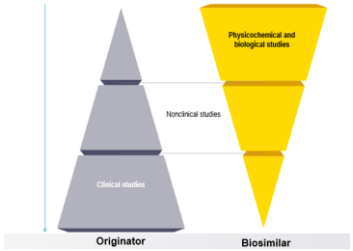
Pembroria®
pembrolizumab

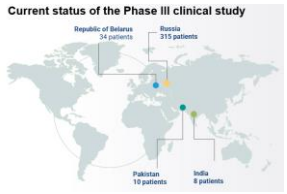
The results of clinical studies of the pembrolizumab biosimilar (Biocad)

December, 2024

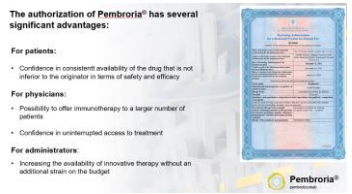
Content



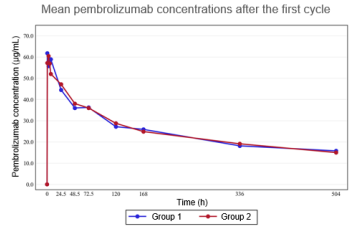
- Introduction and Principles of Biosimilar Development



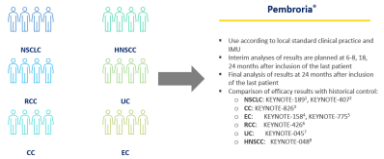
- BCD-201-2 (Phase 3) Study of Pembrolizumab Biosimilar



- Summary



- BCD-201-1 (Phase 1) Study of Pembrolizumab Biosimilar



- Real-World Clinical Data: The Perfection Study

Pembroria®
pembrolizumab

Introduction and Principles of Biosimilar Development

Portfolio of biosimilars that are BIOCAD’s blockbusters

AVEGRA®
bevacizumab

A drug for the treatment of colorectal cancer, ovarian cancer, fallopian tube and primary peritoneal cancer, cervical cancer, lung cancer, kidney cancer, glioblastoma, breast cancer.

>60,000 patients*

ACELLBIA®
rituximab

A drug for the treatment of non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis.

>120,000 patients*

HERTICAD®
trastuzumab

A drug for the treatment of breast cancer and advanced gastric or gastroesophageal junction cancer with tumor HER2 overexpression.

>50,000 patients*

PEMBRORIA®
Pembrolizumab

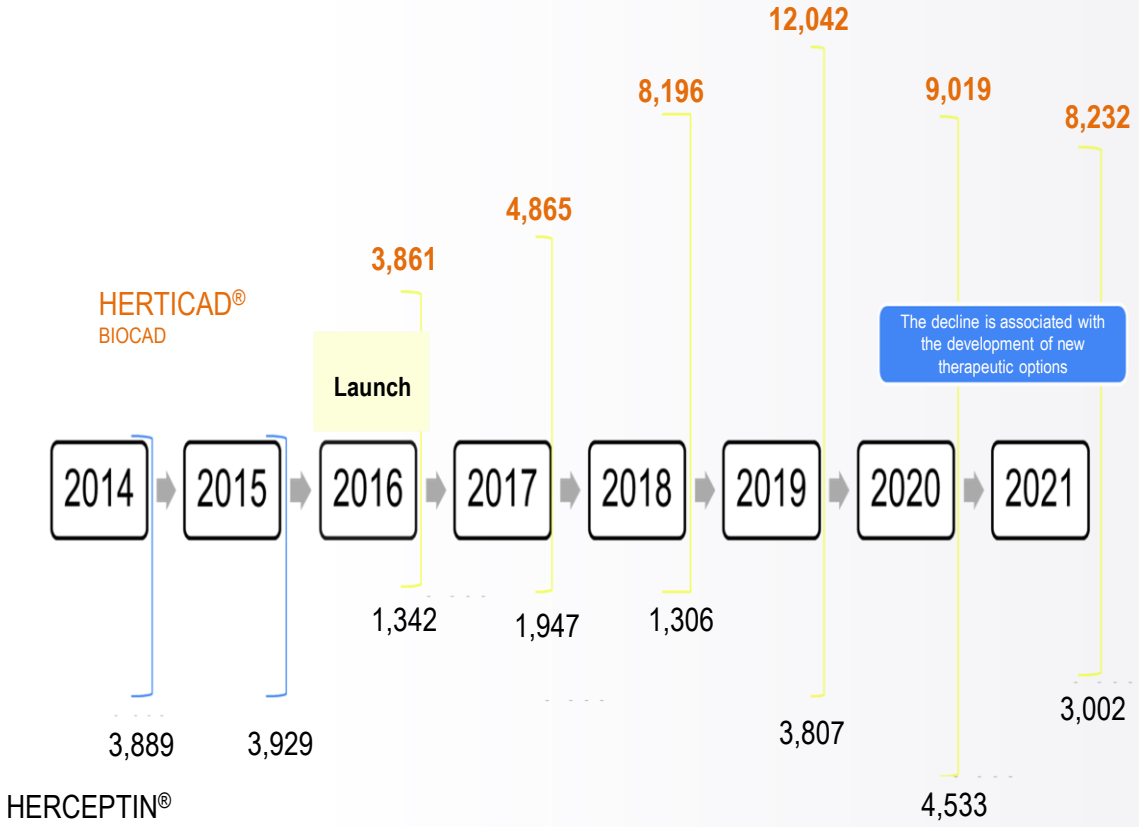
The world’s 1st biosimilar of pembrolizumab

>5 000 patients*

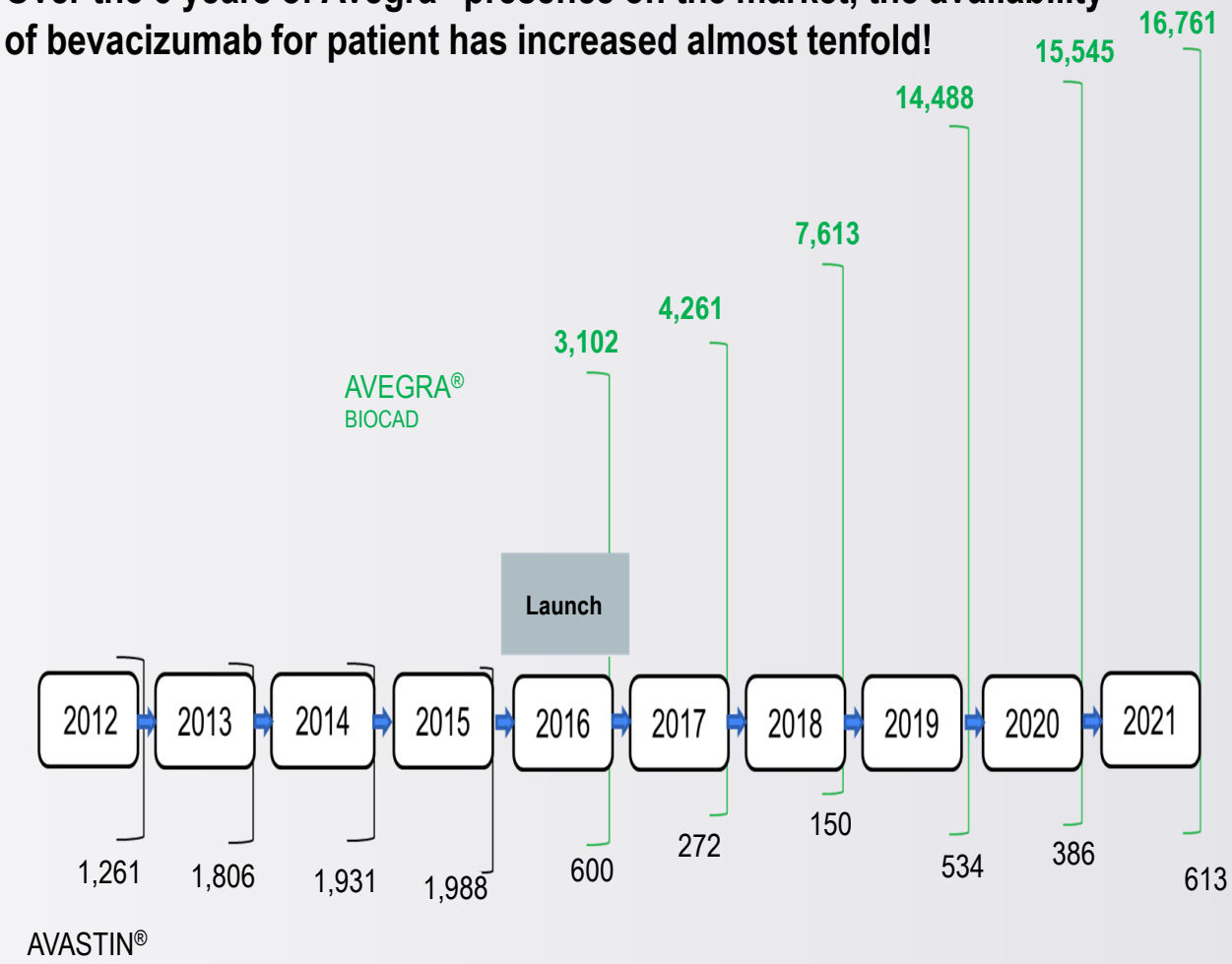
*based on estimations

Increasing patient access to effective therapies through biosimilars

The number of patients on trastuzumab therapy has quadrupled in 5 years after the launch of biosimilar Herticad® by BIOCAD

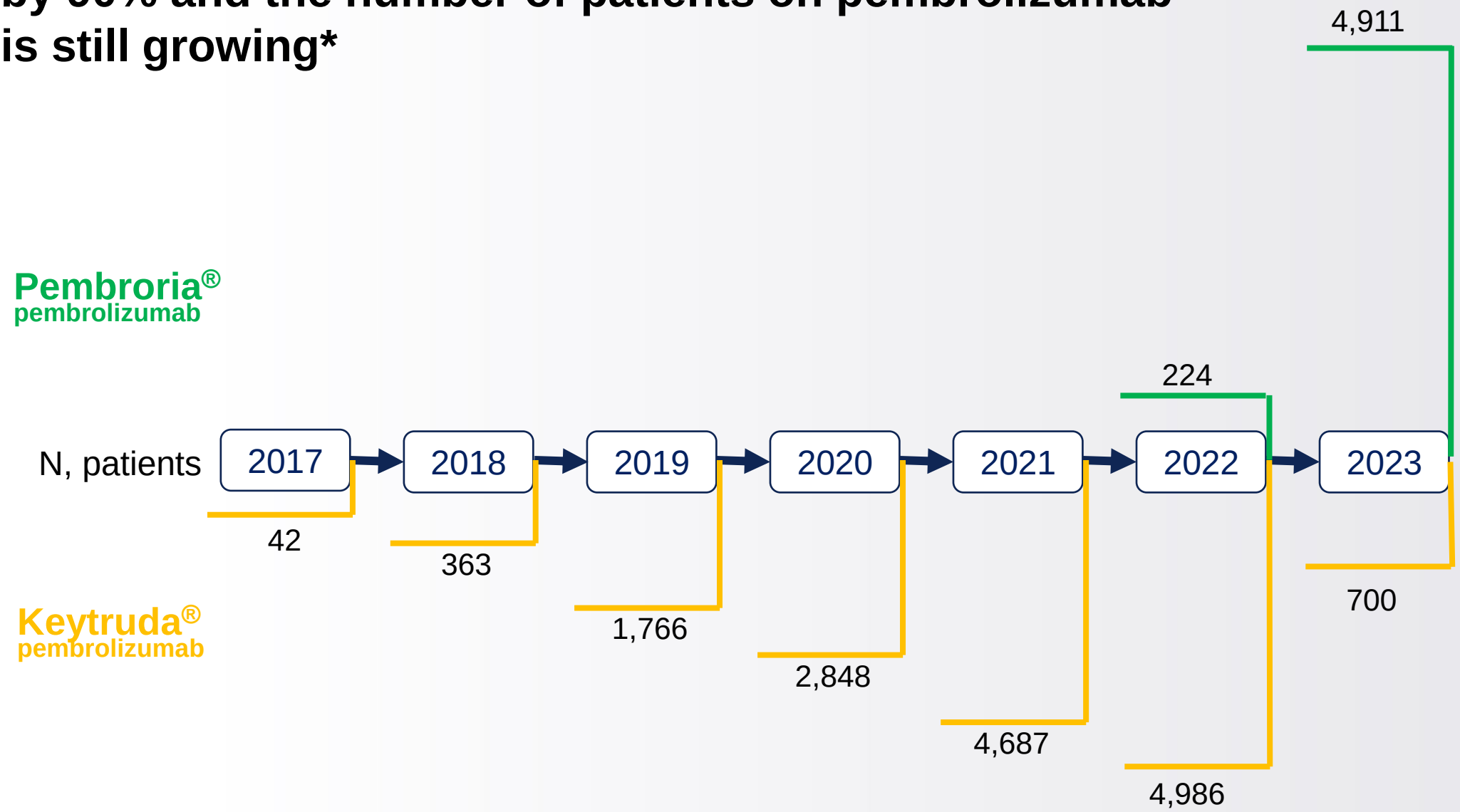


Over the 5 years of Avegra® presence on the market, the availability of bevacizumab for patient has increased almost tenfold!



Calculation procedure:
1 - Calculation of need: quantity of purchased trastuzumab in mg / 7,800 mg (average course dose for a female patient weighing 75 kg based on ...)

In 2023, Pembroria® replaced the originator Keytruda® by 90% and the number of patients on pembrolizumab is still growing*



*Russian market, 2016–2024 (contracts)
Calculation of patients taking into account the course dose of pembrolizumab 200 mg once every 3 weeks

Stages of clinical development of a biosimilar[1,2,3]

The stages of clinical development of a biosimilar for Russia, China, the European Union and the USA are fundamentally similar and include 2 stages:

STAGE 1 includes **demonstration of equivalent pharmacokinetics (PK) of the biosimilar and the originator in terms of $AUC_{0-\infty}$ or AUC_{0-t}** after a single dose in healthy volunteers or patients (**a phase 1 randomized controlled trial**). For subcutaneous products, demonstration of equivalence in terms of C_{max} is also required. In some cases, after the first stage, demonstration of PK equivalence between the biosimilar and the originator in terms of PK after multiple dosing is required (e.g., anticancer drugs with target-mediated clearance, such as trastuzumab). **The equivalence limits for the ratio of PK parameters: 80–125%.**

STAGE 2 includes demonstration of the non-inferior or equivalent efficacy of the biosimilar versus the originator (**a phase 3 randomized controlled trial**)*.

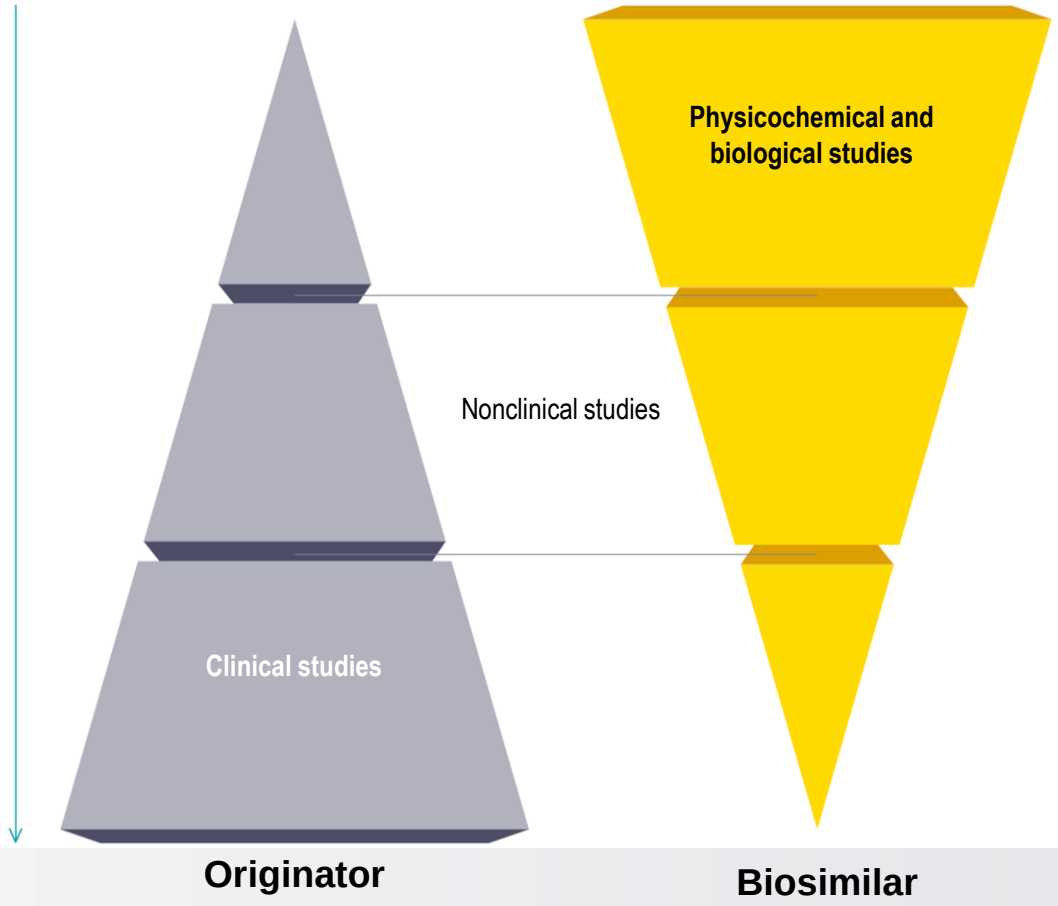
* If sensitive pharmacodynamic markers that have a high correlation with efficacy are available, a comparative pharmacodynamic study may be conducted instead of a comparative efficacy study

1. Eurasian Economic Commission. Decision No. 85 dated November 3, 2016 On Approval of the Rules for Bioequivalence Studies of Medicinal Products in the Eurasian Economic Union (https://docs.eaeunion.org/docs/ru-ru/01411942/cncd_21112016_85)
2. Decision No. 67 dated September 4, 2020 On Amendments to the Rules for Bioequivalence Studies of Medicinal Products in the Eurasian Economic Union (https://docs.eaeunion.org/docs/ru-ru/01411954/cncd_21112016_89)
3. European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010 (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf)

Differences in approaches to studies of biosimilars compared to studies of originator molecules

Physicochemical properties of the molecule, *in vitro* and *in vivo* potency are more important for the authorization of a biosimilar than clinical studies

It is possible to extrapolate the efficacy and safety data obtained for the biosimilar to other indications authorized for the originator.



