.0）	16.2（3.1-24.2）	256.8（65.7-487.7）
D（14）	200	9.4（2.4-24.3）	3.0（1.0-8.0）	5.7（1.5-18.4）	130.6（46.9-473.2）

中央値（範囲）、A：肝機能正常者、B：軽度肝機能低下患者、C：中等度肝機能低下患者、D：重度肝機能低下患者
上記とは異なる用量で投与された14例については記載を省略

16.7 薬物相互作用

*In vitro*試験で、本剤はCYP（1A2、2B6、2C8、2C9、2C19、2D6、2E1及び3A4）及びUGT1A1を阻害し、IC_{50}はそれぞれ7.9～18μM（3.5～7.9μg/mL）及び1.2μM（0.5μg/mL）であった[12]。

外国人固形癌患者24例を対象に本剤がCYP代謝に及ぼす影響について、各種CYPプローブを用いて検討した結果、本剤800mgの1日1回投与ではカフェイン（CYP1A2の基質）、ワルファリン（CYP2C9の基質）及びオメプラゾール（CYP2C19の基質）の薬物動態に意義のある影響を及ぼさなかった。一方、本剤はミダゾラム（CYP3A4の基質）のAUC及びCmaxを約30%増加させ、デキストロメトルファン（CYP2D6の基質）を経口投与後の尿中のデキストロメトルファン／デキストルファン比を33～64%増加させた[13]。

また、*in vitro*試験で、本剤はOATP1B1を阻害し、IC_{50}は0.79μM（0.3μg/mL）であった[14]。［10.参照］

17. 臨床成績

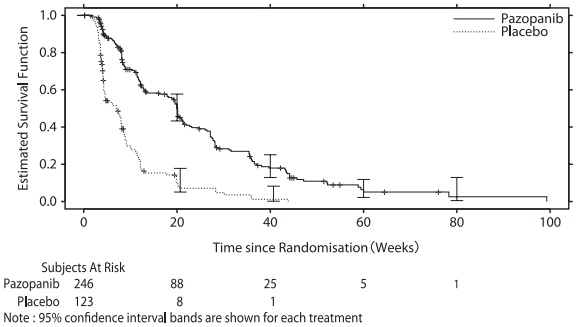
17.1 有効性及び安全性に関する試験

〈悪性軟部腫瘍〉

17.1.1 国際共同第Ⅲ相臨床試験

アントラサイクリン系薬剤を含む前治療に対して病勢進行が認められた転移病変を有する悪性軟部腫瘍患者を対象とした、二重盲検、プラセボ対照試験で、本剤800mgを1日1回経口投与した時の有効性及び安全性を評価した。本試験では、脂肪肉腫、横紋筋肉腫（多形型又は胞巣型を除く）、軟骨肉腫、骨肉腫、ユーイング腫瘍／未熟神経外胚葉性腫瘍、消化管間質腫瘍、隆起性皮膚線維肉腫、炎症性筋線維芽細胞肉腫、悪性中皮腫、子宮の中胚葉性混合腫瘍を組入れ対象から除外した。有効性解析対象例は369例（本剤群246例、プラセボ群123例）であり、このうち47例（本剤群31例、プラセボ群16例）が日本人であった。

主要評価項目である無増悪生存期間（PFS）の中央値は、本剤群で20.0週、プラセボ群で7.0週であり、本剤群のPFSはプラセボ群と比して有意に延長した（ハザード比：0.35、95%信頼区間：0.26～0.48、p＜0.001、両側層別ログランク検定）。



PFSのKaplan-Meier曲線（全体集団、独立判定）

副次的評価項目である全生存期間（OS）の中央値は、本剤群で12.6ヵ月、プラセボ群で10.7ヵ月であり、事前に規定した有意水準（p≤0.04434）には至らなかった（ハザード比：0.87、95.57%信頼区間：0.67～1.13、p＝0.256、両側層別ログランク検定）[15]。

副作用は本剤を投与された240例中（日本人31例を含む）219例（91.3%）に認められた。主な副作用は下痢（130例、54.2%）、疲労（126例、52.5%）、悪心（116例、48.3%）、高血圧（94例、

39.2%）、毛髪変色（93例、38.8%）、食欲減退（82例、34.2%）、体重減少（73例、30.4%）であった。[5.2参照]

17.1.2 外国第Ⅱ相臨床試験

再発又は難治性の悪性軟部腫瘍患者を対象とした、非盲検、非対照試験で、本剤800mg（製造販売用製剤とは異なる製剤）を1日1回経口投与した時の有効性及び安全性について、腫瘍組織型別（脂肪肉腫、平滑筋肉腫、滑膜肉腫、その他）に評価した。本試験では、胎児型横紋筋肉腫、軟骨肉腫、骨肉腫、ユーイング腫瘍／未熟神経外胚葉性腫瘍、消化管間質腫瘍、隆起性皮膚線維肉腫、炎症性筋線維芽細胞肉腫、悪性中皮腫、子宮の中胚葉性混合腫瘍を組入れ対象から除外した。有効性解析対象例は138例であった。

主要評価項目である投与12週時のprogression-free rate（PF率：その時点の評価がCR、PR又はSDであった被験者の割合）は以下のとおりであった[16,17]。

投与12週時のPF率

	脂肪肉腫（N＝19）	平滑筋肉腫（N＝41）	滑膜肉腫（N＝37）	その他（N＝41）
12週時評価				
CR	0	0	0	0
PR	0	1	4	1
SD	5	16	14	16
PF率（%）（90%信頼区間）	26（11.0，47.6）	41（28.4，55.5）	49（34.3，63.2）	41（28.4，55.5）

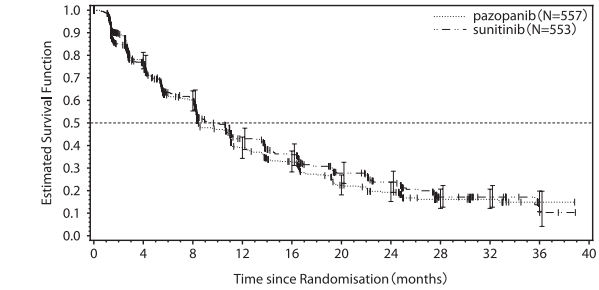
副作用は本剤を投与された142例中127例（89%）に認められた。主な副作用は高血圧（58例、41%）、皮膚色素減少（毛髪を含む）（53例、37%）、疲労（52例、37%）、悪心（51例、36%）、下痢（44例、31%）、嘔吐（35例、25%）であった。[5.2参照]

〈根治切除不能又は転移性の腎細胞癌〉

17.1.3 国際共同第Ⅲ相臨床試験

全身治療による治療歴のない局所進行性又は転移性腎細胞癌患者に本剤800mgを1日1回経口投与した時の有効性及び安全性について、スニチニブ（50mgを1日1回4週間経口投与後に2週間休薬の6週間を1サイクルとして投与）を対照とした非盲検試験で評価した。有効性解析対象例は1110例[注1)]（本剤群557例、スニチニブ群553例）であり、このうち60例（本剤群29例、スニチニブ群31例）が日本人であった。組織学的分類では有効性解析対象1110例のうち1031例（92.9%）が淡明細胞型であった。

主要評価項目であるPFSの中央値は、本剤群で8.4ヵ月、スニチニブ群で9.5ヵ月であり、事前に規定した本剤群のスニチニブ群に対する非劣性の判断基準（ハザード比の95%信頼区間の上限値が1.25を下回る）を満たした（ハザード比：1.0466、95%信頼区間：0.8982～1.2195）。



PFSのKaplan-Meier曲線（全体集団、独立判定）

副次的評価項目であるOSの中間解析（2012年5月時点）では、OSの中央値は、本剤群で28.4ヵ月、スニチニブ群で29.3ヵ月であった（ハザード比：0.908、95%信頼区間：0.762～1.082、p＝0.275、両側層別ログランク検定）[18)]。

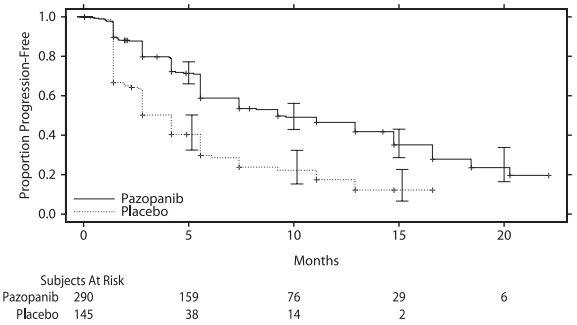
副作用は本剤を投与された554例中（日本人29例を含む）538例（97%）に認められた。主な副作用は下痢（321例、58%）、疲労（273例、49%）、高血圧（240例、43%）、悪心（223例、40%）、手掌・足底発赤知覚不全症候群（159例、29%）であった。

注1）本試験に準じてアジア（中国、韓国及び台湾）で実施された第Ⅱ相臨床試験の被験者183例（本剤群93例、スニチニブ群90例）を含む。

17.1.4 外国第Ⅲ相臨床試験

局所進行性又は転移性腎細胞癌患者（未治療の患者又は1レジメンのサイトカイン治療歴のある患者）を対象とした、プラセボ対照、二重盲検試験で、本剤800mgを1日1回経口投与した時の有効性及び安全性を評価した。有効性解析対象例は435例（本剤群290例、プラセボ群145例）であり、組織学的分類ではこのうち434例（99.8%）が淡明細胞型であった。

主要評価項目であるPFSの中央値は、本剤群で9.2ヵ月、プラセボ群で4.2ヵ月であり、本剤群のPFSはプラセボ群と比して有意に延長した（ハザード比：0.46、95%信頼区間：0.34～0.62、p＜0.0000001、片側層別ログランク検定）。



PFSのKaplan-Meier曲線（全体集団、独立判定）

副次的評価項目であるOSの中央値は、本剤群で22.9ヵ月、プラセボ群で20.5ヵ月であり、有意な差は認められなかった（ハザード比：0.91、95%信頼区間：0.71～1.16、p＝0.224、片側層別ログランク検定）[19)]。

副作用は本剤を投与された290例中257例（89%）に認められた。主な副作用は下痢（44%）、高血圧（37%）、毛髪変色（37%）であった。

17.3 その他

17.3.1 肝機能障害患者を対象とした試験

外国人肝機能障害患者98例（肝機能正常者23例、軽度肝機能低下者23例、中等度肝機能低下者20例、重度肝機能低下者32例）に本剤を1日1回反復経口投与したときの安全性及び薬物動態について評価した（安全性解析対象例97例）。400mgコホートの中等度肝機能障害患者2/4例で用量制限毒性（Grade 4のAST増加1例、Grade 4のAST増加、Grade 4のALT増加及びGrade 3の高ビリルビン血症が1例）が認められ、中等度以上の肝機能障害患者での最大耐用量は200mgであった[11)]。[1.3、7.4、9.3.1、16.6.2参照]

肝機能障害患者での用量制限毒性

投与量（mg）	肝機能			
	正常	軽度低下	中等度低下	重度低下
100	－	－	－	1/6例 ・ビリルビン増加（Grade 4）
200	－	－	1/12例 ・ビリルビン増加（Grade 3）	1/11例 ・下痢（Grade 3）
400	－	1/6例 ・AST増加（Grade 4）	2/4例 ・AST増加（Grade 4） ・AST増加（Grade 4）、ALT増加（Grade 4）、ビリルビン増加（Grade 3）	－
800	0/18例	1/13例 ・胃出血（Grade 5）	－	－

用量制限毒性が評価できなかった27例は記載を省略

18. 薬効薬理

18.1 作用機序

18.1.1 パゾパニブは、血管内皮細胞増殖因子受容体（VEGFR-1、VEGFR-2及びVEGFR-3）、血小板由来増殖因子受容体（PDGFR-α及びPDGFR-β）、並びに幹細胞因子受容体（c-Kit）のリン酸化を阻害した。また、パゾパニブは、マウスに投与した時に肺のVEGFR-2のリン酸化を阻害した[20)]。

18.1.2 パゾパニブは、マウス脈絡膜にレーザー照射で誘発した血管新生、並びにウサギ脈絡膜に血管内皮細胞増殖因子及び塩基性線維芽細胞増殖因子で誘発した血管新生に対して、阻害作用を示した[20)]。

18.2 抗腫瘍効果

18.2.1 悪性軟部腫瘍に対する作用

(1) パゾパニブは、ヒト滑膜肉腫由来SYO-1細胞株、HS-SY-Ⅱ細胞株、1273/99細胞株及びFuji細胞株に対して細胞増殖抑制作用を示した[21]（*in vitro*）。

(2) パゾパニブは、ヒト脂肪肉腫由来SW-872細胞株及びヒト滑膜肉腫由来SYO-1細胞株を皮下移植したマウスにおいて、腫瘍の増殖を抑制した[21,22]（*in vivo*）。

18.2.2 腎細胞癌に対する作用

パゾパニブは、ヒト腎細胞癌由来Caki-2細胞株、ACHN細胞株又はA498細胞株を皮下移植したマウスにおいて、腫瘍の増殖を抑制した[23]（*in vivo*）。

19. 有効成分に関する理化学的知見

一般的名称

パゾパニブ塩酸塩（Pazopanib Hydrochloride）

化学名

5-{4-[(2,3-ジメチル-2*H*-インダゾール-6-イル)(メチル)アミノ]ピリミジン-2-イル}アミノ)-2-メチルベンゼンスルホンアミド一塩酸塩

分子式

$C_{21}H_{23}N_7O_2S \cdot HCl$

分子量

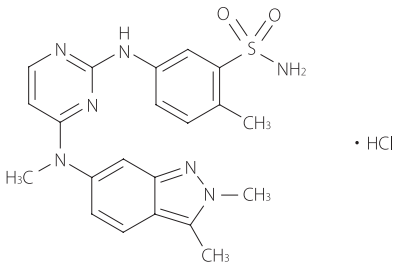
473.98

性状

パゾパニブ塩酸塩は白色～わずかに黄色の粉末である。

pH1.0の緩衝液に溶けにくく、pH7.0の緩衝液にほとんど溶けない。また、メタノールに溶けにくく、水又はエタノールに極めて溶けにくい。

化学構造式



・HCl

22. 包装

20錠［10錠（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）Inada-Inoue, M. et al.：Cancer Chemother. Pharmacol. 2014；73：673-683 ［20153683］

