FDA-approved biosimilars such as bevacizumab-bvzr (ZIRABEV®) are recommended as treatment options in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1-4*†]

INJECTION
Zirabev®
bevacizumab-bvzr
Pfizer

ZIRABEV® (bevacizumab-bvzr)

Product Monograph

BUILDING ONTO THE CLINICAL EXPERIENCE OF BEVACIZUMAB

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar and the reference product.

†NCCN Guidelines® recommend the use of an FDA-approved biosimilar as an appropriate substitute for bevacizumab. See the NCCN Guidelines for detailed recommendations, including specific treatment regimens. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

SELECTED 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 compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies. Non-GI fistulae incidence ranged from <1% to 1.8%, and was highest in patients with cervical cancer. Avoid ZIRABEV 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 for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any internal organ

(continued on next page)

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Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

Indications

ZIRABEV® (bevacizumab-bvzr) is FDA approved for the eligible indications of Avastin® (bevacizumab)[5]

INDICATIONS

Metastatic Colorectal Cancer (mCRC)

ZIRABEV, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with mCRC.

ZIRABEV, 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.

Limitation of Use: ZIRABEV is not indicated for adjuvant treatment of colon cancer.

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

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

Recurrent Glioblastoma (GBM)

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

Metastatic Renal Cell Carcinoma (mRCC)

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

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION

Warnings and Precautions (continued)

- **Surgery and Wound Healing Complications.** The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in bevacizumab-treated patients. In patients who experience wound healing complications during ZIRABEV treatment, withhold ZIRABEV 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 bevacizumab products after resolution of wound healing complications has not been established. Discontinue for wound healing complications of necrotizing fasciitis

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Indications

ZIRABEV® (bevacizumab-bvzr) is FDA approved for the eligible indications of Avastin® (bevacizumab)[5]

INDICATIONS

Persistent, Recurrent, or Metastatic Cervical Cancer (CC)

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

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

ZIRABEV, in combination with carboplatin and paclitaxel, followed by ZIRABEV as a single agent, is indicated for stage III or IV disease following initial surgical resection.

ZIRABEV, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for platinum-resistant recurrent disease in patients who received no more than 2 prior chemotherapy regimens.

ZIRABEV, in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by ZIRABEV as a single agent, is indicated for the treatment of platinum-sensitive recurrent disease.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION

Warnings and Precautions (continued)

- **Hemorrhage.** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding occurred up to 5-fold more frequently in patients receiving bevacizumab. In clinical studies, the incidence of grade ≥3 hemorrhagic events among patients receiving bevacizumab ranged from 0.4% to 7%. Do not administer ZIRABEV to patients with serious hemorrhage or a recent history of hemoptysis (≥1/2 tsp of red blood). Discontinue ZIRABEV in patients who develop grade 3-4 hemorrhage

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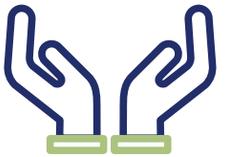
FDA-approved biosimilars such as bevacizumab-bvzr (ZIRABEV®) are recommended as treatment options in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1-4]*

With the largest portfolio of oncology biosimilars—including ZIRABEV® (bevacizumab-bvzr)—Pfizer is committed to expanding options for patient care[6]

Favorable coverage[7]

Potential savings[7]



Support for you and your patients

*NCCN Guidelines® recommend the use of an FDA-approved biosimilar as an appropriate substitute for bevacizumab. See the NCCN Guidelines for detailed recommendations, including specific treatment regimens. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

Pfizer has over 30 years of biologic experience, and more than a decade in the global biosimilars market.[7,8]

SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- Additional serious and sometimes fatal adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:
  - **Arterial thromboembolic events (ATE)** (grade ≥3, 5%, highest in patients with GBM). Discontinue in patients who develop a severe ATE
  - **Renal injury and proteinuria.** Monitor proteinuria during ZIRABEV therapy. Patients with a 2+ or greater urine dipstick reading should undergo 24-hour urine collection. Withhold for proteinuria ≥2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome
    - Grade 3-4 proteinuria ranged from 0.7% to 7% in clinical studies
    - Nephrotic syndrome (<1%)

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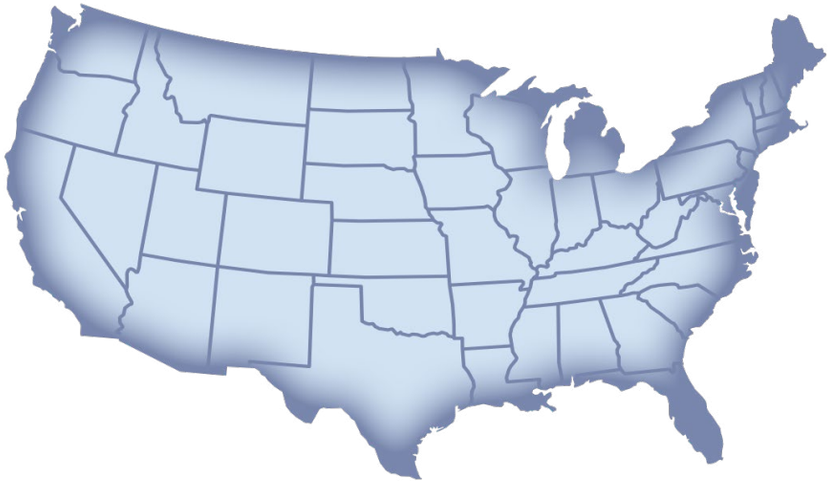
ZIRABEV® (bevacizumab-bvzr) coverage

Learn about access in your area

Coverage for ZIRABEV varies by location. Your Pfizer Sales Representative can share plan-specific commercial and Medicare coverage rates in your region.



Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- Additional serious adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:
  - **Venous thromboembolism events (VTE)** (grade ≥3, 11% seen in Study GOG-0240). Discontinue ZIRABEV in patients with a grade 4 VTE, including pulmonary embolism
  - **Hypertension** (grade 3-4, 5%-18%). Monitor blood pressure during treatment and, for ZIRABEV-associated hypertension, continue monitoring after discontinuation. Withhold for severe hypertension. Discontinue for hypertensive crisis or hypertensive encephalopathy
  - **Posterior reversible encephalopathy syndrome (PRES)** (<0.5%). Discontinue ZIRABEV in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing bevacizumab products, although some patients have experienced ongoing neurologic sequelae

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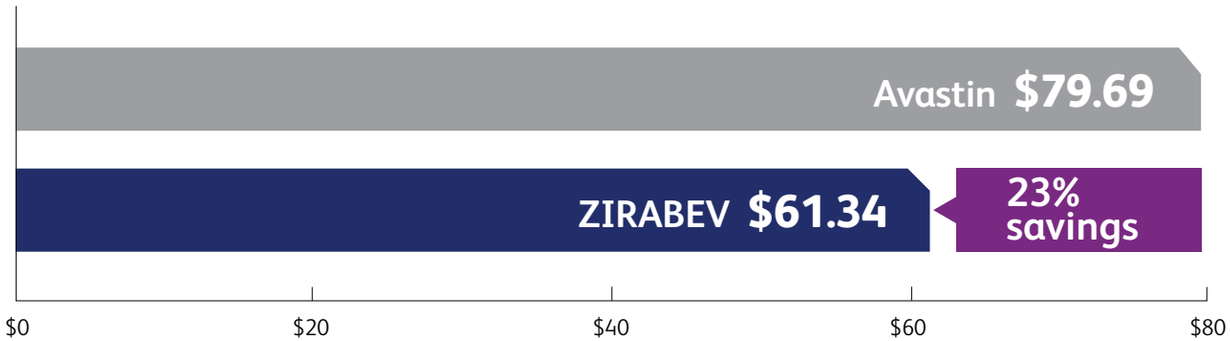
Potential cost savings with ZIRABEV® (bevacizumab-bvzr)

Wholesale acquisition cost (WAC) represents a 23% discount vs Avastin® (bevacizumab) per 10 mg[7]*



An estimated cumulative maximum potential savings over 10 years from implementation of all available biosimilars could reach as much as $150 billion.[9†]

***WAC is a manufacturer's undiscounted or list price to wholesalers/direct purchasers and, therefore, is not inclusive of discounts to payers, providers, distributors, and other purchasing organizations. Data as of October 2022.**

†Estimated reduction in direct spending on biologic drugs between 2017 and 2026 (RAND Corporation). Based on an assumption of a biosimilar market share of 50% and biosimilar prices at 50% of the reference product.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- Additional serious adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included (continued):
  - **Congestive heart failure (CHF)** (grade ≥3 left ventricular dysfunction, 1%). Discontinue ZIRABEV in patients who develop CHF
- **Infusion-related reactions.** Infusion-related reactions with the first dose of bevacizumab occurred in <3% of patients, and severe reactions occurred in 0.4% of patients. Decrease the rate of infusion for mild 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
- **Ovarian failure.** Inform females of reproductive potential of the risk of ovarian failure prior to initiating treatment with ZIRABEV

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Pfizer Oncology Together™ Co-Pay Savings Program for Injectables

Eligible patients may pay as little as **$0** per Tx

Eligible,* commercially insured patients† may pay as little as $0 per ZIRABEV treatment.‡ Limits, terms, and conditions apply.

