アバスチン点滴静注用 100mg/4mL
アバスチン点滴静注用 400mg/16mL
に関する資料

当該資料に記載された情報に係る権利及び内容についての責任は，中外製薬株式会社に帰属するものであり，当該情報を適正使用以外の営利目的に利用することはできません。

中外製薬株式会社

目次

1.5 起原又は発見の経緯及び開発の経緯 2
1.5.1 起原又は発見の経緯 2
1.5.2 非臨床開発の経緯 2
1.5.3 国内における開発・承認申請の経緯 2

図一覧

図 1.5-1 本剤に関する開発の経緯 2

1.5 起原又は発見の経緯及び開発の経緯

1.5.1 起原又は発見の経緯

アバスチン点滴静注用100mg/4mL，同400mg/16mL（以下，本剤）は，ベバシズマブ（遺伝子組換え）（以下，BEV）を有効成分として含有する点滴静脈内注射剤であり，血管内皮増殖因子（Vascular Endothelial Growth Factor; 以下，VEGF）を標的として米国の Genentech 社により創製され，世界で初めて臨床的に有用性を示し，医薬品として承認・臨床応用された血管新生阻害剤である。

1.5.2 非臨床開発の経緯

ヒト HEI193細胞又はマウス Nf2(-/-)細胞をヌードマウスに移植して，脳内腫瘍モデル及び坐骨神経腫瘍モデルを作製し，BEV とバンデタニブ（VEGFR2と EGFR の二重チロシンキナーゼ阻害薬）の効果を検証した結果が2010年に報告されている[1)]。ヒト HEI193細胞を移植したモデルでは，BEV による腫瘍の成長抑制，腫瘍内血管透過性の低下，腫瘍細胞の壊死の増加及び生存期間の延長が観察された。2015年には，ヒト HEI193又はマウス Nf2(-/-)の両細胞をヌードマウスに移植したモデルを用いた B20.4.4（ヒト及びマウスの両 VEGF を中和する抗体）治療において，腫瘍組織浮腫の改善，神経症状の改善，筋萎縮の抑制及び神経再生，腫瘍血管の正常化，並びに放射線療法との併用による生存期間の延長が報告されている[2)]。

本申請に当たり，新たな非臨床試験は実施していない。なお，20[redacted]年[redacted]月に実施した[redacted]相談[redacted]にて「本剤の神経線維腫症2型に係る一変申請にあたり、追加の非臨床試験を実施しないことに異論はない」との見解が示された（[redacted]，20[redacted]年[redacted]月[redacted]日付記録）。

1.5.3 国内における開発・承認申請の経緯

今般，神経線維腫症 II 型患者を対象とした第 II 相多施設共同ランダム化二重盲検実薬対照並行群間比較試験（ FMU2019-01-NF2 試験［ BeatNF2 試験］）において，本剤の有効性及び安全性が確認された。

以上を踏まえ，「神経線維腫症2型」の効能を追加する承認事項一部変更承認申請を行うこととした。

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

図 1.5-1 本剤に関する開発の経緯

試験項目	国内	海外	試験の内容	2019	2020	2021	2022
神経線維腫症 II 型を対象とした臨床試験							
第II相	○		FMU2019-01-NF2	⑩[redacted]			⑥
図中の算用数字は当該試験の開始月及び終了月							

参考文献

1) Wong HK, Lahdenranta J, Kamoun WS, et al. Anti-vascular endothelial growth factor therapies as a novel therapeutic approach to treating neurofibromatosis-related tumors. Cancer Res 2010;70:3483-93.

2) Gao X, Zhao Y, Stemmer-Rachamimov AO, et al. Anti-VEGF treatment improves neurological function and augments radiation response in NF2 schwannoma model. Proc Natl Acad Sci USA 2015;112:14676-81.

目次

1.6 外国における使用状況等に関する資料 2
1.6.1 外国における承認申請状況 2
1.6.2 代表的な添付文書の和訳概要 2
1.6.2.1 米国添付文書の和訳概要 2
1.6.2.2 欧州添付文書の和訳概要 4
1.6.3 米国における添付文書 7
1.6.4 欧州における添付文書 50
1.6.5 Core Data Sheet 122

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

アバスチン点滴静注用100mg/4mL 及び400mg/16mL（以下，本剤）の外国における承認申請状況を以下に記載する。

本剤は，2025年2月時点において，結腸・直腸癌，乳癌，非小細胞肺癌（扁平上皮癌を除く），再発膠芽腫，腎細胞癌，子宮頸癌，上皮性卵巣癌・卵管癌又は原発性腹膜癌及び肝細胞癌のいずれかに対して，欧米を含む世界140カ国で承認・販売されている。

神経線維腫症2型に対しては，2025年7月時点で，いずれの国または地域でも申請もしくは承認されていない。

本剤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にしめし，米国添付文書（2022年9月版），欧州添付文書（2026年1月版）及び最新の企業中核データシート（[redacted]）を，それぞれ1.6.3，1.6.4及び1.6.5に添付する。

1.6.2 代表的な添付文書の和訳概要

1.6.2.1 米国添付文書の和訳概要

1 効能・効果

1.1 転移性結腸・直腸癌

アバスチンは，フルオロウラシル静注をベースとする化学療法との併用で，転移性結腸・直腸癌（mCRC）患者の一次又は二次治療を適応とする。

アバスチンは，フッ化ピリミジン系薬剤-イリノテカン又はフッ化ピリミジン系薬剤-オキサリプラチンベースの化学療法との併用で，ベバシズマブ製剤を含む一次治療後に進行したmCRC 患者の二次治療を適応とする。

使用上の制約:アバスチンは結腸癌の術後補助療法には適応されない ［臨床成績（14.2）参照］ 。

1.2 非扁平上皮非小細胞肺癌の一次治療

アバスチンは，カルボプラチン及びパクリタキセルとの併用で，切除不能な局所進行，再発又は転移性の非扁平上皮非小細胞肺癌（NSCLC）患者の一次治療を適応とする。

1.3 再発膠芽腫

アバスチンは成人の再発性膠芽腫（GBM）の治療を適応とする。

1.4 進行・転移性腎細胞癌

アバスチンはインターフェロンアルファとの併用で転移性腎細胞癌（mRCC）の治療を適応とする。

1.5 治療抵抗性・再発又は転移性子宮頸癌

アバスチンは，パクリタキセル及びシスプラチン又はパクリタキセル及びトポテカンとの併用で，治療抵抗性，再発又は転移性子宮頸癌患者の治療を適応とする。

1.6 上皮性卵巣癌，卵管癌，又は原発性腹膜癌

アバスチンは，カルボプラチン及びパクリタキセルとの併用投与後，アバスチンを単剤投与し，初回外科的切除後のステージ III 又は IV の上皮性卵巣癌，卵管癌又は原発性腹膜癌を有する患者の治療を適応とする。

アバスチンは，パクリタキセル，ペグ化リポソーマルドキソルビシン又はトポテカンとの併用で，化学療法歴が2レジメン以下のプラチナ製剤抵抗性の再発上皮性卵巣癌，卵管癌又は原発性腹膜癌患者の治療を適応とする。

アバスチンは，カルボプラチン及びパクリタキセルとの併用投与又はカルボプラチン及びゲムシタビンとの併用投与後にアバスチンを単剤投与したときの，白金感受性の再発上皮性卵巣癌，卵管癌又は原発性腹膜癌の治療を適応とする。

1.7 肝細胞癌

アバスチンは，アテゾリズマブとの併用で，全身療法歴のない切除不能又は転移性の肝細胞癌（HCC）患者の治療を適応とする。

2 用法・用量

2.1 重要な投与情報

待機手術前に28日間以上中断する。大手術後及び十分な創傷治癒までは少なくとも28日間アバスチンを投与しないこと。

2.2 転移性結腸・直腸癌

静注フルオロウラシルをベースとする化学療法と併用してアバスチンを投与する場合の推奨用量は以下のとおりである。

- ボーラス IFL との併用で，5 mg/kg を2週間間隔で静脈内投与。
- FOLFOX4との併用で10 mg/kg を2週間間隔で静脈内投与。
- ベバシズマブ製剤を含む一次治療で進行が認められた場合，フッ化ピリミジン系薬剤・イリノテカン又はフッ化ピリミジン系薬剤・オキサリプラチンを含む化学療法との併用において，5 mg/kg を2週間間隔で静脈内投与又は7.5 mg/kg を3週間間隔で静脈内投与。

2.3 非扁平上皮非小細胞肺癌の一次治療

カルボプラチン及びパクリタキセルとの併用において，通常，15 mg/kg を3週間間隔で静脈内投与する。

2.4 再発膠芽腫

通常，10 mg/kg を2週間間隔で静脈内投与する。

2.5 進行・転移性腎細胞癌

インターフェロンアルファとの併用において，通常，10 mg/kg を2週間間隔で静脈内投与する。

2.6 治療抵抗性・再発又は転移性子宮頸癌

パクリタキセル及びシスプラチンとの併用又はパクリタキセル及びトポテカンとの併用において，通常，15 mg/kg を3週間間隔で静脈内投与する。

2.7 上皮性卵巣癌，卵管癌，又は原発性腹膜癌

初回外科的切除後のステージ III 又は IV の疾患

カルボプラチン及びパクリタキセルとの併用において，15 mg/kg を3週間間隔で最大6サイクル静脈内投与した後，アバスチン 15 mg/kg を単独で3週間間隔で最大22サイクル又は病勢進行のいずれか早い時点まで静脈内投与する。

再発

プラチナ製剤抵抗性

パクリタキセル，ペグ化リポソーマルドキソルビシン又はトポテカン（毎週）との併用において，通常，10 mg/kg を2週間間隔で静脈内投与する。

トポテカン（3週間間隔）との併用において，通常，15 mg/kg を3週間間隔で静脈内投与する。

プラチナ製剤感受性

カルボプラチン及びパクリタキセルとの併用において，通常，15 mg/kg を3週間間隔で静脈内投与し，6から8サイクル投与した後，アバスチン 15 mg/kg を3週間間隔で疾患進行まで単剤投与する。

カルボプラチン及びゲムシタビンとの併用において，通常，15 mg/kg を3週間間隔で静脈内投与し，6から10サイクル投与した後，アバスチン 15 mg/kg を3週間間隔で単独で病勢進行まで静脈内投与する。

2.8 肝細胞癌

通常，同日にアテゾリズマブとして1,200 mg を静脈内投与した後，15 mg/kg を3週間間隔で，疾患進行又は許容できない毒性の発現まで静脈内投与する。

推奨用量情報については，投与開始前にアテゾリズマブの添付文書を参照のこと。

1.6.2.2 欧州添付文書の和訳概要

4. 臨床関連事項

4.1 適応症

ベバシズマブとフッ化ピリミジン系薬剤をベースとする化学療法との併用は，転移性結腸癌又は直腸癌の成人患者の治療を適応とする。

ベバシズマブとパクリタキセルの併用療法は，転移性乳癌の成人患者の一次治療を適応とする。ヒト上皮成長因子受容体2（HER2）の状態に関する詳細な情報については，5.1項を参照のこと。

ベバシズマブとカペシタビンの併用療法は，タキサン系薬剤又はアントラサイクリン系薬剤を含む他の化学療法による治療が適切ではないと考えられる転移性乳癌の成人患者の一次治療を適応とする。過去12ヵ月以内に術後補助療法としてタキサン系薬剤及びアントラサイクリン系薬剤を含むレジメンの投与を受けた患者は，アバスチンとカペシタビンの併用投与から除外すること。HER2の状態に関する詳細は5.1項を参照のこと。

ベバシズマブは，プラチナ製剤を含む化学療法に加えて，扁平上皮優位の組織型以外の切除不能な進行，転移又は再発の非小細胞肺癌の成人患者の一次治療を適応とする。

ベバシズマブはエルロチニブとの併用で，上皮成長因子受容体（EGFR）活性化変異（5.1項参照）を有する切除不能な進行，転移又は再発の非扁平上皮非小細胞肺癌の成人患者の一次治療を適応とする。

ベバシズマブとインターフェロンアルファ-2a の併用は，進行性及び/又は転移性腎細胞癌の成人患者の一次治療を適応とする。

ベバシズマブは，カルボプラチン及びパクリタキセルとの併用で，進行（国際産婦人科連合（FIGO）病期分類 III B，III C 及び IV 期）上皮性卵巣癌，卵管癌又は原発性腹膜癌を有する成人患者の一次治療を適応とする（5.1項参照）。ベバシズマブは，カルボプラチン及びゲムシタビンとの併用又はカルボプラチン及びパクリタキセルとの併用で，ベバシズマブ又は他の VEGF 阻害薬又は VEGF 受容体標的薬による前治療歴のない，プラチナ製剤感受性の上皮性卵巣癌，卵管癌又は原発性腹膜癌の初回再発成人患者の治療を適応とする。

ベバシズマブとパクリタキセル，トポテカン又はペグ化リポソーマルドキソルビシンの併用投与は，化学療法歴が2レジメン以下であり，ベバシズマブ又は他の VEGF 阻害薬又は VEGF 受容体標的薬による前治療歴がないプラチナ製剤抵抗性の再発上皮性卵巣癌，卵管癌又は原発性腹膜癌の成人患者の治療を適応とする（5.1項参照）。

ベバシズマブは，パクリタキセル及びシスプラチンとの併用，又はプラチナ製剤による治療を受けられない患者では代わりにパクリタキセル及びトポテカンとの併用で，治療抵抗性，再発又は転移性子宮頚癌を有する成人患者の治療を適応とする（5.1項参照）。

4.2 用法・用量

バイアルを振らないこと。

アバスチンは，抗腫瘍薬の使用経験がある医師の監督下で投与しなければならない。

用量

転移性結腸又は直腸癌（mCRC）

通常，アバスチンとして5 mg/kg 又は10 mg/kg（体重）を1回2週間間隔あるいは7.5 mg/kg 又は15 mg/kg（体重）を1回3週間間隔で点滴静注する。

疾患の進行又は許容できない毒性の発現まで投与を継続することが推奨される。

転移性乳癌（mBC）

通常，アバスチンとして10 mg/kg（体重）を2週間間隔又は15 mg/kg（体重）を3週間間隔で点滴静注する。

疾患の進行又は許容できない毒性の発現まで投与を継続することが推奨される。

非小細胞肺癌（NSCLC）

プラチナ製剤を含む化学療法との併用による非扁平上皮 NSCLC の1次治療

プラチナ製剤を含む化学療法に加えてアバスチンを最大6サイクル投与した後，疾患進行までアバスチンを単剤投与する。

通常，アバスチンとして7.5 mg/kg 又は15 mg/kg（体重）を3週間間隔で点滴静注する。

NSCLC 患者における臨床的ベネフィットは，7.5 mg/kg 及び15 mg/kg の両用量で示されている（5.1項参照）。

疾患の進行又は許容できない毒性の発現まで投与を継続することが推奨される。

EGFR 活性化変異を有する非扁平上皮 NSCLC に対するエルロチニブとの併用による一次治療

アバスチンとエルロチニブの併用投与を開始する前に EGFR 変異検査を実施すること。偽陰性や偽陽性の判定を避けるために，十分にバリデートされた頑健な方法を選択することが重要である。

エルロチニブとの併用において，アバスチンとして15 mg/kg（体重）を3週間間隔で点滴静注する。

疾患進行までエルロチニブに加えてアバスチンの投与を継続することが推奨される。

エルロチニブの用法・用量については，エルロチニブの添付文書を参照のこと。

進行性及び/又は転移性腎細胞癌（mRCC）

通常，アバスチンとして10 mg/kg（体重）を2週間間隔で点滴静注する。

疾患の進行又は許容できない毒性の発現まで投与を継続することが推奨される。

上皮性卵巣癌，卵管癌及び原発性腹膜癌

一次治療:カルボプラチン及びパクリタキセルに加えてアバスチンを最大6サイクル投与し，その後，アバスチン単剤を疾患進行，最長15ヵ月又は許容できない毒性の発現のいずれか早い時点まで継続する。

通常，アバスチンとして15 mg/kg（体重）を3週間間隔で点滴静注する。

プラチナ製剤感受性の再発例の治療:アバスチンはカルボプラチン及びゲムシタビンとの併用で6サイクル~最大10サイクル，又はカルボプラチン及びパクリタキセルとの併用で6サイクル~最大8サイクル投与し，その後はアバスチン単剤で病勢進行まで継続する。通常，アバスチンとして15 mg/kg（体重）を3週間間隔で点滴静注する。

プラチナ製剤抵抗性の再発例の治療:アバスチンはパクリタキセル，トポテカン（週1回投与）

又はペグ化リポソームドキソルビシンのいずれかと併用投与されます。通常，アバスチンとして10 mg/kg（体重）を2週間間隔で点滴静注する。トポテカン（3週間ごとに1~5日目に投与）と併用する場合，アバスチンとして15 mg/kg 体重を3週間間隔で点滴静注する。疾患進行又は許容できない毒性が認められるまで投与を継続することが推奨される（5.1項，試験 M022224参照）。

子宮頸癌

アバスチンは，パクリタキセル及びシスプラチン又はパクリタキセル及びトポテカンのいずれかの化学療法レジメンと併用投与する。

通常，アバスチンとして15 mg/kg（体重）を3週間間隔で点滴静注する。

疾患の進行又は許容できない毒性が認められるまで投与を継続することが推奨される（5.1項参照）。

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVASTIN safely and effectively. See full prescribing information for AVASTIN.

AVASTIN® (bevacizumab) injection, for intravenous use
Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	9/2022
Dosage and Administration (2.2)	9/2022
Warnings and Precautions, Infusion-Related Reactions (5.9)	9/2022

----------INDICATIONS AND USAGE----------

Avastin is a vascular endothelial growth factor inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen. (1.1)

  Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer. (1.1)

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. (1.2)
- Recurrent glioblastoma in adults. (1.3)
- Metastatic renal cell carcinoma in combination with interferon alfa. (1.4)
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. (1.5)
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
  - in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection (1.6)
  - in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens (1.6)
  - in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease (1.6)
- Hepatocellular Carcinoma (HCC)
  - in combination with atezolizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy (1.7)

----------DOSAGE AND ADMINISTRATION----------

Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for 28 days following major surgery and until adequate wound healing. (2.1)

Metastatic colorectal cancer (2.2)
- 5 mg/kg every 2 weeks with bolus-IFL
- 10 mg/kg every 2 weeks with FOLFOX4
- 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line bevacizumab product-containing regimen

First-line non–squamous non–small cell lung cancer (2.3)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel

Recurrent glioblastoma (2.4)
- 10 mg/kg every 2 weeks

Metastatic renal cell carcinoma (2.5)
- 10 mg/kg every 2 weeks with interferon alfa

Persistent, recurrent, or metastatic cervical cancer (2.6)
- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan

Stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles

Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.7)
- 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week
- 15 mg/kg every 3 weeks with topotecan given every 3 weeks

Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent
- 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent

Hepatocellular Carcinoma (2.8)
- 15 mg/kg after administration of 1,200 mg of atezolizumab every 3 weeks

Administer as an intravenous infusion after dilution. See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions (2.9, 2.10)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) in a single-dose vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Gastrointestinal Perforations and Fistula: Discontinue for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any organ (5.1)
- Surgery and Wound Healing Complications: In patients who experience wound healing complications during Avastin treatment, withhold Avastin until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days following a major surgery, and until adequate wound healing. The safety of resumption of AVASTIN after resolution of wound healing complication has not been established. Discontinue for wound healing complication of necrotizing fasciitis. (5.2)
- Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage (5.3)
- Arterial Thromboembolic Events (ATE): Discontinue for severe ATE. (5.4)
- Venous Thromboembolic Events (VTE): Discontinue for Grade 4 VTE. (5.5)
- Hypertension: Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy. (5.6)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue. (5.7)
- Renal Injury and Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine. (5.8)
- Infusion-Related Reactions: Decrease rate for infusion-related reactions. Discontinue for severe infusion-related reactions and administer medical therapy. (5.9)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3)
- Ovarian Failure: Advise females of the potential risk. (5.11, 8.3)
- Congestive Heart Failure (CHF): Discontinue Avastin in patients who develop CHF. (5.12)

----------ADVERSE REACTIONS----------

Most common adverse reactions incidence (incidence > 10%) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. 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.

Revised: 9/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Metastatic Colorectal Cancer
- 1.2 First-Line Non-Squamous Non–Small Cell Lung Cancer
- 1.3 Recurrent Glioblastoma
- 1.4 Metastatic Renal Cell Carcinoma
- 1.5 Persistent, Recurrent, or Metastatic Cervical Cancer
- 1.6 Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
- 1.7 Hepatocellular Carcinoma

2 DOSAGE AND ADMINISTRATION
- 2.1 Important Administration Information
- 2.2 Metastatic Colorectal Cancer
- 2.3 First-Line Non-Squamous Non-Small Cell Lung Cancer
- 2.4 Recurrent Glioblastoma
- 2.5 Metastatic Renal Cell Carcinoma
- 2.6 Persistent, Recurrent, or Metastatic Cervical Cancer
- 2.7 Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer
- 2.8 Hepatocellular Carcinoma
- 2.9 Dosage Modifications for Adverse Reactions
- 2.10 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Gastrointestinal Perforations and Fistulae
- 5.2 Surgery and Wound Healing Complications
- 5.3 Hemorrhage
- 5.4 Arterial Thromboembolic Events
- 5.5 Venous Thromboembolic Events
- 5.6 Hypertension
- 5.7 Posterior Reversible Encephalopathy Syndrome (PRES)
- 5.8 Renal Injury and Proteinuria
- 5.9 Infusion-Related Reactions
- 5.10 Embryo-Fetal Toxicity
- 5.11 Ovarian Failure
- 5.12 Congestive Heart Failure

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

7 DRUG INTERACTIONS

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

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

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

14 CLINICAL STUDIES
- 14.1 Metastatic Colorectal Cancer
- 14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer
- 14.3 First-Line Non-Squamous Non-Small Cell Lung Cancer
- 14.4 Recurrent Glioblastoma
- 14.5 Metastatic Renal Cell Carcinoma
- 14.6 Persistent, Recurrent, or Metastatic Cervical Cancer
- 14.7 Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection
- 14.8 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
- 14.9 Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
- 14.10 Hepatocellular Carcinoma

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

Avastin, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first-or second-line treatment of patients with metastatic colorectal cancer (mCRC).

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with mCRC who have progressed on a first-line bevacizumab product-containing regimen.

Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer *[see Clinical Studies (14.2)]*.

1.2 First-Line Non-Squamous Non–Small Cell Lung Cancer

Avastin, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC).

1.3 Recurrent Glioblastoma

Avastin is indicated for the treatment of recurrent glioblastoma (GBM) in adults.

1.4 Metastatic Renal Cell Carcinoma

Avastin, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma (mRCC).

1.5 Persistent, Recurrent, or Metastatic Cervical Cancer

Avastin, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

1.6 Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Avastin, in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.

Avastin, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Avastin, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

1.7 Hepatocellular Carcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Withhold for at least 28 days prior to elective surgery. Do not administer Avastin until at least 28 days following major surgery and until adequate wound healing.

2.2 Metastatic Colorectal Cancer

The recommended dosage when Avastin is administered in combination with intravenous fluorouracil-based chemotherapy is:

- 5 mg/kg intravenously every 2 weeks in combination with bolus-IFL.
- 10 mg/kg intravenously every 2 weeks in combination with FOLFOX4.
- 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line bevacizumab product-containing regimen.

2.3 First-Line Non-Squamous Non-Small Cell Lung Cancer

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel.

2.4 Recurrent Glioblastoma

The recommended dosage is 10 mg/kg intravenously every 2 weeks.

2.5 Metastatic Renal Cell Carcinoma

The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with interferon alfa.

2.6 Persistent, Recurrent, or Metastatic Cervical Cancer

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan.

2.7 Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Stage III or IV Disease Following Initial Surgical Resection

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent for a total of up to 22 cycles or until disease progression, whichever occurs earlier.

Recurrent Disease

Platinum Resistant

The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week).

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks).

Platinum Sensitive

The recommended dosage is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and paclitaxel for 6 to 8 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

The recommended dosage is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and gemcitabine for 6 to 10 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

2.8 Hepatocellular Carcinoma

The recommended dosage is 15 mg/kg intravenously after administration of 1,200 mg of atezolizumab intravenously on the same day, every 3 weeks until disease progression or unacceptable toxicity.

Refer to the Prescribing Information for atezolizumab prior to initiation for recommended dosage information.

2.9 Dosage Modifications for Adverse Reactions

Table 1 describes dosage modifications for specific adverse reactions. No dose reductions for Avastin are recommended.

Table 1: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue Avastin
Wound Healing Complications *[see Warnings and Precautions (5.2)]*.	• Any	Withhold AVASTIN until adequate wound healing.The safety of resumption of AVASTIN after resolution of wound healing complications has not been established.
	• Necrotizing fasciitis	Discontinue Avastin
Hemorrhage *[see Warnings and Precautions (5.3)]*.	• Grade 3 or 4	Discontinue Avastin
	• Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold Avastin
Thromboembolic Events *[see Warnings and Precautions (5.4, 5.5)]*.	• Arterial thromboembolism, severe	Discontinue Avastin
	• Venous thromboembolism, Grade 4	Discontinue Avastin
Hypertension *[see Warnings and Precautions (5.6)]*.	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue Avastin
	• Hypertension, severe	Withhold Avastin if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.7)]*.	• Any	Discontinue Avastin
Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.	• Nephrotic syndrome	Discontinue Avastin
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold Avastin until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*.	• Severe	Discontinue Avastin
	• Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure *[see Warnings and Precautions (5.12)]*.	Any	Discontinue Avastin

2.10 Preparation and Administration

Preparation

- Use appropriate aseptic technique.
- Use sterile needle and syringe to prepare Avastin.
- Visually inspect vial for particulate matter and discoloration prior to preparation for administration. Discard vial if solution is cloudy, discolored or contains particulate matter.
- Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.
- Discard any unused portion left in a vial, as the product contains no preservatives.
- Diluted Avastin solution may be stored at 2°C to 8°C (36°F to 46°F) for up to 8 hours, if not used immediately.
- No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

Administration

- Administer as an intravenous infusion.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated. Administer all subsequent infusions over 30 minutes if second infusion over 60 minutes is tolerated.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) clear to slightly opalescent, colorless to pale brown solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations and Fistulae

Serious, and sometimes fatal, gastrointestinal perforation occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies, with the highest incidence in patients with a history of prior pelvic radiation. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of perforations occurred within 50 days of the first dose *[see Adverse Reactions (6.1)]*.

Serious fistulae (including, tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites) occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from < 1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. The majority of fistulae occurred within 6 months of the first dose. Patients who develop a gastrointestinal vaginal fistula may also have a bowel obstruction and require surgical intervention, as well as a diverting ostomy.

Avoid Avastin in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Discontinue in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ.

5.2 Surgery and Wound Healing Complications

In a controlled clinical study in which Avastin was not administered within 28 days of major surgical procedures, the incidence of wound healing complications, including serious and fatal complications, was 15% in patients with mCRC who underwent surgery while receiving Avastin and 4% in patients who did not receive Avastin. In a controlled clinical study in patients with relapsed or recurrent GBM, the incidence of wound healing events was 5% in patients who received Avastin and 0.7% in patients who did not receive Avastin *[see Adverse Reactions (6.1)]*.

In patients who experience wound healing complications during Avastin treatment, withhold Avastin until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following major surgery and until adequate wound healing. The safety of resumption of AVASTIN after resolution of wound healing complications has not been established *[see Dosage and Administration (2.9)]*.

Necrotizing fasciitis including fatal cases, has been reported in patients receiving Avastin, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue Avastin in patients who develop necrotizing fasciitis.

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, which is most commonly Grade 1 epistaxis, and serious hemorrhage, which in some cases has been fatal. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-5 hemorrhagic events ranged from 0.4% to 7% in patients receiving Avastin *[see Adverse Reactions (6.1)]*.

Serious or fatal pulmonary hemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving Avastin with chemotherapy compared to none of the patients receiving chemotherapy alone.

An evaluation for the presence of varices is recommended within 6 months of initiation of Avastin in patients with HCC. There is lack of clinical data to support the safety of Avastin in patients with variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding because these patients were excluded from clinical trials of Avastin in HCC *[see Clinical Studies (14.10)]*.

Do not administer Avastin to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grades 3-4 hemorrhage.

5.4 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina, occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. Across clinical studies, the incidence of Grades 3-5 ATE was 5% in patients receiving Avastin with chemotherapy compared to ≤2% in patients receiving chemotherapy alone; the highest incidence occurred in patients with GBM. The risk of developing ATE was increased in patients with a history of arterial thromboembolism, diabetes, or >65 years *[see Use in Specific Populations (8.5)]*.

Discontinue in patients who develop a severe ATE. The safety of reinitiating Avastin after an ATE is resolved is not known.

5.5 Venous Thromboembolic Events
An increased risk of venous thromboembolic events (VTE) was observed across clinical studies *[see Adverse Reactions (6.1)]*. In Study GOG-0240, Grades 3-4 VTE occurred in 11% of patients receiving Avastin with chemotherapy compared with 5% of patients receiving chemotherapy alone. In EORTC 26101, the incidence of Grades 3-4 VTE was 5% in patients receiving Avastin with chemotherapy compared to 2% in patients receiving chemotherapy alone.

Discontinue Avastin in patients with a Grade 4 VTE, including pulmonary embolism.

5.6 Hypertension
Severe hypertension occurred at a higher incidence in patients receiving Avastin as compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-4 hypertension ranged from 5% to 18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuing Avastin. Withhold Avastin in patients with severe hypertension that is not controlled with medical management; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

5.7 Posterior Reversible Encephalopathy Syndrome
Posterior reversible encephalopathy syndrome (PRES) was reported in < 0.5% of patients across clinical studies. The onset of symptoms occurred from 16 hours to 1 year after the first dose. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES.

Discontinue Avastin in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing Avastin, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin in patients who developed PRES is not known.

5.8 Renal Injury and Proteinuria
The incidence and severity of proteinuria was higher in patients receiving Avastin as compared to patients receiving chemotherapy. Grade 3 (defined as urine dipstick 4+ or > 3.5 grams of protein per 24 hours) to Grade 4 (defined as nephrotic syndrome) ranged from 0.7% to 7% in clinical studies. The overall incidence of proteinuria (all grades) was only adequately assessed in Study BO17705, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (15 days to 37 months) after initiating Avastin. Median time to resolution was 6.1 months (95% CI: 2.8, 11.3). Proteinuria did not resolve in 40% of patients after median follow-up of 11.2 months and required discontinuation of Avastin in 30% of the patients who developed proteinuria *[see Adverse Reactions (6.1)]*.

In an exploratory, pooled analysis of patients from seven randomized clinical studies, 5% of patients receiving Avastin with chemotherapy experienced Grades 2-4 (defined as urine dipstick 2+ or greater or > 1 gram of protein per 24 hours or nephrotic syndrome) proteinuria. Grades 2-4 proteinuria resolved in 74% of patients. Avastin was reinitiated in 42% of patients. Of the 113 patients who reinitiated Avastin, 48% experienced a second episode of Grades 2-4 proteinuria.

Nephrotic syndrome occurred in < 1% of patients receiving Avastin across clinical studies, in some instances with fatal outcome. In a published case series, kidney biopsy of 6 patients with proteinuria showed findings consistent with thrombotic microangiopathy. Results of a retrospective analysis of 5805 patients who received

Avastin with chemotherapy and 3713 patients who received chemotherapy alone, showed higher rates of elevated serum creatinine levels (between 1.5 to 1.9 times baseline levels) in patients who received Avastin. Serum creatinine levels did not return to baseline in approximately one-third of patients who received Avastin.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Withhold for proteinuria greater than or equal to 2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome.

Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24-hour urine protein [Pearson Correlation 0.39 (95% CI: 0.17, 0.57)].

5.9 Infusion-Related Reactions

Infusion-related reactions reported across clinical studies and postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, anaphylactoid/anaphylactic reactions, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion-related reactions with the first dose occurred in < 3% of patients and severe reactions occurred in 0.4% of patients.

Decrease the rate of infusion for mild, clinically insignificant infusion-related reactions. Interrupt the infusion in patients with clinically significant infusion-related reactions and consider resuming at a slower rate following resolution. Discontinue in patients who develop a severe infusion-related reaction and administer appropriate medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen).

5.10 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, Avastin may cause fetal harm when administered to pregnant women. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.11 Ovarian Failure

The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing Avastin, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving Avastin. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or an FSH level < 30 mIU/mL during the post-treatment period. Long-term effects of Avastin on fertility are unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Avastin *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

5.12 Congestive Heart Failure (CHF)

Avastin is not indicated for use with anthracycline-based chemotherapy. The incidence of Grade ≥ 3 left ventricular dysfunction was 1% in patients receiving Avastin compared to 0.6% of patients receiving chemotherapy alone. Among patients who received prior anthracycline treatment, the rate of CHF was 4% for patients receiving Avastin with chemotherapy as compared to 0.6% for patients receiving chemotherapy alone.

In previously untreated patients with a hematological malignancy, the incidence of CHF and decline in left ventricular ejection fraction (LVEF) were increased in patients receiving Avastin with anthracycline-based chemotherapy compared to patients receiving placebo with the same chemotherapy regimen. The proportion of patients with a decline in LVEF from baseline of ≥ 20% or a decline from baseline of 10% to < 50%, was 10% in patients receiving Avastin with chemotherapy compared to 5% in patients receiving chemotherapy alone. Time to onset of left-ventricular dysfunction or CHF was 1 to 6 months after the first dose in at least 85% of the patients and was resolved in 62% of the patients who developed CHF in the Avastin arm compared to 82% in the placebo arm. Discontinue Avastin in patients who develop CHF.

6 ADVERSE REACTIONS

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

- Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.
- Surgery and Wound Healing Complications *[see Warnings and Precautions (5.2)]*.
- Hemorrhage *[see Warnings and Precautions (5.3)]*.
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.4)]*.
- Venous Thromboembolic Events *[see Warnings and Precautions (5.5)]*.
- Hypertension *[see Warnings and Precautions (5.6)]*.
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.7)]*.
- Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.
- Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*.
- Ovarian Failure *[see Warnings and Precautions (5.11)]*.
- Congestive Heart Failure *[see Warnings and Precautions (5.12)]*.

6.1 Clinical Trials Experience

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

The safety data in Warnings and Precautions and described below reflect exposure to Avastin in 4463 patients including those with mCRC (AVF2107g, E3200), non-squamous NSCLC (E4599), GBM (EORTC 26101), mRCC (BO17705), cervical cancer (GOG-0240), epithelial ovarian, fallopian tube, or primary peritoneal cancer (MO22224, AVF4095, GOG-0213, and GOG-0218), or HCC (IMbrave150) at the recommended dose and schedule for a median of 6 to 23 doses. The most common adverse reactions observed in patients receiving Avastin as a single agent or in combination with other anti-cancer therapies at a rate > 10% were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis.

Across clinical studies, Avastin was discontinued in 8% to 22% of patients because of adverse reactions *[see Clinical Studies (14)]*.

Metastatic Colorectal Cancer

In Combination with bolus-IFL

The safety of Avastin was evaluated in 392 patients who received at least one dose of Avastin in a double-blind, active-controlled study (AVF2107g), which compared Avastin (5 mg/kg every 2 weeks) with bolus-IFL to placebo with bolus-IFL in patients with mCRC *[see Clinical Studies (14.1)]*. Patients were randomized (1:1:1) to placebo with bolus-IFL, Avastin with bolus-IFL, or Avastin with fluorouracil and leucovorin. The demographics of the safety population were similar to the demographics of the efficacy population. All Grades 3–4 adverse reactions and selected Grades 1–2 adverse reactions (i.e., hypertension, proteinuria,

thromboembolic events) were collected in the entire study population. Adverse reactions are presented in Table 2.

Table 2: Grades 3-4 Adverse Reactions Occurring at Higher Incidence (≥2%) in Patients Receiving Avastin vs. Placebo in Study AVF2107g

Adverse Reaction[a]	Avastin with IFL (N=392)	Placebo with IFL (N=396)
Hematology		
Leukopenia	37%	31%
Neutropenia	21%	14%
Gastrointestinal		
Diarrhea	34%	25%
Abdominal pain	8%	5%
Constipation	4%	2%
Vascular		
Hypertension	12%	2%
Deep vein thrombosis	9%	5%
Intra-abdominal thrombosis	3%	1%
Syncope	3%	1%
General		
Asthenia	10%	7%
Pain	8%	5%

a NCI-CTC version 3

In Combination with FOLFOX4

The safety of Avastin was evaluated in 521 patients in an open-label, active-controlled study (E3200) in patients who were previously treated with irinotecan and fluorouracil for initial therapy for mCRC. Patients were randomized (1:1:1) to FOLFOX4, Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity.

The demographics of the safety population were similar to the demographics of the efficacy population.

Selected Grades 3–5 non-hematologic and Grades 4–5 hematologic occurring at a higher incidence (≥2%) in patients receiving Avastin with FOLFOX4 compared to FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse reaction rates due to the reporting mechanisms.

First-Line Non Squamous Non-Small Cell Lung Cancer

The safety of Avastin was evaluated as first-line treatment in 422 patients with unresectable NSCLC who received at least one dose of Avastin in an active-controlled, open-label, multicenter trial (E4599) *[see Clinical Studies (14.3)]*. Chemotherapy naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel and carboplatin with or without Avastin (15 mg/kg every 3 weeks). After completion or upon discontinuation of chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving

therapeutic anticoagulation. The demographics of the safety population were similar to the demographics of the efficacy population.

Only Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions were collected. Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with paclitaxel and carboplatin compared with patients receiving chemotherapy alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thromboembolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Recurrent Glioblastoma

The safety of Avastin was evaluated in a multicenter, randomized, open-label study (EORTC 26101) in patients with recurrent GBM following radiotherapy and temozolomide of whom 278 patients received at least one dose of Avastin and are considered safety evaluable *[see Clinical Studies (14.4)]*. Patients were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine or lomustine alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. In the Avastin with lomustine arm, 22% of patients discontinued treatment due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving Avastin with lomustine, the adverse reaction profile was similar to that observed in other approved indications.

Metastatic Renal Cell Carcinoma

The safety of Avastin was evaluated in 337 patients who received at least one dose of Avastin in a multicenter, double-blind study (BO17705) in patients with mRCC. Patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks) or placebo with interferon alfa *[see Clinical Studies (14.5)]*. Patients were treated until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-5 adverse reactions occurring at a higher incidence (>2%) were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma). Adverse reactions are presented in Table 3.

Table 3: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥5%) of Patients Receiving Avastin vs. Placebo with Interferon Alfa in Study BO17705

Adverse Reaction[a]	Avastin with Interferon Alfa (N=337)	Placebo with Interferon Alfa (N=304)
Metabolism and nutrition		
Decreased appetite	36%	31%
Weight loss	20%	15%
General		
Fatigue	33%	27%
Vascular		
Hypertension	28%	9%
Respiratory, thoracic and mediastinal		
Epistaxis	27%	4%
Dysphonia	5%	0%
Nervous system		
Headache	24%	16%
Gastrointestinal		
Diarrhea	21%	16%
Renal and urinary		
Proteinuria	20%	3%
Musculoskeletal and connective tissue		
Myalgia	19%	14%
Back pain	12%	6%

a NCI-CTC version 3

The following adverse reactions were reported at a 5-fold greater incidence in patients receiving Avastin with interferon-alfa compared to patients receiving placebo with interferon-alfa and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs. 0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs. 1); tinnitus (7 vs. 1); tooth abscess (7 vs. 0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of Avastin was evaluated in 218 patients who received at least one dose of Avastin in a multicenter study (GOG-0240) in patients with persistent, recurrent, or metastatic cervical cancer*[see Clinical Studies (14.6)]*. Patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin (15 mg/kg every 3 weeks), or paclitaxel and topotecan with or without Avastin (15 mg/kg every 3 weeks). The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 218 patients receiving Avastin with chemotherapy compared to 222 patients receiving chemotherapy alone were abdominal pain (12% vs. 10%), hypertension (11% vs. 0.5%), thrombosis (8% vs. 3%), diarrhea (6% vs. 3%), anal fistula (4% vs. 0%), proctalgia (3% vs. 0%), urinary tract infection (8% vs. 6%), cellulitis (3% vs. 0.5%), fatigue (14% vs. 10%), hypokalemia (7% vs. 4%), hyponatremia (4% vs. 1%), dehydration (4% vs. 0.5%), neutropenia (8% vs. 4%), lymphopenia (6% vs. 3%), back pain (6% vs. 3%), and pelvic pain (6% vs. 1%). Adverse reactions are presented in Table 4.

Table 4: Grades 1-4 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0240

Adverse Reaction[a]	Avastin with Chemotherapy (N=218)	Chemotherapy (N=222)
General		
Fatigue	80%	75%
Peripheral edema	15%	22%
Metabolism and nutrition		
Decreased appetite	34%	26%
Hyperglycemia	26%	19%
Hypomagnesemia	24%	15%
Weight loss	21%	7%
Hyponatremia	19%	10%
Hypoalbuminemia	16%	11%
Vascular		
Hypertension	29%	6%
Thrombosis	10%	3%
Infections		
Urinary tract infection	22%	14%
Infection	10%	5%
Nervous system		
Headache	22%	13%
Dysarthria	8%	1%
Psychiatric		
Anxiety	17%	10%
Respiratory, thoracic and mediastinal		
Epistaxis	17%	1%
Renal and urinary		
Increased blood creatinine	16%	10%
Proteinuria	10%	3%
Gastrointestinal		
Stomatitis	15%	10%
Proctalgia	6%	1%
Anal fistula	6%	0%
Reproductive system and breast		
Pelvic pain	14%	8%
Hematology		
Neutropenia	12%	6%
Lymphopenia	12%	5%

a NCI-CTC version 3

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Stage III or IV Following Initial Surgical Resection
The safety of Avastin was evaluated in GOG-0218, a multicenter, randomized, double-blind, placebo controlled, three arm study, which evaluated the addition of Avastin to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection *[see Clinical Studies (14.7)]*. Patients were randomized (1:1:1) to carboplatin and paclitaxel without Avastin (CPP), carboplatin and paclitaxel with Avastin for up to six cycles (CPB15), or carboplatin and paclitaxel with Avastin for six cycles followed by Avastin as a single agent for up to 16 additional doses (CPB15+). Avastin was given at 15 mg/kg every three weeks. On this trial, 1215 patients received at least one dose of Avastin. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the Avastin arms versus the control arm were fatigue (CPB15+ - 9%, CPB15 - 6%, CPP - 6%), hypertension (CPB15+ - 10%, CPB15 - 6%, CPP - 2%), thrombocytopenia (CPB15+ - 21%, CPB15 - 20%, CPP - 15%) and leukopenia (CPB15+ - 51%, CPB15 - 53%, CPP - 50%). Adverse reactions are presented in Table 5.

Table 5: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in GOG-0218

Adverse Reaction[a]	**Avastin with carboplatin and paclitaxel followed by Avastin alone[*] (N=608)**	**Avastin with carboplatin and paclitaxel[**] (N= 607)**	**Carboplatin and paclitaxel[***] (N= 602)**
General			
Fatigue	80%	72%	73%
Gastrointestinal			
Nausea	58%	53%	51%
Diarrhea	38%	40%	34%
Stomatitis	25%	19%	14%
Musculoskeletal and connective tissue			
Arthralgia	41%	33%	35%
Pain in extremity	25%	19%	17%
Muscular weakness	15%	13%	9%
Nervous system			
Headache	34%	26%	21%
Dysarthria	12%	10%	2%
Vascular			
Hypertension	32%	24%	14%
Respiratory, thoracic and mediastinal			
Epistaxis	31%	30%	9%
Dyspnea	26%	28%	20%
Nasal mucosal disorder	10%	7%	4%

a NCI-CTC version 3, * CPB15+, ** CPB15, ***CPP

Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
The safety of Avastin was evaluated in 179 patients who received at least one dose of Avastin in a multicenter, open-label study (MO22224) in which patients were randomized (1:1) to Avastin with chemotherapy or chemotherapy alone in patients with platinum resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within < 6 months from the most recent platinum based therapy *[see Clinical*

Studies (14.8)]. Patients were randomized to receive Avastin 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks. Patients had received no more than 2 prior chemotherapy regimens. The trial excluded patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Patients were treated until disease progression or unacceptable toxicity. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 179 patients receiving Avastin with chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7% vs. 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs. 1.7%).
Adverse reactions are presented in Table 6.

Table 6: Grades 2−4 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study MO22224

Adverse Reaction[a]	Avastin with Chemotherapy (N=179)	Chemotherapy (N=181)
Hematology		
Neutropenia	31%	25%
Vascular		
Hypertension	19%	6%
Nervous system		
Peripheral sensory neuropathy	18%	7%
General		
Mucosal inflammation	13%	6%
Renal and urinary		
Proteinuria	12%	0.6%
Skin and subcutaneous tissue		
Palmar-plantar erythrodysaesthesia	11%	5%
Infections		
Infection	11%	4%
Respiratory, thoracic and mediastinal		
Epistaxis	5%	0%

a NCI-CTC version 3

Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g
The safety of Avastin was evaluated in 247 patients who received at least one dose of Avastin in a double-blind study (AVF4095g) in patients with platinum sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer *[see Clinical Studies (14.9]*. Patients were randomized (1:1) to receive Avastin (15 mg/kg) or placebo every 3 weeks with carboplatin and gemcitabine for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to placebo with chemotherapy were: thrombocytopenia (40% vs. 34%), nausea (4% vs. 1.3%), fatigue (6% vs. 4%), headache (4% vs. 0.9%), proteinuria (10% vs. 0.4%), dyspnea (4% vs. 1.7%), epistaxis (5% vs. 0.4%), and hypertension (17% vs. 0.9%). Adverse reactions are presented in Table 7.

Table 7: Grades 1−5 Adverse Reactions Occurring at a Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Placebo with Chemotherapy in Study AVF4095g

Adverse Reaction[a]	Avastin with Carboplatin and Gemcitabine (N=247)	Placebo with Carboplatin and Gemcitabine (N=233)
General		
Fatigue	82%	75%
Mucosal inflammation	15%	10%
Gastrointestinal		
Nausea	72%	66%
Diarrhea	38%	29%
Stomatitis	15%	7%
Hemorrhoids	8%	3%
Gingival bleeding	7%	0%
Hematology		
Thrombocytopenia	58%	51%
Respiratory, thoracic and mediastinal		
Epistaxis	55%	14%
Dyspnea	30%	24%
Cough	26%	18%
Oropharyngeal pain	16%	10%
Dysphonia	13%	3%
Rhinorrhea	10%	4%
Sinus congestion	8%	2%
Nervous system		
Headache	49%	30%
Dizziness	23%	17%
Vascular		
Hypertension	42%	9%
Musculoskeletal and connective tissue		
Arthralgia	28%	19%
Back pain	21%	13%
Psychiatric		
Insomnia	21%	15%
Renal and urinary		
Proteinuria	20%	3%
Injury and procedural		
Contusion	17%	9%
Infections		
Sinusitis	15%	9%

a NCI-CTC version 3

Study GOG-0213

The safety of Avastin was evaluated in an open-label, controlled study (GOG-0213) in 325 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy*[see Clinical Studies (14.9)]*. Patients were randomized (1:1) to receive carboplatin and paclitaxel for 6 to 8 cycles or Avastin (15 mg/kg every 3 weeks) with carboplatin and paclitaxel for 6 to 8 cycles followed by Avastin as a single agent until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to chemotherapy alone were: hypertension (11% vs. 0.6%), fatigue (8% vs. 3%), febrile neutropenia (6% vs. 3%), proteinuria (8% vs. 0%), abdominal pain (6% vs. 0.9%), hyponatremia (4% vs. 0.9%), headache (3% vs. 0.9%), and pain in extremity (3% vs. 0%).
Adverse reactions are presented in Table 8.

