Saudi Public Assessment Report

Zirabev ®

Active Pharmaceutical Ingredient(s): Bevacizumab

ATC code/CAS no.: L01XC07-bevacizumab

Pharmaceutical/Dosage Form: Concentrate for Solution for Infusion

Dosage Strength: 100 mg/4 ml and 400 mg/16 ml

Marketing Authorisation Holder: Pfizer Saudi Limited, KSA

Shelf life: 36 month

Storage conditions: Store in a refrigerator (2°C -8°C)

Registration No.: 2411200291, 2411200290

Decision and Decision Date: Approved on 26/10/2020

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1. Terms, Definitions, Abbreviations

Term	Explanation
ADA	Antidrug antibodies
AEs	Adverse events
ANOVA	Analysis of variance
ATC	Anatomical therapeutic chemical code
$AUC_{0-\infty}$	Area under the serum concentration-time curve from time 0 to infinite time
AUC_T	Area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration
BOR	Best overall response
CCS	Container closure system
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
C_{max}	Maximum concentration
CQAs	Critical quality attributes
CR	Complete response
CV	Coefficients of variation
DOR	Duration of response
eCTD	Electronic common technical documents
EDTA	Edetate Disodium Dihydrate
EMA	European Medicines Agency
EU	European Union
FDA	United States food and drug authority

FPPs	Finished Pharmaceutical Products
GCP	Good clinical practice
GMP	Good manufacturing practice
HC	Heavy chain
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgG1k	Immunoglobulin G1 kappa
INN	International non-proprietary name
ITT	Intention to treat population
IV	Intravenous
LC	Light chain
mAb	Monoclonal antibody
MAH	Marketing authorisation holder
MCB	Master cell bank
MeSH	Medical subject headings
NA	Not Available
Nab	Neutralizing antibodies
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PF	Pfizer
PFS	Progression-free survival
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PMR	Primary reference material
PP	Per protocol population
PPQ	Process Performance Qualification
PR	Partial response
QAs	Quality attributes

RMP	Reference medicinal product
SAEs	Serious adverse events
SFDA	Saudi food and drug authority
SPC	Summary of Product Characteristics
$t_{½}$	Terminal half-life
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptors
V_{ss}	Volume of distribution at steady state
WCB	Working cell bank

2. Background

2.1 Submission Details

Type of submission: New Biosimilar Drug

Pharmacological class: Antineoplastic and immunomodulating agents, antineoplastic agents, other antineoplastic agents, monoclonal antibodies.

Submitted Indication:

- **Adult with metastasis of colon or rectum cancer:** Zirabev in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of adult patients with metastatic carcinoma of the colon or rectum.
- **Un-resectable advanced and/or metastatic or recurrent non-small lung:** In addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.
- **Advanced and/or metastatic renal cell cancer:** In combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer.
- **Persistent, recurrent, or metastatic carcinoma of the cervix**: In combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

For further information, refer to Summary of Product Characteristics (SPC) in appendix.

2.2 Regulatory Background

This product is considered a New Biosimilar Drug for Saudi regulatory purposes, for the reference medicinal product (RMP) Avastin (Bevacizumab). The Saudi Food and Drug Authority (SFDA) approved the latter in 2014. There are no currently approved biosimilars for Avastin in SFDA.

This product qualified for the following regulatory pathway:

☒ Regular pathway

☐ Abridged

☐ Verification

☐ Priority

Table 1: Regulatory status in other countries:

Country	Product name	Dosage form/Strength	Approval Authority	Date of Approval
Japan	Zirabev	Concentrate for solution for infusion	PMDA	18/6/2019
United States	Zirabev	Concentrate for solution for infusion	FDA	27/6/2019
Canada	Zirabev	Concentrate for solution for infusion	Health Canada	14/6/2019
European Union	Zirabev	Concentrate for solution for infusion	EMA	14/2/2019

3. Scientific discussion about the product:

3.1 Quality aspects

3.1.1 Introduction:

Bevacizumab that has been developed by Pfizer as a proposed biosimilar product to the reference product (RP), Avastin (bevacizumab) for the same indications as the Reference Product Avastin (PF-06439535 as referred by the Applicant) is a humanized immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) with two identical heavy chains (HC) and two identical light chains (LC), covalently linked with four inter-chain disulphide bonds, produced in a Chinese hamster ovary (CHO) cell line, the same cell line used for manufacturing of the reference product Avastin. The confirmed amino acid sequence, the molecular mass (theoretical and experimental) for the deglycosylated molecule and experimental molecular mass including glycosylation, the molecular formula

of the light and heavy chains of Pfizer-bevacizumab number of cysteines, the number of intra and inter disulphide bonds and the general properties are provided.

3.1.2 Active Substance:

- Manufacture, characterization and process controls:
  - Manufacturer:

Several sites were involved in the manufacturing process of Pfizer bevacizumab drug substance but the main process is conducted at Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC USA. The site is covered by a valid GMP certificate.

  - Description of the manufacturing process:

The main steps of the manufacturing process are cell culture, recovery and purification. The process begins with the thawing of cells from the working cell bank (WCB) followed by expansion. During culture expansion and maintenance, critical process parameters and critical material attributes are identified and justified with acceptable ranges. At the end of the production bioreactor, the culture is harvested and clarified by centrifugation and depth filtration to remove cells and debris. After this harvest step, the product proceeds to the purification comprised of several chromatography steps and orthogonal dedicated virus clearance steps, starting with an affinity chromatography step, a virus inactivation step, and ion exchange chromatography steps. The product is then processed through a virus retaining filter (VRF) followed by concentration and solution exchange in an ultrafiltration/diafiltration (UF/DF) step. Lastly, the excipients are added to the product to achieve the final formulation of active substance, followed by final filtration, filling in a suitable container and freezing.

  - Control of materials:

Sufficient data about the description and control of the cell banking system and other raw materials involved in the drug substance manufacturing process was provided. The MCB and WCB were well characterized according to ICH requirements, such as Q5A (R1), Q5B and Q5D guidelines. The provided data indicates that the cell line is robust with respect to critical parameters and demonstrates phenotypic and genotypic stability. The adventitious agents

assays test results indicate that the cell bank is sterile and free of detectable mycoplasma and viruses.

- Control of critical steps and intermediate:

In alignment with ICH Q10, quality systems are in place to support the continuous quality/process verification and change management post approval.

- Process validation:

The validation of the bevacizumab drug substance manufacturing process has been completed and includes three consecutive process performance qualification (PPQ) batches from three independent consecutive thaws of the current working cell bank (WCB). All process parameters (inputs) were maintained within pre-defined limits. All process validation batches met acceptance criteria and conform to the commercial specifications.

- Manufacturing process development:

The process development history indicates that only minor modifications were made in the manufacturing process, with no significant impact on process performance or product. Some process parameters were tightened as the program progressed to process validation to optimize process performance and consistency while remaining within prior established target ranges. All batches used for nonclinical and clinical studies were manufactured at the current commercial facility using the intended commercial process.

- Characterization:

All structure elucidation studies were conducted on bevacizumab manufactured by the commercial manufacturing process. The analytical techniques and methodologies applied to the characterization of bevacizumab are capable of evaluating primary structure, molecular mass, posttranslational modifications, charge and size heterogeneity, extinction coefficient, higher order structure, aggregation and fragmentation, biological activity and degradation pathways. The results indicate that Pfizer bevacizumab has the expected structure and functional properties.

- Control of drug substance:
  - Specifications used for drug substance control including test parameters of identity, purity, impurities, potency and other general tests were assessed and found to comply with ICH Q6B specifications for release and shelf life.
  - Compendial analytical procedures used for batch release and stability studies are clarity, coloration, pH, bioburden and endotoxin. Non-compendial analytical procedures used for batch release and stability studies were demonstrated to be suitable for the intended use. The validation of the analytical methods was described in detail, the results are deemed sufficient and acceptable, and the methods are considered appropriately validated.
  - Batch analysis data from several batches, which demonstrate that manufacturing generates a consistent active substance, have been provided and all results comply with the commercial acceptance criteria available at its time of release.
  - The submitted justification for all release and shelf life test parameters and acceptance criteria are acceptable from the both scientific and regulatory point of view.
- Reference standard:

In-house reference material was used as a reference for analysis of active substance and finished product, generated as follows: a clinical reference material, primary reference material (PRM) and a working reference material (WRM). Both primary reference material (PRM) and working reference material (WRM) have been suitably manufactured, characterized, and found suitable for the intended use.

- Container closure system:

The final container closure system has been appropriately validated and tested for suitability, safety, extractable and leachable. The two sizes of the container were considered during the process validation studies and process manufacture development studies. Container integrity is confirmed visually at the time of use.

- Stability and storage condition:

Primary and supportive stability studies conducted on drug substance batches produced from the intended commercial process have been submitted. The shelf life of the drug substance is 60 months at -20 ± 5°C in the proposed containers. The stability study complies with the GCC Guidelines for Stability Testing of Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs).

