Bevacizumab biosimilar (BCD-021)

Azat Garipov

v1.2024

General information

Description: Bevacizumab is a humanized monoclonal antibody (IgG1). Bevacizumab specifically interacts with human vascular endothelial growth factor (VEGF) and inhibits its binding with receptors on the surface of endothelial cells. As a result of such interaction intracellular signal routs of endothelial cells does not activate and their VEGF dependent growth is further inhibited.

INN: BEVACIZUMAB

Internal code: BCD-021

Dosage form: Concentrate for solution for infusion

Indications:

- Metastatic colorectal cancer
- Local recurrent or advanced breast cancer
- Inoperable or advanced non-squamous NSCLC
- Advanced and/or metastatic renal cell cancer
- Glioblastoma (grade IV glioma)
- Epithelial ovarian, fallopian tube and primary peritoneal cancer
- Persistent, recurrent or metastatic cervical carcinoma

Manufacturer: The full manufacturing cycle and quality control are performed by JSC BIOCAD

BIOCAD bevacizumab in the world

Bevacizumab (JSC BIOCAD) was first approved in the Russian Federation on 25 November 2015

- Supplied to and/or registered in **30+**[1] **countries**
- Approval process ongoing in > **25 countries**

Pharmacovigilance data without unexpected efficacy or safety reports on:

> 3 200 000 vials supplied

> 100 400[2] patients treated

1 Number of countries, where the products are supplied to and/or registered, including temporary quarters and emergency tenders
2 Numbers on this page relevant as of January 2024. The calculation is based on the average recommended doses, average patient weight, and the approximate duration of therapy. The approximate bevacizumab dose for the treatment of one patient (regardless of the indication): 9920 mg

Phase III study of bevacizumab biosimilar BCD-021

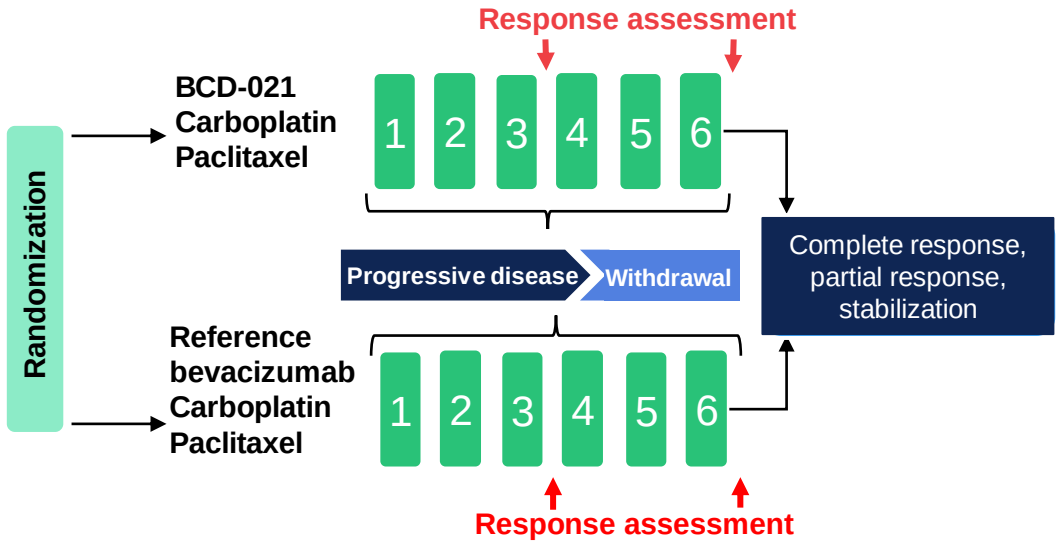
International multicenter randomized double-blind comparative study

Population: 357 adult males and females with advanced unresectable or metastatic (stage IIIb/IV) nonsquamous NSCLC. 14 patients did not receive at least one dose of the study drug or comparator.

Study groups and treatment

Group 1 (BCD-021) n=206:
Day 1 of each 21-day cycle:
paclitaxel - 175 mg/m^2, carboplatin - AUC 6
BCD-021 - 15 mg/kg

Group 2 (reference bevacizumab*) n=137:
Day 1 of each 21-day cycle:
paclitaxel - 175 mg/m^2, carboplatin - AUC 6
reference bevacizumab - 15 mg/kg (1.5 h infusion)



Treatment duration: up to 6 cycles

Primary endpoints
- Objective response rate;
- Equivalence of C_{max} and $AUC_{0\text{-}504h}$ on cycle 1

Reference bevacizumab is Avastin®

Bevacizumab Phase III study
Sample size calculation

Equivalence design was used for the study.
Sample size (n=280) was calculated according to recommendations given by Chow S.C., 2008 (Chow B. et al. “Sample size calculation for clinical trials”, 2nd Edition, 2008), using the following formulas:

Formula for assessment of sample size using risk difference approach

$$n_2 = \frac{\left(\frac{p_1 * (1 - p_1)}{k} + p_2 * (1 - p_2)\right) * \left(z_\alpha + z_{\beta/2}\right)^2}{(\delta - |\varepsilon|)^2}$$

