Vegzelma®

bevacizumab-adcd

Injection 100mg/vial & 400mg/vial

Monograph

Executive Summary

Vegzelma® (bevacizumab-adcd) is biosimilar to Avastin (bevacizumab). Bevacizumab binds VEGF and prevents the interaction of VEGF with 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.[1]

A comprehensive battery of nonclinical in vitro PD studies has demonstrated similar biological activities of Vegzelma and EU-Avastin.[2] In addition, GLP toxicity studies in vivo have been performed to support clinical trials and further confirmed that Vegzelma and EU-Avastin have similar profiles from both a toxicokinetic and immunogenic perspective.[3]

In two phase I trials including Korean and Japanese subjects, Vegzelma demonstrated pharmacokinetic equivalence and similar safety and immunogenicity to reference bevacizumab.[4,5] Additionally, in a phase III trial in non-squamous non-small cell lung cancer (nsNSCLC) patients, Vegzelma was proven to be highly similar and to have no clinically meaningful differences in efficacy from EU-Avastin.[6]

Indications[1]

Metastatic Colorectal Cancer (mCRC)

- Vegzelma, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with mCRC.
- Vegzelma, 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: Vegzelma is not indicated for adjuvant treatment of colon cancer.

First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Vegzelma, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC.

Recurrent Glioblastoma (GBM)

Vegzelma is indicated for the treatment of recurrent GBM in adults.

Metastatic Renal Cell Carcinoma (mRCC)

Vegzelma, in combination with interferon alfa, is indicated for the treatment of mRCC.

Persistent, Recurrent, or Metastatic Cervical Cancer

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

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

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

Select Important Safety Information

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforations and Fistulae: Serious, and sometimes fatal, gastrointestinal perforation occurred at a higher incidence in patients receiving bevacizumab products vs 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. Serious fistulae ranged from <1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. Avoid Vegzelma 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.

Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

EU, European Union; **GLP,** good laboratory practice; **HCPs,** healthcare professionals; **KDR,** kinase insert domain receptor; **PD,** pharmacodynamics; **VEGF,** vascular endothelial growth factor.

Table of Contents

01 | Introduction to Vegzelma 4

02 | Preparation and Administration 8

03 | Clinical Value 11

04 | Important Safety Information 23

05 | References 25

About This Monograph

This monograph compiles important information including 1) pivotal clinical trial data of Vegzelma; 2) information regarding authorization for use; and 3) links to available resources to assist regulatory authorities and HCPs in planning and implementing Vegzelma treatment against cancer.

This guidebook should not supersede local requirements for sites of care or substitute for the medical judgment of treating HCPs. HCPs should review the full Prescribing Information available at Vegzelma.com.

HCP, healthcare professional.

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Injection 100mg/vial & 400mg/vial

01. Introduction to Vegzelma

About Vegzelma (INN: Bevacizumab)

Vegzelma is biosimilar to Avastin (bevacizumab).[1] Bevacizumab binds to VEGF and prevents the interaction of VEGF with 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.[1]

Results from pivotal studies demonstrated therapeutic similarity and PK similarities between Vegzelma and bevacizumab. Vegzelma was well tolerated and showed a comparable safety profile to reference bevacizumab.[6]

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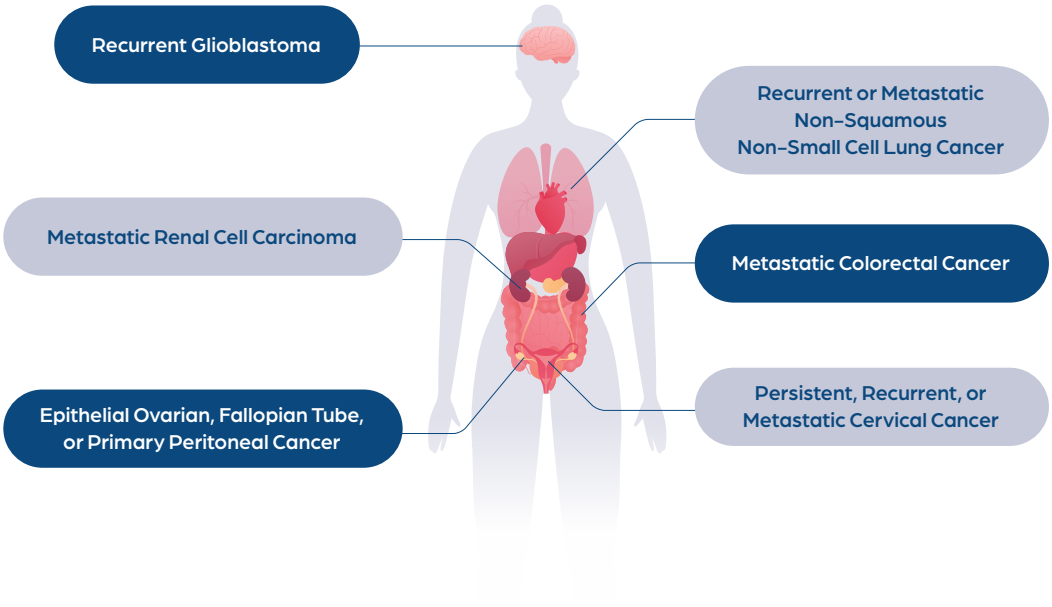
US indication[1,*]



Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

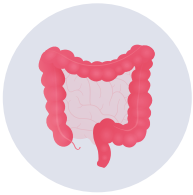
Surgery and Wound Healing Complications: The incidence of surgery and wound healing complications, including serious and fatal complications, was increased in patients receiving bevacizumab products. In patients who experience wound healing complications during treatment, withhold Vegzelma until adequate wound healing. Discontinue Vegzelma in patients who develop necrotizing fasciitis.

*Please refer to the Vegzelma Prescribing Information for more detailed information on the therapeutic indications of Vegzelma.

INN, International Nonproprietary Name; **KDR,** kinase insert domain receptor; **PK,** pharmacokinetics; **US,** United States; **VEGF,** vascular endothelial growth factor.

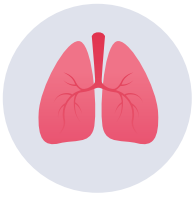
Dosage and administration[1]

Withhold for at least 28 days prior to elective surgery. Do not administer Vegzelma for 28 days following major surgery and until adequate wound healing. Administer as an intravenous infusion after dilution.



Metastatic Colorectal Cancer

- 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

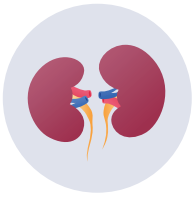


First–Line Non–Squamous Non–Small Cell Lung Cancer

- 15 mg/kg every 3 weeks with carboplatin and paclitaxel

Recurrent Glioblastoma

- 10 mg/kg every 2 weeks



Metastatic Renal Cell Carcinoma

- 10 mg/kg every 2 weeks with interferon alfa

Persistent, Recurrent, or Metastatic Cervical Cancer

- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan

Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

Hemorrhage: Severe or fatal hemorrhage occurred up to 5-fold more frequently in patients receiving bevacizumab products vs chemotherapy alone. Discontinue Vegzelma in patients who develop a Grades 3-4 hemorrhage.

Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

FOLFOX4, 5-fluorouracil, leucovorin, and oxaliplatin; **IFL,** irinotecan, 5-fluorouracil bolus and leucovorin.

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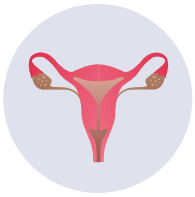
Dosage and administration[1]



Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Stage III or IV disease following initial surgical resection

- 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 disease

- 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 disease

- 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

Dosage forms and strengths[1]

Injection:

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

Warnings and precautions[1]

Gastrointestinal Perforations and Fistula:

Discontinue for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any organ.

Surgery and Wound Healing Complications:

In patients who experience wound healing complications during Vegzelma treatment, withhold Vegzelma until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer Vegzelma for at least 28 days following a major surgery, and until adequate wound healing. The safety of resumption of Vegzelma after resolution of wound healing complication has not been established. Discontinue for wound healing complication of necrotizing fasciitis.

Hemorrhage:

Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage.

Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

Arterial Thromboembolic Events: Serious, sometimes fatal, arterial thromboembolic events (ATE) occurred at a higher incidence in patients receiving bevacizumab vs chemotherapy. Discontinue Vegzelma in patients who develop a severe ATE. The safety of reinitiating bevacizumab products after an ATE is resolved is not known.

Warnings and precautions[1]

- **Arterial Thromboembolic Events (ATE):**
  Discontinue for severe ATE.

- **Venous Thromboembolic Events (VTE):**
  Discontinue for Grade 4 VTE.