3.1.3 Finished Medicinal Product

- Description of the product and pharmaceutical development

The drug product Zirabev® is presented as a liquid concentrate for solution for infusion as a 100 mg/4 mL and 400 mg/16 mL presentations. Both these presentations are supplied in two different pack sizes, 5 mL and 20 mL Type I clear glass vials, sealed with a stopper and an aluminum seal with flip-off plastic cap, respectively. To ensure that a 4 mL and 16 mL nominal volume can be withdrawn from the vial, there is an overfill of approximately 0.3 and 0.5 mL, respectively. Zirabev® finished product is formulated by adding the following excipients: succinate (as a buffering agent), sucrose (as a tonicifier), edetate disodium dihydrate [EDTA] (used as a chelating agent), polysorbate 80 (as a surfactant) and water for injection to reach the target volume. There is no excipient of human or animal origin and no novel excipients. An adequate elemental impurities risk assessment is presented in accordance with ICH Q3D.

- Pharmaceutical development

The manufacturer developed two presentations for Zirabev intended to match the presentations in markets where the corresponding presentation of the Avastin licensed reference product is registered: 100 mg and 400 mg single-dose vials (100 mg/4 mL and 400 mg/16 mL). Drug development was performed in alignment with ICH Q8, Pharmaceutical Development and ICH Q9, Quality Risk Management, utilizing a variety of risk assessment tools in an iterative process for process development and characterization.

- Manufacture of the product and process controls

Zirabev 400 mg/16 mL and 100 mg/4 mL (both 25 mg/mL) presentations are manufactured using the same process steps and controls. The only differences between the presentations are the fill volume and the container closure system. All other manufacturing steps and process parameters are the same.

The batch formula for Zirabev presentations 400 mg/16 mL and 100 mg/4 mL consists of the same bulk Zirabev formulation including 25 mg/mL PF-06439535, 85 mg/mL sucrose, 0.05 mg/mL edetate disodium dihydrate (EDTA), 0.2 mg/mL polysorbate 80, in 20 mM succinate buffer at pH 5.5.

Frozen PF-06439535 active substance is shipped in appropriate containers. The active substance is thawed and transferred to a manufacturing vessel. Dilution buffer is prepared and the active substance is diluted with the buffer to the target protein concentration. The bulk-finished product is then sterile filtered, aseptically filled into vials, stoppered and capped with a crimp seal. Following the capping operation, the vials are visually inspected.

- Process validation:

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Process controls with their control limits for the finished product manufacturing process have been provided and are acceptable.

- Product Specification

The list of test parameters for the finished product specification contains tests for control of identity, purity and impurities, potency and other general tests. The acceptance criteria are applicable from lot release to the end of shelf life. The specification for the finished product release has been set in accordance with Ph. Eur. Requirements and ICH Q6B.

- Container Closure System

Type 1 clear glass vials with chlorobutyl stoppers and crimp seals with flip-off caps. The vial meets USP <660>, Ph. Eur. 3.2.1 and JP 7.01 requirements for Type I glass containers.

- Stability studies

Stability data were provided for primary and supportive drug product batches for both 100 mg/4 mL and 400 mg/16 mL presentations stored under the recommended long term conditions of 5 ± 3°C, accelerated condition (25 ± 2 °C/60 ± 5% relative humidity). In addition, data from thermal stress and photostability conditions were provided. Stability protocol was reviewed and the accumulated data for drug product demonstrates that the quality attributes comply with the commercial acceptance criteria for the corresponding analytical procedures throughout the time points tested. Available long-term stability data are considered representative to support the shelf life of 36 months at 2 - 8°C. The submitted stability data was assessed and follows the GCC Guidelines for Stability Testing of Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs).

3.1.4 Adventitious agents

The only material of animal origin identified is an antiserum used in clone selection, which is derived from sheep and stabilized in bovine serum albumin.

3.1.5 Discussion on chemical, pharmaceutical and biological aspects

Based on the assessment of provided data, the primary structure and identification of posttranslational modifications at the peptide level, subunit level and multi-chain architecture of the intact molecule, and the major and minor product isoforms, as well as extreme conditions studied (phosphate buffer incubation, light-exposure, and oxidation); conclude that Pfizer bevacizumab antibody has the expected structure and biological activity.

3.1.6 Discussion on the comparability studies

Comparability analysis demonstrating the biosimilarity to the reference product Avastin® (both Avastin bevacizumab-EU and Avastin bevacizumab-US) was provided in which the study design was set according to FDA, EMA, and WHO biosimilar guidelines.

The comparability assessment consists of a comparison of PF-06439535 to bevacizumab-EU, PF-06439535 to bevacizumab-US, and bevacizumab-EU to bevacizumab-US. Formulation differences were not considered to influence the analytical studies. Details of

methods used in the characterization and forced degradation studies, including method qualification or validation, are presented.

The biosimilarity assessment performed by the Applicant is considered adequate to confirm the analytical similarity between Pfizer-bevacizumab and Avastin in accordance with SFDA Guideline on Biosimilar Products.

3.2 Clinical Aspects

3.2.1 Clinical Pharmacology

The suggested mechanism of action and drugs in the same pharmacological class Zirabev is biosimilar containing monoclonal antibody consisting of bevacizumab, which is a humanized recombinant immunoglobulin G1 kappa (IgG1k) as an active ingredient. It is designed to bind to vascular endothelial growth factor receptors Flt-1 (VEGFR-1) and kinase insert domain receptor (VEGFR-2) thus inhibiting the vascular endothelial growth factor (VEGF) from binding to its receptors on the surface of endothelial cells. Neutralizing the biological activity of VEGF leads to the inhibition of the vasculogenesis and angiogenesis processes, thus inhibiting tumor progression and growth.

3.2.1.1 Pharmacokinetic studies

- List of pharmacokinetic studies

The PK equivalence of Zirabev to the reference product was investigated primarily in one Phase I clinical trial (a single dose comparative PK study [B7391001] in healthy male subjects). A population PK assessment of Zirabev and the reference product was conducted as a secondary objective in Phase III clinical trial (B7391003) on subjects with newly diagnosed or recurrent Stage IIIB or IV NSCLC.

A pilot phase 1 PK/safety study (B7391002) using EU- approved Bevacizumab in healthy subjects was conducted to assess the inter-subject PK variability and immunogenicity after a single IV dose of 5 mg/kg (Zirabev was not administered in this study). The coefficient of variation (CV%) for AUC0-∞ obtained from this study (21%) was used for the calculation of the sample size of the phase 1 PK study (B7391001).

Table2:

Study	Clinical trials identifier	Objective	Findings	Citation
PK, safety, immunogenicity and tolerability (pivotal).	B7391001	Primary objectives: • To compare the PK of Zirabev to EU- Bevacizumab and Zirabev to US-Bevacizumab. • To compare the PK of EU-Bevacizumab to US-Bevacizumab. Secondary objectives: • To evaluate the single-dose safety, tolerability, and immunogenicity.	Refer to Table 3	Knight B, Rassam D, Liao S, Ewesuedo R. A phase I pharmacokinetics study comparing PF-06439535 (a potential biosimilar) with bevacizumab in healthy male volunteers. Cancer chemotherapy and pharmacology. 2016 Apr 1;77(4):839-46.

Table3: Study B7391001

Title: Phase 1, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06439535 and Bevacizumab Sourced From US and EU Administered to Healthy Male Volunteers.	
Study identifier	B7391001
Design	Phase 1, double blind (sponsor unblinded), randomized (1:1:1), parallel group, single-dose, 3-arm, comparative PK study done in healthy male volunteer.
Total study duration	14 weeks (98 days).
Duration of Run-in phase	28 days.
Duration of main phase	14 weeks (98 days).
Duration of Extension phase	Up to 6 months.
Hypothesis	Equivalence in the PK parameters
Treatment arms	- One hundred two subjects were randomized to Zirabev (n=33), US- Bevacizumab (n=33), or EU- Bevacizumab (n=36). They were administered as IV at a dose of 5 mg/kg over a period of approximately 90 minutes using a calibrated infusion pump.

Randomization	- Randomization to three arms was in 1:1:1 ratio and according to a computer-generated randomization schedule provided by Pfizer. - Prior to dosing a randomization number was allocated manually by an un-blinded Pfizer randomization technician.
Blinding	- The trial was blinded to subjects, investigators, and study monitor. The exception was for the sponsor (to permit real-time interpretation of the safety data and evaluation of the drug concentration-time data), pharmacists, second operator and a study-independent monitor (to review pharmacy drug preparation and drug accountability). - Blinding codes should have only been broken for safety issues (breaking the blind method).
Primary Endpoint	C max, AUCT and AUC0-∞.
Secondary endpoints	CL, Vss and t½.
Statistical analysis:	**Study [B7391001]:** The MAH states that the plan was to recruit 96 subjects to account for 10% drop-out/non-evaluable rate (the aim was to have 87 subjects total [29 per arm] to complete the study). This number would have at least 85% power to establish bioequivalence of Zirabev to EU- and to US- Bevacizumab in the primary PK outcomes (90% confidence intervals [CIs]) using pre-defined margins of 80–125%. The sample size was calculated based on a conservative estimate of CV% for $AUC_{0-\infty}$ and C_{max} of 21% if the true ratio of $AUC_{0-\infty}$ and C_{max} values was equal to 1.05 or less (obtained from the pilot study [B7391002]). The analysis of the primary PK endpoint was performed in the per-protocol (PP) population. The number of subjects included in this set is 97 subjects (Zirabev= 32, EU- Bevacizumab = 33 and US- Bevacizumab =32). The primary and secondary PK parameters were summarized by descriptive statistics. Establishing the PK similarity was based on the results of primary PK parameters which were analyzed by analysis of variance (ANOVA) with treatment as a factor. Safety and tolerability analyses were performed in the safety analysis set. The immunogenicity analysis performed in the full analysis set. **Study [B7391003]:** A descriptive PK assessment was performed in the population PK set (705 subjects) of PF-06439535 vs EU - Bevacizumab (Ctrough and Cmax).
Study Results	**Study [B7391001]:**

Equivalence of the primary outcomes was established in the PP populations as shown in Table 4. The results of the secondary endpoints shown in Table 5. No equivalence testing was conducted for the secondary PK outcomes; instead, they were summarized descriptively and were supportive of biosimilarity.