Table 8: Grades 1−5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0213

Adverse Reaction[a]	Avastin with Carboplatin and Paclitaxel (N=325)	Carboplatin and Paclitaxel (N=332)
Musculoskeletal and connective tissue		
Arthralgia	45%	30%
Myalgia	29%	18%
Pain in extremity	25%	14%
Back pain	17%	10%
Muscular weakness	13%	8%
Neck pain	9%	0%
Vascular		
Hypertension	42%	3%
Gastrointestinal		
Diarrhea	39%	32%
Abdominal pain	33%	28%
Vomiting	33%	25%
Stomatitis	33%	16%
Nervous system		
Headache	38%	20%
Dysarthria	14%	2%
Dizziness	13%	8%
Metabolism and nutrition		
Decreased appetite	35%	25%
Hyperglycemia	31%	24%
Hypomagnesemia	27%	17%
Hyponatremia	17%	6%
Weight loss	15%	4%
Hypocalcemia	12%	5%
Hypoalbuminemia	11%	6%
Hyperkalemia	9%	3%
Respiratory, thoracic and mediastinal		
Epistaxis	33%	2%
Dyspnea	30%	25%
Cough	30%	17%
Rhinitis allergic	17%	4%
Nasal mucosal disorder	14%	3%
Skin and subcutaneous tissue		
Exfoliative rash	23%	16%
Nail disorder	10%	2%
Dry skin	7%	2%
Renal and urinary		
Proteinuria	17%	1%
Increased blood creatinine	13%	5%
Hepatic		

Adverse Reaction[a]	Avastin with Carboplatin and Paclitaxel (N=325)	Carboplatin and Paclitaxel (N=332)
Increased aspartate aminotransferase	15%	9%
General		
Chest pain	8%	2%
Infections		
Sinusitis	7%	2%

a NCI-CTC version 3

Hepatocellular Carcinoma (HCC)

The safety of Avastin in combination with atezolizumab 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 (14.10)]*. Patients received 1,200 mg of atezolizumab intravenously followed by 15 mg/kg Avastin (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 Avastin was 6.9 months (range: 0-16 months) and to atezolizumab was 7.4 months (range: 0-16 months).

Fatal adverse reactions occurred in 4.6% of patients in the Avastin and atezolizumab 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 Avastin and atezolizumab arm. The most frequent serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of Avastin occurred in 15% of patients in the Avastin and atezolizumab arm. The most common adverse reactions leading to Avastin discontinuation were hemorrhages (4.9%), including bleeding varicose vein, hemorrhage and gastrointestinal, subarachnoid, and pulmonary hemorrhages; and increased transaminases or bilirubin (0.9%).

Adverse reactions leading to interruption of Avastin occurred in 46% of patients in the Avastin and atezolizumab arm; the most common (≥ 2%) were proteinuria (6%); infections (6%); hypertension (6%); liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatase (4.6%); gastrointestinal hemorrhages (3%); thrombocytopenia/decreased platelet count (4.3%); and pyrexia (2.4%).

Tables 9 and 10 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received Avastin and atezolizumab in IMbrave150.

Table 9: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving Avastin in IMbrave150

Adverse Reaction	Avastin in combination with atezolizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
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 10: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving Avastin in IMbrave150

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

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Avastin plus atezolizumab (222-323) and sorafenib (90-153) NA = Not applicable.
[1] Graded per NCI CTCAE v4.0

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bevacizumab in the studies described below with the incidence of antibodies in other studies or to other bevacizumab products may be misleading.

In clinical studies for adjuvant treatment of a solid tumor, 0.6% (14/2233) of patients tested positive for treatment-emergent anti-bevacizumab antibodies as detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-bevacizumab antibodies is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Avastin. 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.

General: Polyserositis
Cardiovascular: Pulmonary hypertension, Mesenteric venous occlusion
Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Hepatobiliary disorders: Gallbladder perforation
Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation
Vascular: Arterial (including aortic) aneurysms, dissections, and rupture

7 DRUG INTERACTIONS

Effects of Avastin on Other Drugs

No clinically meaningful effect on the pharmacokinetics of irinotecan or its active metabolite SN38, interferon alfa, carboplatin or paclitaxel was observed when Avastin was administered in combination with these drugs; however, 3 of the 8 patients receiving Avastin with paclitaxel and carboplatin had lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel and carboplatin alone had a greater paclitaxel exposure at Day 63 than at Day 0.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)],* Avastin may cause fetal harm in pregnant women. Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug-associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *(see Data)*. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women 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

Pregnant rabbits dosed with 10 mg/kg to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6–18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included:

reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

8.2 Lactation

Risk Summary
No data are available regarding the presence of bevacizumab in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception
Females
Avastin may 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 Avastin and for 6 months after the last dose.

Infertility
Females
Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first-dose of Avastin. Long-term effects of Avastin on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in patients who received Avastin with chemotherapy (34%) compared to patients who received chemotherapy alone (2%). After discontinuing Avastin with chemotherapy, recovery of ovarian function occurred in 22% of these patients *[see Warnings and Precautions (5.11), Adverse Reactions (6.1)]*.

8.4 Pediatric Use
The safety and effectiveness of Avastin in pediatric patients have not been established.

In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who received Avastin. Avastin is not approved for use in patients under the age of 18 years.

Antitumor activity was not observed among eight pediatric patients with relapsed GBM who received bevacizumab and irinotecan. Addition of Avastin to standard of care did not result in improved event-free survival in pediatric patients enrolled in two randomized clinical studies, one in high grade glioma (n= 121) and one in metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma (n= 154).

Based on the population pharmacokinetics analysis of data from 152 pediatric and young adult patients with cancer (7 months to 21 years of age), bevacizumab clearance normalized by body weight in pediatrics was comparable to that in adults.

Juvenile Animal Toxicity Data
Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use
In an exploratory pooled analysis of 1745 patients from five randomized, controlled studies, 35% of patients were ≥ 65 years old. The overall incidence of ATE was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age; however, the increase in the incidence of ATE was greater in patients ≥ 65 years (8% vs. 3%) as compared to patients < 65 years (2% vs. 1%) *[see Warnings and Precautions (5.4)]*.

11 DESCRIPTION
Bevacizumab is a vascular endothelial growth factor inhibitor. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system.

Avastin (bevacizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brown solution in a single-dose vial for intravenous use. Avastin contains bevacizumab at a concentration of 25 mg/mL in either a 100 mg/4 mL or 400 mg/16 mL single-dose vial.

Each mL of solution contains 25 mg bevacizumab, α,α-trehalose dihydrate (60 mg), polysorbate 20 (0.4 mg), sodium phosphate dibasic, anhydrous (1.2 mg), sodium phosphate monobasic, monohydrate (5.8 mg), and Water for Injection, USP. The pH is 6.2.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

12.3 Pharmacokinetics
The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of Avastin every week, every 2 weeks, or every 3 weeks, bevacizumab pharmacokinetics are linear and the predicted time to reach more than 90% of steady state concentration is 84 days. The accumulation ratio following a dose of 10 mg/kg once every 2 weeks is 2.8.

Population simulations of bevacizumab exposures provide a median trough concentration of 80.3 mcg/mL on Day 84 (10^{th}, 90^{th} percentile: 45, 128) following a dose of 5 mg/kg once every two weeks.

Distribution
The mean (% coefficient of variation [CV%]) central volume of distribution is 2.9 (22%) L.

Elimination
The mean (CV%) clearance is 0.23 (33) L/day. The estimated half-life is 20 days (11 to 50 days).

Specific Populations
The clearance of bevacizumab varied by body weight, sex, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.26 L/day vs. 0.21 L/day) and a larger central volume of distribution (3.2 L vs. 2.7 L) than females. Patients with higher tumor burden (at or above median value of

tumor surface area) had a higher bevacizumab clearance (0.25 L/day vs. 0.20 L/day) than patients with tumor burdens below the median. In Study AVF2107g, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin as compared to females and patients with low tumor burden.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess potential of bevacizumab for carcinogenicity or mutagenicity.

Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea, as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

13.2 Animal Toxicology and/or Pharmacology

Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer

Study AVF2107g

The safety and efficacy of Avastin was evaluated in a double-blind, active-controlled study [AVF2107g (NCT00109070)] in 923 patients with previously untreated mCRC who were randomized (1:1:1) to placebo with bolus-IFL (irinotecan 125 mg/m^2, fluorouracil 500 mg/m^2, and leucovorin 20 mg/m^2 given once weekly for 4 weeks every 6 weeks), Avastin (5 mg/kg every 2 weeks) with bolus-IFL, or Avastin (5 mg/kg every 2 weeks) with fluorouracil and leucovorin. Enrollment to the Avastin with fluorouracil and leucovorin arm was discontinued after enrollment of 110 patients in accordance with the protocol-specified adaptive design. Avastin was continued until disease progression or unacceptable toxicity or for a maximum of 96 weeks. The main outcome measure was overall survival (OS).

The median age was 60 years; 60% were male, 79% were White, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28% received prior adjuvant chemotherapy. The dominant site of disease was extra-abdominal in 56% of patients and was the liver in 38% of patients.

The addition of Avastin improved survival across subgroups defined by age (< 65 years, ≥ 65 years) and sex. Results are presented in Table 11 and Figure 1.

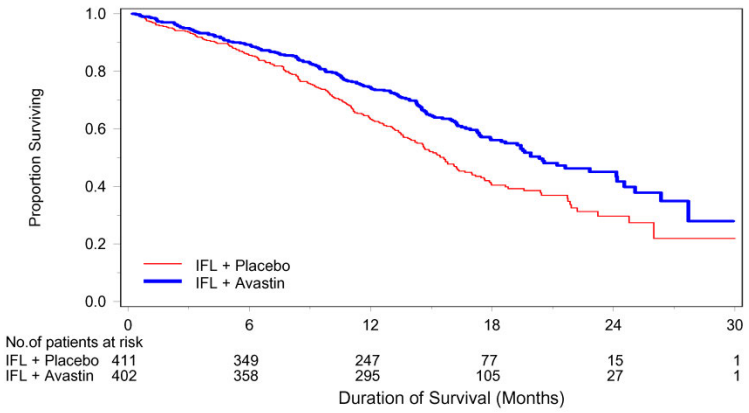
Table 11: Efficacy Results in Study AVF2107g

Efficacy Parameter	Avastin with bolus-IFL (N=402)	Placebo with bolus-IFL (N=411)
Overall Survival		
Median, in months	20.3	15.6
Hazard ratio (95% CI)	0.66 (0.54, 0.81)	
p-value[a]	< 0.001	
Progression-Free Survival		
Median, in months	10.6	6.2
Hazard ratio (95% CI)	0.54 (0.45, 0.66)	
p-value[a]	< 0.001	
Overall Response Rate		
Rate (%)	45%	35%
p-value[b]	< 0.01	
Duration of Response		
Median, in months	10.4	7.1

[a] by stratified log-rank test.

[b] by χ^2 test

Figure 1: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study AVF2107g



Among the 110 patients randomized to Avastin with fluorouracil and leucovorin, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, overall response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study E3200

The safety and efficacy of Avastin were evaluated in a randomized, open-label, active-controlled study [E3200 (NCT00025337)] in 829 patients who were previously treated with irinotecan and fluorouracil for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2 concurrently, then fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; Day 2: leucovorin 200 mg/m^2, then fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; every 2 weeks), Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity. The main outcome measure was OS.

The Avastin alone arm was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee based on evidence of decreased survival compared to FOLFOX4 alone.

The median age was 61 years; 60% were male, 87% were White, 49% had an ECOG performance status of 0, 26% received prior radiation therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan with or without fluorouracil for metastatic disease, and 1% received prior irinotecan and fluorouracil as adjuvant therapy.

The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to FOLFOX4 alone; median OS was 13.0 months vs. 10.8 months [hazard ratio (HR) 0.75 (95% CI: 0.63, 0.89), p-value of 0.001 stratified log-rank test] with clinical benefit seen in subgroups defined by age (< 65 years, ≥ 65 years) and sex. PFS and ORR based on investigator assessment were higher in patients receiving Avastin with FOLFOX4.

Study TRC-0301

The activity of Avastin with fluorouracil (as bolus or infusion) and leucovorin was evaluated in a single arm study [TRC-0301 (NCT00066846)] enrolling 339 patients with mCRC with disease progression following both irinotecan- and oxaliplatin-based chemotherapy. Seventy-three percent of patients received concurrent bolus fluorouracil and leucovorin. One objective partial response was verified in the first 100 evaluable patients for an ORR of 1% (95% CI: 0%, 5.5%).

Study ML18147

The safety and efficacy of Avastin were evaluated in a prospective, randomized, open-label, multinational, controlled study [ML18147 (NCT00700102)] in 820 patients with histologically confirmed mCRC who had progressed on a first-line Avastin containing regimen. Patients were excluded if they progressed within 3 months of initiating first-line chemotherapy and if they received Avastin for less than 3 consecutive months in the first-line setting. Patients were randomized (1:1) within 3 months after discontinuing Avastin as first-line treatment to receive fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy with or without Avastin (5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks). The choice of second-line treatment was contingent upon first-line chemotherapy. Second-line treatment was administered until progressive disease or unacceptable toxicity. The main outcome measure was OS. A secondary outcome measure was ORR.

The median age was 63 years (21 to 84 years); 64% were male, 52% had an ECOG performance status of 1, 44% had an ECOG performance status of 0, 58% received irinotecan-based therapy as first-line treatment, 55% progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each arm.

The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of OS and PFS. There was no significant difference in ORR. Results are presented in Table 12 and Figure 2.

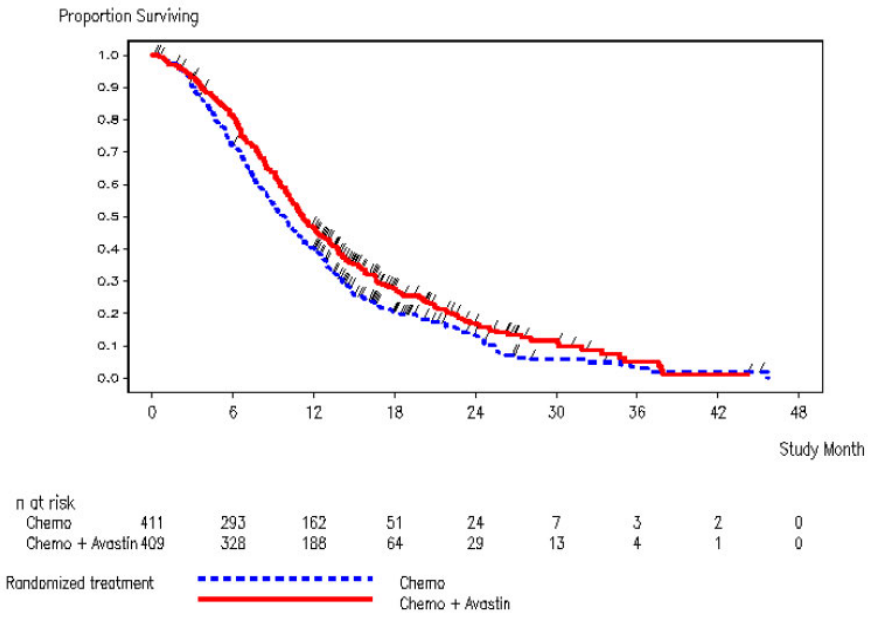
Table 12: Efficacy Results in Study ML18147

Efficacy Parameter	Avastin with Chemotherapy (N=409)	Chemotherapy (N=411)
Overall Survival[a]		
Median, in months	11.2	9.8
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival[b]		
Median, in months	5.7	4.0
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

[a] p=0.0057 by unstratified log-rank test.

[b] p-value < 0.0001 by unstratified log-rank test.

Figure 2: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study ML18147



14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

Lack of efficacy of Avastin as an adjunct to standard chemotherapy for the adjuvant treatment of colon cancer was determined in two randomized, open-label, multicenter clinical studies.

The first study [BO17920 (NCT00112918)] was conducted in 3451 patients with high-risk stage II and III colon cancer, who had undergone surgery for colon cancer with curative intent. Patients were randomized to receive Avastin at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule with FOLFOX4 (N=1155) or on a 3-weekly schedule with XELOX (N=1145) or FOLFOX4 alone (N=1151). The main outcome measure was disease free survival (DFS) in patients with stage III colon cancer.

The median age was 58 years; 54% were male, 84% were White and 29% were ≥ 65 years. Eighty-three percent had stage III disease.

The addition of Avastin to chemotherapy did not improve DFS. As compared to FOLFOX4 alone, the proportion of stage III patients with disease recurrence or with death due to disease progression were numerically higher for patients receiving Avastin with FOLFOX4 or with XELOX. The hazard ratios for DFS were 1.17 (95% CI: 0.98,1.39) for Avastin with FOLFOX4 versus FOLFOX4 alone and 1.07 (95% CI: 0.90, 1.28) for Avastin with XELOX versus FOLFOX4 alone. The hazard ratios for OS were 1.31 (95% CI: 1.03, 1.67) and 1.27 (95% CI: 1, 1.62) for the comparison of Avastin with FOLFOX4 versus FOLFOX4 alone and Avastin with XELOX versus FOLFOX4 alone, respectively. Similar lack of efficacy for DFS was observed in the Avastin-containing arms compared to FOLFOX4 alone in the high-risk stage II cohort.

In a second study [NSABP-C-08 (NCT00096278)], patients with stage II and III colon cancer who had undergone surgery with curative intent, were randomized to receive either Avastin administered at a dose equivalent to 2.5 mg/kg/week with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The median age was 57 years, 50% were male and 87% White. Seventy-five percent had stage III disease. The main outcome was DFS among stage III patients. The HR for DFS was 0.92 (95% CI: 0.77, 1.10). OS was not significantly improved with the addition of Avastin to mFOLFOX6 [HR 0.96 (95% CI: 0.75,1.22)].

14.3 First-Line Non–Squamous Non–Small Cell Lung Cancer

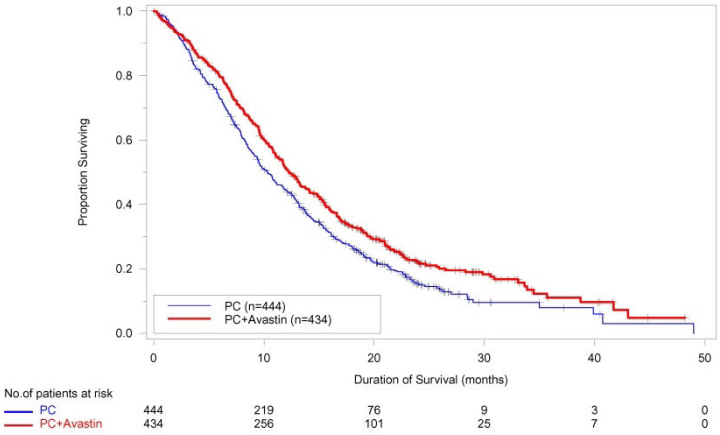
Study E4599

The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study [E4599 (NCT00021060)]. A total of 878 chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC 6) with or without Avastin 15 mg/kg. After completing or discontinuing chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving therapeutic anticoagulation. The main outcome measure was duration of survival.

The median age was 63 years; 54% were male, 43% were ≥ 65 years, and 28% had ≥ 5% weight loss at study entry. Eleven percent had recurrent disease. Of the 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

OS was statistically significantly longer for patients receiving Avastin with paclitaxel and carboplatin compared with those receiving chemotherapy alone. Median OS was 12.3 months vs. 10.3 months [HR 0.80 (95% CI: 0.68, 0.94), final p-value of 0.013, stratified log-rank test]. Based on investigator assessment which was not independently verified, patients were reported to have longer PFS with Avastin with paclitaxel and carboplatin compared to chemotherapy alone. Results are presented in Figure 3.

Figure 3: Kaplan-Meier Curves for Duration of Survival in First-Line Non-Squamous Non-Small Cell Lung Cancer in Study E4599



In an exploratory analysis across patient subgroups, the impact of Avastin on OS was less robust in the following subgroups: women [HR 0.99 (95% CI: 0.79, 1.25)], patients ≥ 65 years [HR 0.91 (95% CI: 0.72, 1.14)] and patients with ≥ 5% weight loss at study entry [HR 0.96 (95% CI: 0.73, 1.26)].

Study BO17704

The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy was studied in another randomized, double-blind, placebo-controlled study [BO17704 (NCT00806923)]. A total of 1043 patients were randomized (1:1:1) to receive cisplatin and gemcitabine with placebo, Avastin 7.5 mg/kg or Avastin 15 mg/kg. The main outcome measure was PFS. Secondary outcome measure was OS.

The median age was 58 years; 36% were female and 29% were ≥ 65 years. Eight percent had recurrent disease and 77% had Stage IV disease.

PFS was significantly higher in both Avastin-containing arms compared to the placebo arm [HR 0.75 (95% CI: 0.62, 0.91), p-value of 0.0026 for Avastin 7.5 mg/kg and HR 0.82 (95% CI: 0.68; 0.98), p-value of 0.0301 for Avastin 15 mg/kg]. The addition of Avastin to cisplatin and gemcitabine failed to demonstrate an improvement in the duration of OS [HR 0.93 (95% CI: 0.78; 1.11), p-value of 0.420 for Avastin 7.5 mg/kg and HR 1.03 (95% CI: 0.86, 1.23), p-value of 0.761 for Avastin 15 mg/kg].

14.4 Recurrent Glioblastoma

Study EORTC 26101

The safety and efficacy of Avastin were evaluated in a multicenter, randomized (2:1), open-label study in patients with recurrent GBM (EORTC 26101, NCT01290939). Patients with first progression following radiotherapy and temozolomide were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine (90 mg/m^2 every 6 weeks) or lomustine (110 mg/m^2 every 6 weeks) alone until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs. >0), steroid use (yes vs. no), largest tumor diameter (≤ 40 vs. > 40 mm), and institution. The main outcome measure was OS. Secondary outcome measures were investigator-assessed PFS and ORR per the modified Response Assessment in Neuro-oncology (RANO) criteria, health related quality of life (HRQoL), cognitive function, and corticosteroid use.

A total of 432 patients were randomized to receive lomustine alone (N=149) or Avastin with lomustine (N=283). The median age was 57 years; 24.8% of patients were ≥ 65 years. The majority of patients with were male (61%); 66% had a WHO performance status score > 0; and in 56% the largest tumor diameter was ≤ 40 mm. Approximately 33% of patients randomized to receive lomustine received Avastin following documented progression.

No difference in OS (HR 0.91, p-value of 0.4578) was observed between arms; therefore, all secondary outcome measures are descriptive only. PFS was longer in the Avastin with lomustine arm [HR 0.52 (95% CI: 0.41, 0.64)] with a median PFS of 4.2 months in the Avastin with lomustine arm and 1.5 months in the lomustine arm. Among the 50% of patients receiving corticosteroids at the time of randomization, a higher percentage of patients in the Avastin with lomustine arm discontinued corticosteroids (23% vs. 12%).

Study AVF3708g and Study NCI 06-C-0064E

The efficacy and safety of Avastin 10 mg/kg every 2 weeks in patients with previously treated GBM were evaluated in one single arm single center study (NCI 06-C-0064E) and a randomized noncomparative multicenter study [AVF3708g (NCT00345163)]. Response rates in both studies were evaluated based on modified WHO criteria that considered corticosteroid use. In AVF3708g, the response rate was 25.9% (95% CI: 17%, 36.1%) with a median duration of response of 4.2 months (95% CI: 3, 5.7). In Study NCI 06-C-0064E, the response rate was 19.6% (95% CI: 10.9%, 31.3%) with a median duration of response of 3.9 months (95% CI: 2.4, 17.4).

14.5 Metastatic Renal Cell Carcinoma

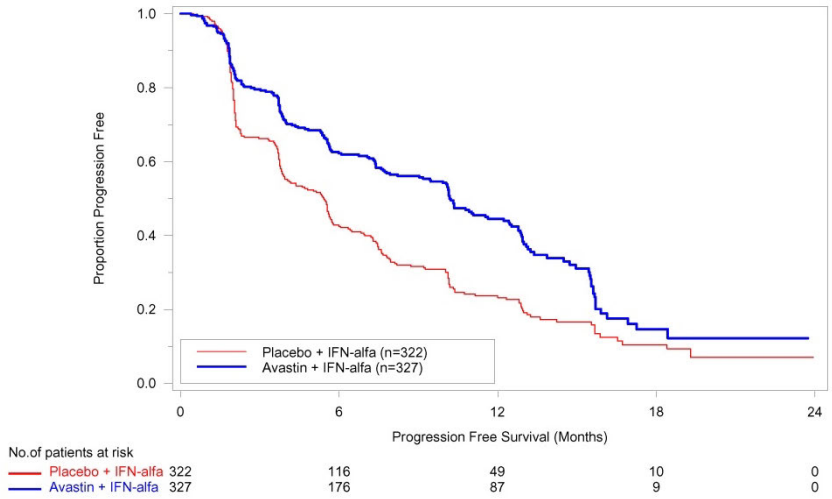
Study BO17705

The safety and efficacy of Avastin were evaluated in patients with treatment-naïve mRCC in a multicenter, randomized, double-blind, international study [BO17705 (NCT00738530)] comparing interferon alfa and Avastin versus interferon alfa and placebo. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks; N = 327) or placebo (every 2 weeks; N = 322) with interferon alfa (9 MIU subcutaneously three times weekly for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 60 years (18 to 82 years); 70% were male and 96% were White. The study population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3–5), and 7% missing.

PFS was statistically significantly prolonged among patients receiving Avastin compared to placebo; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI: 0.49, 0.72), p-value < 0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, p-value < 0.0001, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the patients receiving Avastin with interferon alfa and 21 months in patients receiving interferon alone [HR 0.86, (95% CI: 0.72, 1.04)]. Results are presented in Figure 4.

Figure 4: Kaplan-Meier Curves for Progression-Free Survival in Metastatic Renal Cell Carcinoma in Study BO17705



14.6 Persistent, Recurrent, or Metastatic Cervical Cancer

Study GOG-0240

The safety and efficacy of Avastin were evaluated in patients with persistent, recurrent, or metastatic cervical cancer in a randomized, four-arm, multicenter study comparing Avastin with chemotherapy versus chemotherapy alone [GOG-0240 (NCT00803062)]. A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin, or paclitaxel and topotecan with or without Avastin.

The dosing regimens for Avastin, paclitaxel, cisplatin and topotecan were as follows:

- Day 1: Paclitaxel 135 mg/m^2 over 24 hours, Day 2: cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours, Day 2: cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with Avastin, Days 1-3: topotecan IV 0.75 mg/m^2 over 30 minutes

Patients were treated until disease progression or unacceptable adverse reactions. The main outcome measure was OS. Secondary outcome measures included ORR.

The median age was 48 years (20 to 85 years). Of the 452 patients randomized at baseline, 78% of patients were White, 80% had received prior radiation, 74% had received prior chemotherapy concurrent with radiation, and 32% had a platinum-free interval (PFI) of less than 6 months. Patients had a GOG performance status of 0 (58%) or 1 (42%). Demographic and disease characteristics were balanced across arms.

Results are presented in Figure 5 and Table 13.

Figure 5: Kaplan-Meier Curves for Overall Survival in Persistent, Recurrent, or Metastatic Cervical Cancer in Study GOG-0240

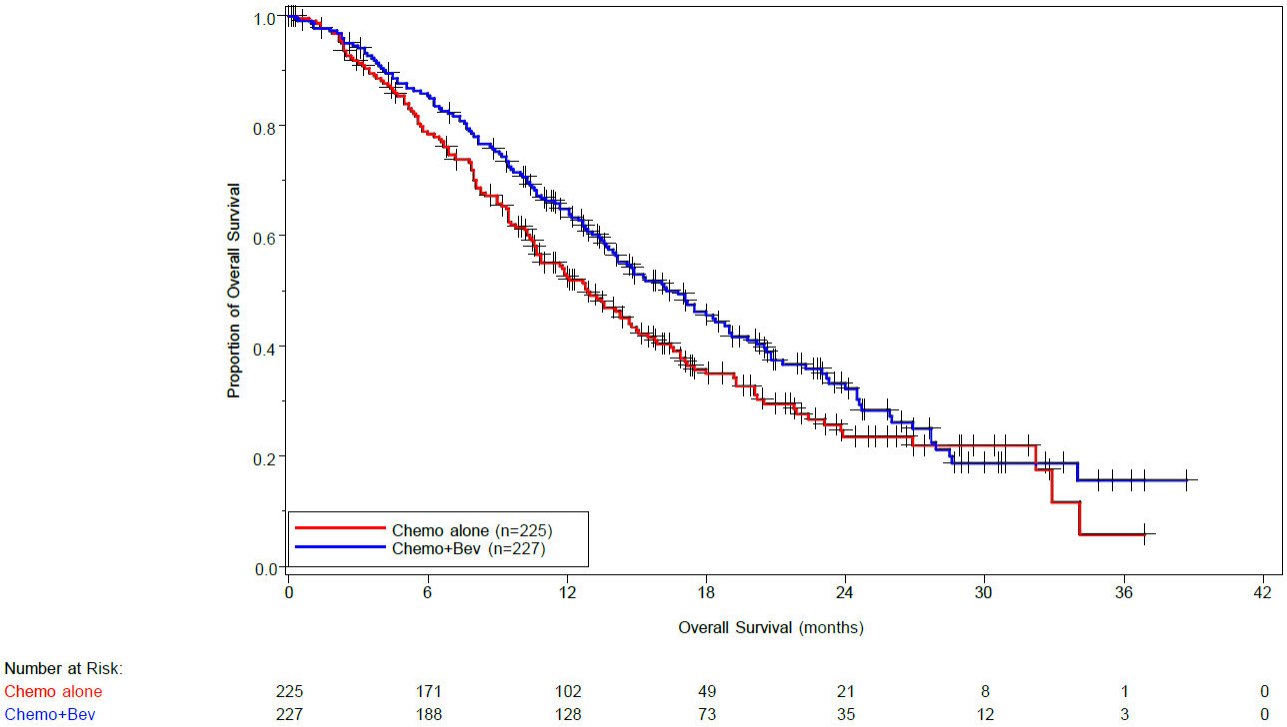


Table 13: Efficacy Results in Study GOG-0240

Efficacy Parameter	Avastin with Chemotherapy (N=227)	Chemotherapy (N=225)
Overall Survival		
Median, in months[a]	16.8	12.9
Hazard ratio (95% CI)	0.74 (0.58, 0.94)	
p-value[b]	0.0132	

[a] Kaplan-Meier estimates.
[b] log-rank test (stratified).

The ORR was higher in patients who received Avastin with chemotherapy [45% (95% CI: 39, 52)] compared to patients who received chemotherapy alone [34% (95% CI: 28,40)].

Table 14: Efficacy Results in Study GOG-0240

Efficacy Parameter	Topotecan and Paclitaxel with or without Avastin (N=223)	Cisplatin and Paclitaxel with or without Avastin (N=229)
Overall Survival		
Median, in months[a]	13.3	15.5
Hazard ratio (95% CI)	1.15 (0.91, 1.46)	
p-value	0.23	

[a] Kaplan-Meier estimates.

The HR for OS with Avastin with cisplatin and paclitaxel as compared to cisplatin and paclitaxel alone was 0.72 (95% CI: 0.51,1.02). The HR for OS with Avastin with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

14.7 Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection

Study GOG-0218

The safety and efficacy of Avastin were evaluated in a multicenter, randomized, double-blind, placebo controlled, three arm study [Study GOG-0218 (NCT00262847)] evaluating the effect of adding Avastin to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer (N=1873) following initial surgical resection. Patients were randomized (1:1:1) to one of the following arms:

- CPP: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent placebo started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent Avastin started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15+: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent Avastin started at cycle 2, followed by Avastin as a single agent every three weeks for a total of up to 22 cycles of therapy (n=623).

The main outcome measure was investigator-assessed PFS. OS was a secondary outcome measure.

The median age was 60 years (range 22-89 years) and 28% of patients were >65 years of age.
Overall, approximately 50% of patients had a GOG PS of 0 at baseline, and 43% a GOG PS score of 1. Patients had either epithelial ovarian cancer (83%), primary peritoneal cancer (15%), or fallopian tube cancer (2%). Serous adenocarcinoma was the most common histologic type (85% in CPP and CPB15 arms, 86% in CPB15+ arm). Overall, approximately 34% of patients had resected FIGO Stage III with residual disease < 1 cm, 40% had resected Stage III with residual disease >1 cm, and 26% had resected Stage IV disease.

The majority of patients in all three treatment arms received subsequent antineoplastic treatment, 78.1% in the CPP arm, 78.6% in the CPB15 arm, and 73.2% in the CPB15+ arm. A higher proportion of patients in the CPP arm (25.3%) and CPB15 arm (26.6%) received at least one anti-angiogenic (including bevacizumab) treatment after discontinuing from study compared with the CPB15+ arm (15.6%).

Study results are presented in Table 15 and Figure 6.

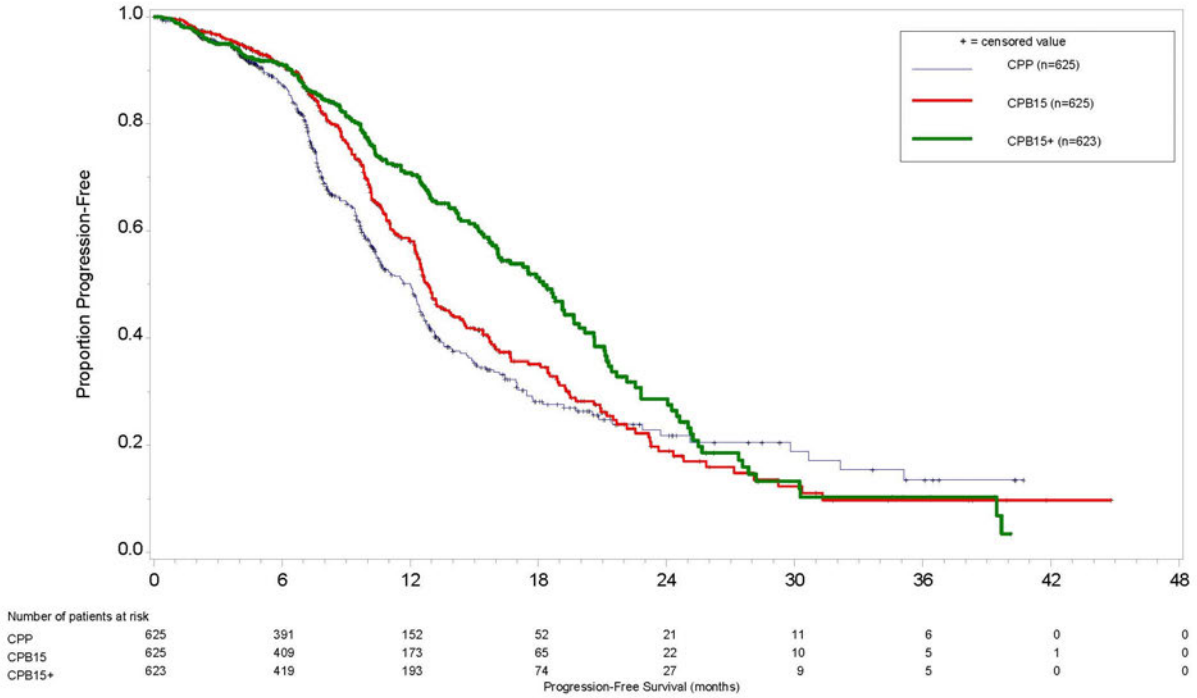
Table 15: Efficacy Results in Study GOG-0218

Efficacy Parameter	**Avastin with carboplatin and paclitaxel followed by Avastin alone (N=623)**	**Avastin with carboplatin and paclitaxel (N=625)**	**Carboplatin and paclitaxel (N= 625)**
Progression-Free Survival per Investigator			
Median, in months	18.2	12.8	12.0
Hazard ratio (95% CI)[a]	0.62 (0.52, 0.75)	0.83 (0.70, 0.98)	
p –value[b]	< 0.0001	NS	
Overall Survival[c]			
Median, in months	43.8	38.8	40.6

Hazard ratio (95% CI)[a]	0.89 (0.76, 1.05)	1.06 (0.90, 1.24)	

NS=not significant
[a] Relative to the control arm; stratified hazard ratio
[b] Two-sided p-value based on re-randomization test
[c] Final overall survival analysis

Figure 6: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection in Study GOG-0218



14.8 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study MO22224

The safety and efficacy of Avastin were evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing Avastin with chemotherapy versus chemotherapy alone in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within <6 months from the most recent platinum-based therapy (N=361). Patients had received no more than 2 prior chemotherapy regimens. Patients received one of the following chemotherapy regimens at the discretion of the investigator: paclitaxel (80 mg/m^2 on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m^2 on day 1 every 4 weeks; or topotecan 4 mg/m^2 on days 1, 8 and 15 every 4 weeks or 1.25 mg/m^2 on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 61 years (25 to 84 years) and 37% of patients were ≥65 years. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥2 times ULN and 31% had ascites at baseline. Seventy-three percent had a PFI of 3 months to 6 months and 27% had PFI of <3 months. ECOG performance status was 0 for 59%, 1 for 34% and 2 for 7% of the patients.

The addition of Avastin to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Results for the ITT population are presented in Table 16 and Figure 7. Results for the separate chemotherapy cohorts are presented in Table 17.

Table 16: Efficacy Results in Study MO22224

Efficacy Parameter	Avastin with Chemotherapy (N=179)	Chemotherapy (N=182)
Progression-Free Survival per Investigator		
Median (95% CI), in months	6.8 (5.6, 7.8)	3.4 (2.1, 3.8)
HR (95% CI)[a]	0.38 (0.30, 0.49)	
p-value[b]	<0.0001	
Overall Survival		
Median (95% CI), in months	16.6 (13.7, 19.0)	13.3 (11.9, 16.4)
HR (95% CI)[a]	0.89 (0.69, 1.14)	
Overall Response Rate		
Number of Patients with Measurable Disease at Baseline	142	144
Rate, % (95% CI)	28% (21%, 36%)	13% (7%, 18%)
Duration of Response		
Median, in months	9.4	5.4

[a] per stratified Cox proportional hazards model
[b] per stratified log-rank test

Figure 7: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study MO22224

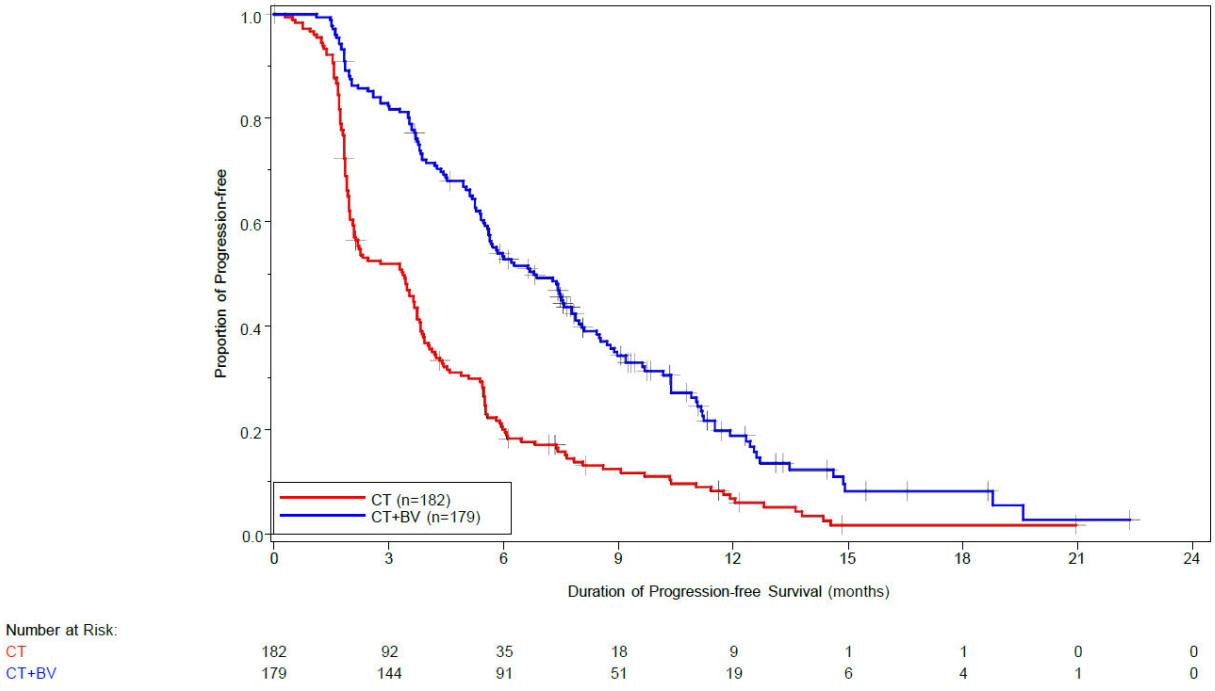


Table 17: Efficacy Results in Study MO22224 by Chemotherapy

Efficacy Parameter	Paclitaxel		Topotecan		Pegylated Liposomal Doxorubicin	
	Avastin with Chemotherapy (N=60)	Chemotherapy (N=55)	Avastin with Chemotherapy (N=57)	Chemotherapy (N=63)	Avastin with Chemotherapy (N=62)	Chemotherapy (N=64)
Progression-Free Survival per Investigator						
Median, in months (95% CI)	9.6 (7.8, 11.5)	3.9 (3.5, 5.5)	6.2 (5.3, 7.6)	2.1 (1.9, 2.3)	5.1 (3.9, 6.3)	3.5 (1.9, 3.9)
Hazard ratio[a] (95% CI)	0.47 (0.31, 0.72)		0.24 (0.15, 0.38)		0.47 (0.32, 0.71)	
Overall Survival						
Median, in months (95% CI)	22.4 (16.7, 26.7)	13.2 (8.2, 19.7)	13.8 (11.0, 18.3)	13.3 (10.4, 18.3)	13.7 (11.0, 18.3)	14.1 (9.9, 17.8)
Hazard ratio [a] (95% CI)	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Overall Response Rate						
Number of patients with measurable disease at baseline	45	43	46	50	51	51
Rate, % (95% CI)	53 (39, 68)	30 (17, 44)	17 (6, 28)	2 (0, 6)	16 (6, 26)	8 (0, 15)
Duration of Response						
Median, in months	11.6	6.8	5.2	NE	8.0	4.6

[a] per stratified Cox proportional hazards model
NE=Not Estimable

14.9 Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g

The safety and efficacy of Avastin were evaluated in a randomized, double-blind, placebo-controlled study [AVF4095g (NCT00434642)] studying Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment (N=484). Patients were randomized (1:1) to receive Avastin (15 mg/kg day 1) or placebo every 3 weeks with carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) a for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The main outcome measures were investigator-assessed PFS. Secondary outcome measures were ORR and OS.

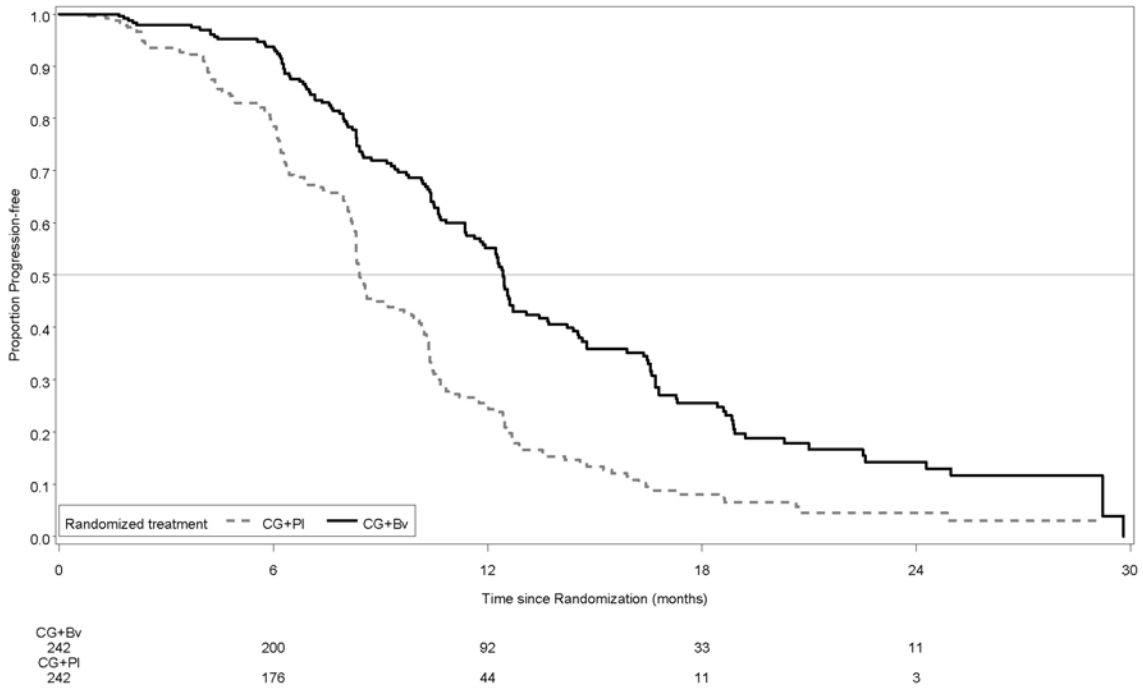
The median age was 61 years (28 to 87 years) and 37% of patients were ≥65 years. All patients had measurable disease at baseline, 74% had baseline CA-125 levels >ULN (35 U/mL). The platinum-free interval (PFI) was 6 months to 12 months in 42 % of patients and >12 months in 58% of patients. The ECOG performance status was 0 or 1 for 99.8% of patients.

A statistically significant prolongation in PFS was demonstrated among patients receiving Avastin with chemotherapy compared to those receiving placebo with chemotherapy (Table 18 and Figure 8). Independent radiology review of PFS was consistent with investigator assessment [HR 0.45 (95% CI: 0.35, 0.58)]. OS was not significantly improved with the addition of Avastin to chemotherapy [HR 0.95 (95% CI: 0.77, 1.17)].