- **Hypertension:**
  Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy.

- **Posterior Reversible Encephalopathy Syndrome (PRES):**
  Discontinue.

- **Renal Injury and Proteinuria:**
  Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine.

- **Infusion-Related Reactions:**
  Decrease rate for infusion-related reactions. Discontinue for severe infusion-related reactions and administer medical therapy.

- **Embryo-Fetal Toxicity:**
  May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception.

- **Ovarian Failure:**
  Advise females of the potential risk.

- **Congestive Heart Failure (CHF):**
  Discontinue Vegzelma in patients who develop CHF.

Adverse reactions[1]

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

Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

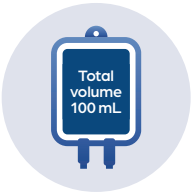
02. Preparation and Administration

Preparation[1]

Use appropriate aseptic technique.

Use sterile needle and syringe to prepare Vegzelma.

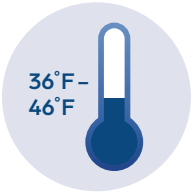
Visually inspect vial for particulate matter and discoloration prior to preparation for administration. Discard vial if solution is cloudy, discolored or contains particulate matter.



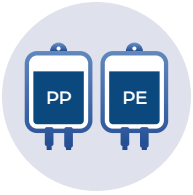
Withdraw necessary amount of Vegzelma and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

Discard any unused portion left in a vial, as the product contains no preservatives.



Diluted Vegzelma solution may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours, or at room temperature up to 30°C (86°F) for up to 4 hours, if not used immediately.



No incompatibilities between Vegzelma and polyolefin (polypropylene and polyethylene) bags have been observed.

Select Important Safety Information

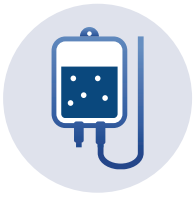
WARNINGS AND PRECAUTIONS (cont.)

Venous Thromboembolic Events: An increased risk of venous thromboembolic events (VTE) was observed across clinical studies. Discontinue Vegzelma in patients with a Grade 4 VTE, including pulmonary embolism.

Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

PE, polyethylene; **PP,** polypropylene; **USP,** United States Pharmacopeia.

Administration[1]



Administer as an **intravenous** infusion.

First infusion: Administer infusion over **90 minutes.**

Second infusion: Administer infusion over **60 minutes** if first infusion is tolerated.

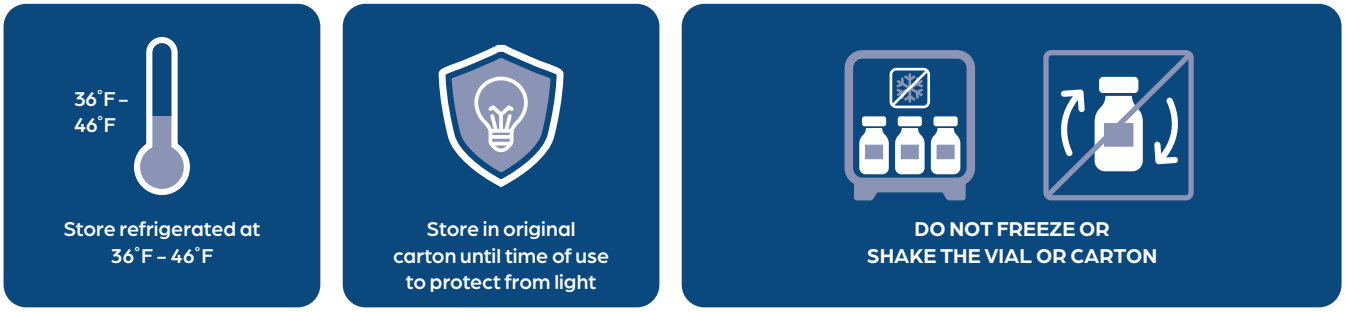
Third and subsequent infusions: Administer all subsequent infusions over **30 minutes** if second infusion over 60 minutes is tolerated.

Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

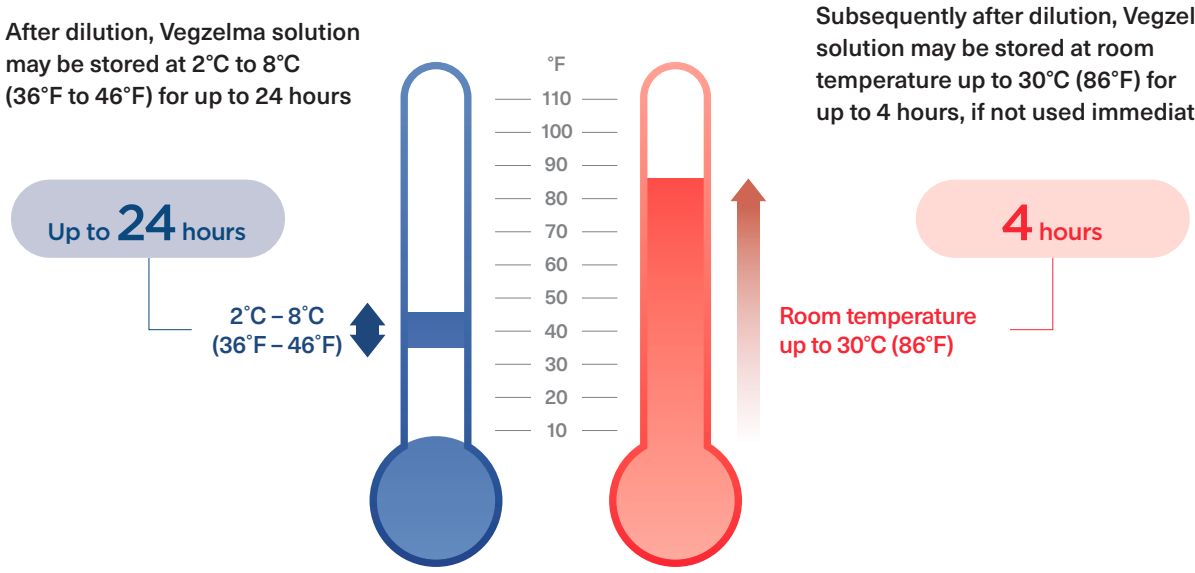
Hypertension: Severe hypertension occurred at a higher incidence in patients receiving bevacizumab products vs chemotherapy alone. Monitor blood pressure every two to three weeks during treatment with Vegzelma. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

Storage[1]



Diluted medicinal product[1]

Diluted Vegzelma solution may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours, or at room temperature up to 30°C (86°F) for up to 4 hours, if not used immediately.



Dilute Vegzelma in 0.9% sodium chloride solution for injection.

Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

Posterior Reversible Encephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) was reported in <0.5% of patients across clinical studies. Discontinue Vegzelma in patients who develop PRES.

Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

03. Clinical Value

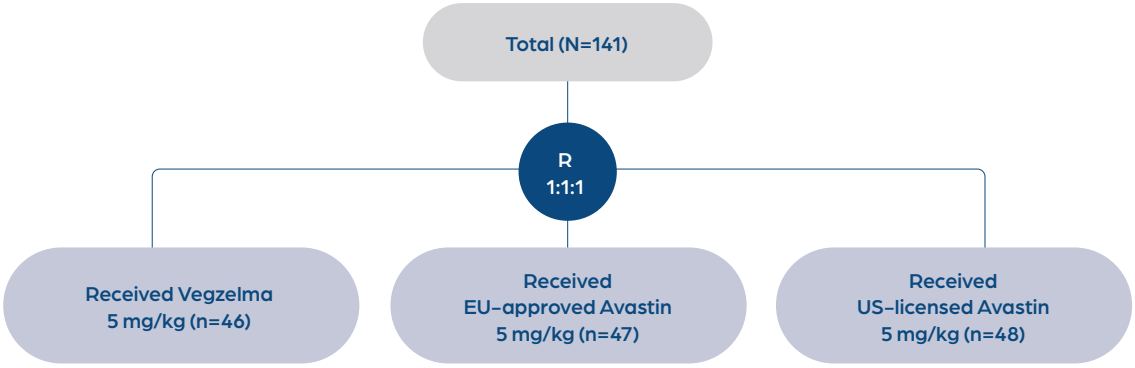
3.1 Phase 1 Study[4]

Phase 1.1: A Randomized, Double-Blind Trial Comparing the Pharmacokinetics of CT-P16, a Candidate Bevacizumab Biosimilar, with its Reference Product in Healthy Adult Males[4]

Study design & objective[4]

A randomized, double-blind, three-arm, parallel-group, single-dose phase I trial designed to demonstrate the pharmacokinetic equivalence of Vegzelma vs. EU-approved Avastin and US-licensed Avastin in healthy male subjects.