European Medicines Agency. *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010*

Principles of clinical trials of medicinal products

Product type	In Russia[1]	Worldwide (EU, USA)
Generic for parenteral administration	No clinical studies required[2]	No clinical studies required
Generic for oral administration	Bioequivalence studies	Bioequivalence studies
Biosimilar	Phase I and III	Phase I and III
Innovative product, including biological one	Phase I, II, and III	Phase I, II, and III

[1] Current data are provided in accordance with the Federal Law N 61-ФЗ “On the circulation of medicinal products” dated April 12, 2010 (as amended on December 29, 2015)

[2] A therapeutic equivalence study was required for authorization of a generic drug for parenteral administration from 2010 to 2015; since 2016, such a study is not required

THE GOAL OF A CLINICAL STUDY OF A BIOSIMILAR IS TO PROOF ITS BIOSIMILARITY TO THE ORIGINATOR, THE ABSENCE OF SIGNIFICANT DIFFERENCES IN PHARMACOKINETICS, PHARMACODYNAMICS, EFFICACY, AND SAFETY

Differences in approaches to studies of biosimilars compared to studies of originators

Development aspects	Biosimilar	Originator
Patient population	Most sensitive	Any
Study design	Comparison with the originator	Superiority over standard therapy
Pharmacokinetics	Parameters for showing similarity to the originator	Parameters for selecting a treatment regimen and other purposes
Efficacy	Efficacy parameters directly reflecting the effect of the product	Long-term efficacy (OS, PFS)
Safety	Similar profile, no unexpected reactions	Acceptable risk/benefit ratio vs. standard therapy
Immunogenicity	Similar *or better* immunogenicity profile	Acceptable risk/benefit ratio vs. standard therapy

European Medicines Agency. *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010*

Non-clinical studies of Pembroria®

- In line with international requirements, all important aspects of the active molecule that can affect the pharmacodynamics and pharmacokinetics of Pembroria® have been characterized in a series of *in vitro* experiments in direct comparison with Keytruda®, including tests for binding to the target receptor (PD-1 receptor), receptors that determine the pharmacotoxicological effects and pharmacokinetics of pembrolizumab, as well as tests for functional potency.

- Data confirming the biosimilarity of Pembroria® and Keytruda for all investigated parameters have been obtained in a series of experiments.

Non-clinical studies of Pembroria®

The results of comparative *in vitro* studies are considered satisfactory and allow concluding that there are no differences in biologic activity between the test biosimilar and the reference drug. Based on this and in accordance with the recommendations set forth in Decision No. 89 of the Council of the Eurasian Economic Commission dated November 3, 2016 On the Approval of the Rules for Investigation of Biological Pharmaceutical Products in the Eurasian Economic Union (Chapter 15.3) and in EMA/CHMP/BMWP/403543/2010 guidelines, ***in vivo* studies are not considered necessary and it can be proceeded to human studies**.

Main clinical studies of Pembroria®

Study BCD-201-1 (Phase 1)

- **Design:** A double-blind, comparative, randomized study of the pharmacokinetics, safety, pharmacodynamics, and immunogenicity of BCD-201 versus Keytruda
- **N** = 131
- **Primary endpoint:** $AUC_{(0-504)}$
- **Secondary endpoints:** PD-1 receptor occupancy on blood cells, ORR, PFS according to RECIST 1.1, etc.
- **Population:** Patients with unresectable, metastatic or recurrent NSCLC (PD-L1 50%+) or melanoma

Study BCD-201-2 (Phase 3)

- **Design:** A double-blind, comparative, randomized study of the efficacy, safety, pharmacokinetics, and immunogenicity of BCD-201 versus Keytruda
- **N** = 366
- **Primary endpoint**: ORR according to RECIST 1.1
- **Population:** Patients with unresectable, metastatic cutaneous melanoma with measurable disease, including data from Phase 1 patients eligible for Phase 3.

Procedures of BCD-201-1 and BCD-201-2 clinical studies are identical

- **Treatment:** BCD-201 (Pembroria®) or Keytruda® 200 mg IV every 3 weeks for 24 weeks (monotherapy)
- **CT:** at baseline, after 12 and 24 weeks of treatment: 4 zones at screening, 3 during therapy + others as needed.

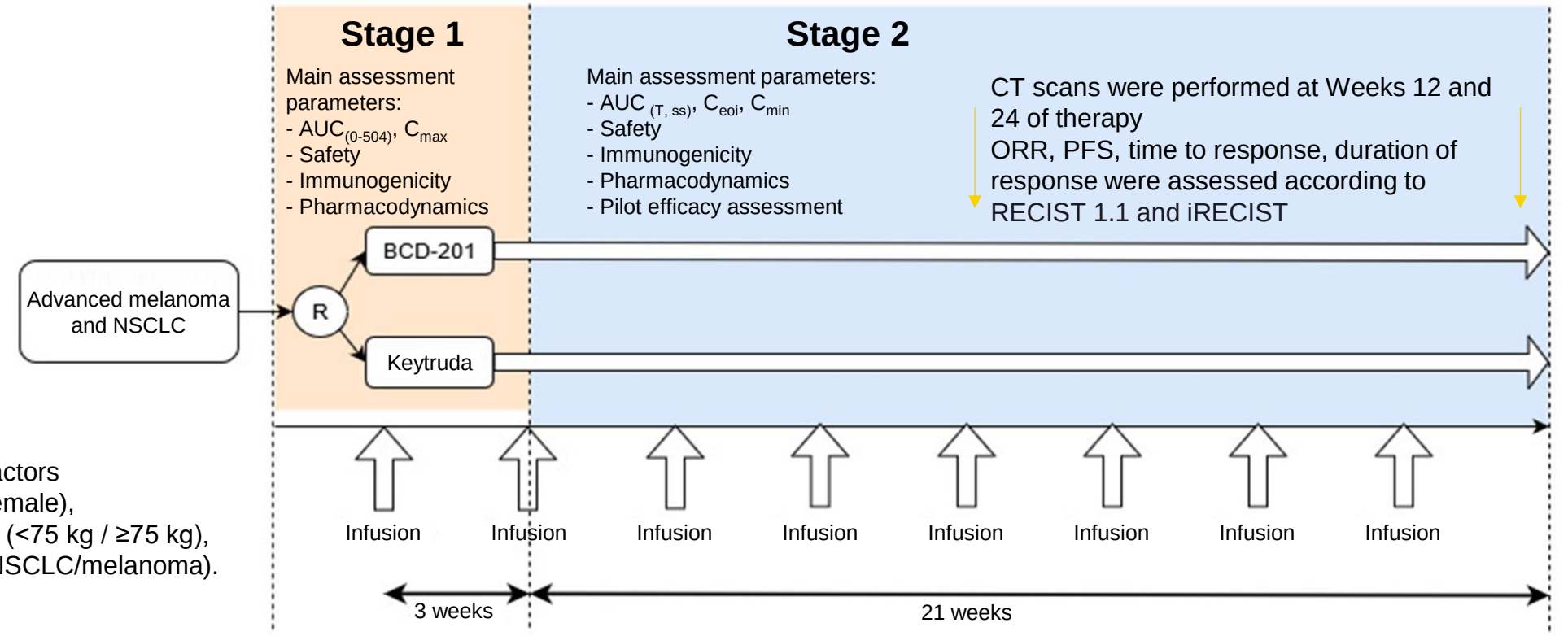
The information presented on the slide is intended for healthcare professionals. Internal data of the company “Report on the results of the clinical study BCD-201-1.”

Pembroria®
pembrolizumab

Study BCD-201-1 (Phase 1)

Design and results

BCD-201-1 study design (Phase I)



Stratification factors
- sex (male/female),
- body weight (<75 kg / ≥75 kg),
- indication (NSCLC/melanoma).

- In the Phase 1 study, the hypothesis of the equivalence of BCD-201 and Keytruda in terms of the pharmacokinetic parameter AUC_{0-504} was tested after the first administration of the drug (0–3 weeks), with equivalence limits of 80.00%–125.00%.
- Moreover, the study assessed the efficacy, safety, and immunogenicity of the study drugs.
- Efficacy data from the Phase 1 study are planned to be included in the Phase 3 study database to demonstrate the equivalent efficacy of BCD-201 and Keytruda. Therefore, the Phase 1 study remains blinded until the hypothesis of the equivalent efficacy of BCD-201 and Keytruda is tested in the Phase 3 study.

Study BCD-201-1:
Patient disposition and analysis population

Parameter	Group 1 (N = 67) n (%)	Group 2 (N = 64) n (%)	Total (N = 131) n (%)
Screened			179
Randomized (ITT)	**67**	**64**	131
Received at least one dose of study therapy (safety population)	66 (98.5)	65 (101.6)*	131 (100)
Immunogenicity population	60 (89.6)	63 (98.4)	119 (90.8)
PK population	65 (97.0)	61 (95.3)	126 (96.2)
PD population	66 (98.5)	62 (96.9)	128 (97.7)

Note: Percentages are calculated based on the ITT population.

**One subject received treatment for another group, to which he was not randomized, throughout the study. This subject was included in the data analysis according to the group assigned at randomization in the ITT population, and according to the actual therapy received in the PP, safety, PK and PD populations.

Study BCD-201-1:
Distribution by disease (ITT population)

Parameter	Group 1 (N = 67) n (%)	Group 2 (N = 64) n (%)	Total (N = 131) n (%)
Randomized (ITT)	67	64	131
NSCLC	24 (35.8)	16 (25.0)	40 (30.5)
Melanoma	43 (64.2)	48 (75.0)	91 (69.5)

Study BCD-201-1:
Demographic and baseline data, NSCLC patients (ITT population)

Parameter	Group 1 (N = 24)	Group 2 (N = 16)
Age (years), mean (range)	66.0 (43–77)	62.4 (44–80)
Sex, n (%)		
Male	19 (79.2)	13 (81.3)
Female	5 (20.8)	3 (18.8)
Race, n (%)		
Caucasian	24 (100)	16 (100)
Duration of disease at screening (months), mean (range)	5.1 (0.16–29.0)	8.1 (0.03–61.2)
Histological type of tumor, n (%)		
Squamous cell lung cancer	11 (45.8)	9 (56.3)
Lung adenocarcinoma	10 (41.7)	6 (37.5)
Large cell lung cancer	1 (4.2)	1 (6.3)
Other	2 (8.3)	0
Presence of distant metastases, n (%)	22 (91.7)	14 (87.5)
ECOG, n (%)		
0	3 (12.5)	0
1	21 (87.5)	16 (100)
Previous therapy		
Surgery	7 (29.2)	7 (43.8)
Neoadjuvant therapy	1 (4.2)	0
Adjuvant therapy	1 (4.2)	0

Study BCD-201-1:
Demographic and baseline data, melanoma patients (ITT population)

Parameter	Group 1 (N = 43)	Group 2 (N = 48)
Age (years), mean (range)	60.7 (19–93)	60.8 (33–88)
Sex, n (%)		
Male	21 (48.8)	19 (39.6)
Female	22 (51.2)	29 (60.4)
Race, n (%)		
Caucasian	42 (97.7)	48 (100)
Black	1 (2.3)	0
Duration of disease at screening (months), mean (range)	25.9 (0.10–156.2)	38.8 (0.23–199.2)
Histological type of tumor, n (%)		
Lentigo maligna melanoma	0	1 (2.1)
Superficial spreading melanoma	6 (14.0)	5 (10.4)
Acral lentiginous melanoma	0	1 (2.1)
Mucosal melanoma	0	1 (2.1)
Nodular melanoma	15 (34.9)	17 (35.4)
Desmoplastic melanoma	0	2 (4.2)
Other	22 (51.2)	21 (43.8)
Presence of distant metastases, n (%)	39 (90.7)	46 (95.8)
Presence of brain metastases, n (%)	4 (9.3)	2 (4.2)
PD-L1, n (%)		
TPS <5%	27 (62.8)	35 (72.9)
TPS ≥5%	10 (23.3)	7 (14.6)
No data available	6 (14.0)	6 (12.5)

Study BCD-201-1:
Demographic and baseline data, melanoma patients (ITT population) (continued)

Parameter	Group 1 (N = 43)	Group 2 (N = 48)
ECOG, n (%)		
0	18 (41.9)	23 (47.9)
1	25 (58.1)	25 (52.1)
Stage according to the 7th edition of the AJCC staging system, n (%)		
M0	4 (9.3)	2 (4.2)
M1a	2 (4.7)	5 (10.4)
M1b	2 (4.7)	2 (4.2)
M1c	35 (81.4)	39 (81.3)
Previous therapy		
Surgery	32 (74.4)	40 (83.3)
Neoadjuvant therapy	1 (2.3)	0
Adjuvant therapy	9 (20.9)	16 (33.3)

The information presented on the slide is intended for healthcare professionals. Internal data of the company “Report on the results of the clinical study BCD-201-1.”

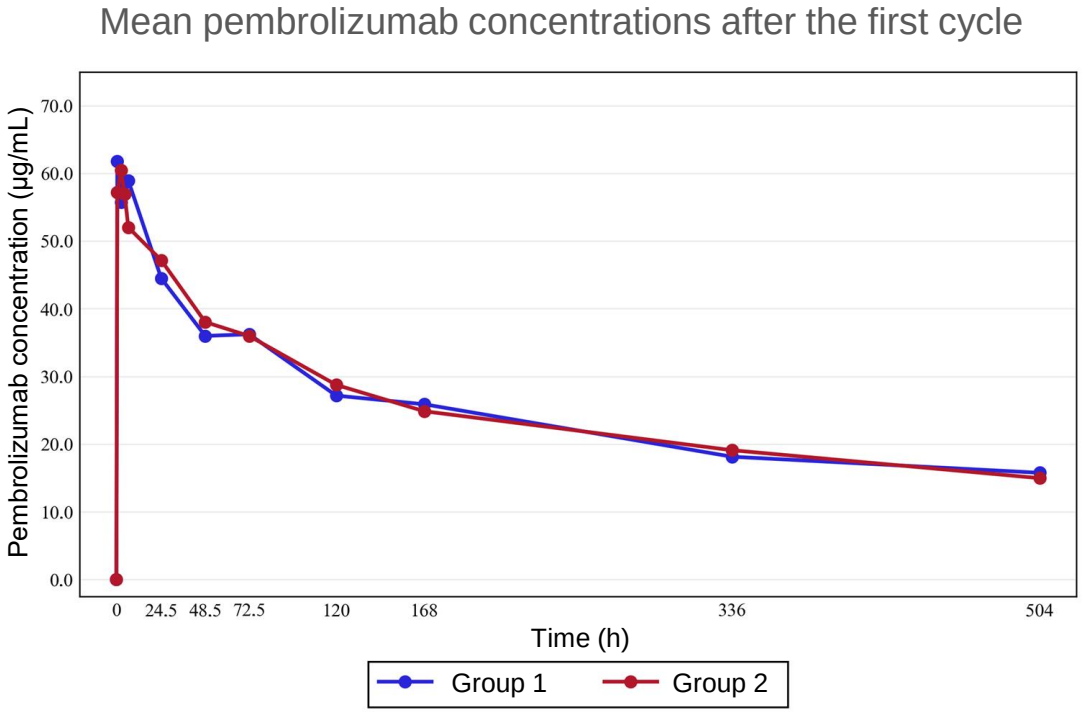
Pharmacokinetic study results support the equivalence of Pembroria® and Keytruda®

- The hypothesis of the drug equivalence in terms of $AUC_{(0-504)}$ was tested using parametric **two-sided 90% confidence intervals for the ratios (G1:G2 and G2:G1) of $AUC_{(0-504)}$ geometric means.**

- The study results **suggest the equivalence of Pembroria® and Keytruda® in terms of the pharmacokinetic parameter $AUC_{(0-504)}$.** The obtained two-sided 90% confidence intervals for the $AUC_{(0-504)}$ ratios are within the limits of equivalence of 80.00–125.00%, regardless of which product Group 1 and Group 2 received.

- Binding anti-pembrolizumab antibodies were not detected in any patient.

- The study is blinded as some patients continued to Ph 3 BCD-201-2



Parameter	N (G1, G2)	90% CI for the ratio of means G1:G2	90% CI for the ratio of means G2:G1	EAEU, EMA requirements
$AUC_{(0-504)}$	65, 61	85.95–109.06%	91.69–116.34%	80.00–125.00%
C_{max}	65, 61	92.41–110.60%	90.41–108.21%	80.00–125.00%

The information presented on the slide is intended for healthcare professionals. Internal data of the company “Report on the results of the clinical study BCD-201-1.”

Study BCD-201-1: Pharmacodynamic study results

- Median lymphocyte PD-1 receptor occupancy was ≥99% on Day 1 in both groups and remained high by Day 22 of the study.
- The differences between the groups in median PD-1 receptor occupancy were less than 1%
- Similar results were obtained in the subpopulations of CD3+, CD4+, CD8+, CD4+HLA-DR+, CD8+HLA-DR+ lymphocytes.