Table 18: Efficacy Results in Study AVF4095g

Efficacy Parameter	Avastin with Gemcitabine and Carboplatin (N=242)	Placebo with Gemcitabine and Carboplatin (N=242)
Progression-Free Survival		
Median, in months	12.4	8.4
Hazard ratio (95% CI)	0.46 (0.37, 0.58)	
p-value	< 0.0001	
Overall Response Rate		
% patients with overall response	78%	57%
p-value	< 0.0001	

Figure 8: Kaplan-Meier Curves for Progression-Free Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study AVF4095g



Study GOG-0213

The safety and efficacy of Avastin were evaluated in a randomized, controlled, open-label study [Study GOG-0213 (NCT00565851)] of Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy (N=673). Patients were randomized (1:1) to receive carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) every 3 weeks for 6 to 8 cycles (N=336) or Avastin (15 mg/kg) every 3 weeks with carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) for 6 to 8 cycles followed by Avastin (15 mg/kg every 3 weeks) as a single agent until disease progression or unacceptable toxicity. The main outcome measure was OS. Other outcome measures were investigator-assessed PFS, and ORR.

The median age was 60 years (23 to 85 years) and 33% of patients were ≥ 65 years. Eighty-three percent had measurable disease at baseline and 74% had abnormal CA-125 levels at baseline. Ten percent of patients had received prior bevacizumab. Twenty-six percent had a PFI of 6 months to 12 months and 74% had a PFI of >12 months. GOG performance status was 0 or 1 for 99% of patients.

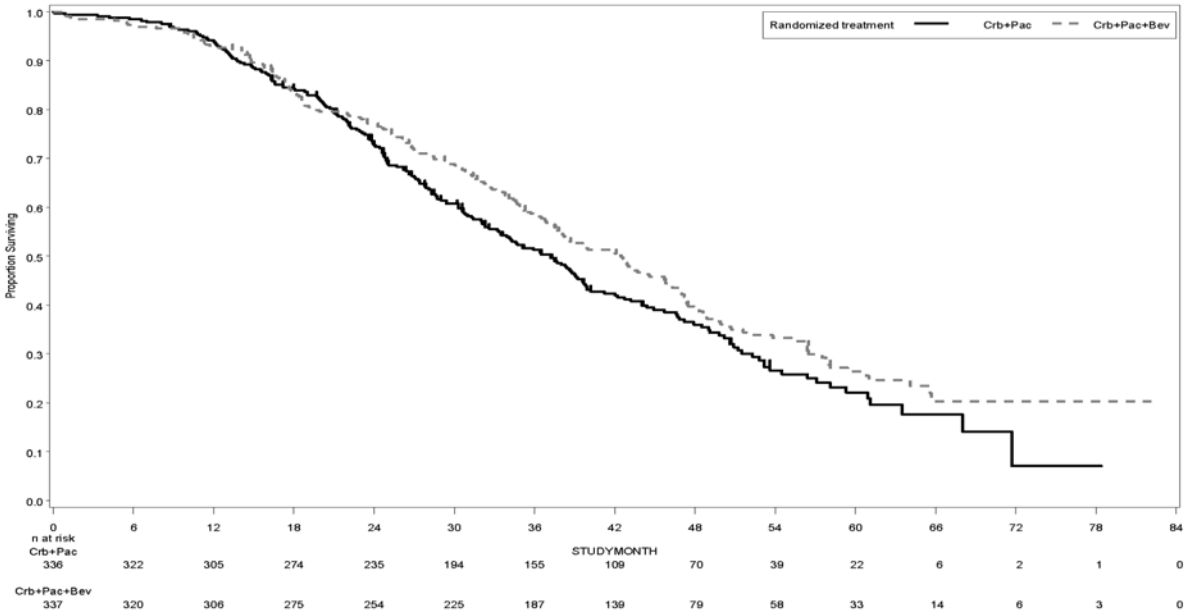
Results are presented in Table 19 and Figure 9.

Table 19: Efficacy Results in Study GOG-0213

Efficacy Parameter	Avastin with Carboplatin and Paclitaxel (N=337)	Carboplatin and Paclitaxel (N=336)
Overall Survival		
Median, in months	42.6	37.3
Hazard ratio (95% CI) (IVRS)[a]	0.84 (0.69, 1.01)	
Hazard ratio (95% CI) (eCRF)[b]	0.82 (0.68, 0.996)	
Progression-Free Survival		
Median, in months	13.8	10.4
Hazard ratio (95% CI) (IVRS)[a]	0.61 (0.51, 0.72)	
Overall Response Rate		
Number of patients with measurable disease at baseline	274	286
Rate, %	213 (78%)	159 (56%)

[a] HR was estimated from Cox proportional hazards models stratified by the duration of treatment free-interval prior to enrolling onto this study per IVRS (interactive voice response system) and secondary surgical debulking status.
[b] HR was estimated from Cox proportional hazards models stratified by the duration of platinum free-interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status.

Figure 9: Kaplan Meier Curves for Overall Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study GOG-0213



14.10 Hepatocellular Carcinoma

The efficacy of Avastin in combination with atezolizumab 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 atezolizumab as an intravenous infusion of 1200 mg, followed by 15 mg/kg Avastin, 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 atezolizumab or Avastin (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.

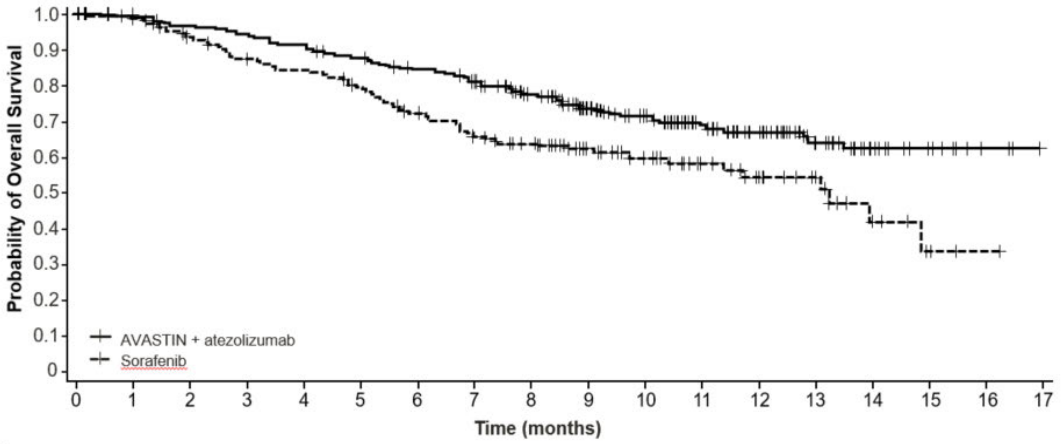
Efficacy results are presented in Table 20 and Figure 10.

Table 20: Efficacy Results from IMbrave150

	Avastin in combination with Atezolizumab (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; N/A=not applicable; RECIST 1.1= Response Evaluation Criteria in Solid Tumors v1.1

Figure 10: Kaplan-Meier Plot of Overall Survival in IMbrave150



No. of Patients at Risk

AVASTIN + atezolizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin (bevacizumab) injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials in the following strengths:

- 100 mg/4 mL (25 mg/mL): carton of one vial (NDC 50242-060-01)
- 400 mg/16 mL (25 mg/mL): carton of one vial (NDC 50242-061-01)

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.

17 PATIENT COUNSELING INFORMATION

Gastrointestinal Perforations and Fistulae: Avastin may increase the risk of developing gastrointestinal perforations and fistulae. Advise patients to immediately contact their healthcare provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, or vomiting *[see Warnings and Precautions (5.1)]*.

Surgery and Wound Healing Complications: Avastin can increase the risk of wound healing complications. Instruct patients not to undergo surgery without first discussing this potential risk with their healthcare provider *[see Warnings and Precautions (5.2)]*.

Hemorrhage: Avastin can increase the risk of hemorrhage. Advise patients to immediately contact their healthcare provider for signs and symptoms of serious or unusual bleeding including coughing or spitting blood *[see Warnings and Precautions (5.3)]*.

Arterial and Venous Thromboembolic Events: Avastin increases the risk of arterial and venous thromboembolic events. Advise patients to immediately contact their healthcare provider for signs and symptoms of arterial or venous thromboembolism *[see Warnings and Precautions (5.4, 5.5)]*.

Hypertension: Avastin can increase blood pressure. Advise patients that they will undergo routine blood pressure monitoring and to contact their healthcare provider if they experience changes in blood pressure *[see Warnings and Precautions (5.6)]*.

Posterior Reversible Leukoencephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) has been associated with Avastin treatment. Advise patients to immediately contact their healthcare provider for new onset or worsening neurological function *[see Warnings and Precautions (5.7)]*.

Renal Injury and Proteinuria: Avastin increases the risk of proteinuria and renal injury, including nephrotic syndrome. Advise patients that treatment with Avastin requires regular monitoring of renal function and to contact their healthcare provider for proteinuria or signs and symptoms of nephrotic syndrome *[see Warnings and Precautions (5.8)]*.

Infusion-Related Reactions: Avastin can cause infusion-related reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.9)]*.

Congestive Heart Failure: Avastin can increase the risk of developing congestive heart failure. Advise patients to contact their healthcare provider immediately for signs and symptoms of CHF *[see Warnings and Precautions (5.12)]*.

Embryo-Fetal Toxicity: Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)]*.

Lactation: Advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

Avastin® (bevacizumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.: 1048

Avastin® is a registered trademark of Genentech, Inc.
©2022 Genentech, Inc.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 25 mg of bevacizumab*.
Each 4 ml vial contains 100 mg of bevacizumab.
Each 16 ml vial contains 400 mg of bevacizumab.
For dilution and other handling recommendations, see section 6.6.

*Bevacizumab is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells.

Excipient with known effect
Each 4 ml vial contains 1.6 mg of polysorbate 20.
Each 16 ml vial contains 6.4 mg of polysorbate 20.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale brown liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.

Bevacizumab in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1.

Bevacizumab in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

Bevacizumab, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

Bevacizumab in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer.

Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. (See section 5.1).
Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents (see section 5.1).

Bevacizumab, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see section 5.1).

4.2 Posology and method of administration

Do not shake the vial.

Avastin must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

Posology

Metastatic carcinoma of the colon or rectum (mCRC)

The recommended dose of Avastin, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks.
It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Metastatic breast cancer (mBC)

The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.
It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Non-small cell lung cancer (NSCLC)

First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy

Avastin is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Avastin as a single agent until disease progression.
The recommended dose of Avastin is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.
Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses (see section 5.1).
It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib

EGFR mutation testing should be performed prior to initiation of treatment with the combination of Avastin and erlotinib. It is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.
The recommended dose of Avastin when used in addition to erlotinib is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that the treatment with Avastin in addition to erlotinib is continued until disease progression.

For the posology and method of administration of erlotinib, please refer to the full erlotinib prescribing information.

Advanced and/or metastatic renal cell cancer (mRCC)

The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion.
It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Epithelial ovarian, fallopian tube and primary peritoneal cancer

Front-line treatment: Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.
The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Treatment of platinum-sensitive recurrent disease: Avastin is administered in combination with either carboplatin and gemcitabine for 6 cycles and up to 10 cycles or in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles, followed by continued use of Avastin as single agent until disease progression. The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Treatment of platinum-resistant recurrent disease: Avastin is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. When Avastin is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity (see section 5.1, study MO22224).

Cervical cancer

Avastin is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan.

The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity (see section 5.1).

Special populations

Elderly patients: No dose adjustment is required in the patients ≥ 65 years of age.

Patients with renal impairment: The safety and efficacy have not been studied in patients with renal impairment (see section 5.2).

Patients with hepatic impairment: The safety and efficacy have not been studied in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of bevacizumab in children aged less than 18 years old 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.

There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovarian, fallopian tube, peritoneum, cervix and kidney.

Method of administration

The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

It should not be administered as an intravenous push or bolus.

Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended as described in section 4.4.

Precautions to be taken before handling or administering the medicinal product

For instructions on dilution of the medicinal product before administration, see section 6.6. Avastin infusions should not be administered or mixed with glucose solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy (see section 4.6).

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.

Gastrointestinal (GI) perforations and Fistulae (see section 4.8)
Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with Avastin and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

GI-vaginal Fistulae in study GOG-0240
Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin are at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae). Prior radiation is a major risk factor for the development of GI-vaginal fistulae and all patients with GI-vaginal fistulae had a history of prior radiation. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae.

Non-GI Fistulae (see section 4.8)
Patients may be at increased risk for the development of fistulae when treated with Avastin. Permanently discontinue Avastin in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. Limited information is available on the continued use of Avastin in patients with other fistulae.
In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Avastin should be considered.

Wound healing complications (see section 4.8)
Avastin may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with Avastin. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypertension (see section 4.8)
An increased incidence of hypertension was observed in Avastin-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting Avastin treatment. There is no information on the effect of Avastin in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy.

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Avastin should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES) (see section 4.8)
There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known.

Proteinuria (see section 4.8)
Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that all Grade (US National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v.3]) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during

therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Avastin. Therapy should be permanently discontinued in patients who develop nephrotic syndrome (NCI-CTCAE v.3).

Arterial thromboembolism (see section 4.8)
In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone.

Patients receiving Avastin plus chemotherapy, with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients with Avastin.

Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions.

Venous thromboembolism (see section 4.8)
Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under Avastin treatment.
Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.
Avastin should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored (NCI-CTCAE v.3).

Haemorrhage
Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy (NCI-CTCAE v.3) (see section 4.8).

Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical trials (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in cases of intracranial bleeding.

There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly (NCI-CTCAE v.3).

Pulmonary haemorrhage/haemoptysis
Patients with non-small cell lung cancer treated with Avastin may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/ haemoptysis (> 2.5 ml of red blood) should not be treated with Avastin.

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Avastin, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Congestive heart failure (CHF) (see section 4.8)
Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Avastin.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all Grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. CHF Grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (NCI-CTCAE v.3) (see section 4.8).

Neutropenia and infections (see section 4.8)
Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions (including anaphylactic shock)/infusion reactions (see section 4.8)
Patients may be at risk of developing infusion/hypersensitivity reactions (including anaphylactic shock). Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Osteonecrosis of the jaw (ONJ) (see section 4.8)
Cases of ONJ have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Avastin and intravenous bisphosphonates are administered simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Avastin. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

Intravitreal use
Avastin is not formulated for intravitreal use.

Eye disorders
Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use
A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

Ovarian failure/fertility
Avastin may impair female fertility (see sections 4.6 and 4.8). Therefore fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with Avastin.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicine contains 1.6 mg of polysorbate 20 in each 100 mg/4 ml vial and 6.4 mg in each 400 mg/16 ml vial which is equivalent to 0.4 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics
No clinically relevant interaction of co-administered chemotherapy on bevacizumab pharmacokinetics was observed based on the results of population pharmacokinetic analyses. There were neither statistically significant nor clinically relevant differences in bevacizumab clearance in patients receiving Avastin monotherapy compared to patients receiving Avastin in combination with interferon alfa-2a, erlotinib or chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents
No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon alfa 2a, erlotinib (and its active metabolite OSI-420), or the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of bevacizumab and sunitinib malate
In two clinical trials of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7 of 19 patients treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination.

MAHA is a haemolytic disorder which can present with red cell fragmentation, anaemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate (see *Hypertension, Proteinuria, PRES* in section 4.4).

Combination with platinum- or taxane-based therapies (see sections 4.4 and 4.8)
Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed mainly in patients treated with platinum- or taxane-based therapies in the treatment of NSCLC and mBC.

Radiotherapy
The safety and efficacy of concomitant administration of radiotherapy and Avastin has not been established.

EGFR monoclonal antibodies in combination with bevacizumab chemotherapy regimens
No interaction studies have been performed. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from

the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential have to use effective contraception during (and up to 6 months after) treatment.

Pregnancy
There are no clinical trial data on the use of Avastin in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and Avastin is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.8). Avastin is contraindicated in pregnancy (see section 4.3).

Breast-feeding
It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development (see section 5.3), women must discontinue breast-feeding during therapy and not breast-feed for at least six months following the last dose of Avastin.

Fertility
Repeat dose toxicity studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 5.3). In a phase III trial in the adjuvant treatment of patients with colon cancer, a substudy with premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on fertility are unknown.

4.7 Effects on ability to drive and use machines

Avastin has no or negligible influence on the ability to drive and use machines. However, somnolence and syncope have been reported with Avastin use (see table 1 in section 4.8). If patients are experiencing symptoms that affect their vision or concentration, or their ability to react, they should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Avastin is based on data from over 5 700 patients with various malignancies, predominantly treated with Avastin in combination with chemotherapy in clinical trials.

The most serious adverse reactions were:

- Gastrointestinal perforations (see section 4.4).
- Haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in non-small cell lung cancer patients (see section 4.4).
- Arterial thromboembolism (see section 4.4).

The most frequently observed adverse reactions across clinical trials in patients receiving Avastin were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with Avastin therapy are likely to be dose-dependent.

Tabulated list of adverse reactions

The adverse reactions listed in this section fall into the following frequency categories: 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).

Tables 1 and 2 list adverse reactions associated with the use of Avastin in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class.

Table 1 provides all adverse reactions by frequency that were determined to have a causal relationship with Avastin through:

- comparative incidences noted between clinical trial treatment arms (with at least a 10% difference compared to the control arm for NCI-CTCAE Grade 1-5 reactions or at least a 2% difference compared to the control arm for NCI-CTCAE Grade 3-5 reactions,
- post-authorisation safety studies,
- spontaneous reporting,
- epidemiological studies\non-interventional or observational studies,
- or through an evaluation of individual case reports.

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse events with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe.

Post-marketing adverse reactions are included in both Tables 1 and 2, where applicable. Detailed information about these post-marketing reactions are provided in Table 3.

Adverse reactions are added to the appropriate frequency category in the tables below according to the highest incidence seen in any indication.
Within each frequency category, adverse reactions are presented in the order of decreasing seriousness.

Some of the adverse reactions are reactions commonly seen with chemotherapy; however, Avastin may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

Table 1: Adverse reactions by frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Abscess[b,d], Cellulitis, Infection, Urinary tract infection		Necrotising fasciitis [a]		
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[b], Thrombo-cytopenia	Anaemia, Lymphopenia				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Immune system disorders		Hypersensitivity, infusion reactions[a,b,d]		Anaphylactic shock		
Metabolism and nutrition disorders	Anorexia, Hypomagnesaemia, Hyponatraemia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalo-pathy syndrome[a,b,d]	Hypertensive encephalo-pathy[a]	
Eye disorders	Eye disorder, Lacrimation increased					
Cardiac disorders		Congestive heart failure[b,d], Supraventricular tachycardia				
Vascular disorders	Hypertension[b,d], Thrombo-embolism (venous)[b,d]	Thrombo-embolism (arterial)[b,d], Haemorrhage[b,d], Deep vein thrombosis				Renal thrombotic microangiopathy[a,b], Hyaline occlusive glomerular microangiopathy[a], Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis, Epistaxis, Cough	Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Hypoxia, Dysphonia[a]				Pulmonary hypertension[a], Nasal septum perforation[a]
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	Gastrointestinal perforation[b,d,] Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[d,e], Gastrointestinal disorder, Proctalgia				Gastrointestinal ulcer[a]
Hepatobiliary disorders						Gallbladder perforation[a,b]
Skin and subcutaneous tissue disorders	Wound healing complications[b,d,] Exfoliative dermatitis, Dry skin, Skin discolouration	Palmar-plantar erythro-dysaesthesia syndrome				
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia	Fistula[b,d], Muscular weakness, Back pain				Osteonecrosis of the jaw[a,b] Non-mandibular osteonecrosis[a,f]
Renal and urinary disorders	Proteinuria[b,d]					
Reproductive system and breast disorders	Ovarian failure[b,c,d]	Pelvic pain				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Congenital, familial, and genetic disorder						Foetal abnormalities[a,b]
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy				
Investigations	Weight decreased					

When events were noted as both all grade and grade 3-5 adverse drug reactions in clinical trials, the highest frequency observed in patients has been reported. Data are unadjusted for the differential time on treatment.

[a] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'
[b] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[c] Based on a substudy from NSABP C-08 with 295 patients
[d] For additional information refer below within section "Further information on selected serious adverse reactions."
[e] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.
[f] Observed in paediatric population only.

Table 2: Severe adverse reactions by frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Cellulitis, Abscess[a,b], Infection, Urinary tract infection				Necrotising fasciitis[c]
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[a], Thrombo-cytopenia	Anaemia, Lymphopenia				
Immune system disorders		Hypersensitivity, infusion reactions [a,b,c]		Anaphylactic shock		
Metabolism and nutrition disorders		Dehydration, Hyponatraemia				
Nervous system disorders	Peripheral sensory neuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible encephalo-pathy syndrome [a,b,c], Hypertensive encephalo-pathy[c]
Cardiac disorders		Congestive heart failure[a,b], Supraventricular tachycardia				
Vascular disorders	Hypertension[a,b]	Thromboembolism arterial[a,b], Haemorrhage[a,b], Thromboembolism (venous)[a,b],				Renal thrombotic microangiopathy[b,c], Hyaline occlusive glomerular

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Deep vein thrombosis				microangiopathy[c], Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders		Pulmonary haemorrhage/ Haemoptysis[a,b], Pulmonary embolism, Epistaxis, Dyspnoea, Hypoxia				Pulmonary hypertension[c], Nasal septum perforation[c]
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[c,d], Gastrointestinal disorder, Stomatitis, Proctalgia				Gastrointestinal perforation[a,b], Gastrointestinal ulcer[c], Rectal haemorrhage
Hepatobiliary disorders						Gallbladder perforation [b,c]
Skin and subcutaneous tissue disorders		Wound healing complications[a,b], Palmar-plantar erythrodysaesthesia syndrome				
Musculoskeletal and connective tissue disorders		Fistula[a,b], Myalgia, Arthralgia, Muscular weakness, Back pain				Osteonecrosis of the jaw[b,c]
Renal and urinary disorders		Proteinuria[a,b]				
Reproductive system and breast disorders		Pelvic pain				Ovarian failure[a,b]
Congenital, familial, and genetic disorder						Foetal abnormalities[a,c]
General disorders and administration site conditions	Asthenia, Fatigue,	Pain, Lethargy, Mucosal inflammation				

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse events with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe. These clinically significant adverse reactions were reported in clinical trials but the grade 3-5 reactions did not meet the threshold of at least a 2% difference compared to the control arm. Table 2 also includes clinically significant adverse reactions that were observed only in the postmarketing setting, therefore, the frequency and NCI-CTCAE grade is not known. These clinically significant reactions have therefore been included in Table 2 within the column entitled "Frequency Not Known."

[a] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).

[b] For additional information refer below within section "Further information on selected serious adverse reactions"

[c] For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'

[d] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

Description of selected serious adverse reactions

Gastrointestinal (GI) perforations and Fistulae (see section 4.4)
Avastin has been associated with serious cases of gastrointestinal perforation.

Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with non-squamous non-small cell lung cancer, up to 1.3% in patients with metastatic breast cancer, up to 2.0% in patients with metastatic renal cell cancer or in patients with ovarian cancer, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2%-1% of all Avastin treated patients.

In Avastin clinical trials, gastrointestinal fistulae (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer.

GI-vaginal Fistulae in study GOG-0240
In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in Avastin-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. The frequency of GI-vaginal fistulae in the group treated with Avastin + chemotherapy was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with no prior radiation and/ or no recurrence inside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving chemotherapy alone were 1.1% vs. 0.8%, respectively. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI Fistulae (see section 4.4)
Avastin use has been associated with serious cases of fistulae including reactions resulting in death.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of Avastin-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Uncommon (≥ 0.1% to < 1%) reports of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

Reactions were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of Avastin, with most reactions occurring within the first 6 months of therapy.

Wound healing (see section 4.4)
As Avastin may adversely impact wound healing, patients who had major surgery within the last 28 days were excluded from participation in phase III clinical trials.

In clinical trials of metastatic carcinoma of the colon or rectum, there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery 28-60 days prior to starting Avastin. An increased incidence of post-operative bleeding or wound healing complication occurring within 60 days of major surgery was observed if the patient was being treated with Avastin at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

Serious wound healing complications, including anastomotic complications, have been reported, some of which had a fatal outcome.

In locally recurrent and metastatic breast cancer trials, Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving Avastin compared with up to 0.9% of patients in the control arms (NCI-CTCAE v.3).

In clinical trials of ovarian cancer, Grade 3-5 wound healing complications were observed in up to 1.8% of patients in the bevacizumab arm versus 0.1% in the control arm (NCI-CTCAE v.3).

Hypertension (see section 4.4)
In clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the Avastin containing arms compared with up to 14% in the control arms. The overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving Avastin ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with Avastin and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

In study JO25567, all grade hypertension was observed in 77.3% of the patients who received Avastin in combination with erlotinib as first-line treatment for non-squamous NSCLC with EGFR activating mutations, compared to 14.3% of patients treated with erlotinib alone. Grade 3 hypertension was 60.0% in patients treated with Avastin in combination with erlotinib compared to 11.7% in patients treated with erlotinib alone. There were no grade 4 or 5 hypertension events.

Hypertension was generally adequately controlled with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of Avastin treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal.

The risk of Avastin-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephalopathy Syndrome (see section 4.4)
There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with PRES, a rare neurological disorder. Presentation may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. The clinical presentation of PRES is often nonspecific, and therefore the diagnosis of PRES requires confirmation by brain imaging, preferably MRI.

In patients developing PRES, early recognition of symptoms with prompt treatment of specific symptoms including control of hypertension (if associated with severe uncontrolled hypertension) is recommended in addition to discontinuation of bevacizumab therapy. Symptoms usually resolve or improve within days after treatment discontinuation, although some patients have experienced some neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known.

Across clinical trials, 8 cases of PRES have been reported. Two of the eight cases did not have radiological confirmation via MRI.

Proteinuria (see section 4.4)
In clinical trials, proteinuria has been reported within the range of 0.7% to 54.7% of patients receiving Avastin.

Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria (NCI-CTCAE v.3). Grade 3 proteinuria was reported in up to 10.9% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. Testing for proteinuria is recommended prior to start of Avastin therapy. In most clinical trials urine protein levels of ≥ 2g/24 hrs led to the holding of Avastin until recovery to < 2g/24 hrs.

Haemorrhage (see section 4.4)
In clinical trials across all indications the overall incidence of NCI-CTCAE v.3 Grade 3-5 bleeding reactions ranged from 0.4% to 6.9% in Avastin treated patients, compared with up to 4.5% of patients in the chemotherapy control group.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 bleeding reactions have been reported in up to 8.3% of patients treated with Avastin in combination with paclitaxel and topotecan compared with up to 4.6% of patients treated with paclitaxel and topotecan.

The haemorrhagic reactions that have been observed in clinical trials were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

Tumour-associated haemorrhage (see section 4.4)
Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in trials in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory substances, treatment with anticoagulants, prior radiotherapy, Avastin therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were Avastin therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent phase III trials, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade reactions were seen with a frequency of up to 9.3% when treated with Avastin plus chemotherapy compared with up to 5% in the patients treated with chemotherapy alone. Grade 3-5 reactions have been observed in up to 2.3% of patients treated with Avastin plus chemotherapy as compared with < 1% with chemotherapy alone (NCI-CTCAE v.3). Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

Gastrointestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal cancer patients, and have been assessed as tumour-associated haemorrhages.

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including cases of central nervous system (CNS) bleeding in patients with CNS metastases (see section 4.4).

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical trials. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with bevacizumab (1.2%) at the time of interim safety analysis (NCI-CTCAE v.3).

Across all clinical trials, mucocutaneous haemorrhage has been seen in up to 50% of Avastin-treated patients. These were most commonly NCI-CTCAE v.3 Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in the Avastin treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common reactions of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Thromboembolism (see section 4.4)

Arterial thromboembolism: An increased incidence of arterial thromboembolic reactions was observed in patients treated with Avastin across indications, including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic reactions.

In clinical trials, the overall incidence of arterial thromboembolic reactions ranged up to 3.8% in the Avastin containing arms compared with up to 2.1% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Avastin compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.7% of patients treated with Avastin in combination with chemotherapy compared to up to 0.5% of patients treated with chemotherapy alone. Myocardial infarction was reported in up to 1.4% of patients treated with Avastin in combination with chemotherapy compared to up to 0.7% of patients treated with chemotherapy alone.

In one clinical trial evaluating Avastin in combination with 5-fluorouracil/folinic acid, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic reactions were observed in 11% (11/100) of patients compared to 5.8% (6/104) in the chemotherapy control group.

Venous thromboembolism: The incidence of venous thromboembolic reactions in clinical trials was similar in patients receiving Avastin in combination with chemotherapy compared to those receiving the control chemotherapy alone. Venous thromboembolic reactions include deep venous thrombosis, pulmonary embolism and thrombophlebitis.

In clinical trials across indications, the overall incidence of venous thromboembolic reactions ranged from 2.8% to 17.3% of Avastin-treated patients compared with 3.2% to 15.6% in the control arms.

Grade 3-5 (NCI-CTCAE v.3) venous thromboembolic reactions have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients treated with chemotherapy alone (across indications, excluding persistent, recurrent, or metastatic cervical cancer).

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 venous thromboembolic events have been reported in up to 15.6% of patients treated with Avastin in combination with paclitaxel and cisplatin compared with up to 7.0% of patients treated with paclitaxel and cisplatin.

Patients who have experienced a venous thromboembolic reaction may be at higher risk for a recurrence if they receive Avastin in combination with chemotherapy versus chemotherapy alone.

Congestive heart failure (CHF)
In clinical trials with Avastin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In four phase III trials (AVF2119g, E2100, BO17708 and AVF3694g) in patients with metastatic breast cancer CHF Grade 3 (NCI-CTCAE v.3) or higher was reported in up to 3.5% of patients treated with Avastin in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of Grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidences of all Grade CHF were similar between the anthracycline + Avastin (6.2%) and the anthracycline + placebo arms (6.0%).

Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of Avastin, patients with pre-existing CHF of NYHA (New York Heart Association) II-IV were excluded, therefore, no information is available on the risk of CHF in this population.

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF.

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m^2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP plus bevacizumab arm. These results suggest that close clinical observation with appropriate cardiac assessments should be considered for patients exposed to cumulative doxorubicin doses greater than 300 mg/m^2 when combined with bevacizumab.

Hypersensitivity reactions (including anaphylactic shock)/infusion reactions (see section 4.4 and *Post-marketing experience* below)
In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Avastin in combination with chemotherapy than with chemotherapy alone. The incidence of these reactions in some clinical trials of Avastin is common (up to 5% in bevacizumab-treated patients).

Infections
From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 infections have been reported in up to 24% of patients treated with Avastin in combination with paclitaxel and topotecan compared with up to 13% of patients treated with paclitaxel and topotecan.

Ovarian failure/fertility (see sections 4.4 and 4.6)
In NSABP C-08, a phase III trial of Avastin in adjuvant treatment of patients with colon cancer, the incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/ml and a negative serum β-HCG pregnancy test, has been evaluated in 295 premenopausal women. New cases of ovarian failure were reported in 2.6% patients in the mFOLFOX-6 group compared to 39% in the mFOLFOX-6 + bevacizumab group. After discontinuation of bevacizumab treatment, ovarian function recovered in 86.2% of these evaluable women. Long term effects of the treatment with bevacizumab on fertility are unknown.

Laboratory abnormalities
Decreased neutrophil count, decreased white blood cell count and presence of urine protein may be associated with Avastin treatment.

Across clinical trials, the following Grade 3 and 4 (NCI-CTCAE v.3) laboratory abnormalities occurred in patients treated with Avastin with at least a 2% difference compared to the corresponding control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased international normalised ratio (INR).

Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5-1.9 times baseline level), both with and without proteinuria, are associated with the use of Avastin. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with Avastin.

Other special populations

Elderly patients
In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic reactions, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs). Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia and thrombocytopenia (NCI-CTCAE v.3); and all Grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with Avastin (see sections 4.4 and 4.8 under *Thromboembolism*). In one clinical trial, the incidence of hypertension of grade ≥ 3 was two-fold higher in patients aged > 65 years than in the younger age group (< 65 years). In a study of platinum-resistant recurrent ovarian cancer patients, alopecia, mucosal inflammation, peripheral sensory neuropathy, proteinuria and hypertension were also reported and occurred at a rate at least 5% higher in the CT + BV arm for bevacizumab-treated patients ≥ 65 years of age compared with bevacizumab-treated patients aged < 65 years.
No increase in the incidence of other reactions, including gastrointestinal perforation, wound healing complications, congestive heart failure, and haemorrhage was observed in elderly patients (> 65 years) receiving Avastin as compared to those aged ≤ 65 years treated with Avastin.

Paediatric population
The safety and efficacy of Avastin in children less than 18 years old have not been established.

In study BO25041 of Avastin added to postoperative radiation therapy (RT) with concomitant and adjuvant temozolomide in paediatric patients with newly diagnosed supratentorial, infratentorial, cerebellar, or peduncular high-grade glioma, the safety profile was comparable with that observed in other tumour types in adults treated with Avastin.

In study BO20924 of Avastin with current standard of care in rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma, the safety profile of Avastin treated children was comparable with that observed in adults treated with Avastin.

Avastin is not approved for use in patients under the age of 18 years. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years treated with Avastin.

Post-marketing experience

Table 3 Adverse reactions reported in post-marketing setting

System organ class (SOC)	*Reactions (frequency*)*
Infections and infestations	Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare) (see also section 4.4)
Immune system disorders	Hypersensitivity reactions and infusion reactions (common); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting (see also section 4.4 and Hypersensitivity reactions (including anaphylactic shock)/infusion reactions above). Anaphylactic shock (rare) (see also section 4.4).
Nervous system disorders	Hypertensive encephalopathy (very rare) (see also section 4.4 and Hypertension in section 4.8) Posterior Reversible Encephalopathy Syndrome (PRES), (rare) (see also section 4.4)
Vascular disorders	Renal thrombotic microangiopathy with or without concomitant sunitinib use, and hyaline occlusive glomerular microangiopathy which may be clinically manifested as proteinuria (not known). For further information on proteinuria see section 4.4 and Proteinuria in section 4.8.
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gall bladder perforation (not known)
Musculoskeletal and connective tissue disorders	Cases of Osteonecrosis of the Jaw (ONJ) have been reported in patients treated with Avastin, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4)
	Cases of non-mandibular osteonecrosis have been observed in Avastin treated paediatric patients (see section 4.8, Paediatric population).
Congenital, familial, and genetic disorder	Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.6)

* if specified, the frequency has been derived from clinical trial data

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

The highest dose tested in humans (20 mg/kg of body weight, intravenous every 2 weeks) was associated with severe migraine in several patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01F G01

Mechanism of action
Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Pharmacodynamic effects
Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

Clinical efficacy and safety

Metastatic carcinoma of the colon or rectum (mCRC)

The safety and efficacy of the recommended dose (5 mg/kg of body weight every two weeks) in metastatic carcinoma of the colon or rectum were studied in three randomised, active-controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. Avastin was combined with two chemotherapy regimens:

- AVF2107g: A weekly schedule of irinotecan/bolus 5-fluorouracil/folinic acid (IFL) for a total of 4 weeks of each 6 week-cycle (Saltz regimen).
- AVF0780g: In combination with bolus 5-fluorouracil/folinic acid (5-FU/FA) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- AVF2192g: In combination with bolus 5-FU/FA for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Three additional studies with bevacizumab have been conducted in mCRC patients: first-line (NO16966), second-line with no previous bevacizumab treatment (E3200), and second-line with previous bevacizumab treatment following disease progression in first-line (ML18147). In these studies, bevacizumab was administered at the following dosing regimens in combination with FOLFOX-4 (5-FU/LV/oxaliplatin), XELOX (capecitabine/oxaliplatin), and fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin:

- NO16966: Avastin 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or Avastin 5 mg/kg every 2 weeks in combination with leucovorin plus 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).

- E3200: Avastin 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in bevacizumab-naïve patients.

- ML18147: Avastin 5.0 mg/kg of body weight every 2 weeks or Avastin 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with bevacizumab. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

AVF2107g
This was a phase III randomised, double-blind, active-controlled clinical trial evaluating Avastin in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL + Avastin (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/FA + Avastin (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of Avastin with the IFL regimen was established and considered acceptable. All treatments were continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an ECOG performance status of 0, 43% had a value of 1 and 0.4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

The primary efficacy variable of the trial was overall survival. The addition of Avastin to IFL resulted in statistically significant increases in overall survival, progression-free survival and overall response rate (see Table 4). The clinical benefit, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved and duration of metastatic disease.

The efficacy results of Avastin in combination with IFL-chemotherapy are displayed in Table 4.

Table 4 Efficacy results for trial AVF2107g

	AVF2107g	
	Arm 1 IFL + placebo	Arm 2 IFL + Avastin[a]
Number of patients	411	402
Overall survival		
Median time (months)	15.6	20.3
95% CI	14.29–16.99	18.46–24.18
Hazard ratio[b]	0.660 (p-value = 0.00004)	
Progression-free survival		
Median time (months)	6.2	10.6
Hazard ratio	0.54 (p-value < 0.0001)	
Overall response rate		
Rate (%)	34.8	44.8
	(p-value = 0.0036)	

[a] 5 mg/kg every 2 weeks.
[b] Relative to control arm.

Among the 110 patients randomised to Arm 3 (5-FU/FA + Avastin) prior to discontinuation of this arm, the median overall survival was 18.3 months and the median progression free survival was 8.8 months.

AVF2192g
This was a phase II randomised, double-blind, active-controlled clinical trial evaluating the efficacy and safety of Avastin in combination with 5-FU/FA as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. One hundred and five patients were randomised to 5-FU/FA + placebo arm and 104 patients to 5-FU/FA + Avastin (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression.
The addition of Avastin 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival as compared to 5-FU/FA chemotherapy alone.

AVF0780g
This was a phase II randomised, active-controlled, open-labelled clinical trial investigating Avastin in combination with 5-FU/FA as first-line treatment of metastatic colorectal cancer. The median age was 64 years. 19% of the patients had received prior chemotherapy and 14% prior radiotherapy. Seventy-one patients were randomised to receive bolus 5-FU/FA or 5-FU/FA + Avastin (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/FA + Avastin (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression-free survival. The addition of Avastin 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, longer progression-free survival, and a trend in longer survival, compared with 5-FU/FA chemotherapy alone (see Table 5). These efficacy data are consistent with the results from trial AVF2107g.

The efficacy data from trials AVF0780g and AVF2192g investigating Avastin in combination with 5-FU/FA-chemotherapy are summarised in Table 5.

Table 5 Efficacy results for trials AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/FA	5-FU/FA + Avastin[a]	5-FU/FA + Avastin[b]	5-FU/FA + placebo	5-FU/FA + Avastin
Number of patients	36	35	33	105	104
Overall survival					
Median time (months)	13.6	17.7	15.2	12.9	16.6
95% CI				10.35–16.95	13.63–19.32
Hazard ratio[c]	-	0.52	1.01		0.79
p-value		0.073	0.978		0.16
Progression-free survival					
Median time (months)	5.2	9.0	7.2	5.5	9.2
Hazard ratio		0.44	0.69		0.5
p-value	-	0.0049	0.217		0.0002
Overall response rate					
Rate (percent)	16.7	40.0	24.2	15.2	26
95% CI	7.0–33.5	24.4–57.8	11.7–42.6	9.2–23.9	18.1–35.6
p-value		0.029	0.43		0.055
Duration of response					
Median time (months)	NR	9.3	5.0	6.8	9.2
25–75 percentile (months)	5.5–NR	6.1–NR	3.8–7.8	5.59–9.17	5.88–13.01

	AVF0780g			AVF2192g	
	5-FU/FA	5-FU/FA + Avastin[a]	5-FU/FA + Avastin[b]	5-FU/FA + placebo	5-FU/FA + Avastin

[a] 5 mg/kg every 2 weeks.
[b] 10 mg/kg every 2 weeks.
[c] Relative to control arm.
NR = not reached.

NO16966

This was a phase III randomised, double-blind (for bevacizumab), clinical trial investigating Avastin 7.5 mg/kg in combination with oral capecitabine and intravenous oxaliplatin (XELOX), administered on a 3-weekly schedule; or Avastin 5 mg/kg in combination with leucovorin with 5-fluorouracil bolus, followed by 5-fluorouracil infusional, with intravenous oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The trial contained two parts: an initial unblinded 2-arm part (Part I) in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4) and a subsequent 2 × 2 factorial 4-arm part (Part II) in which patients were randomised to four treatment groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + Avastin, FOLFOX-4 + Avastin). In Part II, treatment assignment was double-blind with respect to Avastin.

Approximately 350 patients were randomised into each of the 4 trial arms in the Part II of the trial.

Table 6 Treatment regimens in trial NO16966 (mCRC)

	Treatment	Starting dose	Schedule
FOLFOX-4 or FOLFOX-4 + Avastin	Oxaliplatin Leucovorin 5-Fluorouracil	85 mg/m^2 IV 2 h 200 mg/m^2 IV 2 h 400 mg/m^2 IV bolus, 600 mg/m^2 IV 22 h	Oxaliplatin on day 1 Leucovorin on day 1 and 2 5-fluorouracil IV bolus/infusion, each on days 1 and 2
	Placebo or Avastin	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX + Avastin	Oxaliplatin Capecitabine	130 mg/m^2 IV 2 h 1000 mg/m^2 oral bid	Oxaliplatin on day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or Avastin	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, q 3 weeks
5-Fluorouracil: IV bolus injection immediately after leucovorin			

The primary efficacy parameter of the trial was the duration of progression-free survival. In this trial, there were two primary objectives: to show that XELOX was non-inferior to FOLFOX-4 and to show that Avastin in combination with FOLFOX-4 or XELOX chemotherapy was superior to chemotherapy alone. Both co-primary objectives were met:

- Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival and overall survival in the eligible per-protocol population.

- Superiority of the Avastin-containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (Table 7).

Secondary PFS analyses, based on 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with Avastin (analyses shown in Table 7), consistent with the statistically significant benefit observed in the pooled analysis.

Table 7 Key efficacy results for the superiority analysis (ITT population, trial NO16966)

Endpoint (months)	FOLFOX-4 or XELOX + placebo (n = 701)	FOLFOX-4 or XELOX + bevacizumab (n = 699)	P-value
Primary endpoint			
Median PFS**	8.0	9.4	0.0023
Hazard ratio (97.5% CI) [a]	0.83 (0.72–0.95)		
Secondary endpoints			
Median PFS (on treatment)**	7.9	10.4	< 0.0001
Hazard ratio (97.5% CI)	0.63 (0.52–0.75)		
Overall response rate (invest. assessment)**	49.2%	46.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76–1.03)		

* Overall survival analysis at clinical cut-off 31 January 2007
** Primary analysis at clinical cut-off 31 January 2006
[a] Relative to control arm

In the FOLFOX treatment subgroup, the median PFS was 8.6 months in placebo and 9.4 months in bevacizumab treated patients, HR = 0.89, 97.5% CI = [0.73; 1.08]; p-value = 0.1871, the corresponding results in the XELOX treatment subgroup being 7.4 vs. 9.3 months, HR = 0.77, 97.5% CI = [0.63; 0.94]; p-value = 0.0026.

The median overall survival was 20.3 months in placebo and 21.2 months in bevacizumab treated patients in the FOLFOX treatment subgroup, HR = 0.94, 97.5% CI = [0.75; 1.16]; p-value = 0.4937, the corresponding results in the XELOX, treatment subgroup being 19.2 vs. 21.4 months, HR = 0.84, 97.5% CI = [0.68; 1.04]; p-value = 0.0698.

ECOG E3200
This was a phase III randomised, active-controlled, open-label trial investigating Avastin 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusional, with intravenous oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 6 for trial NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 Avastin + FOLFOX-4 and 244 Avastin monotherapy).
The addition of Avastin to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 8).

Table 8 Efficacy results for trial E3200

	E3200	
	FOLFOX-4	FOLFOX-4 + Avastin[a]
Number of patients	292	293
Overall survival		
Median (months)	10.8	13.0
95% CI	10.12–11.86	12.09–14.03
Hazard ratio[b]	0.751 (p-value = 0.0012)	
Progression-free survival		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p-value < 0.0001)	
Objective response rate		
Rate	8.6%	22.2%
	(p-value < 0.0001)	

[a] 10 mg/kg every 2 weeks

[b] Relative to control arm

No significant difference was observed in the duration of overall survival between patients who received Avastin monotherapy compared to patients treated with FOLFOX-4. Progression-free survival and objective response rate were inferior in the Avastin monotherapy arm compared to the FOLFOX-4 arm.

ML18147
This was a phase III randomised, controlled, open-label trial investigating Avastin 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen.

Patients with histologically confirmed mCRC and disease progression were randomised 1:1 within 3 months after discontinuation of bevacizumab first-line therapy to receive fluoropyrimidine/oxaliplatin- or fluoropyrimidine/irinotecan-based chemotherapy (chemotherapy switched depending on first-line chemotherapy) with or without bevacizumab. Treatment was given until progressive disease or unacceptable toxicity. The primary outcome measure was overall survival defined as the time from randomisation until death from any cause.

A total of 820 patients were randomised. The addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen (ITT = 819) (see Table 9).

Table 9 Efficacy results for study ML18147 (ITT population)

	ML18147	
	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy + Avastin[a]
Number of patients	410	409
Overall survival		
Median (months)	9.8	11.2
Hazard ratio (95% confidence interval)	0.81 (0.69, 0.94) (p-value = 0.0062)	
Progression-free survival		
Median (months)	4.1	5.7
Hazard ratio (95% confidence interval)	0.68 (0.59, 0.78) (p-value < 0.0001)	
Objective response rate (ORR)		
Patients included in analysis	406	404
Rate	3.9%	5.4%
	(p-value = 0.3113)	

[a] 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks

Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and the difference was not significant.

Study E3200 used a 5 mg/kg/week equivalent dose of bevacizumab in bevacizumab-naïve patients, while study ML18147 used a 2.5 mg/kg/week equivalent dose of bevacizumab in bevacizumab-pretreated patients. A cross-trial comparison of the efficacy and safety data is limited by differences between these studies, most notably in patient populations, previous bevacizumab exposure and chemotherapy regimens.
Both the 5 mg/kg/week and 2.5 mg/kg/week equivalent doses of bevacizumab provided a statistically significant benefit with regards to OS (HR 0.751 in study E3200; HR 0.81 in study ML18147) and PFS (HR 0.518 in study E3200; HR 0.68 in study ML18147). In terms of safety, there was a higher overall incidence of Grade 3-5 AEs in study E3200 relative to study ML18147.

Metastatic breast cancer (mBC)

Two large phase III trials were designed to investigate the treatment effect of Avastin in combination with two individual chemotherapy agents, as measured by the primary endpoint of PFS. A clinically meaningful and statistically significant improvement in PFS was observed in both trials.

Summarised below are PFS results for the individual chemotherapy agents included in the indication:

- Study E2100 (paclitaxel)
  - Median PFS increase 5.6 months, HR 0.421 (p < 0.0001, 95% CI 0.343; 0.516)
- Study AVF3694g (capecitabine)
  - Median PFS increase 2.9 months, HR 0.69 (p = 0.0002, 95% CI 0.56; 0.84)

Further details of each study and the results are provided below.

ECOG E2100
Trial E2100 was an open-label, randomised, active controlled, multicentre clinical trial evaluating Avastin in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Patients were

randomised to paclitaxel alone (90 mg/m^2 intravenously over 1 hour once weekly for three out of four weeks) or in combination with Avastin (10 mg/kg intravenous infusion every two weeks). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to trial entry. Of the 722 patients in the trial, the majority of patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered unsuitable for trastuzumab therapy. Furthermore, 65% of patients had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastases, including previously treated or resected brain lesions, were excluded.