- This program covers up to **$25,000 per calendar year**§
- There are **no income requirements** for patients to qualify
- Patients enrolled in state- or federally funded prescription insurance programs are not eligible for this program
- For information on enrollment, claims submissions, and reimbursement, visit **PfizerOncologyTogether.com** to download the Co-Pay Savings Program Brochure

***Terms and Conditions:** By using this program, you acknowledge that you currently meet the eligibility criteria and will comply with the terms and conditions described below:

- The Pfizer Oncology Together Co-Pay Savings Program for Injectables for ZIRABEV® is not valid for patients who are enrolled in a state or federally funded insurance program, including but not limited to Medicare, Medicaid, TRICARE, Veterans Affairs health care, a state prescription drug assistance program, or the Government Health Insurance Plan available in Puerto Rico (formerly known as "La Reforma de Salud").
- Program offer is not valid for cash-paying patients.
- Patients prescribed ZIRABEV for hepatocellular carcinoma are not eligible for this co-pay savings program.

Click to view full Terms

†For patients to be eligible for the Injectables Co-Pay Program for ZIRABEV, they must have commercial insurance that covers ZIRABEV and they cannot be enrolled in a state or federally funded insurance program. Whether a co-pay expense is eligible for the Injectables Co-Pay Program for ZIRABEV benefit will be determined at the time the benefit is paid. Co-pay expenses must be in connection with a separately paid claim for ZIRABEV administered in the outpatient setting.
‡The Injectables Co-Pay Program for ZIRABEV will pay the co-pay for ZIRABEV up to the annual assistance limit of $25,000 per calendar year per patient.
§The Injectables Co-Pay Program for ZIRABEV provides assistance for eligible, commercially insured patients prescribed ZIRABEV for co-pays or coinsurance incurred for ZIRABEV up to $25,000 per calendar year. It does not cover or provide support for supplies, services, procedures, or any other physician-related services associated with ZIRABEV treatment.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Pregnancy Warning

- Based on the mechanism of action and animal studies, bevacizumab products may cause fetal harm
- Advise female patients that bevacizumab products may cause fetal harm and to inform their health care provider of a known or suspected pregnancy
- Advise females of reproductive potential to use effective contraception during treatment with ZIRABEV and for 6 months after the last dose of ZIRABEV
- Advise nursing women that breastfeeding is not recommended during treatment with ZIRABEV and for 6 months following their last dose of treatment
- Bevacizumab products may impair fertility

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***Terms and Conditions:** By using this program, you acknowledge that you currently meet the eligibility criteria and will comply with the terms and conditions described below:

- The Pfizer Oncology Together Co-Pay Savings Program for Injectables for ZIRABEV® is not valid for patients who are enrolled in a state or federally funded insurance program, including but not limited to Medicare, Medicaid, TRICARE, Veterans Affairs health care, a state prescription drug assistance program, or the Government Health Insurance Plan available in Puerto Rico (formerly known as "La Reforma de Salud").
- Program offer is not valid for cash-paying patients.
- Patients prescribed ZIRABEV for hepatocellular carcinoma are not eligible for this co-pay savings program.
- With this program, eligible patients may pay as little as $0 co-pay per ZIRABEV treatment, subject to a maximum benefit of $25,000 per calendar year for out-of-pocket expenses for ZIRABEV including co-pays or coinsurances.
- The amount of any benefit is the difference between your co-pay and $0.
- After the maximum of $25,000 you will be responsible for the remaining monthly out-of-pocket costs.
- Patient must have private insurance with coverage of ZIRABEV.
- This offer is not valid when the entire cost of your prescription drug is eligible to be reimbursed by your private insurance plans or other private health or pharmacy benefit programs.
- You must deduct the value of this assistance from any reimbursement request submitted to your private insurance plan, either directly by you or on your behalf.
- You are responsible for reporting use of the program to any private insurer, health plan, or other third party who pays for or reimburses any part of the prescription filled using the program, as may be required.
- You should not use the program if your insurer or health plan prohibits use of manufacturer co-pay assistance programs.
- This program is not valid where prohibited by law.
- This program cannot be combined with any other savings, free trial or similar offer for the specified prescription.
- **Co-pay card will be accepted only at participating pharmacies.**
- **This program is not health insurance.**
- This program is good only in the U.S. and Puerto Rico.
- This program is limited to 1 per person during this offering period and is not transferable.
- No other purchase is necessary.
- Data related to your redemption of the program assistance may be collected, analyzed, and shared with Pfizer, for market research and other purposes related to assessing Pfizer's programs. Data shared with Pfizer will be aggregated and de-identified; it will be combined with data related to other assistance redemptions and will not identify you.
- Pfizer reserves the right to rescind, revoke or amend this program without notice.
- This program may not be available to patients in all states.
- For more information about Pfizer, visit www.pfizer.com.
- For more information about the Pfizer Oncology Together Co-Pay Savings Program for Injectables, visit pfizeroncologytogether.com, call 1-877-744-5675, or write to
  Pfizer Oncology Together Co-Pay Savings Program for Injectables
  P.O. Box 220366
  Charlotte, NC 28222
- Program terms and offer will expire at the end of each calendar year. Before the calendar year ends, you will receive information and eligibility requirements for continued participation.

CLOSE

Navigating access and reimbursement. Together.

Pfizer Oncology together™

Patient Support. Financial Assistance. Together.

If patients need access or reimbursement support, Pfizer Oncology Together is here to help.

Benefits Verification
We can help determine a patient's coverage and out-of-pocket costs.

Prior Authorization (PA) Assistance
We can coordinate with a patient's insurer to determine the PA requirements. After a PA request is submitted, we can follow up with the payer until a final outcome is determined.

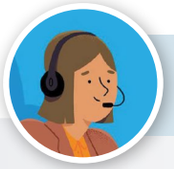
Appeals Assistance
We can review the reasons for a denied claim and provide information on payer requirements. After an appeal is submitted, we can follow up with the payer until a final outcome is determined.

Product Distribution
ZIRABEV is available through most major wholesalers.

Billing and Coding Assistance for IV Products
For your patient claim submissions, we provide easy access to sample forms and template letters, along with billing and coding information for physician's office and hospital outpatient settings of care.

Dedicated Local Support
A Pfizer Oncology Account Specialist can provide detailed information on Pfizer Oncology medications and access resources. In addition, they can help you and your office staff contact a Pfizer Field Reimbursement Manager (FRM) in your area.

FRMs are trained to help address specific access issues—in person or over the phone. They can help educate your staff on our access and reimbursement resources and help address challenging or urgent Pfizer Oncology patient cases you have sent to Pfizer Oncology Together.



FOR LIVE, PERSONALIZED SUPPORT
Call **1-877-744-5675** (Monday–Friday 8 AM–8 PM ET)

VISIT
PfizerOncologyTogether.com

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Most Common Adverse Events

- Across studies, the most common adverse reactions observed in bevacizumab patients at a rate >10% were:
  - Epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis
- Across all studies, bevacizumab was discontinued in 8% to 22% of patients because of adverse reactions

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Pfizer is committed to supporting you and your patients

For commercially insured patients

Co-Pay Savings Program for Injectables

Finding financial support options. Together.

Limits, terms, and conditions apply.
Please see page 7 for terms and conditions.

Eligible patients may pay as little as **$0** per Tx

PfizerBiosimilarsResource.com

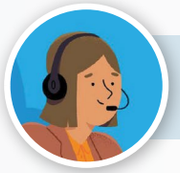
Downloadable tools are available to help support you when implementing Pfizer biosimilars into your practice.

ThisIsLivingWithCancer.com

A free app designed to help manage life with cancer

Help your patients and their caregivers stay connected and get organized by telling them about **LivingWith™**.

The **LivingWith** app is available to anyone living with cancer and their loved ones, and is not specific to ZIRABEV.