PD-1 receptor occupancy, median (IQR*), %	Group 1 N=66	Group 2 N=62
Day 1	99.0 (98.2–99.6)	99.1 (98.6–99.6)
Day 22	97.2 (95.7–98.1)	97.6 (96.3–98.3)
Day 64	97.8 (96.9–98.7)	97.9 (97.1–98.8)
Day 106	98.4 (97.6–99.2)	98.6 (98.3–99.1)
Day 148	98.7 (98.0–99.2)	98.2 (97.2–98.8)

*Interquartile range

The information presented on the slide is intended for healthcare professionals. Internal data of the company “Report on the results of the clinical study BCD-201-1.”

Study BCD-201-1: Pilot efficacy assessment according to RECIST 1.1 (ITT population)

Subgroup Parameter	Group 1, n (%)	Group 2, n (%)
NSCLC	N = 24	N = 16
Complete response (CR)	0	0
Partial response (PR)	6 (25.0)	3 (18.8)
Stable disease (SD)	2 (8.3)	4 (25.0)
Progressive disease (PD)	8 (33.3)	5 (31.3)
Disease control rate (CR+PR+SD)	8 (33.3)	7 (43.8)
Overall response rate (CR+PR)	**6 (25.0)**	**3 (18.8)**
Melanoma	N = 43	N = 48
Complete response (CR)	2 (4.7)	1 (2.1)
Partial response (PR)	9 (20.9)	9 (18.8)
Stable disease (SD)	5 (11.6)	6 (12.5)
Progressive disease (PD)	18 (41.9)	27 (56.3)
Disease control rate (CR+PR+SD)	16 (37.2)	16 (33.3)
Overall response rate (CR+PR)	**11 (25.6)**	**10 (20.8)**

Note: The table does not include the “Not evaluable” and “No data” categories. Therefore, the total number of subjects in the categories may be less than the number of patients in the evaluation population.

Study BCD-201-1: Safety results (24 weeks of therapy, N=131)

Parameter	Group 1 (N = 66) n (%)	Group 2 (N = 65) n (%)
Proportion of subjects with AEs	49 (74.2)	51 (78.5)
Proportion of subjects with grade ≥3 AEs	9 (13.6)	15 (23.1)
Proportion of subjects with AEs related to the study therapy	31 (47.0)	32 (49.2)
Proportion of subjects with any grade immune-related AEs	14 (21.2)	14 (21.5)
Proportion of subjects requiring treatment discontinuation due to AE*	2 (3.0)	2 (3.1)

Note: AE, adverse event.

Study BCD-201-1: Grade ≥3 adverse events (24 weeks of therapy, N=131)

Proportion of subjects with grade ≥3 adverse events, **MedDRA preferred term**	Group 1 (N = 66) n (%)	Group 2 (N = 65) n (%)
Anemia	0	2 (3.1)
Lymphopenia	1 (1.5)	2 (3.1)
Thrombocytopenia	0	2 (3.1)
Pulmonary embolism	2 (3.0)	0
Pulmonary hemorrhage	0	1 (1.5)
Acute respiratory failure	1 (1.5)	0
COVID-19 pneumonia	2 (3.0)	0
Coronavirus infection (COVID-19)	0	1 (1.5)
Chlamydial pneumonia	0	1 (1.5)
Esophagobronchial fistula	1 (1.5)	0
Gastrointestinal bleeding	0	1 (1.5)
Intraabdominal bleeding	1 (1.5)	0
Diarrhea	0	1 (1.5)
Dysphagia	1 (1.5)	0
Weight loss	1 (1.5)	1 (1.5)
Pain in extremity	1 (1.5)	0
Bone pain	0	1 (1.5)
Pathological fracture	0	1 (1.5)
Pericardial effusion	0	1 (1.5)
Hypertension	0	1 (1.5)
Essential hypertension	0	1 (1.5)
Asthenia	0	2 (3.1)
Alanine aminotransferase increased	1 (1.5)	0

Study BCD-201-1: Immune-related adverse events (24 weeks of therapy, N=131)

Proportion of subjects with immune-related adverse events (irAEs), **MedDRA preferred term**	Group 1 (N = 66) n (%)	Group 2 (N = 65) n (%)
Hypothyroidism	4 (6.1)	4 (6.2)
Hyperthyroidism	2 (3.0)	4 (6.2)
Thyroiditis	2 (3.0)	0
Blood thyroid-stimulating hormone level decreased	0	3 (4.6)
Alanine aminotransferase increased	1 (1.5)	0
Aspartate aminotransferase increased	0	1 (1.5)
Transaminases increased	0	1 (1.5)
Rash	3 (4.5)	1 (1.5)
Vitiligo	1 (1.5)	0
Pruritus	0	1 (1.5)
Urticaria	0	1 (1.5)
Dry skin	0	1 (1.5)
Immune-related hepatitis	2 (3.0)	0
Autoimmune hepatitis	1 (1.5)	0
Diarrhea	0	1 (1.5)
Immune-related enterocolitis	0	1 (1.5)
Anemia	0	1 (1.5)
Leukopenia	0	1 (1.5)
Lymphopenia	0	1 (1.5)
Immune-related pulmonary disease	1 (1.5)	0
Non-infectious conjunctivitis	0	1 (1.5)

Note: One case of grade 3 diarrhea was reported. All other irAEs were grade 1–2.

Conclusions

- Based on the analytical data on the pharmacokinetics of Pembroria® (BCD-201) and the originator Keytruda®, the BCD-201-1 study **proved the equivalence** of these products **in terms of $AUC_{(0-504)}$.**

- The results of pharmacodynamic evaluation of the compared drugs showed that the levels of **PD-1 receptor occupancy** on different lymphocyte populations **were similar** when Pembroria® and Keytruda® were used.

- Both drugs had **low immunogenicity**. No cases of binding antibodies to Pembroria ® or Keytruda® were reported.

- The **safety profile** of the compared products was also **similar**.

The information presented on the slide is intended for healthcare professionals. Internal data of the company “Report on the results of the clinical study BCD-201-1.”

Pembroria®
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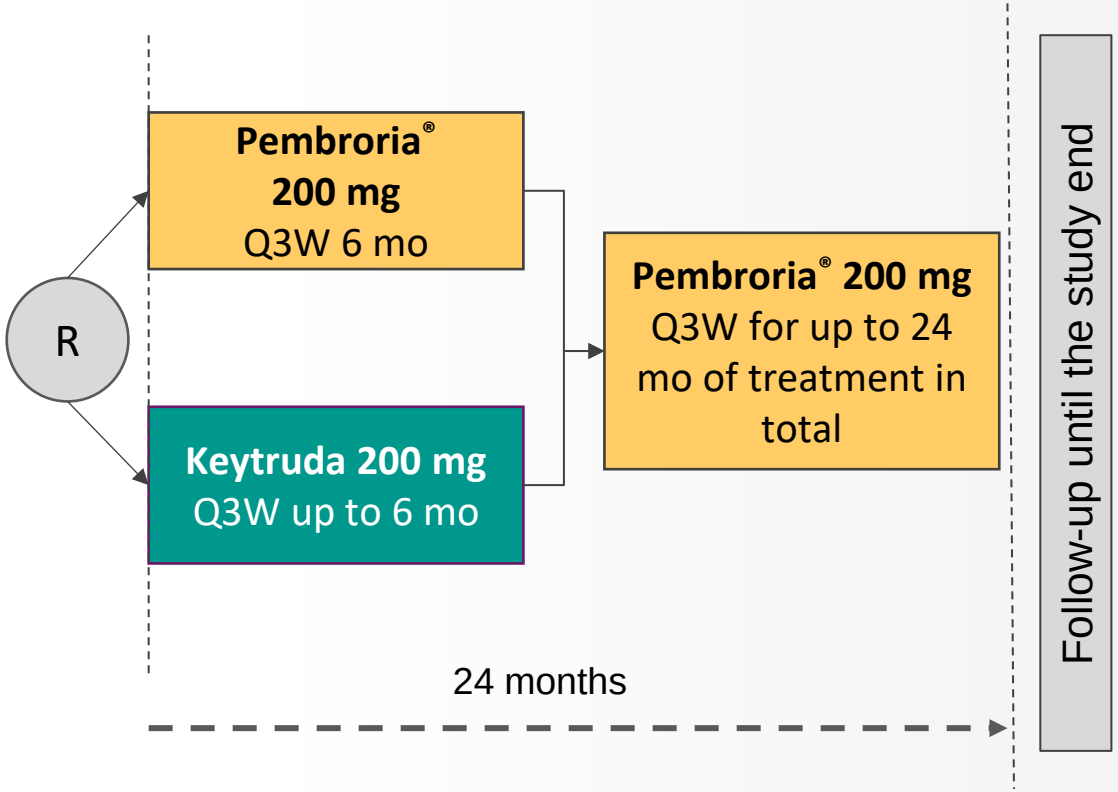
Pembroria®
pembrolizumab

Study BCD-201-2 (Phase 3)

Design and results

Results of the first interim analysis of the randomized, double-blind clinical study of the effectiveness and safety of Pembroria® (JSC BIOCAD) and Keytruda® in subjects with unresectable or metastatic skin melanoma

BCD-201-2 study design (Phase III)



Primary endpoint

- Overall response rate (ORR) per RECIST 1.1 as assessed by the central independent review (CIR).

Secondary effectiveness endpoints

- ORR per iRECIST as assessed by the CIR;
- Duration of response, disease control rate, and time to response per RECIST 1.1 and iRECIST as assessed by the CIR;
- Progression-free survival per RECIST 1.1 and iRECIST as assessed by the CIR;
- Overall survival.

Stratification factors:

- PD-L1 status at screening (TPS PD-L1 ≥ 5% versus TPS PD-L1 < 5%),
- ECOG performance status (ECOG 0 versus ECOG 1)
- disease stage per the AJCC 7th edition (M0/M1a/M1b versus M1c)

Study design:

A double-blind, randomized, comparative, multicenter study

Population:

366 treatment-naive subjects with advanced cutaneous melanoma, with subsequent expansion of the population to 478 subjects

Randomization:

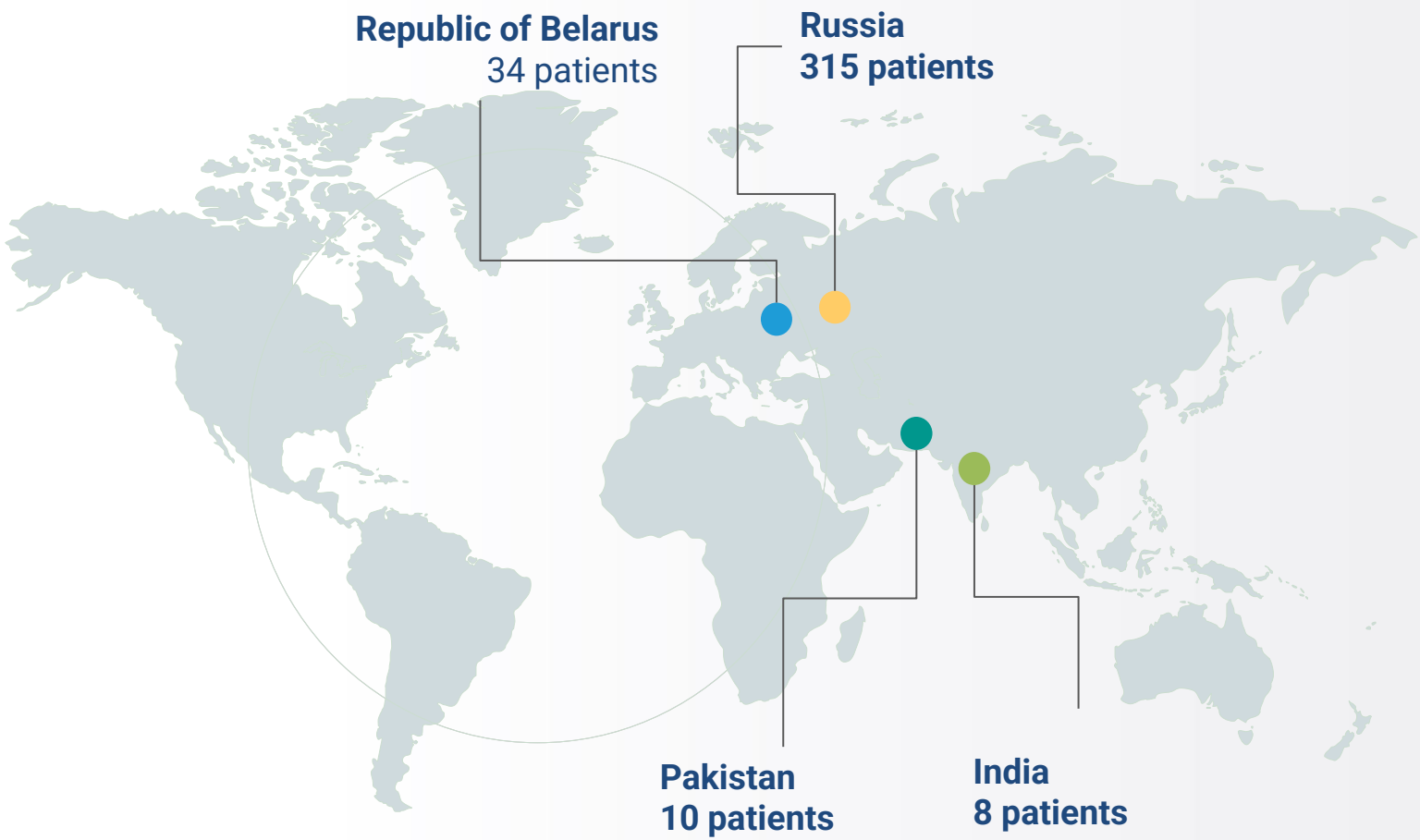
1:1

Demographic and other baseline characteristics of subjects at screening ITT population

Parameter	Group 1 (N = 181)	Group 2 (N = 186)	Total (N = 367)
Age (years)			
Mean	61.6	61.6	61.6
Standard deviation	13.29	14.53	13.92
Sex, n (%)			
Male	84 (46.4)	83 (44.6)	167 (45.5)
Female	97 (53.6)	103 (55.4)	200 (54.5)
Race, n (%)			
Caucasian	170 (93.9)	178 (95.7)	348 (94.8)
Black	1 (0.6)	0	1 (0.3)
Asian	10 (5.5)	8 (4.3)	18 (4.9)
Other	0	0	0
Tumor histology, n (%)			
Superficial spreading melanoma	46 (25.4)	46 (24.7)	92 (25.1)
Nodular melanoma	53 (29.3)	54 (29.0)	107 (29.2)
Lentigo maligna melanoma	3 (1.7)	5 (2.7)	8 (2.2)
Acral lentiginous melanoma	4 (2.2)	3 (1.6)	7 (1.9)
Amelanotic melanoma	8 (4.4)	7 (3.8)	15 (4.1)
Nevoid melanoma	1 (0.6)	4 (2.2)	5 (1.4)
Spitz melanoma	0	0	0
Desmoplastic melanoma	0	1 (0.5)	1 (0.3)
Other	66 (36.5)	66 (35.5)	132 (36.0)

Parameter	Group 1 (N = 181)	Group 2 (N = 186)	Total (N = 367)
Duration of disease at screening (months)			
Mean	22.329	27.367	24.882
Standard deviation	36.3047	35.6633	36.0203
Presence of distant metastases, n (%)			
Yes	167 (92.3)	180 (96.8)	347 (94.6)
Brain	12 (6.6)	7 (3.8)	19 (5.2)
PD-L1, n (%)			
TPS < 1%	65 (35.9)	79 (42.5)	144 (39.2)
TPS ≥ 1%	112 (61.9)	102 (54.8)	214 (58.3)
No data	4 (2.2)	5 (2.7)	9 (2.5)
ECOG, n (%)			
0	92 (50.8)	100 (53.8)	192 (52.3)
1	89 (49.2)	86 (46.2)	175 (47.7)
Stage by the AJCC 7th edition at screening, n (%)			
M0	103 (56.9)	106 (57.0)	209 (56.9)
M1a	18 (9.9)	27 (14.5)	45 (12.3)
M1b	15 (8.3)	6 (3.2)	21 (5.7)
M1c	45 (24.9)	47 (25.3)	92 (25.1)
Prior treatments, n (%)			
Radiotherapy	17 (9.4)	12 (6.5)	29 (7.9)
Surgery	144 (79.6)	158 (84.9)	302 (82.3)
LDH at screening, n (%)			
≤ ULN	142 (78.5)	144 (77.4)	286 (77.9)
> ULN	39 (21.5)	42 (22.6)	81 (22.1)
BRAF mutations, n (%)			
Yes	32 (17.7)	21 (11.3)	53 (14.4)
No	20 (11.0)	32 (17.2)	52 (14.2)
Unknown	129 (71.3)	133 (71.5)	262 (71.4)

Current status of the Phase III clinical study



1 **Russia**
Study approved, completed.

2 **Republic of Belarus**
Study approved, completed.

3 **India**
Study approved, completed.

4 **Pakistan**
Study approved, completed.

- **Enrollment in the Phase III study has now been completed for 367 subjects (July 2023)**
- Since July 2024 additional enrollment (+112 pts)
- The study is blinded. Unblinding will be performed during an analysis of minimum 478 subjects after 24 weeks after the enrollment of the total population
- Report No. 1 containing the results of testing the hypothesis of non-inferiority and the hypothesis of non-superiority of Pembroria® versus Keytruda® was generated.