Overview[4]



Endpoints[4]

Primary pharmacokinetic endpoints	Secondary pharmacokinetic endpoints	Secondary safety/ immunogenicity endpoints
AUC_{inf}, AUC_{last}, C_{max}	T_{max}, V_z, λ_z, $t_{1/2}$, CL, $\%AUC_{ext}$	AEs, vital signs, physical examination, clinical laboratory tests, 12-lead ECG, immunogenicity

Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

Renal Injury and Proteinuria: The incidence and severity of proteinuria were higher in patients receiving bevacizumab products vs chemotherapy. Nephrotic syndrome occurred in <1% of patients receiving bevacizumab products across clinical studies, in some instances with fatal outcome. Discontinue Vegzelma in patients who develop nephrotic syndrome.

AEs, adverse events; **AUC**, area under the concentration-time curve; **AUC_{last}**, AUC from time zero to the last quantifiable concentration; **AUC_{inf}**, AUC from time zero to infinity; **CL**, total body clearance; **C_{max}**, maximum serum concentration; **ECG**, electrocardiogram; **EU**, European Union; **R**, randomization; **T_{max}**, time to C_{max}; **$t_{1/2}$**, terminal half-life; **US**, United States; **V_z**, volume of distribution during the terminal phase; **λ_z**, terminal elimination rate constant; **$\%AUC_{ext}$**, the percentage of AUC_{inf} obtained by extrapolation.

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Study demographics[4]

All subjects were Asian males (N=136); the median age (range) of these subjects was 25.0 (19–53) years. Subject demographics and characteristics were similar across treatment groups.

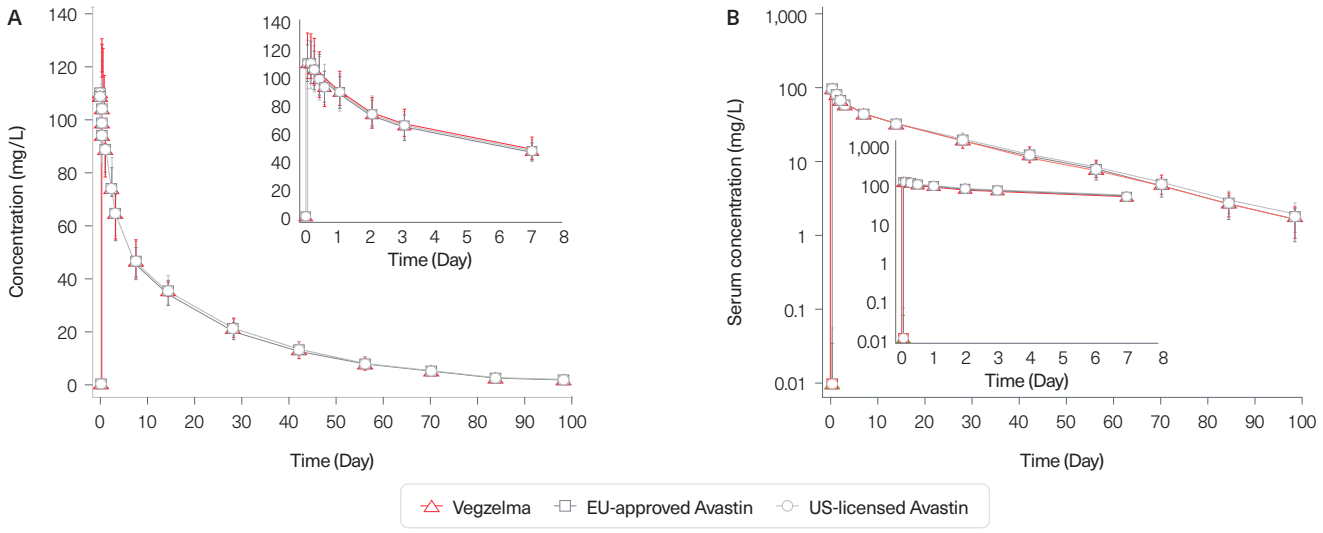
<Baseline demographics and characteristics of subjects: safety population>

Characteristic	Vegzelma (n=46)	EU-approved Avastin (n=47)	US-licensed Avastin (n=48)
Age (years)			
Mean (SD)	28.5 (8.69)	28.4 (7.59)	26.5 (6.28)
Median (range)	25.0 (19-53)	26.0 (21-52)	25.0 (20-52)
Asian race [n (%)]	46 (100)	47 (100)	48 (100)
Male sex [n (%)]	46 (100)	47 (100)	48 (100)
Height (cm)			
Mean (SD)	174.62 (6.589)	174.83 (6.788)	173.14 (4.968)
Median (range)	173.95 (162.6-189.2)	174.40 (161.4-190.9)	173.80 (157.2-182.3)
Weight (kg)			
Mean (SD)	69.93 (9.07)	71.01 (9.42)	69.54 (8.14)
Median (range)	69.90 (51.6-88.2)	70.30 (55.7-92.9)	71.30 (52.7-84.4)
Weight [n (%)]			
<70 kg	23 (50)	22 (46.8)	23 (47.9)
≥70 kg	23 (50)	25 (53.2)	25 (52.1)
BMI (kg/m²)			
Mean (SD)	22.89 (2.310)	23.20 (2.492)	23.17 (2.303)
Median (range)	22.59 (18.0-27.9)	23.36 (19.2-28.7)	23.45 (18.0-28.1)

Pharmacokinetic results[4]

After intravenous administration of a single 5 mg/kg dose of Vegzelma, EU-approved Avastin, or US-licensed Avastin, similar mean bevacizumab serum concentration–time profiles were observed in each treatment group.

<Mean (±SD) serum bevacizumab concentration: A. linear scale; B. semi-logarithmic scale>



Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

Infusion-Related Reactions: In clinical studies, infusion-related reactions with the first dose of bevacizumab products 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 Vegzelma in patients who develop a severe infusion-related reaction and administer appropriate medical therapy.

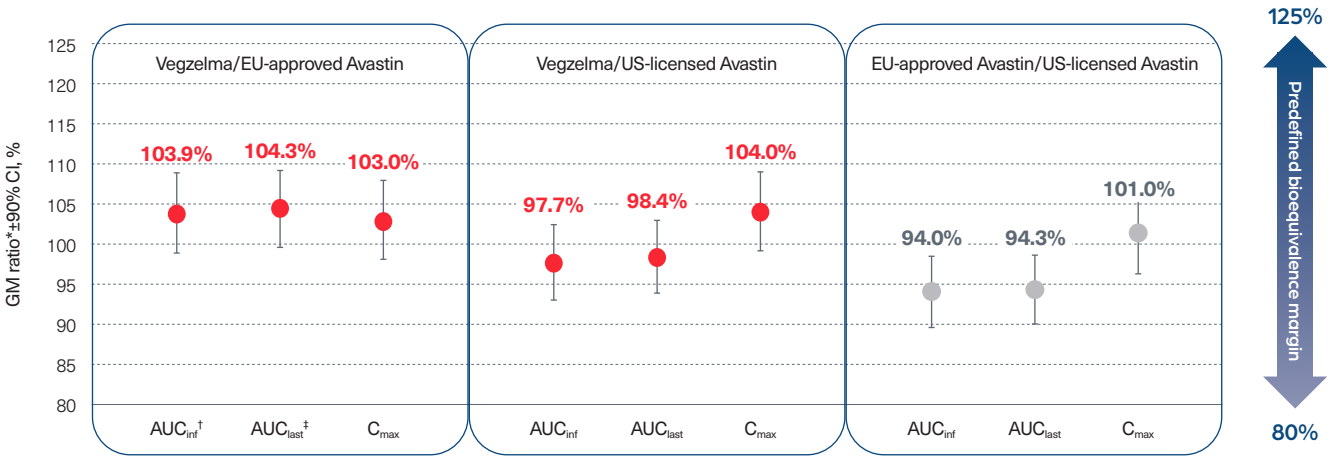
Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

BMI, body mass index; **EU,** European Union; **SD,** standard deviation; **US,** United States.

Pharmacokinetic results[4]

The 90% CIs for the GM ratios of AUC_{inf}, AUC_{last}, and C_{max} for Vegzelma/EU-approved Avastin, Vegzelma/US-licensed Avastin, and EU-approved Avastin/US-licensed Avastin comparisons were all within the bioequivalence margin.