Table 4: Summary of Statistical Comparisons of primary PK Parameters between Test and Reference Products: Per-protocol Analysis Set

Test	Reference	Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
Bevacizumab -Pfizer	Bevacizumab -EU	C_{max} (µg/mL)	141.5	135.5	104.42	98.36 – 110.84
		AUC_T (µg•hr/mL)	40330	40490	99.62	93.69 – 105.93
		$AUC_{0-\infty}$ (µg•hr/mL)	42490	43100	98.58	92.16 – 105.44
Bevacizumab -Pfizer	Bevacizumab -US	C_{max} (µg/mL)	141.5	128.9	109.79	103.38 – 116.60
		AUC_T (µg•hr/mL)	40330	38660	104.32	98.06 – 110.97
		$AUC_{0-\infty}$ (µg•hr/mL)	42490	41120	103.33	96.55 – 110.58
Bevacizumab -EU	Bevacizumab -US	C_{max} (µg/mL)	135.5	128.9	105.15	99.05 – 111.62
		AUC_T (µg•hr/mL)	40490	38660	104.71	98.48 – 111.34
		$AUC_{0-\infty}$ (µg•hr/mL)	43100	41120	104.82	98.00 – 112.12

Table 5: Arithmetic Mean (±SD) Pharmacokinetic Parameter Estimates of Bevacizumab-Pfizer, Bevacizumab-EU, and Bevacizumab-US: Per-protocol Analysis Set

Parameters (units)	Bevacizumab-Pfizer	Bevacizumab-EU	Bevacizumab-US
N, n	32, 32	33, 33	32, 32
C_{max} (µg/mL)	142.9 ± 20.3	137.0 ± 20.5	130.0 ± 18.2
AUC_T (µg•hr/mL)[a]	40840 ± 6411	41010 ± 6711	38920 ± 4566
$AUC_{0-\infty}$ (µg•hr/mL)	43080 ± 7103	43830 ± 8326	41450 ± 5350
CL (mL/hr/kg)	0.119 ± 0.021	0.117 ± 0.022	0.122 ± 0.016
V_{SS} (mL/kg)	62.4 ± 10.6	64.9 ± 9.6	67.7 ± 7.7
$t_{½}$ (hr)	397 ± 63	417 ± 90	413 ± 57

Study [B7391003]:

Consistent with concentration-time profiles, the median Ctrough and Cmax values as well as the corresponding ranges were comparable between PF-06439535 and EU - Bevacizumab arms as shown below in Table 6.

Table 6: Summary of Serum Concentration of PF-06439535 and Bevacizumab-EU vs. Time - PK Population

Visit	Planned Time Post Infusion Start	N	NALQ	Mean	SD	CV (%)	Median	Minimum	Maximum
Concentration Units: ng/mL, Treatment Group: PF-06439535									
Cycle 1 Day 1	0 h	333	6[a]	68.08	705.53	1036	0.0000	0.000	11300
	2 h 30 min	319	309	280000	103260	37	282000	0.000	546000
Cycle 2 Day 1	0 h	310	308	54350	44479	82	49050	0.000	460000
Cycle 3 Day 1	0 h	206	206	81090	48671	60	77450	4040	495000
Cycle 4 Day 1	0 h	277	277	100900	54979	54	94700	1000	475000
Cycle 5 Day 1	0 h	257	256	105300	48469	46	101000	0.000	494000
	1 h 30 min	192	192	360700	131170	36	372500	19700	636000
Concentration Units: ng/mL, Treatment Group: Bevacizumab-EU									
Cycle 1 Day 1	0 h	338	7[a]	116.4	1032.1	886	0.0000	0.000	12300
	2 h 30 min	326	321	302200	100360	33	300000	0.000	525000
Cycle 2 Day 1	0 h	326	324	58930	49452	84	52650	0.000	522000
Cycle 3 Day 1	0 h	211	211	83350	32384	39	79700	5270	259000
Cycle 4 Day 1	0 h	299	298	99750	50531	51	96500	0.000	697000
Cycle 5 Day 1	0 h	271	271	110000	65416	59	106000	5610	723000
	1 h 30 min	201	201	377200	142250	38	387000	28700	1010000

3.2.1.2 Pharmacodynamics studies

NA.

3.2.1.3 Assessors' comment on clinical pharmacology

The PK equivalence of Zirabev to the EU and US versions of the reference product was established in the submitted clinical development program.

3.2.2 Clinical Efficacy

3.2.2.1 Table 7: List of submitted clinical efficacy studies

Study ID	B7391003
No. of study centres / locations	216 Centres.
Design	Efficacy, safety, immunogenicity and PK.
Study Objective	**Primary Objectives:** -To compare the efficacy between PF-06439535 and EU- Bevacizumab. **Secondary Objectives:** To evaluate PF-06439535 and EU- Bevacizumab in the following aspects: -Safety. -Secondary measures of tumor control. -Immunogenicity. -PK.
Subjs by arm entered/ compl.	719 subjects: - PF-06439535= 358. Treated 356. - EU- Bevacizumab= 361. Treated: 358.
Duration	1 year (up to 52 weeks).
Gender **M/F** **Median Age**	The majority of the subjects in the ITT population were male (64.9%) and White (88.7%). The mean age of all subjects was 61.3 years and the mean BMI was 25.5 kg/m2.
Diagnosis **Incl. criteria**	Subjects with Newly diagnosed Stage IIIB or IV NSCLC (according to Revised International System for Staging Lung Cancer Criteria of 2010) or recurrent NSCLC.
Primary endpoint	Efficacy: objective response rate (ORR) based on evaluating the best response achieved by Week 19 and subsequently confirmed by 6 weeks thereafter.

3.2.2.2 Data integrity and GCP

All submitted studies were conducted in compliance with GCP guidelines, as claimed by MAH.

3.2.2.3 Inter-changeability studies

NA.

3.2.2.4 Assessors' comment on the submitted clinical studies

Zirabev approval request was received as an electronic submission in eCTD format. The clinical data and datasets were of acceptable quality. The MAH submitted an indication (metastasis of breast cancer) that is not approved for the reference product Avastin in Saudi Arabia.

Table 8: Study B7391003

Title: A Phase III Randomized, Double-Blind Study of PF-06439535 Plus Paclitaxel-Carboplatin and Bevacizumab Plus Paclitaxel-Carboplatin for the First-Line Treatment of Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer.	
Study identifier	B7391003
Design	Phase 3, multi-national, randomized (1:1 ratio), double blind, 2-arm, parallel Group.
Duration of Run-in phase	≤ 28 days.
Duration of main phase	1 year (up to 52 weeks).
Duration of Extension phase	28-days.
Hypothesis	Equivalence
Treatment arms	719 subjects randomized to : - PF-06439535= 358. Treated 356. - EU- Bevacizumab= 361. Treated: 358. - Both drugs were administered as IV infusion at a dose of 15 mg/kg infusion over 90 minutes. If it was well tolerated, the second infusion may have been administered over 60 minutes. If it was well tolerated, all subsequent infusions may have been administered over 30 minutes for at least 4 cycles and no more than 6 cycles in combination with paclitaxel and carboplatin. - (Details about patients' disposition are available in Appendix B).
Randomization	- Randomization was according to a randomization schedule generated by the Sponsor. - Randomization was stratified by region, sex and smoking history.

Blinding	- The study patients, investigators/study staff, and sponsor's personnel directly involved in the study conduct were blinded. The exception was in situation of the event of an emerging safety issue, the study's pharmacists who responsible for the preparation of the trial's drugs and a limited number of Sponsor's personnel (to monitor the pharmacy records).	
Endpoint and definitions	**Primary endpoints**	Efficacy: objective response rate (ORR) based on evaluating the best response achieved by Week 19 and subsequently confirmed by 6 weeks thereafter.
	Secondary endpoints	– Efficacy: duration of response (DOR), one-year progression-free survival (PFS) rate and one-year survival rate from randomization. – Safety: The type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events (AEs), including cardiotoxicity and infusion-related reactions, and laboratory abnormalities. – Immunogenicity: ADA and Nab against bevacizumab.
Database lock	NA	

Results and Analysis

Statistical analysis

The MAH states that the plan was to recruit 710 subjects accounting for the attrition rate of ~7.5%. Originally, the aim was to have 656 subjects (328 subjects per arm) to yield a power of approximately 90% for achieving equivalence in relative risk under the specified margin with a 5% type I error rate. Based on a meta-analysis of the historical trials of the reference product, the sample size was calculated given the above assumptions and assuming an ORR of 41%. ORR was defined as the percentage of patients within each treatment group who achieved a best overall response (BOR) of complete response (CR) or partial response (PR) by Week 19 and subsequently confirmed on a follow-up tumor assessment by Week 25. In this study, three margins were used to meet the different agencies' requirements (EMA, US FDA and PMDA).