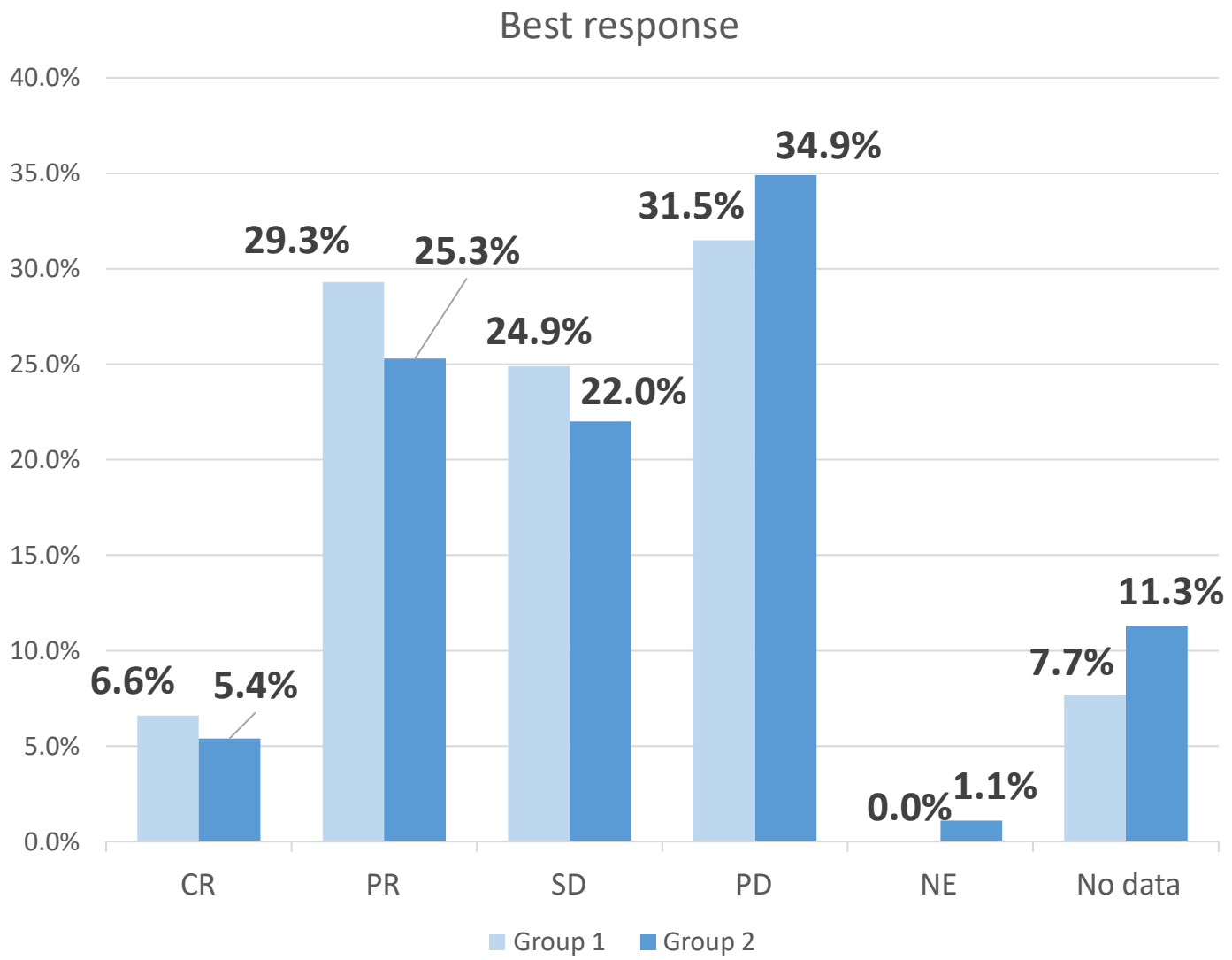
Most patients continued the study

Parameter	Group 1 (N = 181) n (%)	Group 2 (N = 186) n (%)	Total (N = 367) n (%)
Completed the study per protocol	25 (13.8)	28 (15.1)	53 (14.4)
Continue in the study	122 (67.4)	118 (63.4)	240 (65.4)
Discontinued the study prematurely	34 (18.8)	40 (21.5)	74 (20.2)
Informed consent withdrawal	2 (1.1)	6 (3.2)	8 (2.2)
Death	17 (9.4)	21 (11.3)	38 (10.4)
Lost to follow-up	5 (2.8)	7 (3.8)	12 (3.3)
Investigator's decision	10 (5.5)	5 (2.7)	15 (4.1)
Failure to meet eligibility criteria	0	1 (0.5)	1 (0.3)

The non-inferiority of Pembroria® versus Keytruda® was demonstrated regardless of which group actually received Pembroria® and which received Keytruda®

Assessment	Group 1 (N = 181) n (%)	Group 2 (N = 186) n (%)	p-value
Best response			
Complete response (CR)	12 (6.6)	10 (5.4)	
Partial response (PR)	53 (29.3)	47 (25.3)	
Stable disease (SD)	45 (24.9)	41 (22.0)	
Progressive disease (PD)	57 (31.5)	65 (34.9)	
Not evaluable (NE)	0	2 (1.1)	
No data	14 (7.7)	21 (11.3)	
Disease control rate (CR + PR + SD) (95% CI[1])	110 (60.8) (53.3; 67.9)	98 (52.7) (45.3; 60.0)	0.1181[2]
Overall response rate (CR + PR) (95% CI[1])	65 (35.9) (28.9; 43.4)	57 (30.6) (24.1; 37.8)	0.2843[2]

Примечание: [1]Clopper–Pearson method;
[2]Pearson's chi-squared test;
[3]Fisher's exact test.



*The study is currently blinded. The results for the differences between Group 1 to Group 2 and Group 2 to Group 1, respectively, are provided; however, the treatment allocation in these groups is unknown.

Pembroria® and Keytruda® have equivalent effectiveness

Hypothesis Statistics	Group 1 (N = 181) - Group 2 (N = 186)	Group 2 (N = 186) - Group 1 (N = 181)
	Value	Value
Primary non-inferiority hypothesis		
Rate difference (%)	**5.3**	**-5.3**
Right-sided 97.5% CI[1]	-4.4; 100	-14.9; 100
Non-inferiority margin	-15.0	-15.0
Secondary non-superiority hypothesis		
Rate difference (%)	**5.3**	**-5.3**
Left-sided 97.5% CI[1]	-100; 14.9	-100; 4.4
Non-superiority margin	15.0	15.0

An approach of hypothesis hierarchical testing was used in the study. The second hypothesis is tested if the first hypothesis is proven.

After proving the hypothesis of non-inferiority, a secondary hypothesis of non-superiority was tested.

The cumulative results of testing the hypotheses of non-superiority and non-inferiority provide an assessment of the hypothesis of equivalent effectiveness.

CI, confidence interval (one-sided).

[1]CI is calculated using the non-stratified Miettinen-Nurminen method.

*The study is currently blinded. The results for the differences between Group 1 to Group 2 and Group 2 to Group 1, respectively, are provided; however, the treatment allocation in these groups is unknown.

Since the cumulative results of testing the hypotheses of non-superiority and non-inferiority provide an assessment of the hypothesis of equivalent effectiveness, it can be concluded that Pembroria® and Keytruda® have equivalent effectiveness

A subgroup analysis showed a comparable overall response rate in both groups

Subgroup Criteria Evaluation	Group 1 (N = 181) n (%)	Group 2 (N = 186) n (%)	p-value
PD-L1 (<1% / ≥1%)			
TPS PD-L1 ≥ 1%, N1	112	102	
Overall response rate	42 (37.5)	38 (37.3)	0.9705[2]
(95% CI[1])	(28.5; 47.1)	(27.9; 47.4)	
TPS PD-L1 < 1%, N1	65	79	
Overall response rate	22 (33.8)	17 (21.5)	0.0976[2]
(95% CI[1])	(22.6; 46.6)	(13.1; 32.2)	
PD-L1 (<5% / ≥5%)			
TPS PD-L1 ≥ 5%, N1	60	53	
Overall response rate	28 (46.7)	26 (49.1)	0.7996[2]
(95% CI[1])	(33.7; 60.0)	(35.1; 63.2)	
TPS PD-L1 < 5%, N1	117	128	
Overall response rate	36 (30.8)	29 (22.7)	0.1508[2]
(95% CI[1])	(22.6; 40.0)	(15.7; 30.9)	
ECOG performance status			
ECOG 0, N1	92	100	
Overall response rate	34 (37.0)	39 (39.0)	0.7708[2]
(95% CI[1])	(27.1; 47.7)	(29.4; 49.3)	
ECOG 1, N1	89	86	
Overall response rate	31 (34.8)	18 (20.9)	**0.0406[2]**
(95% CI[1])	(25.0; 45.7)	(12.9; 31.0)	
Disease stage per the AJCC 7th edition			
M0, N1	103	106	
Overall response rate	42 (40.8)	34 (32.1)	0.1911[2]
(95% CI[1])	(31.2; 50.9)	(23.3; 41.8)	
M1a/M1b, N1	33	33	
Overall response rate	10 (30.3)	12 (36.4)	0.6015[2]
(95% CI[1])	(15.6; 48.7)	(20.4; 54.9)	

Subgroup Criteria Evaluation	Group 1 (N = 181) n (%)	Group 2 (N = 186) n (%)	p-value
Disease stage per the AJCC 7th edition			
M0/M1a/M1b, N1	136	139	
Overall response rate	52 (38.2)	46 (33.1)	0.3734[2]
(95% CI[1])	(30.0; 47.0)	(25.4; 41.6)	
M1c, N1	45	47	
Overall response rate	13 (28.9)	11 (23.4)	0.5493[2]
(95% CI[1])	(16.4; 44.3)	(12.3; 38.0)	
Lactate dehydrogenase (LDH) level at screening			
≤ ULN, N1	142	144	
Overall response rate	56 (39.4)	45 (31.3)	0.1475[2]
(95% CI[1])	(31.3; 48.0)	(23.8; 39.5)	
> ULN, N1	39	42	
Overall response rate	9 (23.1)	12 (28.6)	0.5729[2]
(95% CI[1])	(11.1; 39.3)	(15.7; 44.6)	
BRAF mutations			
Present, N1	32	21	
Overall response rate	9 (28.1)	9 (42.9)	0.2680[2]
(95% CI[1])	(13.7; 46.7)	(21.8; 66.0)	
Wild-type, N1	20	32	
Overall response rate	8 (40.0)	8 (25.0)	0.2542[2]
(95% CI[1])	(19.1; 63.9)	(11.5; 43.4)	
Brain metastases at screening			
Present, N1	12	7	
Overall response rate	4 (33.3)	3 (42.9)	1.0000[3]
(95% CI[1])	(9.9; 65.1)	(9.9; 81.6)	
None, N1	169	179	
Overall response rate	61 (36.1)	54 (30.2)	0.2401[2]
(95% CI[1])	(28.9; 43.8)	(23.5; 37.5)	

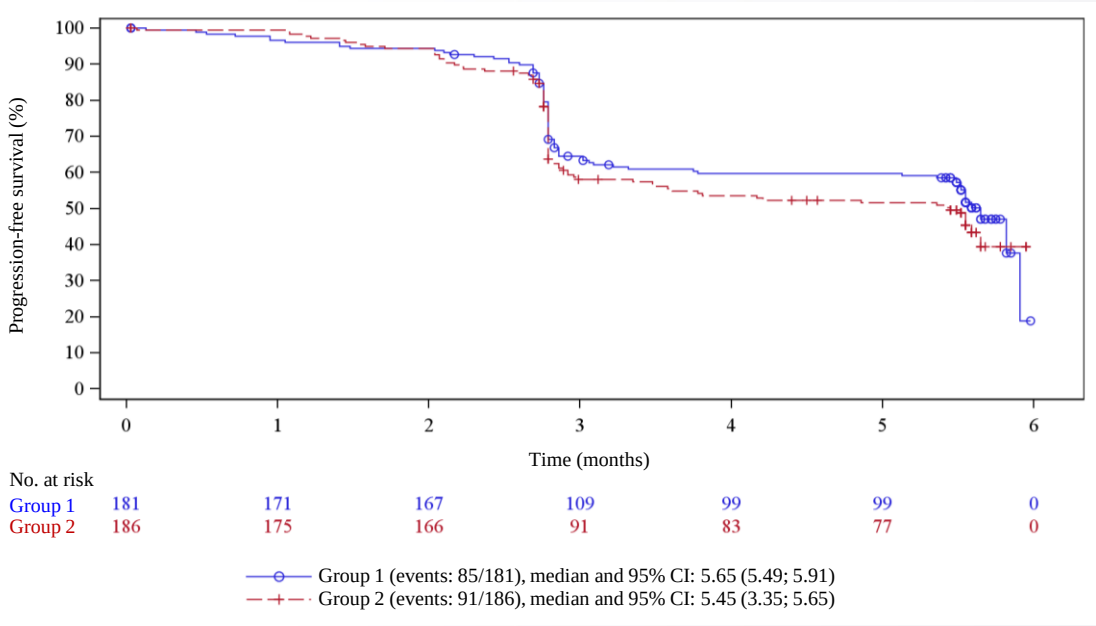
Note: [1]Clopper-Pearson method; [2]Pearson's chi-squared test; [3]Fisher's exact test. N1, number of subjects per group; percentage from N1. Overall response rate (CR + PR), ICR - Independent central review , ITT – intent-to-treat population

Results of the response assessment per RECIST 1.1 by the ICR

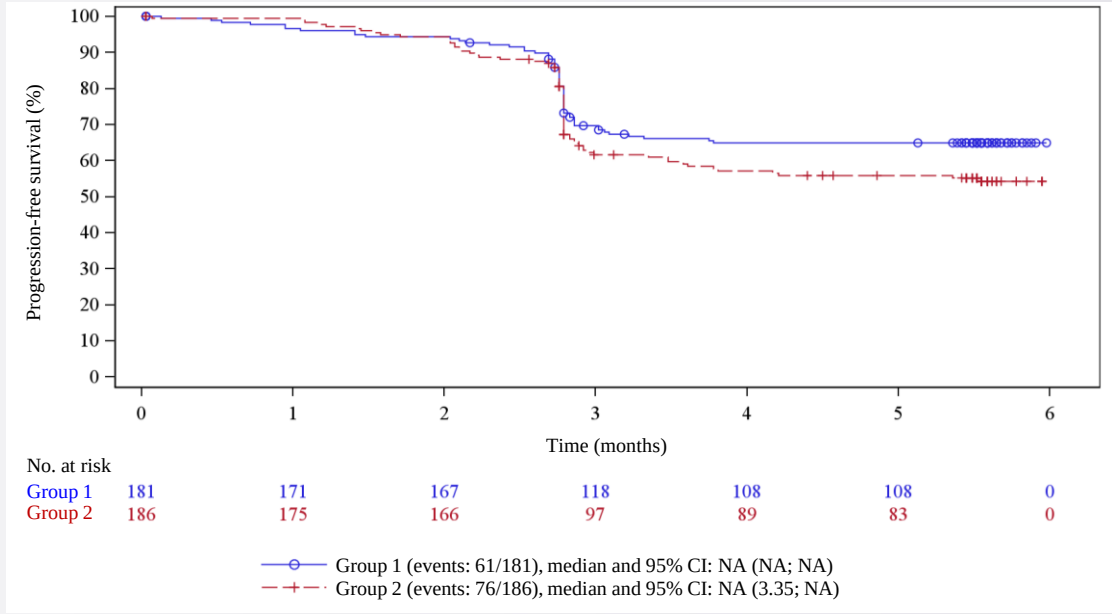
Subgroup analysis. ITT population

Median progression-free survival time was comparable between the groups

Progression-free survival per RECIST 1.1
as assessed by the ICR
ITT population



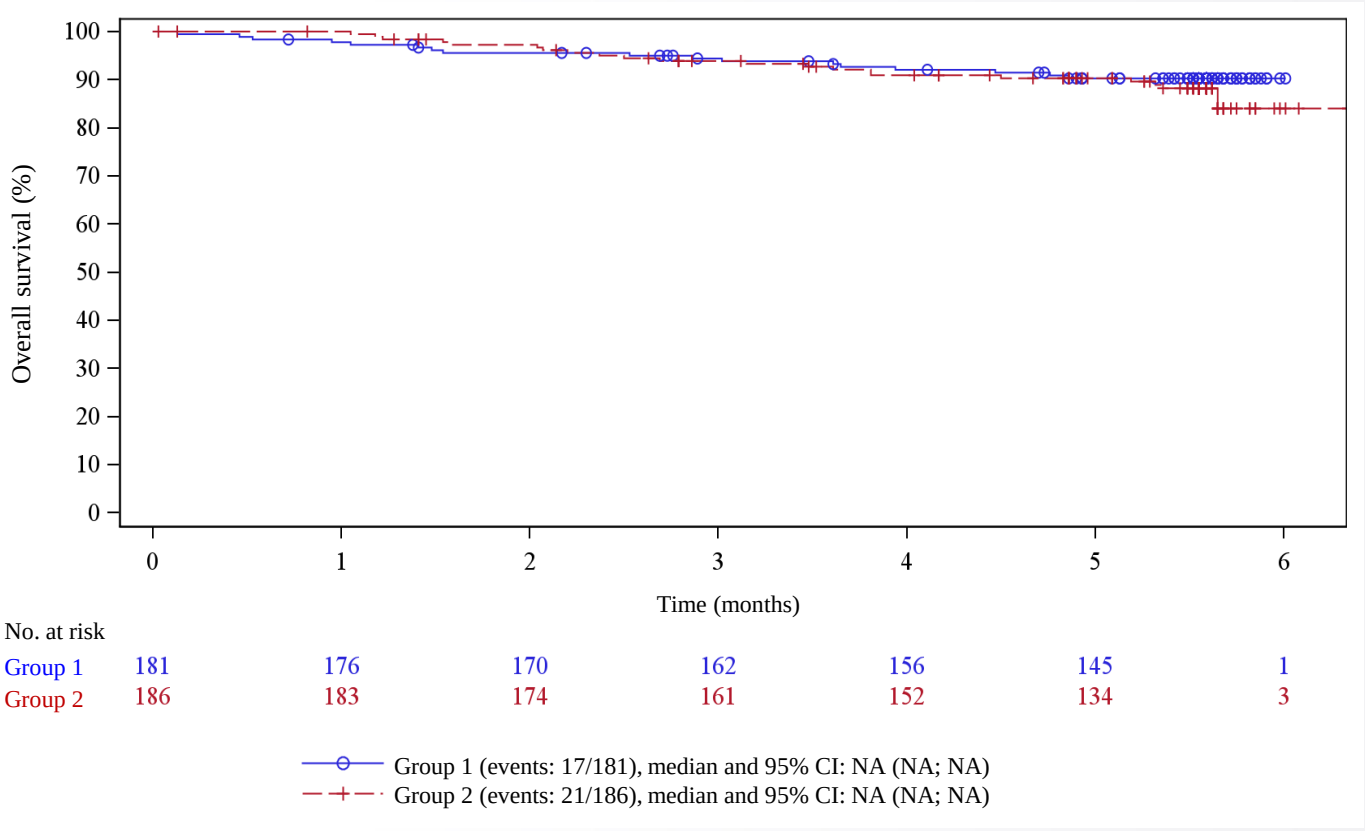
Progression-free survival per iRECIST
as assessed by the ICR
ITT population