Formula for assessment of sample size using risk ratio approach

$$n_2 = \frac{\left(z_\alpha + z_{\beta/2}\right)^2}{(\delta - |\log(RR)|)^2}\left[\frac{1 - p_1}{kp_1} + \frac{1 - p_2}{p_2}\right]$$

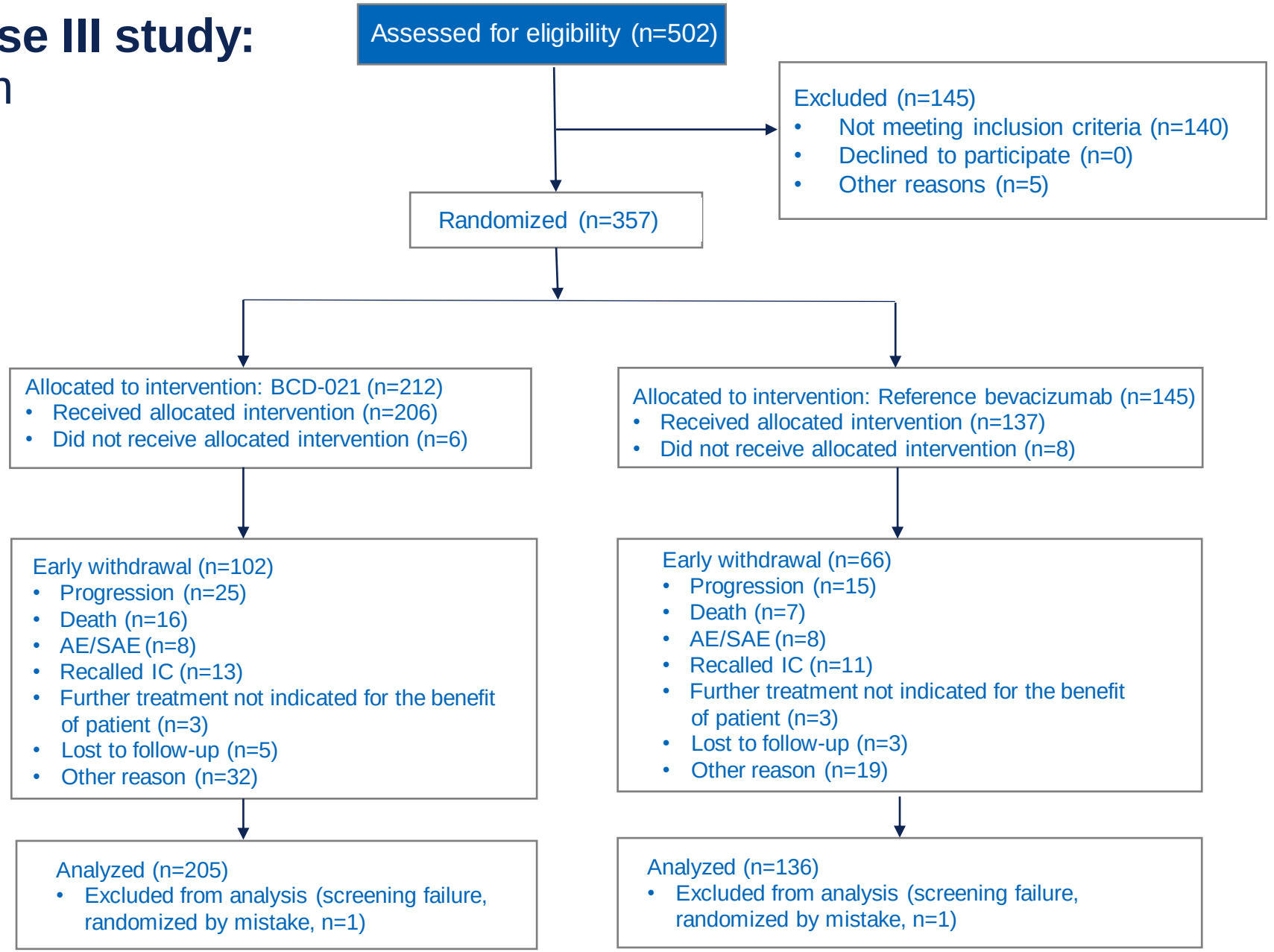
- Equivalence margin* = -18%; 18% for testing equivalence as risk difference (Approach recommended by EMA)
- Equivalence margin* = 67%; 150% for testing equivalence as risk ratio (Approach recommended by FDA)
- Significance level α=0.05
- Statistical power of 80%

* According to ICH E10 Guideline **the margin (delta)** value generally should not be higher than difference between active control and placebo (or absence of treatment).