3）社内資料：海外第Ⅰ相試験（VEG10004）（2012年9月28日承認、CTD2.7.6 VEG10004試験） ［20155743］

4）社内資料：海外第Ⅰ相試験（VEG10005）（2012年9月28日承認、CTD2.7.6 VEG10005試験） ［20155740］

5）社内資料：分布に関する試験（1）（2012年9月28日承認、CTD2.7.2.2.1.1） ［20155741］

6）社内資料：分布に関する試験（2）（2012年9月28日承認、CTD2.7.2.2.1.2） ［20155742］

7）社内資料：分布に関する試験（3）（2012年9月28日承認、CTD2.6.4.4.6） ［20155744］

8）社内資料：分布に関する試験（4）（2012年9月28日承認、CTD2.6.4.4.7） ［20155745］

9）社内資料：代謝に関する試験（1）（2012年9月28日承認、CTD2.7.2.2.1.4） ［20155746］

10）社内資料：海外第Ⅰ,Ⅱ及びⅢ相試験（母集団薬物動態）（2012年9月28日承認、CTD2.7.2.3.2） ［20155832］

11）社内資料：海外第Ⅰ相試験（NCI-8063）（2012年9月28日承認、CTD2.7.6 NCI-8063試験） ［20155747］

12）社内資料：相互作用に関する試験（1）（2012年9月28日承認、CTD 2.6.4.5.5.1.1） ［20155748］

13）社内資料：海外第Ⅰ相試験（VEG10007）（2012年9月28日承認、CTD2.7.6 VEG10007試験） ［20155749］

14）社内資料：相互作用に関する試験（2）（2012年9月28日承認、CTD2.6.4.4.10） ［20155750］

15）社内資料：国際共同第Ⅲ相試験（VEG110727）（2012年9月28日承認、CTD2.7.6 VEG110727試験） ［20155751］

16）社内資料：海外第Ⅱ相試験（VEG20002）（2012年9月28日承認、CTD2.7.6 VEG20002試験） ［20155752］

17）van Glabbeke, M. et al.：Eur. J. Cancer. 2002；38：543-549 ［20152755］

18）社内資料：国際共同第Ⅲ相試験（VEG108844）（2014年3月17日承認、CTD2.7.6 VEG108844試験） ［20155753］

19）社内資料：海外第Ⅲ相試験（VEG105192）（2014年3月17日承認、CTD2.7.6 VEG105192試験） ［20155754］

20）Kumar, R. et al.：Mol. Cancer Ther. 2007；6：2012-2021 ［20153573］

21）Hosaka, S. et al.：J. Orthop. Res. 2012；30：1493-1498 ［20153574］

22）社内資料：薬効薬理試験（1）（2012年9月28日承認、CTD 2.6.2.2.2.3.1） ［20155755］

23）社内資料：薬効薬理試験（2）（2012年9月28日承認、CTD 2.6.2.2.2.3.2） ［20155756］

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

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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投与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。

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の成分に対し重篤な過敏症の既往歴のある患者［11.1.4参照］

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	ヨンデリス点滴静注用0.25mg	ヨンデリス点滴静注用1mg
有効成分	1バイアル中 トラベクテジン0.25mg	1バイアル中 トラベクテジン1mg
添加剤	精製白糖100mg、リン酸二水素カリウム6.8mg、pH調節剤	精製白糖400mg、リン酸二水素カリウム27.2mg、pH調節剤

3.2 製剤の性状

販売名	ヨンデリス点滴静注用0.25mg	ヨンデリス点滴静注用1mg
性状	白色の塊又は粉末（凍結乾燥注射剤）	
pH注）	3.6～4.8	
浸透圧比注）	約1（生理食塩液に対する比）	

注）トラベクテジン0.25mg相当量/5mL生理食塩液又はトラベクテジン1mg相当量/20mL生理食塩液

4. 効能又は効果

悪性軟部腫瘍

5. 効能又は効果に関連する注意

5.1 本剤の化学療法未治療例における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病理組織型以外の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。

5.3「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理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。

6. 用法及び用量

通常、成人にはトラベクテジンとして1回1.2mg/m^2（体表面積）を24時間かけて点滴静注し、少なくとも20日間休薬する。これを1サイクルとして、投与を繰り返す。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

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 薬液が漏出した場合、重度の組織障害を起こすおそれがあるので、中心静脈から投与すること。［14.3.1、14.3.2参照］

7.3 本剤の投与にあたっては、以下の基準を参考に必要に応じて、休薬又は減量すること。［8.1-8.3参照］

・本剤投与開始前の臨床検査値が「投与開始基準」の基準値を満たさない場合は、本剤を投与しない又は基準値に回復するまで投与を延期すること。

投与開始基準

項目	基準値
好中球数	1500/mm^{3}以上
ヘモグロビン	9.0g/dL以上
血小板数	10×10^4/mm^{3}以上
アルブミン	2.5g/dL以上
総ビリルビン	1.5mg/dL以下
AST	施設基準値上限の2.5倍以下
ALT	
ALP注1）	
CK	
クレアチニンクリアランス注2）	30mL/min以上

注1）原疾患に起因する場合を除く。
注2）計算値はCockcroft-Gault式を用いて算出。実測した場合は、実測値にて本基準を満たすこと。

・「減量基準」に該当する副作用が発現した場合は、1段階ごとに減量すること。ただし、最低投与量は0.8mg/m^{2}とする。

減量基準

項目	減量基準
好中球数	500/mm^{3}未満が6日間以上持続する。又は500/mm^{3}未満で発熱、感染を伴う。
血小板数	2.5×10^4/mm^{3}未満
総ビリルビン	1.5mg/dLを超える。
AST	投与後21日目以降に施設基準値上限の2.5倍を超える。
ALT	
ALP	施設基準値上限の2.5倍を超える。
非血液毒性	グレード3注3）以上

注3）CTCAE（Common Terminology Criteria for Adverse Events）version 4.0に準じる。

減量の目安

減量段階	投与量
通常投与量	1.2mg/m^2
1段階減量	1.0mg/m^2
2段階減量	0.8mg/m^2

8. 重要な基本的注意

8.1 肝機能障害があらわれることがあるので、定期的に肝機能検査を行うなど、患者の状態を十分に観察すること。［7.3、11.1.1参照］

8.2 骨髄機能が抑制され、敗血症性ショック等の好中球減少に伴う感染等があらわれることがあるので、本剤投与開始前及び投与中は定期的に血液検査を行うなど、患者の状態を十分に観察すること。［7.3、9.1.1、9.1.2、11.1.2、11.1.5参照］

8.3 横紋筋融解症があらわれることがあるので、筋肉痛、脱力感等の症状を観察するとともに、本剤投与開始前及び投与中は定期的にCKの検査を行うなど、患者の状態を十分に観察すること。［7.3、11.1.3参照］

8.4 心機能障害があらわれることがあるので、本剤投与開始前及び投与中は定期的に心エコー等の心機能検査（左室駆出率の測定を含む）を行うとともに、心機能障害に関連する臨床的な徴候や症状を十分に観察すること。［9.1.3、11.1.6参照］

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 骨髄抑制のある患者

骨髄抑制が増強するおそれがある。[8.2、9.1.2、11.1.2参照]

9.1.2 感染症を合併している患者

骨髄抑制により、感染症が悪化するおそれがある。[8.2、9.1.1、11.1.2、11.1.5参照]

9.1.3 アントラサイクリン系薬剤による治療歴のある患者又は心機能障害のある患者

心機能障害が発現又は増悪するおそれがある。[8.4、11.1.6参照]

9.3 肝機能障害患者

血中濃度が上昇するおそれがある。[16.6.1参照]

9.4 生殖能を有する者

9.4.1 生殖可能な年齢の患者に投与する場合には、性腺に対する影響を考慮すること。[15.2.2参照]

＊9.4.2 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7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、15.2.1参照]

＊9.4.3 男性には、本剤投与中及び最終投与後4カ月間においてバリア法（コンドーム）を用いて避妊する必要性について説明すること。[15.2.1参照]

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。ラットで本剤の胎盤及び胎児への移行が確認されており、胎児への影響又は催奇形性を示す可能性がある。[2.2、9.4.2参照]

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。本剤のヒトでの乳汁移行に関するデータはない。

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

患者の状態を十分に観察し、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。

10. 相互作用

本剤は、主にCYP3A4により代謝される。[16.4.1参照]

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
CYP3A阻害剤（ケトコナゾール注）、クラリスロマイシン、アプレピタント等）[16.7.1参照]	本剤の血漿中濃度が上昇し、副作用の頻度及び重症度が増加するおそれがあるので、CYP3A阻害作用のない又は弱い薬剤への代替を考慮すること。併用が避けられない場合には、患者の状態を慎重に観察し、副作用発現に十分注意すること。	これらの薬剤のCYP3A阻害作用により、本剤の代謝が阻害されると考えられる。
CYP3A誘導剤（リファンピシン、フェノバルビタール、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]	本剤の血漿中濃度が低下し、本剤の有効性が減弱するおそれがあるので、CYP3A誘導作用のない又は弱い薬剤への代替を考慮すること。	これらの薬剤等のCYP3A誘導作用により、本剤の代謝が促進されると考えられる。

注）ケトコナゾールの注射剤及び経口剤は国内未承認である。

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 肝不全、肝機能障害

肝不全（頻度不明）及びAST（47.2%）、ALT（66.7%）等の上昇を伴う肝機能障害があらわれることがある。[8.1参照]

11.1.2 骨髄抑制

好中球減少（83.3%）、白血球減少（55.6%）、血小板減少（36.1%）、貧血（30.6%）、リンパ球減少（22.2%）、発熱性好中球減少症（13.9%）があらわれることがある。[8.2、9.1.1、9.1.2参照]

11.1.3 横紋筋融解症（2.8%）

筋肉痛、脱力感、CK上昇、血中及び尿中ミオグロビン上昇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。[8.3参照]

11.1.4 重篤な過敏症

過敏症（頻度不明）により死亡に至った例も報告されている。[2.1参照]

11.1.5 感染症

肺炎（2.8%）、敗血症性ショック（頻度不明）等があらわれることがある。[8.2、9.1.2参照]

11.1.6 心機能障害

うっ血性心不全（2.8%）及び左室駆出率低下（頻度不明）等の心機能障害があらわれることがある。[8.4、9.1.3参照]

11.2 その他の副作用

	20%以上	5～20%未満	5%未満	頻度不明
消化器	悪心（88.9%）、食欲不振（58.3%）、便秘（47.2%）、嘔吐	口内炎、下痢、味覚異常、消化不良	腹痛	膵炎
肝臓	γ-GTP上昇	ALP上昇、ビリルビン上昇		
精神神経系		頭痛、末梢感覚性神経障害	浮動性めまい	不眠症、錯感覚
呼吸器				咳嗽、呼吸困難
筋骨格系		筋肉痛、CK上昇	関節痛、背部痛	
循環器				潮紅、低血圧
皮膚・皮下組織系			脱毛、注射部位反応	注射部位壊死、注射部位紅斑、注射部位疼痛、皮下溢血
その他	倦怠感（44.4%）	発熱、疲労、浮腫	低カリウム血症、体重減少	脱水、静脈炎、クレアチニン上昇、アルブミン減少

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 本剤の調製にあたっては、溶解時及び希釈時は生理食塩液を使用すること。また、本剤は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。皮膚に本剤、溶解液及び希釈液が付着した場合は、直ちに多量の流水及び石けんでよく洗い流すこと。

14.2 調製方法

14.2.1 無菌的環境下の安全キャビネット内で、0.25mgバイアルには5mL、1mgバイアルには20mLの生理食塩液をシリンジで注入し溶解する。溶解液の使用は、1回のみとする。

14.2.2 完全に溶解するまでバイアルを振とうする。溶解液は無色澄明であることを確認する。

14.2.3 必要な量の溶解液をバイアルから抜き取り、500mL～1000mLの生理食塩液の入った点滴バッグに注入する。

14.2.4 溶解液及び希釈液は調製後速やかに使用すること。溶解から30時間以内に投与を終了すること。

14.3 薬剤投与時の注意

14.3.1 必ず中心静脈からの点滴投与とし、末梢静脈、皮下、筋肉内には投与しないこと。[7.2参照]

14.3.2 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。[7.2参照]

14.3.3 他の薬剤等との配合又は同じ静注ラインでの同時注入は避けること。

15. その他の注意

15.1 臨床使用に基づく情報

海外で、本剤投与後に白血病、骨髄異形成症候群等の悪性腫瘍が発生したとの報告がある。

15.2 非臨床試験に基づく情報

＊15.2.1 遺伝毒性に関して、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の骨髄細胞を用いた小核試験において、陽性の結果が報告されている。[9.4.2、9.4.3参照]

15.2.2 ラットにトラベクテジン50μg/kg/日以上（AUCに基づく用量比較で臨床曝露量未満）を3週間ごとに反復投与したところ、精巣の精上皮変性、精子巨細胞の出現、精巣上体の細胞残屑及び雌において性周期の若干の遅延が認められている。また、サルにトラベクテジン70μg/kg/日（AUCに基づく用量比較で臨床曝露量未満）を3週間ごとに反復投与したところ、未熟精巣の発生頻度増加が認められている。[9.4.1参照]

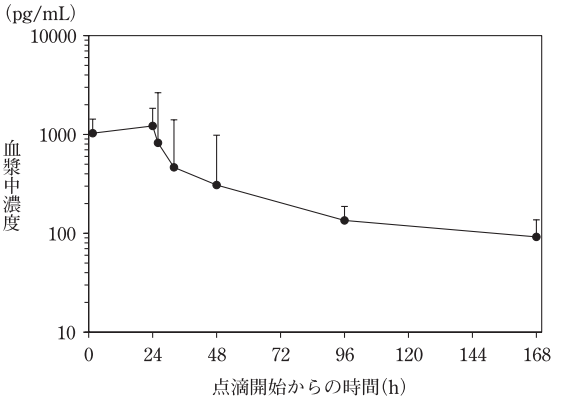
15.2.3 サルにトラベクテジン25μg/kg/日以上（AUCに基づく用量比較で臨床曝露量未満）を3週間ごとに反復投与したところ、網膜浮腫が認められている。

16. 薬物動態

16.1 血中濃度

16.1.1 単回投与

(1) 日本人の悪性軟部腫瘍患者に本剤1.2mg/m^{2}を24時間かけて点滴静注したときの血漿中トラベクテジン濃度は多相性の消失を示し、平均の最終相消失半減期は107時間であった[1~3]。



本剤を1.2mg/m^{2}で24時間点滴静注したときの血漿中トラベクテジン濃度推移

平均値＋標準偏差(n=37)
デキサメタゾンリン酸エステルナトリウム：本剤投与開始約30分前に20mgを静脈内投与

本剤を1.2mg/m^{2}で24時間点滴静注したときのトラベクテジンの薬物動態パラメータ

t_{max} (h)	C_{max} (pg/mL)	AUC_{inf} (ng・h/mL)	$t_{1/2}$ (h)	CL (L/h)	Vd_{ss} (L)
24.3 (1.47, 27.2)	1660 (1720)	66.0 (24.7)	107 (29)	34.3 (10.4)	3040 (1170)

平均値（標準偏差）[t_{max}：中央値（範囲）]、t_{max}及びC_{max}はn=37、その他はn=33
デキサメタゾンリン酸エステルナトリウム：本剤投与開始約30分前に20mgを静脈内投与

(2) 固形癌患者、肉腫患者に本剤を24時間かけて点滴静注[注1)]した場合、0.05~1.8mg/m^{2}の用量範囲でC_{max}及びAUC_{48h}に用量比例性がみられた[4]（外国人データ）。

16.1.2 反復投与

固形癌患者に本剤1.5mg/m^{2}を24時間かけて21日を1サイクルとして反復点滴静注[注1)]したときのC_{max}、AUC_{inf}及びCLについて、サイクル1と2との間に明確な差異は認められなかった[5]（外国人データ）。

本剤を21日サイクルで反復投与したときのサイクル1及び2におけるトラベクテジンの薬物動態パラメータ（1.5mg/m^2、24時間点滴静注[注1)]）

サイクル	t_{max} (h)	C_{max} (pg/mL)	AUC_{inf} (ng・h/mL)	$t_{1/2}$ (h)	CL (L/h)	Vdz (L)
1	24.1 (2.0, 26.5)	1840 (1121)	56.8 (24.9)	103.2 (41.8)	54.7 (23.5)	7509 (3412)
2	23.5 (2.0, 25.6)	1724 (1436)	58.1 (49.0)	77.4 (57.3)	71.0 (51.2)	5655 (3142)