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VISIT
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Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events

- In first-line metastatic colorectal cancer (mCRC), the most common grade 3-4 events in Study 2107, which occurred at a (≥2%) higher incidence in the bevacizumab plus IFL vs IFL groups, were asthenia (10% vs 7%), abdominal pain (8% vs 5%), pain (8% vs 5%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), diarrhea (34% vs 25%), constipation (4% vs 2%), leukopenia (37% vs 31%), and neutropenia (21% vs 14%)

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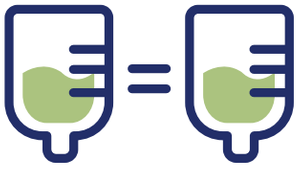
FDA-approved biosimilars such as bevacizumab-bvzr (ZIRABEV®) are recommended as treatment options in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1-4*]

ZIRABEV® (bevacizumab-bvzr) is a biosimilar to Avastin® (bevacizumab)[5]

Approved for eligible indications of Avastin[5]



Same dosing and administration schedule as Avastin[5]

Useful ordering and coding information

*NCCN Guidelines® recommend the use of an FDA-approved biosimilar as an appropriate substitute for bevacizumab. See the NCCN Guidelines for detailed recommendations, including specific treatment regimens. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In second-line mCRC, the most common grade 3-5 (nonhematologic) and 4-5 (hematologic) events in Study E3200, which occurred at a higher incidence (≥2%) in the bevacizumab plus FOLFOX4 vs FOLFOX4 groups, 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 underestimate the true adverse event rates due to the reporting mechanisms used in this study

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Introduction
Dosing and Administration
Ordering and Product Information

ZIRABEV® (bevacizumab-bvzr) has the same dosing and administration schedule as Avastin® (bevacizumab)[5]

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

INDICATIONS	DOSING
Metastatic Colorectal Cancer • In combination with intravenous fluorouracil-based chemotherapy	• 5 mg/kg every 2 weeks intravenously in combination with bolus-IFL • 10 mg/kg every 2 weeks intravenously 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
First-Line Non-Squamous Non-Small Cell Lung Cancer • In combination with carboplatin and paclitaxel	• 15 mg/kg intravenously every 3 weeks
Recurrent Glioblastoma	• 10 mg/kg intravenously every 2 weeks
Metastatic Renal Cell Carcinoma • In combination with interferon alfa	• 10 mg/kg intravenously every 2 weeks

Please see full ZIRABEV Prescribing Information for additional details.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In non-small cell lung cancer (NSCLC), grade 3-5 (nonhematologic) and grade 4-5 (hematologic) adverse events in Study E4599 occurring at a (≥2%) higher incidence in bevacizumab-treated patients vs controls 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%)

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Introduction
Dosing and Administration
Ordering and Product Information

ZIRABEV® (bevacizumab-bvzr) has the same dosing and administration schedule as Avastin® (bevacizumab)[5]

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

INDICATIONS	DOSING
Persistent, Recurrent, or Metastatic Cervical Cancer • In combination with paclitaxel and cisplatin or with paclitaxel and topotecan	• 15 mg/kg intravenously every 3 weeks
Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	
• Stage III or IV disease following initial surgical resection	• 15 mg/kg intravenously 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 or until disease progression, whichever occurs earlier
• Platinum-resistant recurrent disease	• 10 mg/kg intravenously every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week) • 15 mg/kg intravenously every 3 weeks with topotecan (every 3 weeks)
• Platinum-sensitive recurrent disease	• 15 mg/kg intravenously every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent until disease progression • 15 mg/kg intravenously every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent until disease progression

Please see full ZIRABEV Prescribing Information for additional details.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In recurrent glioblastoma (rGBM) Study EORTC 26101, 22% of patients discontinued treatment in the bevacizumab with lomustine arm due to adverse reactions compared with 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
- In metastatic renal cell carcinoma (mRCC), the most common grade 3-5 adverse events in Study BO17705, occurring at a (≥2%) higher incidence in bevacizumab-treated patients vs controls, 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)

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Introduction
Dosing and Administration
Ordering and Product Information

ZIRABEV® (bevacizumab-bvzr) is available in single-dose vials for intravenous infusion[5]

Ordering ZIRABEV—What you need to know[5,10]

Unit of Sale	100 mg/4 mL SDV	400 mg/16 mL SDV
Unit of Sale NDC	0069-0315-01	0069-0342-01
Unit of Sale Quantity	1 vial per carton	1 vial per carton
Unit of Sale List Price*	$613.40	$2,453.60
HCPCS Code	Q5118	
OPPS Status	G: Pass-through payment	

OPPS=Outpatient Prospective Payment System; SDV=single-dose vial.
*As of October 2022.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In persistent, recurrent, or metastatic cervical cancer, grade 3 or 4 adverse reactions in Study GOG-0240, occurring at a higher incidence (≥2%) in 218 patients receiving bevacizumab plus chemotherapy compared to 222 patients receiving chemotherapy alone, were abdominal pain (12% vs 10%), 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%), hypertension (11% vs 0.5%), thrombosis (8% vs 3%), 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%)

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Introduction

Dosing and Administration

Ordering and Product Information

ZIRABEV® (bevacizumab-bvzr) is available in single-dose vials for intravenous infusion[5]

Storage and handling[5]

Available in **100 mg/4 mL SDVs** and **400 mg/16 mL SDVs**

Store in the refrigerator at 2 to 8 °C (36 to 46 °F)

Keep in original carton and protect from light. Do not freeze or shake the vial or carton

Please see the full ZIRABEV Prescribing Information for additional details.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer after primary surgery:
  - 608 patients received carboplatin and paclitaxel plus bevacizumab followed by bevacizumab (CPB15+), 607 patients received carboplatin and paclitaxel plus bevacizumab followed by placebo (CPB15), and 602 patients received carboplatin and paclitaxel plus placebo followed by placebo (CPP)
  - Grade 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the bevacizumab arms vs the chemotherapy-only 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%)

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FDA-approved biosimilars such as bevacizumab-bvzr (ZIRABEV®) are recommended as treatment options in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1-4*]

A totality of evidence supports biosimilarity to Avastin® (bevacizumab)[5,11]

Biosimilarity established based on a totality of evidence[5,11]

Extrapolation allows potential approval for nonstudied indications[11]

No clinically meaningful differences in terms of efficacy or safety[7]

*NCCN Guidelines® recommend the use of an FDA-approved biosimilar as an appropriate substitute for bevacizumab. See the NCCN Guidelines for detailed recommendations, including specific treatment regimens. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (psOC), grade 3-4 adverse reactions in Study AVF4095g, occurring at a higher incidence (≥2%) in 247 patients receiving bevacizumab plus carboplatin and gemcitabine (chemotherapy) compared to 233 patients receiving placebo plus 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%)

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FDA-approved biosimilars such as bevacizumab-bvzr (ZIRABEV®) are recommended treatment options in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1-4*]

ZIRABEV® (bevacizumab-bvzr) was approved by the FDA based on the totality of evidence demonstrating it is highly similar to Avastin® (bevacizumab)[5,7,11]

CLINICAL STUDY	ZIRABEV showed no clinically meaningful difference to Avastin-EU[7*]
CLINICAL PHARMACOLOGY (PK/PD)	ZIRABEV demonstrated PK similarity to Avastin in healthy volunteers[7]
NONCLINICAL	ZIRABEV is similar to Avastin-EU based on TK and toxicity[7]
ANALYTICAL	ZIRABEV is highly similar to Avastin in terms of structure and function[7]

PD=pharmacodynamic; PK=pharmacokinetic; TK=toxicokinetic.
*Product sourced from the EU is often used as a comparator in trials to demonstrate biosimilarity.

Click to view full evidence

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, grade 3-4 adverse reactions in Study GOG-0213, occurring at a higher incidence (≥2%) in 325 patients receiving bevacizumab plus carboplatin and paclitaxel (chemotherapy) compared to 332 patients receiving 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 (3.0% vs 0%)

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CLINICAL STUDY

ZIRABEV showed no clinically meaningful difference to Avastin-EU[7]*

- In a study of patients with NSCLC, ZIRABEV and Avastin-EU demonstrated statistically equivalent objective response rates (ORRs)
  - ORRs were 45.3% and 44.6% for ZIRABEV and Avastin-EU, respectively (90% CI: 0.89-1.16)
- Similarity between ZIRABEV and Avastin-EU fell within the prespecified equivalence margin, supporting no clinically meaningful differences in efficacy

CLINICAL PHARMACOLOGY (PK/PD)

ZIRABEV demonstrated PK similarity to Avastin in healthy volunteers[7]

- In a phase 1 study, the 90% CIs for the test-to-reference ratios of C_{max}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$ were within the predefined bioequivalence acceptance range of 80% to 125% for pairwise comparisons of ZIRABEV to Avastin-EU, ZIRABEV to Avastin-US, and Avastin-EU to Avastin-US

NONCLINICAL

ZIRABEV is similar to Avastin-EU based on TK and toxicity[7]

- In a 1-month comparative toxicity study, ZIRABEV or Avastin-EU administration resulted in the expected pharmacologically mediated response of physeal dysplasia in the distal femur, with similar incidence and severity across all animals dosed with the 2 antibodies

ANALYTICAL

ZIRABEV is highly similar to Avastin in terms of structure and function[7]

Characterization studies included multiple analytical methods supporting quantitative and qualitative similarity assessments, including but not limited to:

- Structural similarity: Identical primary amino acid sequence
  - Peptide mapping data supported identical primary amino acid sequence for ZIRABEV and Avastin-US and Avastin-EU
- Functional similarity: Highly similar inhibition of VEGF-induced cell proliferation
  - Similarity between ZIRABEV, Avastin-US, and Avastin-EU demonstrated by the assessment of dose-response curves and relative potency

$AUC_{0-\tau}$=area under the curve from time 0 to the time of the last quantifiable concentration; $AUC_{0-\infty}$=area under the curve from time 0 to extrapolated infinite time; CI=confidence interval; C_{max}=maximum observed serum concentration; PD=pharmacodynamic; PK=pharmacokinetic; TK=toxicokinetic; VEGF=vascular endothelial growth factor.
*Product sourced from the EU is often used as a comparator in trials to demonstrate biosimilarity.