In the ITT population, the median PFS time per RECIST 1.1 as assessed by the ICR was comparable between the groups and was 5.65 and 5.45 months in Group 1 and Group 2, respectively

ITT – intent-to-treat population, ICR - Independent central review

Overall survival was comparable between Group 1 and Group 2



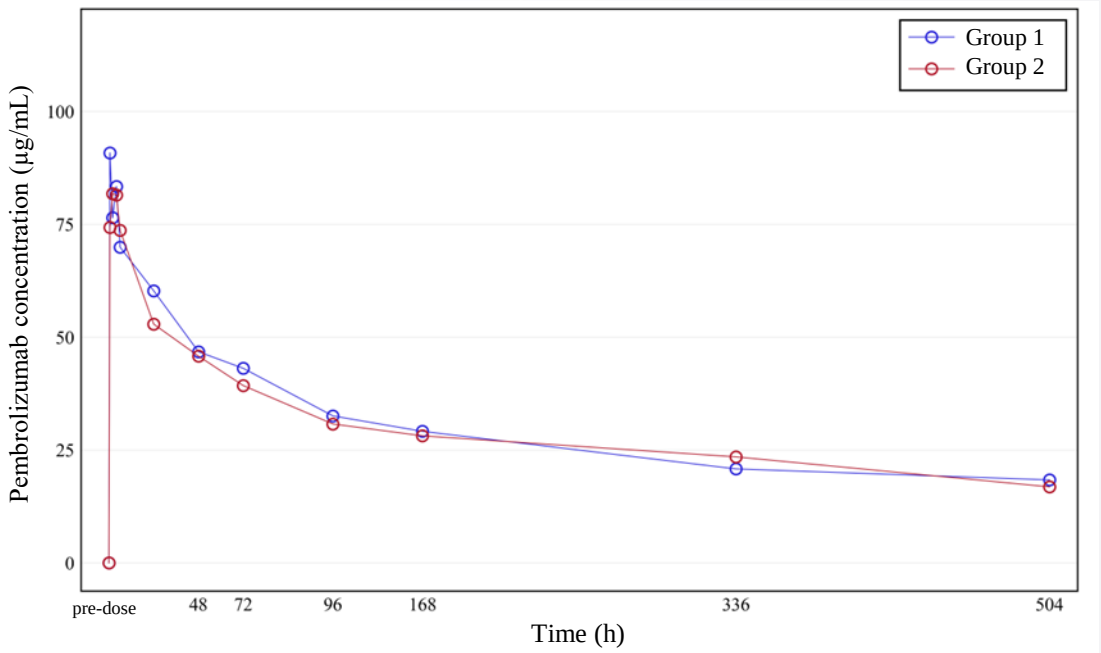
Parameter	Group 1 (N = 181)	Group 2 (N = 186)	HR (Group 1/Group 2) (95% CI)[2]	HR (Group 2/Group 1) (95% CI)[2]	p-value[3]
Number of subjects with event, n (%)	17 (9.4)	21 (11.3)	0.77	1.29	0.4458
Median OS (month) (95% CI)[1]	NA (NA; NA)	NA (NA; NA)	(0.40; 1.50)	(0.67; 2.49)	
24-week OS rate (%)[1]	90.3	88.2			

[1] Kaplan-Meier estimate; [2] stratified Cox model; [3] stratified log-rank test; OS, overall survival; HR, hazard ratio; NA, not applicable. The analysis of data taking into account stratification factors does not include subjects with missing values of stratification factors.

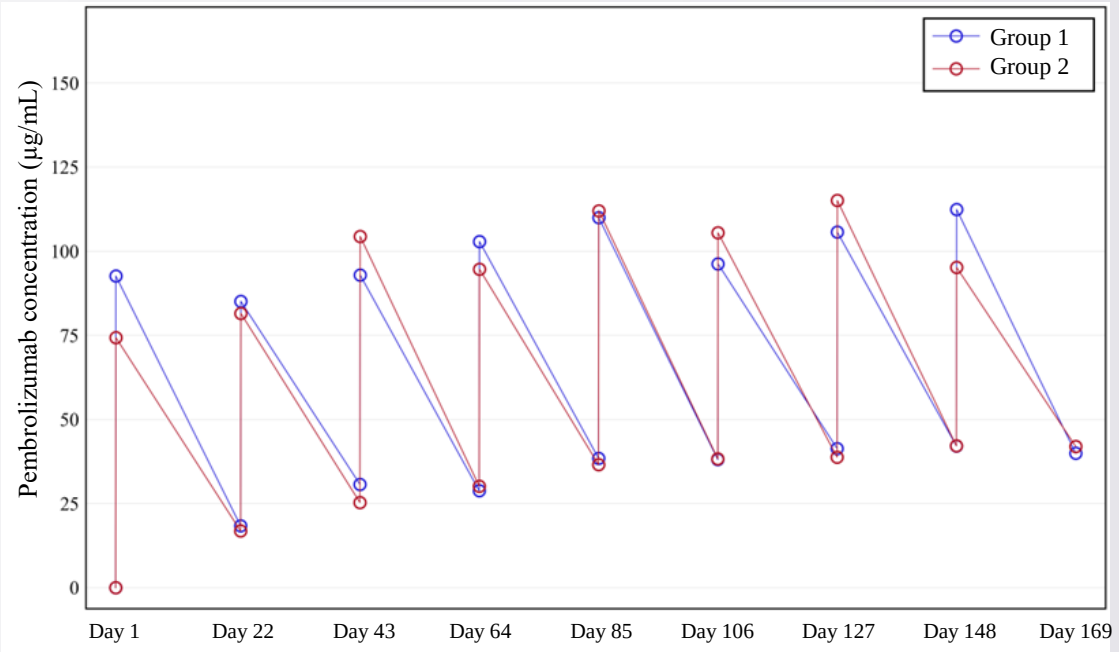
A median OS was not reached in either group. There were no statistically significant differences between the groups in terms of OS.

There are no statistically significant differences between Group 1 and Group 2 across the pharmacokinetic parameters studied

Mean pembrolizumab concentrations after dose 1 (µg/mL) First-dose pharmacokinetics population



Observed concentrations of pembrolizumab after multiple doses (µg/mL) Multiple-dose pharmacokinetics population



There are no statistically significant differences between Group 1 and Group 2 across the pharmacokinetic parameters studied

The concentration-time profiles after multiple doses of Pembroria®/Keytruda® were comparable in Group 1 and Group 2.

Pembroria® and Keytruda® had low immunogenicity

Visit Parameter	Group 1 (N = 173) n (%)	Group 2 (N = 179) n (%)
Visit 1 (Week 1 Day 1)		
BAbs	0	0
NAbs	0	0
Visit 2 (Week 4 Day 22)		
BAbs	3 (1.7)	5 (2.8)
NAbs	0	0
Visit 4 (Week 10 Day 64 ± 2)		
BAbs	3 (1.7)	3 (1.7)
NAbs	0	0
Visit 6 (Week 16 Day 106 ± 2)		
BAbs	4 (2.3)	1 (0.6)
NAbs	0	0
Visit 9 (Week 25)		
BAbs	4 (2.3)	0
NAbs	0	0
At least one positive BAb test	6 (3.5)	5 (2.8)
At least one positive NAb test	0	0

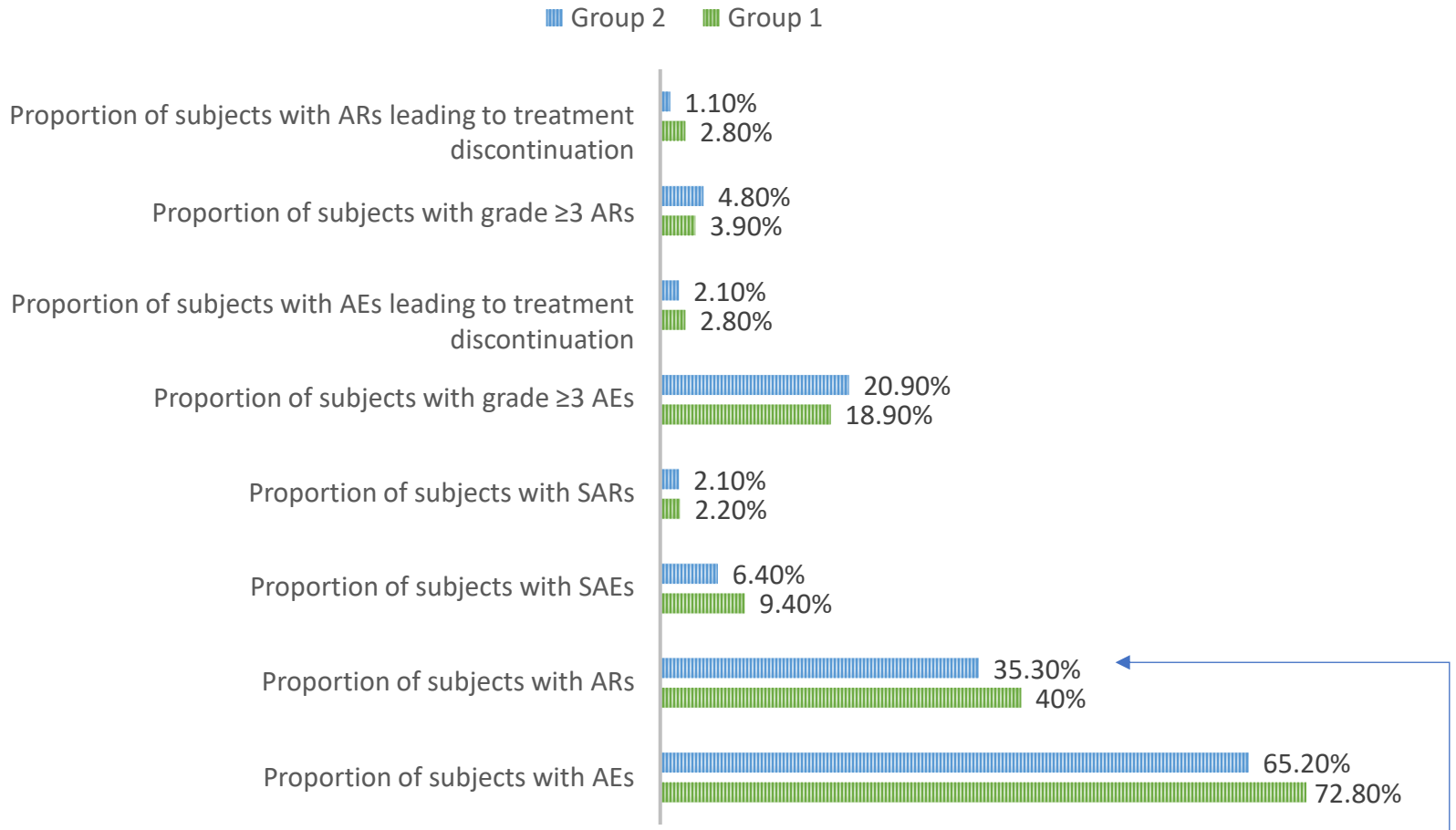
BAbs were detected in 6 and 5 subjects in Groups 1 and 2, respectively.

NAbs were not detected in any of the study subjects.

Note: BAbs, binding antibodies; NAbs, neutralizing antibodies.

Pembroria® and Keytruda® demonstrated satisfactory and comparable safety profiles.

Parameter	Group 1 (N = 180) n (%)	Group 2 (N = 187) n (%)
Proportion of subjects with AEs	131 (72.8)	122 (65.2)
Proportion of subjects with ARs	72 (40.0)	66 (35.3)
Proportion of subjects with SAEs	17 (9.4)	12 (6.4)
Proportion of subjects with SARs	4 (2.2)	4 (2.1)
Proportion of subjects with grade ≥3 AEs	34 (18.9)	39 (20.9)
Proportion of subjects with AEs leading to treatment discontinuation	5 (2.8)	4 (2.1)
Proportion of subjects with grade ≥3 ARs	7 (3.9)	9 (4.8)
Proportion of subjects with ARs leading to treatment discontinuation	5 (2.8)	2 (1.1)



The number of subjects with ARs was comparable between the treatment groups and was 40.0% in Group 1 and 35.3% in Group 2. The majority of reported adverse reactions were Grade 1-2, did not require emergency medical interventions and resolved with favorable outcomes.

AE- adverse events, SAE - serious adverse event, AR – adverse reaction

Conclusions

- In the study BCD-201-1, a pharmacokinetic analysis **demonstrated the equivalence** of Pembroria® and Keytruda® **in terms of the AUC_{0-504}.**
- Pembroria® and Keytruda® produce **comparable levels of PD-1 receptor saturation** in various lymphocyte populations
- Both products demonstrated **low immunogenicity**. No cases of binding antibodies to Pembroria® or Keytruda® were reported.
- **Both products** had **comparable safety profiles.**
- The analysis of BCD-201-2 supported **the equivalent effectiveness of the products being compared**

Pembroria®
pembrolizumab

BIOCAD
Biotechnology Company

UPDATED RESULTS

Multicenter, postmarketing, prospective, non-interventional study of efficacy and safety of BCD - 201® (pembrolizumab biosimilar) in patients with advanced forms of malignant neoplasms of various localizations in real clinical practice.

PERFECTION

assesment of BCD - 201 Real world efficacy and saFEty in multi-Cohort observaTIONal study

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

Why is it important to study the results of real-world clinical practice?

To confirm the results of randomized trials

To study drug activity in a population of patients who do not meet the eligibility criteria for a registrational study

To study the efficacy and tolerability of the drug in various patient subpopulations

To initiate prospective studies based on trends identified in real-world practice

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

AIM

To evaluate the efficacy and safety of BCD -201 in patients with different advanced malignancies in real-world clinical practice.

OBJECTIVES

1. Comparative assessment (historical control) of the efficacy of BCD - 201® in patients with:

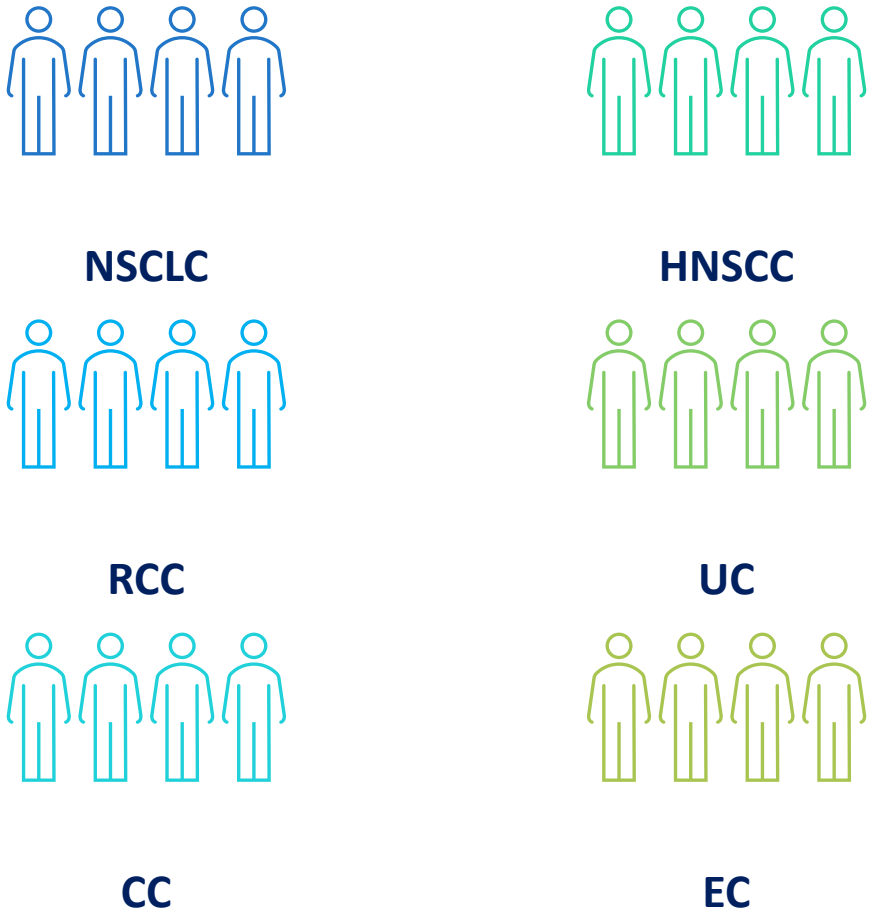
- metastatic NSCLC
- metastatic or inoperable relapsed HNSCC
- locally advanced or metastatic UC
- advanced RCC
- metastatic or relapsed CC
- advanced EC

2. To evaluate the safety of BCD - 201 in patients with different advanced malignancies.

BICCAD Biotechnology Company | BCD - 201® pembrolizumab

NSCLC, non-squamous-cell non-small cell lung cancer. HNSCC, head and neck squamous cell carcinoma. UC, urothelial cancer. RCC, renal cell carcinoma. CC, cervical cancer.
EC, endometrial cancer.