<Statistical analysis of the primary pharmacokinetic endpoints (analysis of covariance)>



*GM ratios were calculated by back-transforming the difference in LS means calculated using an ANCOVA model with treatment as a fixed effect and body weight assessed on day −1 (< 70 vs. ≥ 70 kg) and study site as covariates.; †For four subjects (one from the Vegzelma group, one from the EU-approved Avastin group, and two from the US-licensed Avastin group), AUC_{inf} values were excluded from the statistical analysis because the interval used to calculate λ_z was < 1.5-fold the estimated half-life.; ‡For five subjects (one from the Vegzelma group and four from the US-licensed Avastin group), AUC_{last} values were excluded from the statistical analysis because the subjects withdrew from the study and the last pharmacokinetic samples for these subjects were collected earlier than the planned time (in accordance with the guideline on the investigation of bioequivalence from the EMA).

Inter-individual variation in systemic exposure to bevacizumab (measured as the coefficients of variation of AUC_{inf}, AUC_{last}, and C_{max}) was low (11.8–15.4% across all three treatment groups). Overall, the secondary pharmacokinetic endpoints (t_{max}, V_z, λ_z, $t_{½}$, CL, and $\%AUC_{ext}$) were similar in the three groups.

Pharmacokinetic endpoints		Vegzelma (n=46)	EU-approved Avastin (n=47)	US-licensed Avastin (n=48)
AUC_{inf} (day·mg/L)	Mean (SD)	1,751.45 (252.945)	1,683.89 (208.866)	1,792.41 (240.956)
	Median (range)	1,720.08 (1,260.0-2,254.7)	1,678.92 (1,140.1–2,122.5)	1,787.43 (1,199.4–2,271.9)
AUC_{last} (day·mg/L)	Mean (SD)	1,714.28 (237.258)	1,642.17 (193.722)	1,741.84 (227.659)
	Median (range)	1,699.81 (1,255.2–2,189.2)	1,643.58 (1,131.5–2,068.2)	1,740.89 (1,164.1–2,239.1)
C_{max} (mg/L)	Mean (SD)	117.22 (17.756)	114.06 (15.391)	113.09 (17.402)
	Median (range)	116 (83.6–173.0)	111 (83.2–148.0)	112 (72.6–155.0)
t_{max} (day)	Mean (SD)	0.120 (0.0881)	0.117 (0.0820)	0.125 (0.0801)
	Median (range)	0.104 (0.06–0.50)	0.104 (0.06–0.33)	0.104 (0.06–0.33)
V_z (L)	Mean (SD)	5.352 (1.045)	5.505 (0.705)	5.487 (0.964)
	Median (range)	5.311 (3.30–7.42)	5.449 (4.29–6.97)	5.404 (3.45–8.00)
λ_z (1/day)	Mean (SD)	0.039 (0.0081)	0.039 (0.0076)	0.037 (0.0061)
	Median (range)	0.037 (0.03–0.06)	0.039 (0.02–0.06)	0.037 (0.03–0.05)
$t_{½}$ (day)	Mean (SD)	18.44 (3.281)	18.28 (3.408)	19.29 (3.245)
	Median (range)	18.94 (11.1–24.4)	17.83 (11.5–27.7)	19.00 (14.3–27.6)
CL (L/day)	Mean (SD)	0.20 (0.041)	0.21 (0.035)	0.20 (0.033)
	Median (range)	0.20 (0.1–0.3)	0.21 (0.2–0.3)	0.19 (0.1–0.3)
$\%AUC_{ext}$*	Mean (SD)	3.01 (2.665)	2.68 (1.619)	3.59 (2.810)
	Median (range)	2.63 (0.4–18.3)	2.12 (0.5–8.8)	3.07 (0.8–18.6)

*Two subjects (one in the Vegzelma arm and one in the US-licensed Avastin arm) had $\%AUC_{ext}$ > 10% and were withdrawn (the last pharmacokinetic sampling timepoints were day 55 and 56, respectively).

Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

Embryo-Fetal Toxicity: Bevacizumab products may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Vegzelma and for 6 months after the last dose.

ANCOVA, an analysis of covariance; AUC, area under the concentration–time curve; AUC_{last}, AUC from time zero to the last quantifiable concentration; AUC_{inf}, AUC from time zero to infinity; CI, confidence interval; CL, total body clearance; C_{max}, maximum serum concentration; EMA, European Medicines Agency; EU, European Union; GM, geometric mean; LS, least squares; SD, standard deviation; t_{max}, time to C_{max}, $t_{1/2}$, terminal half-life; US, United States; V_z, volume of distribution during the terminal phase; λ_z, terminal elimination rate constant, $\%AUC_{ext}$, percentage of AUC_{inf} obtained by extrapolation.

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bevacizumab-addc
Injection 100mg/vial & 400mg/vial

Safety profile[4]

Over the course of the study, there were no deaths, TESAEs, or TEAEs leading to discontinuation.

A total of 83 (58.9%) subjects in the safety population reported one or more TEAE during the study (50.0%, 72.3%, and 54.2% in the Vegzelma, EU-approved Avastin, and US-licensed Avastin groups, respectively).

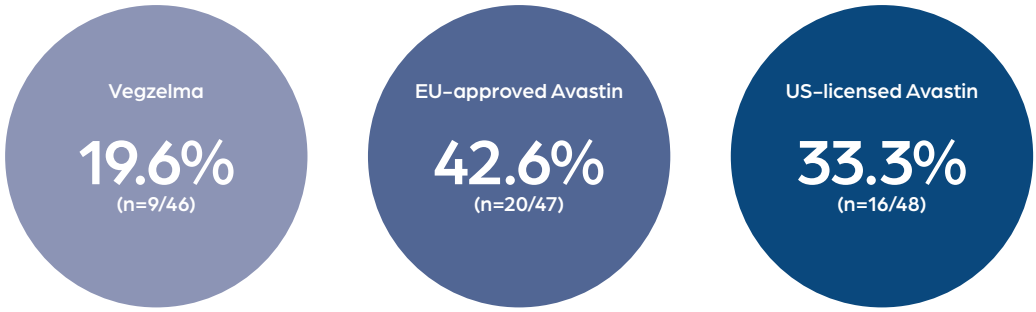
<TEAEs by preferred term: safety population>

TEAEs, n (%)	Vegzelma (n=46)	EU-approved Avastin (n=47)	US-licensed Avastin (n=48)
Total number of TEAEs	52	76	75
Subjects with at least one TEAE	23 (50.0)	34 (72.3)	26 (54.2)
Most common TEAEs*			
Diarrhea	3 (6.5)	6 (12.8)	4 (8.3)
Nasopharyngitis	4 (8.7)	1 (2.1)	6 (12.5)
Blood creatine phosphokinase increased	3 (6.5)	5 (10.6)	4 (8.3)
C-reactive protein increased	2 (4.3)	5 (10.6)	4 (8.3)
Infusion-related reaction	2 (4.3)	2 (4.3)	4 (8.3)
Troponin I increased	1 (2.2)	3 (6.4)	0
Headache	1 (2.2)	2 (4.3)	3 (6.3)
WBC count decreased	1 (2.2)	0	3 (6.3)
Any TEAE related to study drug†	9 (19.6)	20 (42.6)	16 (33.3)
Most common TEAEs related to study drug†,‡			
Diarrhea	3 (6.5)	6 (12.8)	2 (4.2)
C-reactive protein increased	1 (2.2)	4 (8.5)	4 (8.3)
Infusion-related reaction	2 (4.3)	2 (4.3)	4 (8.3)

*TEAEs reported by ≥ 5% subjects in any treatment group; †Considered related (possible, probable, or definite) to study drug by investigator; ‡TEAEs related to study drug reported by ≥ 5% subjects in any treatment group.

A total of 45 subjects reported TEAEs considered by the investigator to be related to study drug. Of these subjects, 9 (19.6%) were in the Vegzelma group, 20 (42.6%) were in the EU-approved Avastin group, and 16 (33.3%) were in the US-licensed Avastin group.

<Any TEAE related to study drug: safety population>



Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

AEs, adverse events; **EU,** European Union; **TEAE,** treatment-emergent adverse event; **TESAEs,** treatment-emergent serious adverse events; **US,** United States; **WBC,** white blood cell.

Immunogenicity results[4]

Levels of immunogenicity, as measured by ADA incidence, were low across all groups, with only seven subjects testing positive for ADAs after study drug administration. No NAbs were detected in any subject who tested positive for ADAs either before or after treatment.

<The positive for ADAs after study drug administration>

Conclusions[4]

- This study has demonstrated that the pharmacokinetics of Vegzelma, EU-approved Avastin, and US-licensed Avastin are equivalent.
- In addition, the safety and immunogenicity profiles of Vegzelma were similar to those of EU-approved and US-licensed Avastin.
- These findings support the continued development of Vegzelma in a phase III clinical study, which is the next step in the totality of evidence approach to establish biosimilarity.

Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

Ovarian Failure: The incidence of ovarian failure was 34% vs 2% in premenopausal women receiving bevacizumab with chemotherapy vs chemotherapy alone for adjuvant treatment of a solid tumor. Inform females of reproductive potential of the risk of ovarian failure prior to initiating treatment with Vegzelma.

ADA, anti-drug antibody; **EU,** European Union; **NAbs,** neutralizing antibodies; **US,** United States.

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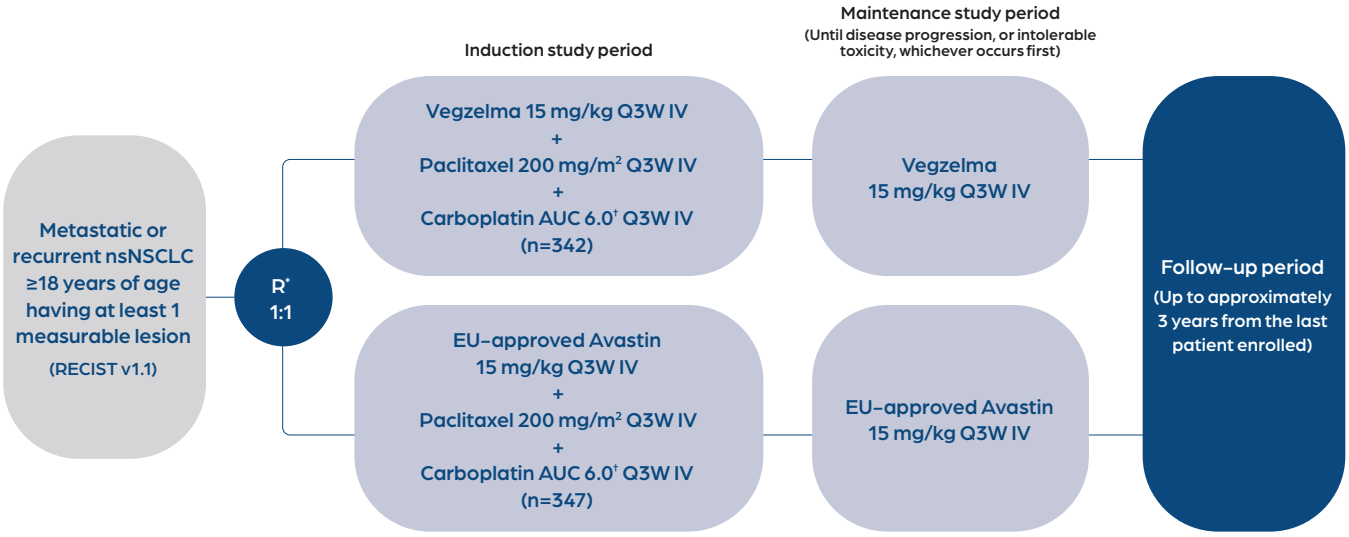
3.2 Phase 3 Study in NSCLC

Study 3.1: Phase III Study Evaluating the Efficacy and Safety of Vegzelma as first-line treatment for metastatic or recurrent nsNSCLC[6]

Study design & objective[6]

A double-blind, randomized, active-controlled, parallel-group, phase 3 study to compare efficacy and safety of Vegzelma and EU-approved Avastin as first-line treatment for metastatic or recurrent nsNSCLC.

Overview[6]



*Randomization was stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and ECOG PS (0 vs. 1).; †mg·min/mL

Main criteria for inclusion[6]

- Male or female with ≥ 18 years of age
- Metastatic or recurrent nsNSCLC diagnosed according to the AJCC 8th edition on Lung Cancer Staging
- At least 1 measurable lesion by RECIST v1.1

Endpoints[6]

Primary efficacy endpoint	Secondary endpoints
ORR during the induction study period	ORR during the whole study period, DoR, TTP, PFS, OS, PK of C_{trough}, QoL, Safety profile

Select Important Safety Information

WARNINGS AND PRECAUTIONS (cont.)

Congestive Heart Failure (CHF): Vegzelma is not indicated for use with anthracycline-based chemotherapy. Discontinue Vegzelma in patients who develop CHF.

Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

AJCC, American Joint Committee on Cancer; **AUC,** area under the curve; **C_{trough},** trough serum concentration; **DoR,** duration of response; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **EU,** European Union; **IV,** intravenous; **NSCLC,** non-small cell lung cancer; **nsNSCLC,** non-squamous non-small cell lung cancer; **ORR,** objective response rate; **OS,** overall survival; **PFS,** progression-free survival; **PK,** pharmacokinetic; **QoL,** quality of life; **Q3W,** every 3 weeks; **R,** randomization; **RECIST,** Response Evaluation Criteria In Solid Tumors; **TTP,** time to progression.

Study demographics[6]

Overall, demographic characteristics were similar between the 2 treatment groups.

<Baseline demographics and characteristics: ITT population>

Characteristic	Vegzelma (n=342)	EU-approved Avastin (n=347)	Total (N=689)
Age (years)			
Mean (SD)	61.3 (9.01)	61.5 (9.42)	61.4 (9.21)
Median	62.0	62.0	62.0
Minimum, Maximum	32, 82	26, 82	26, 82
Sex, n (%)			
Female	119 (34.8)	125 (36.0)	244 (35.4)
Male	223 (65.2)	222 (64.0)	445 (64.6)
Female fertility status*			
Surgically sterilized	13 (10.9)	7 (5.6)	20 (8.2)
Post-menopausal	95 (79.8)	104 (83.2)	199 (81.6)
Potentially able to bear children	11 (9.2)	14 (11.2)	25 (10.2)
Race, n (%)			
American Indian or Alaska Native	9 (2.6)	9 (2.6)	18 (2.6)
Asian	59 (17.3)	55 (15.9)	114 (16.5)
Black or African American	2 (0.6)	1 (0.3)	3 (0.4)
White or Caucasian	264 (77.2)	264 (76.1)	528 (76.6)
Other	8 (2.3)	18 (5.2)	26 (3.8)
Ethnicity, n (%)			
Hispanic or Latino	57 (16.7)	66 (19.0)	123 (17.9)
Non-Hispanic or Non-Latino	282 (82.5)	275 (79.3)	557 (80.8)
Not allowed by investigator country regulations	0	2 (0.6)	2 (0.3)
Unknown	3 (0.9)	4 (1.2)	7 (1.0)
Smoking history, n (%)			
Current smoker	75 (21.9)	88 (25.4)	163 (23.7)
Former smoker	163 (47.7)	148 (42.7)	311 (45.1)
Never smoker	104 (30.4)	111 (32.0)	215 (31.2)
Height (cm)			
n	342	346	688
Mean (SD)	166.85 (9.866)	166.53 (10.034)	166.69 (9.945)
Median	167.00	168.00	167.00
Minimum, Maximum	133.0, 194.0	138.0, 194.0	133.0, 194.0
Weight (kg)			
n	342	346	688
Mean (SD)	68.76 (15.767)	69.78 (15.283)	69.27 (15.523)
Median	67.00	69.00	68.00
Minimum, Maximum	36.0, 131.0	35.0, 126.0	35.0, 131.0
Disease status, n (%)			
Recurrent	25 (7.3)	33 (9.5)	58 (8.4)
Metastatic	317 (92.7)	314 (90.5)	631 (91.6)
Region, n (%)			
EMEA	226 (66.1)	230 (66.3)	456 (66.2)
America	59 (17.3)	62 (17.9)	121 (17.6)
Asia	57 (16.7)	55 (15.9)	112 (16.3)
ECOG PS, n (%)			
Grade 0	105 (30.7)	110 (31.7)	215 (31.2)
Grade 1	237 (69.3)	237 (68.3)	474 (68.8)

*Fertility status was collected for female patients only. Percentages were calculated by using the number of female patients as the denominator.

Select Important Safety Information

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions observed in patients receiving bevacizumab products 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, bevacizumab was discontinued in 8% to 22% of patients because of adverse reactions.

ECOG PS, Eastern Cooperative Oncology Group performance status; **EMEA,** Europe, Middle East, and Africa; **EU,** European Union; **ITT,** intent-to-treat; **SD,** standard deviation.