Study	N (CT/BCT)*	CT ORR	BCT ORR	Risk Ratio
AVF0757	32/34	18.8%	32.4%	0.58
JO19907	59/121	33.9%	56.2%	0.60
AVAiL	327/329	21.7%	34.7%	0.63
E4599	392/381	15.1%	34.9%	0.43
FDA’s meta-analysis	810/865	19.3%	37.7%	0.53

***N: ITT population; CT: chemotherapy; BCT: bevacizumab with chemotherapy**

Bevacizumab Phase III study: CONSORT diagram

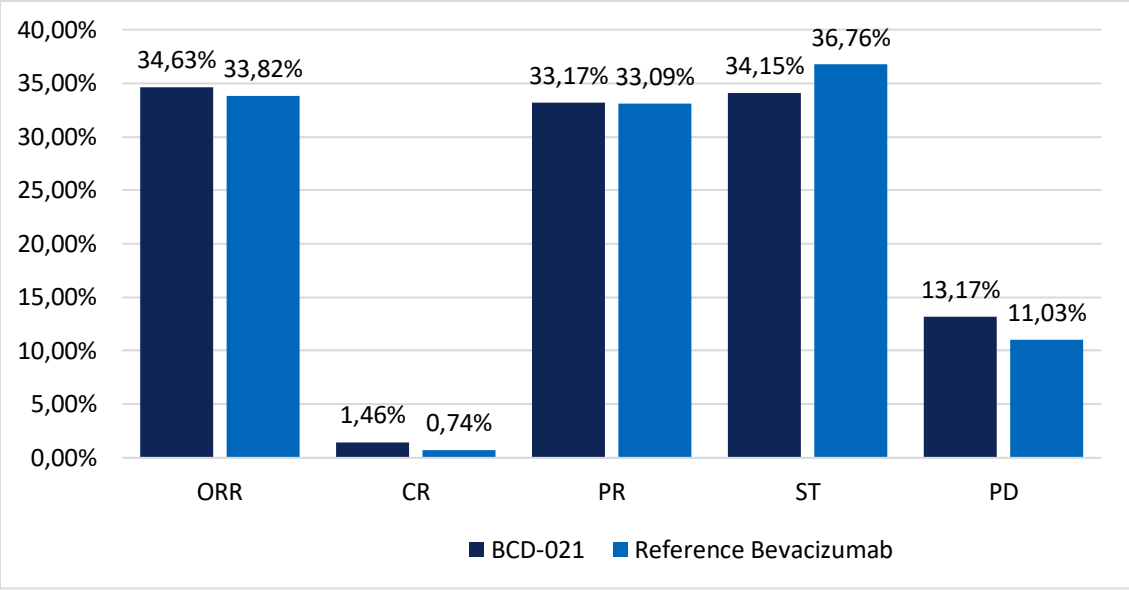


Bevacizumab Phase III study
Efficacy analysis

Primary efficacy endpoint assessment results

Parameter	BCD-021 (n = 205)		Reference bevacizumab (n = 136)		p*
	n	%	n	%	
Objective response rate (ORR)	71	34.63	46	33.82	0.8773
ORR difference, % (95% CI)	**0.81% (-9.47% - 11.09%)**				

* Pearson's χ^2 test



Biosimilarity of BCD-021 to reference bevacizumab was confirmed

- The ORR (primary endpoint) showed no significant differences between the groups
- The estimated 95% CI for ORR difference **(-9.47%; 11.09%)** was within predetermined equivalence margin (-18%; 18%) and margins used for other bevacizumab biosimilars **(-12.5%; 12.5%)**
- The estimated 90% CI for ORR ratio (**79.6%; 131.73%**) was within predetermined equivalence margin (67%; 150%) and margins indicated in guideline for bevacizumab biosimilars (**75.00%; 133.33%**).

Bevacizumab Phase III study
PK analysis

Pharmacokinetic parameter	90% CI	90% CI acceptable range
$AUC_{(0-504)}$ (µg/ml)·h*	80.67–109.69%	80.00% - 125.00%
C_{max} (µg/ml)*	89.12–111.35%	80.00% - 125.00%

- 90% CI for the geometric mean ratios (differences between log values) of $AUC_{(0-504)}$ for BCD-021 and $AUC_{(0-504)}$ for reference bevacizumab were within acceptance range (80.00% - 125.00%) both for Indian and non-Indian patient population. The acceptance range 80.00% - 125.00% is defined by European guideline on biosimilar drug development (EMA/CPMP/EWP/QWP/140198Rev.1/Corr/2010)
- No statistically significant differences in C_{trough} were observed between study groups in any of the therapy cycles

The pharmacokinetics of BCD-021 was equivalent to that of reference bevacizumab both for patients enrolled in India and outside India

*for patients enrolled in Russia, Belarus and Ukraine.

Bevacizumab Phase III study
Safety analysis

Parameter	BCD-021 (n = 206) n(%)	Reference bevacizumab (n = 137) n(%)	p-value*
Any AE/SAE	188 (91.26)	128 (93.43)	0.4651[1]
— **SAE**	28 (13.59)	15 (10.95)	0.4690[1]
— **Therapy-related SAE**	7 (3.40)	3 (2.19)	0.7454[2]
Courses discontinued due to AE/SAE	4 (1.94)	2 (1.46)	1.0000[2]
Deaths[3]	14 (6.80)	8 (5.84)	0.7232[1]

- AEs profiles of BCD-021 and comparator were equivalent.
- Rate of all observed AEs including severe AEs had no statistically significant difference between the groups.
- Most AEs were associated with chemotherapy.
- The most common AEs included hematological and non-hematological disorders, laboratory abnormalities.