CLOSE

incidence (≥2%) in 325 patients receiving bevacizumab plus carboplatin and paclitaxel (chemotherapy) compared to 332 patients receiving 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 (3.0% vs 0%)

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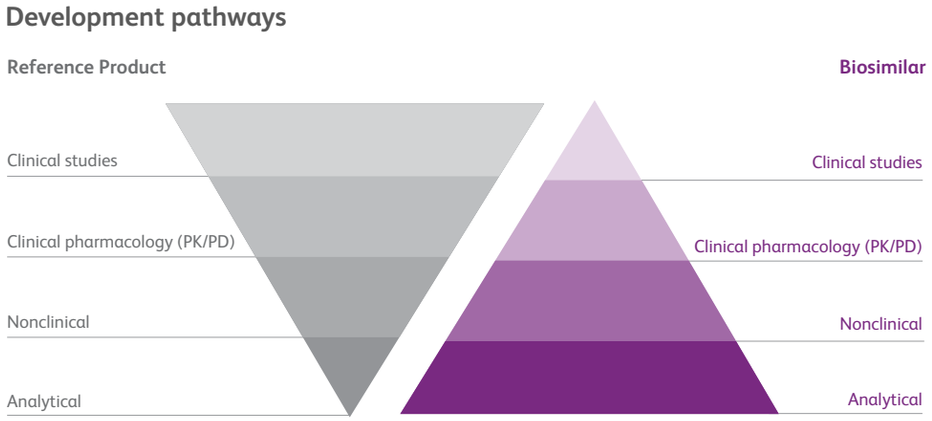
Biosimilars: Highly similar versions of existing biologic medicines[11]

- According to the FDA, a biosimilar is a medicine highly similar to another biological medicine or reference product already marketed in the United States
  - Biosimilars have no clinically meaningful differences in terms of safety, purity, and potency from their reference products

The FDA evaluates biosimilars based on a totality of evidence approach[11,12]



- The goal of biosimilar development is to demonstrate that there are no clinically meaningful differences based on the totality of evidence[11,12]
- Analytical studies are the foundation of biosimilar development and provide the greatest sensitivity for detecting differences between a biosimilar and its reference product[11,12]

Click to enlarge

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (prOC), grade 3-4 adverse reactions in Study MO22224, occurring at a higher incidence (≥2%) in 179 patients receiving bevacizumab plus 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%)

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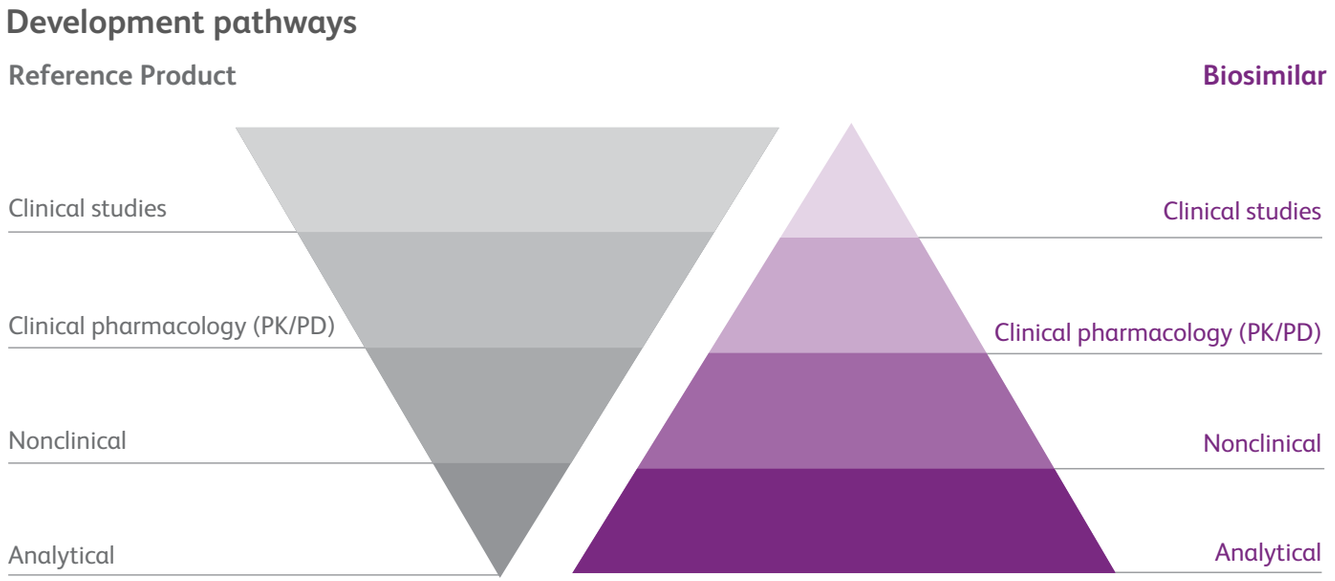
- According to the FDA, a biosimilar is a medicine highly similar to another biological medicine or reference product already marketed in the United States
  - Biosimilars have no clinically meaningful differences in terms of safety, purity, and potency from their reference products

The FDA evaluates biosimilars based on a totality of evidence approach[11,12]



- The goal of biosimilar development is to demonstrate that there are no clinically meaningful differences based on the totality of evidence[11,12]
- Analytical studies are the foundation of biosimilar development and provide the greatest sensitivity for detecting differences between a biosimilar and its reference product[11,12]

CLOSE

Indication-Specific Adverse Events (continued)

- In platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (prOC), grade 3-4 adverse reactions in Study MO22224, occurring at a higher incidence (≥2%) in 179 patients receiving bevacizumab plus 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%)

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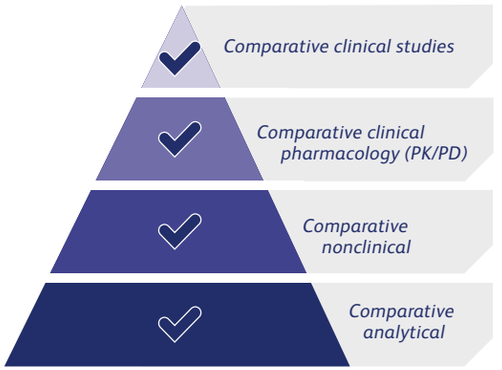
Extrapolation: After biosimilarity is established, allows potential approval for nonstudied indications[11]

Biosimilarity established based on totality of evidence → **Extrapolation for biosimilars**



+ **Scientific justification** to support extrapolation to each approved indication of the reference biologic =

Extrapolated indications, including:
- *Metastatic colorectal cancer*
- *Recurrent glioblastoma*
- *Metastatic renal cell carcinoma*
- *Persistent, recurrent, or metastatic cervical cancer*
- *Epithelial ovarian, fallopian tube, or primary peritoneal cancer*[5]

Extrapolation builds on the thorough analysis of similarity between the biosimilar and reference biologic supported by the scientific evidence generated in robust analytical, nonclinical, and clinical comparability studies. Together with the well-known understanding of the reference biologic, this evidence is carefully analyzed to support scientific justification of extrapolated indications.[11]

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SELECTED 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 compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies. Non-GI fistulae incidence ranged from <1% to 1.8%, and was highest in patients with cervical cancer. Avoid ZIRABEV 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 for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any internal organ

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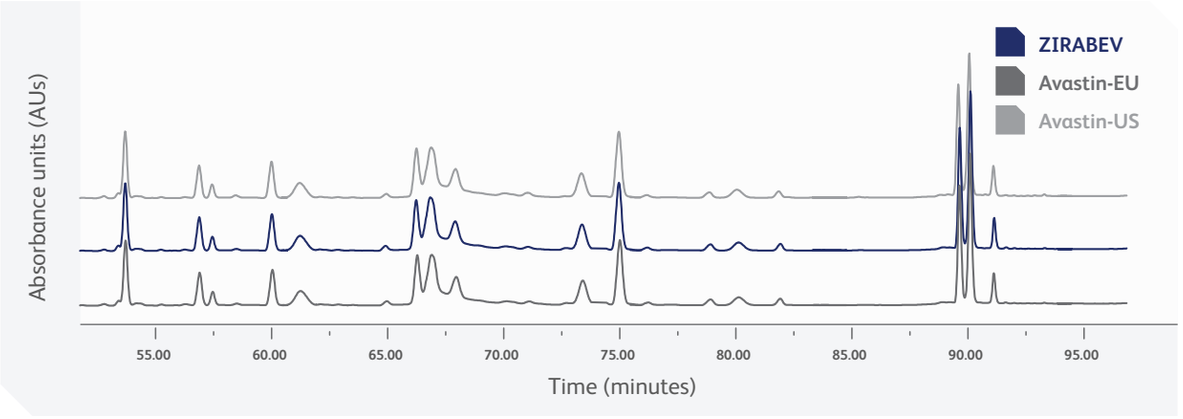
*ZIRABEV® (bevacizumab-bvzr) is highly similar in structure and function to Avastin® (bevacizumab)[7]**

Structural similarity: Identical primary amino acid sequence

Peptide mapping data supported identical primary amino acid sequence for ZIRABEV and Avastin



*A comprehensive analytical approach was used to assess the similarity of ZIRABEV to Avastin-US and Avastin-EU. Two examples are shown above. Extensive structural and functional characterization studies were completed for 3 products as part of the ZIRABEV development program to provide the foundation for the similarity assessment. Characterization studies included multiple orthogonal analytical methods capable of supporting a quantitative and qualitative similarity assessment of bevacizumab attributes. Minor differences between ZIRABEV, Avastin-US, and Avastin-EU were characterized. These minor quantitative differences were demonstrated to not impact in vitro biological activity and are not clinically relevant. (Data not shown here.)