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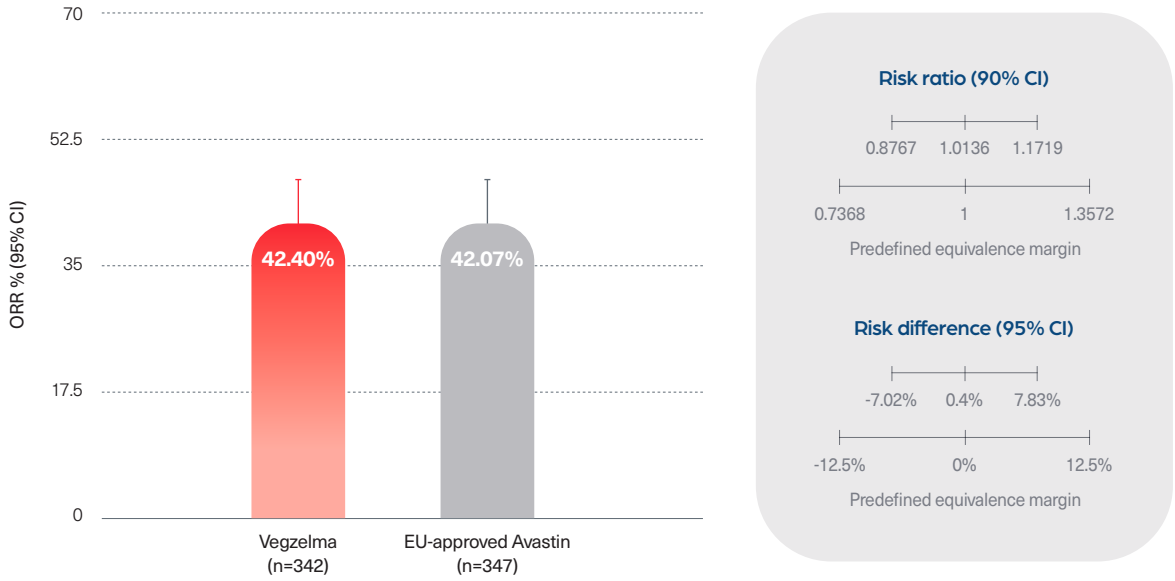
Primary efficacy results[6]

The ORRs were similar in the Vegzelma and EU-approved Avastin treatment groups [42.40% (95% CI: 37.16, 47.64) vs. 42.07% (95% CI: 36.88, 47.27)] and 90% CIs for the risk ratio estimate were within the equivalence margin in ITT population.

<ORR as the primary efficacy endpoint during the induction study period: ITT population>



For BORs, a similar proportion of patients in the Vegzelma and EU-approved Avastin treatment groups had CR [2 patients (0.6%) and 3 patients (0.9%) in the Vegzelma and EU-approved Avastin treatment groups, respectively] and PR [143 patients (41.8%) and 143 patients (41.2%) in the Vegzelma and EU-approved Avastin treatment groups, respectively] in the ITT population.

<BOR during the induction study period : ITT population>

	Vegzelma (n=342)	EU-approved Avastin (n=347)
Best overall response, n (%)		
CR	2 (0.6)	3 (0.9)
PR	143 (41.8)	143 (41.2)
SD	156 (45.6)	140 (40.3)
PD	17 (5.0)	19 (5.5)
Inevaluable	3 (0.9)	3 (0.9)
Missing	21 (6.1)	39 (11.2)

Select Important Safety Information

ADVERSE REACTIONS BY INDICATION

Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment

- **Study AVF2107g:** Grades 3-4 adverse reactions occurring at higher incidence (≥2%) in patients receiving bevacizumab with IFL (N=392) vs placebo with IFL (N=396) were leukopenia (37% vs 31%), neutropenia (21% vs 14%), diarrhea (34% vs 25%), abdominal pain (8% vs 5%), constipation (4% vs 2%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), asthenia (10% vs 7%), and pain (8% vs 5%)

Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

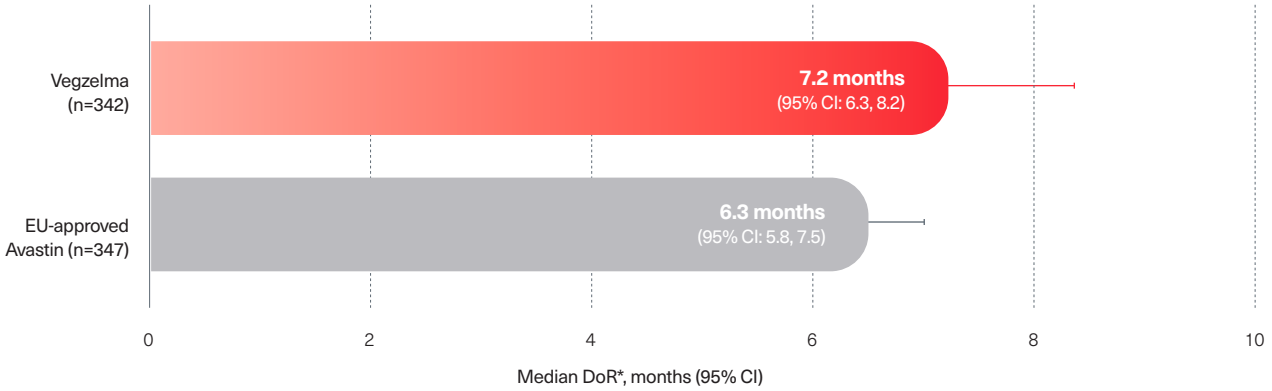
BOR, best overall response; **CI,** confidence interval; **CR,** complete response; **EU,** European Union; **ITT,** intent-to-treat; **ORR,** objective response rate; **PD,** progressive disease; **PR,** partial response; **SD,** stable disease.

Secondary efficacy results[6]

The secondary objective of the study was to evaluate additional efficacy profiles including DoR, TTP, PFS, and OS of Vegzelma compared with EU-approved Avastin.

The median DoR* was similar between the Vegzelma and EU-approved Avastin groups [7.2 months (95% CI: 6.3, 8.2) vs. 6.3 months (95% CI: 5.8, 7.5)].

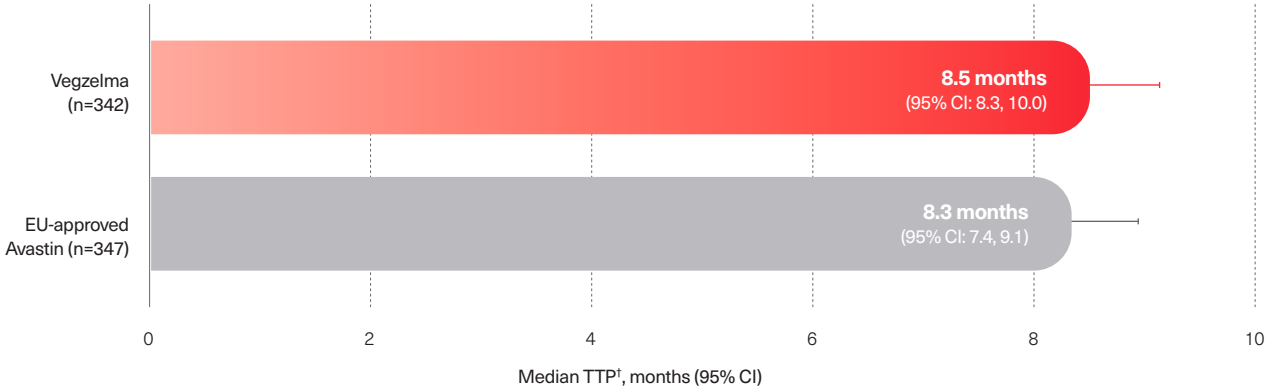
<DoR*: ITT population>



*DoR: the time between initial response (CR or PR) and PD/recurrence or death from any cause, whichever occurred first.

The median TTP† was similar between the Vegzelma and EU-approved Avastin groups [8.5 months (95% CI: 8.3, 10.0) vs. 8.3 months (95% CI: 7.4, 9.1)].

<TTP†: ITT population>



†TTP: the time from randomization to determined PD/recurrence.

Select Important Safety Information

ADVERSE REACTIONS BY INDICATION (cont.)

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

- **Study E3200:** Selected Grades 3-5 (non-hematologic) and Grades 4-5 (hematologic) reactions occurring at a higher incidence (≥2%) in patients receiving bevacizumab with FOLFOX4 (N=521) vs 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%)

CI, confidence interval; **CR,** complete response; **DoR,** duration of response; **EU,** European Union; **ITT,** intent-to-treat; **OS,** overall survival; **PD,** progressive disease; **PFS,** progression-free survival; **PR,** partial response; **TTP,** time to progression.