The analysis of the primary efficacy endpoint was performed in the ITT population (719 subjects) and was based on the Miettinen and Nurminen method without strata for the binomially distributed efficacy endpoint ORR (the outcome was also assessed at week 55

as sensitivity analysis). The analysis was also performed in the PP population (706 subjects) as sensitivity analysis for the primary/secondary endpoints based on the Miettinen and Nurminen method with stratification variables (region, genders and smoking history). In addition, a Cox proportional hazard model and descriptive statistics were used for all secondary efficacy endpoints. For the primary efficacy endpoint and for sensitivity analysis, the missing data on tumor assessment will be considered as a non-responder (i.e., non-CR, non-PR). For the secondary efficacy endpoints, the missing data handling method was censoring.

The results

Equivalence was established in the ITT and PP populations as shown in Table 9 and Table 10. Equivalence in the risk difference was assessed using 95% CIs, while equivalence in the risk ratio was assessed using both 90% and 95% CIs. The results of the sensitivity analysis of the primary efficacy endpoints at week 55 showed consistent results with those from the analysis performed previously at Week 19.

For the secondary efficacy endpoints, the percentages of patients who progressed/died were comparable between the two treatment groups. In addition, the percentages of patients who died due to all causes and being alive at week 55 were approximately similar between the two arms.

Table 9: Summary of Best Overall Response and ORR (Week 19) (Unstratified) – ITT Population

	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Best overall response, n (%)			
Complete response (CR)	9 (2.5)	4 (1.1)	13 (1.8)
Partial response (PR)	153 (42.7)	157 (43.5)	310 (43.1)
Stable disease	154 (43.0)	166 (46.0)	320 (44.5)
Objective progression	15 (4.2)	14 (3.9)	29 (4.0)
Indeterminate[a]	27 (7.5)	20 (5.5)	47 (6.5)
Objective response rate (CR + PR), n (%)	162 (45.3)	161 (44.6)	323 (44.9)
95% exact CI[b]	[40.01, 50.57]	[39.40, 49.89]	[41.25, 48.64]
Treatment comparison (versus bevacizumab-EU)			
Un-stratified risk difference in ORR (%)[c]	0.6531		
95% CI of difference (%)[c]	[-6.6080, 7.9082]		
Treatment comparison (versus bevacizumab-EU)			
Un-stratified risk ratio[d]	1.0146		
95% CI of risk ratio[d]	[0.8628, 1.1933]		
90% CI of risk ratio[d]	[0.8856, 1.1625]		

Table 10: Summary of Best Overall Response (Week 19) - PP Population

	PF-06439535 (N=351) n (%)	Bevacizumab-EU (N=355) n (%)	Total (N=706) n (%)
Best Overall Response			
Complete Response	8 (2.3)	3 (0.8)	11 (1.6)
Partial Response	153 (43.6)	157 (44.2)	310 (43.9)
Stable Disease	153 (43.6)	165 (46.5)	318 (45.0)
Objective Progression	14 (4.0)	13 (3.7)	27 (3.8)
Indeterminate	23 (6.6)	17 (4.8)	40 (5.7)
Objective Response Rate (CR+PR)	161 (45.9)	160 (45.1)	321 (45.5)
95% Exact CI [1]	[40.57, 51.24]	[39.81, 50.41]	[41.75, 49.22]
SD Duration (weeks) [2]			
0 - <6 weeks	7 (4.6)	15 (9.1)	22 (6.9)
6 - <12 weeks	37 (24.2)	23 (13.9)	60 (18.9)
12 - <18 weeks	28 (18.3)	28 (17.0)	56 (17.6)
18 - <24 weeks	30 (19.6)	45 (27.3)	75 (23.6)
>=24 weeks	51 (33.3)	54 (32.7)	105 (33.0)
Treatment Comparison (vs Bevacizumab-EU)			
Un-Stratified Risk Difference in ORR (%) [3]	0.7985		
95% CI of Difference (%) [3]	[-6.5371, 8.1267]		
Stratified Risk Difference in ORR (%) [4]	1.1922		
95% CI of Difference (%) [4]	[-6.1023, 8.4738]		
Treatment Comparison (vs Bevacizumab-EU)			
Un-Stratified Risk Ratio [5]	1.0177		
95% CI of Risk Ratio [5]	[0.8656, 1.1966]		
90% CI of Risk Ratio [5]	[0.8885, 1.1658]		
Stratified Risk Ratio [6]	1.0266		
95% CI of Risk Ratio [6]	[0.8740, 1.2057]		
90% CI of Risk Ratio [6]	[0.8970, 1.1748]		

3.2.2.5 Overall conclusion of clinical efficacy

Equivalence from an efficacy perspective was established in comparison with EU-Bevacizumab using both the EMA, PMDA and FDA criteria. The demonstration of no

clinically meaningful difference between bevacizumab-Pfizer and bevacizumab-EU was based on a sensitive population NSCLC, a choice that was supported by the EMA.

3.2.3 Clinical Safety

3.2.3.1 Patient exposure

Example of a table: Patient exposure

		Patients enrolled	Patients exposed to adverse event	% of patient exposed to adverse event	total number of patients
Study B7391001	Bevacizumab-Pfizer	33	16	(48.5%)	55
	Bevacizumab -EU	36	22	(62.9%)	
	Bevacizumab -US	33	17	(51.5%)	
Study B7391003	Bevacizumab -Pfizer	358	344	(96.6%)	691
	Bevacizumab -EU	3361	347	(96.9%)	

3.2.3.2 Immunogenicity studies

In studyB7391001, from 101 subjects included in the full analysis set, 94 and 91 subjects completed ADA assessments through days 71 and 100, respectively. The results of the immunogenicity analysis of three different arms are shown in Table 11.

Table 11: Summary of ADA Results by Treatment Groups

	Bevacizumab-Pfizer N=33	Bevacizumab-EU N=35	Bevacizumab-US N=33
Total Number of ADA Samples			
Baseline samples	33	35	33
Post-dose samples through Day 71	127	133	127
Post-dose samples through Day 100	157	166	155
Pre-Existing ADA (Baseline ADA)			
Number of subjects tested positive at baseline	0	1	0
Treatment-Emergent ADA			
Number of subjects tested positive through Day 71 (% of total)	2 (6.1%)	1 (2.9%)	2 (6.1%)
Number of subjects tested positive through Day 100 (% of total)[a]	2 (6.1%)	1 (2.9%)	2 (6.1%)

The eight samples that tested positive for ADA were further tested for Nab (none of these samples tested positive).

In study B7391003, the overall immunogenicity rates were low and similar between the treatment arms (5 [1.5%] vs. 5 [1.4%] for PF-06439535 and EU- Bevacizumab, respectively). Of the ADA positive subjects, 0 vs. 3 tested positive for NAb in the PF-06439535 and EU- Bevacizumab, respectively. Table 12 provide results of incidence for ADA positive and negative subjects.

Table 12: Summary of ADA Incidence by Treatment Group - Safety Population

Visit	Criteria	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Cycle 1 (prior to treatment)	n	352	353	705
	Positive	1 (0.3)	3 (0.8)	4 (0.6)
	Negative	350 (99.4)	350 (99.2)	700 (99.3)
	Not tested	1 (0.3)	0	1 (0.1)
Overall (post-treatment)	n	339	350	689
	Positive	5 (1.5)	5 (1.4)	10 (1.5)
	Negative	334 (98.5)	345 (98.6)	679 (98.5)

3.2.3.3 Adverse events

Serious adverse events and deaths

In studyB7391001, the frequency and type of AEs reported were comparable between all three treatment groups (the number of AEs was highest in the EU- Bevacizumab treatment group). Fifty-four percent of subjects experienced 107 AEs, 31 (29%) of these are treatment-related AEs. The majority of the AEs were grade 1 or grade 2, (the most common AE was Upper respiratory tract infection that was experienced by 14 (13.9%) subjects in total).

Two serious adverse events (SAEs) were reported: appendicitis and concussion (both are treatment unrelated). The latter one is considered grade 4. Additional grade 3 AE of musculoskeletal pain occurred in the same subject experienced grade 4 AE. In study B7391003, the most frequently reported AEs were alopecia: 166 (46.6%) vs. 165 (46.1%) patients in the PF-06439535 group and EU-bevacizumab group, respectively. Anemia was

reported in 104 (29.2%) vs. 108 (30.2%) patients in the PF-06439535 group and bevacizumab-EU group, respectively.