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- **Surgery and Wound Healing Complications.** The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in bevacizumab-treated patients. In patients who experience wound healing complications during ZIRABEV treatment, withhold ZIRABEV 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 bevacizumab products after resolution of wound healing complications has not been established. Discontinue for wound healing complications of necrotizing fasciitis

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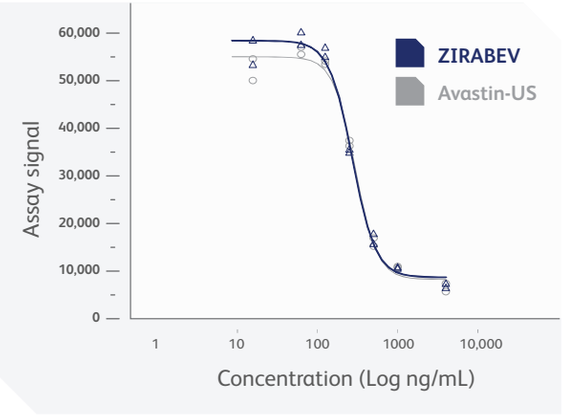
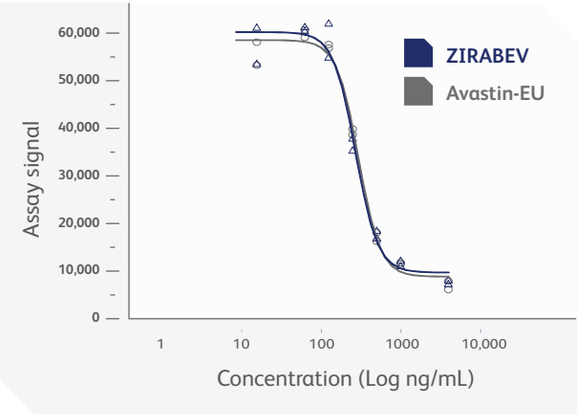
*ZIRABEV® (bevacizumab-bvzr) is highly similar in structure and function to Avastin® (bevacizumab)[7]**

Functional similarity: Inhibition of VEGF-induced cell proliferation highly similar to that of Avastin

Cell growth inhibition assay: Dose-response curve at a constant VEGF concentration





*A comprehensive analytical approach was used to assess the similarity of ZIRABEV to Avastin-US and Avastin-EU. Two examples are shown above. Extensive structural and functional characterization studies were completed for 3 products as part of the ZIRABEV development program to provide the foundation for the similarity assessment. Characterization studies included multiple orthogonal analytical methods capable of supporting a quantitative and qualitative similarity assessment of bevacizumab attributes. Minor differences between ZIRABEV, Avastin-US, and Avastin-EU were characterized. These minor quantitative differences were demonstrated to not impact in vitro biological activity and are not clinically relevant. (Data not shown here.)

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SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- **Hemorrhage.** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding occurred up to 5-fold more frequently in patients receiving bevacizumab. In clinical studies, the incidence of grade ≥3 hemorrhagic events among patients receiving bevacizumab ranged from 0.4% to 7%. Do not administer ZIRABEV to patients with serious hemorrhage or a recent history of hemoptysis (≥1/2 tsp of red blood). Discontinue ZIRABEV in patients who develop grade 3-4 hemorrhage

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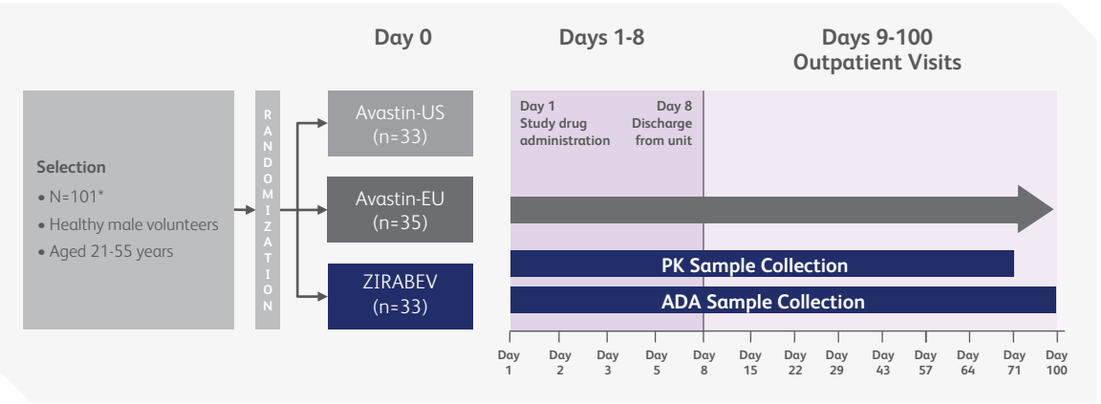
Double-blind, single-dose comparative clinical pharmacology study[7]



PK endpoints

- C_{max}
- $AUC_{0-\tau}$
- $AUC_{0-\infty}$
- Systemic clearance (CL)
- Terminal half-life ($t_{1/2}$)
- Volume of distribution at steady state (V_{ss})

Immunogenicity and safety endpoints

- Incidence of bevacizumab ADAs, including NAbs
- Incidence of AEs

While not shown here, the following endpoints also supported biosimilarity:

- Mean (±SD) PK parameter estimates of CL, $t_{1/2}$, and V_{ss} were comparable across treatment groups
- The 3 treatment groups had a similar ADA profile. No NAb were detected in any of the ADA-positive serum samples
- No clinically meaningful differences in safety profiles were observed between treatment groups

ADA=antidrug antibody; AE=adverse event; NAb=neutralizing antibody; SD=standard deviation.
*The final population used in the PK analysis consisted of 97 subjects; 4 subjects were excluded due to premature study withdrawal, none of which were study-drug related.

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SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- Additional serious and sometimes fatal adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:
  - **Arterial thromboembolic events (ATE)** (grade ≥3, 5%, highest in patients with GBM). Discontinue in patients who develop a severe ATE
  - **Renal injury and proteinuria.** Monitor proteinuria during ZIRABEV therapy. Patients with a 2+ or greater urine dipstick reading should undergo 24-hour urine collection. Withhold for proteinuria ≥2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome
    - Grade 3-4 proteinuria ranged from 0.7% to 7% in clinical studies
    - Nephrotic syndrome (<1%)

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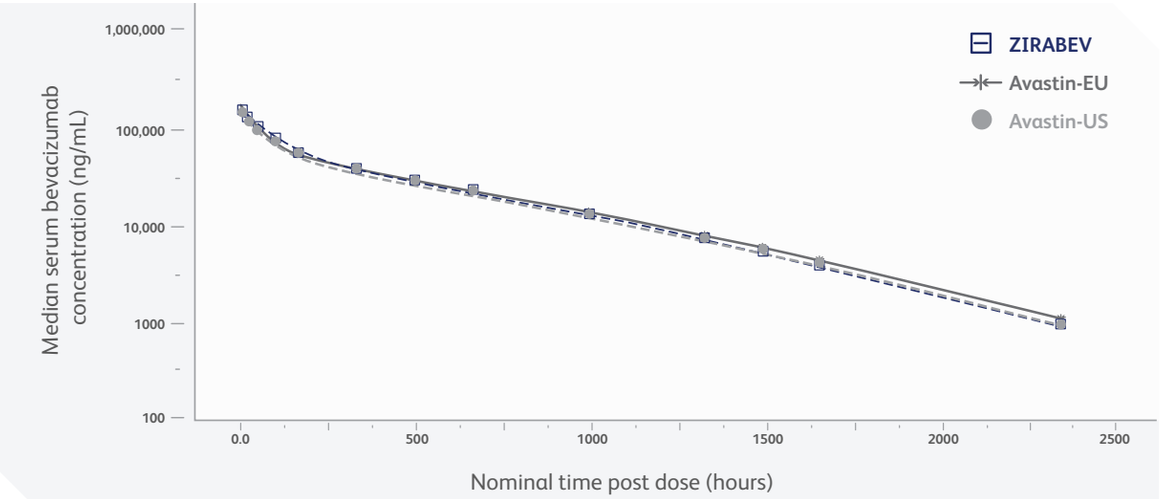
Similar PK profile to Avastin® (bevacizumab) in healthy subjects in a 3-arm study[7]

Median serum concentration-time profile following a single 5-mg/kg dose of ZIRABEV, Avastin-EU, or Avastin-US in healthy subjects—PP population



PP=per protocol.