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024



Pembroria®

- Use according to local standard clinical practice and IMU
- Interim analyses of results are planned at 6-8, 18, 24 months after inclusion of the last patient
- Final analysis of results at 24 months after inclusion of the last patient
- Comparison of efficacy results with historical control:
  - **NSCLC**: KEYNOTE-189[1], KEYNOTE-407[2]
  - **CC**: KEYNOTE-826[3]
  - **EC**: KEYNOTE-158[4], KEYNOTE-775[5]
  - **RCC**: KEYNOTE-426[6]
  - **UC**: KEYNOTE-045[7]
  - **HNSCC**: KEYNOTE-048[8]

1. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005
2. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865
3. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Hoyos Usta E, Yañez E, Gümüş M, Olivera Hurtado de Mendoza M, Samouëlian V, Castonguay V, Arkhipov A, Toker S, Li K, Keefe SM, Monk BJ; KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med. 2021 Nov 11;385(20):1856-1867. doi: 10.1056/NEJMoa2112435. Epub 2021 Sep 18. PMID: 34534429.
4. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol*. 2020;38(1):1-10. doi:10.1200/JCO.19.02105
5. Makker V, Colombo N, Casado Herráez A, et al. Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/KEYNOTE-775. *J Clin Oncol*. 2023;41(16):2904-2910. doi:10.1200/JCO.22.02152
6. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1116-1127. doi:10.1056/NEJMoa1816714
7. Fradet Y, Bellmunt J, Vaughn DJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. *Ann Oncol*. 2019;30(6):970-976. doi:10.1093/annonc/mdz127
8. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study [published correction appears in Lancet. 2020 Jan 25;395(10220):272] [published correction appears in Lancet. 2020 Feb 22;395(10224):564] [published correction appears in Lancet. 2021 Jun 12;397(10291):2252]. *Lancet*. 2019;394(10212):1915-1928. doi:10.1016/S0140-6736(19)32591-7

*The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

THE PERFECTION STUDY DESIGN

Patients

- NSCLC
- HNSCC
- RCC
- UC
- EC
- CC

- General inclusion criteria
- Additional inclusion criteria for each condition

→

Pembroria®
200 mg once every 3 weeks or
400 mg once every 6 weeks
±CHT

- Study duration – 4 years
- Duration of the use of the study therapy:
  - until disease progression,
  - detection of unacceptable toxicity,
  - patient's death,
  - loss of clinical benefit, in the opinion of the investigator, *whichever occurs first*

- **Enrollment period** is 2 years or up to 1500 patients, whichever occurs first.
- **Follow-up period** is 2 years after the inclusion of the last patient.
- **Primary endpoints: ORR** RECIST v1.1, according to the assessment data over 6 months after the start of treatment.
- **Secondary endpoints:**
  - **12 and 24-month** progression-free survival (**PFS**), overall survival (**OS**), duration of response
  - **Safety:** frequency and nature: AEs and SAEs, AEs, AEs of grade 3-4, SARs, immune-related ARs/SARs. The frequency of discontinuation of the study drug due to the development of ARs/SARs.

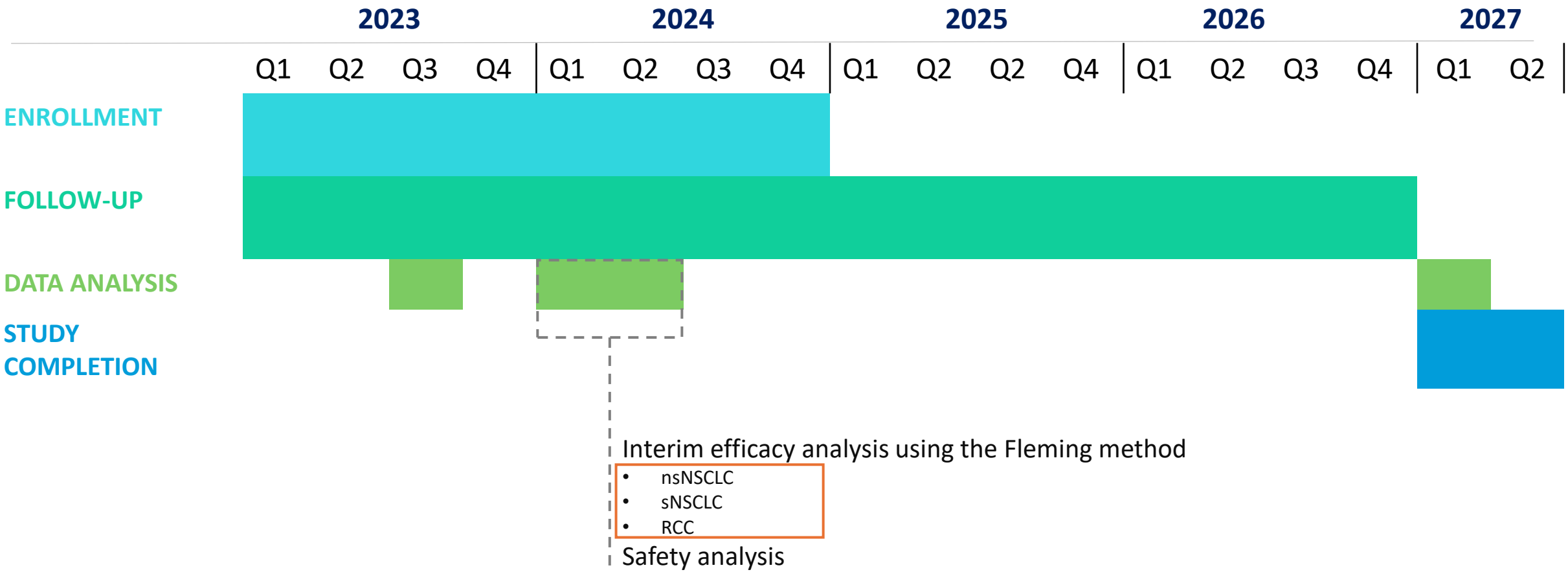
AE, adverse events. SAE, serious adverse events. AR, adverse reactions. SAR, serious adverse reactions.

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

Timeline of the PERFECTION study

52
Study site

637
patients enrolled



Enrollment – 2 years

Follow-up – 2 years

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

BIOCAD

Pre-Specified effectiveness criteria of BCD-201 (Pembroria®) in real-world clinical practice

Condition subgroup	Study code	ORR for therapy based on literature	ORR in the control group to determine P0 and P1	Established boundaries	
				P0	P1
nsNSCLC	**KEYNOTE-189[1]**	**47.6%** (95% CI 42.6; 52.5)	18.9%	**18%**	**42%**
sNSCLC	**KEYNOTE-407[2]**	**62.6%** (95% CI 56.6; 68.3)	38.4%	**35%**	**57%**
RCC	**KEYNOTE-426[5]**	**59.3%** (95% CI 54.5; 63.9)	35.7%	**35%**	**55%**

1.Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Apr 16. PMID: 29658856. 2.Paz-Ares L, Vicente D, Tafreshi A, Robinson A, Soto Parra H, Mazières J, Hermes B, Cicin I, Medgyasszay B, Rodríguez-Cid J, Okamoto I, Lee S, Ramlau R, Vladimirov V, Cheng Y, Deng X, Zhang Y, Bas T, Piperdi B, Halmos B. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. J Thorac Oncol. 2020 Oct;15(10):1657-1669. doi: 10.1016/j.jtho.2020.06.015. Epub 2020 Jun 26. PMID: 32599071. 3.Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, Manzuk L, Piha-Paul SA, Xu L, Zeigenfuss S, Pruitt SK, Leary A. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2019 Jun 10;37(17):1470-1478. doi: 10.1200/JCO.18.01265. Epub 2019 Apr 3. PMID: 30943124. 4. Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, Fujiwara K, Pignata S, Baron-Hay S, Ray-Coquard I, Shapira-Frommer R, Ushijima K, Sakata J, Yonemori K, Kim YM, Guerra EM, Sanli UA, McCormack MM, Smith AD, Keefe S, Bird S, Dutta L, Orlowski RJ, Lorusso D; Study 309–KEYNOTE-775 Investigators. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med. 2022 Feb 3;386(5):437-448. doi: 10.1056/NEJMoa2108330. Epub 2022 Jan 19. PMID: 35045221. 5. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghori R, Joe AK, Pruitt SK, Diaz LA Jr. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020 Jan 1;38(1):1-10. doi: 10.1200/JCO.19.02105. Epub 2019 Nov 4. PMID: 31682550; PMCID: PMC8184060. 6. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Hoyos Usta E, Yañez E, Gümüş M, Olivera Hurtado de Mendoza M, Samouëlian V, Castonguay V, Arkhipov A, Toker S, Li K, Keefe SM, Monk BJ; KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med. 2021 Nov 11;385(20):1856-1867. doi: 10.1056/NEJMoa2112435. Epub 2021 Sep 18. PMID: 34534429. 7. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Mai Y, Poehlein CH, Perini RF, Bajorin DF; KEYNOTE-045 Investigators. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 Mar 16;376(11):1015-1026. doi: 10.1056/NEJMoa1613683. Epub 2017 Feb 17. PMID: 28212060; PMCID: PMC5635424. 8. Burtness B, Rischin D, Greil R, et al. Pembrolizumab Alone or With Chemotherapy for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma in KEYNOTE-048: Subgroup Analysis by Programmed Death Ligand-1 Combined Positive Score. J Clin Oncol. 2022;40(21):2321-2332. doi:10.1200/JCO.21.02198.

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The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

This analysis was perform using Fleming method.

Based on it, cumulative sample size were calculated for each indication as well as accepted and rejected conditions for the null hypothesis

Condition subgroup	Boundary values		Actual power	Actual alfa	Cumulative sample size	Part of assessment	Sample size for part	Conditions for the null hypothesis H0	
	P0	P1						accepted (R ≤ Ag)	rejected (R ≥ Rg)
nsNSCLC	0.18	0.42	0.95	0.044	40	g1	20	3	9
						g2	20	11	12
sNSCLC	0.35	0.57	0.91	0.050	46	g1	23	8	14
						g2	23	21	22
RCC	0.35	0.55	0.90	0.047	53	g1	27	9	16
						g2	26	24	25

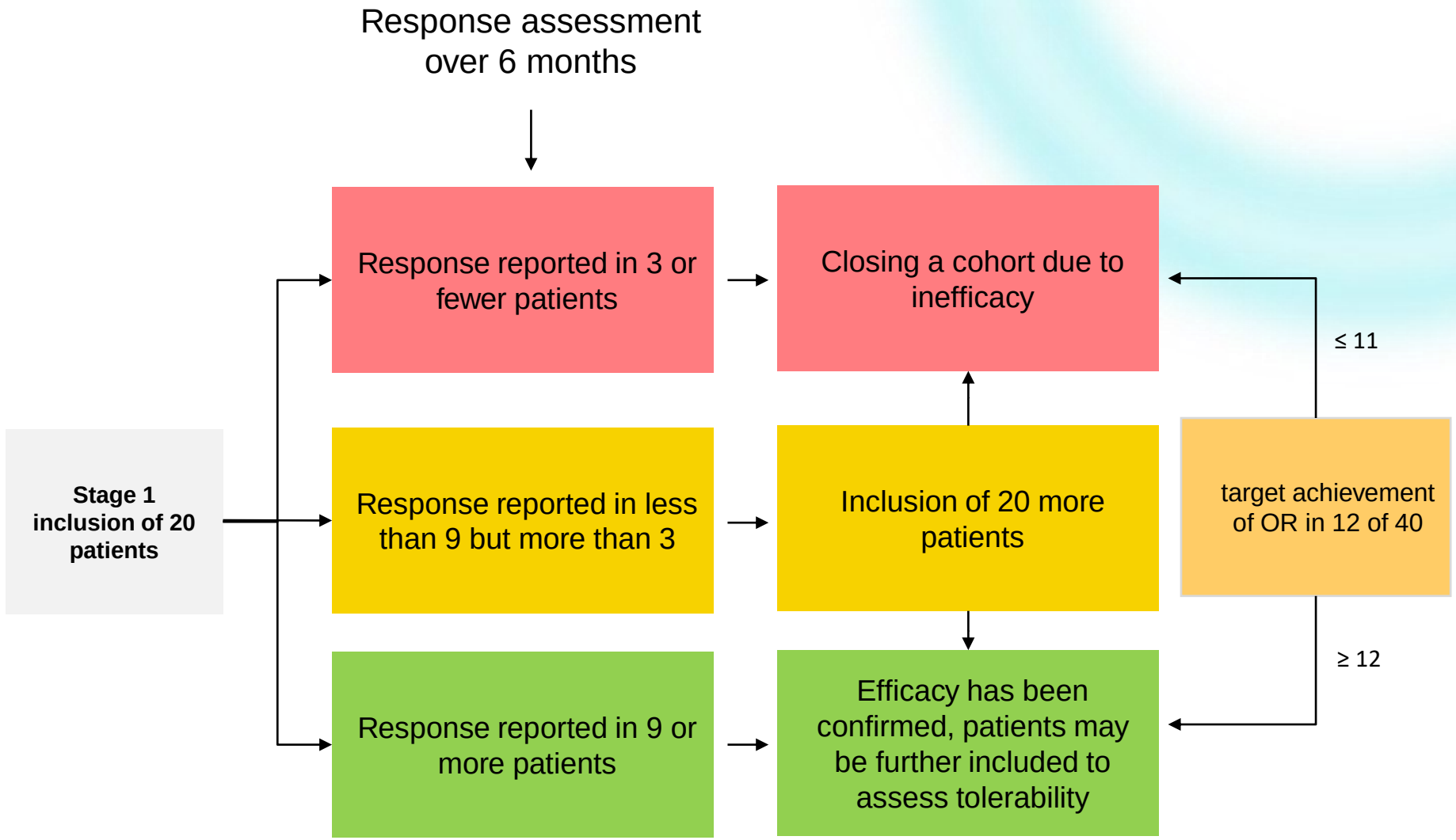
Inclusion in g1 and g2 in accordance with the date of initiation of therapy

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

By June 2024, a sufficient number of patients with nsNSCLC have been enrolled to conduct an efficacy assessment using the Fleming method

PERFECTION: Pembrolizumab + chemotherapy for nsNSCLC

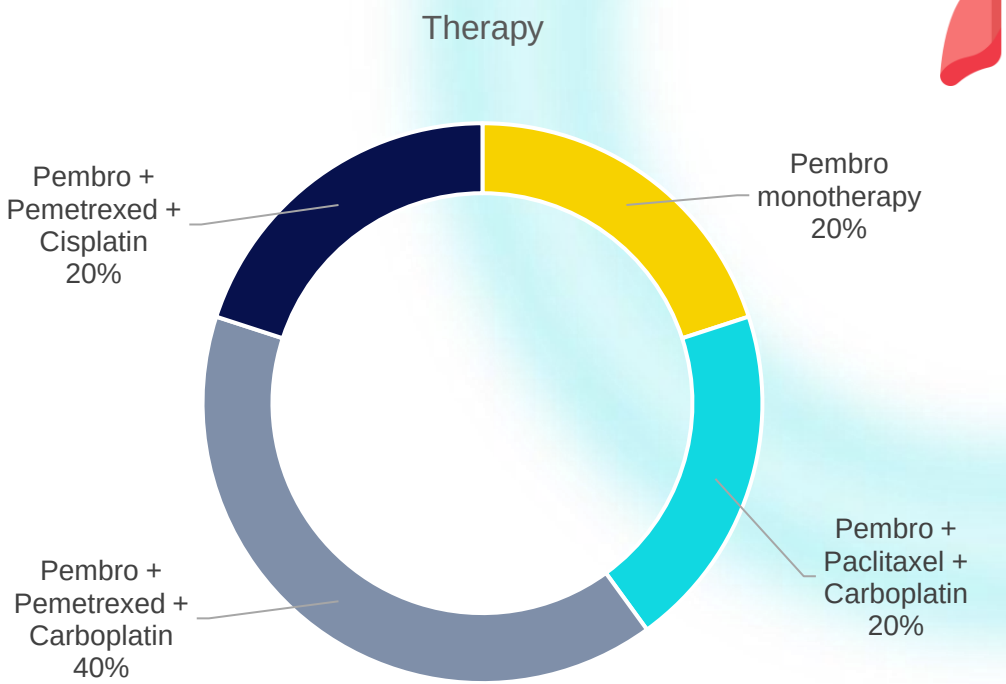
- Histologically and/or cytologically confirmed non-squamous-cell NSCLC
- 1st line therapy
- Any PD-L1 expression level
- The patient was started on therapy with Pemboria® according to the IMU in the following regimen:
  - monotherapy
  - in combination with chemotherapy including a platinum drug and pemetrexed