平均値（標準偏差）[t_{max}：中央値（範囲）]、n=24（サイクル1、t_{max}及びC_{max}はn=23）、n=20（サイクル2）

16.3 分布

*In vitro*試験において、未変化体の血漿蛋白結合率は10~100ng/mLの濃度範囲で97.28~97.77%であり、検討された濃度範囲において、概ね一定であった[6]。

また、*in vitro*試験において、トラベクテジンはP-糖蛋白（P-gp）の基質であることが示された[7]。

16.4 代謝

16.4.1 *In vitro*試験において、トラベクテジンは主にCYP3A4で代謝されることが示された[8]。[10.参照]

16.4.2 ^{14}C標識トラベクテジン1.1mgをヒトに投与したときの総放射能のAUC_{inf}に対する未変化体のAUC_{inf}比について、3時間かけて点滴静注[注1)]した際の6例の平均値は0.082、24時間かけて点滴静注した際の個別値（n=2）はそれぞれ0.077及び0.086であり、血漿中において、未変化体と比較して代謝物の占める割合が大きいことが示唆された[9]（外国人データ）。

16.5 排泄

固形癌患者（n=8）に1.1mgの用量で^{14}C標識トラベクテジンを24時間又は3時間かけて点滴静注[注1)]したとき、17日間までに投与された放射能の57.6%が糞中に排泄され、10日間までに尿中には5.8%が排泄された。未変化体は排泄された放射能の1%未満であった[9]（外国人データ）。

16.6 特定の背景を有する患者

16.6.1 肝機能障害患者

肝機能障害[注2)]を有する固形癌患者に本剤（0.58又は0.9mg/m^{2}投与、各n=3）を3時間かけて点滴静注[注1),注3)]した場合、用量補正したC_{max}及びAUC_{last}は、正常な肝機能の患者（1.3mg/m^{2}投与、n=9）と比較して、それぞれ40%及び97%増加した[10]（外国人データ）。[9.3参照]

16.7 薬物相互作用

16.7.1 ケトコナゾール

固形癌患者（11例）に本剤0.2又は0.58mg/m^{2}を3時間かけて点滴静注[注1),注3)]するとともに、ケトコナゾール[注4)]200mgを本剤の投与12時間前から12時間ごとにそれぞれ計6又は15回反復経口投与した際に、ケトコナゾール非併用時（本剤1.3mg/m^2、用量補正）と比較して、本剤0.58mg/m^{2}投与時（8例）のC_{max}及びAUC_{last}はそれぞれ21及び66%増加した[11]（外国人データ）。[10.2参照]

16.7.2 リファンピシン

固形癌患者（8例）にリファンピシン600mg（第1~6日目）を1日1回反復経口投与するとともに、本剤1.3mg/m^{2}を3時間かけて点滴静注[注1),注3)]（第6日目）した際に、リファンピシン非併用時と比較して、本剤のC_{max}及びAUC_{inf}はそれぞれ22及び38%低下した[12]（外国人データ）。[10.2参照]

16.7.3 その他の薬剤

悪性軟部腫瘍患者（38例）に本剤1.3、1.5又は1.65mg/m^{2}を3時間かけて点滴静注[注1)]するとともに、デキサメタゾン4mgを1日2回、本剤の投与前日から4日間反復経口投与した際に、デキサメタゾン非併用時と比較して、本剤のクリアランス（17例）は28%増加した[13]（外国人データ）。

注1) 本剤の承認用法・用量：1回1.2mg/m^2（体表面積）を24時間かけて点滴静注。1サイクルを21日間として、投与を繰り返す。
注2) 総ビリルビンが施設基準値上限の1.5倍超~3倍以下、かつAST及びALTが施設基準値上限の8倍未満
注3) 本剤投与30分以上前にデキサメタゾンリン酸エステルナトリウム20mgを静脈内投与することとされた。
注4) 経口剤は国内未承認

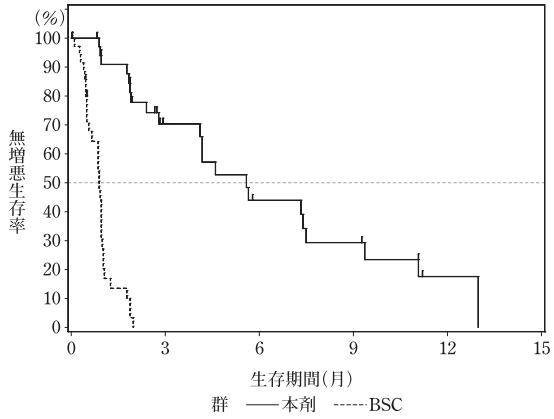
17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国内第Ⅱ相試験

アントラサイクリン系などの使用可能な抗悪性腫瘍剤による治療後に病勢進行が認められた進行又は再発悪性軟部腫瘍患者を対象に、無増悪生存期間（PFS）を主要評価項目とし、本剤（1回1.2mg/m^2）のベストサポーティブケア（BSC）に対する優越性の検討を目的とした第Ⅱ相比較試験を実施した。本試験に登録された患者の組織型は粘液型/円形細胞型脂肪肉腫、滑膜肉腫、胞

巣型横紋筋肉腫、骨外性Ewing肉腫/未熟神経外胚葉性腫瘍、隆起性皮膚線維肉腫、胞巣状軟部肉腫、明細胞肉腫、類血管腫線維性組織球腫、線維形成性小細胞腫瘍、骨外性粘液型軟骨肉腫及び間葉型軟骨肉腫であった。その結果、有効性解析対象例73例（本剤37例、BSC36例）でのPFSにおいて、本剤のBSCに対する優越性が確認された[2,14]。



リスク集合(症例数)

本剤	37	16	9	6	1
BSC	36	—	—	—	—

無増悪生存期間のKaplan-Meier曲線(独立判定)

無増悪生存期間の結果

治療群	症例数	PFS中央値（月）(90%信頼区間)	p値[注1)]	ハザード比[注2)] (90%信頼区間)
本剤	37	5.6 (4.2, 7.5)	<0.0001	0.07 (0.03, 0.14)
BSC	36	0.9 (0.9, 1.0)		

注1）割付調整因子（組織型）を層とした層別ログランク検定のp値として算出した。有意水準は片側0.05であった。
注2）割付調整因子（組織型）にて調整したCox比例ハザードモデルに基づき算出した。

副作用発現率は100%（36/36例）であった。主な副作用は悪心88.9%（32/36例）、好中球数減少83.3%（30/36例）、ALT増加66.7%（24/36例）、食欲減退58.3%（21/36例）、白血球数減少55.6%（20/36例）、便秘47.2%（17/36例）、AST増加47.2%（17/36例）、倦怠感44.4%（16/36例）、嘔吐38.9%（14/36例）、血小板数減少36.1%（13/36例）、貧血30.6%（11/36例）であった。

18. 薬効薬理

18.1 作用機序

本剤は、DNAの副溝部分に結合し、ヌクレオチド除去修復機構を阻害すること等により細胞死及び細胞周期停止を誘導し、腫瘍の増殖を抑制すると考えられている。

また、本剤は、ヒト粘液型脂肪肉腫及びヒトEwing肉腫において染色体転座により発現するそれぞれFUS-CHOPタンパク及びEWS-FLI1タンパクの転写因子としての機能を阻害し、がん関連遺伝子の発現を制御することが報告されている[15~24]。

18.2 抗腫瘍効果

本剤は、ヒト滑膜肉腫由来SYO-1細胞株、ヒトEwing肉腫由来SK-ES-1細胞株、ヒト胞巣型横紋筋肉腫由来SJCRH30細胞株、ヒト骨肉腫由来KHOS/NP細胞株、ヒト横紋筋肉腫由来RD細胞株及びヒト平滑筋肉腫由来SK-LMS-1細胞株を皮下移植したヌードマウスにおいて、腫瘍の増殖を抑制した[25~30]。

19. 有効成分に関する理化学的知見

一般的名称：トラベクテジン（Trabectedin）

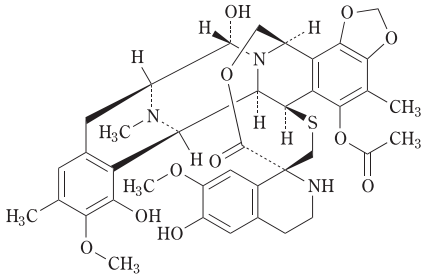
化学名：(1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-6',8,14-Trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-19-oxo-3',4',6a,7,12,13,14,16-octahydro-2'*H*,6*H*-spiro[6,16-(epithiopropanooxymethano)-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinolin-20,1'-isoquinolin]-5-yl acetate

分子式：$C_{39}H_{43}N_3O_{11}S$

分子量：761.84

性　状：白色の粉末である。*N*,*N*-ジメチルホルムアミド、メタノール、エタノール（99.5）又は酢酸（100）に溶けやすく、アセトンにやや溶けやすく、ジクロロメタン又はアセトニトリルに溶けにくく、水にはほとんど溶けない。

化学構造式：



融　点：155～162℃（分解）

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

〈ヨンデリス点滴静注用0.25mg〉

1バイアル

〈ヨンデリス点滴静注用1mg〉

1バイアル

23. 主要文献

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5) Misset J.L : Pharmacokinetics in the study titled "Phase I Pharmacokinetic Study to Determine the Safety of Ecteinascidin-743 (ET-743) Administered as a Continuous Intravenous Infusion Over 24 Hours Every 21 Days In Patients With Solid Tumors"（承認年月日：2015年9月28日、CTD2.7.6.2）
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12) Sharma S : An Open-Label, Multicenter Study to Assess the Potential Effects of Rifampin on the Pharmacokinetics of Trabectedin in Subjects with Advanced Malignancies（承認年月日：2015年9月28日、CTD2.7.2.2、2.7.6.5）
13) Cubedo R : Pharmacokinetics in Phase Ⅱ Clinical Trial of ET-743 as 2nd or 3rd Line treatment in patients with advanced stage and/or metastatic Soft tissue sarcoma（承認年月日：2015年9月28日、CTD2.7.2.2、2.7.6.7）
14) 染色体転座を伴う悪性軟部腫瘍患者を対象としたET-743の第Ⅱ相臨床試験（承認年月日：2015年9月28日、CTD2.7.6.9）
15) Pommier Y, et al. : Biochemistry. 1996 ; 35 (41) : 13303-13309
16) Zewail-Foote M, et al. : J Med Chem. 1999 ; 42 (14) : 2493-2497
17) Takebayashi Y, et al. : Nat Med. 2001 ; 7 (8) : 961-966
18) Tavecchio M, et al. : Eur J Cancer. 2008 ; 44 (4) : 609-618
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25) 小森敏治　他：ヒトユーイング肉腫由来細胞株SK-ES-1のヌードマウス皮下移植腫瘍に対するTrabectedin（ET-743）の抗腫瘍効果（承認年月日：2015年9月28日、CTD2.6.2.2）
26) 小森敏治　他：ヒト胞巣型横紋筋肉腫由来細胞株SJCRH30のヌードマウス皮下移植腫瘍に対するTrabectedin（ET-743）の抗腫瘍効果（承認年月日：2015年9月28日、CTD2.6.2.2）
27) 小森敏治　他：ヒト骨肉腫由来細胞株KHOS/NPのヌードマウス皮下移植腫瘍に対するTrabectedin（ET-743）の抗腫瘍効果（承認年月日：2015年9月28日、CTD2.6.2.2）
28) 小森敏治　他：ヒト横紋筋肉腫由来細胞株RDのヌードマウス皮下移植腫瘍に対するTrabectedin（ET-743）の抗腫瘍効果（承認年月日：2015年9月28日、CTD2.6.2.2）
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30) 小森敏治　他：ヒト滑膜肉腫由来細胞株SYO-1のヌードマウス皮下移植腫瘍に対するTrabectedin（ET-743）の抗腫瘍効果及びその用量反応性（承認年月日：2015年9月28日、CTD2.6.2.2）

24. 文献請求先及び問い合わせ先

大鵬薬品工業株式会社　医薬品情報課
〒101-8444　東京都千代田区神田錦町1-27
TEL　0120-20-4527

26. 製造販売業者等

26.1 製造販売元

大鵬薬品工業株式会社
東京都千代田区神田錦町1-27

26.2 提携先

Pharma Mar, S.A.
スペイン

2022年1月改訂（第1版）

日本標準商品分類番号
874291

貯　　法：室温保存
有効期間：4年

承認番号	22300AMX00520000
販売開始	2011年7月

抗悪性腫瘍剤
エリブリンメシル酸塩製剤

毒薬、処方箋医薬品[注]

ハラヴェン®静注1mg
Halaven® Injection

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、緊急時に十分な対応が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、本剤による治療開始に先立ち、患者又はその家族に有効性及び危険性を十分に説明し、同意を得てから投与すること。

1.2 骨髄抑制があらわれることがあるので、頻回に血液検査を行うなど、患者の状態を十分に観察すること。また、「2.禁忌」、「8.重要な基本的注意」及び「9.特定の背景を有する患者に関する注意」の項を参照し、適応患者の選択を慎重に行うこと。[2.1、8.1、9.1.1、9.2、9.3、9.8、11.1.1参照]

2. 禁忌（次の患者には投与しないこと）

2.1 高度な骨髄抑制のある患者
［骨髄抑制を悪化させる可能性がある。］[1.2参照]
2.2 本剤の成分に対し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	ハラヴェン静注1mg
有効成分	エリブリンメシル酸塩　1.0mg （1バイアル（2.0mL）中の分量）
添加剤	無水エタノール　0.10mL （1バイアル（2.0mL）中の分量）
	塩酸　適量 （1バイアル（2.0mL）中の分量）
	水酸化ナトリウム　適量 （1バイアル（2.0mL）中の分量）

3.2 製剤の性状

販売名	ハラヴェン静注1mg
性状	無色澄明の液
pH	6.0～9.0
浸透圧比	約3（0.5mg／mL、希釈しない場合） （生理食塩液に対する比）
	約1（0.0203mg／mL[注]） （生理食塩液に対する比）

注）平均的な体表面積から換算した投与量（2.03mg）を生理食塩液で100mLに希釈した時の濃度
（エリブリンメシル酸塩2.03mg相当量／100mL生理食塩液）

4. 効能又は効果

手術不能又は再発乳癌、悪性軟部腫瘍

5. 効能又は効果に関連する注意

〈手術不能又は再発乳癌〉

5.1 本剤の術前・術後補助化学療法における有効性及び安全性は確立していない。
5.2 本剤の投与を行う場合には、アントラサイクリン系抗悪性腫瘍剤及びタキサン系抗悪性腫瘍剤を含む化学療法を施行後の増悪若しくは再発例を対象とすること。

〈悪性軟部腫瘍〉

5.3 本剤の化学療法未治療例における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理解した上で、適応患者の選択を行うこと。[17.1.3、17.1.4参照]

6. 用法及び用量

通常、成人には、エリブリンメシル酸塩として、1日1回1.4mg／m^2（体表面積）を2～5分間かけて、週1回、静脈内投与する。これを2週連続で行い、3週目は休薬する。これを1サイクルとして、投与を繰り返す。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

7.1 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 本剤の投与にあたっては、以下の基準を参考に必要に応じて、投与を延期、減量又は休薬すること。

〈各サイクル1週目〉

投与開始基準	下記の基準を満たさない場合、投与を延期する。 ・好中球数：1,000／mm^3以上 ・血小板数：75,000／mm^3以上 ・非血液毒性：Grade2[注1]以下
減量基準	前サイクルにおいて以下の副作用等が発現した場合、減量した上で投与する[注2]。 ・7日間を超えて継続する好中球数減少（500／mm^3未満） ・発熱又は感染を伴う好中球数減少（1,000／mm^3未満） ・血小板数減少（25,000／mm^3未満） ・輸血を要する血小板数減少（50,000／mm^3未満） ・Grade3[注1]以上の非血液毒性 ・副作用等により、2週目に休薬した場合