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SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- Additional serious adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:
  - **Venous thromboembolism events (VTE)** (grade ≥3, 11% seen in Study GOG-0240). Discontinue ZIRABEV in patients with a grade 4 VTE, including pulmonary embolism
  - **Hypertension** (grade 3-4, 5%-18%). Monitor blood pressure during treatment and, for ZIRABEV-associated hypertension, continue monitoring after discontinuation. Withhold for severe hypertension. Discontinue for hypertensive crisis or hypertensive encephalopathy
  - **Posterior reversible encephalopathy syndrome (PRES)** (<0.5%). Discontinue ZIRABEV in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing bevacizumab products, although some patients have experienced ongoing neurologic sequelae

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Similar PK profile to Avastin® (bevacizumab) in healthy subjects in a 3-arm study[7]

Test	Reference	Parameter	Adjusted Geometric Means		Ratio (%)	90% CI (%)
			Test	Reference		
ZIRABEV	Avastin-EU	C_{max}	141.5	135.5	104.42	98.36-110.84
		$AUC_{0-\tau}$	40,330	40,490	99.62	93.69-105.93
		$AUC_{0-\infty}$	42,490	43,100	98.58	92.16-105.44
ZIRABEV	Avastin-US	C_{max}	141.5	128.9	109.79	103.38-116.60
		$AUC_{0-\tau}$	40,330	38,660	104.32	98.06-110.97
		$AUC_{0-\infty}$	42,490	41,120	103.33	96.55-110.58
Avastin-EU	Avastin-US	C_{max}	135.5	128.9	105.15	99.05-111.62
		$AUC_{0-\tau}$	40,490	38,660	104.71	98.48-111.34
		$AUC_{0-\infty}$	43,100	41,120	104.82	98.00-112.12

ANOVA=analysis of variance.

90% CIs of the geometric mean (GM) ratio for C_{max} and AUC were within the prespecified equivalence criteria of 80%–125%.[7]

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- Additional serious adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included (continued):
  - **Congestive heart failure (CHF)** (grade ≥3 left ventricular dysfunction, 1%). Discontinue ZIRABEV in patients who develop CHF
- **Infusion-related reactions.** Infusion-related reactions with the first dose of bevacizumab occurred in <3% of patients, and severe reactions occurred in 0.4% of patients. Decrease the rate of infusion for mild 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
- **Ovarian failure.** Inform females of reproductive potential of the risk of ovarian failure prior to initiating treatment with ZIRABEV

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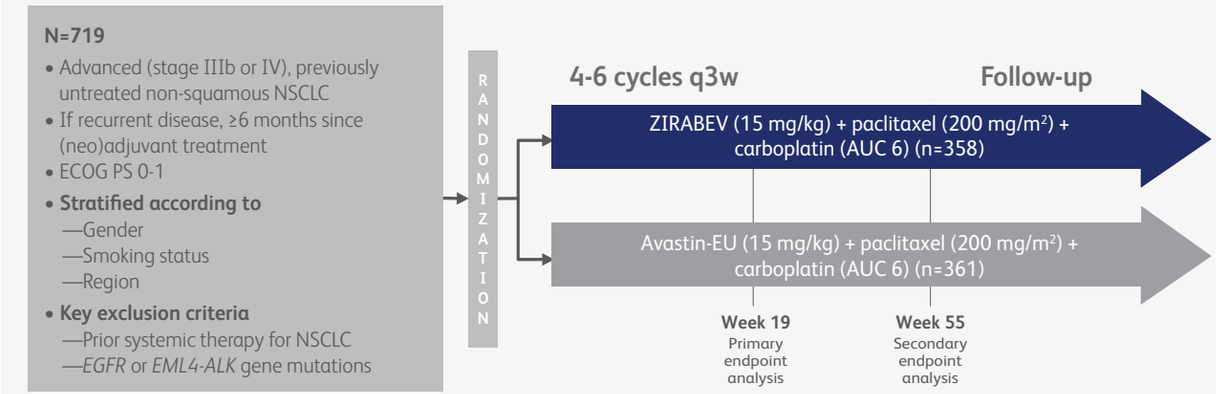
Comparative clinical trial in patients with advanced non-squamous NSCLC[7]



ECOG PS=Eastern Cooperative Oncology Group performance status; q3w=every 3 weeks.

Study Design
Primary Endpoint
Secondary Endpoints

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION

Pregnancy Warning

- Based on the mechanism of action and animal studies, bevacizumab products may cause fetal harm
- Advise female patients that bevacizumab products may cause fetal harm and to inform their health care provider of a known or suspected pregnancy
- Advise females of reproductive potential to use effective contraception during treatment with ZIRABEV and for 6 months after the last dose of ZIRABEV
- Advise nursing women that breastfeeding is not recommended during treatment with ZIRABEV and for 6 months following their last dose of treatment
- Bevacizumab products may impair fertility

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Comparative clinical trial in patients with advanced non-squamous NSCLC[7]

Primary endpoint

- ORR at week 19 (confirmed by week 25)

Secondary endpoints

- DOR
- 1-year PFS rate
- 1-year OS rate
- Safety
- Immunogenicity
- Peak and trough concentrations for ZIRABEV and Avastin-EU

While not shown here, the following endpoints also supported biosimilarity[7]:

- No statistically significant or clinically meaningful differences between the 2 treatment groups were observed for DOR
- Trough and apparent peak serum bevacizumab concentrations were comparable for both treatments
- The observed rate of ADA and NAb was low, with comparable percentages of patients with ADA and NAb observed for the 2 treatment groups. Given the low number of patients with ADA (1.5% for ZIRABEV and 1.4% for Avastin-EU post treatment), the association between immunogenicity and safety could not be evaluated. The patients with ADA did not experience serious IRRs or anaphylactic reactions

DOR=duration of response; IRR=infusion-related reaction; OS=overall survival; PFS=progression-free survival.

Study Design
Primary Endpoint
Secondary Endpoints

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION

Most Common Adverse Events

- Across studies, the most common adverse reactions observed in bevacizumab patients at a rate >10% were:
  - Epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis
- Across all studies, bevacizumab was discontinued in 8% to 22% of patients because of adverse reactions

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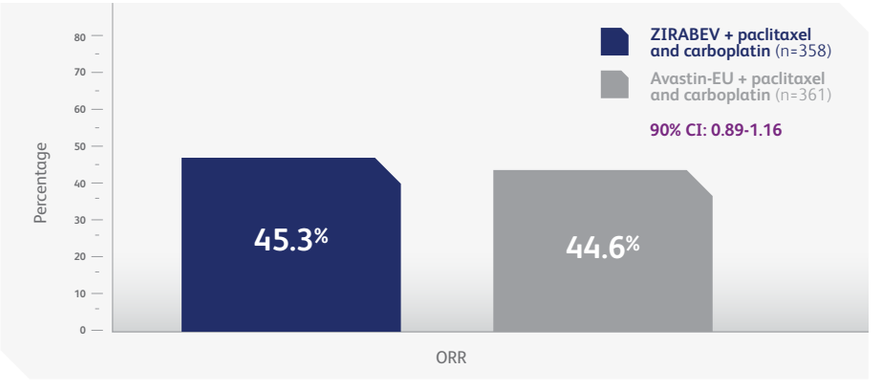
Primary endpoint: In patients with NSCLC, ZIRABEV® (bevacizumab-bvzr) demonstrated similar ORR to Avastin® (bevacizumab)*[7]



Study design: A phase 3, randomized, double-blind study of ZIRABEV or Avastin-EU in combination with paclitaxel and carboplatin for the first-line treatment of treatment-naïve patients with advanced non-squamous NSCLC. Primary endpoint: ORR by week 19, confirmed by week 25.

- Similarity between ZIRABEV and Avastin-EU is indicated by the 90% CI for the risk ratio,† which fell within the prespecified equivalence margin

CR=complete response; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.
*ORR was defined as the percent of patients within each treatment group who achieved a best overall response of CR or PR by week 19 in accordance with RECIST v1.1, which was subsequently confirmed on a follow-up tumor assessment by week 25.
†Risk ratio and associated 90% CI were based on the Miettinen and Nurminen method.