The proportion of SAEs were generally similar between two arms, 81 (22.8%) vs. 80 (22.3%) patients in PF-06439535 group and EU-bevacizumab group, respectively. The most common reported SAEs were pneumonia (8 [2.2%] vs. 6 [1.7%]), febrile neutropenia (5 [1.4] vs.7 [2.0%]), and neutropenia (4 [1.1%] vs. 6 [1.7%] patients in PF-06439535 group and EU-bevacizumab group, respectively.

The reported cases of deaths were 293 and were mainly due to the underlying disease: 256 (35.6%) vs. (129 [36.0%] patients in the PF-06439535 group and EU-bevacizumab group, respectively.

3.2.3.4 Assessor's overall conclusions on clinical safety

The safety and immunogenicity profiles of Zirabev vs. US-EU Bevacizumab appeared generally similar in both studies.

3.2.4 Discussion on clinical efficacy and safety aspects

Based on the submitted clinical development program, the similarity of Zirabev to both the EU and US Avastin was demonstrated with no concerns about safety and immunogenicity.

4. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Bleeding/haemorrhage Pulmonary haemorrhage Proteinuria Arterial thromboembolic events (ATE) Hypertension Congestive heart failure Wound-healing complications Gastrointestinal perforations Posterior reversible encephalopathy syndrome (PRES) Neutropenia Venous thromboembolic events (VTE)

	Fistula (other than gastrointestinal) Thrombotic microangiopathy Pulmonary hypertension Ovarian failure Hypersensitivity reactions/infusion reactions Gallbladder perforation Peripheral sensory neuropathy Cardiac disorders (excluding CHF and ATE) Osteonecrosis of the jaw Necrotizing fasciitis Adverse events following off-label intravitreal use Embryo-foetal development disturbance Osteonecrosis in children
Important potential risks	None
Missing information	Safety profile of the different treatment combinations in patients with non-squamous NSCLC Long-term effects of bevacizumab when used in the paediatric population Safety and efficacy in patients with renal impairment Safety and efficacy in patients with hepatic impairment Use in lactating women

4.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

- Congestive Heart Failure
- Arterial Thromboembolic Events
- Interstitial Lung Disease
- Osteonecrosis of the Jaw

4.2. Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities planned or ongoing to assess the effectiveness of risk minimization measures.

4.3. Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SPC addressed to patients and healthcare professionals

- Important advice on the medicine's packaging;
- The authorised pack size
- The medicine's legal status.

In addition to these measures, adverse event information is continuously collected and periodically analyzed, including the PSUR assessment, so that immediate action can be taken if necessary.

Artwork and Trade Name assessment (Available in appendix)

Proposed trade Name	Dosage Form
Zirabev	Concentrate for solution for infusion

Look –alike/Sound-alike (LA/SA) Error Risk Potential:

Zirabev name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN and USAN STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	SFDA	Shared File/ Excel Sheet	Martindale	Stem Book 2018
Zirabev	NO	NO	Yes at FDA	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Zirabev is accepted.

Outer and Inner Package:

Based on the submitted data, the proposed artwork is accepted.

5. Overall Conclusion

Based on a review of data on quality, safety and efficacy, SFDA considered that the benefit/risk profile of Zirabev was favourrible and decided to grant the marketing authorisation of Zirabev for the treatment of the following indication:

- **Adult with metastasis of colon or rectum cancer:** Zirabev in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of adult patients with metastatic carcinoma of the colon or rectum.
- **Un-resectable advanced and/or metastatic or recurrent non-small lung:** In addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic, or recurrent non-small cell lung cancer other than predominantly squamous cell histology.
- **Advanced and/or metastatic renal cell cancer:** In combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer.
- **Persistent, recurrent, or metastatic carcinoma of the cervix**: In combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

Appendix

A. Artwork

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Zirabev 25 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 25 mg of bevacizumab*.

Each 4 ml vial contains 100 mg of bevacizumab.

Each 16 ml vial contains 400 mg of bevacizumab.

For dilution and other handling recommendations, see section 6.6.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colorless to pale brown liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

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

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

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

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

4.2. Posology and method of administration

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

Posology

Metastatic carcinoma of the colon or rectum (mCRC)

The recommended dose of Zirabev, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks.

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Metastatic breast cancer (mBC)

The recommended dose of Zirabev is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Non-small cell lung cancer (NSCLC)

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

Zirabev is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Zirabev as a single agent until disease progression.

The recommended dose of Zirabev is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses (see section 5.1).

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Advanced and/or metastatic renal cell cancer (mRCC)

The recommended dose of Zirabev is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion.

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Cervical cancer

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

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

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

Special populations

Elderly patients

No dose adjustment is required in the elderly.

Patients with renal impairment

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

Patients with hepatic impairment

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

Paediatric population

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

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

Method of administration

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

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

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

Precautions to be taken before handling or administering the medicinal product

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

4.3. Contraindications

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

- Pregnancy (see section 4.6).

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Gastrointestinal (GI) perforations and fistulae (see section 4.8)

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

I-vaginal fistulae in study GOG-0240

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

Non-GI fistulae (see section 4.8)

Patients may be at increased risk for the development of fistulae when treated with bevacizumab. Permanently discontinue Zirabev in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. Limited information is available on the continued use of bevacizumab in patients with other fistulae.

In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Zirabev should be considered.

Wound healing complications (see section 4.8)

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

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

Hypertension (see section 4.8)

An increased incidence of hypertension was observed in bevacizumab-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre -existing hypertension should be adequately controlled before starting Zirabev treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy.

Monitoring of blood pressure is generally recommended during therapy.

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

Posterior reversible encephalopathy syndrome (PRES) (see section 4.8)

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

Proteinuria (see section 4.8)

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that all Grade (US National Cancer Institute- Common Terminology Criteria for Adverse Events [NCI-CTCAE v.3]) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome (NCI-CTCAE v.3).

Arterial thromboembolism (see section 4.8)

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

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

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

Venous thromboembolism (see section 4.8)

Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.

Zirabev should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored (NCI-CTCAE v.3).

Haemorrhage

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

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

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

Pulmonary haemorrhage/haemoptysis

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

Congestive heart failure (CHF) (see section 4.8)

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

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

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

Neutropenia and infections (see section 4.8)

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

Hypersensitivity reactions/infusion reactions (see section 4.8)

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

Osteonecrosis of the jaw (ONJ) (see section 4.8)

Cases of ONJ have been reported in cancer patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which

ONJ is an identified risk. Caution should be exercised when Zirabev and intravenous bisphosphonates are administered simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Zirabev. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

Intravitreal use

Zirabev is not formulated for intravitreal use.

Eye disorders

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

Systemic effects following intravitreal use

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

Ovarian failure/fertility

Bevacizumab may impair female fertility (see sections 4.6 and 4.8). Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Zirabev.

4.5. Interaction with other medicinal products and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

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

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon alpha 2a, erlotinib (and its active metabolite OSI-420), or the

chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of bevacizumab and sunitinib malate

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

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

Combination with platinum- or taxane-based therapies (see sections 4.4 and 4.8)

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

Radiotherapy

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

EGFR monoclonal antibodies in combination with bevacizumab chemotherapy regimens

No interaction studies have been performed. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab -containing chemotherapy. Results from the randomized phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.

4.6. Fertility, pregnancy, and lactation

Women of childbearing potential

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

Pregnancy

There are no clinical trial data on the use of bevacizumab in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and bevacizumab is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. In the post-marketing

setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.8). Bevacizumab is contraindicated in pregnancy (see section 4.3).

Breast-feeding

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

Fertility

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

4.7. Effects on ability to drive and use machines

Bevacizumab has no or negligible influence on the ability to drive and use machines. However, somnolence and syncope have been reported with bevacizumab use (see table 1 in section 4.8).

If patients are experiencing symptoms that affect their vision or concentration, or their ability to react, they should be advised not to drive and use machines until symptoms abate.

4.8. Undesirable effects

Summary of the safety profile

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

The most serious adverse reactions were:

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

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

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

Tabulated list of adverse reactions

The adverse reactions listed in this section fall into the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Tables 1 and 2 list adverse reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications.

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

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

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

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

Adverse reactions are added to the appropriate frequency category in the tables below according to the highest incidence seen in any indication.

Within each frequency category, adverse reactions are presented in the order of decreasing seriousness.

Some of the adverse reactions are reactions commonly seen with chemotherapy; however, bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents.

Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

Table 1: Adverse reactions by frequency

System organ class	Very common	Common	Rare
Infections and infestations		Sepsis, Abscess[b,d], Cellulitis, Infection, Urinary tract infection	Necrotising fasciitisa
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[b], Thrombo-cytopenia	Anaemia, Lymphopenia	
Immune system disorders		Hypersensitivity, Infusion reactions [a,b,d]	
Metabolism and nutrition disorders	Anorexia, Hypomagnesaemia, Hyponatraemia	Dehydration	
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence	Posterior reversible encephalo-pathy syndrome[a,b,d]
Eye disorders	Eye disorder, Lacrimation increased		
Cardiac disorders		Congestive heart failure[b,d,] Supraventricular tachycardia	
Vascular disorders	Hypertension[b,d], Thrombo-embolism (venous)[b,d]	Thrombo-embolism (arterial)[b,d,] Haemorrhage[b,d,] Deep vein thrombosis	

Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis, Epistaxis, Cough	Pulmonary haemorrhage/ Haemoptysis[b,d,] Pulmonary embolism, Hypoxia, Dysphonia[a]	
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	Gastrointestinal perforation[b,d], Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal Fistulae [d,e], Gastrointestinal disorder, Proctalgia	
Hepatobiliary disorders			
Skin and subcutaneous tissue disorders	Wound healing complications[b,d], Exfoliative dermatitis, Dry skin, Skin discoloration	Palmar-plantar erythro-dysaesthesia syndrome	
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia	Fistula[b,d], Muscular weakness, Back pain	

Renal and urinary disorders	Proteinuria[b,d]		
Reproductive system and breast disorders	Ovarian failure[b,c,d]	Pelvic pain	
Congenital, familial, and genetic disorder			
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy	
Investigations	Weight decreased		

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

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

[c]Based on a substudy from NSABP C-08 with 295 patients

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

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

[f]Observed in pediatric population only

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

Table 2: Severe adverse reactions by frequency

System organ class	Very common	Common	Frequency not known
Infections and infestations		Sepsis, Cellulitis, Abscess[a,b], Infection, Urinary tract infection	Necrotising fasciitisc
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia[a], Thrombo-cytopenia	Anaemia, Lymphopenia	
Immune system disorders			Hypersensitivity, Infusion reactions[a,b,c]
Metabolism and nutrition disorders		Dehydration, Hyponatraemia	
Nervous system disorders	Peripheral sensory neuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache	Posterior reversible encephalopathy syndrome [a,b,c], Hypertensive encephalopathy[c]
Cardiac disorders		Congestive heart failure[a,b], Supraventricular tachycardia	
Vascular disorders	Hypertension[a,b]	Thromboembolism arterial[a,b], Haemorrhage[a,b], Thromboembolism (venous)[a,b], Deep vein thrombosis	Renal thrombotic microangiopathy
Respiratory, thoracic and mediastinal disorders		Pulmonary haemorrhage/ Haemoptysis[a,b], Pulmonary embolism, Epistaxis, Dyspnoea, Hypoxia	Pulmonary hypertension[c], Nasal septum perforation[c]

Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[c,d], Gastrointestinal disorder, Stomatitis, Proctalgia	Gastrointestinal perforation[a,b], Gastrointestinal ulcer[c], Rectal haemorrhage
Hepatobiliary disorders			Gallbladder perforation [b,c]
Skin and subcutaneous tissue disorders		Wound healing complications[a,b], Palmar-plantar erythrodysaesthesia syndrome	
Musculoskeletal and connective tissue disorders		Fistula[a,b], Myalgia, Arthralgia, Muscular weakness, Back pain	Osteonecrosis of the jaw[b,c]
Renal and urinary disorders		Proteinuria[a,b]	
Reproductive system and breast disorders		Pelvic pain	Ovarian failure[a,b]
Congenital, familial, and genetic disorder			Foetal abnormalities[a,c]
General disorders and administration site conditions	Asthenia, Fatigue,	Pain, Lethargy, Mucosal inflammation	

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

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

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

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

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

Description of selected serious adverse reactions

Gastrointestinal (GI) perforations and fistulae (see section 4.4)

Bevacizumab has been associated with serious cases of gastrointestinal perforation.

Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with non-squamous non-small cell lung cancer, up to 1.3% in patients with metastatic breast cancer, up to 2.0% in patients with metastatic renal cell cancer or in patients with ovarian cancer, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation. The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases, underlying intra-abdominal inflammation was present, from either gastric ulcer disease, tumor necrosis, diverticulitis, or chemotherapy-associated colitis.

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

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

GI-vaginal fistulae in study GOG-0240

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in bevacizumab-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. The frequency of GI-vaginal fistulae in the group treated with bevacizumab + chemotherapy was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with no prior radiation and/ or no recurrence inside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving

chemotherapy alone were 1.1% vs. 0.8%, respectively. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI fistulae (see section 4.4)

Bevacizumab use has been associated with serious cases of fistulae including reactions resulting in death.

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

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

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

Wound healing (see section 4.4)

As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days were excluded from participation in phase III clinical trials.

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

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

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

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

Hypertension (see section 4.4)

In clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the bevacizumab containing arms compared with up to 14% in the control arms. The overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in

up to 1.0% of patients treated with bevacizumab and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

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

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

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

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

Posterior reversible encephalopathy syndrome (see section 4.4)

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

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

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

Proteinuria (see section 4.4)

In clinical trials, proteinuria has been reported within the range of 0.7% to 54.7% of patients receiving bevacizumab.

Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria (NCI-CTCAE v.3). Grade 3 proteinuria was reported in up to 10.9% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. Testing for proteinuria is recommended prior to start of Zirabev

therapy. In most clinical trials urine protein levels of ≥ 2 g/24 hrs led to the holding of bevacizumab until recovery to < 2 g/24 hrs.

Haemorrhage (see section 4.4)

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

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

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

Tumour-associated haemorrhage (see section 4.4)

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

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

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

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

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical trials. In an exploratory retrospective

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

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

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

Thromboembolism (see section 4.4)

Arterial thromboembolism

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

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

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

Venous thromboembolism

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

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

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

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

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

Congestive heart failure (CHF)

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

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

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

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

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m2. This phase III clinical trial compared rituximab /cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to R- CHOP

without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP plus bevacizumab arm. These results suggest that close clinical observation with appropriate cardiac assessments should be considered for patients exposed to cumulative doxorubicin doses greater than 300 mg/m2 when combined with bevacizumab.

Hypersensitivity reactions/infusion reactions (see section 4.4 and Post-marketing experience below)

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapy than with chemotherapy alone. The incidence of these reactions in some clinical trials of bevacizumab is common (up to 5% in bevacizumab- treated patients).

Infections

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

Ovarian failure/fertility (see sections 4.4 and 4.6)

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

Laboratory abnormalities

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

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

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

Other special populations

Elderly patients

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic reactions, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs). Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia and thrombocytopenia (NCI-CTCAE v.3); and all Grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with bevacizumab (see sections 4.4 and 4.8 under Thromboembolism). In one clinical trial, the incidence of hypertension of grade ≥ 3 was two fold higher in patients aged > 65 years than in the younger age group (<65 years). In a study of platinum-resistant recurrent ovarian cancer patients, alopecia, mucosal inflammation, peripheral sensory neuropathy, proteinuria and hypertension were also reported and occurred at a rate at least 5% higher in the CT + BV arm for bevacizumab-treated patients ≥ 65 years of age compared with bevacizumab-treated patients aged < 65 years.

No increase in the incidence of other reactions, including gastrointestinal perforation, wound healing complications, congestive heart failure, and haemorrhage was observed in elderly patients (> 65 years) receiving bevacizumab as compared to those aged ≤ 65 years treated with bevacizumab.

Paediatric population

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

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

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

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

Post-marketing experience

Table 3: Adverse reactions reported in post-marketing setting

System organ class (SOC)	Reactions (frequency*)
Infections and Infestations	Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare) (see also section 4.4)

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

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

Reporting of suspected adverse reactions

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

To report any side effects:

- The National Pharmacovigilance Centre (NPC):
  - SFDA Call Center: 19999
  - E-mail: npc.drug@sfda.gov.sa
  - Website: https://ade.sfda.gov.sa/

Other GCC States

Please contact the relevant competent authority

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, other antineoplastic agents, monoclonal antibodies, ATC code: L01X C07

Zirabev is a biosimilar medicinal product.

Mechanism of action

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

Pharmacodynamic effects

Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast,

pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

Clinical efficacy

Metastatic carcinoma of the colon or rectum (mCRC)

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

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

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

- NO16966: Bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or bevacizumab 5 mg/kg every 2 weeks in combination with leucovorin plus 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).
- E3200: Bevacizumab 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in bevacizumab-naïve patients.
- ML18147: Bevacizumab 5.0 mg/kg of body weight every 2 weeks or bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first -line treatment with bevacizumab. Use of irinotecan- or oxaliplatin-containing regimen was switched depending.

AVF2107g

This was a phase III randomised, double-blind, active-controlled clinical trial evaluating bevacizumab in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1)

or IFL + bevacizumab (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/FA + bevacizumab (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of bevacizumab with the IFL regimen was established and considered acceptable. All treatments were continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an ECOG performance status of 0, 43% had a value of 1 and 0.4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

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

The efficacy results of bevacizumab in combination with IFL-chemotherapy are displayed in Table4.

Table 4: Efficacy results for trial AVF2107g

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

[a]5 mg/kg every 2 weeks

[b]Relative to control arm

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

AVF2192g

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

AVF0780g

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

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

Table 5: Efficacy results for trials AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/FA	5-FU/FA + bevacizumab[a]	5-FU/FA + bevacizumab[b]	5-FU/FA + placebo	5-FU/FA + bevacizumab
Number of patients	36	35	33	105	104

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

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

NO16966

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

patients were randomised to four treatment groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + bevacizumab, FOLFOX-4 + bevacizumab). In Part II, treatment assignment was double-blind with respect to bevacizumab.