In trial E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with Avastin as a single agent continued until disease progression. The patient characteristics were similar across the trial arms. The primary endpoint of this trial was progression free survival (PFS), based on trial investigators' assessment of disease progression. In addition, an independent review of the primary endpoint was also conducted. The results of this trial are presented in Table 10.

Table 10 Trial E2100 efficacy results

Progression-free survival				
	Investigator assessment*		IRF assessment	
	Paclitaxel (n = 354)	Paclitaxel/ Avastin (n = 368)	Paclitaxel (n = 354)	Paclitaxel/ Avastin (n = 368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343; 0.516)		0.483 (0.385; 0.607)	
p-value	< 0.0001		< 0.0001	
Response rates (for patients with measurable disease)				
	Investigator assessment		IRF assessment	
	Paclitaxel (n = 273)	Paclitaxel/ Avastin (n = 252)	Paclitaxel (n = 243)	Paclitaxel/ Avastin (n = 229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	< 0.0001		< 0.0001	

* primary analysis

Overall survival		
	Paclitaxel (n = 354)	Paclitaxel/ Avastin (n = 368)
Median OS (months)	24.8	26.5
HR (95% CI)	0.869 (0.722; 1.046)	
p-value	0.1374	

The clinical benefit of Avastin as measured by PFS was seen in all pre-specified subgroups tested (including disease-free interval, number of metastatic sites, prior receipt of adjuvant chemotherapy and oestrogen receptor (ER) status).

AVF3694g
Study AVF3694g was a phase III, multicentre, randomised, placebo-controlled trial designed to evaluate the efficacy and safety of Avastin in combination with chemotherapy compared to chemotherapy plus placebo as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer.

Chemotherapy was chosen at the investigator's discretion prior to randomisation in a 2:1 ratio to receive either chemotherapy plus Avastin or chemotherapy plus placebo. The choices of chemotherapy included capecitabine, taxane (protein-bound paclitaxel, docetaxel), and anthracycline-based agents (doxorubicin/ cyclophosphamide, epirubicin/ cyclophosphamide, 5-fluorouracil/ doxorubicin/ cyclophosphamide, 5-fluorouracil/epirubicin/cyclophosphamide) given every three weeks (q3w). Avastin or placebo was administered at a dose of 15 mg/kg q3w.

This study included a blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and medicinal product (Avastin or placebo) every 3 weeks until disease progression, treatment-limiting toxicity, or death. On documented disease progression, patients who entered the optional open-label phase could receive open-label Avastin together with a wide-range of second line therapies.

Statistical analyses were performed independently for 1) patients who received capecitabine in combination with Avastin or placebo; 2) patients who received taxane-based or anthracycline-based chemotherapy in combination with Avastin or placebo. The primary endpoint of the study was PFS by investigator assessment. In addition, the primary endpoint was also assessed by an independent review committee (IRC).

The results of this study from the final protocol defined analyses for progression free survival and response rates for the independently powered capecitabine cohort of Study AVF3694g are presented in Table 11 Results from an exploratory overall survival analysis which include an additional 7 months of follow-up (approximately 46% of patients had died) are also presented. The percentage of patients who received Avastin in the open-label phase was 62.1% in the capecitabine + placebo arm and 49.9% in the capecitabine + Avastin arm.

Table 11 Efficacy results for study AVF3694g: – Capecitabine[a] and Avastin/Placebo (Cap + Avastin/Pl)

Progression-free survival[b]				
	Investigator Assessment		IRC Assessment	
	Cap + Pl (n = 206)	Cap + Avastin (n = 409)	Cap + Pl (n = 206)	Cap + Avastin (n = 409)
Median PFS (months)	5.7	8.6	6.2	9.8
Hazard ratio vs placebo arm (95% CI)	0.69 (0.56; 0.84)		0.68 (0.54; 0.86)	
p-value	0.0002		0.0011	
Response rate (for patients with measurable disease)[b]				
	Cap + Pl (n = 161)		Cap + Avastin (n = 325)	
% pts with objective response	23.6		35.4	
p-value	0.0097			
Overall survival[b]				
HR (95% CI)	0.88 (0.69; 1.13)			
p-value (exploratory)	0.33			

[a]1 000 mg/m^2 oral twice daily for 14 days administered every 3 weeks

[b]Stratified analysis included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression; data from those patients were censored at the last tumour assessment prior to starting NPT.

An unstratified analysis of PFS (investigator assessed) was performed that did not censor for non-protocol therapy prior to disease progression. The results of these analyses were very similar to the primary PFS results.

Non-small cell lung cancer (NSCLC)

First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy

The safety and efficacy of Avastin, in addition to platinum-based chemotherapy, in the first-line treatment of patients with non-squamous non-small cell lung cancer (NSCLC), was investigated in trials E4599 and BO17704. An overall survival benefit has been demonstrated in trial E4599 with a 15 mg/kg/q3wk dose of bevacizumab. Trial BO17704 has demonstrated that both 7.5 mg/kg/q3wk and 15 mg/kg/q3wk bevacizumab doses increase progression free survival and response rate.

E4599
E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating Avastin as first-line treatment of patients with locally advanced (stage IIIb with malignant pleural effusion), metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2) and carboplatin AUC = 6.0, both by intravenous infusion (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC in combination with Avastin at a dose of 15 mg/kg intravenous infusion day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the Avastin + carboplatin–paclitaxel arm continued to receive Avastin as a single agent every 3 weeks until disease progression. 878 patients were randomised to the two arms.

During the trial, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of Avastin and 21.1% (89/422) of patients received 13 or more administrations of Avastin.

The primary endpoint was duration of survival. Results are presented in Table 12.

Table 12 Efficacy results for trial E4599

	Arm 1 Carboplatin/ Paclitaxel	Arm 2 Carboplatin/ Paclitaxel + Avastin 15 mg/kg q 3 weeks
Number of patients	444	434
Overall survival		
Median (months)	10.3	12.3
Hazard ratio	0.80 (p = 0.003) 95% CI (0.69; 0.93)	
Progression-free survival		
Median (months)	4.8	6.4
Hazard ratio	0.65 (p < 0.0001) 95% CI (0.56; 0.76)	
Overall response rate		
Rate (percent)	12.9	29.0 (p < 0.0001)

In an exploratory analysis, the extent of Avastin benefit on overall survival was less pronounced in the subgroup of patients who did not have adenocarcinoma histology.

BO17704
Trial BO17704 was a randomised, double-blind phase III trial of Avastin in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced (stage IIIb with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression free survival, secondary endpoints for the trial included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 intravenous infusion on day 1 and gemcitabine 1250 mg/m^2 intravenous infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with Avastin at a dose of 7.5 or 15 mg/kg intravenous infusion day 1 of every 3-week cycle. In the Avastin-containing arms, patients could receive Avastin as a single-agent every 3 weeks until disease progression or unacceptable toxicity. Trial results show

that 94% (277/296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti-cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 13.

Table 13 Efficacy results for trial BO17704

	Cisplatin/Gemcitabine + placebo	Cisplatin/Gemcitabine + Avastin 7.5 mg/kg q 3 weeks	Cisplatin/Gemcitabine + Avastin 15 mg/kg q 3 weeks
Number of patients	347	345	351
Progression-free survival Median (months) Hazard ratio	6.1	6.7 (p = 0.0026) 0.75 [0.62; 0.91]	6.5 (p = 0.0301) 0.82 [0.68; 0.98]
Best overall response rate[a]	20.1%	34.1% (p < 0.0001)	30.4% (p = 0.0023)
Overall survival			
Median (months) Hazard ratio	13.1	13.6 (p = 0.4203) 0.93 [0.78; 1.11]	13.4 (p = 0.7613) 1.03 [0.86, 1.23]

[a] patients with measurable disease at baseline

First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib

JO25567
Study JO25567 was a randomised, open-label, multi-centre phase II study conducted in Japan to evaluate the efficacy and safety of Avastin used in addition to erlotinib in patients with non-squamous NSCLC with EGFR activating mutations (exon 19 deletion or exon 21 L858R mutation) who had not received prior systemic therapy for stage IIIB/IV or recurrent disease.

The primary endpoint was progression-free survival (PFS) based on independent review assessment. Secondary endpoints included overall survival, response rate, disease control rate, duration of response, and safety.

EGFR mutation status was determined for each patient prior to patient screening and 154 patients were randomised to receive either erlotinib + Avastin (erlotinib 150 mg oral daily + Avastin [15 mg/kg intravenously every 3 weeks]) or erlotinib monotherapy (150 mg oral daily) until disease progression (PD) or unacceptable toxicity. In the absence of PD, discontinuation of one component of study treatment in the erlotinib + Avastin arm did not lead to discontinuation of the other component of study treatment as specified in the study protocol.

The efficacy results of the study are presented in Table 14.

Table 14 Efficacy results for study JO25567

	Erlotinib N = 77#	**Erlotinib + Avastin N = 75#**
PFS^ (months)		
Median	9.7	16.0
HR (95% CI)	0.54 (0.36; 0.79)	
p-value	0.0015	
Overall response rate		
Rate (n)	63.6% (49)	69.3% (52)
p-value	0.4951	
Overall survival* (months)		
Median	47.4	47.0
HR (95% CI)	0.81 (0.53; 1.23)	
p-value	0.3267	

A total of 154 patients (ECOG Performance Status 0 or 1) were randomised. However two of the randomised patients discontinued the study before receiving any study treatment

^ Blinded independent review (protocol-defined primary analysis)

* Exploratory analysis: final OS analysis at clinical cut off on 31 October 2017, approx. 59% of patients had died.

CI, confidence interval; HR, Hazard ratio from unstratified Cox regression analysis; NR, not reached.

Advanced and/or metastatic renal cell cancer (mRCC)

Avastin in combination with interferon alfa-2a for the first-line treatment of advanced and/ or metastatic renal cell cancer (BO17705)

This was a phase III randomised double-blind trial conducted to evaluate the efficacy and safety of Avastin in combination with interferon (IFN) alfa-2a versus IFN alfa-2a alone as first-line treatment in mRCC. The 649 randomised patients (641 treated) had Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases and adequate organ function. Patients were nephrectomised for primary renal cell carcinoma. Avastin 10 mg/kg was given every 2 weeks until disease progression. IFN alfa-2a was given up to 52 weeks or until disease progression at a recommended starting dose of 9 MIU three times a week, allowing a dose reduction to 3 MIU three times a week in 2 steps. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the trial including progression-free survival. The addition of Avastin to IFN-alpha-2a significantly increased PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR = 0.91). A high proportion of patients (approximately 63% IFN/placebo; 55% Avastin/IFN) received a variety of non-specified post-trial anti-cancer therapies, including antineoplastic agents, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 15

Table 15 Efficacy results for trial BO17705

	BO17705	
	Placebo + IFN[a]	Bv[b] + IFN[a]
Number of patients	322	327
Progression-free survival		
Median (months)	5.4	10.2
Hazard ratio	0.63	
95% CI	0.52, 0.75	
	(p-value < 0.0001)	
Objective response rate (%) in Patients with measurable disease		
N	289	306
Response rate	12.8%	31.4%
	(p-value < 0.0001)	
Overall survival		
Median (months)	21.3	23.3
Hazard ratio	0.91	
95% CI	0.76, 1.10	
	(p-value 0.3360)	

[a] Interferon alfa-2a 9 MIU 3×/week

[b] Bevacizumab 10 mg/kg q 2 wk

An exploratory multivariate Cox regression model using backward selection indicated that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to trial entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63; 0.96], p = 0.0219), indicating a 22% reduction in the risk of death for patients in the Avastin + IFN alfa-2a arm compared to IFN alfa-2a arm.

Ninety-seven patients in the IFN alfa-2a arm and 131 patients in the Avastin arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU three times a week as pre-specified in the protocol. Dose-reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of Avastin and IFN alfa-2a based on PFS event free rates over time, as shown by a sub-group analysis. The 131 patients in the Avastin + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the trial, exhibited at 6, 12 and 18 months PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving Avastin + IFN alfa-2a.

AVF2938

This was a randomised, double-blind, phase II clinical trial investigating Avastin 10 mg/kg in a 2 weekly schedule with the same dose of Avastin in combination with 150 mg daily erlotinib, in patients with metastatic clear cell RCC. A total of 104 patients were randomised to treatment in this trial, 53 to Avastin 10 mg/kg every 2 weeks plus placebo and 51 to Avastin 10 mg/kg every 2 weeks plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the Avastin + Placebo arm and the Avastin + Erlotinib arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response. The addition of erlotinib to bevacizumab did not result

in an improvement in OS (HR = 1.764; p = 0.1789), duration of objective response (6.7 vs 9.1 months) or time to symptom progression (HR = 1.172; p = 0.5076).

AVF0890
This was a randomised phase II trial conducted to compare the efficacy and safety of bevacizumab versus placebo. A total of 116 patients were randomised to receive bevacizumab 3 mg/kg every 2 weeks (n = 39), 10 mg/kg every 2 weeks; (n = 37), or placebo (n = 40).
An interim analysis showed there was a significant prolongation of the time to progression of disease in the 10 mg/kg group as compared with the placebo group (hazard ratio, 2.55; p < 0.001). There was a small difference, of borderline significance, between the time to progression of disease in the 3 mg/kg group and that in the placebo group (hazard ratio, 1.26; p = 0.053). Four patients had objective (partial) response, and all of these had received the 10 mg/kg dose bevacizumab; the ORR for the 10 mg/kg dose was 10%.

Epithelial ovarian, fallopian tube and primary peritoneal cancer

Front-line treatment of ovarian cancer

The safety and efficacy of Avastin in the front-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) that evaluated the effect of the addition of Avastin to carboplatin and paclitaxel compared to the chemotherapy regimen alone.

GOG-0218
The GOG-0218 study was a phase III multicentre, randomised, double-blind, placebo-controlled, three arm study evaluating the effect of adding Avastin to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with advanced (stages IIIB, IIIC and IV according to FIGO staging version dated 1988) epithelial ovarian, fallopian tube or primary peritoneal cancer.

Patients who had received prior therapy with bevacizumab or prior systemic anticancer therapy for ovarian cancer (e.g. chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) or previous radiotherapy to the abdomen or pelvis were excluded from the study.

A total of 1873 patients were randomised in equal proportions to the following three arms:

- CPP arm: Five cycles of placebo (started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of Avastin (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of Avastin (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by continued use of Avastin (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The majority of patients included in the study were White (87% in all three arms); the median age was 60 years in CPP and CPB15 arms and 59 years in CPB15+ arm; and 29% of patients in CPP or CPB15 and 26% in CPB15+ were over 65 years of age. Overall approximately 50% of patients had a GOG PS of 0 at baseline, 43% a GOG PS score of 1, and 7% a GOG PS score of 2. Most patients had EOC (82% in CPP and CPB15, 85% in CPB15+) followed by PPC (16% in CPP, 15% in CPB15, 13% in CPB15+) and FTC (1% in CPP, 3% in CPB15, 2% in CPB15+). The majority of patients had serous adenocarcinoma histologic type (85% in CPP and CPB15, 86% in CPB15+). Overall approximately 34% of patients were FIGO stage III optimally debulked with gross residual disease, 40% stage III sub-optimally debulked, and 26% were stage IV patients.

The primary endpoint was PFS based on investigator's assessment of disease progression based on radiological scans or CA 125 levels, or symptomatic deterioration per protocol. In addition, a

prespecified analysis of the data censoring for CA-125 progression events was conducted, as well as an independent review of PFS as determined by radiological scans.

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting, patients who received bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone (CPB15+), had a clinically meaningful and statistically significant improvement in PFS.

In patients who only received bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone (CPB15), no clinically meaningful benefit in PFS was observed.

The results of this study are summarised in Table 16.

Table 16 Efficacy results from study GOG-0218

Progression-free survival [1]			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)
Median PFS (months)	10.6	11.6	14.7
Hazard ratio (95% CI) [2]		0.89 (0.78, 1.02)	0.70 (0.61, 0.81)
p-value [3, 4]		0.0437	< 0.0001
Objective response rate [5]			
	CPP (n = 396)	CPB15 (n = 393)	CPB15+ (n = 403)
% pts with objective response	63.4	66.2	66.0
p-value		0.2341	0.2041
Overall survival [6]			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)
Median OS (months)	40.6	38.8	43.8
Hazard ratio (95% CI) [2]		1.07 (0.91, 1.25)	0.88 (0.75, 1.04)
p-value [3]		0.2197	0.0641

[1] Investigator assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February, 2010.
[2] Relative to the control arm; stratified hazard ratio.
[3] One-sided log-rank p-value
[4] Subject to a p-value boundary of 0.0116.
[5] Patients with measurable disease at baseline.
[6] Final overall survival analysis performed when 46.9% of the patients had died.

Prespecified PFS analyses were conducted, all with a cut-off date of 29 September 2009. The results of these prespecified analyses are as follows:

- The protocol specified analysis of investigator-assessed PFS (without censoring for CA-125 progression or non-protocol therapy [NPT]) shows a stratified hazard ratio of 0.71 (95% CI: 0.61-0.83, 1-sided log-rank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 10.4 months in the CPP arm and 14.1 months in the CPB15+ arm.

- The primary analysis of investigator-assessed PFS (censoring for CA-125 progressions and NPT) shows a stratified hazard ratio of 0.62 (95% CI: 0.52-0.75, 1-sided log-rank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 12.0 months in the CPP arm and 18.2 months in the CPB15+ arm.

- The analysis of PFS as determined by the independent review committee (censoring for NPT) shows a stratified hazard ratio of 0.62 (95% CI: 0.50-0.77, 1-sided log-rank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 13.1 in the CPP arm and 19.1 months in the CPB15+ arm.

PFS subgroup analyses by disease stage and debulking status are summarised in Table 17. These results demonstrate robustness of the analysis of PFS as shown in Table 16.

Table 17 PFS[1] results by disease stage and debulking status from study GOG-0218

Randomised patients stage III optimally debulked disease [2,3]			
	CPP (n = 219)	CPB15 (n = 204)	CPB15+ (n = 216)
Median PFS (months)	12.4	14.3	17.5
Hazard ratio (95% CI)[4]		0.81 (0.62, 1.05)	0.66 (0.50, 0.86)
Randomised patients with stage III suboptimally debulked disease[3]			
	CPP (n = 253)	CPB15 (n = 256)	CPB15+ (n = 242)
Median PFS (months)	10.1	10.9	13.9
Hazard ratio (95% CI)[4]		0.93 (0.77, 1.14)	0.78 (0.63, 0.96)
Randomised patients with stage IV disease			
	CPP (n = 153)	CPB15 (n = 165)	CPB15+ (n = 165)
Median PFS (months)	9.5	10.4	12.8
Hazard Ratio (95% CI)[4]		0.90 (0.70, 1.16)	0.64 (0.49, 0.82)

[1] Investigator assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February, 2010
[2] With gross residual disease.
[3] 3.7% of the overall randomised patient population had stage IIIB disease.
[4] Relative to the control arm.

BO17707 (ICON7)
BO17707 was a phase III, two arm, multicentre, randomised, controlled, open-label study comparing the effect of adding Avastin to carboplatin plus paclitaxel in patients with FIGO stage I or IIA (Grade 3 or clear cell histology only; n = 142), or FIGO stage IIB - IV (all Grades and all histological types, n = 1386) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery (NCI-CTCAE v.3). FIGO staging version dated 1988 was used in this trial.

Patients who had received prior therapy with bevacizumab or prior systemic anticancer therapy for ovarian cancer (e.g. chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) or previous radiotherapy to the abdomen or pelvis were excluded from the study.

A total of 1528 patients were randomised in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles of 3 weeks duration
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles of 3 weeks plus Avastin (7.5 mg/kg q3w) for up to 12 months (Avastin was started at cycle 2 of chemotherapy if treatment was initiated within 4 weeks of surgery or at cycle 1 if treatment was initiated more than 4 weeks after surgery).

The majority of patients included in the study were White (96%), the median age was 57 years in both treatment arms, 25% of patients in each treatment arm were 65 years of age or over, and

approximately 50% of patients had an ECOG PS of 1; 7% of patients in each treatment arm had an ECOG PS of 2. The majority of patients had EOC (87.7%) followed by PPC (6.9%) and FTC (3.7%) or a mixture of the three origins (1.7%). Most patients were FIGO stage III (both 68%) followed by FIGO stage IV (13% and 14%), FIGO stage II (10% and 11%) and FIGO stage I (9% and 7%). The majority of the patients in each treatment arm (74% and 71%) had poorly differentiated (Grade 3) primary tumours at baseline. The incidence of each histologic sub-type of EOC was similar between the treatment arms; 69% of patients in each treatment arm had serous adenocarcinoma histologic type.

The primary endpoint was PFS as assessed by the investigator using RECIST.

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting, patients who received bevacizumab at a dose of 7.5 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab for up to 18 cycles had a statistically significant improvement in PFS.

The results of this study are summarised in Table 18.

Table 18 Efficacy results from study BO17707 (ICON7)

Progression-free survival		
	CP (n = 764)	CPB7.5+ (n = 764)
Median PFS (months) 2	16.9	19.3
Hazard ratio [95% CI] 2	0.86 [0.75; 0.98] (p-value = 0.0185)	
Objective response rate [1]		
	CP (n = 277)	CPB7.5+ (n = 272)
Response rate	54.9%	64.7%
	(p-value = 0.0188)	
Overall survival [3]		
	CP (n = 764)	CPB7.5+ (n = 764)
Median (months)	58.0	57.4
Hazard ratio [95% CI]	0.99 [0. 85; 1. 15] (p-value = 0. 8910)	

[1] In patients with measurable disease at baseline.
[2] Investigator assessed PFS analysis with data cut-off date of 30 November 2010.
[3] Final overall survival analysis performed when 46.7% of the patients had died with data cut-off date of 31 March 2013.

The primary analysis of investigator-assessed PFS with a data cut-off date of 28 February 2010 shows an unstratified hazard ratio of 0.79 (95% CI: 0.68-0.91, 2-sided log-rank p-value 0.0010) with a median PFS of 16.0 months in the CP arm and 18.3 months in the CPB7.5+ arm.

PFS subgroup analyses by disease stage and debulking status are summarised in Table 19. These results demonstrate robustness of the primary analysis of PFS as shown in Table 18.

Table 19 PFS[1] results by disease stage and debulking status from study BO17707 (ICON7)

Randomised patients with stage III optimally debulked disease [2,3]		
	CP (n = 368)	CPB7.5+ (n = 383)
Median PFS (months)	17.7	19.3
Hazard ratio (95% CI) [4]		0.89 (0.74, 1.07)
Randomised patients with stage III suboptimally debulked disease[3]		
	CP (n = 154)	CPB7.5+ (n = 140)
Median PFS (months)	10.1	16.9
Hazard ratio (95% CI)4		0.67 (0.52, 0.87)
Randomised patients with stage IV disease		
	CP (n = 97)	CPB7.5+ (n = 104)
Median PFS (months)	10.1	13.5
Hazard ratio (95% CI)4		0.74 (0.55, 1.01)

[1] Investigator assessed PFS analysis with data cut-off date of 30 November 2010.
[2] With or without gross residual disease.
[3] 5.8% of the overall randomised patient population had stage IIIB disease.
[4] Relative to the control arm.

Recurrent ovarian cancer

The safety and efficacy of Avastin in the treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer was studied in three phase III trials (AVF4095g , MO22224 and GOG-0213) with different patient populations and chemotherapy regimens.

- AVF4095g evaluated the efficacy and safety of bevacizumab in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent in patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.
- GOG-0213 evaluated the efficacy and safety of bevacizumab in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent in patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.
- MO22224 evaluated the efficacy and safety of bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.

AVF4095g
The safety and efficacy of Avastin in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment, was studied in a phase III randomised, double-blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding Avastin to carboplatin and gemcitabine chemotherapy and continuing Avastin as a single agent to progression, to carboplatin and gemcitabine alone.

Only patients with histologically documented ovarian, primary peritoneal, or fallopian tube carcinoma that had recurred > 6 months after platinum-based chemotherapy and who had not received chemotherapy in the recurrent setting and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents were included in the study.

A total of 484 patients with measurable disease were randomised 1:1 to either:

- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo (every 3 weeks) alone until disease progression or unacceptable toxicity
- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent Avastin (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by Avastin (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity

The primary endpoint was progression-free survival based on investigator assessment using modified RECIST 1.0. Additional endpoints included objective response, duration of response, overall survival and safety. An independent review of the primary endpoint was also conducted.

The results of this study are summarised in Table 20.

Table 20 Efficacy results from study AVF4095g

Progression-free survival				
	Investigator Assessment		IRC Assessment	
	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)
Not censored for NPT				
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.524 [0.425, 0.645]		0.480 [0.377, 0.613]	
p –value	< 0.0001		< 0.0001	
Censored for NPT				
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.484 [0.388, 0.605]		0.451 [0.351, 0.580]	
p–value	< 0.0001		< 0.0001	
Objective response rate				
	Investigator Assessment		IRC Assessment	
	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)
% pts with objective response	57.4%	78.5%	53.7%	74.8%
p –value	< 0.0001		< 0.0001	
Overall survival				
	Placebo + C/G (n = 242)		Avastin + C/G (n = 242)	
Median OS (months)	32.9		33.6	
Hazard ratio (95% CI)	0.952 [0.771, 1.176]			
p-value	0.6479			

PFS subgroup analyses depending on recurrence since last platinum therapy are summarised in Table 21.

Table 21 Progression-free survival by time from last platinum therapy to recurrence

	Investigator Assessment	
Time from last platinum therapy to recurrence	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)
6–12 months (n = 202)		
Median	8.0	11.9
Hazard ratio (95% CI)	0.41 (0.29–0.58)	
> 12 months (n = 282)		
Median	9.7	12.4
Hazard ratio (95% CI)	0.55 (0.41–0.73)	

GOG-0213
GOG-0213, a phase III randomised controlled open label trial, studied the safety and efficacy of Avastin in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting. There was no exclusion criterion for prior anti-angiogenic therapy. The study evaluated the effect of adding Avastin to carboplatin + paclitaxel and continuing Avastin as a single agent until disease progression or unacceptable toxicity compared to carboplatin + paclitaxel alone.

A total of 673 patients were randomised in equal proportions to the following two treatment arms:
- CP arm: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 intravenously) every 3 weeks for 6 and up to 8 cycles.
- CPB arm: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 intravenously) and concurrent Avastin (15 mg/kg) every 3 weeks for 6 and up to 8 cycles, followed by Avastin (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

Most patients in both the CP arm (80.4%) and the CPB arm (78.9%) were White. The median age was 60.0 years in the CP arm and 59.0 years in the CPB arm. The majority of patients (CP: 64.6%; CPB: 68.8%) were in the age category < 65 years. At baseline, most patients in both treatment arms had a GOG PS of 0 (CP: 82.4%: CPB; 80.7%) or 1 (CP: 16.7%: CPB; 18.1%). A GOG PS of 2 at baseline was reported in 0.9% of patients in the CP arm and in 1.2% of patients in the CPB arm."

The primary efficacy endpoint was overall survival (OS). The main secondary efficacy endpoint was progression-free survival (PFS). Results are presented in Table 22.

Table 22 Efficacy results[1,2] from study GOG-0213

Primary endpoint		
Overall survival (OS)	CP (n = 336)	CPB (n = 337)
Median OS (months)	37.3	42.6
Hazard ratio (95% CI) (eCRF)[a]	0.823 [CI: 0.680, 0.996]	
p-Value	0.0447	
Hazard ratio (95% CI) (registration form)[b]	0.838 [CI: 0.693, 1.014]	
p-Value	0.0683	
Secondary endpoint		
Progression-free survival (PFS)	CP (n = 336)	CPB (n = 337)
Median PFS (months)	10.2	13.8
Hazard ratio (95% CI)	0.613 [CI: 0.521, 0.721]	
p-value	< 0.0001	

1 Final Analysis [2] Tumour assessments and response evaluations were determined by the investigators using the GOG RECIST criteria (Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228Y247).

[a] Hazard ratio was estimated from Cox proportional hazards models stratified by the duration of platinum free-interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status Yes/No (Yes=randomised to undergo cytoreduction or randomised to not undergo cytoreduction; No= not a candidate or did not consent to cytoreduction). [b] stratified by the duration of treatment free-interval prior to enrolling onto this study per the registration form, and secondary surgical debulking status Yes/No.

The trial met its primary objective of OS improvement. Treatment with Avastin at 15 mg/kg every 3 weeks in combination with chemotherapy (carboplatin and paclitaxel) for 6 and up to 8 cycles, followed by Avastin until disease progression or unacceptable toxicity resulted, when data were derived from eCRF, in a clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin and paclitaxel alone.

MO22224

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. This study was designed as an open-label, randomised, two-arm phase III evaluation of bevacizumab plus chemotherapy (CT + BV) versus chemotherapy alone (CT).

A total of 361 patients were enrolled into this study and administered either chemotherapy (paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD) alone or in combination with bevacizumab:

- CT Arm (chemotherapy alone):
  - Paclitaxel 80 mg/m^2 as a 1-hour intravenous infusion on Days 1, 8, 15, and 22 every 4 weeks.
  - Topotecan 4 mg/m^2 as a 30-minute intravenous infusion on Days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on Days 1–5 every 3 weeks.
  - PLD 40 mg/m^2 as a 1 mg/min intravenous infusion on Day 1 only every 4 weeks. After Cycle 1, the medicinal product could be delivered as a 1-hour infusion.
- CT + BV Arm (chemotherapy plus bevacizumab):
  - The chosen chemotherapy was combined with bevacizumab 10 mg/kg intravenously every 2 weeks (or bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m^2 on Days 1–5 every 3 weeks).

Eligible patients had epithelial ovarian, fallopian tube or primary peritoneal cancer that progressed within <6 months of previous platinum therapy consisting of a minimum of 4 platinum therapy cycles. Patients should have had a life expectancy of ≥ 12 weeks and no prior radiotherapy to the pelvis or abdomen. Most patients were FIGO stage IIIC or stage IV. The majority of patients in both arms had an ECOG Performance Status (PS) of 0 (CT: 56.4% vs. CT + BV: 61.2%). The percentage of patients with an ECOG PS of 1 or ≥ 2 was 38.7% and 5.0% in the CT arm, and 29.8% and 9.0% in the CT + BV arm. Information on race exists for 29.3% of patients and nearly all patients were white. The median age of patients was 61.0 (range: 25–84) years. A total of 16 patients (4.4%) were > 75 years old. The overall rates of discontinuation due to adverse events were 8.8% in the CT arm and 43.6% in the CT + BV arm (mostly due to Grade 2-3 adverse events) and the median time to discontinuation in the CT + BV arm was 5.2 months compared with 2.4 months in the CT arm. The rates of discontinuation due to adverse events in the subgroup of patients > 65 years old were 8.8% in the CT arm and 50.0% in the CT + BV arm. The HR for PFS was 0.47 (95% CI: 0.35, 0.62) and 0.45 (95% CI: 0.31, 0.67) for the < 65 and ≥ 65 subgroups, respectively.

The primary endpoint was progression-free-survival, with secondary endpoints including objective response rate and overall survival. Results are presented in Table 23.

Table 23 Efficacy Results from Study MO22224

Primary endpoint		
Progression-free survival*		
	CT (n = 182)	CT + BV (n = 179)
Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296, 0.485]	
p-value	< 0.0001	
Secondary Endpoints		
Objective response rate**		
	CT (n = 144)	CT + BV (n = 142)
% patients with objective response	18 (12.5%)	40 (28.2%)
p –value	0.0007	
Overall survival (final analysis)***		
	CT (n = 182)	CT + BV (n = 179)
Median OS (months)	13.3	16.6
Hazard ratio (95% CI)	0.870 [0.678, 1.116]	
p-value	0.2711	

All analyses presented in this table are stratified analyses.
* Primary analysis was performed with a data cut-off date of 14 November 2011.
**Randomised Patients with Measurable Disease at Baseline.
***The final analysis of overall survival was performed when 266 deaths, which account for 73.7% of enrolled patients, were observed.

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (paclitaxel, topotecan or PLD) alone in the recurrent platinum-resistant setting, patients who received bevacizumab at a dose of 10 mg/kg every 2 weeks (or 15 mg/kg every 3 weeks if used in combination with 1.25 mg/m^2 topotecan on Days 1–5 every 3 weeks) in combination with chemotherapy and continued to receive bevacizumab until disease progression or unacceptable toxicity, had a statistically significant improvement in PFS. The exploratory PFS and OS analyses by chemotherapy cohort (paclitaxel, topotecan and PLD) are summarised in Table 24.

Table 24: Exploratory PFS and OS analyses by chemotherapy cohort

	CT	CT+BV
Paclitaxel	n = 115	
Median PFS (months)	3.9	9.2
Hazard ratio (95% CI)	0.47 [0.31, 0.72]	
Median OS (months)	13.2	22.4
Hazard ratio (95% CI)	0.64 [0.41, 0.99]	
Topotecan	n = 120	
Median PFS (months)	2.1	6.2
Hazard ratio (95% CI)	0.28 [0.18, 0.44]	
Median OS (months)	13.3	13.8
Hazard ratio (95% CI)	1.07 [0.70, 1.63]	
PLD	n = 126	
Median PFS (months)	3.5	5.1
Hazard ratio (95% CI)	0.53 [0.36, 0.77]	
Median OS (months)	14.1	13.7
Hazard ratio (95% CI)	0.91 [0.61, 1.35]	

Cervical Cancer

GOG-0240
The efficacy and safety of Avastin in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) in the treatment for patients with persistent, recurrent or metastatic carcinoma of the cervix was evaluated in study GOG-0240, a randomised, four-arm, open label, multi-centre phase III trial.

A total of 452 patients were randomised to receive either:

- Paclitaxel 135 mg/m^2 intravenously over 24 hours on Day 1 and cisplatin 50 mg/m^2 intravenously on Day 2, every 3 weeks (q3w); or
  Paclitaxel 175 mg/m^2 intravenously over 3 hours on Day 1 and cisplatin 50 mg/m^2 intravenously on Day 2 (q3w); or
  Paclitaxel 175 mg/m^2 intravenously over 3 hours on Day 1 and cisplatin 50 mg/m^2 intravenously on Day 1 (q3w)

- Paclitaxel 135 mg/m^2 intravenously over 24 hours on Day 1 and cisplatin 50 mg/m^2 intravenously on Day 2 plus bevacizumab 15 mg/kg intravenously on Day 2 (q3w); or
  Paclitaxel 175 mg/m^2 intravenously over 3 hours on Day 1 and cisplatin 50 mg/m^2 intravenously on Day 2 plus bevacizumab 15 mg/kg intravenously on Day 2 (q3w); or
  Paclitaxel 175 mg/m^2 intravenously over 3 hours on Day 1 and cisplatin 50 mg/m^2 intravenously on Day 1 plus bevacizumab 15 mg/kg intravenously on Day 1 (q3w)

- Paclitaxel 175 mg/m^2 intravenously over 3 hours on Day 1 and topotecan 0.75 mg/m^2 intravenously over 30 minutes on days 1-3 (q3w)

- Paclitaxel 175 mg/m^2 intravenously over 3 hours on Day 1 and topotecan 0.75 mg/m^2 intravenously over 30 minutes on Days 1-3 plus bevacizumab 15 mg/kg intravenously on Day 1 (q3w)

Eligible patients had persistent, recurrent or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with

surgery and/or radiation therapy and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

The median age was 46.0 years (range: 20–83) in the Chemo alone group and 48.0 years (range: 22-85) in the Chemo + Avastin group; with 9.3% of patients in the Chemo alone group and 7.5% of patients in the Chemo + Avastin group over the age of 65 years.

Of the 452 patients randomised at baseline, the majority of patients were white (80.0% in the Chemo alone group and 75.3% in the Chemo + Avastin group), had squamous cell carcinoma (67.1% in the Chemo alone group and 69.6% in the Chemo + Avastin group), had persistent/recurrent disease (83.6% in the Chemo alone group and 82.8% in the Chemo + Avastin group), had 1-2 metastatic sites (72.0% in the Chemo alone group and 76.2% in the Chemo + Avastin group), had lymph node involvement (50.2% in the Chemo alone group and 56.4% in the Chemo + Avastin group), and had a platinum free interval ≥ 6 months (72.5% in the Chemo alone group and 64.4% in the Chemo + Avastin group).

The primary efficacy endpoint was overall survival. Secondary efficacy endpoints included progression-free survival and objective response rate.
Results from the primary analysis and the follow-up analysis are presented by Avastin Treatment and by Trial Treatment in Table 25 and Table 26, respectively.

Table 25 Efficacy results from study GOG-0240 by Avastin treatment

	Chemotherapy (n = 225)	Chemotherapy + Avastin (n = 227)
Primary endpoint		
Overall survival – Primary analysis[6]		
Median (months)[1]	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58, 0.94] (p-value[5] = 0.0132)	
Overall survival – Follow-up analysis[7]		
Median (months)[1]	13.3	16.8
Hazard ratio [95% CI]	0.76 [0.62, 0.94] (p-value[5,8] = 0.0126)	
Secondary endpoints		
Progression-free survival – Primary analysis[6]		
Median PFS (months)[1]	6.0	8.3
Hazard ratio [95% CI]	0.66 [0.54, 0.81] (p-value[5] < 0.0001)	
Best overall response – Primary analysis[6]		
Responders (response rate[2])	76 (33.8%)	103 (45.4%)
95% CI for response rates[3]	[27.6%, 40.4%]	[38.8%, 52.1%]
Difference in response rates	11.60%	
95% CI for difference in response rates[4]	[2.4%, 20.8%]	
p-value (chi-squared test)	0.0117	

[1] Kaplan-Meier estimates
[2] Patients and percentage of patients with best overall response of confirmed CR or PR; percentage calculated on patients with measurable disease at baseline
[3] 95% CI for one sample binomial using Pearson-Clopper method
[4] Approximate 95% CI for difference of two rates using Hauck-Anderson method
[5] log-rank test (stratified)
[6] Primary analysis was performed with a data cut-off date of 12 December 2012 and is considered the final analysis
[7] Follow-up analysis was performed with a data cut-off date of 07 March 2014
[8] p-value displayed for descriptive purpose only

Table 26 Overall survival results from study GOG-0240 by Trial Treatment

Treatment Comparison	Other Factor	Overall survival – Primary analysis[1] Hazard Ratio (95% CI)	Overall survival - Follow-up analysis[2] Hazard Ratio (95% CI)
Avastin vs. No Avastin	Cisplatin+ Paclitaxel	0.72 (0.51, 1.02) (17.5 vs.14.3 months; p = 0.0609)	0.75 (0.55, 1.01) (17.5 vs.15.0 months; p = 0.0584)
	Topotecan+ Paclitaxel	0.76 (0.55, 1.06) (14.9 vs. 11.9 months; p = 0.1061)	0.79 (0.59, 1.07) (16.2 vs. 12.0 months; p = 0.1342)
Topotecan+ Paclitaxel vs. Cisplatin+ Paclitaxel	Avastin	1.15 (0.82, 1.61) (14.9 vs. 17.5 months; p = 0.4146)	1.15 (0.85, 1.56) (16.2 vs 17.5 months; p = 0.3769)
	No Avastin	1.13 (0.81, 1.57) (11.9 vs.14.3 months; p = 0.4825)	1.08 (0.80, 1.45) (12.0 vs 15.0 months; p = 0.6267)

[1] Primary analysis was performed with a data cut-off date of 12 December 2012 and is considered the final analysis
[2] Follow-up analysis was performed with a data cut-off date of 07 March 2014; all p-values are displayed for descriptive purpose only

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies, in all subsets of the paediatric population, in breast carcinoma, adenocarcinoma of the colon and rectum, lung carcinoma (small cell and non-small cell carcinoma), kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney), ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours), fallopian tube carcinoma (excluding rhabdomyosarcoma and germ cell tumours), peritoneal carcinoma (excluding blastomas and sarcomas) and cervix and corpus uteri carcinoma.

High-grade glioma
Anti-tumour activity was not observed in two earlier studies among a total of 30 children aged > 3 years old with relapsed or progressive high-grade glioma when treated with bevacizumab and irinotecan (CPT-11). There is insufficient information to determine the safety and efficacy of bevacizumab in children with newly-diagnosed high-grade glioma.

- In a single-arm study (PBTC-022), 18 children with recurrent or progressive non-pontine high-grade glioma (including 8 with glioblastoma [WHO Grade IV], 9 with anaplastic astrocytoma [Grade III] and 1 with anaplastic oligodendroglioma [Grade III]) were treated with bevacizumab (10 mg/kg) two weeks apart and then with bevacizumab in combination with CPT-11 (125-350 mg/m²) once every two weeks until progression. There were no objective (partial or complete) radiological responses (MacDonald criteria). Toxicity and adverse reactions included arterial hypertension and fatigue as well as CNS ischaemia with acute neurological deficit.

- In a retrospective single institution series, 12 consecutive (2005 to 2008) children with relapsed or progressive high-grade glioma (3 with WHO Grade IV, 9 with Grade III) were treated with

bevacizumab (10 mg/kg) and irinotecan (125 mg/m²) every 2 weeks. There were no complete responses and 2 partial responses (MacDonald criteria).

In a randomised phase II study (BO25041) a total of 121 patients aged ≥ 3 years to < 18 years with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG) were treated with post operative radiation therapy (RT) and adjuvant temozolomide (T) with and without bevacizumab: 10 mg/kg every 2 weeks intravenously.

The study did not meet its primary endpoint of demonstrating a significant improvement of EFS (Central Radiology Review Committee (CRRC)-assessed) when bevacizumab was added to the RT/T arm compared with RT/T alone (HR = 1.44; 95% CI: 0.90, 2.30). These results were consistent with those from various sensitivity analyses and in clinically relevant subgroups. The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone.

Addition of Avastin to RT/T did not demonstrate clinical benefit in study BO25041 in 60 evaluable children patients with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG) (See section 4.2 for information on paediatric use).

Soft tissue sarcoma
In a randomised phase II study (BO20924) a total of 154 patients aged ≥ 6 months to < 18 years with newly diagnosed metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma were treated with standard of care (Induction IVADO/IVA+/- local therapy followed by Maintenance Vinorelbine and cyclophosphamide) with or without bevacizumab (2.5 mg/kg/week) for a total duration of treatment of approximately 18 months. At the time of the final primary analysis, the primary endpoint of EFS by independent central review did not show a statistically significant difference between the two treatment arms, with HR of 0.93 (95% CI: 0.61, 1.41; p-value = 0.72). The difference in ORR per independent central review was 18% (CI: 0.6%, 35.3%) between the two treatment arms in the few patients who had evaluable tumour at baseline and had a confirmed response prior to receiving any local therapy : 27/75 patients (36.0%, 95% CI: 25.2%, 47.9%) in the Chemo arm and 34/63 patients (54.0%, 95% CI: 40.9%, 66.6%) in the Bv + Chemo arm. The final Overall Survival (OS) analyses showed no significant clinical benefit from addition of bevacizumab to chemotherapy in this patient population.

Addition of Avastin to standard of care did not demonstrate clinical benefit in clinical trial BO20924, in 71 evaluable children (from age 6 months to less than 18 years old) patients with metastatic Rhabdomyosarcoma and non-Rhabdomyosarcoma Soft Tissue Sarcoma.
(See section 4.2 for information on paediatric use).

The incidence of AEs, including Grade ≥ 3 AEs and SAEs, was similar between the two treatment arms. No AEs leading to death occurred in either treatment arm; all deaths were attributed to disease progression. Bevacizumab addition to multimodal standard of care treatment seemed to be tolerated in this paediatric population.

5.2 Pharmacokinetic properties

The pharmacokinetic data for bevacizumab are available from ten clinical trials in patients with solid tumours. In all clinical trials, bevacizumab was administered as an intravenous infusion. The rate of infusion was based on tolerability, with an initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Distribution
The typical value for central volume (V_c) was 2.73 l and 3.28 l for female and male patients respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (V_p) was 1.69 l and 2.35 l for female and male patients

respectively, when bevacizumab is co-administered with anti-neoplastic agents. After correcting for body weight, male patients had a larger V_c (+ 20%) than female patients.

Biotransformation
Assessment of bevacizumab metabolism in rabbits following a single intravenous dose of ^{125}I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. The metabolism and elimination of bevacizumab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.

Elimination
The value for clearance is, on average, equal to 0.188 and 0.220 l/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+ 17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

Pharmacokinetics in special populations
The population pharmacokinetics were analysed in adult and paediatric patients to evaluate the effects of demographic characteristics. In adults, the results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Renal impairment
No trials have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients since the kidneys are not a major organ for bevacizumab metabolism or excretion.

Hepatic impairment
No trials have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment since the liver is not a major organ for bevacizumab metabolism or excretion.

Paediatric population
The pharmacokinetics of bevacizumab were evaluated in 152 children, adolescents and young adults (7 months to 21 years, 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and volume of distribution of bevacizumab were comparable between paediatric and young adult patients when normalised by body weight, with exposure trending lower as body weight decreased. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account.

The pharmacokinetics of bevacizumab was well characterised by the paediatric population PK model for 70 patients in Study BO20924 ((1.4 to 17.6 years; 11.6 to 77.5 kg) and 59 patients in Study BO25041 (1 to 17 years; 11.2 to 82.3 kg). In Study BO20924, bevacizumab exposure was generally lower compared to a typical adult patient at the same dose. In Study BO25041, bevacizumab exposure was similar compared to a typical adult at the same dose. In both studies, bevacizumab exposure trended lower as body weight decreased.

5.3 Preclinical safety data

In studies of up to 26 weeks duration in cynomolgus monkeys, physeal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations. In rabbits, bevacizumab was shown to inhibit wound healing at doses below the proposed clinical dose. Effects on wound healing were shown to be fully reversible.

Studies to evaluate the mutagenic and carcinogenic potential of bevacizumab have not been performed.

No specific studies in animals have been conducted to evaluate the effect on fertility. An adverse effect on female fertility can however be expected as repeat dose toxicity studies in animals have shown inhibition of the maturation of ovarian follicles and a decrease/absence of corpora lutea and associated decrease in ovarian and uterus weight as well as a decrease in the number of menstrual cycles.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal malformations. Adverse foetal outcomes were observed at all tested doses, of which the lowest dose resulted in average serum concentrations approximately 3 times larger than in humans receiving 5 mg/kg every 2 weeks. Information on foetal malformations observed in the post marketing setting are provided in section 4.6 Fertility, Pregnancy and Lactation and 4.8 Undesirable Effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Sodium phosphate
Polysorbate 20 (E 432)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

A concentration dependent degradation profile of bevacizumab was observed when diluted with glucose solutions (5%).

6.3 Shelf life

Vial (unopened)

3 years.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 30 days at 2 °C to 8 °C plus an additional 48 hours at 2 °C to 30 °C in sodium chloride 9 mg/ml (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °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

4 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 100 mg of bevacizumab.
16 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 400 mg of bevacizumab.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Do not shake the vial.

Avastin should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution. A sterile needle and syringe should be used to prepare Avastin.