〈各サイクル2週目〉

投与開始基準	下記の基準を満たさない場合、投与を延期する。 ・好中球数：1,000／mm^3以上 ・血小板数：75,000／mm^3以上 ・非血液毒性：Grade2[注1]以下
投与再開基準	投与延期後1週間以内に上記の投与開始基準を満たした場合、減量して投与する[注2]。
休薬基準	投与延期後1週間以内に上記の投与開始基準を満たさない場合は、休薬する。

注1）Common Terminology Criteria for Adverse Events（CTCAE）に基づく。
注2）減量を行う際、次の用量を参考にすること。

減量前の投与量 → 減量後の投与量
1.4mg／m^2 → 1.1mg／m^2
1.1mg／m^2 → 0.7mg／m^2
0.7mg／m^2 → 投与中止を考慮

8. 重要な基本的注意

8.1 骨髄抑制があらわれることがあるので、頻回に血液検査を行うなど、患者の状態を十分に観察し、感染症の発現に注意すること。[1.2、9.1.1、11.1.1参照]
8.2 QT間隔延長があらわれたとの報告があるので、投与開始前は心電図検査及び電解質検査を行うこと。本剤投与中は適宜心電図検査を行うなど患者の状態を十分に観察すること。
8.3 肝機能障害があらわれることがあるので、本剤投与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。[11.1.4参照]
8.4 間質性肺炎があらわれることがあるので、胸部X線検査を行うなどして、患者の状態を十分に観察すること。[11.1.5参照]

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 骨髄抑制のある患者［1.2、8.1、11.1.1参照］

9.2 腎機能障害患者

本剤のAUCが増加する傾向がある。[1.2、16.6.1参照]

9.3 肝機能障害患者
肝機能障害を有する患者に投与する場合は、減量を考慮すること。本剤のAUCが増加し、好中球減少の発現頻度が高くなる傾向がある。[1.2、16.6.2参照]
9.4 生殖能を有する者
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。動物実験（ラット、イヌ）において精巣毒性が認められている。
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）で胚致死作用及び催奇形作用が報告されている。[2.3参照]
9.6 授乳婦
授乳しないことが望ましい。本剤が乳汁に移行する可能性があり、乳児が乳汁を介して摂取した場合、乳児に重篤な副作用が発現するおそれがある。
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
患者の状態を十分に観察し、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く、骨髄抑制や消化器症状等の副作用があらわれやすい。[1.2参照]

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
抗悪性腫瘍剤 放射線照射	併用により、骨髄抑制が増強するおそれがある。併用する場合には、患者の状態を十分に観察し、必要に応じて減量又は休薬期間の延長を行うこと。	ともに骨髄抑制作用を有し、骨髄抑制が増強するおそれがある。

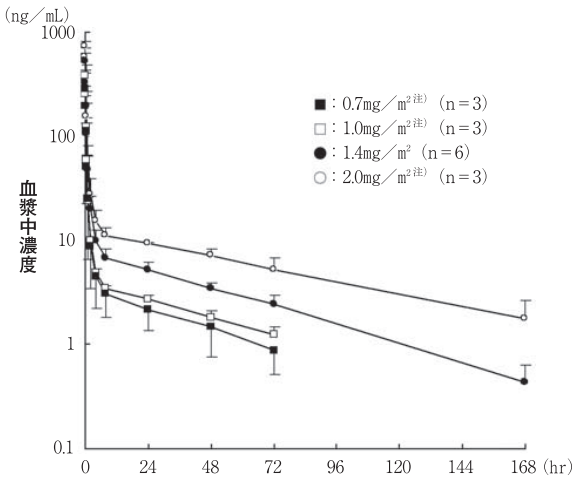
11. 副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。
11.1 重大な副作用
11.1.1 骨髄抑制
白血球減少（99.2%）、好中球減少（98.5%）、リンパ球減少（63.6%）、貧血（23.5%）、ヘモグロビン減少（21.2%）、発熱性好中球減少（12.1%）、血小板減少（9.1%）、赤血球減少（3.8%）、汎血球減少（頻度不明）等があらわれることがある。異常が認められた場合には、減量や休薬等を行い、必要に応じて、G-CSF製剤や抗生剤の投与等の適切な処置を行うこと。Grade3以上の白血球及び好中球減少の最低値は、ともに投与開始14日後（中央値）にあらわれ、最低値発現日からともに7日後（中央値）に回復した。[1.2、8.1、9.1.1参照]
11.1.2 感染症（頻度不明）
敗血症、肺炎等があらわれることがある。
11.1.3 末梢神経障害（末梢性ニューロパチー）（28.0%）
観察を十分に行い、しびれ等の症状が認められた場合には、減量や休薬等の適切な処置を行うこと。
11.1.4 肝機能障害（8.3%）[8.3参照]
11.1.5 間質性肺炎（1.5%）[8.4参照]
11.1.6 皮膚粘膜眼症候群（Stevens-Johnson症候群）、多形紅斑（いずれも頻度不明）
11.2 その他の副作用

	30%以上	5～30%未満	5%未満	頻度不明
血液			血小板増加	
消化器	悪心(40.2%)、口内炎(34.1%)	嘔吐、便秘、下痢、腹痛	口唇炎、口内乾燥、口の感覚鈍麻、流涎過多、歯痛、歯肉痛、歯周炎、舌炎、舌苔、嚥下障害、腹部不快感、消化不良、胃腸粘膜障害、胃炎、裂肛、肛門周囲痛	膵炎、粘膜の炎症
全身症状	疲労(34.1%)、発熱(31.1%)	倦怠感、浮腫	無力症、疼痛、インフルエンザ様疾患	
精神神経系		味覚異常、頭痛、めまい	同名性半盲、傾眠、不眠症、不安、感覚鈍麻、感覚障害	
代謝	食欲減退(34.8%)	血中アルブミン、カリウム、リンの低下、総コレステロールの上昇、耐糖能障害	血中ナトリウム、クロール、カルシウム、総蛋白、血糖の低下、血中リン、トリグリセリドの上昇	
筋骨格系		筋肉痛、関節痛	頸部痛、背部痛、肢径部痛、四肢痛、筋固縮、筋痙縮、関節炎、変形性関節症	骨痛
呼吸器		咳嗽、口腔咽頭痛	呼吸困難、鼻出血、鼻漏、口腔咽頭不快感、上気道炎、胸膜炎、放射線性肺臓炎、発声障害、肺塞栓症、喀血、胸水	
皮膚	脱毛症(46.2%)	発疹	湿疹、蕁麻疹、そう痒症、光線過敏性反応、皮膚乾燥、皮膚筋炎	
肝臓		AST、ALT、Al-P、γ-GTP、LDHの上昇	総ビリルビンの上昇、脂肪肝	
循環器			動悸、血圧上昇、頻脈、心電図QT延長、心室性期外収縮	
泌尿器		蛋白尿、尿潜血	尿意切迫、BUN、血中クレアチニンの上昇、尿路感染、排尿障害、腎不全	
感覚器			結膜炎、眼の異常感、複視、眼脂、眼痛、眼乾燥、流涙増加、耳漏、耳鳴、白内障	
その他		CK、CRPの上昇、体重減少	注射部位反応(そう痒感等)、注射部位漏出、胸痛、口渇、過敏症、膣分泌物、血管炎、出血、ほてり、体重増加、不規則月経	

14. 適用上の注意
14.1 薬剤調製時の注意
14.1.1 本剤を他の医薬品と混注しないこと。
14.1.2 本剤を5%ブドウ糖注射液で希釈した場合、反応生成物が検出されるため、希釈する場合は日本薬局方生理食塩液を使用すること。また、0.01mg／mL未満の濃度に希釈しないこと。
14.1.3 調製時には手袋、ゴーグル及び保護衣の着用が望ましい。本剤が皮膚に付着した場合には、直ちに石鹸及び多量の流水で洗い流すこと。また、粘膜に付着した場合には、直ちに多量の流水で洗い流すこと。
14.2 薬剤投与時の注意
14.2.1 本剤をシリンジに入れ、室温で保存した場合は6時間以内、冷蔵で保存した場合は24時間以内に投与すること。

15. その他の注意
15.1 臨床使用に基づく情報
前治療歴を有する患者において、本剤の投与後に骨髄異形成症候群（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
日本人固形がん患者15例に本剤0.7注)、1.0注)、1.4又は2.0注)mg／m^2を2～10分間かけて静脈内投与したとき、本剤は3相性の消失推移を示した[1)]。



本剤静脈内投与時の血漿中エリブリン濃度（第1日目）

薬物動態パラメータ（1.4mg／m²投与時）

	C_{max} (ng／mL)	$AUC_{0\text{-}inf}$ (ng・hr／mL)	$t_{1/2}$ (hr)	CL (L／hr／m²)	V_{ss} (L／m²)
第1日目	519.4±107.2	672.7±113.7	39.4±8.3	1.89±0.33	76.3±19.2
第8日目	544.4±52.5	698.5±128.8	38.6±5.2	1.82±0.34	67.8±12.4

（第1日目n＝6、第8日目n＝5、平均値±標準偏差）

注）本剤の承認された用量は、成人1日1回1.4mg／m²（体表面積）である。

16.3 分布

*In vitro*試験におけるエリブリン（100～1,000ng／mL）のヒト血漿蛋白結合率は48.92～65.07%であった[2]。

ラットに^{14}C標識エリブリン酢酸塩0.75mg／kgを単回静脈内投与したとき、投与後7日目までに多くの組織に放射能が分布していた。特に、肺、膀胱、腎皮質、腎髄質、肝臓、脾臓、甲状腺、胃、唾液腺で高い放射能が認められ、中枢神経系では低かった。

イヌに^{14}C標識エリブリン酢酸塩0.08mg／kgを単回静脈内投与したとき、血液中放射能／血漿中放射能の比は0.94～1.25であった[3]。

16.4 代謝

固形がん患者6例に^{14}C標識体を単回静脈内投与したとき、血漿中の放射能の大部分が未変化体であった。また、投与後168時間までに尿糞中に排泄された放射能の78.6%が未変化体であった[4]（外国人データ）。

*In vitro*試験の結果から、CYP3A4が主にエリブリンの代謝に寄与すると考えられた[5]。

16.5 排泄

固形がん患者6例に^{14}C標識体を単回投与したとき、投与後168時間までに、投与した放射能の8.9%が尿中に、77.6%が糞中に排泄された。尿糞中の放射能のうち、78.6%が未変化体として排泄された[4]（外国人データ）。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

固形がん患者19例の腎機能をクレアチニンクリアランスによって、正常（≥80mL／min）、中等度腎機能障害（30-50mL／min）及び重度腎機能障害（15-29mL／min）に分類し、それぞれ本剤を1.4mg／m²、1.4mg／m²及び0.7mg／m²投与した際の薬物動態パラメータにおいて、腎機能の低下に伴い半減期は変化しないものの、クリアランスの低下、AUC（投与量補正時）の増加及びC_{max}（投与量補正時）の増加が認められた[8]（外国人データ）。[9.2参照]

腎機能正常患者及び腎機能障害患者における薬物動態パラメータ

	正常 (N＝6)	中等度 (N＝7)	重度 (N＝6)
用量（mg／m²）	1.4	1.4	0.7
C_{max}（ng／mL／mg）注）	109±50.4	140±51.6	236±176
$AUC_{0\text{-}inf}$（ng・hr／mL／mg）注）	408±224	595±299[a)]	575±232
$t_{1/2}$（hr）	43.4±15.3	43.9±10.9[a)]	38.7±12.5
CL（L／hr）	3.13±1.65	2.07±1.03[a)]	2.01±0.875
V_{ss}（L）	144±73.7	86.5±32.7[a)]	66.6±26.8

注）エリブリン1mgあたりに補正した数値を示す。

a）n＝6

16.6.2 肝機能障害患者

固形がん患者18例の肝機能をChild-Pugh分類によって、正常、軽度肝機能障害（Child-Pugh A）及び中等度肝機能障害（Child-Pugh B）に分類し、それぞれ本剤を1.4mg／m²、1.1mg／m²及び0.7mg／m²投与した際の薬物動態パラメータにおいて、肝機能の低下に伴いクリアランスの低下、半減期の延長、AUC（投与量補正時）の増加及びC_{max}（投与量補正時）の増加が認められた[7]（外国人データ）。[9.3参照]

肝機能正常患者及び肝機能障害患者における薬物動態パラメータ

	正常 (N＝6)	Child-Pugh A (N＝7)	Child-Pugh B (N＝5)
用量（mg／m²）	1.4	1.1	0.7
C_{max}（ng／mL／mg）注）	72.0±20.2	83.9±28.5	100±46.2
$AUC_{0\text{-}inf}$（ng・hr／mL／mg）注）	229±58.3	420±175.4	646±412.6
$t_{1/2}$（hr）	36.1±8.65	41.1±12.73	65.9±18.50
CL（L／hr）	4.57±0.959	2.75±1.094	2.06±1.028
V_{ss}（L）	166±50.1	113±29.1	149±81.5

注）エリブリン1mgあたりに補正した数値を示す。

16.6.3 高齢者

母集団薬物動態解析より、エリブリンのクリアランスは、65歳以上の患者と65歳未満の患者において有意な差は認められなかった[6]。

16.7 薬物相互作用

16.7.1 その他

*In vitro*試験においてエリブリンはCYP3A4に対して可逆的な競合阻害作用（Ki：3～17μmol／L）を示したが、CYP1A2、CYP2C9、CYP2C19、CYP2D6及びCYP2E1に対してはほとんど阻害作用を示さなかった。また、ヒト肝細胞においてCYP1A、CYP2C9、CYP2C19及びCYP3Aの酵素活性及び蛋白発現量に影響を及ぼさなかった[5]。

外国人固形がん患者10例に本剤とケトコナゾールを併用投与した際に、エリブリンの薬物動態パラメータはケトコナゾールの影響を受けなかった[9]。

外国人固形がん患者11例にリファンピシンを反復投与した後に本剤と併用投与した際に、エリブリンの薬物動態パラメータはリファンピシンの影響を受けなかった[10]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈手術不能又は再発乳癌〉

17.1.1 進行又は再発乳癌を対象とした国内臨床第Ⅱ相試験

アントラサイクリン系薬剤及びタキサン系薬剤を含む前治療を有する進行又は再発乳癌患者に対し、奏効率は21.3%（17／80例）であった[11]。

安全性解析対象症例81例中全例に副作用が認められた。主な副作用は、好中球減少（98.8%）、白血球減少（98.8%）、脱毛症（58.0%）、リンパ球減少（54.3%）、疲労（44.4%）、食欲減退（43.2%）、悪心（42.0%）、口内炎（39.5%）、味覚異常（33.3%）、ヘモグロビン減少（32.1%）、ASTの上昇（29.6%）、ALTの上昇（27.2%）、CKの上昇（25.9%）、発熱（24.7%）、末梢神経障害（24.7%）、γ-GTPの上昇（19.8%）、耐糖能障害（16.0%）、嘔吐（14.8%）、頭痛（14.8%）、発熱性好中球減少（14.8%）、下痢（13.6%）、Al-Pの上昇（13.6%）、LDHの上昇（12.3%）、筋肉痛（12.3%）、発疹（12.3%）、便秘（12.3%）、血小板減少（11.1%）、倦怠感（11.1%）であった。（試験終了時の集計）