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

Table 6: Treatment regimens in trial NO16966 (mCRC)

	Treatment	Starting dose	Schedule
FOLFOX-4 or FOLFOX-4 + bevacizumab	Oxaliplatin Leucovorin 5-Fluorouracil	85 mg/m2 intravenous 2 h 200 mg/m2 intravenous 2 h 400 mg/m2 intravenous bolus, 600 mg/m2 intravenous 22 h	Oxaliplatin on day 1 Leucovorin on day 1 and 2 5-fluorouracil intravenous bolus/infusion, each on days 1 and 2
	Placebo or bevacizumab	5 mg/kg intravenous 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX + bevacizumab	Oxaliplatin Capecitabine	130 mg/m^2 intravenous 2 h 1000 mg/m^2 oral bid	Oxaliplatin on day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or bevacizumab	7.5 mg/kg intravenous 30-90 min	Day 1, prior to XELOX, q3 weeks
5-Fluorouracil: intravenous bolus injection immediately after leucovorin			

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

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

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

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

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

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

[a]relative to control arm

*Overall survival analysis at clinical cut-off 31 January 2007
**Primary analysis at clinical cut-off 31 January 2006

In the FOLFOX treatment subgroup, the median PFS was 8.6 months in placebo and 9.4 months in bevacizumab treated patients, HR = 0.89, 97.5% CI = [0.73; 1.08]; p-value = 0.1871, the corresponding results in the XELOX treatment subgroup being 7.4 vs. 9.3 months, HR = 0.77, 97.5% CI = [0.63; 0.94]; p-value = 0.0026.
The median overall survival was 20.3 months in placebo and 21.2 months in bevacizumab treated patients in the FOLFOX treatment subgroup, HR=0.94, 97.5% CI = [0.75; 1.16]; p-value = 0.4937,

the corresponding results in the XELOX, treatment subgroup being 19.2 vs. 21.4 months, HR = 0.84, 97.5% CI = [0.68; 1.04]; p-value = 0.0698.

ECOG E3200

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

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

Table 8: Efficacy results for trial E3200

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

[a]10 mg/kg every 2 weeks [b]Relative to control arm

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

ML18147

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

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

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

Table 9: Efficacy results for study ML18147 (ITT population)

	ML18147	
	Fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy	Fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy + bevacizumab[a]
Number of patients	410	409
Overall survival		
Median (months)	9.8	11.2
Hazard ratio (95% confidence interval)	0.81 (0.69 - 0.94) (p-value = 0.0062)	
Progression-free survival		
Median (months)	4.1	5.7
Hazard ratio (95% confidence interval)	0.68 (0.59 - 0.78) (p-value < 0.0001)	

Objective response rate (ORR)		
Patients included in analysis	406	404
Rate	3.9%	5.4%
	(p-value = 0.3113)	

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

Statistically significant improvements in progression-free survival were also observed.

Objective response rate was low in both treatment arms and the difference was not significant.
Study E3200 used a 5 mg/kg/week equivalent dose of bevacizumab in bevacizumab-naïve patients, while study ML18147 used a 2.5 mg/kg/week equivalent dose of bevacizumab in bevacizumab-pretreated patients. A cross-trial comparison of the efficacy and safety data is limited by differences between these studies, most notably in patient populations, previous bevacizumab exposure and chemotherapy regimens. Both the 5 mg/kg/week and 2.5 mg/kg/week equivalent doses of bevacizumab provided a statistically significant benefit with regards to OS (HR 0.751 in study E3200; HR 0.81 in study ML18147) and PFS (HR 0.518 in study E3200; HR 0.68 in study ML18147). In terms of safety, there was a higher overall incidence of Grade 3-5 AEs in study E3200 relative to study ML18147.

Metastatic breast cancer (mBC)

ECOG E2100
Trial E2100 was an open-label, randomised, active controlled, multicentre clinical trial evaluating bevacizumab in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Patients were randomised to paclitaxel alone (90 mg/m2 intravenous over 1 hour once weekly for three out of four weeks) or in combination with bevacizumab (10 mg/kg intravenous infusion every two weeks). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to trial entry. Of the 722 patients in the trial, the majority of patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered unsuitable for trastuzumab therapy. Furthermore, 65% of patients had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastases, including previously treated or resected brain lesions, were excluded.
In trial E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with bevacizumab as a single agent continued until disease progression. The patient characteristics were similar across the trial arms.

The primary endpoint of this trial was progression free survival (PFS), based on trial investigators' assessment of disease progression. In addition, an independent review of the primary endpoint was also conducted. The results of this trial are presented in Table 10.

Table 10: Trial E2100 efficacy results

Progression-free survival				
	Investigator assessment*		IRF assessment	
	Paclitaxel (n=354)	Paclitaxel/ bevacizumab (n=368)	Paclitaxel (n=354)	Paclitaxel/ bevacizumab (n=368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343; 0.516)		0.483 (0.385; 0.607)	
p-value	< 0.0001		< 0.0001	
Response rates (for patients with measurable disease)				
	Investigator assessment		IRF assessment	
	Paclitaxel (n=273)	Paclitaxel/ bevacizumab (n=252)	Paclitaxel (n=243)	Paclitaxel/ bevacizumab (n=229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	< 0.0001		< 0.0001	
Overall survival				
	Paclitaxel (n=354)		Paclitaxel/ bevacizumab (n=368)	
Median OS (months)	24.8		26.5	
HR (95% CI)	0.869 (0.722; 1.046)			
p-value	0.1374			

*primary analysis

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

Non-small cell lung cancer (NSCLC)

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

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

E4599

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

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m2) and carboplatin AUC = 6.0, both by intravenous infusion (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC in combination with bevacizumab at a dose of 15 mg/kg intravenous infusion day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the bevacizumab + carboplatin–paclitaxel arm continued to receive bevacizumab as a single agent every 3 weeks until disease progression. 878 patients were randomised to the two arms.

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

The primary endpoint was duration of survival. Results are presented in Table 11.

Table 11: Efficacy results for trial E4599

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

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

BO17704

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

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m2 intravenous infusion on day 1 and gemcitabine 1250 mg/m2 intravenous infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with bevacizumab at a dose of 7.5 or 15 mg/kg intravenous infusion day 1 of every 3-week cycle. In the bevacizumab-containing arms, patients could receive bevacizumab as a single-agent every 3 weeks until disease progression or unacceptable toxicity. Trial results show that 94% (277 / 296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti- cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 12.

Table 12: Efficacy results for trial BO17704

	Cisplatin/Gemcitabine + placebo	Cisplatin/Gemcitabine + bevacizumab 7.5 mg/kg q 3 weeks	Cisplatin/Gemcitabine + bevacizumab 15 mg/kg q 3 weeks
Number of patients	347	345	351
Progression-free survival			
Median (months)	6.1	6.7	6.5
Hazard ratio		0.75 (p=0.0026) [0.62; 0.91]	0.82 (p=0.0301) [0.68; 0.98]
Best overall response rate[a]	20.1%	34.1% (p < 0.0001)	30.4% (p=0.0023)

[a] patients with measurable disease at baseline

Advanced and/or metastatic renal cell cancer (mRCC)

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

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

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

The efficacy results are presented in Table 13.

Table 13: Efficacy results for trial BO17705

	Placebo + IFN[a]	Bv[b] + IFN[a]
Number of patients	322	327
Progression-free survival		
Median (months)	5.4	10.2
Hazard ratio (95% CI)	6.3 (0.52, 0.75) (p-value < 0.0001)	
Objective response rate (%) in Patients with measurable disease		
N	289	306
Response rate	12.8%	31.4%
	(p-value < 0.0001)	

Overall survival		
Median (months)	21.3	23.3
Hazard ratio	0.91 95% CI (0.76, 1.10) (p-value 0.3360)	

[a] Interferon alfa-2a 9 MIU 3x/week
[b] Bevacizumab 10 mg/kg q 2 wk

An exploratory multivariate Cox regression model using backward selection indicated that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to trial entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63;

0.96], p=0.0219), indicating a 22% reduction in the risk of death for patients in the bevacizumab + IFN alfa-2a arm compared to IFN alfa-2a arm.

Ninety seven (97) patients in the IFN alfa-2a arm and 131 patients in the bevacizumab arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU three times a week as pre -specified in the protocol. Dose-reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of bevacizumab and IFN alfa-2a based on PFS event free rates over time, as shown by a sub-group analysis. The 131 patients in the bevacizumab + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the trial, exhibited at 6, 12 and 18 months PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving bevacizumab + IFN alfa-2a.

AVF2938

This was a randomised, double-blind, phase II clinical trial investigating bevacizumab 10 mg/kg in a 2 weekly schedule with the same dose of bevacizumab in combination with 150 mg daily erlotinib, in patients with metastatic clear cell RCC. A total of 104 patients were randomised to treatment in this trial, 53 to bevacizumab 10 mg/kg every 2 weeks plus placebo and 51 to bevacizumab 10 mg/kg every 2 weeks plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the bevacizumab + Placebo arm and the bevacizumab + Erlotinib arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response. The addition of erlotinib to bevacizumab did not result in an improvement in OS (HR = 1.764; p=0.1789), duration of objective response (6.7 vs 9.1 months) or time to symptom progression (HR = 1.172; p=0.5076).