1 - Pearsons χ2 test; 2 - Two-tailed Fisher's exact test
3 - This tabulation does not include the lethal outcome in patient who was randomized but did not receive a single dose of the study drug

Bevacizumab Phase III clinical study
Immunogenicity analysis

Parameter	BCD-021 (n = 206) n(%)	Reference bevacizumab (n = 137) n(%)	p-value*
Binding antibodies (Screening)	1 (0.49)	2 (1.46)	0.5661[2]
Binding antibodies (throughout the study)	9 (4.37)	10 (7.30)	0.2452[1]
Neutralizing antibodies (Screening and/or throughout the study)	4 (1.94)	5 (3.65)	0.4924[2]

By now there is no data indicating the relation of neutralizing antibodies to bevacizumab to AE, loss of drug efficacy and/or pharmacokinetics. The clinical significance of these antibody responses is unknown.

[1] - Pearson's chi-squared test, [2] - Fisher's exact test;

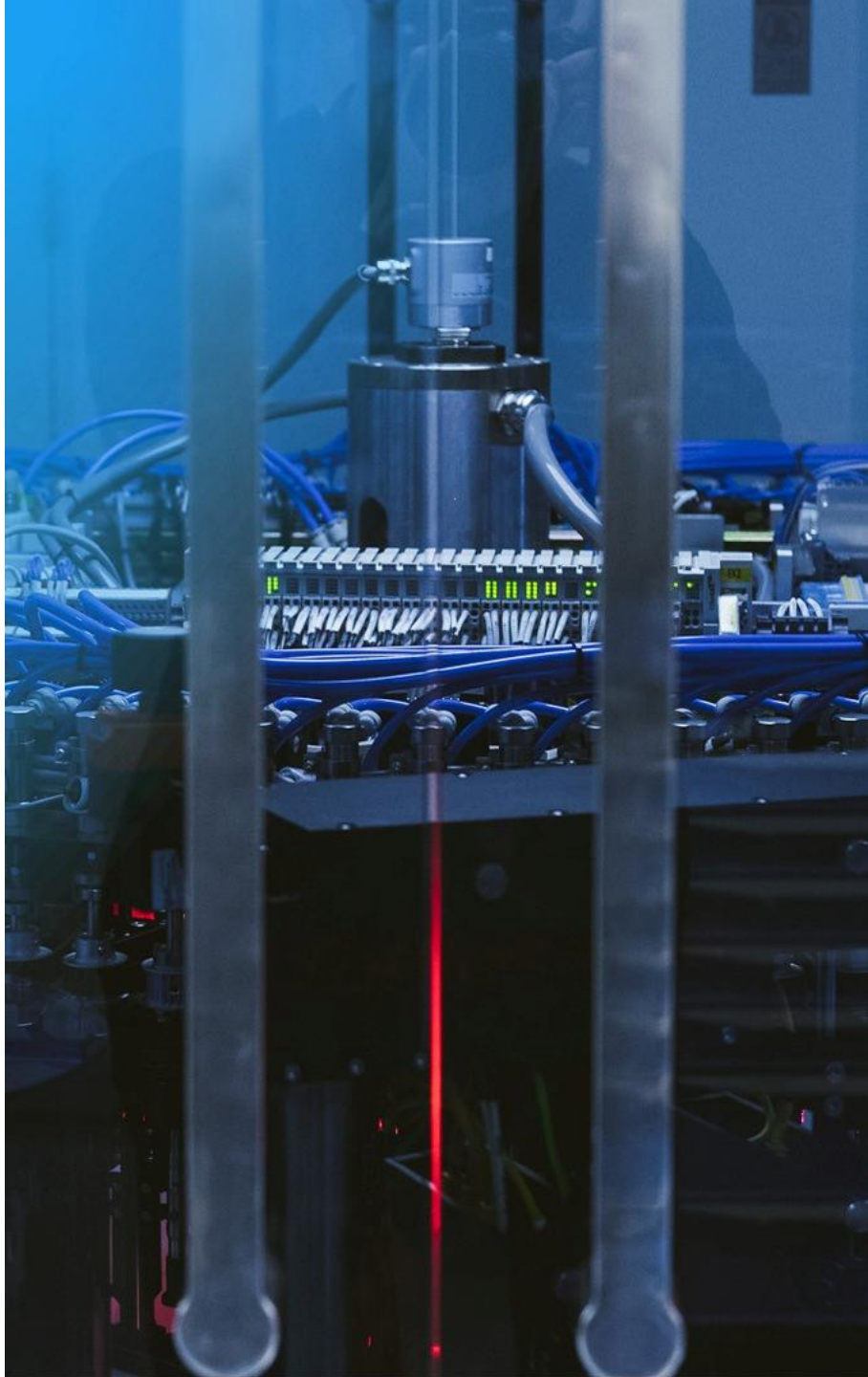
Conclusions

The pharmacokinetics analysis has found no differences between the BCD-021 and reference drug groups