17.1.2 進行又は再発乳癌を対象とした外国臨床第Ⅲ相試験

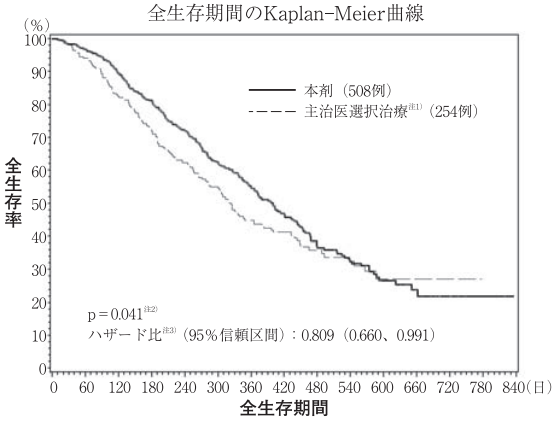
アントラサイクリン系薬剤及びタキサン系薬剤を含む前治療2～5レジメンの進行又は再発乳癌患者（762例）において、主治医選択治療を比較対照とし、全生存期間を主要評価項目として本剤の主治医選択治療に対する優越性の検証を目的とした第Ⅲ相比較試験が実施された。

その結果、全生存期間において、本剤の主治医選択治療に対する優越性が確認された。

本剤投与群における全生存期間の中央値は399日であった[12]。

安全性解析対象症例のうち本剤が投与された503例中475例（94.4%）に副作用が認められた。主な副作用は、好中球減少（52.7%）、脱毛症（44.3%）、末梢神経障害（31.6%）、悪心（29.8%）、疲労（25.6%）、白血球減少（24.1%）、無力症（22.3%）、貧血（16.7%）、食欲減退（16.5%）、便秘（15.1%）、発熱（13.5%）、嘔吐（12.9%）、下痢（12.9%）、体重減少（11.7%）、頭痛（10.3%）であった。（試験終了時の集計）

全生存期間のKaplan-Meier曲線



注1）主治医選択治療のうち、10例以上で使用された薬剤は以下の通り。

薬剤名：例数（%）	
ビノレルビン：61（24.0）	パクリタキセル：26（10.2）
ゲムシタビン：46（18.1）	ドキソルビシン：23（9.1）
カペシタビン：44（17.3）	ドセタキセル：10（3.9）

注2）HER2／neu、カペシタビン前治療歴及び地域を層とした層別log-rank検定

注3）本剤／主治医選択治療
HER2／neu、カペシタビン前治療歴及び地域を層としたCox回帰モデルに基づき算出した。

〈悪性軟部腫瘍〉

17.1.3 進行又は再発悪性軟部腫瘍を対象とした国内臨床第Ⅱ相試験

1レジメン以上の前治療歴を有する進行又は再発の悪性軟部腫瘍患者（51例）に対し、有効性及び安全性を評価した。有効性は2つの腫瘍組織型群別（平滑筋肉腫又は脂肪肉腫群、その他組織型群）に評価を行った。本試験では、胎児性横紋筋肉腫、軟骨肉腫、骨肉腫、ユーイング肉腫／未熟神経外胚葉性腫瘍、消化管間質腫瘍、隆起性皮膚線維肉腫、炎症性筋線維芽細胞腫、神経芽細胞腫、悪性中皮腫、子宮の中胚葉性混合腫瘍を組み入れ対象から除外した。

主要評価項目である投与12週時のprogression-free rate（PF率：その時点の評価がCR、PR又はSDであった被験者の割合）は以下の通りであった[13]。

投与12週時のPF率

	脂肪肉腫／平滑筋肉腫（N=35）	その他組織型（N=16）
12週時評価		
CR	0	0
PR	0	0
SD	21	5
PF率（%）（90%信頼区間）	60（44.7,74.0）	31（13.2,54.8）

安全性解析対象症例51例中全例に副作用が認められた。主な副作用は、白血球減少（100.0%）、好中球減少（98.0%）、リンパ球減少（78.4%）、貧血（47.1%）、発熱（41.2%）、倦怠感（39.2%）、悪心（37.3%）、末梢神経障害（33.3%）、脱毛症（27.5%）、口内炎（25.5%）、味覚異常（23.5%）、ALTの上昇（23.5%）、ASTの上昇（23.5%）、食欲減退（21.6%）、疲労（17.6%）、便秘（15.7%）、発疹（15.7%）、血中アルブミンの低下（15.7%）、LDHの上昇（15.7%）、鼻咽頭炎（13.7%）、CKの上昇（13.7%）、蛋白尿（13.7%）、頭痛（11.8%）、上気道感染（11.8%）、血中リンの低下（11.8%）、肝機能障害（11.8%）であった。（効能追加承認時の集計）[5.4参照]

17.1.4 進行又は再発悪性軟部腫瘍を対象とした外国臨床第Ⅲ相試験

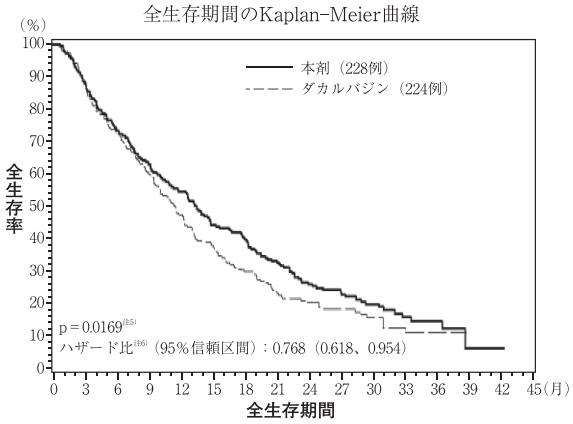
2レジメン以上の前治療歴を有する進行又は再発の脂肪肉腫及び平滑筋肉腫患者（452例）において、ダカルバジン注4)を比較対照とし、全生存期間を主要評価項目として本剤のダカルバジンに対する優越性の検証を目的とした第Ⅲ相比較試験が実施された。その結果、全生存期間において、本剤のダカルバジンに対する優越性が確認された。

本剤投与群における全生存期間の中央値は13.5ヵ月であった[14]。

安全性解析対象症例のうち本剤が投与された226 例中210例（92.9%）に副作用が認められた。主な副作用は、好中球減少（50.0%）、疲労（36.7%）、脱毛症（34.5%）、悪心（33.2%）、末梢神経障害（26.1%）、貧血（24.3%）、白血球減少（22.6%）、便秘（16.8%）、無力症（15.9%）、発熱（14.6%）、食欲減退（14.2%）、下痢（13.3%）、口内炎（12.8%）、嘔吐（11.9%）、頭痛（10.2%）であった。（効能追加承認時の集計）[5.4参照]

注4）ダカルバジンは悪性軟部腫瘍に対して国内未承認

全生存期間のKaplan-Meier曲線



注5）組織型、地域、前化学療法のレジメン数を層とした層別log-rank検定

注6）本剤／ダカルバジン
組織型、地域、前化学療法のレジメン数を層としたCox回帰モデルに基づき算出した。

18. 薬効薬理

18.1 作用機序

エリブリンメシル酸塩は、チューブリンの重合を阻害して微小管の伸長を抑制することで正常な紡錘体形成を妨げる。その結果、G_2／M期で細胞分裂を停止させてアポトーシスによる細胞死を誘導し、腫瘍増殖抑制作用を示す[15)~18)]。

18.2 抗腫瘍効果

18.2.1 *in vitro*試験

(1) エリブリンメシル酸塩は、ヒト乳癌由来細胞株（MDA-MB-231、MDA-MB-435、MDA-MB-468及びHCC1806）に対して、細胞増殖抑制作用を示した[15)、19)]。

(2) β-チューブリン変異を有するパクリタキセル耐性ヒト卵巣癌由来細胞株（1A9PTX10及び1A9PTX22）に対して、エリブリンメシル酸塩の細胞増殖抑制作用は減弱しなかった[19)]。

18.2.2 *in vivo*試験

エリブリンメシル酸塩は、ヒト乳癌由来細胞株（MDA-MB-435、MX-1及びUISO-BCA-1）、ヒト線維肉腫由来細胞株（HT-1080）、ヒト平滑筋肉腫由来細胞株（SK-LMS-1）及びヒトユーイング肉腫由来細胞株（A673）皮下移植マウスに対して、腫瘍増殖抑制作用を示し、実験終了時点まで腫瘍の完全退縮が維持されていたマウスも観察された[15)、20)、21)]。

19. 有効成分に関する理化学的知見

一般名：エリブリンメシル酸塩（Eribulin Mesilate）

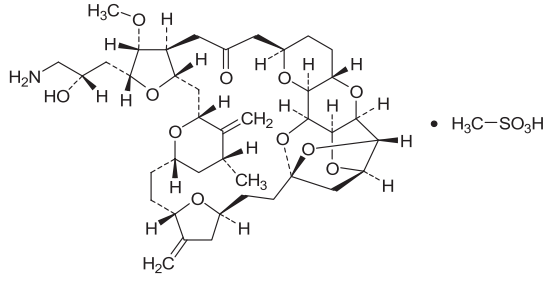
化学名：(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-2-[(2*S*)-3-Amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one monomethanesulfonate

分子式：$C_{40}H_{59}NO_{11}$・CH_4O_3S

分子量：826.00

性　状：エリブリンメシル酸塩は白色の粉末である。
本品は水、メタノール、エタノール(99.5)及びジメチルスルホキシドに溶けやすい。
本品は吸湿性である。

構造式：



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。

22．包装

2.0mL［1バイアル］

23．主要文献

1）社内資料：日本人固形がん患者を対象とした臨床第Ⅰ相試験（国内試験）（2011年4月22日承認、CTD 2.7.6.3） [HAL-0050]
2）社内資料：エリブリンメシル酸塩の血漿たん白結合（2011年4月22日承認、CTD 2.6.4.4.3） [HAL-0051]
3）社内資料：^{14}C-エリブリン酢酸塩由来放射能の分布（ラット、イヌ）（2011年4月22日承認、CTD 2.6.4.4.2.2） [HAL-0052]
4）社内資料：固形がん患者を対象としたマスバランス試験（外国試験）（2011年4月22日承認、CTD 2.7.6.4） [HAL-0053]
5）社内資料：エリブリンメシル酸塩の*in vitro*代謝（2011年4月22日承認、CTD 2.6.4.5.3） [HAL-0054]
6）社内資料：エリブリンメシル酸塩の母集団薬物動態解析（2011年4月22日承認、CTD 2.7.2.3.2.3） [HAL-0055]
7）Devriese L. A. et al.：Cancer Chemother. Pharmacol., 2012；70（6）：823-832 [HAL-0168]
8）Tan A. R. et al.：Cancer Chemother. Pharmacol., 2015；76（5）：1051-1061 [HAL-0638]
9）Devriese L. A. et al.：Invest. New Drugs, 2013；31（2）：381-389 [HAL-0119]
10）Devriese L. A. et al.：Br. J. Clin. Pharmacol., 2013；75（2）：507-515 [HAL-0135]
11）社内資料：進行又は再発乳癌を対象とした臨床第Ⅱ相試験（国内試験）（2011年4月22日承認、CTD 2.7.6.11） [HAL-0058]
12）社内資料：進行又は再発乳癌を対象とした臨床第Ⅲ相試験（外国試験）（2011年4月22日承認、CTD 2.7.6.12） [HAL-0059]
13）社内資料：進行又は再発悪性軟部腫瘍を対象とした臨床第Ⅱ相試験（国内試験）（2016年2月29日承認、CTD 2.7.6.3） [HAL-0342]
14）社内資料：進行又は再発悪性軟部腫瘍を対象とした臨床第Ⅲ相試験（外国試験）（2016年2月29日承認、CTD 2.7.6.1） [HAL-0343]
15）Towle M. J. et al.：Cancer Res., 2001；61（3）：1013-1021 [HAL-0002]
16）Kuznetsov G. et al.：Cancer Res., 2004；64（16）：5760-5766 [HAL-0003]
17）Jordan M. A. et al.：Mol. Cancer Ther., 2005；4（7）：1086-1095 [HAL-0004]
18）社内資料：エリブリンメシル酸塩の作用機序に関する検討（2011年4月22日承認、CTD 2.6.2.2.1.2） [HAL-0060]
19）社内資料：エリブリンメシル酸塩のがん細胞増殖抑制作用（*in vitro*）（2011年4月22日承認、CTD 2.6.2.2.1.1） [HAL-0061]
20）社内資料：エリブリンメシル酸塩の抗腫瘍効果（*in vivo*）（2011年4月22日承認、CTD 2.6.2.2.2.1） [HAL-0062]
21）社内資料：エリブリンメシル酸塩と他の抗がん剤の併用効果（*in vivo*）（2011年4月22日承認、CTD 2.6.2.2.2.4） [HAL-0063]

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（輸入元）

エーザイ株式会社
東京都文京区小石川4-6-10

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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
〈テセントリク点滴静注1200mg〉
○ 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
〈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
〈製剤共通〉
○ 切除不能な胞巣状軟部肉腫

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・効果にて製造販売承認されている。

以下に示すように，海外で実施された第 II 相臨床試験である ML39345試験（NCI 試験）の結果に加えて，本邦において国内第 II 相臨床試験である NCCH1907/MK008試験（ALBERT 試験）の結果が得られ，胞巣状軟部肉腫（ASPS）患者に対して本剤の有用性が示されたことから「切除不能な胞巣状軟部肉腫」の効能・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。

ML39345試験（NCI 試験）の試験概要

成人（18歳以上）及び小児/若年者（2歳以上18歳未満）の，測定可能病変を有する治癒切除不能 ASPS 患者に対し本剤を投与する第 II 相非盲検単群試験を，米国で実施した。

NCI 試験の monotherapy arm では，Simon の2段階デザインを採用した。最初に9例の患者を登録し，1例以上の患者で奏効が認められた場合，患者を15例追加登録することとした。患者24例中3例以上（12.5%以上）の患者で奏効が認められた場合，有効性をさらに検討する価値があると判断することとした。最終的に，NCI 試験の monotherapy arm の予定被験者数は53例とした。

本剤の用法・用量は，21日を1サイクルとし，成人（18歳以上）被験者には1200 mg，小児/若年者（2歳以上18歳未満）の被験者には15 mg/kg（最大1200 mg），各サイクルの Day 1に静脈内投与した。2年以上本剤投与を継続した被験者には，2年間までの treatment holiday を許容した。

NCCH1907/MK008試験（ALBERT 試験）の試験概要

16歳以上の，測定可能病変を有する治癒切除不能 ASPS 患者を対象に，本剤の有効性及び安全性を評価する第 II 相非盲検単群試験を，本邦で実施した。予定登録被験者数は20例とした。

本剤の用法・用量は，21日を1サイクルとし，成人（18歳以上）被験者には1200 mg，16歳以上18歳未満の被験者には15 mg/kg（最大1200 mg），各サイクルの Day 1に静脈内投与した。

NCI 試験及び ALBERT 試験の結果概要

NCI 試験では，最初に登録された19例を対象に主解析が実施されており，19例中8例で奏効（独立評価機関による評価）が確認され、真の奏効割合が事前に設定した閾値奏効割合5%を上回ると考えられたため、被験者数を50例に拡大した。

NCI 試験及び ALBERT 試験では，奏効割合（Independent Review Committee; IRC 評価）を主要評価項目とした。

NCI 試験及び ALBERT 試験の奏効割合（IRC 評価）は，24.5%（95%CI：13.34～38.87%）及び10.0%（95%CI：1.2～31.7%）であった（表 1.8.1.1.1-1）。ALBERT 試験においては，95%信頼区間の下限は事前に設定した閾値奏効割合5%を下回った。