The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 mg/ml to 16.5 mg/ml. In the majority of the occasions the necessary amount of Avastin can be diluted with 0.9% sodium chloride solution for injection to a total volume of 100 ml.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

No incompatibilities between Avastin and polyvinyl chloride or polyolefine bags or infusion sets have been observed.

Avastin is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/300/001 – 100 mg/4 ml vial
EU/1/04/300/002 – 400 mg/16 ml vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 January 2005
Date of latest renewal: 17 November 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA): https://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

Genentech, Inc.
1 Antibody Way
Oceanside, CA 92056
USA

F. Hoffmann-La Roche AG
Grenzacherstrasse 124
4058 Basel
Switzerland

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barrell-Str. 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion
bevacizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg bevacizumab.

3. LIST OF EXCIPIENTS

Trehalose dihydrate, sodium phosphate, polysorbate 20, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 4 ml
100 mg/4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use

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

This medicinal product does not contain any preservative

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the diluted medicine

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(S)

EU/1/04/300/001

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 the 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(S) OF ADMINISTRATION

Avastin 25 mg/ml concentrate for solution for infusion
bevacizumab
IV

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

100 mg/4 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion
bevacizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 mg bevacizumab.

3. LIST OF EXCIPIENTS

Trehalose dihydrate, sodium phosphate, polysorbate 20, water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 16 ml
400 mg/16 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use

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

This medicinal product does not contain any preservative

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the diluted medicine

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(S)

EU/1/04/300/002

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 the 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(S) OF ADMINISTRATION

Avastin 25 mg/ml concentrate for solution for infusion
bevacizumab
IV

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

400 mg/16 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Avastin 25 mg/ml concentrate for solution for infusion
bevacizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet:

1. What Avastin is and what it is used for
2. What you need to know before you use Avastin
3. How to use Avastin
4. Possible side effects
5. How to store Avastin
6. Contents of the pack and other information

1. What Avastin is and what it is used for

Avastin contains the active substance bevacizumab, which is a humanised monoclonal antibody (a type of protein that is normally made by the immune system to help defend the body from infection and cancer). Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. The VEGF protein causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once bevacizumab is bound to VEGF, tumour growth is prevented by blocking the growth of the blood vessels which provide the nutrients and oxygen to the tumour.

Avastin is a medicine used for the treatment of adult patients with advanced cancer in the large bowel, i.e., in the colon or rectum. Avastin will be administered in combination with chemotherapy treatment containing a fluoropyrimidine medicine.

Avastin is also used for the treatment of adult patients with metastatic breast cancer. When used for patients with breast cancer, it will be administered with a chemotherapy medicinal product called paclitaxel or capecitabine.

Avastin is also used for the treatment of adult patients with advanced non-small cell lung cancer. Avastin will be administered together with a chemotherapy regimen containing platinum.

Avastin is also used for the treatment of adult patients with advanced non-small cell lung cancer when cancer cells have specific mutations of a protein called epidermal growth factor receptor (EGFR). Avastin will be administered in combination with erlotinib.

Avastin is also used for treatment of adult patients with advanced kidney cancer. When used for patients with kidney cancer, it will be administered with another type of medicine called interferon.

Avastin is also used for the treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. When used for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, it will be administered in combination with carboplatin and paclitaxel.

When used for those adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has come back at least 6 months after the last time they were treated

with a chemotherapy regimen containing a platinum agent, Avastin will be administered in combination with carboplatin and gemcitabine or with carboplatin and paclitaxel.

When used for those adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has come back before 6 months after the last time they were treated with a chemotherapy regimen containing a platinum agent, Avastin will be administered in combination with paclitaxel, or topotecan, or pegylated liposomal doxorubicin.

Avastin is also used for the treatment of adult patients with persistent, recurrent or metastatic cervical cancer. Avastin will be administered in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy.

2. What you need to know before you use Avastin

Do not use Avastin if
- you are allergic (hypersensitive) to bevacizumab or to any of the other ingredients of this medicine (listed in section 6).
- you are allergic (hypersensitive) to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- you are pregnant.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Avastin

- It is possible that Avastin may increase the risk of developing holes in the gut wall. If you have conditions causing inflammation inside the abdomen (e.g. diverticulitis, stomach ulcers, colitis associated with chemotherapy), please discuss this with your doctor.

- Avastin may increase the risk of developing an abnormal connection or passageway between two organs or vessels. The risk of developing connections between the vagina and any parts of the gut can increase if you have persistent, recurrent or metastatic cervical cancer.

- This medicine can increase the risk of bleeding or increase the risk of problems with wound healing after surgery. If you are going to have an operation, if you have had major surgery within the last 28 days or if you still have an unhealed wound following surgery, you should not receive this medicine.

- Avastin may increase the risk of developing serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing.

- Avastin can increase the incidence of high blood pressure. If you have high blood pressure which is not well controlled with blood pressure medicines, please consult your doctor as it is important to make sure that your blood pressure is under control before starting Avastin treatment.

- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

- This medicine increases the risk of having protein in your urine especially if you already have high blood pressure.

- The risk of developing blood clots in your arteries (a type of blood vessel) can increase if you are over 65 years old, if you have diabetes, or if you have had previous blood clots in your arteries. Please talk to your doctor since blood clots can lead to heart attack and stroke.

- Avastin can also increase the risk of developing blood clots in your veins (a type of blood vessel).

- This medicine may cause bleeding, especially tumour-related bleeding. Please consult your doctor if you or your family tend to suffer from bleeding problems or you are taking medicines to thin the blood for any reason.

- It is possible that Avastin may cause bleeding in and around your brain. Please discuss this with your doctor if you have metastatic cancer affecting your brain.

- It is possible that Avastin can increase the risk of bleeding in your lungs, including coughing or spitting blood. Please discuss with your doctor if you noticed this previously.

- Avastin can increase the risk of developing a weak heart. It is important that your doctor knows if you have ever received anthracyclines (for example doxorubicin, a specific type of chemotherapy used to treat some cancers) or had radiotherapy to your chest, or if you have heart disease.

- This medicine may cause infections and a decreased number of your neutrophils (a type of blood cell important for your protection against bacteria).

- It is possible that Avastin can cause hypersensitivity (including anaphylactic shock) and/or infusion reactions (reactions related to your injection of the medicine). Please let your doctor, pharmacist or nurse know if you have previously experienced problems after injections, such as dizziness/feeling of fainting, breathlessness, swelling or skin rash.

- A rare neurological side effect named posterior reversible encephalopathy syndrome (PRES) has been associated with Avastin treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

Please consult your doctor, even if these above statements were only applicable to you in the past.

Before you are given Avastin or while you are being treated with Avastin:
- if you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth tell your doctor and dentist immediately.
- if you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with Avastin, in particular when you are also receiving or have received an injection of bisphosphonate into your blood.

You may be advised to have a dental check-up before you start treatment with Avastin.

Children and adolescents
Avastin use is not recommended in children and adolescents under the age of 18 years because the safety and benefit have not been established in these patient populations.

Death of bone tissue (osteonecrosis) in bones other than the jaw have been reported in patients under 18 years old when treated with Avastin.

Other medicines and Avastin
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Combinations of Avastin with another medicine called sunitinib malate (prescribed for renal and gastrointestinal cancer) may cause severe side effects. Discuss with your doctor to make sure that you do not combine these medicines.

Tell your doctor if you are using platinum- or taxane-based therapies for lung or metastatic breast cancer. These therapies in combination with Avastin may increase the risk of severe side effects.

Please tell your doctor if you have recently received, or are receiving, radiotherapy.

Pregnancy, breast-feeding and fertility
You must not use this medicine if you are pregnant. Avastin may cause damage to your unborn baby as it may stop the formation of new blood vessels. Your doctor should advise you about using contraception during treatment with Avastin and for at least 6 months after the last dose of Avastin.

Tell your doctor straightaway if you are pregnant, become pregnant during treatment with this medicine, or plan to become pregnant in the near future.

You must not breast-feed your baby during treatment with Avastin and for at least 6 months after the last dose of Avastin, as this medicine may interfere with the growth and development of your baby.

Avastin may impair female fertility. Please consult your doctor for more information.

Ask your doctor, pharmacist or nurse for advice before taking any medicine.

Driving and using machines
Avastin has not been shown to reduce your ability to drive or to use any tools or machines. However, sleepiness and fainting have been reported with Avastin use. If you experience symptoms that affect your vision or concentration, or your ability to react, do not drive and use machines until symptoms disappear.

Avastin contains sodium and polysorbate 20
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicine contains 1.6 mg of polysorbate 20 in each 100 mg/4 ml vial and 6.4 mg in each 400 mg/16 ml vial which is equivalent to 0.4 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Avastin

Dosage and frequency of administration
The dose of Avastin needed depends on your body weight and the kind of cancer to be treated. The recommended dose is 5 mg, 7.5 mg, 10 mg or 15 mg per kilogram of your body weight. Your doctor will prescribe a dose of Avastin that is right for you. You will be treated with Avastin once every 2 or 3 weeks. The number of infusions that you receive will depend on how you are responding to treatment; you should continue to receive this medicine until Avastin fails to stop your tumour growing. Your doctor will discuss this with you.

Method and route of administration
Do not shake the vial. Avastin is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the Avastin vial will be diluted with sodium chloride solution before use. A doctor or nurse will give you this diluted Avastin solution by intravenous infusion (a drip into your vein). The first infusion will be given to you over 90 minutes. If this is well-tolerated the second infusion may be given over 60 minutes. Later infusions may be given to you over 30 minutes.

The administration of Avastin should be temporarily discontinued
- if you develop severe high blood pressure requiring treatment with blood pressure medicines,
- if you have problems with wound healing following surgery,

- if you undergo surgery.

The administration of Avastin should be permanently discontinued if you develop
- severe high blood pressure which cannot be controlled by blood pressure medicines; or a sudden severe rise in blood pressure,
- presence of protein in your urine accompanied by swelling of your body,
- a hole in your gut wall,
- an abnormal tube-like connection or passage between the windpipe and the gullet, between internal organs and skin, between the vagina and any parts of the gut or between other tissues that are not normally connected (fistula), and are judged by your doctor to be severe,
- serious infections of the skin or deeper layers under the skin,
- a blood clot in your arteries,
- a blood clot in the blood vessels of your lungs,
- any severe bleeding.

If too much Avastin is given
- you may develop a severe migraine. If this happens you should talk to your doctor, pharmacist or nurse immediately.

If a dose of Avastin is missed
- your doctor will decide when you should be given your next dose of Avastin. You should discuss this with your doctor.

If you stop treatment with Avastin
Stopping your treatment with Avastin may stop the effect on tumour growth. Do not stop treatment with Avastin unless you have discussed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

The side effects listed below were seen when Avastin was given together with chemotherapy. This does not necessarily mean that these side effects were strictly caused by Avastin.

Allergic reactions
If you have an allergic reaction, tell your doctor or a member of the medical staff straight away. The signs may include: difficulty in breathing or chest pain. You could also experience redness or flushing of the skin or a rash, chills and shivering, feeling sick (nausea) or being sick (vomiting), swelling, light-headedness, fast heartbeat and loss of consciousness.

You should seek help immediately if you suffer from any of the below mentioned side effects.

Severe side effects, which may be **very common** (may affect more than 1 in 10 people), include:
- high blood pressure,
- feeling of numbness or tingling in hands or feet,
- decreased number of cells in the blood, including white cells that help to fight against infections (this may be accompanied by fever), and cells that help the blood to clot,
- feeling weak and having no energy,
- tiredness,
- diarrhoea, nausea, vomiting and abdominal pain.

Severe side effects, which may be **common** (may affect up to 1 in 10 people), include:
- perforation of the gut,
- bleeding, including bleeding in the lungs in patients with non-small cell lung cancer,
- blocking of the arteries by a blood clot,
- blocking of the veins by a blood clot,
- blocking of the blood vessels of the lungs by a blood clot,
- blocking of the veins of the legs by a blood clot,
- heart failure,
- problems with wound healing after surgery,
- redness, peeling, tenderness, pain, or blistering on the fingers or feet,
- decreased number of red cells in the blood,
- lack of energy,
- stomach and intestinal disorder,
- muscle and joint pain, muscular weakness,
- dry mouth in combination with thirst and/or reduced or darkened urine,
- inflammation of the moist lining of mouth and gut, lungs and air passages, reproductive, and urinary tracts,
- sores in the mouth and the tube from the mouth to the stomach, which may be painful and cause difficulty swallowing,
- pain, including headache, back pain and pain in the pelvis and anal regions,
- localised pus collection,
- infection, and in particular infection in the blood or bladder,
- reduced blood supply to the brain or stroke,
- sleepiness,
- nose bleed,
- increase in heart rate (pulse),
- blockage in the gut or bowel,
- abnormal urine test (protein in the urine),
- shortness of breath or low levels of oxygen in the blood,
- infections of the skin or deeper layers under the skin,
- fistula: abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between vagina and the gut in patients with cervical cancer,
- allergic reactions (the signs may include breathing difficulty, facial redness, rash, low blood pressure or high blood pressure, low oxygen in your blood, chest pain, or nausea/vomiting).

Severe side effects, which may be **rare** (may affect up to 1 in 1 000 people), include:
- sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness (anaphylactic shock).

Severe side effects of **unknown** frequency (frequency cannot be estimated from the available data), include:
- serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing,
- a negative effect on a woman's ability to have children (see the paragraphs below the list of side effects for further recommendations),
- a brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES),
- symptoms that suggest changes in normal brain function (headaches, vision changes, confusion, or seizures), and high blood pressure,
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections),
- clogging of a very small blood vessel(s) in the kidney,
- abnormally high blood pressure in the blood vessels of the lungs which makes the right side of the heart work harder than normal,
- a hole in the cartilage wall separating the nostrils of the nose,

- a hole in the stomach or intestines,
- an open sore or hole in the lining of the stomach or small intestine (the signs may include abdominal pain, feeling bloated, black tarry stools or blood in your stools (faeces) or blood in your vomit),
- bleeding from the lower part of the large bowel,
- lesions in the gums with an exposed jaw bone that does not heal and may be associated with pain and inflammation of the surrounding tissue (see the paragraphs below the list of side effects for further recommendations),
- hole in the gall bladder (symptoms and signs may include abdominal pain, fever, and nausea/vomiting).

You should seek help as soon as possible if you suffer from any of the below mentioned side effects.

Very common (may affect more than 1 in 10 people) side effects, which were not severe, include:
- constipation,
- loss of appetite,
- fever,
- problems with the eyes (including increased production of tears),
- changes in speech,
- change in the sense of taste,
- runny nose,
- dry skin, flaking and inflammation of the skin, change in skin colour,
- loss of body weight,
- nose bleeds.

Common (may affect up to 1 in 10 people) side effects, which were not severe, include:
- voice changes and hoarseness.

Patients older than 65 years have an increased risk of experiencing the following side effects:
- blood clot in the arteries which can lead to a stroke or a heart attack,
- reduction in the number of white cells in the blood, and cells that help the blood clot,
- diarrhoea,
- sickness,
- headache,
- fatigue,
- high blood pressure.

Avastin may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood, in particular neutrophils (one type of white blood cell which helps protect against infections) in the blood; presence of protein in the urine; decreased blood potassium, sodium or phosphorous (a mineral); increased blood sugar; increased blood alkaline phosphatase (an enzyme); increased serum creatinine (a protein measured by a blood test to see how well your kidneys are working); decreased haemoglobin (found in red blood cells, which carry oxygen), which may be severe.

Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs and symptoms of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience any of them.

Pre-menopausal women (women who have a menstrual cycle) may notice that their periods become irregular or are missed and may experience impaired fertility. If you are considering having children you should discuss this with your doctor before your treatment starts.

Avastin has been developed and made to treat cancer by injecting it into the bloodstream. It has not been developed or made for injection into the eye. It is therefore not authorised to be used in this way. When Avastin is injected directly into the eye (unapproved use), the following side effects may occur:

- Infection or inflammation of the eye globe,
- Redness of the eye, small particles or spots in your vision (floaters), eye pain,
- Seeing flashes of light with floaters, progressing to a loss of some of your vision,
- Increased eye pressure,
- Bleeding in the eye.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist 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 Avastin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the vial label after the abbreviation 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.

Infusion solutions should be used immediately after dilution. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless the infusion solutions have been prepared in a sterile environment. When dilution has taken place in a sterile environment, Avastin is stable for 30 days at 2 °C to 8 °C plus an additional 48 hours at 2 °C to 30 °C.

Do not use Avastin if you notice any particulate matter or discolouration prior to administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Avastin contains

- The active substance is bevacizumab. Each ml of concentrate contains 25 mg of bevacizumab, corresponding to 1.4 to 16.5 mg/ml when diluted as recommended.
  Each 4 ml vial contains 100 mg of bevacizumab, corresponding to 1.4 mg/ml when diluted as recommended.
  Each 16 ml vial contains 400 mg of bevacizumab, corresponding to 16.5 mg/ml when diluted as recommended
- The other ingredients are trehalose dihydrate, sodium phosphate, polysorbate 20 (E 432) (see section 2 ‘Avastin contains sodium and polysorbate 20’) and water for injections.

What Avastin looks like and contents of the pack
Avastin is a concentrate for solution for infusion. The concentrate is a clear, colourless to pale brown liquid in a glass vial with a rubber stopper. Each vial contains 100 mg bevacizumab in 4 ml of solution or 400 mg bevacizumab in 16 ml of solution. Each pack of Avastin contains one vial.

Marketing Authorisation Holder
Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

Manufacturer
Roche Pharma AG
Emil-Barell-Str. 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien,
Luxembourg/Luxemburg
N.V. Roche S.A.
België/Belgique/Belgien
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел.: +359 2 474 5444

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Danmark
Roche Pharmaceuticals A/S
Tlf.: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα, Κύπρος
Roche (Hellas) A.E.
Ελλάδα
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Magyarország
Roche (Magyarország) Kft.
Tel.: +36 1 279 4500

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438000

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel.: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o.
Tel: + 385 1 47 22 333

Ireland, Malta
Roche Products (Ireland) Ltd.
Ireland/L-Irlanda
Tel: +353 (0) 1 469 0700

Ísland
Roche Pharmaceuticals A/S
c/o Icepharma hf
Sími:+354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

次頁以降は非公表のため削除

CORE DATA SHEET [redacted]

[redacted]

AVASTIN®

Bevacizumab

[redacted]

目次

1.7 同種同効品一覧表 2

1.7 同種同効品一覧表

本邦で神経線維腫症2型の効能を取得している品目はないため，本剤の同種同効品に該当する薬剤はない。

目次

1.8 添付文書（案） 2
1.8.1 効能又は効果，用法及び用量の設定根拠 2
1.8.1.1 効能又は効果及び用法及び用量 2
1.8.1.2 効能又は効果の設定理由 3
1.8.1.3 効能又は効果に関連する注意の設定理由 6
1.8.1.4 用法及び用量の設定理由 6
1.8.1.5 用法及び用量に関連する注意の設定理由 7
1.8.2 使用上の注意の設定の根拠 12
添付文書（案） 20

最新の添付文書を参照すること。

1.8 添付文書（案）

1.8.1 効能又は効果，用法及び用量の設定根拠

1.8.1.1 効能又は効果及び用法及び用量

4. 効能又は効果

〇治癒切除不能な進行・再発の結腸・直腸癌
〇扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌
〇手術不能又は再発乳癌
〇悪性神経膠腫
〇卵巣癌
〇進行又は再発の子宮頸癌
〇切除不能な肝細胞癌
〇神経線維腫症2型

5. 効能又は効果に関連する注意

〈治癒切除不能な進行・再発の結腸・直腸癌及び扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌〉
（変更なし）
〈手術不能又は再発乳癌〉
（変更なし）
〈悪性神経膠腫〉
（変更なし）
〈卵巣癌〉
（変更なし）
〈進行又は再発の子宮頸癌〉
（変更なし）
〈切除不能な肝細胞癌〉
（変更なし）
〈神経線維腫症2型〉
5.12「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。[17.1.19参照]

6. 用法及び用量

〈治癒切除不能な進行・再発の結腸・直腸癌〉
他の抗悪性腫瘍剤との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回5mg/kg（体重）又は10mg/kg（体重）を点滴静脈内注射する。投与間隔は2週間以上とする。
他の抗悪性腫瘍剤との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回7.5mg/kg（体重）を点滴静脈内注射する。投与間隔は3週間以上とする。
〈扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌，進行又は再発の子宮頸癌〉
他の抗悪性腫瘍剤との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回15mg/kg（体重）を点滴静脈内注射する。投与間隔は3週間以上とする。
〈手術不能又は再発乳癌〉
パクリタキセルとの併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回10mg/kg（体重）を点滴静脈内注射する。投与間隔は2週間以上とする。
〈悪性神経膠腫〉
通常，成人にはベバシズマブ（遺伝子組換え）として1回10mg/kg（体重）を2週間間隔又は

1回15mg/kg（体重）を3週間間隔で点滴静脈内注射する。なお，患者の状態により投与間隔は適宜延長すること。

〈卵巣癌〉

他の抗悪性腫瘍剤との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回10mg/kg（体重）を2週間間隔又は1回15mg/kg（体重）を3週間間隔で点滴静脈内注射する。なお，患者の状態により投与間隔は適宜延長すること。

〈切除不能な肝細胞癌〉

アテゾリズマブ（遺伝子組換え）との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回15mg/kg（体重）を点滴静脈内注射する。投与間隔は3週間以上とする。

〈神経線維腫症2型〉

通常，成人にはベバシズマブ（遺伝子組換え）として1回5mg/kg（体重）を2週間間隔で点滴静脈内注射する。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤と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た上で，選択すること。［17.1.1-17.1.19参照］

7.2 再発悪性神経膠腫及び神経線維腫症2型以外における本剤単独投与での有効性及び安全性は確立していない。

7.3 初回投与時は90分かけて点滴静注する。初回投与の忍容性が良好であれば，2回目の投与は60分間で行っても良い。2回目の投与においても忍容性が良好であれば，それ以降の投与は30分間投与とすることができる。

〈治癒切除不能な進行・再発の結腸・直腸癌〉

（変更なし）

〈扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌〉

（変更なし）

〈手術不能又は再発乳癌〉

（変更なし）

〈悪性神経膠腫〉

（変更なし）

〈卵巣癌〉

（変更なし）

〈進行又は再発の子宮頸癌〉

（変更なし）

〈神経線維腫症2型〉

7.14 本剤による再治療は，本剤の治療により症状が維持又は改善した後，一定期間経過して治療を要する程度にまで症状が悪化した場合に行うこと。［17.1.19参照］

7.15 本剤の継続投与は，「17.臨床成績」の項の内容を熟知した上で，患者の状態に応じて検討すること。［17.1.19参照］

注）追加，変更箇所に下線を付した。

1.8.1.2 効能又は効果の設定理由

神経線維腫症2型は，両側聴神経鞘腫を主徴とする遺伝性疾患であり，厚生労働省の特定疾患（難病）に指定されている極めて希少な疾患である。神経鞘腫，髄膜腫など多数の中枢神経腫瘍が発生するため治療が困難であり，既存の治療法である手術療法や定位放射線治療は腫瘍の制御には有効だが，聴力温存は期待できない。また，発生する腫瘍は病理学的には良性腫瘍

に分類される。長期間にわたり無症状で経過することもあるが，特に若年者では腫瘍が成長して，急速に難聴などの神経症状が進行することがある。長年にわたり腫瘍が多発する場合や両側聴神経鞘腫など頭蓋内腫瘍の成長を制御できない場合には，患者の QOL は著しく低下し，生命予後も芳しくない。過去の調査では，5年，10年，20年生存率はそれぞれ85%，67%，38%とされている[1)]。

2009年に抗 VEGF 抗体であるベバシズマブの神経線維腫症2型の聴神経腫瘍に対する有効性が米国の Plotkin SR らによって New England Journal of Medicine 誌に初めて報告され[2)]，その後の追試報告をまとめると，腫瘍縮小がみられた割合は50%を超えており，聴力改善がみられた割合も50%強であるなど，有効性が示唆されている[3)]。こうした結果報告を受けて，米国及び欧州では神経線維腫症2型の聴神経腫瘍に対して，ベバシズマブの投与が推奨されるガイドラインが発表されている[4),5)]。また，ベバシズマブは既に複数の癌種で多くの使用経験が蓄積されており，安全性も確立している。

FMU2019-01-NF2試験（以下，本試験）は，聴神経腫瘍を有する神経線維腫症2型の患者を対象とした，ベバシズマブの初期治療の有効性と安全性の評価に加えて，再治療の有効性を評価する多施設共同二重盲検無作為化比較試験である。主要評価項目は，治療開始24週時点でのベースラインとの比較による，最高語音明瞭度の評価に基づく聴力改善患者（以下，レスポンダー）の割合とした。レスポンダーの定義は，少なくとも標的病変の一方において，最高語音明瞭度の値がベースラインの値から20%以上改善し，かつ，その値が50%以上であり，かつ標的病変において最高語音明瞭度の値が20%以上増悪していない被験者とした。初期治療期間は48週間で，ベバシズマブ投与群（以下，本剤投与群）とベバシズマブ初期非投与群（以下，プラセボ群）に1:1で無作為に割り付け，24週時以降は全例にベバシズマブを46週時まで投与した。48週時以降は，48週時にレスポンダーと判定され，かつ，担当医により症状増悪（基準：48週時点の最高語音明瞭度と比較して20%以上悪化）と判断された場合に，最長96週時まで2週間間隔で6回までのベバシズマブの再治療を可能とした。

主要評価項目である24週時点のレスポンダーの割合（95%信頼区間）は，本剤投与群で16.1%（5.5, 33.7），プラセボ群で3.2%（0.1, 16.7）であり，統計学的に有意な差は認められなかった（P=0.0858，χ^2検定）が，本剤投与群がプラセボ群を数値的に上回っていた。

副次的評価項目である24週，36週及び48週における最高語音明瞭度及び聴神経腫瘍体積のスクリーニング時からの変化量の平均値は表 1.8.1.2-1のとおりであった。48週継続投与した本剤投与群において状態悪化が緩やかになる傾向が認められている。

表 1.8.1.2-1　24週，36週及び48週におけるスクリーニング時からの変化量の平均値（%）（FAS）

	最高語音明瞭度の変化量の平均値（%）（95%信頼区間）		**聴神経腫瘍体積の縮小率の平均値（%）（95%信頼区間）**	
投与群	本剤 N=30	プラセボ N=31	本剤 N=30	プラセボ N=31
24週	9.459 (3.970, 14.949)	-2.103 (-8.193, 3.988)	14.06 (8.918, 19.202)	-7.012 (-11.149, -2.875)
36週	9.135 (2.930, 15.340)	1.744 (-3.398, 7.425)	14.267 (7.570, 20.964)	6.807 (0.581, 13.032)
48週	8.081 (1.553, 14.609)	2.564 (-3.472, 8.600)	14.579 (8.814, 20.344)	8.668 (2.218, 15.118)

副次的評価項目として，聴神経腫瘍体積のベースラインからの縮小率で評価した奏効割合を検討した。奏効の定義は，少なくとも標的病変の一方において，腫瘍体積がベースラインから20%以上縮小し，標的病変において腫瘍体積が20%以上増大していない被験者とした。その結果，治療開始12週及び24週時点では，本剤投与群の奏効割合がプラセボ群の奏効割合を上回っ

ていた（表 1.8.1.2-2）。

表 1.8.1.2-2　聴神経腫瘍体積：評価時点毎の奏効割合(%)（FAS)

		12週	24週	36週	48週
本剤投与群	被験者数	30	30	30	30
	奏効例数	6	10	11	9
	奏効割合(%)	20.0	33.3	36.7	30.0
	95%信頼区間(%)	7.7～38.6	17.3～52.8	19.9～56.1	14.7～49.4
プラセボ群	被験者数	31	31	31	31
	奏効例数	0	1	8	10
	奏効割合(%)	0	3.2	25.8	32.3
	95%信頼区間(%)	0.0～11.2	0.1～16.7	11.9～44.6	16.7～51.4
差	奏効割合(%)	20.0	30.1	10.9	-2.3
	95%信頼区間(%)	5.7～34.3	12.1～48.1	-12.3～34.0	-25.5～21.0
P 値（χ^2検定）		0.0087	0.0022	0.3598	0.8490

全般的な安全性において，投与群間に顕著な差は認められなかった。ベバシズマブ投与期間（プラセボ群の初期治療から22週時までのプラセボ投与期間を除いた全被験者での投与期間）及び経過観察期間における有害事象の集計においても，高血圧の副作用の頻度が高かったものの，重篤な副作用はなく，投与中止・休薬を要した副作用についても，蛋白尿を除き複数の被験者で発現した事象は認められなかった。

以上の結果より，本試験において主要評価項目で統計学的有意差は得られなかったが，最高語音明瞭度や聴神経腫瘍体積などの複数の評価項目で，プラセボ群と比較して本剤投与群において改善傾向がみられた。また，安全性についても，投与群間に顕著な差はなく，臨床的に重要な安全性上の懸念事項は認められなかった。

本試験において，聴神経腫瘍以外に対するベバシズマブの有効性は検証していない。神経線維腫症2型は聴神経腫瘍に代表される前庭神経鞘腫を主徴とする疾患であるが，三叉神経鞘腫や髄膜腫など複数の腫瘍型が多発性に生じ，複合的な症状を呈する疾患である。神経線維腫症2型患者のうち約9割が聴神経腫瘍を併発しており，その他の部位の腫瘍に比べて頻度が高い。三叉神経鞘腫は両側29%，片側15%で，髄膜腫は49%でそれぞれ併発している[6)]。三叉神経鞘腫は顔面麻痺や顔の痛みを引き起こす可能性があり，髄膜腫は進行性の神経学的欠損，発作，頭蓋内圧亢進，死亡を引き起こす可能性がある[2),7),8)]。また，頭蓋内非前庭神経鞘腫は複数の脳神経障害を引き起こす可能性がある[13)]。聴神経腫瘍以外の腫瘍型は非常に希少であるため検証的試験の実施が困難であり，これらの腫瘍を有する神経線維腫症2型患者にベバシズマブを投与した際の有効性及び安全性のデータは限定的である。Nakhate らの研究では[14)]，頭蓋内非前庭神経鞘腫及び髄膜腫を有する神経線維腫症2型患者を対象にベバシズマブを投与した結果，腫瘍当たりの奏効割合は非前庭神経鞘腫で42%（5/12個），髄膜腫で13%（5/40個）であり，非前庭神経鞘腫の奏効割合は前庭神経鞘腫の奏効割合の37%と同程度であったと報告がある。ベバシズマブの髄膜腫への有効性は限定的であるとの報告が多いが，ベバシズマブは非前庭神経鞘腫に対して持続的な有効性を有することが示唆されている。以上のことより，聴神経腫瘍以外の腫瘍型を有する神経線維腫症2型患者に対してもベバシズマブ投与により腫瘍増大や聴力低下が抑制される可能性が考えられる。

本試験は聴神経腫瘍の病勢進行に伴う聴力障害が認められていない患者を対象としていない。聴力障害が認められていない患者に対しても，何らかの症状が見られた場合や腫瘍の増大が明らかな場合，手術による腫瘍の摘出と定位放射線治療を検討する。一般に，腫瘍が小さいうちに手術すれば術後の神経障害のリスクは低く，聴力が温存できる可能性があるが，大きな腫瘍

の手術では聴力温存は困難で，術後顔面神経麻痺やその他の神経障害を合併することもある。外科手術の他に，小さな腫瘍には定位放射線治療も有効であるが，放射線治療に伴う聴力低下のリスクがある[1)]。本試験において，ベバシズマブ投与により聴神経腫瘍体積が縮小する傾向が認められており，臨床的に重要な安全性上の懸念事項は認められていない。そのため，聴力障害が認められていない患者に対しても，ベバシズマブ投与による腫瘍縮小の効果が期待され，聴力温存が困難な可能性がある手術及び放射線治療の介入が延期又は回避できる可能性が考えられる。

本試験は放射線既治療の神経線維腫症2型患者は除外されている。放射線既治療の神経線維腫症2型患者に対してベバシズマブを投与した臨床研究報告及び症例報告はいずれも症例数が少なく，有効性及び安全性のデータは限定的である[7),8)]。神経線維腫症2型患者の放射線治療は，長期的な腫瘍制御に一定の有効性があるものの，単発性腫瘍への有効性が概ね9割であるのに比べて，多発性腫瘍では7～8割程度と明らかに低く[9)-11)]，聴力温存が困難である等の課題がある。放射線既治療の神経線維腫症2型において，現時点で保険収載された有効な薬物治療は無く，手術や放射線治療は聴力低下，聴力喪失をきたすリスクが高く，聴力改善効果が期待できないばかりか，課題が大きいことから，聴力を損なうことなく腫瘍の増大を制御できる安全な治療法が求められている。本試験において，本剤投与群がプラセボ群と比較して聴力改善の傾向が認められており，臨床的に重要な安全性上の懸念事項は認められていない。以上より，放射線既治療の患者に対してもベバシズマブ投与が QOL の改善に寄与することが期待され，ベネフィットがリスクを上回ると考えられることにより，治療選択肢のひとつになり得ると考える。

これらの結果を総合的に判断し，神経線維腫症2型患者に対し，ベバシズマブ投与を治療選択肢にすることは臨床的意義が大きく，ベネフィットがリスクを上回ると考えられることから，効能又は効果を「神経線維腫症2型」と設定した。

1.8.1.3 効能又は効果に関連する注意の設定理由

「臨床成績」の項の内容を熟知し，ベバシズマブ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が重要であることから，効能又は効果に関連する注意として注意喚起することとした。

なお，審査の過程において効能又は効果に関連する注意は，以下の記載となった。

5.12 臨床試験において、前庭神経鞘腫以外の病変に対する本剤の有効性及び安全性は検討されていない。［17.1.19参照］

5.13 「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。［17.1.19 参照］

1.8.1.4 用法及び用量の設定理由

本邦において，ベバシズマブは，「治癒切除不能な進行・再発の結腸・直腸癌」，「扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌」，「手術不能又は再発乳癌」，「悪性神経膠腫」，「卵巣癌」，「進行又は再発の子宮頸癌」又は「切除不能な肝細胞癌」に係る効能・効果に対して，1回5～15mg/kg（体重）を点滴静脈内注射し，投与間隔は2週間以上又は3週間以上で承認されている。

ベバシズマブ（遺伝子組換え）の1回5 mg/kg（体重），2週間間隔での点滴静脈内注射は，神経線維腫症2型患者を対象とした本試験において，主要評価項目（治療開始24週時点での最高語音明瞭度による評価に基づく聴力改善患者［レスポンダー］の割合）で統計学的有意差は得られなかったものの，最高語音明瞭度，聴神経腫瘍体積を主とする複数の評価項目で，プラ

セボ群と比較して本剤投与群において改善傾向がみられた。安全性について，本剤投与群とプラセボ群の間で顕著な差はなく，臨床的に重要な安全性上の懸念事項は認められなかった。

有効性の観点で，本試験の用法・用量設定の根拠となった30例以上の症例で検討した2つの後方視的臨床研究の概要について以下に示す。

① Plotkin SR らの報告[3] （31症例，2012年）

ベバシズマブ1回5 mg/kg（体重）を2週間間隔で点滴静脈内注射し，聴力（最高語音明瞭度）と腫瘍体積を主たる評価項目としている。治療期間の中央値は14カ月であった。57%（13/23例）に聴力改善があり，55%（17/31例）に体積縮小がみられたが，両評価項目とも効果発現までの期間の中央値は3カ月であった。90%の症例が1年後に聴力を維持，61%が3年後まで維持した。また，88%が1年後まで安定又は縮小した腫瘍体積を維持し，54%が3年後まで維持した。忍容性は良好であったとされている。このように，神経線維腫症2型の進行性の聴神経腫瘍に対してベバシズマブ5 mg/kg（体重）2週間間隔での治療は，聴力・腫瘍体積に対して50%以上で奏効し，大半の患者で聴力の温存又は改善があったとしている。

② Morris KA らの報告[15] （61症例，2016年）

ベバシズマブ1回5 mg/kg（体重）を2週間間隔，又は1回7.5 mg/kg（体重）を3週間間隔で点滴静脈内注射し，6カ月間以上あるいは3カ月毎の画像診断で腫瘍のさらなる縮小がみられなくなるまで続けられた。画像診断で安定した状態の患者については，その後，維持療法として4週間間隔で1回2.5～5 mg/kg（体重）の点滴静脈内注射が行われた。その結果，ベバシズマブによる腫瘍増大の抑制，聴力ならびに QOL の改善が認められたとしている。39%の症例に腫瘍縮小（20%以上の腫瘍体積縮小）があり，51%に治療以前には増大がみられた腫瘍の安定化があった。聴力評価が可能な症例の86%に聴力の維持又は改善がみられた。結果として，手術件数が減少し，手術による聴力低下の危険の回避にもつながったとされている。

安全性の観点で，本試験の用法・用量設定の根拠となったイギリスで行われた神経線維腫症2型（80症例）のコホート研究（ベバシズマブの初期治療の用量としては[16]，1回7.5 mg/kg［体重］の3週間間隔及び1回5 mg/kg［体重］の2週間間隔）について，以下に示す。

最も高頻度に認められた副作用は，疲労，高血圧，感染であった。ロジスティック回帰モデルによる分析の結果，年齢（30歳以上）と初期治療の用量（1回7.5 mg/kg［体重］3週間間隔）が高血圧の発症の独立した予測因子であることが特定された。ベバシズマブの初期投与量として1回7.5 mg/kg（体重） を3週間間隔で投与する群では，40%（10/25例）が高血圧を発症したのに対し，1回5 mg/kg（体重）を2週間間隔で投与する群では，16%（9/55例）であった（両側 Fisher's exact test，p = 0.045）。このように副作用の観点からは，ベバシズマブの初期治療の用量は1回7.5 mg/kg（体重）の3週間間隔投与と比べて，1回5 mg/kg（体重）の2週間間隔投与が望ましいことが示唆されている。

以上，有効性，安全性の観点から，神経線維腫症2型患者に対するベバシズマブの用法及び用量を「通常，成人にはベバシズマブ（遺伝子組換え）として1回5 mg/kg（体重）を2週間間隔で点滴静脈内注射する。」と設定した。

1.8.1.5 用法及び用量に関連する注意の設定理由

本試験でみられた有効性及び安全性は，神経線維腫症2型におけるベバシズマブ単独投与のため，「効能共通」の注意喚起として「再発悪性神経膠腫及び神経線維腫症2型以外における本剤単独投与での有効性及び安全性は確立していない。」とした。

ベバシズマブによる治療は，治療中の有効性が確認されている反面，治療中止に伴い治療効果が消失し再増悪することが報告されている。Douwes らの報告[18] では，ベバシズマブ投与中止後の臨床的サーベイランスは11例で実施され，その期間の中央値は29.2カ月（範囲：2.7～52.4）であった。投与中止後，症状の更なる改善がみられた患者はおらず，3例（27%）は症状が安定していたが，8例（73%）は症状が悪化した。2回目又は3回目の治療コースを受けた全4例は最初の投与中止後に症状が悪化した。2回目の治療コース後，1例で症状の改善，1例で

症状の安定，2例で症状の悪化がみられた。3例（1例が症状安定，2例が症状悪化）がベバシズマブの3回目の治療コースを受けた。その後，症状の改善，安定維持，悪化がそれぞれ1例で認められた。また，これまでの複数の癌種での患者の使用経験から，ベバシズマブは長期間の継続投与により，高血圧や蛋白尿など副作用の発現頻度が高くなることが知られている。癌患者に比べて長期の生存が期待され治療期間が長くなることが見込まれる神経線維腫症2型患者においては，ベバシズマブの長期間の継続投与の安全性とその効果を勘案して治療計画を立案する必要がある。

本試験で得られた長期投与時の有効性について，本剤投与群の最高語音明瞭度の48週におけるベースラインからの変化量の平均値は8.838%（95%信頼区間：2.485～15.191）であり，48週の投与期間を通じて腫瘍縮小及び増悪抑制が一貫して持続していた。加えて，本剤投与群の48週時点の聴神経腫瘍体積の奏効割合は30.0%，腫瘍縮小率は14.579%であり，腫瘍体積についても48週の投与期間を通じて腫瘍縮小及び増悪抑制は持続していた（表 1.8.1.2-1及び表 1.8.1.2-2）。本試験で得られた長期投与時の安全性について，ベバシズマブ投与期間（プラセボ群の初期治療から22週時までのプラセボ投与期間を除いた全被験者での投与期間）及び経過観察期間における有害事象の発現率は88.5%であり，このうち Grade 3以上の有害事象の発現率は14.8%であった。主な有害事象は高血圧（21.3%），発熱，上咽頭炎及び鼻出血（各13.1%）等であった。重篤な有害事象のうち，ベバシズマブとの因果関係を否定できない有害事象の報告はなく，投与中止・休薬を要した副作用について蛋白尿を除き複数の被験者で発現した事象はなかった。ベバシズマブの投与開始後48週までに発現した副作用については概ね管理可能であった。

これまでに報告されているベバシズマブを長期投与した臨床試験の有効性及び安全性の概要を以下に示す。

① Poltkin らの報告[17)]（20例，2023年）

ベバシズマブ1回10 mg/kg を6カ月間2週間間隔投与した後に，維持療法として，1回5 mg/kg を18カ月間3週間間隔投与している。この試験の聴覚機能の指標は，本試験と同様に最高語音明瞭度を用いており，難聴の定義はベースラインと比較して単語認識スコア又は純音平均聴力の統計的に有意な低下とした。維持療法中の標的耳における難聴の無発生率は，48週後で95%，72週後で89%，98週後で70%であり，疾患の無進行は，48週後で94%，72週後で89%，98週後で89%と，多くの症例でベバシズマブによる治療効果が長期間継続していたと考えられる。安全性について，治療関連有害事象が95%，Grade 3以上の治療関連有害事象が35%に認められた。主な有害事象は高血圧（65%），不規則月経（46%），疲労（30%），蛋白尿（15%）であった。Grade 3の有害事象による1例の投与中止，Grade 1または2の有害事象による2例の患者希望による投与中止が報告された。維持療法期間に新たな安全性シグナルは検出されなかった。

② Morris KA らの報告[15)]（61症例，2016年）

61例にベバシズマブ1回5 mg/kg を2週間間隔投与又は1回7.5 mg/kg を3週間間隔投与し，腫瘍縮小が見られなくなるまで投与している。有効性について，32%（15/47例）の患者で部分奏効，51%（24/47例）の患者で安定が認められた。部分奏効の持続期間の中央値は15カ月（範囲：3～33カ月）であり，ベバシズマブ投与の追跡期間と同等であったことが示されている。安全性について，82%（50/61例）に有害事象（主な副作用：疲労，頻発過多月経，高血圧）を認め，Grade 3以上の有害事象は13%（8/61例）であった。ベバシズマブに関連する死亡の報告はなかった。

③ ベバシズマブの神経線維腫症2型に対する適応外使用としての報告

長期投与に関連する国内副作用報告としてベバシズマブ投与（1回10 mg/kg 2週間間隔投与にて開始）中に腎機能悪化，腫瘍内出血，くも膜下出血をきたし，休薬・投与間隔の延長（2ヶ月間隔にて投与）を要したが7年以上投与継続中の症例や，COVID-19感染，鎖骨骨折手術による休薬以外はベバシズマブ投与を1回10 mg/kg 2週間隔投与で4年間継続した症例が報告されていた。

本試験及び公表されている論文から，一貫して長期投与時の有効性は見られており，安全性の観点でも長期投与による新たな安全性シグナルは見られず管理可能であった。

長期投与が想定される根拠としては以下の通りである。本試験においてベバシズマブを休薬する48週以降から96週までの経過観察を実施した症例における最高語音明瞭度及び腫瘍体積の経過観察結果から，休薬後に聴力低下や腫瘍体積が増大する傾向が認められている（表 1.8.1.5-1及び表 1.8.1.5-2）。

表 1.8.1.5-1　最高語音明瞭度の48週以降におけるベースラインからの変化量（%）の記述統計量

時点	群	標的病変数	平均	最小値	中央値	最大値
60週	本剤投与群	23	7.30	-10.00	2.00	56.00
	プラセボ群	25	0.48	-58.00	2.00	50.00
72週	本剤投与群	21	2.29	-20.00	0.00	44.00
	プラセボ群	20	-6.50	-64.00	-2.00	24.00
84週	本剤投与群	13	-0.62	-28.00	0.00	34.00
	プラセボ群	12	-13.17	-46.00	-11.00	24.00
96週	本剤投与群	13	-1.38	-34.00	0.00	34.00
	プラセボ群	8	-16.50	-48.00	-19.00	16.00

表 1.8.1.5-2　腫瘍体積の48週以降におけるベースラインからの縮小率（%）の記述統計量

時点	群	標的病変数	平均	最小値	中央値	最大値
60週	本剤投与群	36	12.81	-22.22	10.64	59.26
	プラセボ群	39	9.77	-40.18	6.23	69.91
72週	本剤投与群	36	11.56	-27.10	10.13	59.26
	プラセボ群	39	6.56	-40.18	3.49	68.46
84週	本剤投与群	36	6.55	-33.33	7.06	59.26
	プラセボ群	39	4.45	-57.76	4.49	69.30
96週	本剤投与群	36	6.51	-50.58	7.54	59.26
	プラセボ群	39	4.41	-57.76	4.49	63.33

また，海外の臨床研究にて，ベバシズマブの休薬により聴力の悪化や腫瘍体積の増大が認められており，QOL 低下又は外科的治療が必要となることが想定される。よって，聴力の改善または維持，あるいは腫瘍体積の縮小や維持期間の延長が認められる場合は，副作用を鑑み，投与期間について検討した上で，ベバシズマブを継続投与することが望ましいと考える。

神経線維腫症2型患者に対する治療として実臨床で想定される治療形態のひとつとして，初期治療期間終了後に有効性の評価と経過観察を行い，有効例においては，治療を一旦終了し，その後の再増悪時に再治療を行って機能維持を図る方法が考えられる。

本試験では，初期治療の有効性と安全性の評価に加えて，副次目的として，ベバシズマブによる腫瘍体積縮小効果・再治療の効果の有無等を評価することにより，再治療の評価を行った。48週の初期治療の後，再治療を実施した被験者は2名であり，うち1名で聴神経腫瘍体積の縮小率に基づく奏効と判定されていることから，少数例ながら，ベバシズマブの再治療の一定の効果が示唆されている。いずれもプラセボ群の30代男性症例であり，48週の初期治療を完了している。1症例目は，48週時点で最高語音明瞭度が86%と，スクリーニング時点の52%と比べて大幅な聴力改善があり，レスポンダーと判定された。約6カ月経過時点で聴力の著明な悪化及び腫瘍増大がみられ，その際の純音聴力検査では，115 dB とスケールアウトし聴力を喪失した状態にあったため，最高語音明瞭度検査は測定不能として実施されなかった。12週間の再治療を実施した結果，純音聴力は61.3 dB，最高語音明瞭度は48%と著明な回復が得られたものの，本試験のレスポンダー判定の基準である最高語音明瞭度50%以上とならなかったため無効と判定された。腫瘍体積についても，再治療開始時点を基準として18.9%の縮小がみられたが，縮

小率が20%を下回っており無効と判定された。すなわち，1症例目は本試験で設定した基準を満たしていないものの，臨床的には聴力，腫瘍体積ともに一定の改善がみられた症例と考えられた。2症例目は，48週時点で最高語音明瞭度が62%と，スクリーニング時点の28%と比べて大幅な聴力改善があり，レスポンダーと判定された。約8カ月経過時点で聴力の顕著な悪化がみられ，その際の純音聴力検査では68.8 dB であり，48週時点に比べてむしろ良い結果であったが，最高語音明瞭度は42%と，20%の低下が認められたことに加え，腫瘍体積も48週時点と比べて増大していた。12週間の再治療を実施した結果，純音聴力は71.3 dB，最高語音明瞭度は46%と回復を認めなかったが，増悪も認めなかった。一方，腫瘍体積は26.8%の縮小が得られ奏効と判定された。すなわち，2症例目の再治療では聴力の改善を認めなかったが，腫瘍体積の明らかな縮小がみられた。以上，2症例ではあるが，48週時点で有効であったがその後再増悪した症例に再治療を行うことで，聴力ならびに腫瘍体積が一定の改善又は維持する効果が期待できることが示唆される。また，再治療における継続投与については，本試験の再治療で腫瘍体積の縮小傾向及び聴力の改善傾向が得られた症例において，12 週間の再治療終了後，腫瘍の増大及び聴力低下を来たし手術と放射線治療が必要となった事例もあることから，再治療においても，臨床的有用性が認められる場合は，ベバシズマブを継続投与することが望ましいと考える。

なお，福島県立医科大学脳神経外科で実施した臨床研究（厚生労働科学研究費補助金 難治性疾患等克服事業 神経皮膚症候群に関する調査研究平成23～25年度総合研究報告書）の報告後に[19]，6症例を加えた合計10症例（17腫瘍）について検討した結果では[20]，ベバシズマブ投与終了後，再増悪した1症例（1腫瘍）において，ベバシズマブの再治療を行ったところ，腫瘍縮小効果が再び観察されている。

このように，ベバシズマブによる再治療については，一定の効果が期待できることから，用法及び用量に関連する注意は，「本剤による再治療は，本剤の治療により症状が維持又は改善した後，一定期間経過して治療を要する程度にまで症状が悪化した場合に行うこと。」とした。

また，「17.臨床成績」の項の内容を熟知した上で，患者の状態に応じて検討することが重要であることから，用法・用量に関連する注意として注意喚起することとした。

なお，審査の過程において用法及び用量に関連する注意は，以下の記載となった。

〈効能共通〉

7.1 本剤と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た上で，選択すること。［17.1.1-17.1.19参照］

7.2 再発悪性神経膠腫及び神経線維腫症2型以外における本剤単独投与での有効性及び安全性は確立していない。

7.3 初回投与時は90分かけて点滴静注する。初回投与の忍容性が良好であれば，2回目の投与は60分間で行っても良い。2回目の投与においても忍容性が良好であれば，それ以降の投与は30分間投与とすることができる。

〈神経線維腫症2型〉

7.14 本剤の継続投与及び再治療は、「17.臨床成績」の項の内容を熟知した上で、患者の状態に応じて検討すること。［17.1.19 参照］

参考文献

1） 神経線維腫症 II 型（指定難病34）概要・診断基準等.（厚生労働省作成）. 難病情報センターWebsite. https://www.nanbyou.or.jp/entry/275. Accessed May 29, 2025.