There was no statistically significant difference in primary efficacy endpoint (ORR) between the groups. Therefore, equivalent efficacy of BCD-021 and reference bevacizumab was confirmed

The safety analysis has shown that BCD-021 and reference bevacizumab have similar safety and low immunogenicity

The data obtained demonstrate the therapeutic equivalence of bevacizumab biosimilar BCD-021 and the reference drug



Bevacizumab biosimilar BCD-021 phase 3 study publication in BMC Cancer journal

Stroyakovskiy *et al. BMC Cancer* (2022) 22:129
https://doi.org/10.1186/s12885-022-09243-7

BMC Cancer

RESEARCH Open Access

Randomized double-blind clinical trial comparing safety and efficacy of the biosimilar BCD-021 with reference bevacizumab

Daniil L. Stroyakovskiy[1], Natalya V. Fadeeva[2], Marina P. Matrosova[3], Konstantin G. Shelepen[4], Grigoriy A. Adamchuk[5], Bodhisatta Roy[6], Rajnish Nagarkar[7], Mahesh Kalloli[8], Daria Zhuravleva[9], Georgiy D. Voevodin[9], Mariya S. Shustova[9] and Fedor Kryukov[9*]

Reference:
Stroyakovskiy DL, Fadeeva NV, Matrosova MP, Shelepen KG, Adamchuk GA, Roy B, Nagarkar R, Kalloli M, Zhuravleva D, Voevodin GD, Shustova MS, Kryukov F. Randomized double-blind clinical trial comparing safety and efficacy of the biosimilar BCD-021 with reference bevacizumab. BMC Cancer. 2022 Feb 1;22(1):129. doi: 10.1186/s12885-022-09243-7. PMID: 35105329; PMCID: PMC8808992.
https://bmccancer.biomedcentral.com/articles/10.1186/s12885-022-09243-7

Multicentre prospective observational post-authorisation study of safety and effectiveness of bevacizumab (Avegra®, BIOCAD) in patients with metastatic colorectal cancer in real world practice: **APOLLON-11** & **SOYUZ-APOLLON***

Tryakin A., et al., 2023, Annals of Oncology

Version 4.2023

About the APOLLON-11 & SOYUZ-APOLLON study

The aim of the study was to evaluate the safety and effectiveness of long-term continuous use of Avegra® BIOCAD (INN: bevacizumab) in patients with metastatic colorectal cancer (mCRC) in routine clinical practice

This presentation demonstrates the final results of a multicentre prospective observational authorisation study of the safety and efficacy of Avegra® BIOCAD (INN: bevacizumab) in combination with chemotherapy in patients with mCRC

Depending on the geography the study was divided into Apollon-11, conducted in Moscow, and Soyuz-Apollon, conducted in 18 regions of Russia. The final analysis summarizes pooled results of all regions (Apollon-11 + Soyuz-Apollon)

Tryakin, A. et al., 2023. 125P Final results of APOLLON-11 and SOYUZ-APOLLON study: Multicentre prospective observational post-authorization study of bevacizumab biosimilar in patients with metastatic colorectal cancer in real-world practice, Annals of Oncology, Elsevier BV.
doi: 10.1016/j.annonc.2023.10.260.
https://www.annalsofoncology.org/article/S0923-7534(23)04466-6/fulltext

Study geography

18 regions in Russia

28 centers
56 investigators

438 patients

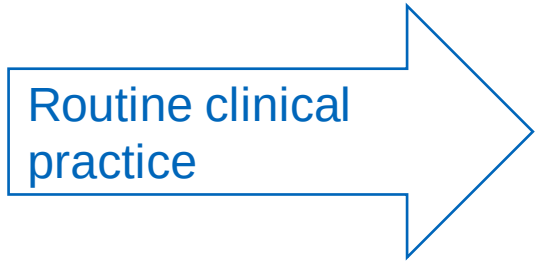
Started – December 2019

Final analysis – January 2023

Study design

- Patients with mCRC (n=438)
- 1st line chemotherapy + bevacizumab
- ECOG 0-1

Median follow-up 7.4 mo



Primary safety endpoints:

- Adverse reactions (CTCAE v5.0)
- Treatment discontinuation due to adverse reactions

Secondary effectiveness endpoints:

- Objective response rate
- Progression-free survival
- Overall survival

Baseline characteristics

Characteristic		n=438	
		n	%
Age	Median (min–max), years	62 (28-87)	
Gender	Male	239	54.6
	Female	199	45.4
ECOG	0	166	37.9
	1	272	62.1
Tumor localization	Left-side	294	67.1
	Right-side	144	32.9
KRAS mutation	Yes	85	19.4
	No	126	28.8
	Unknown	227	51.8
NRAS mutation	Yes	23	5.3
	No	174	39.7
	Unknown	241	55.0
BRAF mutation	Yes	12	2.7
	No	163	37.2
	Unknown	263	60.0