表 1.8.1.1.1-1 奏効割合（IRC 評価）の要約（NCI 試験及び ALBERT 試験，有効性解析対象集団）

治験	NCI 試験	ALBERT 試験
N	49	20
奏効数	12	2
奏効割合（IRC 評価）(95%CI)	24.5% (13.34～38.87%)	10.0% (1.2～31.7%)
CR (%)	0	2 (10%*)
PR (%)	12 (24.5%)	0
SD (%)	24 (49.0%)	14 (70%*)
PD (%)	10 (20.4%)	4 (20%*)
評価不能等 (%)	3 (6.1%)	0

RECIST v1.1。確定（confirmed）のみ。

*: 解析計画及び解析結果に含まれない，手元計算に基づく参考値。

データカットオフ日：NCI 試験2021年9月1日，ALBERT 試験2022年3月3日

［5.3.5.2-2 Table 8，5.3.5.2-1 Table 14.2-2-1及び Table 14.4.6-1を改変］

NCI 試験の安全性解析対象集団49例で，有害事象は49例（100.0%）に認められた。

発現割合が40%以上の事象は，疲労27例（55.1%），高血糖26例（53.1%），リンパ球数減少22例（44.9%），悪心，高血圧及び頭痛各21例（42.9%），咳嗽20例（40.8%）であった。

ALBERT 試験の安全性解析対象集団20例で，有害事象は20例（100.0%）に認められた。

発現割合が20%以上の事象は，発熱8例（40.0%），リンパ球数減少6例（30.0%），アスパラギン酸アミノトランスフェラーゼ増加，頭痛及び貧血各5例（25.0%），アラニンアミノトランスフェラーゼ増加及び好中球数減少各4例（20.0%）であった。

NCI 試験及び ALBERT 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。

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。

以上のことから，ASPS 患者に対する本剤の忍容性が示された。ASPS 患者での本剤の安全性プロファイルは，他の悪性腫瘍の患者での本剤の安全性プロファイルと同様であり，本剤の新たな安全性シグナルは認められなかった。

以上，NCI 試験及び ALBERT 試験で得られた有効性及び安全性の結果から，ASPS 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・効果に「切除不能な胞巣状軟部肉腫」を設定した。

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60分かけて3週間間隔で点滴静注する。なお、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。 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60分かけて3週間間隔で点滴静注する。なお、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。 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60分かけて3週間間隔で点滴静注する。なお、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。
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60分かけて3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。なお、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。
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60分かけて3週間間隔で点滴静注する。なお、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。
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60分かけて3週間間隔で点滴静注する。なお、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。
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60分かけて2週間間隔で点滴静注する。なお、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。
切除不能な胞巣状軟部肉腫	通常、18歳以上の患者にはアテゾリズマブ（遺伝子組換え）として1回1200mg を60分かけて3週間間隔で点滴静注する。通常、2歳以上18歳未満の患者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60分かけて3週間間隔で点滴静注する。なお、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。

7. 用法及び用量に関連する注意

〈効能共通〉

（省略）

〈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〉

（省略）

〈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〉

（省略）

〈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〉

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〉

（省略）

注）追加，変更箇所に下線を付した。

1.8.1.2.1 用法及び用量の設定根拠

2歳以上の ASPS 患者を対象に15 mg/kg Q3W（18歳未満，最大1200 mg/body）又は1200 mg/body Q3W（18歳以上）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。

NCI 試験では，21日を1サイクルとし，成人（18歳以上）被験者には1200 mg，小児/若年者（2歳以上18歳未満）の被験者には15mg/kg（最大1200mg），各サイクルの Day 1に静脈内投与した。

ALBERT 試験では，21日を1サイクルとし，成人（18歳以上）被験者には1200 mg，16歳以上18歳未満の被験者には15 mg/kg（最大1200 mg），各サイクルの Day 1に静脈内投与した。

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週間間隔投与法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項に記載した通り，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週間間隔投与法の設定は忍容性があると判断した。

成人集団での民族差は，テセントリク点滴静注1200 mg 初回申請資料（CTD 2.7.2.3.8章「民族差の検討」）に記載の通り，popPK の解析結果及びトラフ濃度推移から薬物動態に民族差がないことが確認されており，その後の適応追加時においても民族差は認められていない。また，本剤は ICH E5（補遺 D）に基づく評価においても民族的要因による影響を受けづらい薬物であると考えられる。

ASPS 小児患者集団での薬物動態データは得られていないものの，CTD 2.7.2.3.2章「母集団薬物動態解析 及び母集団薬物動態（popPK）モデルを用いた曝露量のシミュレーション結果」に記載の通り，小児を含む固形がん患者を対象として実施した臨床試験（GO29664）のデータを用いて構築した popPK モデルのシミュレーション結果から，アテゾリズマブの薬物動態パラメータ及び薬物動態に影響を与える因子は，小児及び若年成人と成人で類似することが確認された。また，アテゾリズマブの曝露量［Area Under the Curve（AUC），maximum drug concentration（C_{max}）及び minimum drug concentration （C_{min}）］は，15 mg/kg 又は1200 mg/body の Q3W 投与時，2歳以上12歳未満及び12歳以上18歳未満の年齢集団と18歳以上の若年成人及び成人で大きな差異は認められず，成人の薬物動態から小児の薬物動態の外挿による予測は可能であると考えられた。2歳以上12歳未満の年齢集団では，Cycle 1の AUC 及び C_{max} が15 mg/kg 投与の成人と比べて20%程度低いものの，Cycle 1及び定常状態における C_{min} は成人と類似しており，その値はアテゾリズマブのターゲット血清中濃度である6 μg/mL を十分上回っており，成人と同様の有効性が期待できると考えられた。

また，GO29664試験の安全性解析対象集団87例において，有害事象は85例（97.7%）に認められた。発現割合が20%以上の事象は，発熱36例（41.4%），疲労31例（35.6%），便秘29例（33.3%），貧血25例（28.7%），咳嗽22例（25.3%），嘔吐21例（24.1%），下痢19例（21.8%），食欲減退及び頭痛各18例（20.7%）であった。GO29664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。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。また，CTD 表2.5.5.1-3「安全性の概要（GO29664試験，安全性解析対象集団，年齢群別）」及び表2.5.5.3-3「いずれかの群で発現割合が10%以上の有害事象の重症度別の要約（GO29664試験，安全性解析対象集団）」より，2歳未満，2歳以上12歳未満及び12歳以上18歳未満の年齢集団と18歳以上の年齢集団で安全性について大きな差異は認められなかった。

以上のことから，非日本人の薬物動態から日本人の薬物動態の外挿及び，成人の薬物動態から小児の薬物動態の外挿による予測は可能であり，日本人 ASPS 患者に対する用法及び用量は，米国での承認用法及び用量である15 mg/kg Q3W（18歳未満，最大1200 mg/body）又は1200 mg/body Q3W（18歳以上）が適切であると考えた。

GO29664試験の試験概要

30歳未満（成人及び小児：体重3 kg 以上）の前治療歴のある固形癌患者を対象にアテゾリズマブの用法用量を検討した試験である。予定登録被験者数は約100例とした。

本剤の用法・用量は、成人（18歳以上）には1200 mg の固定用量で，小児（2歳以上）には15 mg/kg（最大1200 mg），3週間毎に，8カ月まで点滴静脈内投与した。8カ月時点で臨床的利益が継続している患者は，Medical Monitor の承認のもと，治験薬を継続することを可能とした。

1.8.1.2.2 用法及び用量に関連する注意の設定根拠

現時点では切除不能な ASPS に対し，他の抗悪性腫瘍剤との併用療法に関する有効性及び安全性は確立されていないことから，併用療法に関する注意が必要と考え，7.4項に「切除不能な胞巣状軟部肉腫」を追加した。

なお，審査の過程において，用法及び用量は以下の記載となった。

【用法及び用量】

効能又は効果	用法及び用量
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60分かけて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60分かけて3週間間隔で点滴静注する。なお、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。

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、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	変更なし

の状態を十分に観察すること。[11.1.18参照]	
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> 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。	ALBERT試験（2022年3月3日カットオフデータ）、ML39345試験（2021年9月1日カットオフデータ）に基づき変更した。 2歳未満を対象とした、切除不能な胞巣状軟部肉腫に対する臨床試験は実施していないことから追記した。
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（2.9%） [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（5.9%）、ALT増加（5.9%）、Al-P増加（2.0%）、γ-GTP増加(0.8%)、ビリルビン増加(1.4%)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（1.3%） 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%)	ALBERT試験（2022年3月3日カットオフデータ）、ML39345試験（2021年9月1日カットオフデータ）に基づき変更した。

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（0.5%）、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（0.2%）、髄膜炎（0.2%）、脊髄炎（頻度不明）
11.1.10 神経障害
末梢性ニューロパチー（3.2%）、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（0.2%）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 Infusion reaction（2.5%）
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。
11.1.18 発熱性好中球減少症（2.8%注）
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]

ALBERT 試験（2022年3月3日カットオフデータ）、ML39345 試験（2021年9月1日カットオフデータ）に基づき変更した。

CCDS 改訂に伴い「血中 CK 増加」を追記した。

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、浮動性めまい、味覚異常、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（10.3%）、食欲減退、便秘	嘔吐、口内炎、腹痛、口内乾燥	腹部膨満、嚥下障害、消化不良、リパーゼ増加、アミラーゼ増加	
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、口腔咽頭痛、胸水、しゃっくり、喀血、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、紅斑、ざ瘡様皮膚炎	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、血小板減少、好中球減少	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、血中甲状腺刺激ホルモン増加、高血糖、低アルブミン血症、脱水	血中甲状腺刺激ホルモン減少、高カリウム血症、低リン血症、低カルシウム血症		
その他	疲労（14.8%）、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、胸痛、過敏症、血中乳酸脱水素酵素増加、疼痛		

注）発現頻度は、IMpower150試験から集計した。

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。	本剤は抗体製剤であるため、安定性及び無菌性の維持の観点から、溶解後の残液は廃棄し、再使用や保存はしないことが必要なため設定した。

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

貯　　法：2～8℃保存
有効期間：36 箇月

日本標準商品分類番号
874291

	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

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

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

〈テセントリク点滴静注 1200mg〉
○ 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
〈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
〈製剤共通〉
○ 切除不能な胞巣状軟部肉腫

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

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）

6. 用法及び用量

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 60 分かけて 3 週間間隔で点滴静注する。なお、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。 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 60 分かけて 3 週間間隔で点滴静注する。なお、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。 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 60 分かけて 3 週間間隔で点滴静注する。なお、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。
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 60 分かけて 3 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。なお、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。
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 60 分かけて 3 週間間隔で点滴静注する。なお、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。
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 60 分かけて 3 週間間隔で点滴静注する。なお、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。
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 60 分かけて 2 週間間隔で点滴静注する。なお、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。
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 60 分かけて 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

効能又は効果	用法及び用量
	子組換え）として1回15mg/kg（体重）（最大1200mg）を60分かけて3週間間隔で点滴静注する。なお、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。

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。
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	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	左記の状態が回復するまで、本剤を休薬する。

副作用	程度	処置
	候性の甲状腺機能亢進症	
	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。
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。

副作用	程度	処置
	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〉

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]

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、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。[11.1.18 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〉

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。

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（2.9%）

[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（5.9%）、ALT 増加（5.9%）、Al-P 増加（2.0%）、γ-GTP 増加（0.8%）、ビリルビン増加（1.4%）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**（1.3%）

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（0.5%）、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（0.2%）**、髄膜炎**（0.2%）**、脊髄炎（頻度不明）**

11.1.10 神経障害

末梢性ニューロパチー（3.2%）、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（0.2%）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 Infusion reaction（2.5%）

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。

11.1.18 発熱性好中球減少症（2.8%[注)]）

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]

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、浮動性めまい、味覚異常、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（10.3%）、食欲減退、便秘	嘔吐、口内炎、腹痛、口内乾燥	腹部膨満、嚥下障害、消化不良、リパーゼ増加、アミラーゼ増加	
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、口腔咽頭痛、胸水、しゃっくり、喀血、低酸素症、鼻閉	
皮膚	発疹、そう痒症	脱毛症、斑状丘疹	蕁麻疹、皮膚炎、	

	5%以上	1%以上～5%未満	1%未満	頻度不明
		状皮疹、皮膚乾燥、紅斑、ざ瘡様皮膚炎	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、血小板減少、好中球減少	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、血中甲状腺刺激ホルモン増加、高血糖、低アルブミン血症、脱水	血中甲状腺刺激ホルモン減少、高カリウム血症、低リン血症、低カルシウム血症	
その他	疲労（14.8%）、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、胸痛、過敏症、血中乳酸脱水素酵素増加、疼痛	

注）発現頻度は、IMpower150 試験から集計した。

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。

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

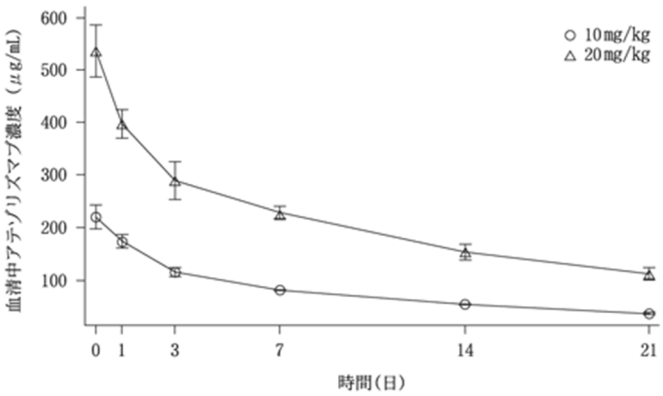
16.1 血中濃度

16.1.1 単回投与

日本人の進行固形癌患者 3 例ずつに本剤 10 又は 20mg/kg を 90 分（±15 分）間点滴静注[注1)] 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 週間間隔又は 840mg を 2 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）

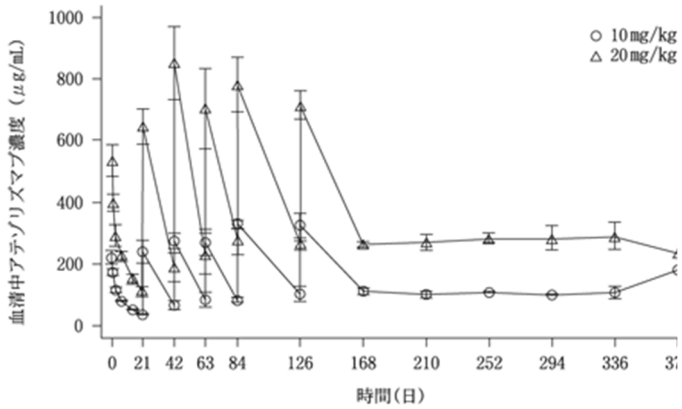
投与量 (mg/kg)	C_{max}* (μg/mL)	AUC_{inf} (μg・day/mL)	$V_{d,ss}$ (L)	CL (L/day)	$t_{1/2}$ (day)
10	220± 21.9	2290± 101	3.72 ± 1.14	0.236± 0.0572	11.7± 0.969
20	536± 49.4	6630± 668	3.82 ± 0.718	0.213± 0.0609	13.0± 1.32

*C_{max}：初回投与時（Cycle 1 Day 1）の投与後 30 分の採血

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）[2)]

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）[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	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)

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）[4)]［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)