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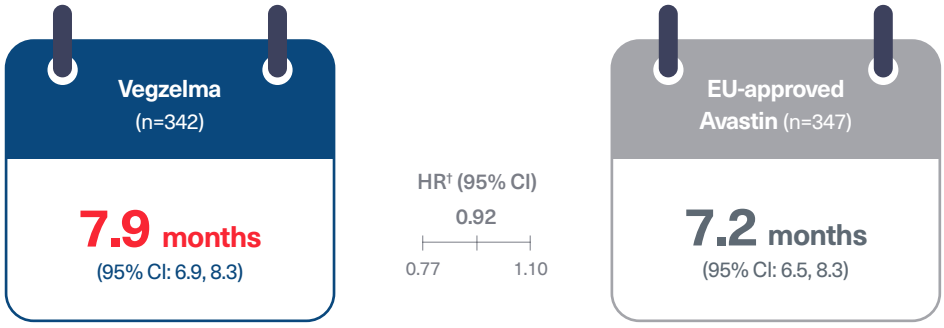
Secondary efficacy results

In the ITT population, 248 (72.5%) patients and 246 (70.9%) patients had died or had PD/recurrence in the Vegzelma and EU-approved Avastin treatment groups, respectively.[6]

The median PFS* was similar between the Vegzelma and EU-approved Avastin groups [7.9 months (95% CI: 6.9, 8.3) vs. 7.2 months (95% CI: 6.5, 8.3)], with the HR† of 0.92 (95% CI: 0.77, 1.10).[6]

<PFS*: ITT population[6]>

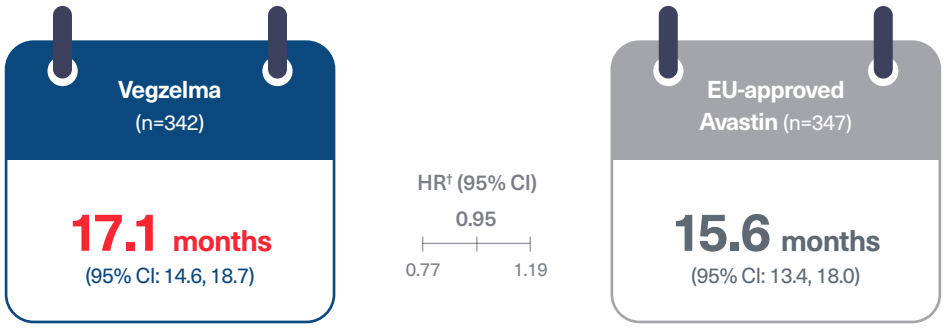


*PFS: the time from randomization to determined PD/recurrence or death from any cause, whichever occurred first[6]; †HR: a measure of how often a particular event happens in one group compared to how often it happens in another group, over time.[7]

In the ITT population, 164 (48.0%) patients and 168 (48.4%) patients had died in the Vegzelma and EU-approved Avastin treatment groups, respectively.[6]

The median OS‡ was similar between the Vegzelma and EU-approved Avastin groups [17.1 months (95% CI: 14.6, 18.7) vs. 15.6 months (95% CI: 13.4, 18.0)], with the HR† of 0.95 (95% CI: 0.77, 1.19).[6]

<OS‡: ITT population[6]>



†HR: a measure of how often a particular event happens in one group compared to how often it happens in another group, over time[7]; ‡OS: the time from randomization to death from any cause.[6]

Select Important Safety Information

ADVERSE REACTIONS BY INDICATION (cont.)

Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment

- **Study E4599:** Grades 3-5 (non-hematologic) and Grades 4-5 (hematologic) adverse reactions occurring at a higher incidence (≥2%) in patients receiving bevacizumab with paclitaxel and carboplatin (N=422) vs 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%)

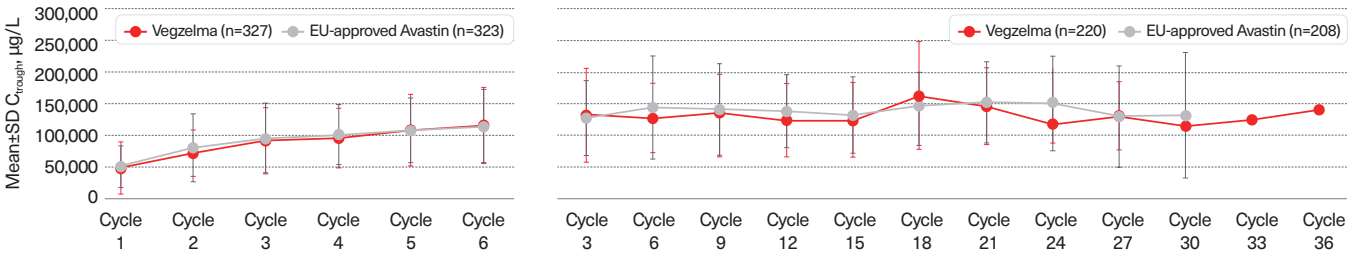
Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

CI, confidence interval; **EU,** European Union; **HR,** hazard ratio; **ITT,** intent-to-treat; **OS,** overall survival; **PD,** progressive disease; **PFS,** progression-free survival.

Pharmacokinetic results[6]

The mean C_{trough} at each cycle during the induction and maintenance periods were similar between the Vegzelma and EU-approved Avastin in the PK population.

<Mean C_{trough} of bevacizumab at each cycles>



Induction study period

No. of patients	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Vegzelma	318	302	283	268	252	246
EU-approved Avastin	316	287	269	254	238	228

Maintenance study period

Cycle 3	Cycle 6	Cycle 9	Cycle 12	Cycle 15	Cycle 18	Cycle 21	Cycle 24	Cycle 27	Cycle 30	Cycle 33	Cycle 36
204	147	104	58	42	23	14	11	7	2	1	1
188	119	97	68	44	33	14	11	5	3	0	0

Safety profile[6]

Overall, 5,533 TEAEs were reported in 652 (94.6%) patients [332 (96.2%) patients and 320 (93.0%) patients in the Vegzelma and EU-approved Avastin treatment groups, respectively].

The majority of TEAEs were grade 1 or 2 in severity and TEAEs with severity of grade 3 or higher was similar between the 2 treatment groups.

<TEAEs during the whole study period: Safety population>

	TEAE		TEAEs grade 3 or higher		TESAEs		TEAEs leading to study drug discontinuation		TEAEs leading to death	
	Vegzelma (n=345)	EU-approved Avastin (n=344)	Vegzelma (n=345)	EU-approved Avastin (n=344)	Vegzelma (n=345)	EU-approved Avastin (n=344)	Vegzelma (n=345)	EU-approved Avastin (n=344)	Vegzelma (n=345)	EU-approved Avastin (n=344)
Total events	2,957	2,576	313	269	99	95	56	55	23	24
No. of patients (%)	332 (96.2%)	320 (93.0%)	151 (43.8%)	144 (41.9%)	69 (20.0%)	73 (21.2%)	55 (15.9%)	55 (16.0%)	23 (6.7%)	24 (7.0%)
Related to the study drug	178 (51.6%)	174 (50.6%)	52 (15.1%)	49 (14.2%)	18 (5.2%)	23 (6.7%)	22 (6.4%)	21 (6.1%)	3 (0.9%)	7 (2.0%)
Unrelated to the study drug	318 (92.2%)	307 (89.2%)	126 (36.5%)	115 (33.4%)	55 (15.9%)	54 (15.7%)	33 (9.6%)	34 (9.9%)	20 (5.8%)	17 (4.9%)

The majority of laboratory parameters had no CTCAE grade or were CTCAE grade 1 (mild) or grade 2 (moderate) for each laboratory parameter.

Select Important Safety Information

ADVERSE REACTIONS BY INDICATION (cont.)

Recurrent glioblastoma in adults

- **Study EORTC 26101:** In the bevacizumab with lomustine arm (N=278), 22% of patients discontinued treatment due to adverse reactions vs 10% of patients in the lomustine arm. In patients receiving bevacizumab with lomustine, the adverse reaction profile was similar to that observed in other approved indications

CTCAE, Common Terminology Criteria for Adverse Events; **C_{trough},** trough serum concentration; **EU,** European Union; **PK,** pharmacokinetic; **SD,** standard deviation; **TEAEs,** treatment-emergent adverse events; **TESAEs,** treatment-emergent serious adverse events.