Treatment profile

First-line chemotherapy regimens	n=438	
	n	%
FOLFOX/FOLFOX 6 + bev	**248**	**56.6**
XELOX + bev	**113**	**25.8**
FOLFIRI + bev	30	6.8
FOLFOXIRI + bev	15	3.4
XELIRI + bev	9	2.1
Other	23	5.3

Safety (1)

Bevacizumab infusions (n=436)	
Median (min-max)	8 (1-37)

Safety characteristic	N=436	
	n	%
Adverse reactions	48	**11.0**
Treatment discontinuation due to AR	12	**2.8**
Serious adverse events (SAEs)	9	2.1
Adverse events (AEs), grade 3-5	21	4.8
Adverse reactions (ARs), grade 3-5	12	2.3
At least one infusion reaction	13	3.0
Grade 1 infusion reaction	11	2.5
Grade 2 infusion reaction	2	0.5

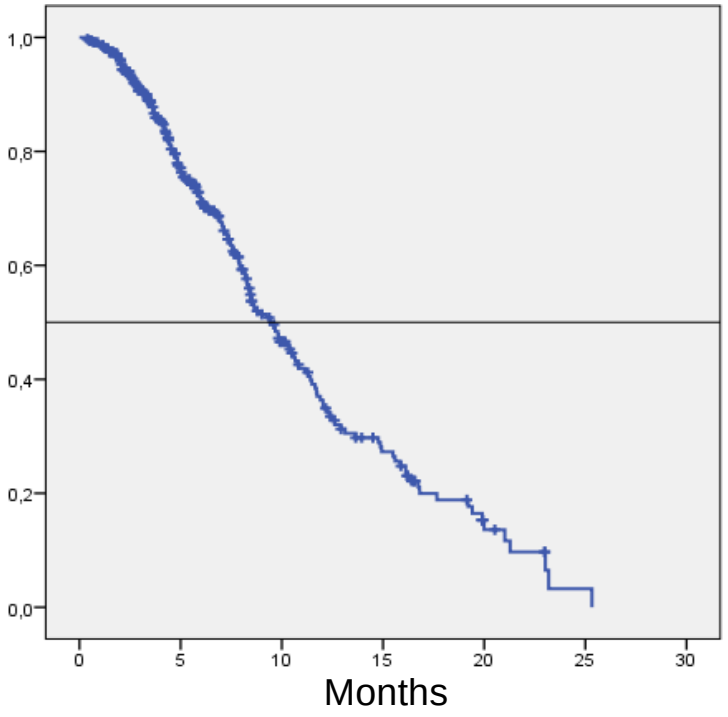
Safety (2)

Adverse reactions	N=436	
	n	%
Anemia	1	0,2%
Asthenia	4	0,9%
Headache	4	0,9%
Diarrhea*	5	1,1%
Gastrointestinal bleeding*	3	0,7%
Ecchymosis	2	0,5%
Hemoptysis	1	0,2%
Leukopenia*	3	0,7%
Neutropenia*	4	0,9%
Nose bleeds	1	0,2%
Gastrointestinal perforation*	1	0,2%
Hypertension*	14	3,2%
Fatigue	1	0,2%
Hot flush	1	0,2%
Proteinuria	1	0,2%
Nausea and vomiting symptoms	1	0,2%
Deep vein thrombosis	1	0,2%
Thrombocytopenia	2	0,5%

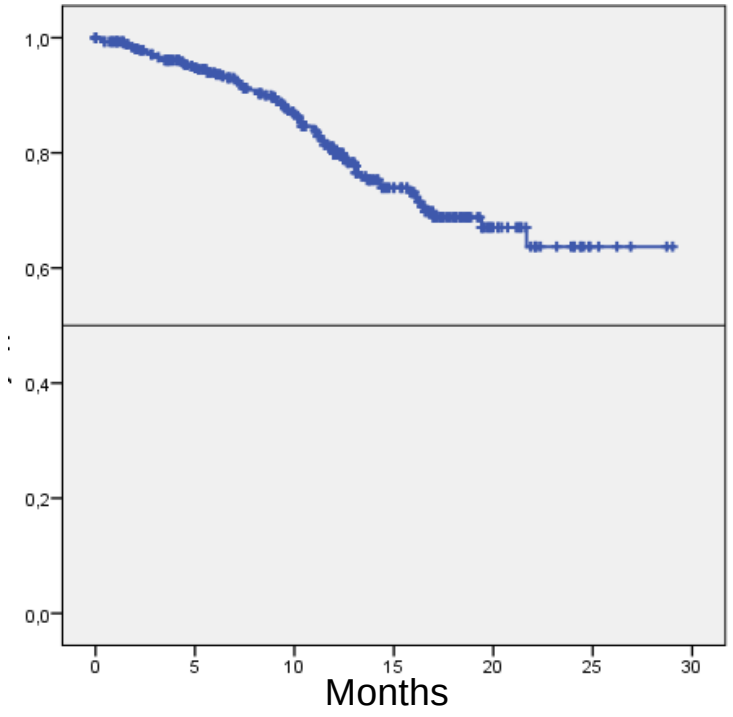
Effectiveness: Response to treatment and survival