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）

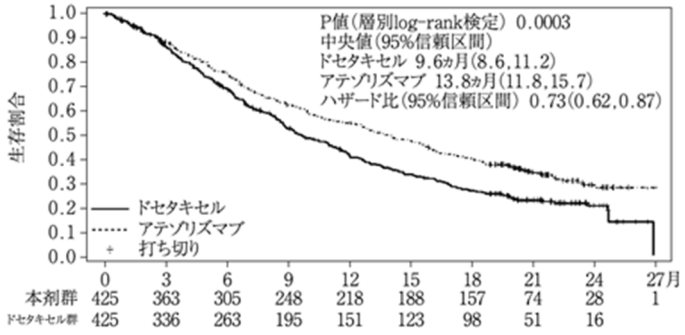
プラチナ製剤を含む化学療法歴[注1)]のある切除不能な進行・再発の非小細胞肺癌患者1225例（本剤群613例、ドセタキセル群612例）を対象に、本剤とドセタキセルとの有効性及び安全性を比較する第Ⅲ相試験を実施した。

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[5)]。

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[6)]。

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)

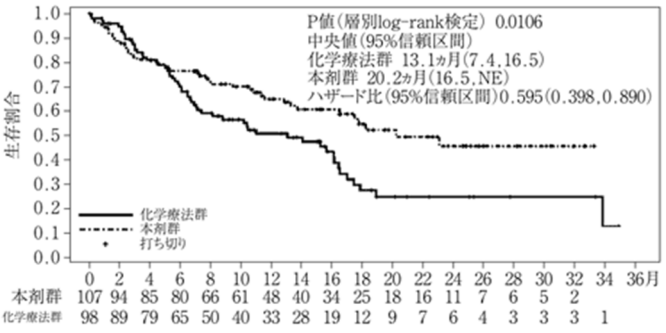
化学療法歴のない[注2)]、PD-L1 陽性（腫瘍細胞又は腫瘍浸潤免疫細胞における PD-L1 発現率が 1%以上）の切除不能な進行・再発の非小細胞肺癌患者 572 例（日本人 51 例を含む）を対象に、本剤 1200 mg（本剤群）の有効性及び安全性を、プラチナ製剤（シスプラチン又はカルボプラチン）及びペメトレキセド又はゲムシタビンの併用投与（化学療法群）と比較する第Ⅲ相試験を実施した。中間解析の結果、*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者を除く 554 例の ITT-WT 集団のうち TC3/IC3-WT[注3)] 集団 205 例（日本人 24 例を含む）において、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[7)]。

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[8)]。

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）

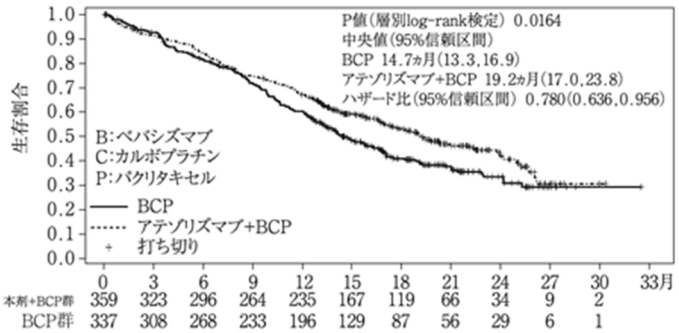
化学療法歴のない[注4)]、扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌患者 1202 例（日本人 93 例を含む）を対象に、本剤 1200mg と他の抗悪性腫瘍剤（カルボプラチン＋パクリタキセル［A 群、402 例］、又はカルボプラチン＋パクリタキセル＋ベバシズマブ（遺伝子組換え）［B 群、400 例］）の併用投与の有効性及び安全性を、併用化学療法（カルボプラチン＋パクリタキセル＋ベバシズマブ（遺伝子組換え）［C 群、400 例］）と比較する第Ⅲ相試験を実施した[注5)]。2018 年 1 月 22 日の中間解析の結果、*EGFR* 遺伝子変異陽性又は *ALK* 融合遺伝子陽性の患者を除く 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[9)]。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］）[10)]。

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[10)]。

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）



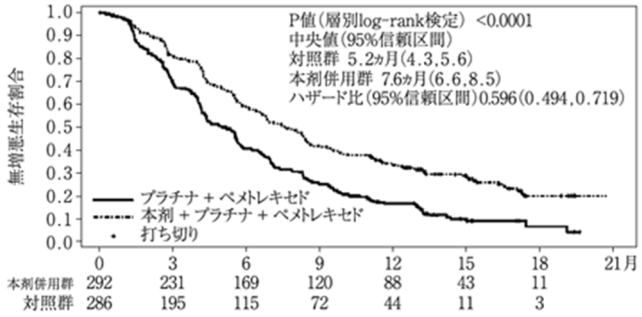
17.1.4 国際共同第Ⅲ相臨床試験（IMpower132 試験）

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[11]。

注6）本剤1200mg、カルボプラチンAUC6又はシスプラチン75mg/m²、ペメトレキセド500mg/m²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。

IMpower132試験の無増悪生存期間のKaplan-Meier曲線（全患者集団）



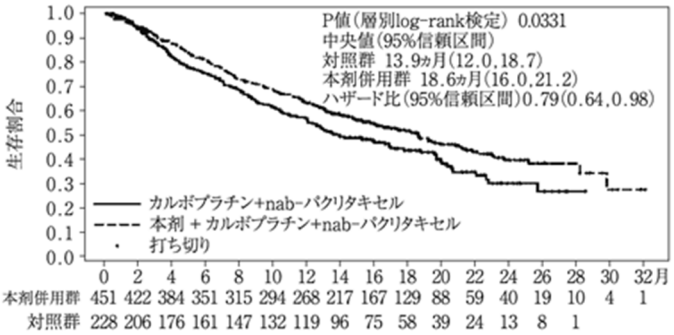
17.1.5 海外第Ⅲ相臨床試験（IMpower130試験）

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[12]。
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[13]。

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/m²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〉

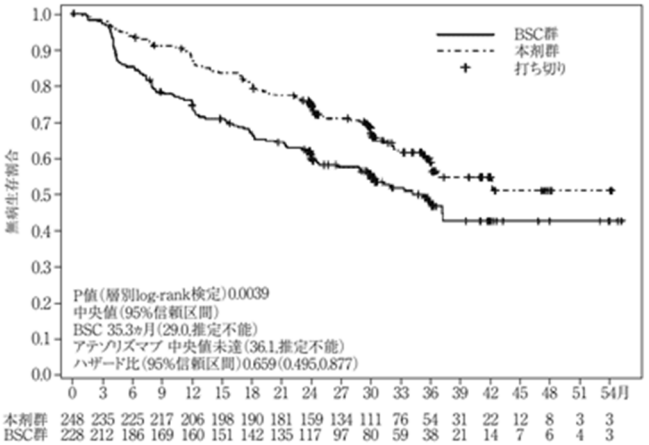
17.1.6 国際共同第Ⅲ相臨床試験（IMpower010試験）

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[14]。
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[15]。

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[15]。

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］	

＊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	248	NE［NE, NE］	0.772*2［0.509, 1.170］
	BSC	228	NE［NE, NE］	
1≦TC＜50%	本剤	133	NE［NE, NE］	1.218*3［0.705, 2.104］
	BSC	114	NE［NE, NE］	
TC≧50%	本剤	115	NE［NE, NE］	0.366*3［0.181, 0.742］
	BSC	114	NE［NE, NE］	

＊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）

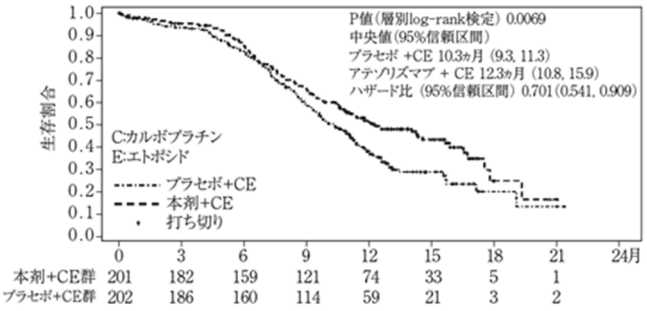
化学療法歴のない進展型小細胞肺癌患者[注11] 403 例（日本人 42 例を含む）を対象に、本剤 1200mg とカルボプラチン＋エトポシドの併用療法（本剤群、201 例）の 3 週間間隔投与の有効性及び安全性をプラセボとカルボプラチン＋エトポシドの併用療法（プラセボ群、202 例）と比較する第Ⅰ/Ⅲ相ランダム化試験を実施した[注12]。中間解析の結果、全患者集団において、本剤群でプラセボ群と比較して主要評価項目である全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］：0.701［0.541, 0.909］、P=0.0069［層別 log-rank 検定］、有意水準両側 0.0193）、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[16]。

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[17]。

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）

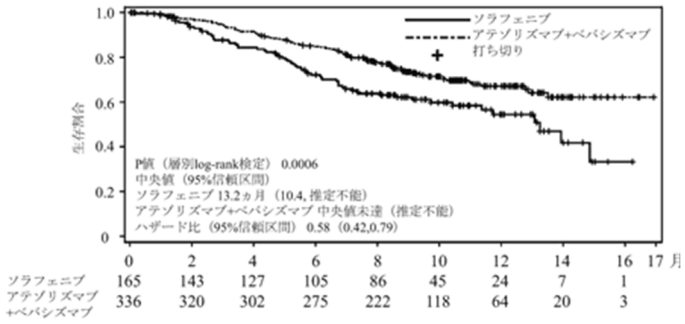
全身化学療法歴のない Child-Pugh 分類 A の切除不能な肝細胞癌患者[注13] 501 例（日本人 61 例を含む）を対象に、本剤 1200mg とベバシズマブ（遺伝子組換え）（本剤併用群、336 例）の併用投与の有効性及び安全性を、ソラフェニブ（対照群、165 例）と比較する第Ⅲ相ランダム化試験を実施した[注14]。中間解析の結果、501 例（日本人 61 例を含む）の ITT 集団において、本剤併用群で対照群と比較して、主要評価項目の一つである全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］0.58［0.42, 0.79］、P=0.0006［層別 log-rank 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[18]。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[18]。

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。

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〉

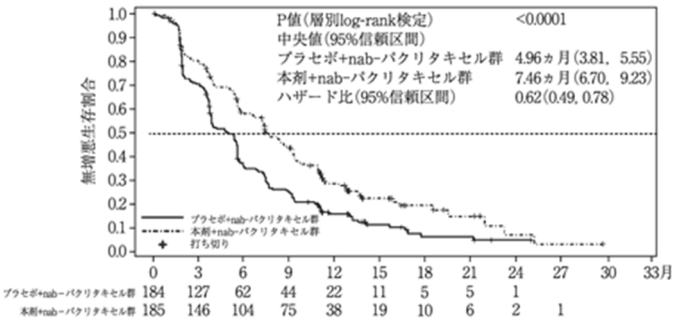
17.1.9 国際共同第Ⅲ相臨床試験（IMpassion130 試験）

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[19)]。

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[20)]。

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[21)]。

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[22)]。

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[23)]。

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。

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

1) Mizugaki H, et al. Invest New Drugs. 2016;34 (5) :596-603
2) 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）
3) 社内資料：薬物動態解析報告書（IMpassion130 試験）
4) 社内資料：海外第Ⅰ/Ⅱ相試験（GO29664 試験）
5) Rittmeyer A, et al. Lancet. 2017;389 (10066) :255-265
6) 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）
7) Herbst R, et al. N Engl J Med. 2020;383 (14) :1328-1339
8) 社内資料：国際共同第Ⅲ相臨床試験（IMpower110 試験）
9) Socinski MA, et al. N Engl J Med. 2018;378 (24) :2288-2301
10) 社内資料：国際共同第Ⅲ相臨床試験（IMpower150 試験）
11) 社内資料：国際共同第Ⅲ相臨床試験（IMpower132 試験）
12) West H, et al. Lancet Oncol. 2019;20 (7) :924-937
13) 社内資料：海外第Ⅲ相臨床試験（IMpower130 試験）
14) Felip E, et al. Lancet. 2021;398 (10308) :1344-1357
15) 社内資料：国際共同第Ⅲ相臨床試験（IMpower010 試験）
16) Horn L, et al. N Engl J Med. 2018;379 (23) : 2220-2229
17) 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）
18) 社内資料：国際共同第Ⅲ相臨床試験（IMbrave150 試験）
19) Schmid P, et al. N Engl J Med. 2018;379 (22) : 2108-2121
20) 社内資料：国際共同第Ⅲ相臨床試験（IMpassion130 試験）
21) 社内資料：海外第Ⅱ相臨床試験（ML39345 試験）
22) 社内資料：国内第Ⅱ相臨床試験（ALBERT 試験）
23) 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
ロシュ グループ

® F. ホフマン・ラ・ロシュ社（スイス） 登録商標

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>〈テセントリク点滴静注1200mg〉
○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
〈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>
<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60分かけて3週間間隔で点滴静注する。なお、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。

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60分かけて3週間間隔で点滴静注する。なお、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。

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60分かけて3週間間隔で点滴静注する。なお、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。</td></tr>
<tr><td>PD-L1 陽性の非小細胞肺癌における術後補助療法</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60分かけて 3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。なお、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。</td></tr>
<tr><td>進展型小細胞肺癌</td><td>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60分かけて3週間間隔で点滴静注する。なお、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。</td></tr>
<tr><td>切除不能な</td><td>ベバシズマブ（遺伝子組換え）との併用において、通常、成</td></tr>
</table>
</td></tr>
</table>

	肝細胞癌	人にはアテゾリズマブ（遺伝子組換え）として1回1200mg を60分かけて3週間間隔で点滴静注する。なお、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。
	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60分かけて2週間間隔で点滴静注する。なお、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。
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。

副　作　用	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試験及び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）のうち本剤が投与された被験者の3259例中2279例（69.9%）に副作用が発現した。 試験全体 副作用　例数 疲労　473 下痢　366 悪心　334 発疹　276 食欲減退　269　等 試験全体 臨床検査値異常　例数 血小板減少　209 好中球減少　191 ALT増加　188 AST増加　188 白血球減少　102　等
会　　社	中外製薬株式会社　製剤：輸入

（変　更）

<table>
<tr><td>化学名・別名</td><td></td></tr>
<tr><td>構　造　式</td><td></td></tr>
<tr><td>効能・効果</td><td>〈テセントリク点滴静注1200mg〉
○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
〈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
〈製剤共通〉
○切除不能な胞巣状軟部肉腫</td></tr>
<tr><td>用法・用量</td><td>
<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60分かけて3週間間隔で点滴静注する。なお、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。

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60分かけて3週間間隔で点滴静注する。なお、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。