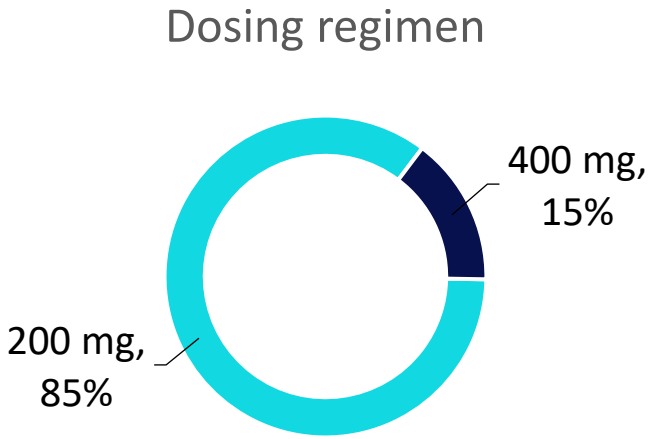


The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

PERFECTION: Characteristics of patients with nsNSCLC

Characteristics	g1 N=20
Median age (interval), years	64 (40 – 74)
Men	17 (85%)
Women	3 (15%)
ECOG PS 0	7 (35%)
ECOG PS 1	13 (65%)
Current smoker	12 (60%)
Histologic type	
adenocarcinoma	20 (100%)
Metastases at the beginning of therapy	19 (95%)
Brain metastases	0 (0%)
Liver metastases	2 (10%)
Lung metastases	9 (45%)
PD-L1 expression level established	9 (45%)
PD-L1 expression	
TPS < 1%	1 (11,1%)
TPS 1%-49 %	3 (33,3%)
TPS ≥ 50%	5 (55.5%)
Previous therapy	
Yes	2 (10%)
Surgery for the underlying disease	6 (30%)





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The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

Results of the efficacy assessment in nsNSCLC using Fleming method

Condition subgroup	Cumulative sample size	Part of assessment	Sample size for part	Conditions for the null hypothesis H0		Objective response reported
				accepted (R ≤ Ag)	rejected (R ≥ Rg)	
nsNSCLC	40	g1	20	3	9	11
		g2	20	11	12	

55%
ORR

Objective response reported in 11 of 20 patients – the null hypothesis was rejected – the regimen proved to be consistent with the original scheme

BIOCAD Biotechnology Company | BCD - 201® pembrolizumab

Inclusion in g1 and g2 in accordance with the date of initiation of therapy

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

Objective response rate for non-squamous-cell non small cells lung cancer cohort in PERFECTION is comparable with results obtained in Keytruda registration clinical trials

PERFECTION
nsNSCLC
Pembroria®

- Histologically and/or cytologically confirmed non-squamous-cell NSCLC
- 1st line therapy
- Any PD-L1 expression level
- The patient was started on therapy with Pemboria® according to the IMU in the following regimen:
  - in combination with chemotherapy including a platinum drug and pemetrexed

By June 2024, a sufficient number of patients in nsNSCLC g1 and g2 have been enrolled to conduct an efficacy assessment using the Fleming method
Efficacy was assessed in 40 patients:

- **Objective response was reported in 11/20 – 55%**

KEYNOTE-189/042
nsNSCLC

- **Patients with previously untreated nsNSCLC**
- stage IV
- ECOG 0-1
- any PD-L1 status
- no activating EGFR/ALK mutations
- no symptomatic CNS metastases or pneumonitis requiring treatment

KN-189
- 410 patients were included in the experimental group
  Objective response was reported in 48.3%

KN-042
- 299 patients were included in the experimental group
  Objective response was reported in 39%

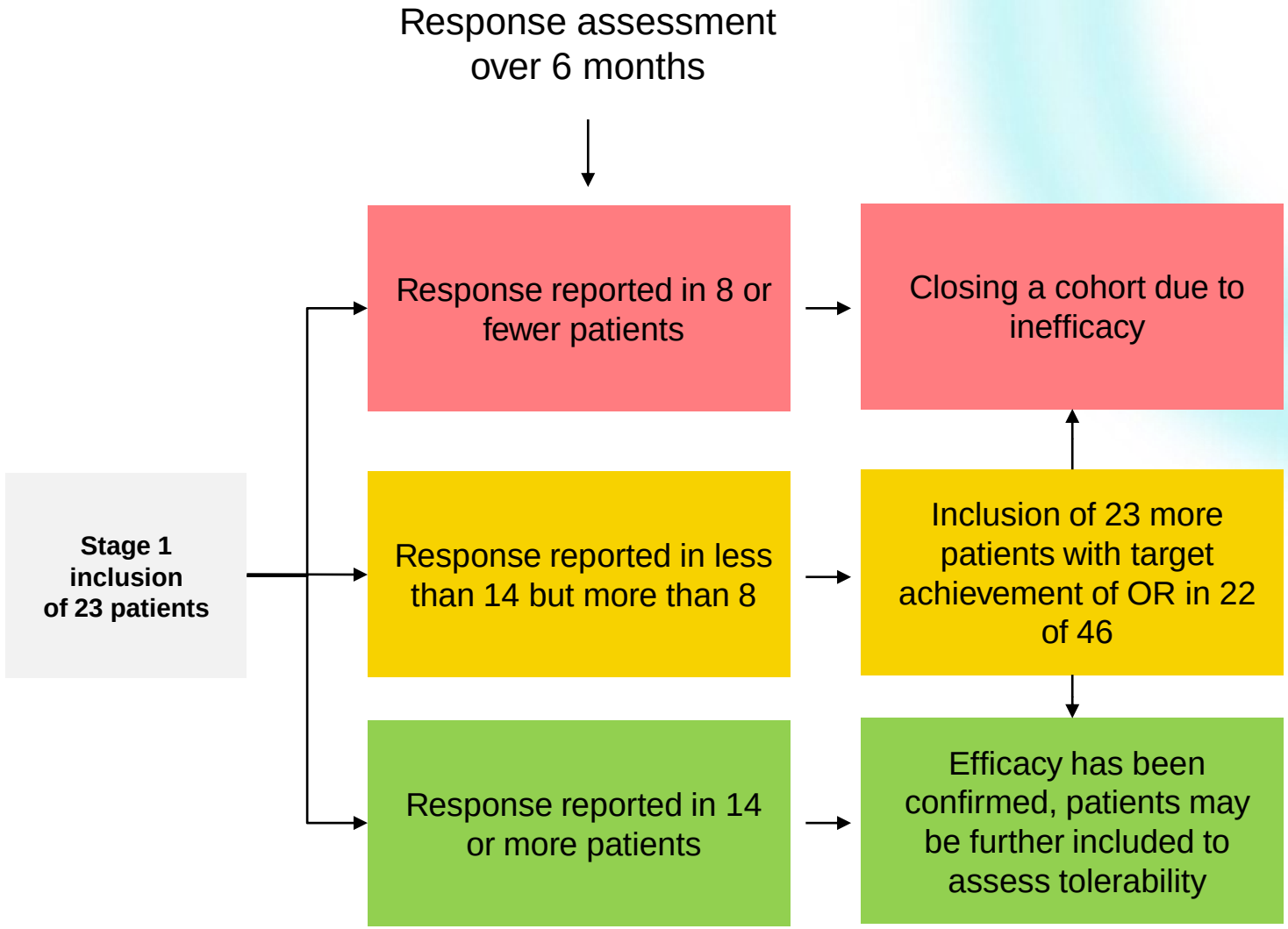
BICCAD Biotechnology Company | BCD - 201® pembrolizumab

Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol. 2023;41(11):1992-1998. doi:10.1200/JCO.22.0198
https://www.keytrudahcp.com/efficacy/nsclc-first-line-monotherapy/

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

PERFECTION: Pembrolizumab + chemotherapy for sNSCLC

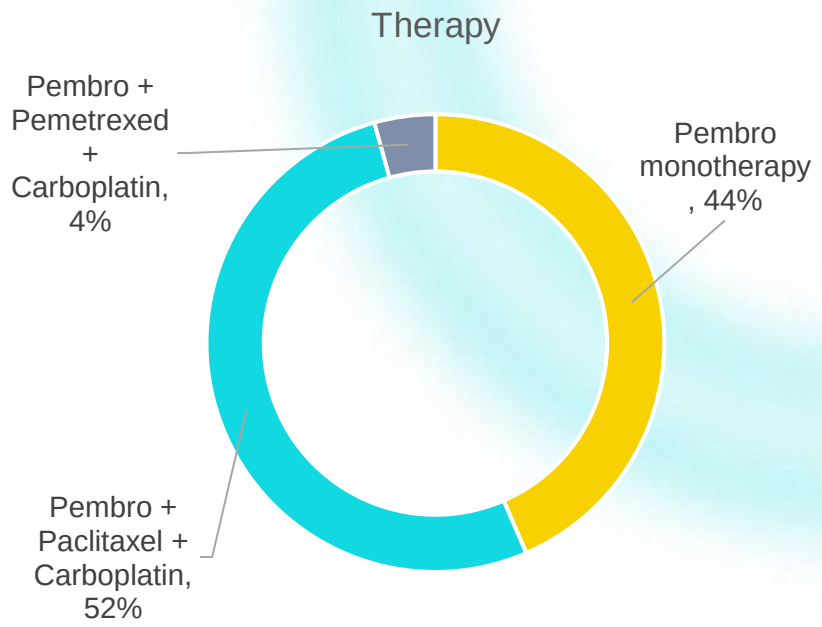
- Histologically and/or cytologically confirmed squamous-cell NSCLC
- 1st line therapy
- The patient was started on therapy with Pemboria® according to the IMU in the following regimen:
  - In combination with paclitaxel and platinum drugs
  - Monotherapy

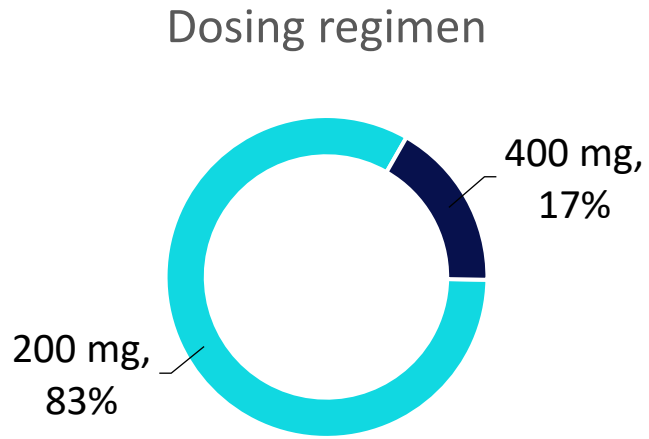


The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

PERFECTION: Characteristics of patients with sNSCLC

Characteristics	g1 N=23	g2 N=23	Total N=46
Median age (interval), years	65 (37 – 78)	67 (44 – 75)	66 (37 – 78)
Men	18 (78.3%)	22 (95.7%)	40 (87%)
Women	5 (21.7%)	1 (4.3%)	6 (13%)
ECOG PS 0	8 (34.8%)	8 (34.8%)	16 (34.8%)
ECOG PS 1	15 (65.2%)	15 (65.2%)	30 (65.2%)
Current smoker	13 (52.2%)	12 (56.5%)	6 (54.3%)
Histologic type			
squamous-cell NSCLC	23 (100%)	23 (100%)	46 (100%)
Metastases at the beginning of therapy	21 (91.3%)	21 (91.3%)	42 (91.3%)
Brain metastases	5 (21.7%)	1 (4%)	6 (13%)
Lung metastases	11 (47.8%)	12 (52%)	23 (50%)
Liver metastases	1 (4.3%)	3 (1.3%)	4 (8.6%)
PD-L1 expression level established	19 (86.2%)	13 (56.5%)	32 (69.6%)
PD-L1 expression			
TPS < 1%	5 (21.7%)	2 (8.7%)	7 (15.2%)
TPS 1%-49 %	4 (17.3%)	5 (21.7%)	9 (19.5%)
TPS ≥ 50%	10 (43.5%)	6 (26.1%)	16 (34.8%)
Previous therapy			
Yes	1 (4.3%)	4 (17.4%)	5 (10.9%)
Surgery for the underlying disease	4 (17.4%)	5 (21.7%)	9 (19.6%)





BIOCAD Biotechnology Company | Pembroria® pembrolizumab

The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

Results of the efficacy assessment in sNSCLC using Fleming method

Condition subgroup	Cumulative sample size	Part of assessment	Sample size for part	Conditions for the null hypothesis H0		Objective response reported
				accepted (R ≤ Ag)	rejected (R ≥ Rg)	
sNSCLC	46	g1	23	8	14	11
		g2	23	21	22	22

47.8%
ORR

Objective response reported in 22 of 46 patients – the null hypothesis was rejected – the regimen proved to be consistent with the original scheme

Inclusion in g1 and g2 in accordance with the date of initiation of therapy

Objective response rate for squamous-cell non small cells lung cancer cohort in PERFECTION is comparable with results of Keytruda registration clinical trials

PERFECTION

sNSCLC

Pembroria®

- Histologically and/or cytologically confirmed squamous-cell NSCLC
- 1st line therapy
- The patient was started on therapy with Pemboria® according to the IMU in the following regimen:
  - In combination with paclitaxel and platinum drugs
  - Monotherapy

By June 2024, a sufficient number of patients in sNSCLC g1 and g2 have been enrolled to conduct an efficacy assessment using the Fleming method
Efficacy was assessed in 46 patients:

- **Objective response was reported in 22/46 – 47.8%**

KEYNOTE-407/042

sNSCLC

- Previously untreated squamous NSCLC
- stage IV
- ECOG performance status 0-1
- Availability of a tumor sample for determining PD-L1 expression
- Absence of symptomatic brain metastases
- Absence of pneumonitis requiring systemic steroids
- (N = 559)

KN-407

- 278 patients were included in the experimental group
  Objective response was reported in 57.9%

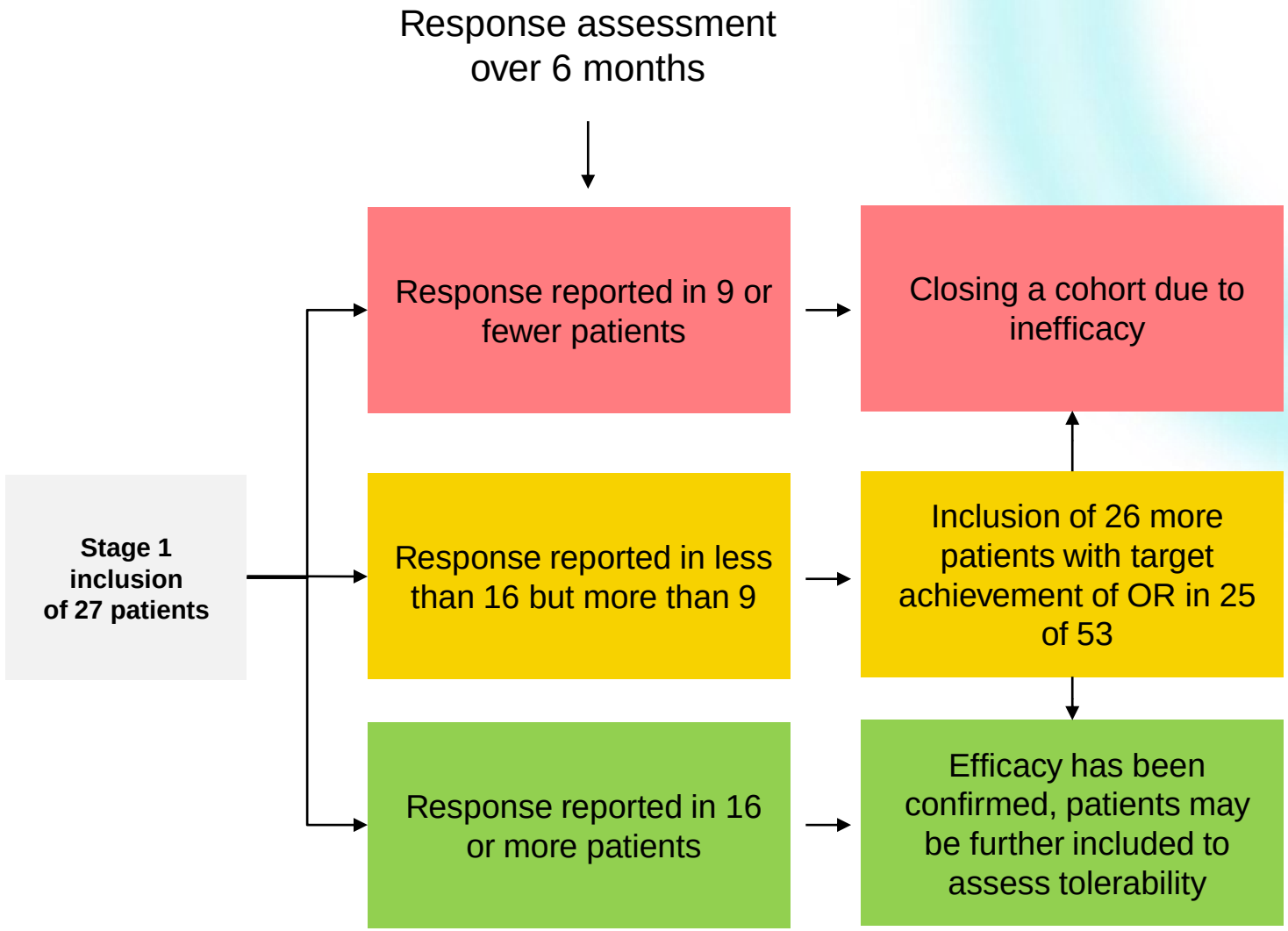
KN-042

- 299 patients were included in the experimental group
  Objective response was reported in 39%

Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865

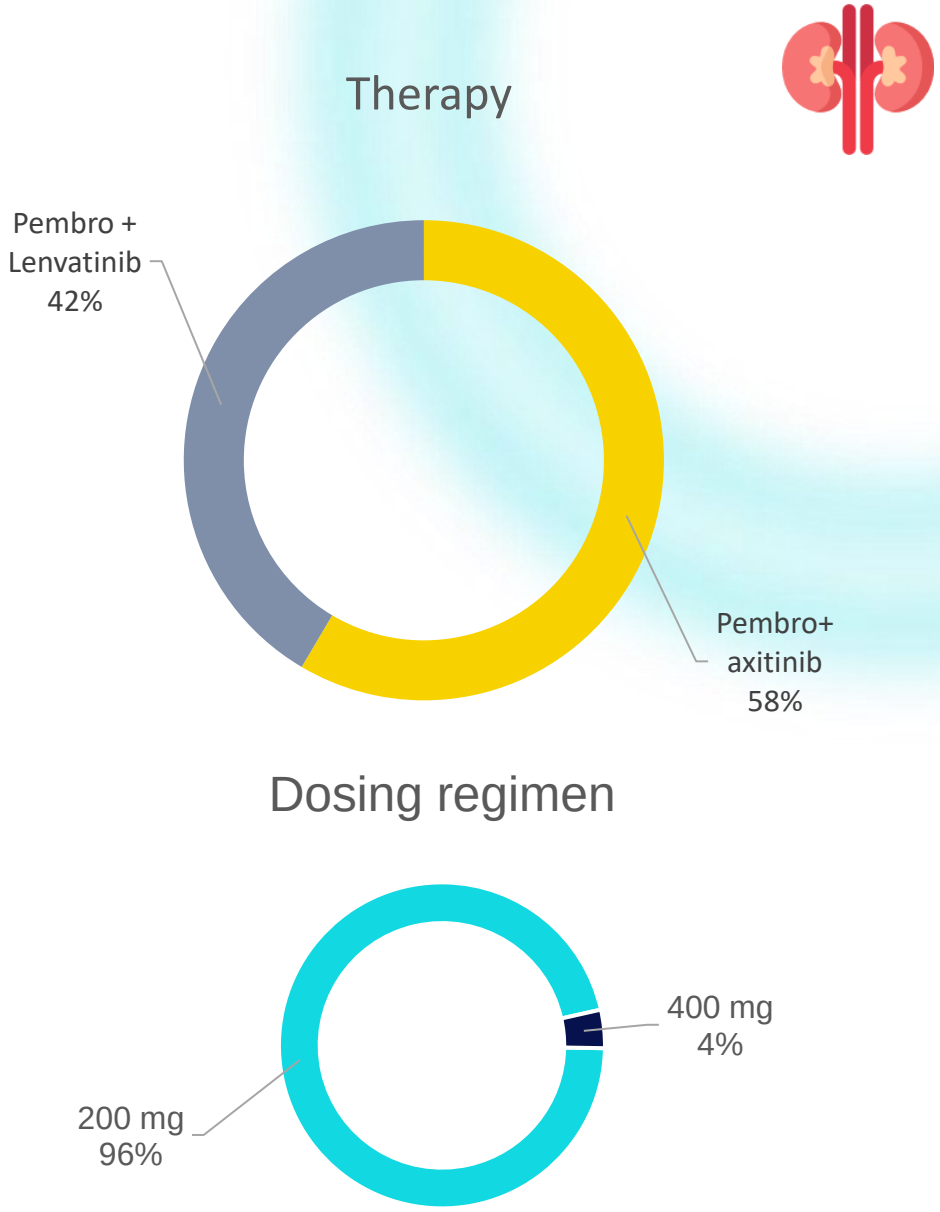
PERFECTION: Pembrolizumab + TKI for RCC

- Histologically and/or cytologically confirmed advanced renal cell carcinoma
- Any prognosis according to the IMDC prognostic model
- 1st line therapy
- The patient was started on therapy with Pemboria® according to the IMU in the following regimen:
  - in combination with axitinib
  - in combination with levantinib



PERFECTION: Characteristics of patients with sNSCLC

Characteristics	g1 N=27	g2 N=26	Total N=53
Median age (interval), years	62 (41 – 76)	64,5 (42 – 74)	63 (41 – 76)
Men	15 (55,6%)	14 (53,8%)	29 (54,7%)
Women	12 (44,4%)	12 (46,2%)	24 (45,3%)
ECOG PS 0	12 (44,4%)	12 (46,2%)	24 (45,3%)
ECOG PS 1	15 (55,6%)	14 (53,8%)	29 (54,7%)
Current smoker	2 (7,4%)	5 (19,2%)	7 (13,2%)
Metastases			
Metastases at the beginning of therapy	24 (88,9%)	24 (92,3%)	48 (90,6%)
Retroperitoneal lymph node metastasis	3 (11,1%)	5 (19,2%)	8 (15%)
Lung metastases	12 (44,4%)	17 (65,3%)	29 (54,7%)
Liver metastases	4 (14,8%)	3 (11,5%)	7 (13,3%)
Peritoneal metastases	3 (11,1%)	3 (11,5%)	6 (11,4%)
The IMDC Risk Score			
Favorable	8 (29,6%)	4 (15,4%)	12 (22,6%)
Intermediate	17 (63%)	16 (61,5%)	33 (62,3%)
Poor	2 (7,4%)	6 (23,1)	8 (15,1%)
Previous therapy			
No	27 (100%)	26 (100%)	53 (100%)
Surgery for the primary disease	17 (63%)	20 (76,9%)	37 (69,8%)



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The results were presented at the White Nights Congress in St. Petersburg, Russia, July 5th 2024

Results of the efficacy assessment

Condition subgroup	Cumulative sample size	Part of assessment	Sample size for part	Conditions for the null hypothesis H0		Objective response reported
				accepted (R ≤ Ag)	rejected (R ≥ Rg)	
RCC	53	g1	27	9	16	13
		g2	26	24	25	31

58.5%
ORR

Objective response reported in 31 of 53 patients – the null hypothesis was rejected – the regimen proved to be consistent with the original scheme

BICCAD Biotechnology Company | BCD - 201® pembrolizumab

Inclusion in g1 and g2 in accordance with the date of initiation of therapy

PERFECTION: Safety assessment results of BCD-201 (Pembroria®)

nsNSCLC

- Patients with AEs – 1/20 (5%)
  - Blood and lymphatic system disorders
- In g1 no ARs were reported

sNSCLC

- Patients with AEs – 3/46 (6.5%)
  - Blood and lymphatic system disorders
  - Gastrointestinal disorders
  - Nausea
- Patients with AEs – 1/46 (2.2%)
  - Gastrointestinal disorders CTCAE v 5.0 grade – 2.

RCC

- Patients with AEs – 6/453 (11.3%)
- disorders of the skin and subcutaneous tissues
- disorders of the liver and biliary tract
- kidney and urinary tract disorders
- endocrine system disorders
- swelling of the nasopharynx, urticaria on axitinib
- Patients with ARs – 3/46 (5.7%)
- immune-mediated hepatitis. Severity according to CTCAE v 5.0 – 4.
- immune-mediated nephritis. Severity according to CTCAE v 5.0 – 2.
- disorders of the endocrine system. Severity according to CTCAE v 5.0 – 1

PERFECTION STUDY: **In real-world clinical practice, BCD-201 (Pembroria®) demonstrates a favorable safety profile.**

PERFECTION STUDY: INTERIM ANALYSIS

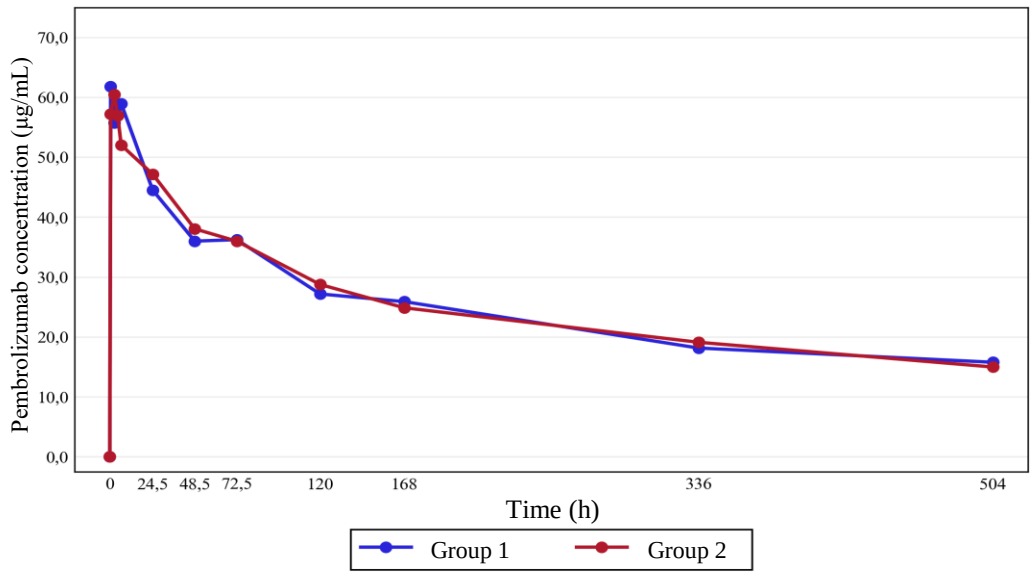
In real-world clinical practice, BCD-201(Pembroria®) demonstrates similar efficacy and tolerability results to the original molecule.

Pembroria®
pembrolizumab

Summary

The results of the phase I clinical study BCD-201-1 support the equivalence of Pembroria® and Keytruda® based on the AUC_{0-504}

Mean pembrolizumab concentrations after the first cycle



Study BCD-201-1: Pilot Effectiveness Assessment per RECIST 1.1 (ITT population)

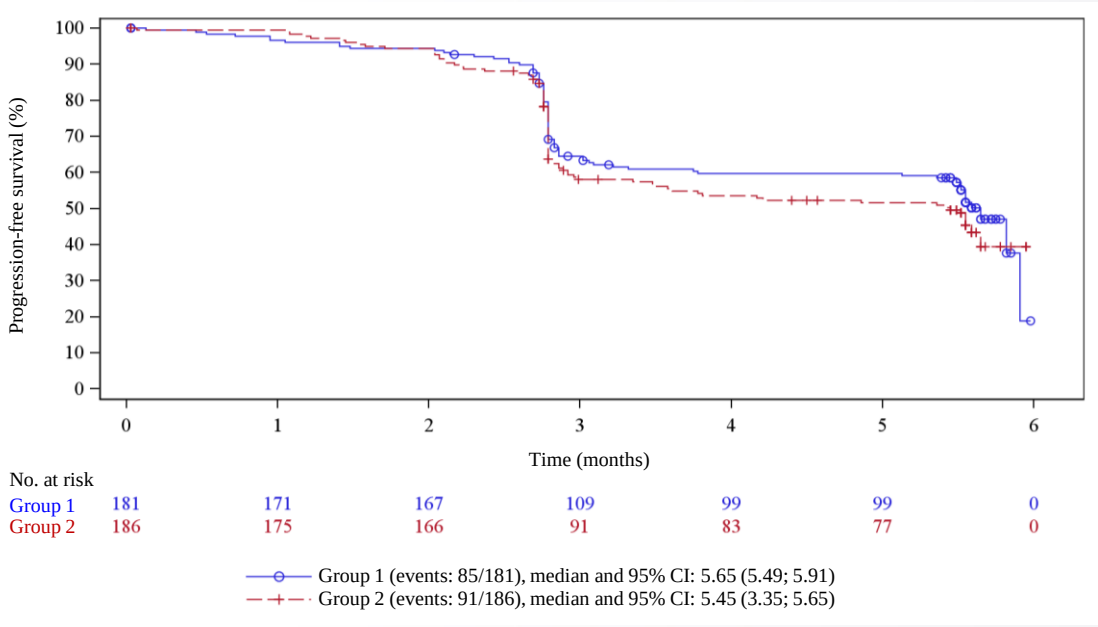
Subgroup Assessment	Group 1, n (%)	Group 2, n (%)
NSCLC	N = 24	N = 16
Complete response (CR)	0	0
Partial response (PR)	6 (25.0)	3 (18.8)
Stable disease (SD)	2 (8.3)	4 (25.0)
Progressive disease (PD)	8 (33.3)	5 (31.3)
Disease control rate (CR + PR + SD)	8 (33.3)	7 (43.8)
Overall response rate (CR + PR)	**6 (25.0)**	**3 (18.8)**
Melanoma	N = 43	N = 48
Complete response (CR)	2 (4.7)	1 (2.1)
Partial response (PR)	9 (20.9)	9 (18.8)
Stable disease (SD)	5 (11.6)	6 (12.5)
Progressive disease (PD)	18 (41.9)	27 (56.3)
Disease control rate (CR + PR + SD)	16 (37.2)	16 (33.3)
Overall response rate (CR + PR)	**11 (25.6)**	**10 (20.8)**

Note: The table does not include the “Not evaluable” and “No data” categories. Therefore, the total number of subjects in the categories may be less than the number of patients in the evaluation population.

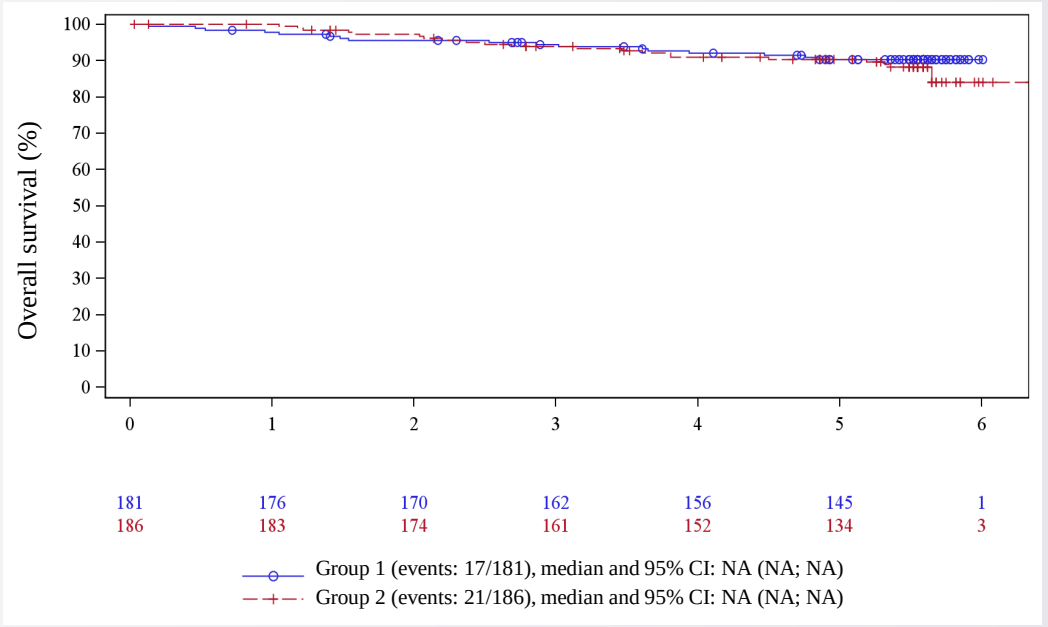
Parameter	N (Group 1, Group 2)	90% CI for the ratio of means G1:G2	90% CI for the ratio of means G2:G1	EAEU, EMA requirements
AUC_{0-504}	65, 61	85.95–109.06%	91.69–116.34%	80.00–125.00%
C_{max}	65, 61	92.41–110.60%	90.41–108.21%	80.00–125.00%

The analysis of phase III study BCD-201-2 supported the equivalent effectiveness of the products being compared

Progression-free survival per RECIST 1.1 as assessed by the ICR
ITT population



Overal survival



In the ITT population, the median PFS time per RECIST 1.1 as assessed by the ICR was comparable between the groups and was 5.65 and 5.45 months in Group 1 and Group 2, respectively

A median OS was not reached in either group. There were no statistically significant differences between the groups in terms of OS.

ITT – intent-to-treat population, ICR - Independent central review, PFS – progression-free survival

The authorization of Pembroria® has several significant advantages:

For patients:

- Confidence in consistentt availability of the drug that is not inferior to the originator in terms of safety and efficacy

For physicians:

- Possibility to offer immunotherapy to a larger number of patients

- Confidence in uninterrupted access to treatment

For administrators:

- Increasing the availability of innovative therapy without an additional strain on the budget

MINISTRY OF HEALTH
OF THE RUSSIAN FEDERATION

Marketing Authorization for a Medicinal Product for Human Use

ЛП-008684
(number of the marketing authorization for the medicinal product)

Name of the holder (owner) of the Marketing Authorization for the medicinal product	PK-137 Limited Liability Company (PK-137 LLC)
Address of the holder (owner) of the Marketing Authorization for the medicinal product	124460, Moscow, Intracity Territory of the Silino Municipal District, Zelenograd, Proyezd 5557-y, d. 2
Date of Marketing Authorization for the medicinal product	**December 2, 2022**
Validity period of the Marketing Authorization for the medicinal product	November 31, 2025
Date of variations to the Marketing Authorization for the medicinal product (date of renewal of the Marketing Authorization for the medicinal product)	January 22, 2024
Information about the authorized medicinal product:	
Trade name	**Pembroria®**
International non-proprietary, or generic, or chemical name	Pembrolizumab
Dosage form	concentrate for solution for infusion
Strength	25 mg/mL
Qualitative and quantitative composition of active ingredients and qualitative composition of excipients	
pembrolizumab 25.0 mg, excipients (trehalose dihydrate, glycine, poloxamer 188, histidine hydrochloride monohydrate, histidine, water for injection)	
Presentation (dosage form, strength, primary packaging, quantity of dosage form per primary packaging, quantity of primary packaging per consumer packaging, package contents)	concentrate for solution for infusion, 25 mg/mL (vial) 4 mL × 1 (carton)
Details of the regulatory documentation	ЛП-008684-140823

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