2） Plotkin SR, Stemmer-Rachamimov AO, Barker FG 2nd, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. N Engl J Med. 2009; 361(4):358-67.

3） Plotkin SR, Merker VL, Halpin C, et al. Bevacizumab for progressive vestibular schwannoma in neurofibromatosis type 2: a retrospective review of 31 patients. Otol Neurotol 2012;33(6):1046-52.
4） EANO guideline on the diagnosis and treatment of vestibular schwannoma Neuro Oncol. 2019 Oct 28;22(1):31–45
5） NCCN Guidelines Central Nervous System Cancers ; https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1425. Accessed Aug 1, 2025.
6） Iwatate K, Yokoo T, Iwatate E, et al. Population characteristics and progressive disability in neurofibromatosis type 2. World Neurosurg 2017;106:653-60.
7） Lu VM, Ravindran K, Graffeo CS, et al. Efficacy and safety of bevacizumab for vestibular schwannoma in neurofibromatosis type 2: a systematic review and meta-analysis of treatment outcomes. Neuro Oncol 2019;144:239-48.
8） Eminowicz GK, Raman R, Conibear, et al. Bevacizumab treatment for vestibular schwannomas in neurofibromatosis type two: report of two cases, including responses after prior gamma knife and vascular endothelial growth factor inhibition therapy. J Laryngol Otol 2012;126(1):79-82.
9） Hasegawa T, Kato T, Naito T, et al. Long-term outcomes of sporadic vestibular schwannomas treated with recent stereotactic radiosurgery techniques. Int J Radiat Oncol Biol Phys 2020;108:725-33.
10） Shrivastava M, Emmanouil B, Mathew R, et al. Stereotactic radiosurgery and radiotherapy for vestibular schwannoma in NF2-related schwannomatosis. Laryngoscope 2024;134:2364-71.
11） Puataweepong P, Dhanacha M, Ruangkanchanasetr R, et al. Long-term clinical outcomes of stereotactic radiotherapy for bilateral vestibular schwannomas in neurofibromatosis type 2 patients. J Neurooncol 2023;164:587-95.
12） Wang J, Landry AP, Raleigh DR, et al. Meningioma: International Consortium on Meningiomas consensus review on scientific advances and treatment paradigms for clinicians, researchers, and patients. Neuro Oncol 2024;26(10):1742-80
13） Aboukais R, Zairi F, Bonne NX, et al. Causes of mortality in neurofibromatosis type 2. Br J Neurosurg 2015;29(1):37-40
14） Nakhate V, Ly Ina. Effect of bevacizumab on non-target intracranial meningiomas and non-vestibular schwannomas in NF2-related schwannomatosis: NF104. Neuro Oncol 2025;173:751-7
15） Morris KA, Golding JF, Axon PR, et al. Bevacizumab in neurofibromatosis type 2 (NF2) related vestibular schwannomas: a nationally coordinated approach to delivery and prospective evaluation. Neurooncol Pract. 2016;3(4):281-9.
16） Morris KA, Golding JF, Blesing C, et al. Toxicity profile of bevacizumab in the UK neurofibromatosis type 2 cohort. J Neurooncol. 2017;131(1):117-24.
17） Plotkin SR, Allen J, Dhall G, Campian JL, Clapp DW, Fisher MJ, et al. Multicenter, prospective, phase II study of maintenance bevacizumab for children and adults with NF2-related schwannomatosis and progressive vestibular schwannoma. Neuro Oncol 2023;25:1498-506.
18） Douwes J PJ, Hensen EF, Jansen JC, et al. Bevacizumab treatment for patients with NF2-related schwannomatosis: a single center experience. Cancers 2024;16(8):1479
19） 齋藤清，市川優寛，佐藤拓ら．神経線維腫症2型に伴う聴神経腫瘍に対する bevacizumab の腫瘍縮小効果．厚生労働省科学研究費補助金 難治性疾患等克服研究事業 神経皮膚症候群に関する調査研究平成23～25年度　総合研究報告書
20） Fujii M, Ichikawa M, Iwatate K, et al. Bevacizumab therapy of neurofibromatosis type 2 associated vestibular schwannoma in japanese patients. Neurol Med Chir (Tokyo) 2020;60(2):75-82.

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 〈効能共通〉 1.1 消化管穿孔があらわれ，死亡に至る例が報告されている。本剤の投与中に，消化管穿孔と診断された場合は，本剤の投与を中止し，適切な処置を行い，以降，本剤を再投与しないこと。［9.1.1，11.1.2参照］ 1.2 創傷治癒遅延による合併症（創し開，術後出血等）があらわれることがある。 1.2.1 手術後の患者に本剤を投与する場合は，術創の状態を確認し，投与の可否を検討すること。大きな手術の術創が治癒していない場合は，治療上の有益性が危険性を上回ると判断される場合を除き，本剤を投与しないこと。［8.1，9.1.2，11.1.4参照］ 1.2.2 本剤の投与中に創傷治癒遅延による合併症があらわれた場合は，創傷が治癒するまで本剤の投与を中止し，適切な処置を行うこと。［8.1，9.1.2，11.1.4参照］ 1.2.3 本剤の投与終了後に手術を行う場合は，本剤の投与終了からその後の手術まで十分な期間をおくこと。［8.1，9.1.2，11.1.4参照］ 1.3 本剤の投与により腫瘍関連出血のリスクが高まるおそれがある。脳腫瘍（脳転移を含む）を有する患者に本剤を投与した場合，脳出血があらわれるおそれがある。本剤の投与中に重度の出血があらわれた場合は，本剤の投与を中止し，適切な処置を行い，以降，本剤を再投与しないこと。［8.4，9.1.3，11.1.5参照］ 1.4 本剤の投与により，肺出血（喀血）があらわれ，死亡に至る例が報告されている。観察を十分に行い，肺出血（喀血）があらわれた場合は，本剤の投与を中止し，適切な処置を行い，以降，本剤を再投与しないこと。［2.2，11.1.5参照］ 1.5 脳卒中，一過性脳虚血発作，心筋梗塞，狭心症，脳虚血，脳梗塞等の動脈血栓塞栓症があらわれ，死亡に至る例が報告されている。観察を十分に行い異常が認められた場合には，本剤の投与を中止し，適切な処置を行うこと。動脈血栓塞栓症があらわれた患者には，本剤を再投与しないこと。［9.1.5，11.1.6参照］ 1.6 高血圧性脳症又は高血圧性クリーゼがあらわれ，死亡に至る例が報告されている。これらの事象があらわれた場合は，本剤の投与を中止し，適切な処置を行うこと。このような患者には，以降，本剤を再投与しないこと。また，本剤の投与期間中は血圧を定期的に測定すること。［8.2，11.1.7参照］ 1.7 可逆性後白質脳症症候群があらわれることがある。可逆性後白質脳症症候群が疑われた場合は，本剤の投与を中止し，適切な処置を行うこと。［11.1.8参照］ 〈治癒切除不能な進行・再発の結腸・直腸癌、扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌、手術不能又は再発乳癌、悪性神経膠腫、卵巣癌、進行又は再発の子宮頸癌、切除不能な肝細胞癌〉 1.8 本剤を含むがん化学療法は，緊急時に十分対応できる医療施設において，がん化学療法に十分な知識・経験を持つ医師のもとで，本療法が適切と判断される症例についてのみ実施すること。また，治療開始に先立ち，患者又はその家族に有効性及び危険性を十分説明し，同意を得てから投与すること。 〈神経線維腫症2型〉	神経線維腫症2型の治療における医師要件の注意事項として，1.9項に新たに記載を追加した。記載追加にあたり，効能共通の注意事項を先頭に移動させた。

1.9 本剤は，緊急時に十分対応できる医療施設において，本剤と神経線維腫症2型の治療についての十分な知識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 本剤の成分に対し過敏症の既往歴のある患者 2.2 喀血（2.5mL 以上の鮮血の喀出）の既往のある患者［1.4，11.1.5参照］	変更なし
8. 重要な基本的注意 8.1 創傷治癒遅延による合併症があらわれることがある。本剤の投与終了後に手術を行う場合は，本剤の投与終了からその後の手術まで十分な期間をおくこと。本剤の最終投与から手術までの適切な間隔は明らかになっていないが，本剤の半減期を考慮すること。［1.2.1-1.2.3，9.1.2，11.1.4，16.1.1参照］ 8.2 高血圧があらわれることがあるので，投与期間中は血圧を定期的に測定し，適切な処置を行うこと。 ［1.6，11.1.7参照］ 8.3 蛋白尿があらわれることがあるので，投与期間中は尿蛋白を定期的に検査することが望ましい。［11.1.9参照］ 8.4 脳転移を疑う症状がなく，本剤の投与が開始された患者においても，慎重に患者を観察し，神経学的異常が疑われた場合には脳転移及び脳出血の可能性を考慮して，本剤の投与中止を含めて適切な対応を行うこと。［1.3，9.1.3，11.1.5参照］ 8.5 骨髄抑制があらわれることがあるので，定期的に血液検査を行うなど観察を十分に行うこと。［11.1.10参照］ 8.6 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。［11.1.14参照］ 8.7 卵巣癌に対して，他の抗悪性腫瘍剤との併用において本剤を1回10mg/kg（体重），2週間間隔で使用する際には，関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議　公知申請への該当性に係る報告書」[1)] 等）を熟読すること。	8.4項について「本剤を含むがん化学療法」から「本剤の投与」へ文言の軽微修正を行った。
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 消化管など腹腔内の炎症を合併している患者 消化管穿孔があらわれるおそれがある。［1.1，11.1.2参照］ 9.1.2 大きな手術の術創が治癒していない患者 創傷治癒遅延による合併症があらわれるおそれがある。臨床試験において大きな手術後28日間経過していない患者に本剤を投与した経験はない。［1.2.1-1.2.3，8.1，11.1.4参照］ 9.1.3 脳転移を有する患者 脳腫瘍（脳転移を含む）を有する患者に本剤を投与する場合は，観察を十分に行い，脳出血が疑われるような症状が認められた場合は，本剤の投与中止を含めて適切な対応を行うこと。脳転移を有する患者で脳出血を認めた例が報告され，また，初発膠芽腫患者を対象とした国際共同臨床試験において，本剤の投与により脳出血の発現率が高くなる傾向が認められている。［1.3，8.4，11.1.5参照］ 9.1.4 先天性出血素因，凝固系異常のある患者 出血があらわれるおそれがある。	変更なし

9.1.5 血栓塞栓症の既往のある患者 心筋梗塞，脳梗塞，深部静脈血栓症，肺塞栓症などがあらわれるおそれがある。［1.5，11.1.6参照］ 9.1.6 糖尿病の患者 動脈血栓塞栓症の発現リスクが高くなるおそれがある。 9.1.7 高血圧症の患者 高血圧が悪化するおそれがある。蛋白尿の発現率が上昇することがある。 9.1.8 うっ血性心不全又は冠動脈疾患などの重篤な心疾患のある患者 うっ血性心不全が悪化又はあらわれるおそれがある。［11.1.12参照］ 9.4 生殖能を有する者 妊娠する可能性がある女性には，本剤投与中及び最終投与後6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］ 9.5 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。本剤を投与された患者で奇形を有する児の出産が報告されている。また，本剤をウサギ（器官形成期）に投与したところ，胚・胎児毒性及び催奇形性が認められた。［9.4，15.2.1参照］ 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 は乳汁中に移行することが知られている。 9.7 小児等 9.7.1 小児等を対象とした臨床試験は実施していない。 9.7.2 小児等で骨壊死（顎以外の部位）があらわれるとの報告がある。 9.8 高齢者 患者の状態を十分に観察しながら慎重に投与すること。海外臨床試験において，65歳未満の患者と比較し，65歳以上の患者で本剤投与による脳卒中，一過性脳虚血発作，心筋梗塞等の動脈血栓塞栓症の発現率の上昇が認められた。	
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 ショック，アナフィラキシー（1.9%） ショック，アナフィラキシー・infusion reaction（蕁麻疹，呼吸困難，口唇浮腫，咽頭浮腫等）があらわれることがある。過敏症状が認められた場合は，本剤の投与を中止し，薬物治療（アドレナリン，副腎皮質ステロイド剤，抗ヒスタミン剤等）等の適切な処置をすること。 11.1.2 消化管穿孔（0.9%） 死亡に至る例が報告されている。消化管穿孔と診断された場合は，重篤な消化管穿孔が再発するおそれがあるので，本剤を再投与しないこと。［1.1，9.1.1 参照］ 11.1.3 瘻孔（0.3%） 消化管瘻（腸管皮膚瘻，腸管瘻，気管食道瘻等）又は消化管以外の瘻孔（気管支胸膜瘻，泌尿生殖器瘻，胆管瘻等）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。また，気管食道瘻又は重度の瘻孔があらわれた患者では，本剤を再投与しないこと。子宮頸癌を対象とした海外臨床試験では，消化管腔	BeatNF2 試験（2022 年 6 月 28 日カットオフデータ）に基づき下線部を変更した。なお，その他の副作用について，発現頻度の更新に伴う事象名の順序変更については下線付与していない。

瘻（直腸腟瘻等）（8.3%），消化管瘻（直腸瘻）（0.5%），消化管以外の瘻（膀胱腟瘻等）（1.8%）が認められており，また発現例の多くは，骨盤部への放射線治療歴のある患者であったことが報告されている。

11.1.4 創傷治癒遅延

創傷治癒に影響を及ぼす可能性が考えられ，創傷治癒遅延による創し開（0.5%）及び術後出血（0.4%）等の合併症があらわれることがある。創傷治癒遅延による合併症があらわれた場合は，創傷が治癒するまで本剤の投与を中止し，適切な処置を行うこと。［1.2.1-1.2.3，8.1，9.1.2 参照］

11.1.5 出血（19.3%）

腫瘍関連出血を含む，消化管出血（吐血，下血）（1.9%），肺出血（血痰・喀血）（1.2%），脳出血（0.1%）等があらわれることがある。また，鼻出血（15.0%），歯肉出血（1.4%），腟出血（0.1%未満）等の粘膜出血があらわれることがある。重度の出血においては死亡に至る例が報告されているため，肺出血（喀血）又は重度の出血があらわれた場合は，本剤の投与を中止し，適切な処置を行うこと。また，このような出血があらわれた患者では，重度の出血が再発するおそれがあるので，本剤を再投与しないこと。［1.3，1.4，2.2，8.4，9.1.3 参照］

11.1.6 血栓塞栓症

脳卒中（頻度不明），一過性脳虚血発作（0.1%），心筋梗塞（0.1%未満），狭心症（0.1%），脳虚血（頻度不明），脳梗塞（0.2%）等の動脈血栓塞栓症，及び深部静脈血栓症（0.2%），肺塞栓症（0.1%）等の静脈血栓塞栓症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。動脈血栓塞栓症があらわれた患者では，再発時に死亡に至る可能性もあるので，本剤を再投与しないこと。［1.5，9.1.5 参照］

11.1.7 高血圧性脳症（頻度不明），高血圧性クリーゼ（頻度不明）

コントロール不能の高血圧，高血圧性脳症，高血圧性クリーゼがあらわれた場合には，本剤の投与を中止し，適切な処置を行うこと。また，高血圧性脳症，高血圧性クリーゼが再発するおそれがあるので，このような患者には本剤を再投与しないこと。高血圧の発現率は本剤の用量に相関して上昇する傾向が示唆されている。［1.6，8.2 参照］

11.1.8 可逆性後白質脳症症候群（0.1%未満）

可逆性後白質脳症症候群（症状：痙攣発作，頭痛，精神状態変化，視覚障害，皮質盲等）があらわれることがあり，高血圧を伴う例と伴わない例が報告されている。観察を十分に行い，可逆性後白質脳症症候群が疑われた場合は，本剤の投与を中止し，血圧のコントロール，抗痙攣薬の投与等の適切な処置を行うこと。［1.7 参照］

11.1.9 ネフローゼ症候群（0.1%未満）

高度の蛋白尿等の異常が認められた場合には，投与を中止し，適切な処置を行うこと。蛋白尿の発現率は本剤の用量に相関して上昇する傾向が示唆されている。［8.3 参照］

11.1.10 骨髄抑制

他の抗悪性腫瘍剤との併用において汎血球減少症（0.1%未満），好中球減少（24.0%），白血球減少（23.8%），貧血（8.5%），血小板減少（10.2%）があらわれることがある。なお，臨床試験で他の抗悪性腫瘍剤に本剤を併用した群において，併用していない群と比較して，高度の好中球減少症，発熱性好中球減少症の発現頻度が高まることが報告されている。［8.5 参照］

11.1.11 感染症（9.9%）

好中球減少の有無にかかわらず肺炎（0.6%），敗血症（0.2%），壊死性筋膜炎

（頻度不明）等の感染症があらわれ，死亡に至る例が報告されている。なお，壊死性筋膜炎については，創傷治癒遅延，消化管穿孔，瘻孔に続発した例が報告されている。

11.1.12 うっ血性心不全（0.1%未満）

乳癌を対象とした海外臨床試験では，グレード3以上の左室機能不全が2.2%の頻度で認められており，また発現例の多くは，アントラサイクリン系薬剤の投与歴，左胸壁への放射線治療歴等のある患者であったことが報告されている。［9.1.8参照］

11.1.13 間質性肺炎（0.4%）

11.1.14 血栓性微小血管症（頻度不明）

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。［8.6参照］

11.1.15 動脈解離（0.1%未満）

大動脈解離を含む動脈解離があらわれることがある。

11.2 その他の副作用

	5%以上	1～5%未満	1%未満	頻度不明
精神神経系	神経毒性（末梢性感覚ニューロパシー，末梢性運動ニューロパシー，感覚神経障害等）（15.5%）	味覚異常，頭痛，不眠症，浮動性めまい	神経痛，体位性めまい，不安，嗅覚錯誤，失神，傾眠，痙攣，構語障害	
消化器	食欲減退（14.5%），悪心（13.9%），口内炎（11.5%），下痢，嘔吐，便秘	腹痛，歯肉炎，口唇炎，胃不快感	歯周病，胃炎，消化不良，消化管潰瘍，歯痛，痔核，齲歯，歯肉痛，腸炎，逆流性食道炎，腸閉塞，胃腸炎，舌炎，肛門周囲痛，歯の脱落	胃腸障害
泌尿器	尿蛋白陽性（10.5%）	尿中血陽性	BUN増加，血中クレアチニン増加	
肝臓	肝機能異常（AST上昇，ALT上昇，γ-GTP増加，LDH増加等）	血中ビリルビン増加		
血液・凝固		リンパ球数減少，フィブリンDダイマー増加	INR増加，フィブリノゲン増加，白血球数増加，APTT延長，好中球数増加，プロトロンビン時間延長	
心・血管系	高血圧（18.2%）		動悸，洞性頻脈	上室性頻脈

皮膚	脱毛症(10.5%)，発疹	色素沈着，手足症候群，爪の障害，瘙痒症	紅斑，蕁麻疹，皮膚乾燥，皮膚剥脱，皮膚炎，爪囲炎，爪色素沈着，過角化	皮膚変色，剥脱性皮膚炎
筋・骨格	関節痛	筋痛，背部痛	四肢痛，筋骨格硬直，筋力低下，筋骨格痛（肩部痛，殿部痛等），側腹部痛	
呼吸器		発声障害，しゃっくり，咽頭喉頭痛，鼻漏	咳嗽，呼吸困難，鼻炎，気管支炎，低酸素症	肺高血圧症
眼			結膜炎，流涙増加，霧視	眼障害
代謝		血中コレステロール増加，血中アルブミン減少	血中ナトリウム減少，血中リン減少，血中尿酸増加，高カリウム血症，総蛋白減少，高脂血症，血中カルシウム減少，尿中ブドウ糖陽性，高カルシウム血症，血中クロール減少，高血糖，甲状腺機能低下症，高マグネシウム血症，血中ナトリウム増加，低マグネシウム血症，低カリウム血症	
その他	疲労・倦怠感(15.3%)，発熱	上気道感染（鼻咽頭炎等），体重減少，Al-P 上昇，末梢性浮腫，潮紅，注射部位反応（疼痛等），CRP 上昇	膀胱炎，無力症，ほてり，体重増加，胸痛，胸部不快感，膿瘍，カテーテル関連合併症（感染，炎症等），口腔ヘルペス，耳鳴，脱水，回転性めまい，毛包炎，顔面浮腫，静脈炎，帯状疱疹，熱感，不規則月経，感染性腸炎，耳不快感，疼痛，尿路感染	蜂巣炎，鼻中隔穿孔，卵巣機能不全（無月経等），骨盤痛

注）発現頻度は治癒切除不能な進行・再発の結腸・直腸癌に対する国内臨床試験［JO18157試験，JO18158試験及び JO19380試験］，未治療の扁平上皮癌を除く進行・再発の非小細胞肺癌に対する国内臨床試験［JO19907試験］，手術不能又は再発乳癌に対する国内臨床試験［JO19901試験］，初発の膠芽腫に対する国際共同臨床試験［BO21990試験］（国内症例），再発悪性神経膠腫

<table>
<tr><td>に対する国内臨床試験［JO22506試験］，卵巣癌に対する国際共同臨床試験［GOG-0218試験］（国内症例），進行又は再発の子宮頸癌に対する国内臨床試験［JO29569試験］，切除不能な肝細胞癌に対する国際共同臨床試験［YO40245試験］（国内症例），神経線維腫症2型に対する国内臨床試験［FMU2019-01-NF2試験］及び製造販売後の特定使用成績調査を含む。</td><td></td></tr>
<tr><td>14. 適用上の注意
14.1 薬剤調製時の注意
14.1.1 本剤の投与時には必要量を注射筒で抜き取り，日局生理食塩液に添加して約100mL とする。

〈必要抜き取り量計算式〉
$$抜き取り量（mL）＝体重（kg）\times\frac{1回投与量(mg/kg)}{25\ (mg/mL)}$$
<table><tr><th>1回投与量</th><th>必要抜き取り量（mL）計算式</th></tr><tr><td>5mg/kg</td><td>抜き取り量(mL)＝体重(kg)×0.2(mL/kg)</td></tr><tr><td>7.5mg/kg</td><td>抜き取り量(mL)＝体重(kg)×0.3(mL/kg)</td></tr><tr><td>10mg/kg</td><td>抜き取り量(mL)＝体重(kg)×0.4(mL/kg)</td></tr><tr><td>15mg/kg</td><td>抜き取り量(mL)＝体重(kg)×0.6(mL/kg)</td></tr></table>
14.1.2 日局生理食塩液以外は使用しないこと。
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。
14.2 薬剤投与時の注意
本剤とブドウ糖溶液を混合した場合，ベバシズマブの力価の減弱が生じるおそれがあるため，ブドウ糖溶液との混合を避け，本剤とブドウ糖溶液の同じ点滴ラインを用いた同時投与は行わないこと。</td><td>変更なし</td></tr>
<tr><td>15. その他の注意
15.1 臨床使用に基づく情報
15.1.1 海外臨床試験において本剤と化学療法を併用した閉経前女性患者は，化学療法のみを実施した患者と比較して，卵巣機能不全（β-HCG 妊娠検査陰性で3カ月以上継続する無月経かつ FSH≧30MIU/mL）の発現率が高いとの報告があり，妊孕性低下の可能性が示唆された。なお，本剤中止後にほとんどの患者で卵巣機能の回復が認められているが，本剤の妊孕性への長期的な影響は不明である。
15.1.2 本剤投与後に顎骨壊死が発現したとの報告があり，多くはビスホスホネート系製剤を投与中あるいは投与経験がある患者であった。また，本剤を含む血管新生阻害薬とビスホスホネート系製剤を併用時に顎骨壊死の発現が増加する可能性が示唆されたとの報告がある。
15.1.3 適応外疾患に対する硝子体内（用法・用量外）投与例において，網膜剥離，眼内炎，硝子体出血，網膜出血等の眼障害があらわれることが報告されている。本剤を硝子体内投与するにあたって，本剤の不適切な無菌操作下での小</td><td>変更なし</td></tr>
</table>

分けにより，重篤な眼感染症があらわれ，失明に至った例が海外で報告されている。また，海外において，心筋梗塞，脳卒中等があらわれることが報告されている1-3)。 15.2 非臨床試験に基づく情報 15.2.1 ウサギの胚・胎児試験（10～100mg/kg を器官形成期投与）において，胎児体重の減少，吸収胚の増加，外形・骨格異常を有する胎児の増加が認められた。［9.4，9.5参照］ 15.2.2 若齢カニクイザルでは本剤の反復投与（2～50mg/kg，週1回又は週2回投与）により，長骨成長板で骨端軟骨異形成が認められた。	

Confidential - 秘

202X 年 X 月改訂（第 X 版、効能変更、用法及び用量変更）

貯　　法：2～8℃保存
有効期間：36 箇月

日本標準商品分類番号
874291

	点滴静注用 100mg/4mL	点滴静注用 400mg/16mL
承認番号	21900AMX00910	21900AMX00921
販売開始	2007 年 6 月	

抗悪性腫瘍剤／
抗 VEGF 注1) ヒト化モノクローナル抗体
ベバシズマブ（遺伝子組換え）注
生物由来製品、劇薬、処方箋医薬品注2)

アバスチン®点滴静注用 100mg/4mL
アバスチン®点滴静注用 400mg/16mL
AVASTIN ®for Intravenous Infusion

注 1）VEGF：Vascular Endothelial Growth Factor
（血管内皮増殖因子）
注 2）注意―医師等の処方箋により使用すること

1. 警告

〈効能共通〉

1.1 消化管穿孔があらわれ、死亡に至る例が報告されている。本剤の投与中に、消化管穿孔と診断された場合は、本剤の投与を中止し、適切な処置を行い、以降、本剤を再投与しないこと。[9.1.1、11.1.2 参照]

1.2 創傷治癒遅延による合併症（創し開、術後出血等）があらわれることがある。

1.2.1 手術後の患者に本剤を投与する場合は、術創の状態を確認し、投与の可否を検討すること。大きな手術の術創が治癒していない場合は、治療上の有益性が危険性を上回ると判断される場合を除き、本剤を投与しないこと。[8.1、9.1.2、11.1.4 参照]

1.2.2 本剤の投与中に創傷治癒遅延による合併症があらわれた場合は、創傷が治癒するまで本剤の投与を中止し、適切な処置を行うこと。[8.1、9.1.2、11.1.4 参照]

1.2.3 本剤の投与終了後に手術を行う場合は、本剤の投与終了からその後の手術まで十分な期間をおくこと。[8.1、9.1.2、11.1.4 参照]

1.3 本剤の投与により腫瘍関連出血のリスクが高まるおそれがある。脳腫瘍（脳転移を含む）を有する患者に本剤を投与した場合、脳出血があらわれるおそれがある。本剤の投与中に重度の出血があらわれた場合は、本剤の投与を中止し、適切な処置を行い、以降、本剤を再投与しないこと。[8.4、9.1.3、11.1.5 参照]

1.4 本剤の投与により、肺出血（喀血）があらわれ、死亡に至る例が報告されている。観察を十分に行い、肺出血（喀血）があらわれた場合は、本剤の投与を中止し、適切な処置を行い、以降、本剤を再投与しないこと。[2.2、11.1.5 参照]

1.5 脳卒中、一過性脳虚血発作、心筋梗塞、狭心症、脳虚血、脳梗塞等の動脈血栓塞栓症があらわれ、死亡に至る例が報告されている。観察を十分に行い異常が認められた場合には、本剤の投与を中止し、適切な処置を行うこと。動脈血栓塞栓症があらわれた患者には、本剤を再投与しないこと。[9.1.5、11.1.6 参照]

1.6 高血圧性脳症又は高血圧性クリーゼがあらわれ、死亡に至る例が報告されている。これらの事象があらわれた場合は、本剤の投与を中止し、適切な処置を行うこと。このような患者には、以降、本剤を再投与しないこと。また、本剤の投与期間中は血圧を定期的に測定すること。[8.2、11.1.7 参照]

1.7 可逆性後白質脳症症候群があらわれることがある。可逆性後白質脳症症候群が疑われた場合は、本剤の投与を中止し、適切な処置を行うこと。[11.1.8 参照]

〈治癒切除不能な進行・再発の結腸・直腸癌、扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌、手術不能又は再発乳癌、悪性神経膠腫、卵巣癌、進行又は再発の子宮頸癌、切除不能な肝細胞癌〉

1.8 本剤を含むがん化学療法は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本療法が適切と判断される症例についてのみ実施すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

〈神経線維腫症 2 型〉

1.9 本剤は、緊急時に十分対応できる医療施設において、本剤と神経線維腫症 2 型の治療についての十分な知識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 本剤の成分に対し過敏症の既往歴のある患者

2.2 喀血（2.5mL 以上の鮮血の喀出）の既往のある患者
［1.4、11.1.5 参照］

3. 組成・性状

3.1 組成

販売名	アバスチン点滴静注用 100mg/4mL	アバスチン点滴静注用 400mg/16mL

Confidential - 秘

Confidential - 秘

有効成分	ベバシズマブ（遺伝子組換え）注) 100mg	ベバシズマブ（遺伝子組換え）注) 400mg
添加剤	トレハロース水和物 240mg	トレハロース水和物 960mg
	リン酸二水素ナトリウム一水和物 23.2mg	リン酸二水素ナトリウム一水和物 92.8mg
	無水リン酸一水素ナトリウム 4.8mg	無水リン酸一水素ナトリウム 19.2mg
	ポリソルベート 20 1.6mg	ポリソルベート 20 6.4mg

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。製造工程の培地成分としてブタ由来成分（ペプトン）を使用している。

3.2 製剤の性状

販売名	アバスチン点滴静注用 100mg/4mL	アバスチン点滴静注用 400mg/16mL
剤形	注射剤（バイアル）	
性状	澄明～乳白光を呈する、無色～微褐色の液	
pH	5.9～6.3	
浸透圧比	約 1（日局生理食塩液に対する比）	

4. 効能又は効果

○ 治癒切除不能な進行・再発の結腸・直腸癌
○ 扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌
○ 手術不能又は再発乳癌
○ 悪性神経膠腫
○ 卵巣癌
○ 進行又は再発の子宮頸癌
○ 切除不能な肝細胞癌
○ 神経線維腫症 2 型

5. 効能又は効果に関連する注意

〈治癒切除不能な進行・再発の結腸・直腸癌及び扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌〉

5.1 術後補助療法において、本剤の有効性及び安全性は確認されていない。

5.2 「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。[17.1.1-17.1.11 参照]

〈手術不能又は再発乳癌〉

5.3 術後薬物療法において、本剤の有効性及び安全性は確認されていない。

5.4 延命効果は示されていない。[17.1.13 参照]

5.5 「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、HER 2 及びホルモン受容体の発現状況等を踏まえて本剤投与の必要性を検討し、適応患者の選択を行うこと。[17.1.12、17.1.13 参照]

〈悪性神経膠腫〉

5.6 「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、治療歴、病理組織型等を踏まえて適応患者の選択を行うこと。[17.1.14、17.1.15 参照]

〈卵巣癌〉

5.7 FIGO StageⅢ以上の卵巣癌患者に投与すること。

5.8 「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。[17.1.16 参照]

〈進行又は再発の子宮頸癌〉

5.9 「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.17 参照]

〈切除不能な肝細胞癌〉

5.10 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。

5.11 「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、臨床試験に組み入れられた患者の肝機能障害の程度等を踏まえて適応患者の選択を行うこと。[17.1.18 参照]

〈神経線維腫症 2 型〉

5.12 臨床試験において、前庭神経鞘腫以外の病変に対する本剤の有効性及び安全性は検討されていない。[17.1.19 参照]

5.13 「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。[17.1.19 参照]

6. 用法及び用量

〈治癒切除不能な進行・再発の結腸・直腸癌〉

他の抗悪性腫瘍剤との併用において、通常、成人にはベバシズマブ（遺伝子組換え）として 1 回 5mg/kg（体重）又は 10mg/kg（体重）を点滴静脈内注射する。投与間隔は 2 週間以上とする。

他の抗悪性腫瘍剤との併用において、通常、成人にはベバシズマブ（遺伝子組換え）として 1 回 7.5mg/kg（体重）を点滴静脈内注射する。投与間隔は 3 週間以上とする。

〈扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌、進行又は再発の子宮頸癌〉

他の抗悪性腫瘍剤との併用において、通常、成人にはベバシズマブ（遺伝子組換え）として 1 回 15mg/kg（体重）を点滴静脈内注射する。投与間隔は 3 週間以上とする。

〈手術不能又は再発乳癌〉

パクリタキセルとの併用において、通常、成人にはベバシズマブ（遺伝子組換え）として 1 回 10mg/kg（体重）を点滴静脈内注射する。投与間隔は 2 週間以上とする。

〈悪性神経膠腫〉

通常、成人にはベバシズマブ（遺伝子組換え）として 1 回 10mg/kg（体重）を 2 週間間隔又は 1 回 15mg/kg（体重）を 3 週間間隔で点滴静脈内注射する。なお、患者の状態により投与間隔は適宜延長すること。

〈卵巣癌〉

他の抗悪性腫瘍剤との併用において、通常、成人にはベバシズマブ（遺伝子組換え）として 1 回 10mg/kg（体重）を 2 週間間隔又は 1 回 15mg/kg（体重）を 3 週間間隔で点滴静脈内注射する。なお、患者の状態により投与間隔は適宜延長すること。

〈切除不能な肝細胞癌〉

アテゾリズマブ（遺伝子組換え）との併用において、通常、成人にはベバシズマブ（遺伝子組換え）として 1 回 15mg/kg（体重）を点滴静脈内注射する。投与間隔は 3 週間以上とする。

〈神経線維腫症 2 型〉

通常、成人にはベバシズマブ（遺伝子組換え）として 1 回 5mg/kg（体重）を 2 週間間隔で点滴静脈内注射する。

Confidential - 秘

Confidential - 秘

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤と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た上で、選択すること。[17.1.1-17.1.19 参照]

7.2 再発悪性神経膠腫及び神経線維腫症2型以外における本剤単独投与での有効性及び安全性は確立していない。

7.3 初回投与時は90分かけて点滴静注する。初回投与の忍容性が良好であれば、2回目の投与は60分間で行っても良い。2回目の投与においても忍容性が良好であれば、それ以降の投与は30分間投与とすることができる。

〈治癒切除不能な進行・再発の結腸・直腸癌〉

7.4 本剤は、フッ化ピリミジン系薬剤を含む他の抗悪性腫瘍剤との併用により投与すること。[17.1.1-17.1.7 参照]

7.5 本剤の用法・用量は、「17. 臨床成績」の項の内容を熟知した上で、本剤と併用する他の抗悪性腫瘍剤及び患者のがん化学療法歴に応じて選択すること。[17.1.1-17.1.7 参照]

〈扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌〉

7.6 本剤は白金系抗悪性腫瘍剤を含む他の抗悪性腫瘍剤との併用により開始すること。[17.1.8-17.1.11 参照]

〈手術不能又は再発乳癌〉

7.7 本剤はパクリタキセルとの併用により開始すること。[17.1.12、17.1.13 参照]

〈悪性神経膠腫〉

7.8 初発悪性神経膠腫の場合は、本剤は放射線照射及びテモゾロミドとの併用により開始すること。[17.1.15 参照]

7.9 本剤の用法・用量は、「17. 臨床成績」の項の内容を熟知した上で、患者の治療歴に応じて選択すること。[17.1.14、17.1.15 参照]

〈卵巣癌〉

7.10 本剤と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、国内外の最新のガイドライン等を参考にした上で選択すること。[17.1.16 参照]

7.11 本剤とカルボプラチン及びパクリタキセルを併用する場合は、併用投与終了後も本剤単独投与を継続すること（本剤を継続投与しない場合の有効性は確認されていない）。[17.1.16 参照]

〈進行又は再発の子宮頸癌〉

7.12 本剤はパクリタキセルを含む他の抗悪性腫瘍剤との併用により開始すること。[17.1.17 参照]

7.13 日本人患者においては、本剤はパクリタキセル及びノギテカンとの併用投与の経験はない。

〈神経線維腫症2型〉

7.14 本剤の継続投与及び再治療は、「17. 臨床成績」の項の内容を熟知した上で、患者の状態に応じて検討すること。[17.1.19 参照]

8. 重要な基本的注意

8.1 創傷治癒遅延による合併症があらわれることがある。本剤の投与終了後に手術を行う場合は、本剤の投与終了からその後の手術まで十分な期間をおくこと。本剤の最終投与から手術までの適切な間隔は明らかになっていないが、本剤の半減期を考慮すること。[1.2.1-1.2.3、9.1.2、11.1.4、16.1.1 参照]

8.2 高血圧があらわれることがあるので、投与期間中は血圧を定期的に測定し、適切な処置を行うこと。[1.6、11.1.7 参照]

8.3 蛋白尿があらわれることがあるので、投与期間中は尿蛋白を定期的に検査することが望ましい。[11.1.9 参照]

8.4 脳転移を疑う症状がなく、本剤の投与が開始された患者においても、慎重に患者を観察し、神経学的異常が疑われた場合には脳転移及び脳出血の可能性を考慮して、本剤の投与中止を含めて適切な対応を行うこと。[1.3、9.1.3、11.1.5 参照]

8.5 骨髄抑制があらわれることがあるので、定期的に血液検査を行うなど観察を十分に行うこと。[11.1.10 参照]

8.6 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。[11.1.14 参照]

8.7 卵巣癌に対して、他の抗悪性腫瘍剤との併用において本剤を1回10mg/kg（体重）、2週間間隔で使用する際には、関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議　公知申請への該当性に係る報告書」[1)] 等）を熟読すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 消化管など腹腔内の炎症を合併している患者

消化管穿孔があらわれるおそれがある。[1.1、11.1.2 参照]

9.1.2 大きな手術の術創が治癒していない患者

創傷治癒遅延による合併症があらわれるおそれがある。臨床試験において大きな手術後28日間経過していない患者に本剤を投与した経験はない。[1.2.1-1.2.3、8.1、11.1.4 参照]

9.1.3 脳転移を有する患者

脳腫瘍（脳転移を含む）を有する患者に本剤を投与する場合は、観察を十分に行い、脳出血が疑われるような症状が認められた場合は、本剤の投与中止を含めて適切な対応を行うこと。脳転移を有する患者で脳出血を認めた例が報告され、また、初発膠芽腫患者を対象とした国際共同臨床試験において、本剤の投与により脳出血の発現率が高くなる傾向が認められている。[1.3、8.4、11.1.5 参照]

9.1.4 先天性出血素因、凝固系異常のある患者

出血があらわれるおそれがある。

9.1.5 血栓塞栓症の既往のある患者

心筋梗塞、脳梗塞、深部静脈血栓症、肺塞栓症などがあらわれるおそれがある。[1.5、11.1.6 参照]

9.1.6 糖尿病の患者

動脈血栓塞栓症の発現リスクが高くなるおそれがある。

9.1.7 高血圧症の患者

高血圧が悪化するおそれがある。蛋白尿の発現率が上昇することがある。

9.1.8 うっ血性心不全又は冠動脈疾患などの重篤な心疾患のある患者

うっ血性心不全が悪化又はあらわれるおそれがある。[11.1.12 参照]

9.4 生殖能を有する者

妊娠する可能性がある女性には、本剤投与中及び最終投与後6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]

9.5 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。本剤を投与された患者で奇形を有する児の出産

Confidential - 秘

Confidential - 秘

が報告されている。また、本剤をウサギ（器官形成期）に投与したところ、胚・胎児毒性及び催奇形性が認められた。[9.4、15.2.1 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 は乳汁中に移行することが知られている。

9.7 小児等

9.7.1 小児等を対象とした臨床試験は実施していない。

9.7.2 小児等で骨壊死（顎以外の部位）があらわれるとの報告がある。

9.8 高齢者

患者の状態を十分に観察しながら慎重に投与すること。海外臨床試験において、65 歳未満の患者と比較し、65 歳以上の患者で本剤投与による脳卒中、一過性脳虚血発作、心筋梗塞等の動脈血栓塞栓症の発現率の上昇が認められた。

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
抗凝固剤 ヘパリン ワルファリン等	出血があらわれるおそれがある。	出血リスクを増強させるおそれがある。

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 ショック、アナフィラキシー（1.9%）

ショック、アナフィラキシー・infusion reaction（蕁麻疹、呼吸困難、口唇浮腫、咽頭浮腫等）があらわれることがある。過敏症状が認められた場合は、本剤の投与を中止し、薬物治療（アドレナリン、副腎皮質ステロイド剤、抗ヒスタミン剤等）等の適切な処置をすること。

11.1.2 消化管穿孔（0.9%）

死亡に至る例が報告されている。消化管穿孔と診断された場合は、重篤な消化管穿孔が再発するおそれがあるので、本剤を再投与しないこと。[1.1、9.1.1 参照]

11.1.3 瘻孔（0.3%）

消化管瘻（腸管皮膚瘻、腸管瘻、気管食道瘻等）又は消化管以外の瘻孔（気管支胸膜瘻、泌尿生殖器瘻、胆管瘻等）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。また、気管食道瘻又は重度の瘻孔があらわれた患者では、本剤を再投与しないこと。子宮頸癌を対象とした海外臨床試験では、消化管腟瘻（直腸腟瘻等）（8.3%）、消化管瘻（直腸瘻）（0.5%）、消化管以外の瘻（膀胱腟瘻等）（1.8%）が認められており、また発現例の多くは、骨盤部への放射線治療歴のある患者であったことが報告されている。

11.1.4 創傷治癒遅延

創傷治癒に影響を及ぼす可能性が考えられ、創傷治癒遅延による創し開（0.5%）及び術後出血（0.4%）等の合併症があらわれることがある。創傷治癒遅延による合併症があらわれた場合は、創傷が治癒するまで本剤の投与を中止し、適切な処置を行うこと。[1.2.1-1.2.3、8.1、9.1.2 参照]

11.1.5 出血（19.3%）

腫瘍関連出血を含む、消化管出血（吐血、下血）（1.9%）、肺出血（血痰・喀血）（1.2%）、脳出血（0.1%）等があらわれることがある。また、鼻出血（15.0%）、歯肉出血（1.4%）、腟出血（0.1%未満）等の粘膜出血があらわれることがある。重度の出血においては死亡に至る例が報告されているため、肺出血（喀血）又は重度の出血があらわれた場合は、本剤の投与を中止し、適切な処置を行うこと。また、このような出血があらわれた患者では、重度の出血が再発するおそれがあるので、本剤を再投与しないこと。[1.3、1.4、2.2、8.4、9.1.3 参照]

11.1.6 血栓塞栓症

脳卒中（頻度不明）、一過性脳虚血発作（0.1%）、心筋梗塞（0.1%未満）、狭心症（0.1%）、脳虚血（頻度不明）、脳梗塞（0.2%）等の動脈血栓塞栓症、及び深部静脈血栓症（0.2%）、肺塞栓症（0.1%）等の静脈血栓塞栓症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。動脈血栓塞栓症があらわれた患者では、再発時に死亡に至る可能性もあるので、本剤を再投与しないこと。[1.5、9.1.5 参照]

11.1.7 高血圧性脳症（頻度不明）、**高血圧性クリーゼ**（頻度不明）

コントロール不能の高血圧、高血圧性脳症、高血圧性クリーゼがあらわれた場合には、本剤の投与を中止し、適切な処置を行うこと。また、高血圧性脳症、高血圧性クリーゼが再発するおそれがあるので、このような患者には本剤を再投与しないこと。高血圧の発現率は本剤の用量に相関して上昇する傾向が示唆されている。[1.6、8.2 参照]

11.1.8 可逆性後白質脳症症候群（0.1%未満）

可逆性後白質脳症症候群（症状：痙攣発作、頭痛、精神状態変化、視覚障害、皮質盲等）があらわれることがあり、高血圧を伴う例と伴わない例が報告されている。観察を十分に行い、可逆性後白質脳症症候群が疑われた場合は、本剤の投与を中止し、血圧のコントロール、抗痙攣薬の投与等の適切な処置を行うこと。[1.7 参照]