AVF0890

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

Cervical cancer

GOG-0240

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

A total of 452 patients were randomised to receive either:

- Paclitaxel 135 mg/m2 intravenous over 24 hours on Day 1 and cisplatin 50 mg/m2 intravenous on Day 2, every 3 weeks (q3w); or
  - Paclitaxel 175 mg/m2 intravenous over 3 hours on Day 1 and cisplatin 50 mg/m2 intravenous on Day 2 (q3w); or
  - Paclitaxel 175 mg/m2 intravenous over 3 hours on Day 1 and cisplatin 50 mg/m2 intravenous on Day 1 (q3w).
- Paclitaxel 135 mg/m2 intravenous over 24 hours on Day 1 and cisplatin 50 mg/m2 intravenous on Day 2 plus bevacizumab 15 mg/kg intravenous on Day 2 (q3w); or
  - Paclitaxel 175 mg/m2 intravenous over 3 hours on Day 1 and cisplatin 50 mg/m2 intravenous on Day 2 plus bevacizumab 15 mg/kg intravenous on Day 2 (q3w); or
  - Paclitaxel 175 mg/m2 intravenous over 3 hours on Day 1 and cisplatin 50 mg/m2 intravenous on Day 1 plus bevacizumab 15 mg/kg intravenous on Day 1 (q3w).
- Paclitaxel 175 mg/m2 intravenous over 3 hours on Day 1 and topotecan 0.75 mg/m2 intravenous over 30 minutes on days 1-3 (q3w).
- Paclitaxel 175 mg/m2 intravenous over 3 hours on Day 1 and topotecan 0.75 mg/m2 intravenous over 30 minutes on Days 1-3 plus bevacizumab 15 mg/kg intravenous on Day 1 (q3w).

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

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

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

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

The primary efficacy endpoint was overall survival. Secondary efficacy endpoints included progression-free survival and objective response rate. Results from the primary analysis and the follow-up analysis are presented by bevacizumab Treatment and by Trial Treatment in Table 14 and Table 15, respectively.

Table 14: Efficacy results from study GOG-0240 by bevacizumab treatment

	Chemotherapy (n=225)	Chemo + bevacizumab (n=227)
Primary endpoint		
Overall survival – Primary analysis[6]		
Median (months)[1]	12.9	16.8
Hazard ratio [95% CI]	0.74[0.58, 0.94] (p-value[5] = 0.0132)	
Overall survival-follow-up analysis[7]		
Median (months)[1]	13.3	16.8
Hazard ratio [95% CI]	0.76[0.62, 0.94] (p-value[5,8] = 0.0126)	
Secondary endpoint		

Progression-free survival – Primary analysis[6]		
Median (months)[1]	6.0	8.3
Hazard ratio [95% CI]	0.66[0.54, 0.81] (p-value[5] <0.0001)	
Best overall response – Primary analysis[6]		
Responders (Response rate[2])	76 (33.8%)	103 (45.4%)
95% CI for response rates[3]	[27.6%, 40.4%]	[38.8%, 52.1%]
Difference in response rates	11.60%	
95% CI for difference in response rates[4]	[2.4%, 20.8%]	
p-value (Chi-squared test)	0.0117	

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

Table 15 Overall survival results from study GOG-0240 by trial treatment

Treatment comparison	Other factor	Overall survival – primary analysis[1] Hazard ratio (95% CI)	Overall survival - follow-up analysis[2] Hazard ratio (95% CI)
Bevacizumab vs. No Bevacizumab	Cisplatin+ Paclitaxel	0.72 (0.51, 1.02) (17.5 vs.14.3 months; p = 0.0609)	0.75 (0.55, 1.01) (17.5 vs.15.0 months; p = 0.0584)
	Topotecan+	0.76 (0.55, 1.06)	0.79 (0.59, 1.07)

	Paclitaxel	(14.9 vs. 11.9 months; p = 0.1061)	(16.2 vs. 12.0 months; p = 0.1342)
Topotecan+ Paclitaxel vs. Cisplatin+ Paclitaxel	Bevacizumab	1.15 (0.82, 1.61)	1.15 (0.85, 1.56)
		(14.9 vs. 17.5 months; p = 0.4146)	(16.2 vs 17.5 months; p = 0.3769)
	No Bevacizumab	1.13 (0.81, 1.57)	1.08 (0.80, 1.45)
		(11.9 vs.14.3 months; p = 0.4825)	(12.0 vs 15.0 months; p = 0.6267)

[1] Primary analysis was performed with a data cut-off date of 12 December 2012 and is considered the final analysis.

[2] Follow-up analysis was performed with a data cut-off date of 07 March 2014; all p-values are displayed for descriptive purpose only.

Paediatric population

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

High-grade glioma

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

- In a single-arm study (PBTC-022), 18 children with recurrent or progressive non-pontine high-grade glioma (including 8 with glioblastoma [WHO Grade IV], 9 with anaplastic astrocytoma [Grade III] and 1 with anaplastic oligodendroglioma [Grade III]) were treated with bevacizumab (10 mg/kg) two weeks apart and then with bevacizumab in combination with CPT-11 (125-350 mg/m²) once every two weeks until progression. There were no objective (partial or complete) radiological responses (MacDonald criteria). Toxicity and adverse reactions included arterial hypertension and fatigue as well as CNS ischaemia with acute neurological deficit.
- In a retrospective single institution series, 12 consecutive (2005 to 2008) children with relapsed or progressive high-grade glioma (3 with WHO Grade IV, 9 with Grade III) were

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

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

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

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

Soft tissue sarcoma

In a randomized phase II study (BO20924) a total of 154 patients aged ≥ 6 months to <18 years with newly diagnosed metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma were treated with standard of care (Induction IVADO/IVA+/- local therapy followed by Maintenance Vinorelbine and cyclophosphamide) with or without bevacizumab (2.5 mg/kg/week) for a total duration of treatment of approximately 18 months. At the time of the final primary analysis, the primary endpoint of EFS by independent central review did not show a statistically significant difference between the two treatment arms, with HR of 0.93 (95% CI: 0.61, 1.41; p-value = 0.72).

The difference in ORR per independent central review was 18% (CI: 0.6%, 35.3%) between the two treatment arms in the few patients who had evaluable tumor at baseline and had a confirmed response prior to receiving any local therapy: 27/75 patients (36.0%, 95% CI: 25.2%, 47.9%) in the Chemo arm and 34/63 patients (54.0%, 95% CI: 40.9%, 66.6%) in the Bv +Chemo arm. The secondary endpoint of Overall Survival (OS) was not mature. Until mature OS results and safety data are available, no definitive conclusion can be drawn on the benefit/risk balance.

Addition of bevacizumab to standard of care did not demonstrate clinical benefit in clinical trial BO20924, in 71 evaluable children (from age 6 months to less than 18 years old) patients with metastatic Rhabdomyosarcoma and non-Rhabdomyosarcoma Soft Tissue Sarcoma.

(See section 4.2 for information on paediatric use).

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

5.2. Pharmacokinetic properties

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

Distribution

The typical value for central volume (Vc) was 2.73 L and 3.28 L for female and male patients respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (Vp) was 1.69 L and 2.35 L for female and male patients respectively, when bevacizumab is co-administered with anti-neoplastic agents. After correcting for body weight, male patients had a larger Vc (+ 20%) than female patients.

Biotransformation

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

Elimination

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

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

Pharmacokinetics in special populations

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

Renal impairment

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

Hepatic impairment

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

Paediatric population

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

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

5.3. Preclinical safety data

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Name of ingredients	Function	Unit Formula for the 100mg/4ml (mg/vial)	Unit Formula for the 400mg/16ml (mg/vial)
Bevacizumab (PF-06439535)	Active ingredient	100	400
Succinic Acid	Buffer component	9.44	37.76
Sucrose	Tonicifier	340	1360
Edetate Disodium Dihydrate (EDTA)	Chelator	0.2	0.8
Polysorbate 80	Surfactant	0.8	3.2
Sodium Hydroxide	pH adjustment	q.s. to pH 5.5	q.s. to pH 5.5
Water for injection	Solvent	q.s. to 4.0 mL	q.s. to 16.0 mL

* q.s. mean quantity sufficient.

6.2. Incompatibilities

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

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

6.3. Shelf life

Vial (unopened)

Do not use ZIRABEV after the expiry date which is stated on the vial label after EXP:.The expiry date refers to the last day of that month.

Shelf life: 3 years

Diluted medicinal product

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

6.4. Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

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

Pack of 1 vial.

6.6. Special precautions for disposal and other handling

Zirabev should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

Once the vial has been opened, the dilution must be performed immediately. The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 mg/ml to 16.5 mg/ml. In the majority of the occasions the necessary amount of Zirabev can be diluted with 0.9% sodium chloride solution for injection to a total volume of 100 mL.

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

No incompatibilities between Zirabev and polyvinyl chloride or polyolefin bags or infusion sets have been observed.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG

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