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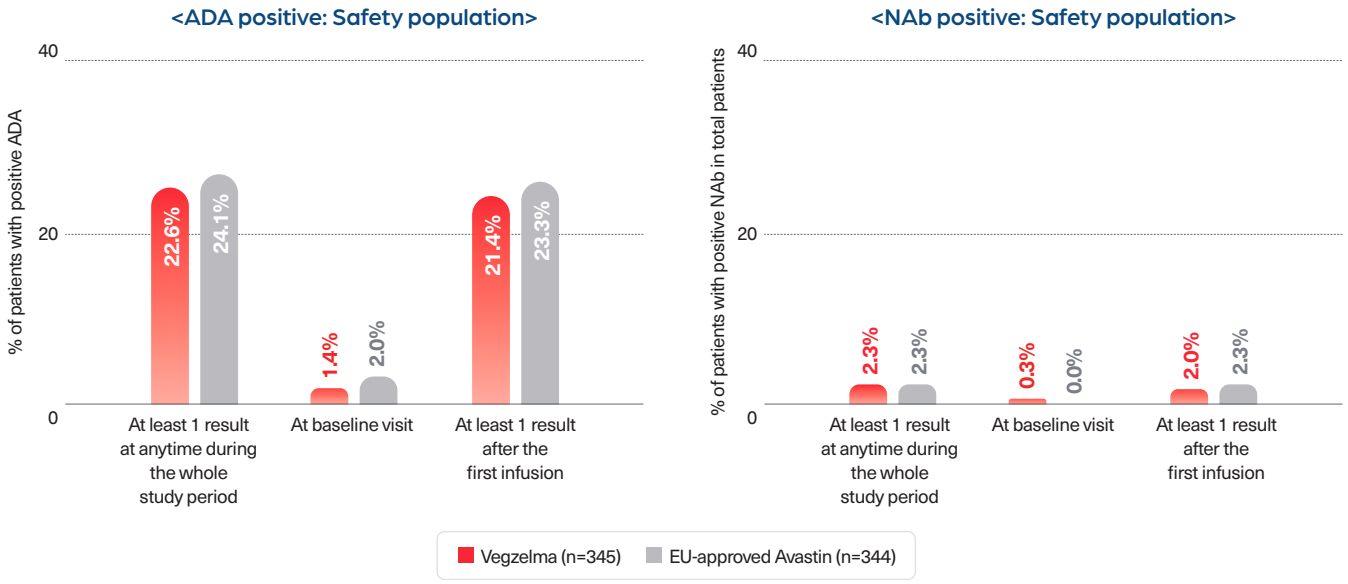
Immunogenicity results[6]

The majority of patients had negative ADA test results at each time point.

In general, the proportion of patients with positive ADA and NAb results at any time during the study period was similar in the Vegzelma and EU-approved Avastin treatment groups.



Conclusions[6]

- The efficacy of Vegzelma was equivalent to that of the EU-approved Avastin for primary efficacy endpoint as determined by ORR during the induction study period. The efficacy results of Vegzelma throughout the study were similar to those of EU-approved Avastin for secondary efficacy endpoints (time-to-event analyses).
- The PK of Vegzelma to EU-approved Avastin in terms of C_{trough} was found to be similar.
- Vegzelma was well tolerated and the safety profile of Vegzelma during the study period was similar to that of EU-approved Avastin.

Select Important Safety Information

ADVERSE REACTIONS BY INDICATION (cont.)

Metastatic renal cell carcinoma in combination with interferon alfa

- **Study BO17705:** Grades 3-5 adverse reactions occurring at a higher incidence (>2%) in patients receiving bevacizumab with interferon alfa (N=337) vs placebo with interferon alfa (N=304) 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)

Please see the Important Safety Information throughout and on pages 25-26, and the accompanying full Prescribing Information.

ADA, anti-drug antibodies; C_{trough}, trough serum concentration; EU, European Union; NAb, neutralizing antibody; ORR, objective response rate; PK, pharmacokinetic.

04. Important Safety Information

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforations and Fistulae: Serious, and sometimes fatal, gastrointestinal perforation occurred at a higher incidence in patients receiving bevacizumab products vs 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. Serious fistulae ranged from <1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. Avoid Vegzelma 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.

Surgery and Wound Healing Complications: The incidence of surgery and wound healing complications, including serious and fatal complications, was increased in patients receiving bevacizumab products. In patients who experience wound healing complications during treatment, withhold Vegzelma until adequate wound healing. Discontinue Vegzelma in patients who develop necrotizing fasciitis.

Hemorrhage: Severe or fatal hemorrhage occurred up to 5-fold more frequently in patients receiving bevacizumab products vs chemotherapy alone. Discontinue Vegzelma in patients who develop a Grades 3-4 hemorrhage.

Arterial Thromboembolic Events: Serious, sometimes fatal, arterial thromboembolic events (ATE) occurred at a higher incidence in patients receiving bevacizumab vs chemotherapy. Discontinue Vegzelma in patients who develop a severe ATE. The safety of reinitiating bevacizumab products after an ATE is resolved is not known.

Venous Thromboembolic Events: An increased risk of venous thromboembolic events (VTE) was observed across clinical studies. Discontinue Vegzelma in patients with a Grade 4 VTE, including pulmonary embolism.

Hypertension: Severe hypertension occurred at a higher incidence in patients receiving bevacizumab products vs chemotherapy alone. Monitor blood pressure every two to three weeks during treatment with Vegzelma. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) was reported in <0.5% of patients across clinical studies. Discontinue Vegzelma in patients who develop PRES.

Renal Injury and Proteinuria: The incidence and severity of proteinuria was higher in patients receiving bevacizumab products vs chemotherapy. Nephrotic syndrome occurred in <1% of patients receiving bevacizumab products across clinical studies, in some instances with fatal outcome. Discontinue Vegzelma in patients who develop nephrotic syndrome.

Infusion-Related Reactions: In clinical studies, infusion-related reactions with the first dose of bevacizumab products 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 Vegzelma in patients who develop a severe infusion-related reaction and administer appropriate medical therapy.

Embryo-Fetal Toxicity: Bevacizumab products may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Vegzelma and for 6 months after the last dose.

Ovarian Failure: The incidence of ovarian failure was 34% vs 2% in premenopausal women receiving bevacizumab with chemotherapy vs chemotherapy alone for adjuvant treatment of a solid tumor. Inform females of reproductive potential of the risk of ovarian failure prior to initiating treatment with Vegzelma.

Congestive Heart Failure (CHF): Vegzelma is not indicated for use with anthracycline-based chemotherapy. Discontinue Vegzelma in patients who develop CHF.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions observed in patients receiving bevacizumab products 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, bevacizumab was discontinued in 8% to 22% of patients because of adverse reactions.

Please see the Important Safety Information continued on the next page, and the accompanying full Prescribing Information.

Important Safety Information (cont.)

ADVERSE REACTIONS BY INDICATION

Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment

- **Study AVF2107g:** Grades 3-4 adverse reactions occurring at higher incidence (≥2%) in patients receiving bevacizumab with IFL (N=392) vs placebo with IFL (N=396) were leukopenia (37% vs 31%), neutropenia (21% vs 14%), diarrhea (34% vs 25%), abdominal pain (8% vs 5%), constipation (4% vs 2%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), asthenia (10% vs 7%), and pain (8% vs 5%)

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

- **Study E3200:** Selected Grades 3-5 (non-hematologic) and Grades 4-5 (hematologic) reactions occurring at a higher incidence (≥2%) in patients receiving bevacizumab with FOLFOX4 (N=521) vs 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%)

Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment

- **Study E4599:** Grades 3-5 (non-hematologic) and Grades 4-5 (hematologic) adverse reactions occurring at a higher incidence (≥2%) in patients receiving bevacizumab with paclitaxel and carboplatin (N=422) vs 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 in adults

- **Study EORTC 26101:** In the bevacizumab with lomustine arm (N=278), 22% of patients discontinued treatment due to adverse reactions vs 10% of patients in the lomustine arm. In patients receiving bevacizumab with lomustine, the adverse reaction profile was similar to that observed in other approved indications

Metastatic renal cell carcinoma in combination with interferon alfa

- **Study BO17705:** Grades 3-5 adverse reactions occurring at a higher incidence (>2%) in patients receiving bevacizumab with interferon alfa (N=337) vs placebo with interferon alfa (N=304) 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)

Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan

- **Study GOG-0240:** Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in patients receiving bevacizumab with chemotherapy (N=218) vs chemotherapy alone (N=222) 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%)

Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by Vegzelma as a single agent, for stage III or IV disease following initial surgical resection

- **Study GOG-0218:** Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the bevacizumab arms (N=608, N=607) vs control arm (N=602) 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%)

Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens

- **Study MO22224:** Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in patients receiving bevacizumab with chemotherapy (N=179) vs chemotherapy alone (N=181) were hypertension (6.7% vs 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs 1.7%)

Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Vegzelma as a single agent, for platinum-sensitive recurrent disease

- **Study AVF4095g:** Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in patients receiving bevacizumab with chemotherapy (N=247) vs placebo with chemotherapy (N=233) 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%)

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please see accompanying full Prescribing Information for complete information.

05. References

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