The comparative clinical trial evaluated patients with NSCLC, a sensitive population for detecting potential between-product differences when establishing biosimilarity.[7]

Study Design
Primary Endpoint
Secondary Endpoints

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events

- In first-line metastatic colorectal cancer (mCRC), the most common grade 3-4 events in Study 2107, which occurred at a (≥2%) higher incidence in the bevacizumab plus IFL vs IFL groups, were asthenia (10% vs 7%), abdominal pain (8% vs 5%), pain (8% vs 5%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), diarrhea (34% vs 25%), constipation (4% vs 2%), leukopenia (37% vs 31%), and neutropenia (21% vs 14%)

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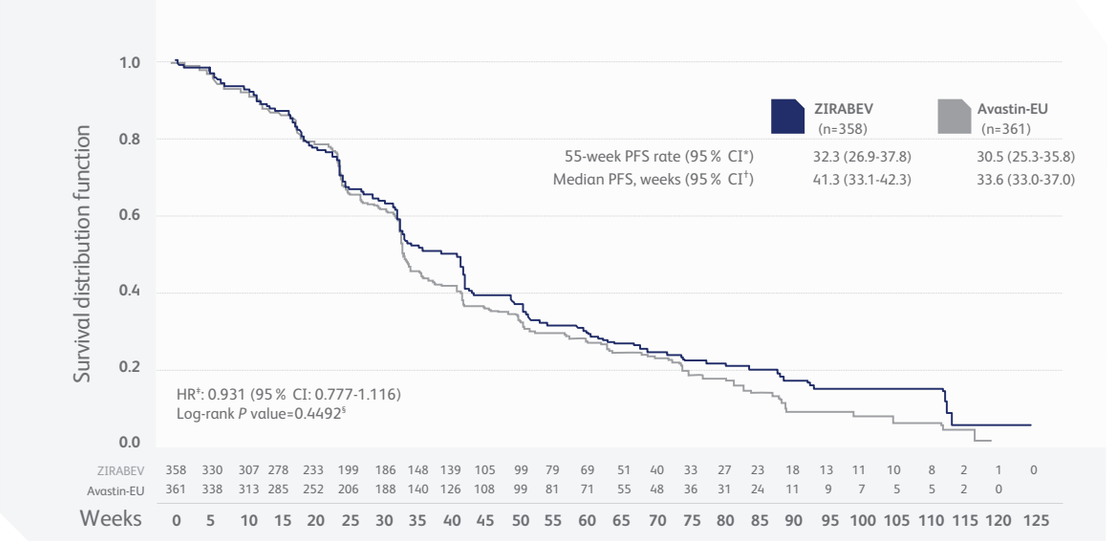
Secondary endpoint: No significant differences in 1-year PFS rate[7]

Kaplan-Meier plot of PFS—ITT population (55-week analysis)[7]



HR=hazard ratio; ITT=intent to treat.
*Estimated from the Kaplan-Meier curve, calculated from the product limit method.
†Based on the Brookmeyer and Crowley method.
‡Based on the Cox proportional hazards model stratified by smoking, sex, and region.
§This is a 2-sided *P* value from log-rank test stratified by smoking, sex, and region.

Study Design
Primary Endpoint
Secondary Endpoints

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In second-line mCRC, the most common grade 3-5 (nonhematologic) and 4-5 (hematologic) events in Study E3200, which occurred at a higher incidence (≥2%) in the bevacizumab plus FOLFOX4 vs FOLFOX4 groups, 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 underestimate the true adverse event rates due to the reporting mechanisms used in this study

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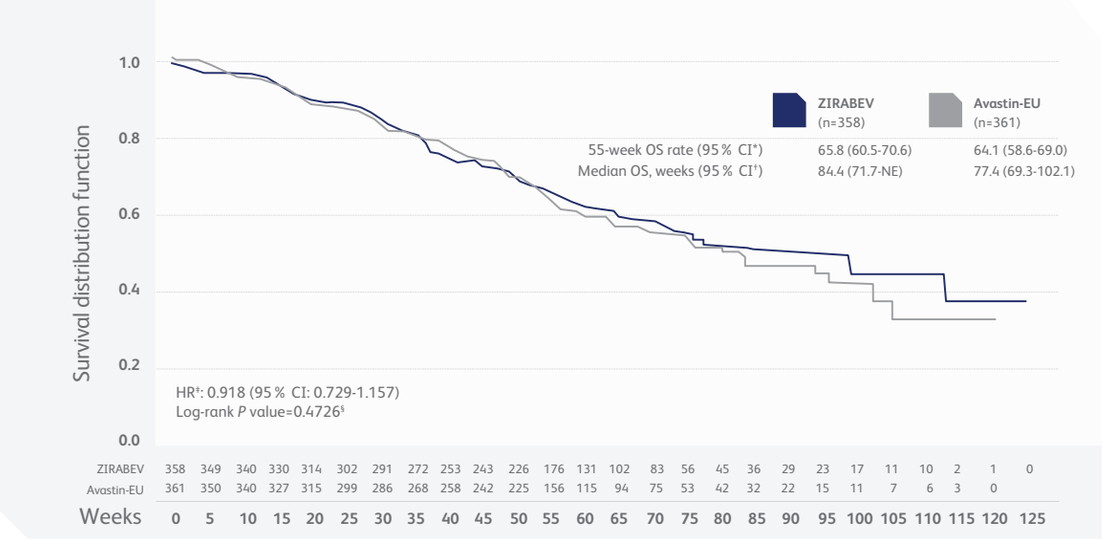
Secondary endpoint: No significant differences in 1-year OS rate[7]

Kaplan-Meier plot of OS—ITT population (55-week analysis)[7]



NE=not evaluable.
*Estimated from the Kaplan-Meier curve, calculated from the product limit method.
†Based on the Brookmeyer and Crowley method.
‡Based on the Cox proportional hazards model stratified by smoking, sex, and region.
§This is a 2-sided *P* value from log-rank test stratified by smoking, sex, and region.

Study Design
Primary Endpoint
Secondary Endpoints

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In non-small cell lung cancer (NSCLC), grade 3-5 (nonhematologic) and grade 4-5 (hematologic) adverse events in Study E4599 occurring at a (≥2%) higher incidence in bevacizumab-treated patients vs controls 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%)

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ZIRABEV® (bevacizumab-bvzr) showed a safety profile similar to Avastin® (bevacizumab)[5,7]

No significant differences in adverse events of special interest[7]

Treatment-emergent adverse events of special interest (all causalities–tier 1, grade 3 or higher)—safety population

	ZIRABEV (n=356)	Avastin-EU (n=358)
Categories, n (%)		
Hypertension, only grade 3 or higher	34 (9.6)	32 (8.9)
Venous thromboembolic events	8 (2.2)	4 (1.1)
Bleeding/hemorrhage, including pulmonary hemorrhage	8 (2.2)	7 (2.0)
Cardiac disorders	10 (2.8)	12 (3.4)
Arterial thromboembolic events	6 (1.7)	6 (1.7)
Proteinuria/nephrotic syndrome	4 (1.1)	5 (1.4)
Congestive heart failure	1 (0.3)	3 (0.8)
Gastrointestinal perforation	0	2 (0.6)

- No clinically meaningful safety differences were identified between the 2 treatment groups
- No new safety signals were identified with ZIRABEV compared with the known adverse event profile of Avastin

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION

Indication-Specific Adverse Events (continued)

- In recurrent glioblastoma (rGBM) Study EORTC 26101, 22% of patients discontinued treatment in the bevacizumab with lomustine arm due to adverse reactions compared with 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
- In metastatic renal cell carcinoma (mRCC), the most common grade 3-5 adverse events in Study BO17705, occurring at a (≥2%) higher incidence in bevacizumab-treated patients vs controls, 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)

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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 compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies. Non-GI fistulae incidence ranged from <1% to 1.8%, and was highest in patients with cervical cancer. Avoid ZIRABEV 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 for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any internal organ
- **Surgery and Wound Healing Complications.** The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in bevacizumab-treated patients. In patients who experience wound healing complications during ZIRABEV treatment, withhold ZIRABEV 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 bevacizumab products after resolution of wound healing complications has not been established. Discontinue for wound healing complications of necrotizing fasciitis
- **Hemorrhage.** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding occurred up to 5-fold more frequently in patients receiving bevacizumab. In clinical studies, the incidence of grade ≥3 hemorrhagic events among patients receiving bevacizumab ranged from 0.4% to 7%. Do not administer ZIRABEV to patients with serious hemorrhage or a recent history of hemoptysis (≥1/2 tsp of red blood). Discontinue ZIRABEV in patients who develop grade 3-4 hemorrhage
- Additional serious and sometimes fatal adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:
  - **Arterial thromboembolic events (ATE)** (grade ≥3, 5%, highest in patients with GBM). Discontinue in patients who develop a severe ATE
  - **Renal injury and proteinuria.** Monitor proteinuria during ZIRABEV therapy. Patients with a 2+ or greater urine dipstick reading should undergo 24-hour urine collection. Withhold for proteinuria ≥2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Indication-Specific Adverse Events (continued)

- In persistent, recurrent, or metastatic cervical cancer, grade 3 or 4 adverse reactions in Study GOG-0240, occurring at a higher incidence (≥2%) in 218 patients receiving bevacizumab plus chemotherapy compared to 222 patients receiving chemotherapy alone, were abdominal pain (12% vs 10%), 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%), hypertension (11% vs 0.5%), thrombosis (8% vs 3%), 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%)

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Important Safety Information

- Grade 3-4 proteinuria ranged from 0.7% to 7% in clinical studies
- Nephrotic syndrome (<1%)