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60分かけて3週間間隔で点滴静注する。なお、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。</td></tr>
<tr><td>PD-L1陽性の非小細胞肺癌における術後補助療法</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60分かけて3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。なお、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。</td></tr>
<tr><td>進展型小細胞肺癌</td><td>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60分かけて3週間間隔で点滴静注する。なお、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。</td></tr>
<tr><td>切除不能な肝細胞癌</td><td>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60分かけて3週間間隔で点滴静注する。なお、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。</td></tr>
<tr><td>PD-L1陽性のホルモン受容体陰性</td><td>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60分かけて2週間間隔で点滴静注する。なお、初回</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td><table>
<tr><td>かつHER2陰性の手術不能又は再発乳癌</td><td>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。</td></tr>
<tr><td>切除不能な胞巣状軟部肉腫</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60分かけて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60分かけて3週間間隔で点滴静注する。なお、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。</td></tr>
</table></td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td></td></tr>
<tr><td>毒　　性</td><td></td></tr>
<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 試験のうち本剤が投与された被験者の3328例中2342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>216</td><td></td></tr>
<tr><td>下痢</td><td>372</td><td></td><td>好中球減少</td><td>199</td><td></td></tr>
<tr><td>悪心</td><td>343</td><td></td><td>AST 増加</td><td>198</td><td></td></tr>
<tr><td>発疹</td><td>287</td><td></td><td>ALT 増加</td><td>197</td><td></td></tr>
<tr><td>食欲減退</td><td>274</td><td>等</td><td>白血球減少</td><td>114</td><td>等</td></tr>
</table></td></tr>
<tr><td>会　　社</td><td></td></tr>
</table>

（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							

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
5.3.2.3　他のヒト生体試料を用いた試験報告書							
該当資料なし							
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							
5.3.3.5-1	—	PPK of Atezolizumab in Pediatric and Young Adult Patients with Previously Treated Solid Tumors	—	海外	—	評価	あり

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
5.3.3.5-2	—	MODELING AND SIMULATION REPORT POPULATION PK SIMULATIONS OF ATEZOLIZUMAB IN PEDIATRIC PATIENTS	—	海外	—	評価	あり
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							

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
	5.3.5.2-1	—	切除不能胞巣状軟部肉腫に対するアテゾリズマブ療法の多施設共同第II 相医師主導治験 治験実施計画書番号：NCCH1907/MK008 治験総括報告書	2020 年5 月[redacted]日（最初の被験者の同意取得日） 治験終了日：2022 年3 月[redacted]日（最後の被験者の最終観察日）	国内	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_body	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_synopsis	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり

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
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1611	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1612	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1613	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり

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
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1614	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1615	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1616	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり

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
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1618	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1619	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_16110	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり

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
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_16111	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_16113	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1621	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり

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
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1622	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1623	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1624	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり

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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
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1625	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1626	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1627	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり

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	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
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1628	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-2	—	Primary CSR Study ML39345, (P10005) Report No. 1110042 May, 2022 （NCI試験）_1629	First Patient Enrolled: [redacted]-Apr-2017 Data cutoff: 01-Sep-2021	海外	—	評価	あり
	5.3.5.2-3	—	Primary CSR Study GO29664, Report No. 1080984, August 2018.	First Patient Enrolled: [redacted]Nov 2015 Last Patient Entered: [redacted] 20[redacted] Data cut-off: 02 Apr 2018	海外	—	評価	あり

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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
5.3.5.2-4	—	Final CSR Study GO29664, Report No. 1095866, November 2019.	First Patient Enrolled: [redacted]-Nov-2015 Data cut-off: 06-Jun-2019 Last Patient Last Visit: [redacted]-Jun-2019	海外	—	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							
5.3.5.3-1	—	Integrated Statistical Analysis Report Atezolizumab, ASPS	—	国内	—	参考	なし
5.3.5.4　その他の試験報告書							
該当資料なし							
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 1122480 & テセントリク安全性定期報告	—	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							

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5.3.7.1-1	—	症例一覧表		国内		評価	なし
5.3.7.2　有害事象一覧表							
5.3.7.2-1	—	有害事象一覧表（ALBERT試験）		国内		評価	なし
5.3.7.2-2	—	有害事象一覧表（NCI試験）		海外		評価	なし
5.3.7.2-3	—	有害事象一覧表（GO29664試験Data cut-off 02 Apr 2018）		海外		評価	なし
5.3.7.2-4	—	有害事象一覧表（GO29664試験Data cut-off 06 Jun 2019）		海外		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（ALBERT試験）		国内		評価	なし
5.3.7.3-2	—	重篤な有害事象一覧表（NCI試験）		海外		評価	なし
5.3.7.3-3	—	重篤な有害事象一覧表（GO29664試験Data cut-off 02 Apr 2018）		海外		評価	なし
5.3.7.3-4	—	重篤な有害事象一覧表（GO29664試験Data cut-off 06 Jun 2019）		海外		評価	なし

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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
5.3.7.4　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（ALBERT試験）		国内		評価	なし
5.3.7.4-2	—	臨床検査値異常一覧表（NCI試験）		海外		評価	なし
5.3.7.4-3	—	臨床検査値異常一覧表（GO29664試験Data cut-off 02 Apr 2018）		海外		評価	なし
5.3.7.4-4	—	臨床検査値異常一覧表（GO29664試験Data cut-off 06 Jun 2019）		海外		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

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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	Ferrari A, Sultan I, Huang TT, et al.	Soft tissue sarcoma across the age spectrum: a population-based study from the Surveillance Epidemiology and End Results database.	Pediatr Blood Cancer. 2011;57(6):943-949	2.5-1)
5.4-2	Wang H, Jacobson A, Harmon DC, et al.	Prognostic factors in alveolar soft part sarcoma: A SEER analysis.	J Surg Oncol. 2016;113(5):581-586	2.5-3)
5.4-3	Wang Y, Du B, Yang M, He W.	Paediatric orbital alveolar soft part sarcoma recurrence during long-term follow-up: a report of 3 cases and a review of the literature.	BMC Ophthalmol. 2020;20(1):60	2.5-4)
5.4-4	Ogose A, Yazawa Y, Ueda T, et al.	Alveolar soft part sarcoma in Japan: multi-institutional study of 57 patients from the Japanese Musculoskeletal Oncology Group.	Oncology. 2003;65(1):7-13	2.5-5)
5.4-5	Ogura K, Beppu Y, Chuman H, et al.	Alveolar soft part sarcoma: a single-center 26-patient case series and review of the literature.	Sarcoma. 2012;2012:907179	2.5-6)
5.4-6	松井寿夫, 牧山尚也, 金森昌彦, 前田明夫.	術前化学療法が有効であった胞巣状軟部肉腫の1例	癌と化学療法．1991;18(3):481-484	2.5-7)
5.4-7	Paoluzzi L, Maki RG.	Diagnosis, Prognosis, and Treatment of Alveolar Soft-Part Sarcoma: A Review.	JAMA Oncol. 2019;5(2):254-260	2.5-8)

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5.4　参考文献

CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-8	Orbach D, Brennan B, Casanova M, et al.	Paediatric and adolescent alveolar soft part sarcoma: A joint series from European cooperative groups.	Pediatr Blood Cancer. 2013;60(11):1826-1832	2.5-9)
5.4-9	National Comprehensive Cancer Network.	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®) Soft Tissue Sarcoma. Version 3. 2023	—	2.5-10)
5.4-10	Gronchi A, Miah AB, Dei Tos AP, et al.	Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up☆.	Ann Oncol. 2021;32(11):1348-1365	2.5-11)
5.4-11	Portera CA Jr, Ho V, Patel SR, et al.	Alveolar soft part sarcoma: clinical course and patterns of metastasis in 70 patients treated at a single institution.	Cancer. 2001;91(3):585-591	2.5-12) 2.7.3-1)
5.4-12	Reichardt P, Lindner T, Pink D, Thuss-Patience PC, Kretzschmar A, Dörken B.	Chemotherapy in alveolar soft part sarcomas. What do we know?.	Eur J Cancer 2003;39(11):1511-1516	2.5-13)
5.4-13	Stacchiotti S, Negri T, Zaffaroni N, et al.	Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect.	Ann Oncol. 2011;22(7):1682-1690	2.5-14)

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CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-14	Li T, Wang L, Wang H, et al.	A retrospective analysis of 14 consecutive Chinese patients with unresectable or metastatic alveolar soft part sarcoma treated with sunitinib.	Invest New Drugs. 2016;34(6):701-706	2.5-15)
5.4-15	Stacchiotti S, Mir O, Le Cesne A, et al.	Activity of Pazopanib and Trabectedin in Advanced Alveolar Soft Part Sarcoma.	Oncologist. 2018;23(1):62-70	2.5-16) 2.7.3-3)
5.4-16	Liu J, Fan Z, Li S, et al.	Target therapy for metastatic alveolar soft part sarcoma: a retrospective study with 47 cases.	Ann Transl Med. 2020;8(22):1493	2.5-17)
5.4-17	Urakawa H, Kawai A, Goto T, et al.	Phase II trial of pazopanib in patients with metastatic or unresectable chemoresistant sarcomas: A Japanese Musculoskeletal Oncology Group study.	Cancer Sci. 2020;111(9):3303-3312	2.5-18)
5.4-18	Nakamura T, Matsumine A, Kawai A, et al.	The clinical outcome of pazopanib treatment in Japanese patients with relapsed soft tissue sarcoma: A Japanese Musculoskeletal Oncology Group (JMOG) study.	Cancer. 2016;122(9):1408-1416	2.5-19)
5.4-19	Groisberg R, Hong DS, Behrang A, et al.	Characteristics and outcomes of patients with advanced sarcoma enrolled in early phase immunotherapy trials.	J Immunother Cancer. 2017;5(1):100	2.5-20)
5.4-20	Wilky BA, Trucco MM, Subhawong TK, et al.	Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial.	Lancet Oncol. 2019;20(6):837-848	2.5-21)
5.4-21	Alshamsan B, Badran A, Alshibany A, et al.	Real-World Outcome and Prognostic Factors of Pazopanib in Advanced Soft Tissue Sarcoma.	Cancer Manag Res. 2021;13:6755-6766	2.5-22)

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CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-22	Kim M, Kim TM, Keam B, et al.	A Phase II Trial of Pazopanib in Patients with Metastatic Alveolar Soft Part Sarcoma.	Oncologist. 2019;24(1):20-e29	2.5-23)
5.4-23	[redacted]	Atezolizumab_ASPS_C-CATデータ解析計画報告書_v1.00	中外製薬株式会社 社内報告書	2.5-24)
5.4-24	[redacted]	Atezolizumab_ASPS_MasterKeyデータ解析計画報告書_v1.00	中外製薬株式会社 社内報告書	2.5-25) 273-5)
5.4-25	Moreno Tellez C, Leyfman Y, D'Angelo SP, Wilky BA, Dufresne A.	Immunotherapy in Sarcoma: Where Do Things Stand?	Surg Oncol Clin N Am. 2022;31(3):381-397	2.5-26)
5.4-26	Yang Y, Beeraka NM, Liu J, et al.	Comparative Combinatorial Implications and Theranostics of Immunotherapy in the Impediment of Alveolar Soft Part Sarcoma.	Curr Pharm Des. 2022;28(41):3404-3412	2.5-27)
5.4-27	Shi Y, Cai Q, Jiang Y, et al.	Activity and Safety of Geptanolimab (GB226) for Patients with Unresectable, Recurrent, or Metastatic Alveolar Soft Part Sarcoma: A Phase II, Single-arm Study.	Clin Cancer Res. 2020;26(24):6445-6452	2.5-28)
5.4-28	Yang J, Dong L, Yang S, et al.	Safety and clinical efficacy of toripalimab, a PD-1 mAb, in patients with advanced or recurrent malignancies in a phase I study.	Eur J Cancer. 2020;130:182-192	2.5-29)
5.4-29	D'Angelo SP, Mahoney MR, Van Tine BA, et al.	Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials.	Lancet Oncol. 2018;19(3):416-426	2.5-30)

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5.4　参考文献

CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-30	菅原正登.	希少がん疾患各論 骨軟部腫瘍・肉腫 胞巣状軟部肉腫の診断と治療.	日本臨床. 2021 79 (suppl1) :548-551	2.5-31)
5.4-31	Flores RJ, Harrison DJ, Federman NC, et al.	Alveolar soft part sarcoma in children and young adults: A report of 69 cases.	Pediatr Blood Cancer. 2018;65(5):e26953	2.5-32)
5.4-32	Huan C, Kelly ML, Steele R, Shapira I, Gottesman SR, Roman CA.	Transcription factors TFE3 and TFEB are critical for CD40 ligand expression and thymus-dependent humoral immunity.	Nat Immunol. 2006;7(10):1082-1091	2.5-33)
5.4-33	Kobos R, Nagai M, Tsuda M, et al.	Combining integrated genomics and functional genomics to dissect the biology of a cancer-associated, aberrant transcription factor, the ASPSCR1-TFE3 fusion oncoprotein.	J Pathol. 2013;229(5):743-754	2.5-34)
5.4-34	Ogose A, Kawashima H, Hotta T, et al.	Frequent expression of human leukocyte antigen class I and the status of intratumoral immune cells in alveolar soft part sarcoma.	Oncol Lett. 2017;13(4):2169-2176	2.5-35)
5.4-35	O'Sullivan Coyne G, Naqash AR, Sankaran H, Chen AP.	Advances in the management of alveolar soft part sarcoma.	Curr Probl Cancer. 2021;45(4):100775	2.5-36)

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CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-36	Goldberg JM, Fisher DE, Demetri GD, et al.	Biologic Activity of Autologous, Granulocyte-Macrophage Colony-Stimulating Factor Secreting Alveolar Soft-Part Sarcoma and Clear Cell Sarcoma Vaccines.	Clin Cancer Res. 2015;21(14):3178-3186	2.5-37)
5.4-37	Brohl AS, Sindiri S, Wei JS, et al.	Immuno-transcriptomic profiling of extracranial pediatric solid malignancies.	Cell Rep. 2021;37(8):110047.	2.5-38)
5.4-38	D'Angelo SP, Shoushtari AN, Agaram NP, et al.	Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment.	Hum Pathol. 2015;46(3):357-365	2.5-39)
5.4-39	Kostine M, Cleven AH, de Miranda NF, Italiano A, Cleton-Jansen AM, Bové e JV.	Analysis of PD-L1, T-cell infiltrate and HLA expression in chondrosarcoma indicates potential for response to immunotherapy specifically in the dedifferentiated subtype.	Mod Pathol. 2016;29(9):1028-1037	2.5-40)
5.4-40	Kim C, Kim EK, Jung H, et al.	Prognostic implications of PD-L1 expression in patients with soft tissue sarcoma.	BMC Cancer. 2016;16:434	2.5-41)
5.4-41	Groisberg R, Roszik J, Conley AP, et al.	Genomics, Morphoproteomics, and Treatment Patterns of Patients with Alveolar Soft Part Sarcoma and Response to Multiple Experimental Therapies.	Mol Cancer Ther. 2020;19(5):1165-1172	2.5-42)
5.4-42	Chen A	Phase II Study of Atezolizumab in Patients with Alveolar Soft Part Sarcoma.	Connective Tissue Oncology Society (CTOS) 2019 Annual Meeting.	2.5-43) 2.7.3-2)

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CTD No	著者	表題	掲載誌・その他	引用CTD No
5.4-43	Kavanagh JJ, Gershenson DM, Choi H, et al.	Multi-institutional phase 2 study of TLK286 (TELCYTA, a glutathione S-transferase P1-1 activated glutathione analog prodrug) in patients with platinum and paclitaxel refractory or resistant ovarian cancer.	Int J Gynecol Cancer.2005;15(4):593-600	2.5-44)
5.4-44	Bezjak A, Tu D, Seymour L, et al.	Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21.	J Clin Oncol. 2006;24(24):3831-3837	2.5-45)
5.4-45	Kris MG, Natale RB, Herbst RS, et al.	Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial.	JAMA. 2003;290(16):2149-2158	2.5-46)
5.4-46	山東雅紀，赤羽和久，田口泰郎，新宮優二，法水信治，坂本英至.	進行・再発乳癌に対するbevacizumab + paclitaxelの使用経験.	日臨外会誌 2015;76:2885-2891	2.5-47)

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