ORR, % (95% CI)	**39.4 (34.2 – 44.8), 2.9% CR**
PFS, median (95% CI)	**9.4** (8.1 – 10,7)
OS, median (95% CI)	Not reached (NR-NR)

Progression-free survival (PFS), n=357

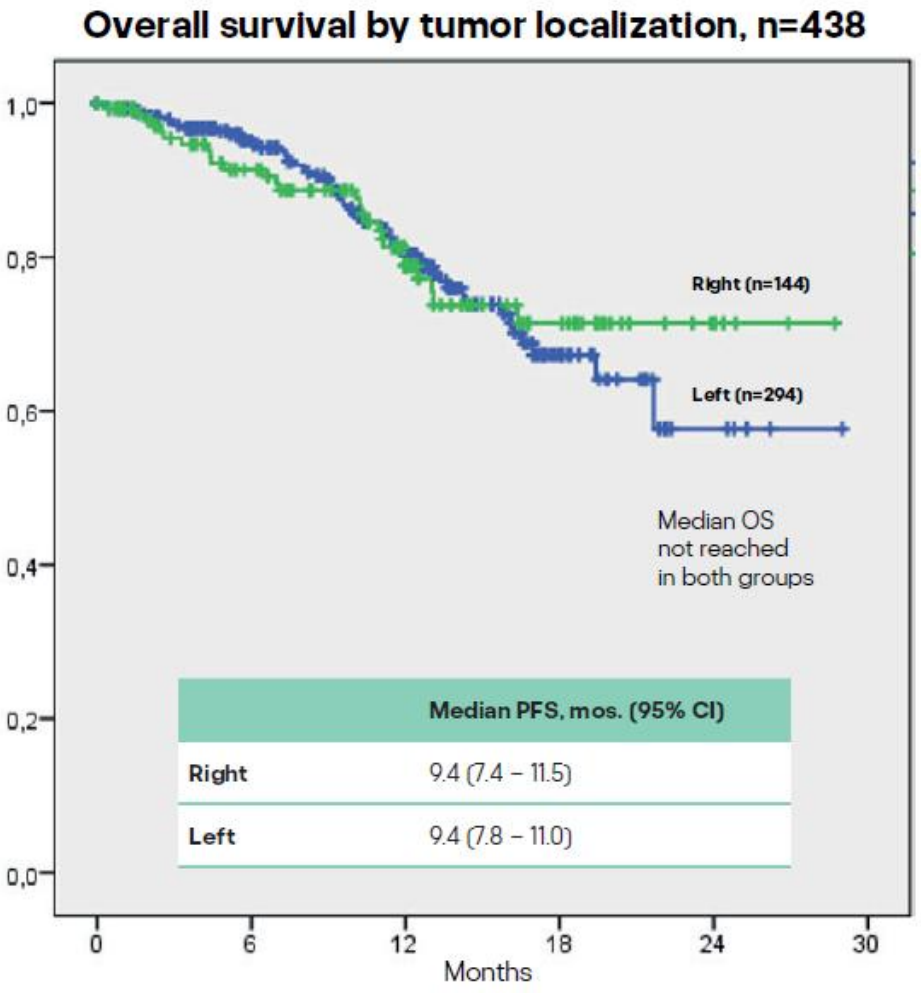


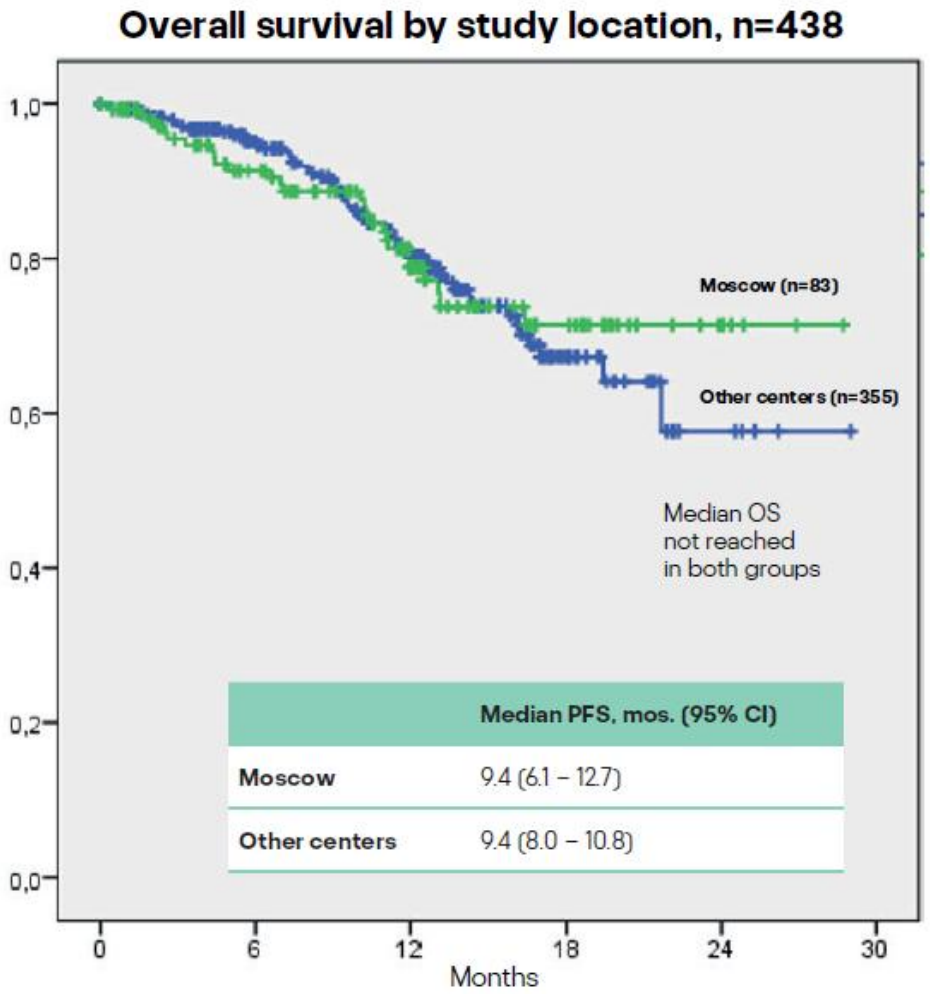
Overall survival (OS), n=438



ORR, objective response rate; CR, complete responses

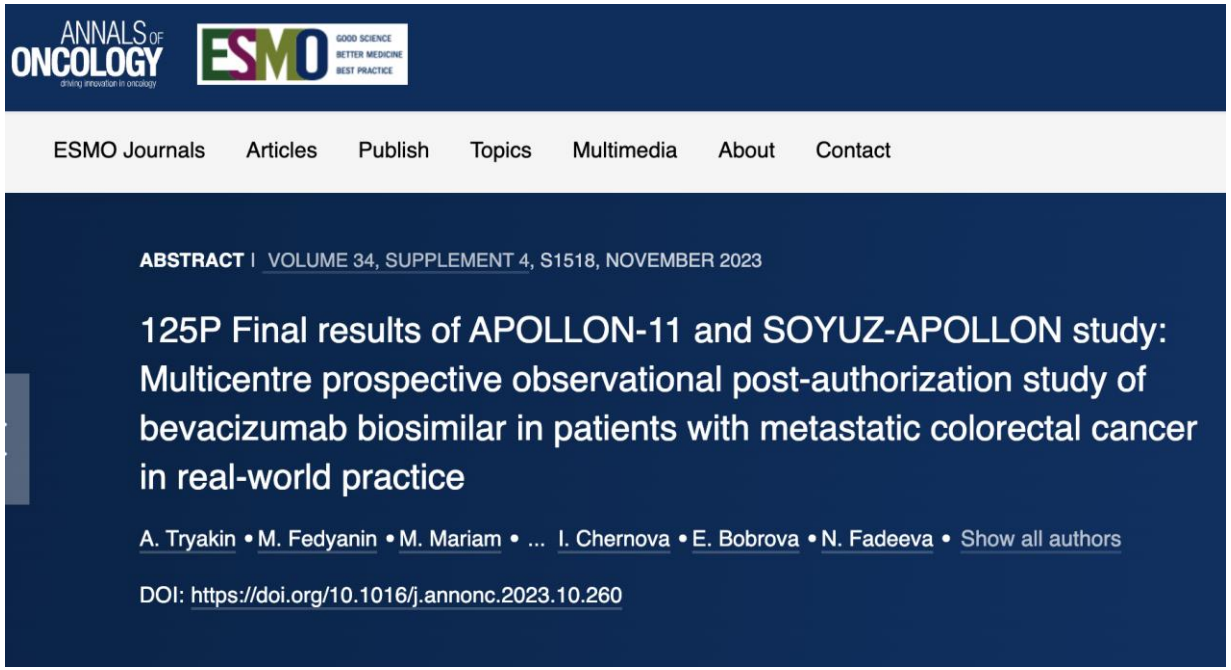
Effectiveness: tumor side and study location subanalysis





CONCLUSION

Post-authorisation study of bevacizumab biosimilar Avegra® (BIOCAD) confirmed expected safety profile and effectiveness in patients with mCRC



REFERENCE:

Tryakin, A. et al., 2023. 125P Final results of APOLLON-11 and SOYUZ-APOLLON study: Multicentre prospective observational post-authorization study of bevacizumab biosimilar in patients with metastatic colorectal cancer in real-world practice, Annals of Oncology, Elsevier BV. doi: 10.1016/j.annonc.2023.10.260. https://www.annalsofoncology.org/article/S0923-7534(23)04466-6/fulltext