11.1.9 ネフローゼ症候群（0.1%未満）

高度の蛋白尿等の異常が認められた場合には、投与を中止し、適切な処置を行うこと。蛋白尿の発現率は本剤の用量に相関して上昇する傾向が示唆されている。[8.3 参照]

11.1.10 骨髄抑制

他の抗悪性腫瘍剤との併用において汎血球減少症（0.1%未満）、好中球減少（24.0%）、白血球減少（23.8%）、貧血（8.5%）、血小板減少（10.2%）があらわれることがある。なお、臨床試験で他の抗悪性腫瘍剤に本剤を併用した群において、併用していない群と比較して、高度の好中球減少症、発熱性好中球減少症の発現頻度が高まることが報告されている。[8.5 参照]

11.1.11 感染症（9.9%）

好中球減少の有無にかかわらず肺炎（0.6%）、敗血症（0.2%）、壊死性筋膜炎（頻度不明）等の感染症があらわれ、死亡に至る例が報告されている。なお、壊死性筋膜炎については、創傷治癒遅延、消化管穿孔、瘻孔に続発した例が報告されている。

11.1.12 うっ血性心不全（0.1%未満）

Confidential - 秘

Confidential - 秘

乳癌を対象とした海外臨床試験では、グレード3以上の左室機能不全が2.2%の頻度で認められており、また発現例の多くは、アントラサイクリン系薬剤の投与歴、左胸壁への放射線治療歴等のある患者であったことが報告されている。[9.1.8 参照]

11.1.13 間質性肺炎（0.4%）

11.1.14 血栓性微小血管症（頻度不明）

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。[8.6 参照]

11.1.15 動脈解離（0.1%未満）

大動脈解離を含む動脈解離があらわれることがある。

11.2 その他の副作用

	5%以上	1～5%未満	1%未満	頻度不明
精神神経系	神経毒性（末梢性感覚ニューロパシー、末梢性運動ニューロパシー、感覚神経障害等）（15.5%）	味覚異常、頭痛、不眠症、浮動性めまい	神経痛、体位性めまい、不安、嗅覚錯誤、失神、傾眠、痙攣、構語障害	
消化器	食欲減退（14.5%）、悪心（13.9%）、口内炎（11.5%）、下痢、嘔吐、便秘	腹痛、歯肉炎、口唇炎、胃不快感	歯周病、胃炎、消化不良、消化管潰瘍、歯痛、痔核、齲歯、歯肉痛、腸炎、逆流性食道炎、腸閉塞、胃腸炎、舌炎、肛門周囲痛、歯の脱落	胃腸障害
泌尿器	尿蛋白陽性（10.5%）	尿中血陽性	BUN増加、血中クレアチニン増加	
肝臓	肝機能異常（AST上昇、ALT上昇、γ-GTP増加、LDH増加等）	血中ビリルビン増加		
血液・凝固		リンパ球数減少、フィブリンDダイマー増加	INR増加、フィブリノゲン増加、白血球数増加、APTT延長、好中球数増加、プロトロンビン時間延長	
心・血管系	高血圧（18.2%）		動悸、洞性頻脈	上室性頻脈
皮膚	脱毛症（10.5%）、発疹	色素沈着、手足症候群、爪の障害、瘙痒症	紅斑、蕁麻疹、皮膚乾燥、皮膚剥脱、皮膚炎、爪囲炎、爪色素沈着、過角化	皮膚変色、剥脱性皮膚炎
筋・骨格	関節痛	筋痛、背部痛	四肢痛、筋骨格硬直、筋力低下、筋骨格痛（肩部痛、殿部痛等）、側腹部痛	
呼吸器		発声障害、しゃっくり、咽頭喉頭痛、鼻漏	咳嗽、呼吸困難、鼻炎、気管支炎、低酸素症	肺高血圧症
眼			結膜炎、流涙増加、霧視	眼障害
代謝		血中コレステロール増加、血中アルブミン減少	血中ナトリウム減少、血中リン減少、血中尿酸増加、高カリウム血症、総蛋白減少、高脂血症、血中カルシウム減少、尿中ブドウ糖陽性、高カルシウム血症、血中クロール減少、高血糖、甲状腺機能低下症、高マグネシウム血症、血中ナトリウム増加、低マグネシウム血症、低カリウム血症	
その他	疲労・倦怠感（15.3%）、発熱	上気道感染（鼻咽頭炎等）、体重減少、Al-P上	膀胱炎、無力症、ほてり、体重増加、胸痛、	蜂巣炎、鼻中隔穿孔、卵巣機能不

Confidential - 秘

Confidential - 秘

	5%以上	1～5%未満	1%未満	頻度不明
		昇、末梢性浮腫、潮紅、注射部位反応（疼痛等）、CRP上昇	胸部不快感、膿瘍、カテーテル関連合併症（感染、炎症等）、口腔ヘルペス、耳鳴、脱水、回転性めまい、毛包炎、顔面浮腫、静脈炎、帯状疱疹、熱感、不規則月経、感染性腸炎、耳不快感、疼痛、尿路感染	全（無月経等）、骨盤痛

注）発現頻度は治癒切除不能な進行・再発の結腸・直腸癌に対する国内臨床試験［JO18157 試験、JO18158 試験及び JO19380 試験］、未治療の扁平上皮癌を除く進行・再発の非小細胞肺癌に対する国内臨床試験［JO19907 試験］、手術不能又は再発乳癌に対する国内臨床試験［JO19901 試験］、初発の膠芽腫に対する国際共同臨床試験［BO21990 試験］（国内症例）、再発悪性神経膠腫に対する国内臨床試験［JO22506 試験］、卵巣癌に対する国際共同臨床試験［GOG-0218 試験］（国内症例）、進行又は再発の子宮頸癌に対する国内臨床試験［JO29569 試験］、切除不能な肝細胞癌に対する国際共同臨床試験［YO40245 試験］（国内症例）、神経線維腫症 2 型に対する国内臨床試験［FMU2019-01-NF2 試験］及び製造販売後の特定使用成績調査を含む。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 本剤の投与時には必要量を注射筒で抜き取り、日局生理食塩液に添加して約 100mL とする。

〈必要抜き取り量計算式〉

$$\text{抜き取り量（mL）} = \text{体重（kg）} \times \frac{\text{1回投与量（mg/kg）}}{\text{25（mg/mL）}}$$

1 回投与量	必要抜き取り量（mL）計算式
5mg/kg	抜き取り量（mL）＝体重（kg）×0.2（mL/kg）
7.5mg/kg	抜き取り量（mL）＝体重（kg）×0.3（mL/kg）
10mg/kg	抜き取り量（mL）＝体重（kg）×0.4（mL/kg）
15mg/kg	抜き取り量（mL）＝体重（kg）×0.6（mL/kg）

14.1.2 日局生理食塩液以外は使用しないこと。

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。

14.2 薬剤投与時の注意

本剤とブドウ糖溶液を混合した場合、ベバシズマブの力価の減弱が生じるおそれがあるため、ブドウ糖溶液との混合を避け、本剤とブドウ糖溶液の同じ点滴ラインを用いた同時投与は行わないこと。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 海外臨床試験において本剤と化学療法を併用した閉経前女性患者は、化学療法のみを実施した患者と比較して、卵巣機能不全（β-HCG 妊娠検査陰性で 3 カ月以上継続する無月経かつ FSH≧30MIU/mL）の発現率が高いとの報告があり、妊孕性低下の可能性が示唆された。なお、本剤中止後にほとんどの患者で卵巣機能の回復が認められているが、本剤の妊孕性への長期的な影響は不明である。

15.1.2 本剤投与後に顎骨壊死が発現したとの報告があり、多くはビスホスホネート系製剤を投与中あるいは投与経験がある患者であった。また、本剤を含む血管新生阻害薬とビスホスホネート系製剤を併用時に顎骨壊死の発現が増加する可能性が示唆されたとの報告がある。

15.1.3 適応外疾患に対する硝子体内（用法・用量外）投与例において、網膜剥離、眼内炎、硝子体出血、網膜出血等の眼障害があらわれることが報告されている。本剤を硝子体内投与するにあたって、本剤の不適切な無菌操作下での小分けにより、重篤な眼感染症があらわれ、失明に至った例が海外で報告されている。また、海外において、心筋梗塞、脳卒中等があらわれることが報告されている[2)-4)]。

15.2 非臨床試験に基づく情報

15.2.1 ウサギの胚・胎児試験（10～100mg/kg を器官形成期投与）において、胎児体重の減少、吸収胚の増加、外形・骨格異常を有する胎児の増加が認められた。［9.4、9.5 参照］

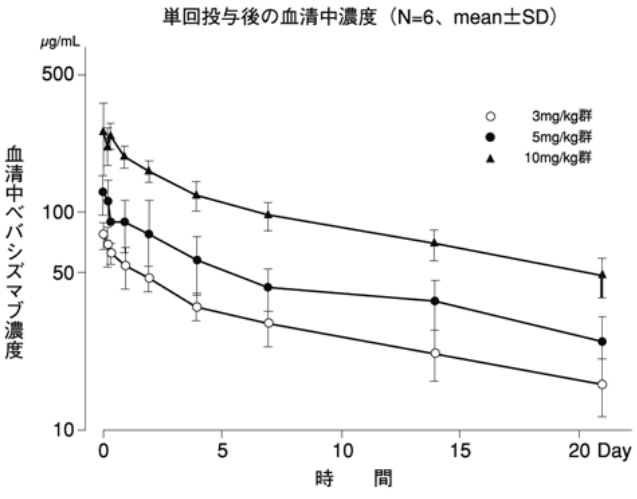
15.2.2 若齢カニクイザルでは本剤の反復投与（2～50mg/kg、週 1 回又は週 2 回投与）により、長骨成長板で骨端軟骨異形成が認められた。

16. 薬物動態

16.1 血中濃度

16.1.1 単回投与

結腸・直腸癌患者 18 例にベバシズマブ 3、5 又は 10mg/kg[注1)] を 90 分間点滴静注したときの血清中濃度は以下のとおりであった。ベバシズマブの血清中からの消失は緩やかで、AUC は投与量に比例して増加した[5)]。［8.1 参照］



単回投与時の薬物動態パラメータ

Confidential - 秘

Confidential - 秘

投与量 (mg/kg)	AUC_{inf} (μg・day/mL)	V_d (mL/kg)	CL (mL/day/kg)	$t_{1/2}$ (day)
3	852.3±237.4	62.50±11.10	3.80±1.20	12.33±4.52
5	1387.2±426.9	73.47±18.34	3.94±1.34	13.40±2.82
10	2810.9±344.8	60.26±8.93	3.61±0.48	11.68±1.74

N=6、mean±SD

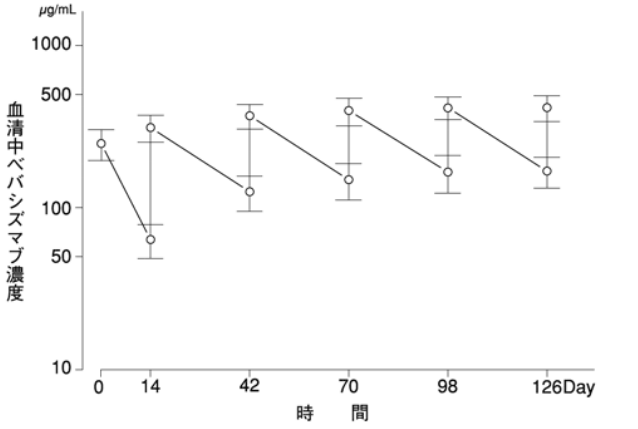
注 1）本剤の治癒切除不能な進行・再発の結腸・直腸癌に対する承認用量は 1 回 5mg/kg、7.5mg/kg 及び 10mg/kg である。

16.1.2 反復投与

〈手術不能又は再発乳癌〉

転移・再発乳癌患者にパクリタキセルとの併用によりベバシズマブ 10mg/kg の点滴静注を 2 週間隔で繰り返したときの血清中ベバシズマブ濃度推移は以下のとおりであった。初回投与 70 日後（投与 6 回目）の最低及び最高血清中濃度は各々149.0±37.4（47 例）及び 397.8±77.9（43 例）μg/mL であり、投与 6 回目以降の濃度はほぼ一定の値を示した [6]。

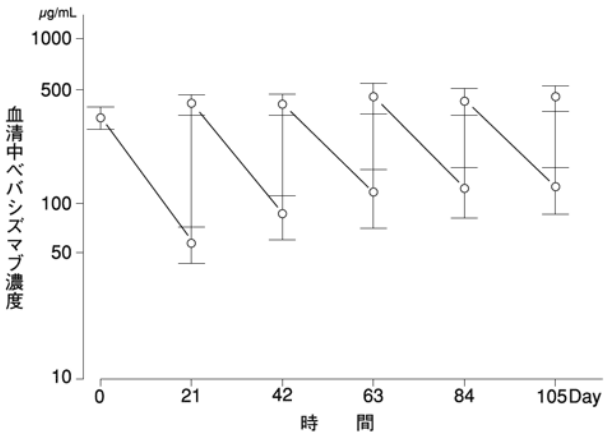
反復投与時（10mg/kg/2週間）の血清中濃度（N=31～67、mean±SD）



〈扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌〉

非小細胞肺癌患者 53 例にカルボプラチン・パクリタキセル療法との併用によりベバシズマブ 15mg/kg の点滴静注を 3 週間隔で繰り返したときの血清中ベバシズマブ濃度推移は以下のとおりであった。初回投与 63 日後（投与 4 回目）の最低及び最高血清中濃度は各々115.9±45.6（20 例）及び 450.3±97.3（19 例）μg/mL であり、投与 4 回目以降の濃度はほぼ一定の値を示した [7]。

反復投与時（15mg/kg/3週間）の血清中濃度（N=8～53、mean±SD）



16.1.3 母集団薬物動態解析の成績

491 例の患者に 1～20mg/kg 注 2) の用量のベバシズマブを 1 週間隔、2 週間隔、若しくは 3 週間隔で点滴静注したときの血清中濃度を用い、母集団薬物動態解析を実施した。2-コンパートメントモデルで解析したときの男性のクリアランスは 0.262L/day、女性は 0.207L/day であった。また、中心コンパートメントの分布容積については、男性は 3.25L、女性は 2.66L であった（外国人データ）。

注 2）本剤の承認用量は 1 回 5mg/kg、7.5mg/kg、10mg/kg 及び 15mg/kg である。

16.3 分布

ウサギに ^{125}I 標識ベバシズマブを単回静脈内投与したところ、いずれの組織においても特異的な取り込みは認められず、本剤の分布はほぼ血漿に限られていた [8]。

16.5 排泄

ウサギに ^{125}I 標識ベバシズマブを単回静脈内投与したところ、投与 48 時間後の尿中に未変化体は検出されなかった [9]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈治癒切除不能な進行・再発の結腸・直腸癌〉

17.1.1 国内第Ⅰ/Ⅱ相試験（JO19380 試験）

未治療の進行・再発結腸・直腸癌患者を対象に、カペシタビン・オキサリプラチン療法（XELOX 療法）と本剤 1 回 7.5mg/kg 併用投与（21 日を 1 サイクルとし、第 1 日目に、他剤投与に先立ち本剤を投与）による第Ⅰ/Ⅱ相試験を実施した。奏効率は 71.9%（PR41/57 例）であった。無増悪生存期間の中央値は 336.0 日（95%信頼区間：293－380 日）であった。[5.2、7.1、7.4、7.5 参照]

副作用発現率は、XELOX 療法＋本剤群で 100%（58/58 例）であった。主な副作用は、末梢性感覚ニューロパシー 93.1%（54/58 例）、食欲不振 89.7%（52/58 例）、疲労 82.8%（48/58 例）、手掌・足底発赤知覚不全症候群 77.6%（45/58 例）、悪心 74.1%（43/58 例）であった [10]。

17.1.2 国内安全性確認試験（JO18158 試験）

進行・再発結腸・直腸癌を対象に、オキサリプラチン・フルオロウラシル・レボホリナートカルシウム療法（FOLFOX 4 療法）と本剤の併用投与による安全性確認試験を、未治療例注 1) には本剤 5mg/kg、既治療例注 2) には 10mg/kg の用量（14 日を 1 サイクルとし、第 1 日目に、他剤投与に先立ち本剤を投与）により実施した。奏効率は未治療例 79.4%（PR27/34 例）で、既治療例で 47.8%（PR11/23 例）で、全例で SD 以上であった（主治医評価）。[5.2、7.1、7.4、7.5 参照]

注 1）未治療例：初発進行病巣又は再発巣（術後補助療法終了後 6 カ月以上経過して確認されたもの）に対する化学療法を受けていない患者

注 2）既治療例：先行化学療法において病勢進行・再発の認められた患者

副作用発現率は、本剤 5mg/kg 群で 100%（38/38 例）、本剤 10mg/kg 群で 100%（26/26 例）であった。主な副作用は、本剤 5mg/kg 群で食欲不振 97.4%（37/38 例）、好中球数減少 92.1%（35/38 例）、悪心 86.8%（33/38 例）、白血球数減少 78.9%（30/38 例）、下痢 73.7%（28/38 例）であり、本剤 10mg/kg 群で白血球数減少 100%（26/26 例）、好中球数減少 96.2%（25/26 例）、食欲不振 88.5%（23/26

Confidential - 秘

Confidential - 秘

例）、悪心 84.6%（22/26 例）、血小板数減少 80.8%（21/26 例）であった[11]。

17.1.3 国内第Ⅰ相試験（J018157 試験）

既治療又は未治療の進行・再発結腸・直腸癌患者 18 例を対象としたフルオロウラシル・レボホリナートカルシウム療法（5-FU/*l*-LV 療法）と本剤の併用投与（14 日を 1 サイクルとし、第 1 日目に、他剤投与終了直後に本剤を投与）による第Ⅰ相試験を実施した。奏効率は 16.7%（PR3/18 例）で、5mg/kg では 6 例全例が SD、10mg/kg では 6 例中 2 例が PR、4 例が SD であった。［5.2、7.1、7.4、7.5 参照］

副作用発現率は、5-FU/*l*-LV 療法＋本剤 5mg/kg 群で 100%（6/6 例）、5-FU/*l*-LV 療法＋本剤 10mg/kg 群で 100%（6/6 例）であった。主な副作用は、5-FU/*l*-LV 療法＋本剤 5mg/kg 群で好中球数減少 66.7%（4/6 例）、白血球数減少 66.7%（4/6 例）、血小板数減少 66.7%（4/6 例）、口内炎 66.7%（4/6 例）であり、5-FU/*l*-LV 療法＋本剤 10mg/kg 群で食欲不振 83.3%（5/6 例）、悪心 66.7%（4/6 例）、鼻出血 66.7%（4/6 例）、高血圧 66.7%（4/6 例）であった[12]。

17.1.4 海外第Ⅲ相無作為化比較試験（NO16966 試験）

未治療の転移性結腸・直腸癌患者において、オキサリプラチン・フルオロウラシル・ホリナートカルシウム療法（FOLFOX 4 療法）又は XELOX 療法に本剤又はプラセボを投与する 2×2 要因の二重盲検比較試験を実施した。本剤の用量は、FOLFOX 4 療法との併用では 5mg/kg（14 日を 1 サイクルとし、第 1 日目に他剤投与に先立ち本剤を投与）、XELOX 療法との併用では 7.5mg/kg（21 日を 1 サイクルとし、第 1 日目に他剤投与に先立ち本剤を投与）とした。その結果、主要解析において、本剤併用群ではこれらの FOLFOX 4 療法又は XELOX 療法の化学療法のみを受けた場合に比べ、有意な無増悪生存期間の延長が認められた。副次的解析の FOLFOX 4 療法＋本剤群と FOLFOX 4 療法＋プラセボ群の比較では有意な差は認められなかったが、XELOX 療法＋本剤群と XELOX 療法＋プラセボ群の比較では有意な無増悪生存期間の延長が認められた。また、副次的評価項目である生存期間については、化学療法に本剤を併用することにより延長傾向が認められた。［5.2、7.1、7.4、7.5 参照］

NO16966 試験の有効性（優越性検定）に関する成績

投与群	無増悪生存期間[注3]		生存期間[注4]	
	中央値（月）	ハザード比	中央値（月）	ハザード比
化学療法[注5]＋プラセボ群（n＝701）	8.02	0.83 P＝0.0023	19.91	0.89 P＝0.0769
化学療法[注5]＋アバスチン群（n＝699）	9.36		21.22	
XELOX 療法＋プラセボ群（n＝350）	7.39	0.77 P＝0.0026	19.19	0.84 P＝0.0698
XELOX 療法＋アバスチン群（n＝350）	9.26		21.36	
FOLFOX 4 療法＋プラセボ群（n＝351）	8.57	0.89 P＝0.1871	20.34	0.94 P＝0.4937
FOLFOX 4 療法＋アバスチン群（n＝349）	9.40		21.16	

注 3）カットオフ日：2006 年 1 月 31 日、主治医評価による無増悪生存期間

注 4）カットオフ日：2007 年 1 月 31 日

注 5）化学療法：FOLFOX 4 療法又は XELOX 療法

副作用発現率は、FOLFOX 4 療法＋本剤群で 98.2%（335/341 例）、XELOX 療法＋本剤群で 98.9%（349/353 例）であった。主な副作用は、FOLFOX 4 療法＋本剤群で悪心 62%（213/341 例）、下痢 60%（205/341 例）、好中球減少症 55%（188/341 例）、口内炎 40%（137/341 例）、錯感覚 39%（133/341 例）、嘔吐 37%（127/341 例）、疲労 37%（127/341 例）、鼻出血 29%（99/341 例）、無力症 26%（90/341 例）、食欲不振 26%（88/341 例）であり、XELOX 療法＋本剤群で悪心 64%（226/353 例）、下痢 62%（220/353 例）、嘔吐 44%（157/353 例）、手掌・足底発赤知覚不全症候群 39%（139/353 例）、錯感覚 37%（131/353 例）、疲労 36%（127/353 例）、口内炎 29%（101/353 例）、食欲不振 28%（100/353 例）、無力症 21%（73/353 例）、末梢性ニューロパシー20%（69/353 例）、好中球減少症 20%（69/353 例）であった[13]。

17.1.5 海外第Ⅲ相無作為化比較試験（E3200 試験）

イリノテカン塩酸塩水和物及びフルオロウラシルの治療が無効となった進行又は転移性の結腸・直腸癌患者を対象に、FOLFOX 4 療法群を対照とし、FOLFOX 4 療法に本剤 10mg/kg（14 日を 1 サイクルとし、第 1 日目に他剤に先立ち本剤を投与）を併用したときの有効性を検討した。その結果、本剤併用群においては、FOLFOX 4 療法群に比べ有意な生存期間の延長が認められた。また、副次的評価項目についても、無増悪生存期間の延長と高い奏効率が認められた。［5.2、7.1、7.4、7.5 参照］

E3200 試験の有効性に関する成績

投与群	奏効率		無増悪生存期間		生存期間	
	%（有効例）	P 値	中央値（月）	ハザード比	中央値（月）	ハザード比
FOLFOX 4 療法群（n＝292）	8.6（25）	P＜0.0001	4.5	0.518 P＜0.0001	10.8	0.751 P＝0.0012
FOLFOX 4 療法＋アバスチン群（n＝293）	22.2（65）		7.5		13.0	

Grade3 以上（血液毒性については Grade4 以上）の副作用発現率は、FOLFOX 4 療法＋本剤群で 76.3%（219/287 例）であった。FOLFOX 4 療法群との発現率の差が 2%以上であった主な副作用は、疲労 18.5%（53/287 例）、下痢 17.8%（51/287 例）、神経障害－感覚性 16.4%（47/287 例）、悪心 10.8%（31/287 例）、嘔吐 10.1%（29/287 例）、脱水 8.7%（25/287 例）、高血圧 6.3%（18/287 例）、腹痛 5.9%（17/287 例）、呼吸困難 5.9%（17/287 例）、神経障害－その他 5.2%（15/287 例）であった[14]。

17.1.6 海外第Ⅲ相二重盲検無作為化比較試験（AVF2107g 試験）

Confidential - 秘

Confidential - 秘

未治療の転移性結腸・直腸癌患者を対象に、イリノテカン塩酸塩水和物・フルオロウラシル・ホリナートカルシウム療法（IFL 療法）を対照群とし、IFL 療法に本剤 5mg/kg（14 日を 1 サイクルとし、第 1 日目に他剤投与終了後に本剤を投与）又はプラセボを併用投与した。その結果、本剤併用群では IFL 療法単独に比べ有意な生存期間及び無増悪生存期間の延長が認められた[15]。［5.2、7.1、7.4、7.5 参照］

AVF2107g 試験の有効性に関する成績

投与群	無増悪生存期間		生存期間	
	中央値（月）	ハザード比	中央値（月）	ハザード比
IFL 療法＋プラセボ群（n＝411）	6.28	0.577 P＜0.0001	15.80	0.714 P＜0.0001
IFL 療法＋アバスチン群（n＝402）	10.58		20.37	

有害事象発現率は、IFL 療法＋本剤群で 96.7%（379/392 例）であった。主な有害事象は、下痢 74.7%（293/392 例）、白血球減少症 44.4%（174/392 例）、無力症 32.4%（127/392 例）、悪心 29.8%（117/392 例）、蛋白尿 28.8%（113/392 例）、腹痛 26.5%（104/392 例）、高血圧 24.5%（96/392 例）、嘔吐 21.7%（85/392 例）、疼痛 19.4%（76/392 例）、食欲不振 15.8%（62/392 例）であった[16]。

17.1.7 海外第Ⅱ相二重盲検無作為化比較試験（AVF2192g 試験）

イリノテカン塩酸塩水和物の治療に不適と考えられる未治療の転移性結腸・直腸癌患者を対象に、フルオロウラシル・ホリナートカルシウム療法（5-FU/LV 療法）を対照群とし、5-FU/LV 療法に本剤 5mg/kg を併用投与（14 日を 1 サイクルとし、第 1 日目に他剤投与終了後に本剤を投与）したときの有効性を検討した。その結果、本剤併用群では、5-FU/LV 療法単独に比べ有意な無増悪生存期間の延長が認められた[17]。［5.2、7.1、7.4、7.5 参照］

AVF2192g 試験の有効性に関する成績

投与群	無増悪生存期間		生存期間	
	中央値（月）	ハザード比	中央値（月）	ハザード比
5-FU/LV 療法＋プラセボ群（n＝105）	5.52	0.496 P＝0.0002	13.24	0.766 P＝0.0942
5-FU/LV 療法＋アバスチン群（n＝104）	9.17		16.56	

有害事象発現率は、5-FU/LV 療法＋本剤群で 100%（100/100 例）であった。主な有害事象は、下痢 84.0%（84/100 例）、無力症 76.0%（76/100 例）、悪心 65.0%（65/100 例）、腹痛 47.0%（47/100 例）、食欲不振 43.0%（43/100 例）、嘔吐 40.0%（40/100 例）、蛋白尿 38.0%（38/100 例）、疼痛 33.0%（33/100 例）、高血圧 32.0%（32/100 例）、便秘 26.0%（26/100 例）、貧血 26.0%（26/100 例）であった[18]。

未治療の転移性結腸・直腸癌を対象とした 5-FU/LV 療法に本剤を併用した、上記試験を含む 3 試験の併合解析が行われ、本剤併用群において、対照群に比し生存期間、無増悪生存期間に有意な延長が認められたとの報告がある[19]。

〈扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌〉

17.1.8 国内第Ⅱ相試験（J019907 試験）

未治療の扁平上皮癌を除く進行・再発の非小細胞肺癌患者を対象に、カルボプラチン・パクリタキセル療法（CP 療法）を対照群とし、CP 療法に本剤 15mg/kg を併用（21 日を 1 サイクルとし、第 1 日目に、他剤投与終了後に本剤を投与）した第Ⅱ相試験を実施した。CP 療法は両群とも 6 サイクルまでとし、本剤の投与は CP 療法の中止又は終了後も同一用法・用量で病勢進行まで継続した。その結果、本剤併用群では、CP 療法に比べ有意な無増悪生存期間の延長及び奏効率の改善が認められた。［5.2、7.1、7.6 参照］

J019907 試験の有効性に関する成績

投与群	無増悪生存期間		奏効率	
	中央値（月）	ハザード比	%	P 値
CP 療法単独群（n＝58）	5.9	0.61 P＝0.0090	31.0	P＝0.0013
CP 療法＋アバスチン群（n＝117）	6.9		60.7	

副作用発現率は、CP 療法＋本剤群で 100%（125/125 例）であった。主な副作用は、好中球数減少 96.8%（121/125 例）、脱毛症 95.2%（119/125 例）、白血球数減少 94.4%（118/125 例）、末梢性ニューロパシー88.0%（110/125 例）、ヘモグロビン減少 84.0%（105/125 例）であった[20]。

17.1.9 海外第Ⅱ/Ⅲ相無作為化比較試験（E4599 試験）

未治療の扁平上皮癌を除く進行・再発の非小細胞肺癌患者を対象に、CP 療法を対照群とし、CP 療法に本剤 15mg/kg を併用（21 日を 1 サイクルとし、第 1 日目に他剤投与終了後に本剤を投与）したときの有効性を検討した。CP 療法はいずれの群でも 6 サイクルまでとし、本剤の投与は CP 療法の中止又は終了後も同一用法・用量で病勢進行まで継続した。その結果、本剤併用群では、CP 療法に比べ有意な生存期間の延長が認められた[21]。［5.2、7.1、7.6 参照］

E4599 試験の有効性に関する成績

投与群	無増悪生存期間		生存期間	
	中央値（月）	ハザード比	中央値（月）	ハザード比
CP 療法単独群（n＝433）	4.5	0.66 P＜0.001	10.3	0.79 P＝0.003
CP 療法＋アバスチン 15mg/kg 群（n＝417）	6.2		12.3	

Grade3 以上の副作用発現率は、本剤 15mg/kg＋CP 療法群で 69.1%（295/427 例）であった。主な Grade3 以上の副作用は、好中球数減少 25.8%（110/427 例）、疲労 14.5%（62/427 例）、呼吸困難 9.6%（41/427 例）、末梢性感覚ニューロパシー9.1%（39/427 例）、高血圧 6.3%（27/427 例）、感染 5.4%（23/427 例）、悪心 4.9%（21/427 例）、食欲不振 4.9%（21/427 例）、脱水 4.7%（20/427 例）、嘔吐 4.4%（19/427 例）であった[22]。

Confidential - 秘

Confidential - 秘

17.1.10 海外第Ⅲ相二重盲検無作為化比較試験（B017704 試験）

未治療の扁平上皮癌を除く進行・再発の非小細胞肺癌患者を対象に、シスプラチン・ゲムシタビン塩酸塩療法（GC 療法、ゲムシタビン塩酸塩は国内未承認用法・用量を使用）を対照群とし、GC 療法に本剤 7.5mg/kg 注6)（未承認）又は 15mg/kg を併用投与（21 日を 1 サイクルとし、第 1 日目に他剤投与終了後に本剤を投与）したときの有効性を検討した。GC 療法はいずれの群でも 6 サイクルまでとし、本剤の投与は GC 療法の中止又は終了後も同一用法・用量で病勢進行まで継続した。その結果、本剤 7.5mg/kg 及び 15mg/kg 併用群の両群で、GC 療法に比べ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た。[5.2、7.1、7.6 参照]

B017704 試験の有効性に関する成績

投与群	無増悪生存期間		生存期間	
	中央値（月）	ハザード比	中央値（月）	ハザード比
GC 療法＋プラセボ群（n＝347）	6.1	0.82 P＝0.0301	13.1	1.03 P＝0.7613
GC 療法＋アバスチン 15mg/kg 群（n＝351）	6.5		13.4	
GC 療法＋アバスチン 7.5mg/kg 群（n＝345）	6.7	0.75 P＝0.0082	13.6	0.93 P＝0.4203

注 6）本剤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に対する承認用量は 1 回 15mg/kg である。

副作用発現率は、本剤 7.5mg/kg 注6) ＋GC 療法群で 95.5%（315/330 例）、本剤 15mg/kg＋GC 療法群で 95.4%（314/329 例）であった。主な副作用は、本剤 7.5mg/kg 注6) ＋GC 療法群で悪心 54.8%（181/330 例）、好中球減少症 48.5%（160/330 例）、嘔吐 47.0%（155/330 例）、血小板減少症 37.0%（122/330 例）、貧血 33.3%（110/330 例）、疲労 27.9%（92/330 例）、食欲不振 24.5%（81/330 例）、鼻出血 23.9%（79/330 例）、便秘 20.9%（69/330 例）、高血圧 20.9%（69/330 例）であり、本剤 15mg/kg＋GC 療法群で悪心 55.6%（183/329 例）、好中球減少症 45.9%（151/329 例）、嘔吐 45.3%（149/329 例）、血小板減少症 34.3%（113/329 例）、疲労 30.7%（101/329 例）、貧血 30.4%（100/329 例）、鼻出血 28.9%（95/329 例）、高血圧 28.9%（95/329 例）、食欲不振 27.4%（90/329 例）、脱毛症 21.3%（70/329 例）であった[23]。

17.1.11 海外第Ⅱ相無作為化比較試験（AVF0757g 試験）

未治療の進行・再発の非小細胞肺癌患者を対象に、CP 療法を対照群とし、CP 療法に本剤 7.5mg/kg 注6)（未承認）又は 15mg/kg を併用（21 日を 1 サイクルとし、第 1 日目に他剤投与終了後に本剤を投与）したときの有効性を検討した。CP 療法はいずれの群でも 6 サイクルまでとし、本剤の投与は CP 療法の中止又は終了後も同一用法・用量で病勢進行又は 18 サイクルまで継続した。扁平上皮癌患者を除いて解析した結果、本剤 15mg/kg 併用群では、CP 療法に比べ Time to disease progression（TTP）の有意な延長及び奏効率の改善が認められた。[5.2、7.1、7.6 参照]

AVF0757g 試験の有効性に関する成績

投与群	TTP		奏効率	
	中央値（月）	ハザード比	%	P 値
CP 療法単独群（n＝25）	4.0	—	12.0	—
CP 療法＋アバスチン 15mg/kg 群（n＝32）	7.4	0.41 P＝0.0028	31.3	P＝0.0857
CP 療法＋アバスチン 7.5mg/kg 群（n＝22）	4.3	0.85 P＝0.5963	31.8	P＝0.0976

副作用発現率は、本剤 7.5mg/kg 注6) ＋CP 療法群で 81.8%（18/22 例）、本剤 15mg/kg＋CP 療法群で 90.3%（28/31 例）であった。主な副作用は、本剤 7.5mg/kg 注6) ＋CP 療法群で鼻出血 36.4%（8/22 例）、発疹 31.8%（7/22 例）、疲労 27.3%（6/22 例）、好中球減少症 22.7%（5/22 例）、関節痛 22.7%（5/22 例）、悪心 13.6%（3/22 例）、喀血 13.6%（3/22 例）、下痢 9.1%（2/22 例）、口内炎 9.1%（2/22 例）、呼吸困難 9.1%（2/22 例）、脱毛症 9.1%（2/22 例）であり、本剤 15mg/kg＋CP 療法群で疲労 41.9%（13/31 例）、鼻出血 35.5%（11/31 例）、下痢 29.0%（9/31 例）、関節痛 22.6%（7/31 例）、悪心 19.4%（6/31 例）、口内炎 19.4%（6/31 例）、無力症 19.4%（6/31 例）、脱毛症 19.4%（6/31 例）、好中球減少症 16.1%（5/31 例）、頭痛 16.1%（5/31 例）、発疹 16.1%（5/31 例）であった[24]。

〈手術不能又は再発乳癌〉

17.1.12 国内第Ⅱ相試験（J019901 試験）

HER 2 陰性で転移・再発乳癌に対する化学療法未治療患者を対象に、パクリタキセルと本剤 10mg/kg を併用（28 日を 1 サイクルとし、第 1 日目、8 日目、15 日目にパクリタキセルを、第 1 日目、15 日目に本剤を投与）した第Ⅱ相試験を実施した。有害事象によりいずれかの薬剤を中止した場合、もう一方の薬剤を単剤にて、同一用法・用量で病勢進行まで継続投与可能とした。無増悪生存期間の中央値は 12.9 カ月（95% 信頼区間：11.1-18.2 カ月）、奏効率は 73.5%（CR 5/117 例、PR 81/117 例）であった[25]。[5.5、7.1、7.7 参照]

副作用発現率は、本剤 10mg/kg＋パクリタキセルで 100%（120/120 例）であった。主な副作用は、脱毛症 98.3%（118/120 例）、白血球数減少 85.0%（102/120 例）、好中球数減少 75.8%（91/120 例）、末梢性ニューロパシー 75.0%（90/120 例）、鼻出血 70.8%（85/120 例）、尿中蛋白陽性 59.2%（71/120 例）、爪の障害 53.3%（64/120 例）、疲労 50.8%（61/120 例）、食欲不振 50.8%（61/120 例）、味覚異常 48.3%（58/120 例）であった[26]。

17.1.13 海外第Ⅲ相無作為化比較試験（E2100 試験）

HER 2 陰性注7) で転移・再発乳癌に対する化学療法未治療患者を対象に、パクリタキセル（PTX）療法を対照群とし、PTX 療法に本剤 10mg/kg を併用（28 日を 1 サイクルとし、第 1 日目、8 日目、15 日目に PTX を、第 1 日目、15 日目に PTX 投与終了後に本剤を投与）したときの有効

Confidential - 秘

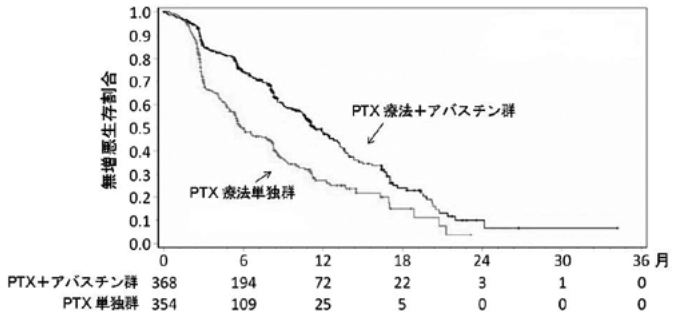
Confidential - 秘

性を検討した。有害事象によりいずれかの薬剤を中止した場合、もう一方の薬剤を単剤にて、同一用法・用量で病勢進行まで継続投与可能とした。第1回中間解析（2005年2月9日データカットオフ）の結果に基づき、試験は早期有効中止された。本剤併用群では、PTX療法単独に比べ主要評価項目である無増悪生存期間（独立判定委員会評価）の有意な延長が認められた。一方、副次的評価項目である生存期間については、PTX療法に本剤を併用することによる有意な延長は認められなかった[27]。［5.4、5.5、7.1、7.7 参照］

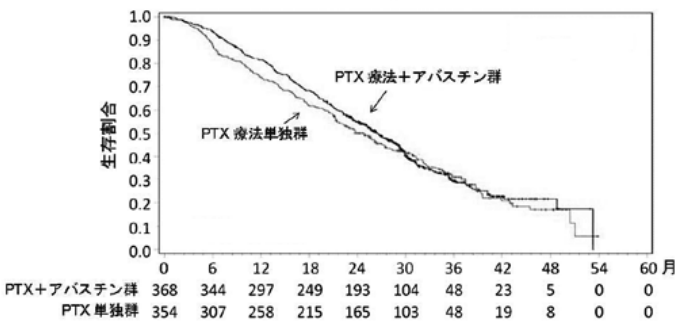
E2100試験の有効性に関する成績

投与群	無増悪生存期間		生存期間	
	中央値（月）	ハザード比	中央値（月）	ハザード比
PTX療法単独群（n＝354）	5.8	0.483 P＜0.0001	24.8	0.869 P＝0.1374
PTX療法＋アバスチン群（n＝368）	11.3		26.5	

E2100試験の無増悪生存期間のKaplan-Meier曲線



E2100試験の生存期間のKaplan-Meier曲線



注7）E2100試験では、トラスツズマブ（遺伝子組換え）既治療のHER 2陽性乳癌患者、及びトラスツズマブ（遺伝子組換え）を含む治療が適応にならないHER 2発現不明乳癌患者も登録可能であった。

Grade3以上（血液毒性についてはGrade4以上）の副作用発現率は、本剤＋PTX療法群で67.8%（246/363例）であった。主な副作用は、末梢性感覚ニューロパシー24.2%（88/363例）、高血圧15.2%（55/363例）、疲労10.5%（38/363例）、感染9.6%（35/363例）、好中球数減少5.5%（20/363例）、筋力低下4.4%（16/363例）、呼吸困難4.4%（16/363例）、下痢3.9%（14/363例）、嘔吐3.9%（14/363例）、悪心3.9%（14/363例）であった[28]。

〈悪性神経膠腫〉

17.1.14 国内第Ⅱ相試験（JO22506試験）

既治療の再発悪性神経膠腫患者（膠芽腫29例、退形成性星細胞腫1例、退形成性乏突起星細胞腫1例）を対象に、本剤10mg/kgの2週間隔投与時の有効性を検討した。再発の膠芽腫患者29例における6カ月無増悪生存率は33.9%、1年生存率は34.5%、奏効率は27.6%であった。無増悪生存期間及び生存期間の中央値はそれぞれ3.3カ月及び10.5カ月であった[29]。［5.6、7.1、7.9 参照］

副作用発現率は、96.8%（30/31例）であった。主な副作用は、尿中蛋白陽性41.9%（13/31例）、高血圧32.3%（10/31例）、下痢22.6%（7/31例）、鼻出血22.6%（7/31例）、ALT増加16.1%（5/31例）、好中球数減少16.1%（5/31例）、白血球数減少16.1%（5/31例）、血中Al-P増加12.9%（4/31例）、便秘9.7%（3/31例）、口内炎9.7%（3/31例）であった[30]。

17.1.15 国際共同第Ⅲ相二重盲検無作為化比較試験（BO21990試験）

初発の膠芽腫患者を対象に、放射線照射とテモゾロミドによる術後補助療法（RT/T療法）に本剤又はプラセボを併用する二重盲検無作為化比較試験を実施した。本剤の用量は、放射線照射とテモゾロミド（1日1回連日投与）の併用期間（6週間）中は、10mg/kg（第1日目から2週間隔、4回投与）とし、テモゾロミドの4週間休薬期間中は本剤も休薬した。その後、テモゾロミドの維持療法期間（28日を1サイクルとし、第1日目から第5日目まで1日1回投与を6サイクルまで実施）中は、本剤10mg/kg（28日を1サイクルとして、第1日目、15日目に投与）を併用投与した。テモゾロミド維持療法終了後は本剤の用量を15mg/kg（21日を1サイクルとし、第1日目に投与）とし、病勢進行まで継続投与した。その結果、本剤併用群では、プラセボ併用群に比べ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た。もう1つの主要評価項目である生存期間には、有意な延長は認められなかった[31]。［5.6、7.1、7.8、7.9 参照］

BO21990試験の有効性に関する成績

投与群	無増悪生存期間		生存期間	
	中央値（月）	ハザード比	中央値（月）	ハザード比
RT/T療法＋プラセボ群（n＝463）注8）	6.2	0.64 P＜0.0001	16.7	0.88 P＝0.0987
RT/T療法＋アバスチン群（n＝458）注9）	10.6		16.8	

注8）日本人患者25例を含む。
注9）日本人患者19例を含む。

副作用発現率は、本剤＋RT/T療法群で92.7%（430/464例）であった。主な副作用は、悪心39.9%（185/464例）、脱毛症35.1%（163/464例）、疲労33.2%（154/464例）、血小板減少症31.3%（145/464例）、高血圧29.3%（136/464例）、嘔吐23.5%（109/464例）、鼻出血16.4%（76/464例）、食欲減退16.2%（75/464例）、便秘15.5%

Confidential - 秘

Confidential - 秘

（72/464 例）、好中球減少症 13.6%（63/464 例）であった[32)]。

〈卵巣癌〉

17.1.16 国際共同第Ⅲ相二重盲検無作為化比較試験（GOG-0218 試験）

化学療法未治療の上皮性卵巣癌、卵管癌、原発性腹膜癌患者を対象に、カルボプラチン・パクリタキセル療法（CP 療法）を対照群（CPP 群[注 10)]）とし、CP 療法に本剤 15mg/kg を併用投与した CPB15 群[注 11)] 及び本剤 15mg/kg を併用・継続投与した CPB15＋群[注 12)] の 3 群による有効性を検討した。CP 療法はいずれの群でも 6 サイクルまでとし、本剤又はプラセボは投与開始から病勢進行又は 21 サイクルまで投与した。その結果、CPB15＋群で、CPP 群に比べ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た。なお、CPB15 群では、有意な無増悪生存期間の延長は認められなかった。[5.8、7.1、7.10、7.11 参照]

注 10）21 日を 1 サイクルとし、CP 療法の 2 サイクル目から第 1 日目に他剤投与終了後にプラセボを投与し、CP 療法の中止又は終了後もプラセボを継続投与した群

注 11）21 日を 1 サイクルとし、CP 療法の 2 サイクル目から第 1 日目に他剤投与終了後に本剤を投与し、CP 療法の中止又は終了後はプラセボを継続投与した群

注 12）21 日を 1 サイクルとし、CP 療法の 2 サイクル目から第 1 日目に他剤投与終了後に本剤を投与し、CP 療法の中止又は終了後も本剤を継続投与した群

GOG-0218 試験の有効性に関する成績

投与群	無増悪生存期間[注 13)]			生存期間[注 14)]		
	イベント数	中央値（月）	ハザード比	イベント数	中央値（月）	ハザード比
CPP 群（n＝625）	375	10.4	—	299	40.6	—
CPB15 群（n＝625）	356	11.8	0.84 片側 P＝0.0118[注 15)]	309	38.8	1.065 片側 P＝0.2197
CPB15＋群（n＝623）	317	14.1	0.71 片側 P＜0.0001[注 15)]	270	43.8	0.879 片側 P＝0.0641

注 13）カットオフ日：2009 年 9 月 29 日

注 14）カットオフ日：2011 年 8 月 26 日

注 15）有意水準 0.0116

日本人部分集団における有効性に関する成績[注 16)]

投与群	無増悪生存期間[注 17)]		
	イベント数	中央値（月）	ハザード比［95%信頼区間］
CPP 群（n＝20）	8	14.5	—
CPB15 群（n＝12）	3	NE[注 18)]	0.44［0.09、2.20］
CPB15＋群（n＝12）	3	NE[注 18)]	0.71［0.14、3.77］

注 16）日本人部分集団のイベント数は少なく、有効性について結論は得られていない。

注 17）カットオフ日：2010 年 2 月 25 日

注 18）NE：not estimable

副作用発現率は、CPB15 群で 99.2%（602/607 例）、CPB15＋群で 99.7%（606/608 例）であった。主な副作用は、CPB15 群で好中球数減少 94.6%（574/607 例）、白血球数減少 94.4%（573/607 例）、ヘモグロビン減少 90.0%（546/607 例）、疲労 69.7%（423/607 例）、血小板数減少 69.2%（420/607 例）、末梢性感覚ニューロパシー63.1%（383/607 例）、脱毛症 49.9%（303/607 例）、悪心 49.4%（300/607 例）、便秘 41.2%（250/607 例）、下痢 31.8%（193/607 例）であり、CPB15＋群で好中球数減少 94.7%（576/608 例）、白血球数減少 94.1%（572/608 例）、ヘモグロビン減少 90.3%（549/608 例）、疲労 77.5%（471/608 例）、血小板数減少 70.4%（428/608 例）、末梢性感覚ニューロパシー63.5%（386/608 例）、悪心 55.1%（335/608 例）、脱毛症 50.3%（306/608 例）、便秘 42.9%（261/608 例）、関節痛 34.2%（208/608 例）であった[33) 注 19)]。