- Additional serious adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:
  - **Venous thromboembolism events (VTE)** (grade ≥3, 11% seen in Study GOG-0240). Discontinue ZIRABEV in patients with a grade 4 VTE, including pulmonary embolism
  - **Hypertension** (grade 3-4, 5%-18%). Monitor blood pressure during treatment and, for ZIRABEV-associated hypertension, continue monitoring after discontinuation. Withhold for severe hypertension. Discontinue for hypertensive crisis or hypertensive encephalopathy
  - **Posterior reversible encephalopathy syndrome (PRES)** (<0.5%). Discontinue ZIRABEV in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing bevacizumab products, although some patients have experienced ongoing neurologic sequelae
  - **Congestive heart failure (CHF)** (grade ≥3 left ventricular dysfunction, 1%). Discontinue ZIRABEV in patients who develop CHF
- **Infusion-related reactions.** Infusion-related reactions with the first dose of bevacizumab occurred in <3% of patients, and severe reactions occurred in 0.4% of patients. Decrease the rate of infusion for mild 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
- **Ovarian failure.** Inform females of reproductive potential of the risk of ovarian failure prior to initiating treatment with ZIRABEV

Pregnancy Warning

- Based on the mechanism of action and animal studies, bevacizumab products may cause fetal harm
- Advise female patients that bevacizumab products may cause fetal harm and to inform their health care provider of a known or suspected pregnancy

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION

Indication-Specific Adverse Events (continued)

- In stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer after primary surgery:
  - 608 patients received carboplatin and paclitaxel plus bevacizumab followed by bevacizumab (CPB15+), 607 patients received carboplatin and paclitaxel plus bevacizumab followed by placebo (CPB15), and 602 patients received carboplatin and paclitaxel plus placebo followed by placebo (CPP)
  - Grade 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the bevacizumab arms vs the chemotherapy-only 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%)

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Important Safety Information

- Advise females of reproductive potential to use effective contraception during treatment with ZIRABEV and for 6 months after the last dose of ZIRABEV
- Advise nursing women that breastfeeding is not recommended during treatment with ZIRABEV and for 6 months following their last dose of treatment
- Bevacizumab products may impair fertility

Most Common Adverse Events

- Across studies, the most common adverse reactions observed in bevacizumab patients at a rate >10% were:
  - Epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis
- Across all studies, bevacizumab was discontinued in 8% to 22% of patients because of adverse reactions

Indication-Specific Adverse Events

- In first-line metastatic colorectal cancer (mCRC), the most common grade 3-4 events in Study 2107, which occurred at a (≥2%) higher incidence in the bevacizumab plus IFL vs IFL groups, were asthenia (10% vs 7%), abdominal pain (8% vs 5%), pain (8% vs 5%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), diarrhea (34% vs 25%), constipation (4% vs 2%), leukopenia (37% vs 31%), and neutropenia (21% vs 14%)
- In second-line mCRC, the most common grade 3-5 (nonhematologic) and 4-5 (hematologic) events in Study E3200, which occurred at a higher incidence (≥2%) in the bevacizumab plus FOLFOX4 vs FOLFOX4 groups, 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 underestimate the true adverse event rates due to the reporting mechanisms used in this study

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION

Indication-Specific Adverse Events (continued)

- In platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (psOC), grade 3-4 adverse reactions in Study AVF4095g, occurring at a higher incidence (≥2%) in 247 patients receiving bevacizumab plus carboplatin and gemcitabine (chemotherapy) compared to 233 patients receiving placebo plus 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%)

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Important Safety Information

- In non-small cell lung cancer (NSCLC), grade 3-5 (nonhematologic) and grade 4-5 (hematologic) adverse events in Study E4599 occurring at a (≥2%) higher incidence in bevacizumab-treated patients vs controls 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%)
- In recurrent glioblastoma (rGBM) Study EORTC 26101, 22% of patients discontinued treatment in the bevacizumab with lomustine arm due to adverse reactions compared with 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
- In metastatic renal cell carcinoma (mRCC), the most common grade 3-5 adverse events in Study BO17705, occurring at a (≥2%) higher incidence in bevacizumab-treated patients vs controls, 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)
- In persistent, recurrent, or metastatic cervical cancer, grade 3 or 4 adverse reactions in Study GOG-0240, occurring at a higher incidence (≥2%) in 218 patients receiving bevacizumab plus chemotherapy compared to 222 patients receiving chemotherapy alone, were abdominal pain (12% vs 10%), 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%), hypertension (11% vs 0.5%), thrombosis (8% vs 3%), 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%)
- In stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer after primary surgery:
  - 608 patients received carboplatin and paclitaxel plus bevacizumab followed by bevacizumab (CPB15+), 607 patients received carboplatin and paclitaxel plus bevacizumab followed by placebo (CPB15), and 602 patients received carboplatin and paclitaxel plus placebo followed by placebo (CPP)

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SELECTED SAFETY INFORMATION

Indication-Specific Adverse Events (continued)

- In platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, grade 3-4 adverse reactions in Study GOG-0213, occurring at a higher incidence (≥2%) in 325 patients receiving bevacizumab plus carboplatin and paclitaxel (chemotherapy) compared to 332 patients receiving 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 (3.0% vs 0%)

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Important Safety Information

- Grade 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the bevacizumab arms vs the chemotherapy-only 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%)

- In platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (psOC), grade 3-4 adverse reactions in Study AVF4095g, occurring at a higher incidence (≥2%) in 247 patients receiving bevacizumab plus carboplatin and gemcitabine (chemotherapy) compared to 233 patients receiving placebo plus 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%)
- In platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, grade 3-4 adverse reactions in Study GOG-0213, occurring at a higher incidence (≥2%) in 325 patients receiving bevacizumab plus carboplatin and paclitaxel (chemotherapy) compared to 332 patients receiving 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 (3.0% vs 0%)
- In platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (prOC), grade 3-4 adverse reactions in Study MO22224, occurring at a higher incidence (≥2%) in 179 patients receiving bevacizumab plus 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%)

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SELECTED SAFETY INFORMATION

Indication-Specific Adverse Events (continued)

- In platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (prOC), grade 3-4 adverse reactions in Study MO22224, occurring at a higher incidence (≥2%) in 179 patients receiving bevacizumab plus 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%)

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Important Safety Information

INDICATIONS

Metastatic Colorectal Cancer

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

ZIRABEV, 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.

Limitation of Use: ZIRABEV is not indicated for adjuvant treatment of colon cancer.

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

ZIRABEV, 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).

Recurrent Glioblastoma

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

Metastatic Renal Cell Carcinoma

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

Persistent, Recurrent, or Metastatic Cervical Cancer

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

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED 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 compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies. Non-GI fistulae incidence ranged from <1% to 1.8%, and was highest in patients with cervical cancer. Avoid ZIRABEV 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 for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any internal organ

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Important Safety Information

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

ZIRABEV, in combination with carboplatin and paclitaxel, followed by ZIRABEV 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.

ZIRABEV, 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.

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

Please see Important Safety Information and Indications on pages 30-36 and full Prescribing Information, also available at ZirabevHCP.com.

SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- **Surgery and Wound Healing Complications.** The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in bevacizumab-treated patients. In patients who experience wound healing complications during ZIRABEV treatment, withhold ZIRABEV 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 bevacizumab products after resolution of wound healing complications has not been established. Discontinue for wound healing complications of necrotizing fasciitis

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Summary

References

ZIRABEV® (bevacizumab-bvzr): Pfizer Oncology's commitment to building onto the clinical experience of bevacizumab

With the largest portfolio of oncology biosimilars—including ZIRABEV—Pfizer is committed to expanding options for patient care[6]

Favorable coverage[7]

Potential savings[7]

Support for you and your patients

Approved for the eligible indications of Avastin® (bevacizumab)[5]

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Realize the full potential of biosimilars. Ask about the Pfizer Oncology Biosimilars Portfolio

SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- **Hemorrhage.** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding occurred up to 5-fold more frequently in patients receiving bevacizumab. In clinical studies, the incidence of grade ≥3 hemorrhagic events among patients receiving bevacizumab ranged from 0.4% to 7%. Do not administer ZIRABEV to patients with serious hemorrhage or a recent history of hemoptysis (≥1/2 tsp of red blood). Discontinue ZIRABEV in patients who develop grade 3-4 hemorrhage

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Summary

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.5.2021. © 2021 National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the guideline, go online to NCCN.org.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.2.2021. © 2021 National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the guideline, go online to NCCN.org.
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.4.2021. © 2021 National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the guideline, go online to NCCN.org.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer V.1.2021. © 2021 National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the guideline, go online to NCCN.org.
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SELECTED SAFETY INFORMATION
Warnings and Precautions (continued)

- Additional serious and sometimes fatal adverse events with increased incidence in the bevacizumab-treated arm vs chemotherapy arm included:
  - **Arterial thromboembolic events (ATE)** (grade ≥3, 5%, highest in patients with GBM). Discontinue in patients who develop a severe ATE
  - **Renal injury and proteinuria.** Monitor proteinuria during ZIRABEV therapy. Patients with a 2+ or greater urine dipstick reading should undergo 24-hour urine collection. Withhold for proteinuria ≥2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome
    - Grade 3-4 proteinuria ranged from 0.7% to 7% in clinical studies
    - Nephrotic syndrome (<1%)

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