注 19）カットオフ日：2010 年 2 月 5 日

〈進行又は再発の子宮頸癌〉

17.1.17 海外第Ⅲ相無作為化比較試験（GOG-0240 試験）

全身化学療法未治療の手術又は放射線療法による根治療法の対象とならない進行又は再発[注 20)] の子宮頸癌患者を対象に、化学療法（シスプラチン・パクリタキセル療法[注 21)] 又はパクリタキセル・ノギテカン塩酸塩療法[注 22)]）を対照群とし、化学療法に本剤 15mg/kg を併用[注 23)] したときの有効性を検討した。その結果、本剤併用群では、対照群に比べ主要評価項目である生存期間の有意な延長が認められた[34)]。[5.9、7.1、7.12 参照]

GOG-0240 試験の有効性に関する成績

投与群	生存期間	
	中央値（月）	ハザード比
化学療法群（n＝225）	12.9	0.74 片側 P＝0.0066[注 24)]
化学療法＋アバスチン群（n＝227）	16.8	

注 20）FIGO 分類ⅣB 期及び治療抵抗性を含む。

注 21）21 日を 1 サイクルとし、以下の①～③から患者ごとに選択。

①第 1 日目にパクリタキセル 135mg/m^2 を 24 時間かけて静脈内投与し、第 2 日目にシスプラチン 50mg/m^2 を静脈内投与する。

②第 1 日目にパクリタキセル 175mg/m^2 を 3 時間かけて静脈内投与し、シスプラチン 50mg/m^2 を静脈内投与する。

③第 1 日目にパクリタキセル 175mg/m^2 を 3 時間かけて静脈内投与し、第 2 日目にシスプラチン 50mg/m^2 を静脈内投与する。

注 22）21 日を 1 サイクルとし、第 1 日目にパクリタキセル 175mg/m^2 を 3 時間かけて静脈内投与し、第 1～3 日目にノギテカン塩酸塩 0.75mg/m^2 を静脈内投与する。

注 23）シスプラチン・パクリタキセル療法との併用の場合：21 日を 1 サイクルとし、第 1 又は 2 日目に他剤投与終了後に本剤 15mg/kg を静脈内投与する。
パクリタキセル・ノギテカン塩酸塩療法との併用の場合：21 日を 1 サイクルとし、第 1 日目に他剤投与終了後に本剤 15mg/kg を静脈内投与する。

注 24）有意水準 0.0140

Confidential - 秘

Confidential - 秘

副作用発現率は、化学療法＋本剤群で 98.2%（214/218 例）であった。主な副作用は、疲労 79.4%（173/218 例）、脱毛症 61.9%（135/218 例）、悪心 61.9%（135/218 例）、末梢性感覚ニューロパシー60.1%（131/218 例）、便秘 45.9%（100/218 例）、下痢 36.7%（80/218 例）、嘔吐 33.5%（73/218 例）、食欲減退 33.5%（73/218 例）、高血圧 28.9%（63/218 例）、腹痛 27.5%（60/218 例）であった[35]。

〈切除不能な肝細胞癌〉

17.1.18 国際共同第Ⅲ相臨床試験（Y040245（IMbrave150）試験）

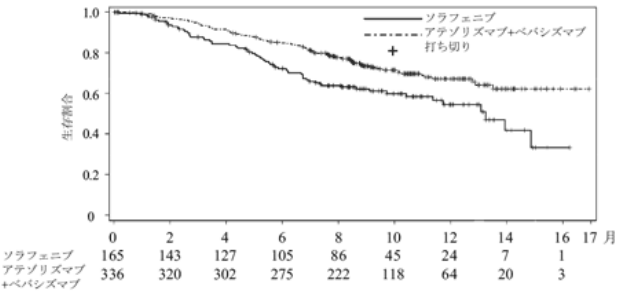
全身化学療法歴のない Child-Pugh 分類 A の切除不能な肝細胞癌患者[注25] 501 例（日本人 61 例を含む）を対象に、本剤 15mg/kg とアテゾリズマブ（遺伝子組換え）（本剤併用群、336 例）の併用投与の有効性及び安全性を、ソラフェニブ（対照群、165 例）と比較する第Ⅲ相ランダム化試験を実施した[注26]。中間解析の結果、501 例（日本人 61 例を含む）の ITT 集団において、本剤併用群で対照群と比較して、主要評価項目の一つである全生存期間の有意な延長が認められ（ハザード比［95%信頼区間］0.58［0.42，0.79］、P=0.0006［層別 log-rank 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。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］）。［5.11、7.1 参照］

本剤とアテゾリズマブ（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[36]。

注 25）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 26）本剤併用群では本剤 15mg/kg 及びアテゾリズマブ（遺伝子組換え）1200mg 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。

Y040245（IMbrave150）試験の全生存期間の Kaplan-Meier 曲線（ITT 集団）



〈神経線維腫症 2 型〉

17.1.19 国内第Ⅱ相試験（FMU2019-01-NF2 試験）（jRCT2080224914）

前庭神経鞘腫を有する神経線維腫症 2 型患者 62 例を対象に、本剤 5mg/kg の 2 週間間隔投与の有効性、安全性をプラセボと比較する第Ⅱ相無作為化比較試験を実施した。初期治療期間は 48 週間で、前半 22 週時までは本剤 5mg/kg 又はプラセボを 2 週間間隔で投与し、24 週以降 46 週時までは全例に本剤 5mg/kg を 2 週間間隔で投与した。初期治療期完了後（治験薬投与開始 48 週時）からは経過観察期間（治験薬投与開始 96 週時まで）であり、初期治療期完了後に最高語音明瞭度の評価に基づきレスポンダー[注27]と判定され、かつ経過観察期間中に再増悪[注28]したと担当医により判断された場合には、再治療として、本剤 5mg/kg を 2 週間間隔で 6 回投与可能とされた。また、治験薬に不忍容の場合には休薬又は中止することとされた。

主要評価項目である治験薬投与開始 24 週時点の最高語音明瞭度の評価に基づくレスポンダー[注27]の割合は下表のとおりであり、本剤群とプラセボ群の間に統計学的に有意な差は認められなかった。

24 週時点のレスポンダー[注27]の割合

本剤（N=31）例数（割合（%））［95%信頼区間］	プラセボ（N=31）例数（割合（%））［95%信頼区間］	群間差［95%信頼区間］	P 値[注29]
5（16.1）［5.5，33.7］	1（3.2）［0.1，16.7］	12.9［-1.5，27.3］	0.0858

治験薬投与開始 48 週時点までの最高語音明瞭度及び前庭神経鞘腫の腫瘍体積のベースラインからの変化量の平均値は下表のとおりであった。

48 週時点までのベースラインからの変化量

	最高語音明瞭度（%）の変化量（平均値±標準偏差）		前庭神経鞘腫の腫瘍体積減少率（%）（平均値±標準偏差）	
投与群	本剤	プラセボ[注30]	本剤	プラセボ[注30]
標的病変[注31]数	37	39	36	39
ベースライン値[注32]	46.7±23.1	41.5±26.6	4.4±4.7	5.9±5.9
24 週	9.5±16.5	-2.1±18.8	14.1±15.2	-7.0±12.8
36 週	9.1±18.6	1.7±17.5	14.3±19.8	6.8±19.2

Confidential - 秘

Confidential - 秘

48 週	8.1±19.6	2.6±18.6	14.6±17.0	8.7±19.9

また、経過観察期である治験薬投与開始 96 週時点の最高語音明瞭度及び前庭神経鞘腫の腫瘍体積のベースラインからの変化量の記述統計量は下表のとおりであった。
[5.12、5.13、7.1、7.14 参照]

96 週時点のベースラインからの変化量

	最高語音明瞭度（%）の変化量		前庭神経鞘腫の腫瘍体積減少率（%）	
投与群	本剤	プラセボ 注 30)	本剤	プラセボ 注 30)
標的病変 注 31) 数	13	8	36	39
平均値±標準偏差	-1.4±18.0	-16.5±20.3	6.5±19.6	4.4±25.4
中央値	0.0	-19.0	7.5	4.5
最小値，最大値	-34.0，34.0	-48.0，16.0	-50.6，59.3	-57.8，63.3

注 27）少なくとも標的病変 注 31) の一方において、最高語音明瞭度（%）のベースラインからの変化量が+20%以上、かつ、その値が 50%以上。標的病変 注 31) において最高語音明瞭度のベースラインからの変化量が-20%を超えない。
注 28）最高語音明瞭度（%）の値が治験薬投与開始 48 週時と比較して 20%以上悪化。
注 29）χ^2 検定、有意水準両側 0.05
注 30）24 週以降は本剤を投与した。
注 31）放射線未治療かつ最高語音明瞭度が 80%以下かつ純音聴力検査による平均聴力レベル（4 分法）0～100dB である病変。
注 32）「最高語音明瞭度」での単位は（%）、「前庭神経鞘腫の腫瘍体積」での単位は（cm^3）。

本剤が投与された 61 例において 57.4%(35/61 例)に副作用が認められた。主な副作用（10%以上）は高血圧 18.0%（11/61 例）であった [37]。

18. 薬効薬理

18.1 作用機序

ベバシズマブは、ヒト血管内皮増殖因子（VEGF）に対する遺伝子組換え型ヒト化モノクローナル抗体である。VEGF は、血管内皮細胞の細胞分裂促進・生存を制御するとともに血管透過性の亢進に関与するサイトカインであり、種々の癌細胞及び神経線維腫症 2 型患者の前庭神経鞘腫において発現が亢進している [38)-40)]。ベバシズマブは、ヒト VEGF と特異的に結合することにより、VEGF と血管内皮細胞上に発現している VEGF 受容体との結合を阻害する [41)]。ベバシズマブは VEGF の生物活性を阻止することにより、腫瘍組織での血管新生を抑制し、腫瘍の増殖を阻害する [41),42)]。また、VEGF により亢進した血管透過性を低下させ、腫瘍組織で亢進した間質圧を低減する [42)]。神経線維腫症 2 型患者の前庭神経鞘腫においても、VEGF の生物活性を阻害することにより、腫瘍体積を減少させると考えられる [40)]。

18.2 抗腫瘍効果

ヒト癌細胞株をヌードマウス又はヌードラットに移植し、ベバシズマブ又は親抗体（マウス抗体）である A4.6.1 抗体を投与することにより、大腸癌（COLO205、HM7、LSLiM6）、肺癌（A549）、乳癌（MX-1、MDA-MB-435）、膠芽腫（U-87MG）、卵巣癌（SKOV-3）等広範な癌腫に対し抗腫瘍活性を認めた [43)-47)]。また、ヒト大腸癌（HM7）を用いた実験的癌転移モデルにおいて、肝臓への転移を抑制した [43)]。化学療法あるいは放射線療法にベバシズマブ又は親抗体を併用することにより、抗腫瘍効果の増強作用を示した [43)-47)]。神経線維腫症 2 型患者のシュワン細胞腫由来のヒト HEI193 細胞株をヌードマウスの頭蓋内又は坐骨神経に移植したモデルにおいて、ベバシズマブの腫瘍成長抑制効果が観察された。[48)]

19. 有効成分に関する理化学的知見

一般的名称：ベバシズマブ（遺伝子組換え）
(Bevacizumab (Genetical Recombination))
(JAN)
分子式：軽鎖（1-214 残基）（$C_{1034}H_{1591}N_{273}O_{338}S_6$）
重鎖（1-453 残基）（$C_{2235}H_{3413}N_{585}O_{678}S_{16}$）
分子量：約 149,000
構造式：アミノ酸 214 個の軽鎖 2 分子とアミノ酸 453 個の重鎖 2 分子からなる糖タンパク質

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

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

〈アバスチン点滴静注用 100mg/4mL〉
4mL×1 バイアル
〈アバスチン点滴静注用 400mg/16mL〉
16mL×1 バイアル

23. 主要文献

1) 医療上の必要性の高い未承認薬・適応外薬検討会議公知申請への該当性に係る報告書：ベバシズマブ（遺伝子組換え）（卵巣癌　10mg/kg 2 週間間隔投与追加）
2) The CATT Research Group, et al. N Engl J Med. 2011;364:1897-908.
3) Curtis LH, et al. Arch Ophthalmol. 2010;128:1273-9.
4) Gower EW, et al. ARVO 2011 E-Abstract Poster 6644.
5) 単回投与時の薬物動態（国内第Ⅰ相試験 JO18157）（2007 年 4 月 18 日承認、申請資料概要 2.7.2.2.2.1）
6) 反復投与時の血中濃度（国内第Ⅱ相試験 JO19901）（2011 年 9 月 26 日承認、申請資料概要 2.7.2.2）
7) 反復投与時の血中濃度（国内第Ⅱ相試験 JO19907）（2011 年 9 月 26 日承認、申請資料概要 2.7.2.3）
8) ウサギ分布試験（2007 年 4 月 18 日承認、申請資料概要 2.6.4.4.1）
9) ウサギ排泄試験（2007 年 4 月 18 日承認、申請資料概要 2.6.4.6.1）
10) 社内資料：国内第Ⅰ/Ⅱ相試験（JO19380 試験）
11) 社内資料：国内安全性確認試験（JO18158 試験）

Confidential - 秘

Confidential - 秘

12) 社内資料：国内第Ⅰ相試験（JO18157 試験）
13) 社内資料：海外第Ⅲ相比較試験（NO16966 試験）
14) 海外第Ⅲ相比較試験（E3200 試験）（2007 年 4 月 18 日承認、申請資料概要 2.7.6.7）
15) 海外第Ⅲ相比較試験（AVF2107g 試験）（2007 年 4 月 18 日承認、申請資料概要 2.7.6.4）
16) 社内資料：海外第Ⅲ相比較試験（AVF2107g 試験）
17) 海外第Ⅱ相比較試験（AVF2192g 試験）（2007 年 4 月 18 日承認、申請資料概要 2.7.6.5）
18) 社内資料：海外第Ⅱ相比較試験（AVF2192g 試験）
19) Kabbinavar FF, et al. J Clin Oncol. 2005;23:3706-12.
20) 社内資料：国内第Ⅱ相試験（JO19907 試験）
21) Sandler A, et al. N Engl J Med. 2006;355:2542-50.
22) 社内資料：海外第Ⅱ/Ⅲ相比較試験（E4599 試験）
23) 社内資料：海外第Ⅲ相比較試験（BO17704 試験）
24) 社内資料：海外第Ⅱ相比較試験（AVF0757g 試験）
25) 国内第Ⅱ相試験（JO19901 試験）（2011 年 9 月 26 日承認、申請資料概要 2.7.6.6）
26) 国内第Ⅱ相試験（JO19901 試験）（2011 年 9 月 26 日承認、申請資料概要 2.7.4.2.1.1）
27) 海外第Ⅲ相比較試験（E2100 試験）（2011 年 9 月 26 日承認、申請資料概要 2.7.3.3）
28) 社内資料：海外第Ⅲ相比較試験（E2100 試験）
29) 国内第Ⅱ相試験（JO22506 試験）（2013 年 6 月 14 日承認、申請資料概要 2.7.6.1.3）
30) 国内第Ⅱ相試験（JO22506 試験）（2013 年 6 月 14 日承認、申請資料概要（再発）2.7.4.2.1.1）
31) 社内資料：国際共同第Ⅲ相比較試験（BO21990 試験）
32) 国際共同第Ⅲ相比較試験（BO21990 試験）（2013 年 6 月 14 日承認、申請資料概要（初発）2.7.4.2.1.1）
33) 社内資料：国際共同第Ⅲ相比較試験（GOG-0218 試験）
34) 海外第Ⅲ相比較試験（GOG-0240 試験）（2016 年 5 月 23 日承認、申請資料概要 2.7.6.1.1）
35) 海外第Ⅲ相比較試験（GOG-0240 試験）（2016 年 5 月 23 日承認、申請資料概要 2.7.6.2.1）
36) 社内資料：国際共同第Ⅲ相試験（YO40245 試験）
37) 社内資料：国内第Ⅱ相比較試験（FMU2019-01-NF2 試験）
38) Ferrara N, et al. Nat Med. 2003;9:669-76.
39) Ferrara N, et al. Endocr Rev. 1997;18:4-25.
40) Plotkin SR, et al. N Engl J Med. 2009;361:358-67
41) Presta LG, et al. Cancer Res. 1997;57:4593-9.
42) Willett CG, et al. Nat Med. 2004;10:145-7.
43) Gerber H-P, et al. Cancer Res. 2005;65:671-80.
44) Yanagisawa M, et al. Oncol Rep. 2009;22:241-7.
45) 社内資料：ヒト肺癌 xenograft モデルにおける抗腫瘍効果の検討
46) ヒト乳癌 xenograft モデルにおける抗腫瘍効果の検討（2011 年 9 月 26 日承認、申請資料概要 2.6.2.2.1 及び 2.6.2.5.1）
47) ヒト膠芽腫 xenograft モデルにおける抗腫瘍効果の検討（2013 年 6 月 14 日承認、申請資料概要 2.6.2.2.1 及び 2.6.2.5.1）
48) Wong HK, et al. Cancer Res 2010;70:3483-93.

24. 文献請求先及び問い合わせ先

中外製薬株式会社　メディカルインフォメーション部
〒103-8324　東京都中央区日本橋室町 2-1-1
電話：0120-189706
Fax：0120-189705
https://www.chugai-pharm.co.jp/

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

®登録商標

Confidential - 秘

目次

1.10 毒薬・劇薬等の指定審査資料のまとめ 2

1.10 毒薬・劇薬等の指定審査資料のまとめ

（現　行）

<table>
<tr><td>化学名・別名</td><td>マウス抗ヒト血管内皮増殖因子モノクローナル抗体の相補性決定部及びヒトIgG1に由来するフレームワーク部と定常部からなるヒト化モノクローナル抗体をコードするcDNAの発現により，チャイニーズハムスター卵巣細胞で産生される214個のアミノ酸残基（$C_{1034}H_{1591}N_{273}O_{338}S_6$；分子量：23446.71）の軽鎖2分子と453個のアミノ酸残基（$C_{2235}H_{3413}N_{585}O_{678}S_{16}$；分子量：49838.57：C末端のリジン1残基が欠損しているものを含む）の重鎖2分子からなる糖タンパク質（分子量：約149,000）。</td></tr>
<tr><td>構造式</td><td>アミノ酸配列は別紙のとおり</td></tr>
<tr><td>効能・効果</td><td>治癒切除不能な進行・再発の結腸・直腸癌
扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌
手術不能又は再発乳癌
悪性神経膠腫
卵巣癌
進行又は再発の子宮頸癌
切除不能な肝細胞癌</td></tr>
<tr><td>用法・用量</td><td>
<table>
<tr><th>効能・効果</th><th>用法・用量</th></tr>
<tr><td rowspan="2">治癒切除不能な進行・再発の結腸・直腸癌</td><td>他の抗悪性腫瘍剤との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回5mg/kg（体重）又は10mg/kg（体重）を点滴静脈内注射する。投与間隔は2週間以上とする。</td></tr>
<tr><td>他の抗悪性腫瘍剤との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回7.5mg/kg（体重）を点滴静脈内注射する。投与間隔は3週間以上とする。</td></tr>
<tr><td>扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌</td><td rowspan="2">他の抗悪性腫瘍剤との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回15mg/kg（体重）を点滴静脈内注射する。投与間隔は3週間以上とする。</td></tr>
<tr><td>進行又は再発の子宮頸癌</td></tr>
<tr><td>手術不能又は再発乳癌</td><td>パクリタキセルとの併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回10mg/kg（体重）を点滴静脈内注射する。投与間隔は2週間以上とする。</td></tr>
<tr><td>悪性神経膠腫</td><td>通常，成人にはベバシズマブ（遺伝子組換え）として1回10mg/kg（体重）を2週間間隔又は1回15mg/kg（体重）を3週間間隔で点滴静脈内注射する。なお，患者の状態により投与間隔は適宜延長すること。</td></tr>
<tr><td>卵巣癌</td><td>他の抗悪性腫瘍剤との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回10mg/kg（体重）を2週間間隔又は1回15mg/kg（体重）を3週間間隔で点滴静脈内注射する。</td></tr>
</table>
</td></tr>
</table>

	なお，患者の状態により投与間隔は適宜延長すること。
切除不能な肝細胞癌	アテゾリズマブ（遺伝子組換え）との併用において，通常，成人にはベバシズマブ（遺伝子組換え）として1回15mg/kg（体重）を点滴静脈内注射する。投与間隔は3週間以上とする。

劇薬等の指定	生物由来製品*，劇薬，処方箋医薬品
市販名及び有効成分・分量	製剤：アバスチン点滴静注用100mg/4mL アバスチン点滴静注用400mg/16mL （1バイアル中ベバシズマブ（遺伝子組換え）として100mg 又は400mg含有）

毒性

【亜急性】

動物種	投与期間	投与経路	投与量(mg/kg)	無毒性量(mg/kg)	主な所見
サル	4週間	静脈内	2,10,50(週2回)	2	・10mg/kg 以上雄で骨端軟骨の異形成
サル	13週間	静脈内	2,10,50(週2回)	<2	・2mg/kg 以上雄，10mg/kg 以上雌で骨端軟骨異形成 ・10mg/kg 以上雌で卵巣・子宮重量低下，黄体数減少あるいは欠失

【慢性】

動物種	投与期間	投与経路	投与量(mg/kg)	無毒性量(mg/kg)	主な所見
サル	26週間	静脈内	2,10,50(週1回，10mg/kgのみ週1回及び2回投与の2群を設置)	<2	・2mg/kg 以上雌雄で骨端軟骨異形成 ・10mg/kg 以上（投与頻度に関わらず）雌で月経周期の異常，子宮重量減少，子宮内膜増殖の減少，10mg/kg（週2回）及び50mg/kg で卵胞成熟阻害，黄体欠失

副作用

副作用・臨床検査値異常発現率

〈卵巣癌〉

卵巣癌に対する国際共同臨床試験の安全性評価対象例（国内症例）24例中24例（100%）に407件の副作用が認められた。

副作用の種類	例数(%)
ヘモグロビン減少	24(100)
好中球数減少	24(100)
白血球数減少	24(100)
血小板数減少	23(95.8)
悪心	22(91.7)

等

〈悪性神経膠腫〉

初発膠芽腫を対象にした国際共同臨床試験の国内症例の安全性評価症例19例全例（100%）に178件の副作用が認められた。

副作用の種類	例数(%)
脱毛症	19(100.0)
便秘	14(73.7)
食欲減退	12(63.2)
悪心	11(57.9)

等

再発悪性神経膠腫を対象にした国内臨床試験における安全性評価対象例31例中30例（96.8%）に129件の副作用が認められた。

副作用の種類	例数(%)
尿中蛋白陽性	13(41.9)
高血圧	10(32.3)
下痢	7(22.6)
鼻出血	7(22.6)

等

〈手術不能又は再発乳癌〉

国内臨床試験における安全性評価対象例120例に認められた副作用は，120例（100.0%）2,529件であった。

副作用の種類	例数(%)
脱毛症	118(98.3)
白血球数減少	102(85.0)
好中球数減少	91(75.8)
末梢性ニューロパシー	90(75.0)
鼻出血	85(70.8)

等

〈扁平上皮癌を除く切除不能な進行・再発の非小細胞肺癌〉

国内臨床試験における安全性評価対象例125例中125例（100.0%）2,783件に副作用が認められた。

副作用の種類	例数(%)
好中球減少症	121(96.8)
脱毛症	119(95.2)
白血球数減少	118(94.4)
神経毒性	117(93.6)
ヘモグロビン減少	105(84.0)
関節痛	101(80.8)

等

〈治癒切除不能な進行・再発の結腸・直腸癌〉

国内臨床試験における安全性評価対象例140例及び製造販売後の特定使用成績調査における安全性評価対象例2,696例の計2,814例中1,789例（63.6%）6,738件に副作用が認められた。

副作用の種類	例数(%)
好中球減少症	529(18.8)
白血球数減少	520(18.5)
高血圧	415(14.6)
鼻出血	281(10.0)
食欲不振	277(9.84)

等

〈進行又は再発の子宮頸癌〉

国内臨床試験における安全性評価対象例7例中7例（100.0%）に20件の副作

<table>
<tr><td></td><td>用が認められた。

<table>
<tr><td>副作用の種類</td><td>例数(%)</td></tr>
<tr><td>高血圧</td><td>3(42.9)</td></tr>
<tr><td>倦怠感</td><td>2(28.6)</td></tr>
<tr><td>好中球数減少</td><td>2(28.6)</td></tr>
</table>
等

〈切除不能な肝細胞癌〉
切除不能な肝細胞癌を対象にした国際共同臨床試験の国内症例の安全性評価対象例35例中31例（88.6%）に109件の副作用が認められた。

<table>
<tr><td>副作用の種類</td><td>例数(%)</td></tr>
<tr><td>高血圧</td><td>15(42.9)</td></tr>
<tr><td>発声障害</td><td>10(28.6)</td></tr>
<tr><td>発熱</td><td>6(17.1)</td></tr>
<tr><td>蛋白尿</td><td>5(14.3)</td></tr>
<tr><td>倦怠感</td><td>5(14.3)</td></tr>
</table>
等</td></tr>
<tr><td>会社</td><td>中外製薬株式会社　製剤：輸入</td></tr>
</table>

* 平成19年4月18日付厚生労働省告示第163号により指定された。

（追加）

<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>神経線維腫症2型</td></tr>
<tr><td>用法・用量</td><td>
<table>
<tr><th>効能・効果</th><th>用法・用量</th></tr>
<tr><td>神経線維腫症2型</td><td>通常，成人にはベバシズマブ（遺伝子組換え）として1回5mg/kg（体重）を2週間間隔で点滴静脈内注射する。</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>副作用・臨床検査値異常発現率
〈神経線維腫症2型〉
神経線維腫症2型を対象にした国内臨床試験における安全性評価対象例61例中35例（57.4%）に87件の副作用が認められた。
<table>
<tr><th>副作用の種類</th><th>例数(%)</th></tr>
<tr><td>高血圧</td><td>11(18.0)</td></tr>
<tr><td>蛋白尿</td><td>6(9.84)</td></tr>
<tr><td>鼻出血</td><td>6(9.84)</td></tr>
<tr><td>アスパラギン酸アミノトランスフェラーゼ増加</td><td>4(6.56)</td></tr>
<tr><td>アラニンアミノトランスフェラーゼ増加</td><td>4(6.56)</td></tr>
<tr><td>痔出血</td><td>4(6.56)</td></tr>
</table>
等</td></tr>
<tr><td>会　　社</td><td></td></tr>
</table>

別紙

ベバシズマブ（遺伝子組換え）のアミノ酸配列

```
  1 Asp-Ile-Gln-Met-Thr-Gln-Ser-Pro-Ser-Ser-Leu-Ser-Ala-Ser-Val-Gly-Asp-Arg-Val-Thr-Ile-Thr-Cys-Ser-Ala-
 26 Ser-Gln-Asp-Ile-Ser-Asn-Tyr-Leu-Asn-Trp-Tyr-Gln-Gln-Lys-Pro-Gly-Lys-Ala-Pro-Lys-Val-Leu-Ile-Tyr-Phe-
 51 Thr-Ser-Ser-Leu-His-Ser-Gly-Val-Pro-Ser-Arg-Phe-Ser-Gly-Ser-Gly-Ser-Gly-Thr-Asp-Phe-Thr-Leu-Thr-Ile-
 76 Ser-Ser-Leu-Gln-Pro-Glu-Asp-Phe-Ala-Thr-Tyr-Tyr-Cys-Gln-Gln-Tyr-Ser-Thr-Val-Pro-Trp-Thr-Phe-Gly-Gln-
101 Gly-Thr-Lys-Val-Glu-Ile-Lys-Arg-Thr-Val-Ala-Ala-Pro-Ser-Val-Phe-Ile-Phe-Pro-Pro-Ser-Asp-Glu-Gln-Leu-
126 Lys-Ser-Gly-Thr-Ala-Ser-Val-Val-Cys-Leu-Leu-Asn-Asn-Phe-Tyr-Pro-Arg-Glu-Ala-Lys-Val-Gln-Trp-Lys-Val-
151 Asp-Asn-Ala-Leu-Gln-Ser-Gly-Asn-Ser-Gln-Glu-Ser-Val-Thr-Glu-Gln-Asp-Ser-Lys-Asp-Ser-Thr-Tyr-Ser-Leu-
176 Ser-Ser-Thr-Leu-Thr-Leu-Ser-Lys-Ala-Asp-Tyr-Glu-Lys-His-Lys-Val-Tyr-Ala-Cys-Glu-Val-Thr-His-Gln-Gly-
201 Leu-Ser-Ser-Pro-Val-Thr-Lys-Ser-Phe-Asn-Arg-Gly-Glu-Cys
```

軽鎖

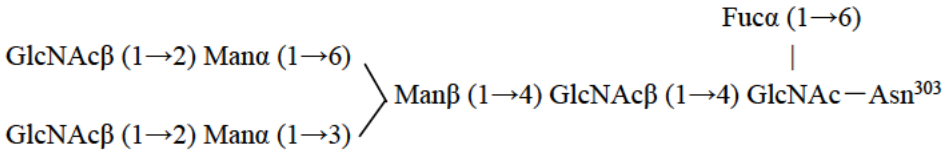
```
  1 Glu-Val-Gln-Leu-Val-Glu-Ser-Gly-Gly-Gly-Leu-Val-Gln-Pro-Gly-Gly-Ser-Leu-Arg-Leu-Ser-Cys-Ala-Ala-Ser-
 26 Gly-Tyr-Thr-Phe-Thr-Asn-Tyr-Gly-Met-Asn-Trp-Val-Arg-Gln-Ala-Pro-Gly-Lys-Gly-Leu-Glu-Trp-Val-Gly-Trp-
 51 Ile-Asn-Thr-Tyr-Thr-Gly-Glu-Pro-Thr-Tyr-Ala-Ala-Asp-Phe-Lys-Arg-Arg-Phe-Thr-Phe-Ser-Leu-Asp-Thr-Ser-
 76 Lys-Ser-Thr-Ala-Tyr-Leu-Gln-Met-Asn-Ser-Leu-Arg-Ala-Glu-Asp-Thr-Ala-Val-Tyr-Tyr-Cys-Ala-Lys-Tyr-Pro-
101 His-Tyr-Tyr-Gly-Ser-Ser-His-Trp-Tyr-Phe-Asp-Val-Trp-Gly-Gln-Gly-Thr-Leu-Val-Thr-Val-Ser-Ser-Ala-Ser-
126 Thr-Lys-Gly-Pro-Ser-Val-Phe-Pro-Leu-Ala-Pro-Ser-Ser-Lys-Ser-Thr-Ser-Gly-Gly-Thr-Ala-Ala-Leu-Gly-Cys-
151 Leu-Val-Lys-Asp-Tyr-Phe-Pro-Glu-Pro-Val-Thr-Val-Ser-Trp-Asn-Ser-Gly-Ala-Leu-Thr-Ser-Gly-Val-His-Thr-
176 Phe-Pro-Ala-Val-Leu-Gln-Ser-Ser-Gly-Leu-Tyr-Ser-Leu-Ser-Ser-Val-Val-Thr-Val-Pro-Ser-Ser-Ser-Leu-Gly-
201 Thr-Gln-Thr-Tyr-Ile-Cys-Asn-Val-Asn-His-Lys-Pro-Ser-Asn-Thr-Lys-Val-Asp-Lys-Lys-Val-Glu-Pro-Lys-Ser-
226 Cys-Asp-Lys-Thr-His-Thr-Cys*-Pro-Pro-Cys**-Pro-Ala-Pro-Glu-Leu-Leu-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-
251 Pro-Lys-Pro-Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-Val-Val-Asp-Val-Ser-His-Glu-
276 Asp-Pro-Glu-Val-Lys-Phe-Asn-Trp-Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-Glu-Glu-
301 Gln-Tyr-Asn-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-
326 Lsy-Cys-Lys-Val-Ser-Asn-Lys-Ala-Leu-Pro-Ala-Pro-Ile-Glu-Lys-Thr-Ile-Ser-Lys-Ala-Lys-Gly-Gln-Pro-Arg-
351 Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-Pro-Ser-Arg-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-Leu-Val-
376 Lsy-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-
401 Pro-Pro-Val-Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Lys-Leu-Thr-Val-Asp-Lys-Ser-Arg-Trp-Gln-Gln-
426 Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-Leu-Ser-
451 Pro-Gly-Lys
```

Asn：糖鎖結合部位

*, **：重鎖同士のジスルフィド結合部位

重鎖

主な糖鎖構造



Man：マンノース，Fuc：フコース，GlcNAc：N-アセチルグルコサミン

第4部（モジュール4）：非臨床試験報告書　添付資料一覧

4.3　参考文献

CTD No	著者	表題	掲載誌・その他	引用CTD No
4.3-1	Kim KJ, Li B, Houck K, et al.	The vascular endothelial growth factor proteins:identification of biologically relevant regions by neutralizing monoclonal antibodies.	Growth Factors 1992;7:53-64.	2.4 1) 2.6.1 1)
4.3-2	Presta LG, Chen H, O'Connor SJ, et al.	Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders.	Cancer Res 1997;57:4593-9.	2.4 2) 2.6.1 2)
4.3-3	Ferrara N, Houck K, Jakeman L, et al.	Molecular and biological properties of the vascular endothelial growth factor family of proteins.	Endocr Rev 1992;13:18-32.	2.4 3) 2.6.1 3)
4.3-4	Ferrara N, Davis-Smyth T.	The biology of vascular endothelial growth factor.	Endocr Rev 1997;18:4-25.	2.4 4) 2.6.1 4)
4.3-5	Ferrara N.	Vascular endothelial growth factor: basic science and clinical progress.	Endocr Rev 2004;25:581-611.	2.4 5) 2.6.1 5)
4.3-6	Hoeben A, Landuyt B, Highley MS, et al.	Vascular endothelial growth factor and angiogenesis.	Pharmcol Rev 2004;56:549-80.	2.4 6) 2.6.1 6)
4.3-7	Gerber H-P, Ferrara N.	Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies.	Cancer Res 2005;65:671-80.	2.4 7)
4.3-8	Wong HK, Lahdenranta J, Kamoun WS, et al.	Anti-vascular endothelial growth factor therapies as a novel therapeutic approach to treating neurofibromatosis-related tumors.	Cancer Res 2010;70:3483-93.	2.4 8) 2.6.1 11) 2.6.2 4)
4.3-9	Gao X, Zhao Y, Stemmer-Rachamimov AO, et al.	Anti-VEGF treatment improves neurological function and augments radiation response in NF2 schwannoma model.	Proc Natl Acad Sci USA 2015;112:14676-81.	2.4 9) 2.6.2 5)
4.3-10	Jain RK.	Molecular regulation of vessel maturation.	Nat Med 2003;9:685-93.	2.4 10)
4.3-11	Carmeliet P.	Angiogenesis in health and disease.	Nat Med 2003;9:653-60.	2.4 11)
4.3-12	Willett CG, Boucher Y, di Tomaso E, et al.	Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.	Nat Med 2004;10:145-7.	2.4 12)
4.3-13	Tong RT, Boucher Y, Kozin SV, et al.	Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors.	Cancer Res 2004;64:3731-6.	2.4 13)
4.3-14	Plotkin SR, Stemmer-Rachamimov AO, Barker II FG, et al.	Hearing improvement after bevacizumab in patients with neurofibromatosis type 2.	N Engl J Med. 2009;361:358-67.	2.4 14) 2.6.1 10) 2.6.2 1)
4.3-15	Chaudhry IH, O'Donovan DG, Brenchley PEC, et al.	Vascular endothelial growth factor expression correlates with tumor grade and vascularity in gliomas.	Histopathology 2001;39:409-15.	2.6.1 7)
4.3-16	Schmidt NO, Westphal M, Hagel C, et al.	Levels of vascular endothelial growth factor, hepatocyte growth factor/scatter factor and basic fibroblast growth factor in human gliomas and their relation to angiogenesis.	Int J Cancer 1999;84:10-8.	2.6.1 8)
4.3-17	Yao Y, Kubota T, Sato K, et al.	Prognostic value of vascular endothelial growth factor and its receptors Flt-1 and Flk-1 in astrocytic tumors.	Acta Neurochir (Wien) 2001;143:159-66.	2.6.1 9)
4.3-18	Plotkin SR, Merker VL, Halpin C, et al.	Bevacizumab for progressive vestibular schwannoma in neurofibromatosis type 2: a retrospective review of 31 patients.	Otol Neurotol 2012;33:1046-52.	2.6.2 2)
4.3-19	Morris KA, Golding JF, Axon PR, et al.	Bevacizumab in neurofibromatosis type 2 (NF2) related vestibular schwannomas: a nationally coordinated approach to delivery and prospective evaluation.	Neurooncol Pract 2016;3:281-9.	2.6.2 3)

Confidential - 秘

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

. Confidential - 秘

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
5.3.1　生物薬剤学試験報告書						
5.3.1.1　バイオアベイラビリティ（BA）試験報告書						
該当資料なし						
5.3.1.2　比較BA試験及び生物学的同等性（BE）試験報告書						
該当資料なし						
5.3.1.3　In Vitro-In Vivoの関連を検討した試験報告書						
該当資料なし						
5.3.1.4　生物学的及び理化学的分析法検討報告書						
該当資料なし						
5.3.2　ヒト生体試料を用いた薬物動態関連の試験報告書						
5.3.2.1　血漿蛋白結合試験報告書						
該当資料なし						
5.3.2.2　肝代謝及び薬物相互作用試験報告書						
該当資料なし						
5.3.2.3　他のヒト生体試料を用いた試験報告書						
該当資料なし						

. Confidential - 秘

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
5.3.3　臨床薬物動態（PK）試験報告書						
5.3.3.1　健康被験者におけるPK及び初期忍容性試験報告書						
該当資料なし						
5.3.3.2　患者におけるPK及び初期忍容性試験報告書						
該当資料なし						
5.3.3.3　内因性要因を検討したPK試験報告書						
該当資料なし						
5.3.3.4　外因性要因を検討したPK試験報告書						
該当資料なし						
5.3.3.5　ポピュレーションPK試験報告書						
該当資料なし						
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						

. Confidential - 秘

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
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						
5.3.5.1-1	齋藤 清	神経線維腫症II型に対するベバシズマブの有効性及び安全性を検討する多施設共同二重盲検無作為化比較試験（BeatNF2 trial）総括報告書	2019年10月1日～2022年6月28日	国内	FMU2019-01-NF2	評価
5.3.5.2　非対照試験報告書						
該当資料なし						
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	[redacted]	Integrated Statistical Analysis Report Bevacizumab, NF2	2019年10月1日～2022年6月28	国内	FMU2019-01-NF2	参考
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 1136616	—	国内/海外	—	参考
5.3.7　患者データ一覧表及び症例記録						
5.3.7.1　症例一覧表						
5.3.7.1-1		症例一覧表（FMU2019-01-NF2試験）	2019年10月1日～2022年6月28	国内	FMU2019-01-NF2	評価
5.3.7.2　副作用一覧表						
5.3.7.2-1		副作用一覧表（FMU2019-01-NF2試験）	2019年10月1日～2022年6月28	国内	FMU2019-01-NF2	評価

. Confidential - 秘

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
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（FMU2019-01-NF2試験）	2019年10月1日 ～2022年6月28	国内	FMU2019-01-NF2	評価
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（FMU2019-01-NF2試験）	2019年10月1日 ～2022年6月28	国内	FMU2019-01-NF2	評価
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（FMU2019-01-NF2試験）	2019年10月1日 ～2022年6月28	国内	FMU2019-01-NF2	評価

. Confidential - 秘

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.4　参考文献

CTD No	著者	表題	掲載誌・その他
5.4-1	Dhaenens BAE, Ferner RE, Evans DG, Heimann G, Potratz C, van de Ketterij	Lessons learned from drug trials in neurofibromatosis: A systematic review.	Eur J Med Genet 2021;64:104281.
5.4-2	Evans DG.	Neurofibromatosis type 2 (NF2): a clinical and molecular review.	Orphanet J Rare Dis 2009;4:16.
5.4-3	Blakeley JO, Plotkin SR.	Therapeutic advances for the tumors associated with neurofibromatosis type 1, type 2, and schwannomatosis.	Neuro Oncol 2016;18:624-38.
5.4-4	Mota M, Shevde LA.	Merlin regulates signaling events at the nexus of development and cancer.	Cell Commun Signal 2020;18:63.
5.4-5	Evans DG, Huson SM, Donnai D, Neary W, Blair V, Newton V, Harris R.	A clinical study of type 2 neurofibromatosis.	Q J Med 1992;84:603-18.
5.4-6	Korf BR.	Neurofibromatosis.	Handb Clin Neurol 2013;111:333-40.
5.4-7	Lee TJ, Chopra M, Kim RH, Parkin PC, Barnett-Tapia C.	Incidence and prevalence of neurofibromatosis type 1 and 2: a systematic review and meta-analysis.	Orphanet J Rare Dis 2023;18:292.
5.4-8	Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, et al.	Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service.	Am J Med Genet A 2010;152A:327-32.
5.4-9	Goldbrunner R, Weller M, Regis J, Lund-Johansen M, Stavrinou P, Reuss	EANO guideline on the diagnosis and treatment of vestibular schwannoma.	Neuro Oncol 2020;22:31-45.
5.4-10	National Comprehensive Cancer Network.	NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. Version 5.2024.-M	NCCN Guidelines for Patients
5.4-11	Olson JJ, Kalkanis SN, Ryken TC.	Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Treatment of Adults With Vestibular Schwannomas: Executive Summary.	Neurosurgery 2018;82:129-34.
5.4-12	Blakeley JO, Ye X, Duda DG, Halpin CF, Bergner AL, Muzikansky A, et al.	Efficacy and Biomarker Study of Bevacizumab for Hearing Loss Resulting From Neurofibromatosis Type 2-Associated Vestibular Schwannomas.	J Clin Oncol 2016;34:1669-75.
5.4-13	Plotkin SR, Merker VL, Halpin C, Jennings D, McKenna MJ, Harris GJ, et al.	Bevacizumab for progressive vestibular schwannoma in neurofibromatosis type 2: a retrospective review of 31 patients.	Otol Neurotol 2012;33:1046-52.
5.4-14	Morris KA, Golding JF, Axon PR, Afridi S	Bevacizumab in neurofibromatosis type 2 (NF2) related vestibular schwannomas: a nationally coordinated approach to delivery and prospective evaluation.	Neurooncol Pract 2016;3:281-9.
5.4-15	Douwes JPJ, Hensen EF, Jansen JC, Gel	Bevacizumab Treatment for Patients with NF2-Related Schwannomatosis: A Single Center Experience.	Cancers (Basel) 2024;16:1479.
5.4-16	Fujii M, Ichikawa M, Iwatate K, Bakhit M	Bevacizumab Therapy of Neurofibromatosis Type 2 Associated Vestibular Schwannoma in Japanese Patients.	Neurol Med Chir (Tokyo) 2020;60:75-82.
5.4-17	Plotkin SR, Ardern-Holmes SL, Barker F	Hearing and facial function outcomes for neurofibromatosis 2 clinical trials.	Neurology 2013;81(21 Suppl 1):S25-32.
5.4-18	Huang V, Bergner AL, Halpin C, Merker VL, Sheridan MR, Widemann BC, et al.	Improvement in Patient-reported Hearing After Treatment With Bevacizumab in People With Neurofibromatosis Type 2.	Otol Neurotol 2018;39:632-8.
5.4-19	Koos WT, Day JD, Matula C, Levy DI.	Neurotopographic considerations in the microsurgical treatment of small acoustic neurinomas.	J Neurosurg 1998;88:506-12.

Confidential - 秘

第5部（モジュール5）：臨床試験報告書　添付資料一覧

5.4　参考文献

CTD No	著者	表題	掲載誌・その他
5.4-20	Iwatate K, Yokoo T, Iwatate E, Ichikawa M, Sato T, Fujii M, et al.	Population Characteristics and Progressive Disability in Neurofibromatosis Type 2.	World Neurosurg 2017;106:653-60.
5.4-21	小寺一興.	A-2 語音明瞭度と補聴器の効果と適応.	補聴器フィッティングの考え方　改訂第3版. 東京：診断と治療社；2010年. 4-5ペー
5.4-22	Plotkin SR, Allen J, Dhall G, Campian JL, Clapp DW, Fisher MJ, et al.	Multicenter, prospective, phase II study of maintenance bevacizumab for children and adults with NF2-related schwannomatosis and progressive vestibular schwannoma.	Neuro Oncol 2023;25:1498-506.
5.4-23	Plotkin SR, Messiaen L, Legius E, Pancza P, Avery RA, Blakeley JO, et al.	Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: An international consensus recommendation.	Genet Med 2022;24:1967-77.

Confidential - 秘

提出すべき資料がない項目リスト

セクション	項目	表題
第3部	品質に関する文書	
第4部	非臨床試験報告書	
	4.2.1.1	効力を裏付ける試験
	4.2.1.2	副次的薬理試験
	4.2.1.3	安全性薬理試験
	4.2.1.4	薬力学的薬物相互作用試験
	4.2.2.1	分析法及びバリデーション報告書
	4.2.2.6	薬物動態学的薬物相互作用（非臨床）
	4.2.2.7	その他の薬物動態試験
	4.2.3.1	単回投与毒性試験
	4.2.3.2	反復投与毒性試験
	4.2.3.3	遺伝毒性試験
	4.2.3.4	がん原性試験
	4.2.3.5	生殖発生毒性試験
	4.2.3.6	局所刺激性試験
	4.2.3.7	その他の毒性試験
第5部	臨床試験報告書	
	5.3.1.1	バイオアベイラビリティ（BA）試験報告書
	5.3.1.2	比較BA試験及び生物学的同等性（BE）試験報告書
	5.3.1.3	In Vitro-In Vivoの関連を検討した試験報告書
	5.3.1.4	生物学的及び理化学的分析法検討報告書
	5.3.2.1	血漿蛋白結合試験報告書
	5.3.2.2	肝代謝及び薬物相互作用試験報告書
	5.3.2.3	他のヒト生体試料を用いた試験報告書
	5.3.3.1	健康被験者におけるPK及び初期忍容性試験報告書
	5.3.3.2	患者におけるPK及び初期忍容性試験報告書
	5.3.3.3	内因性要因を検討したPK試験報告書
	5.3.3.4	外因性要因を検討したPK試験報告書
	5.3.3.5	ポピュレーションPK試験報告書
	5.3.4.1	健康被験者におけるPD試験及びPK　PD試験報告書
	5.3.4.2	患者におけるPD試験及びPK　PD試験報告書
	5.3.5.2	非対照試験報告書
	5.3.5.4	その他の試験報告書

Confidential - 秘