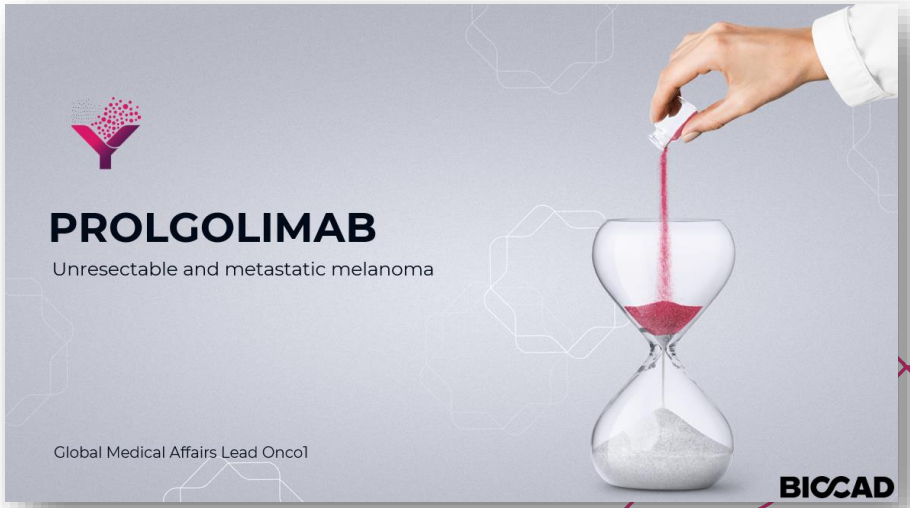
Content

Press here to read the prolgolimab presentation in NSCLC



Press here to read the prolgolimab presentation in melanoma

PROLGOLIMAB

NSCLC

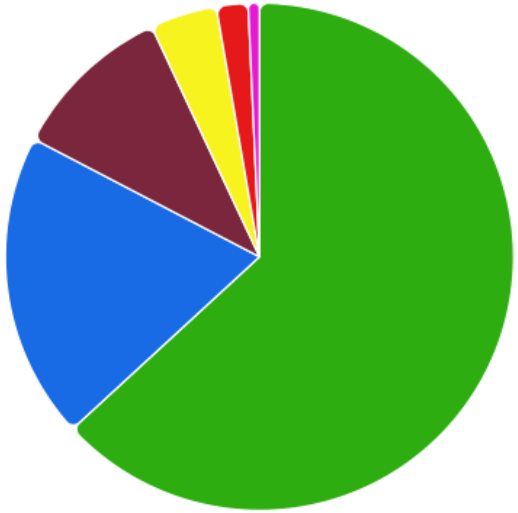
Global Medical Affairs Lead

BIOCAD

Lung cancer is the most common and most deadly cancer worldwide

World data

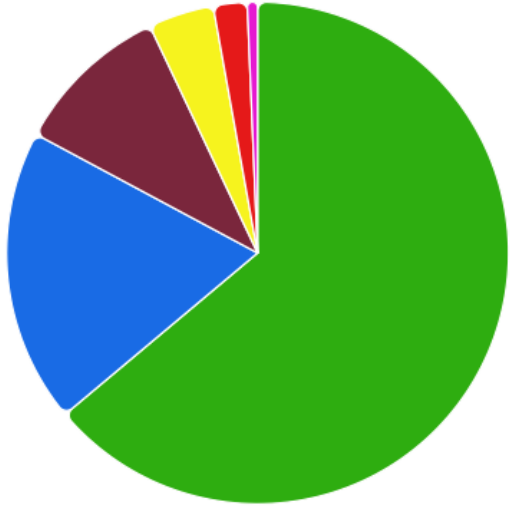
Incidence



Continent	Cases	Percent
Asia	1 566 355	63.1%
Europe	484 306	19.5%
Northern America	257 284	10.4%
Latin America and the Caribbean	105 306	4.2%
Africa	49 831	2.0%
Oceania	17 593	0.71%

Incidence, both sexes

Prevalence



Continent	Prev. cases	Percent
Asia	2 058 202	63.9%
Europe	610 169	18.9%
Northern America	325 855	10.1%
Latin America and the Caribbean	135 918	4.2%
Africa	70 142	2.2%
Oceania	21 175	0.66%

5-year prevalence, both sexes

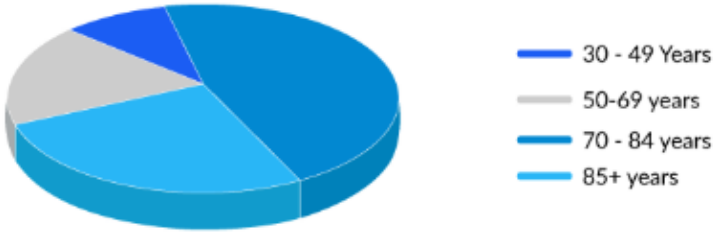
Incidence

Rank	Cases	ASR (World)
1	2 480 675	23.6

Mortality

Rank	Deaths	ASR (World)
1	1 817 469	16.8

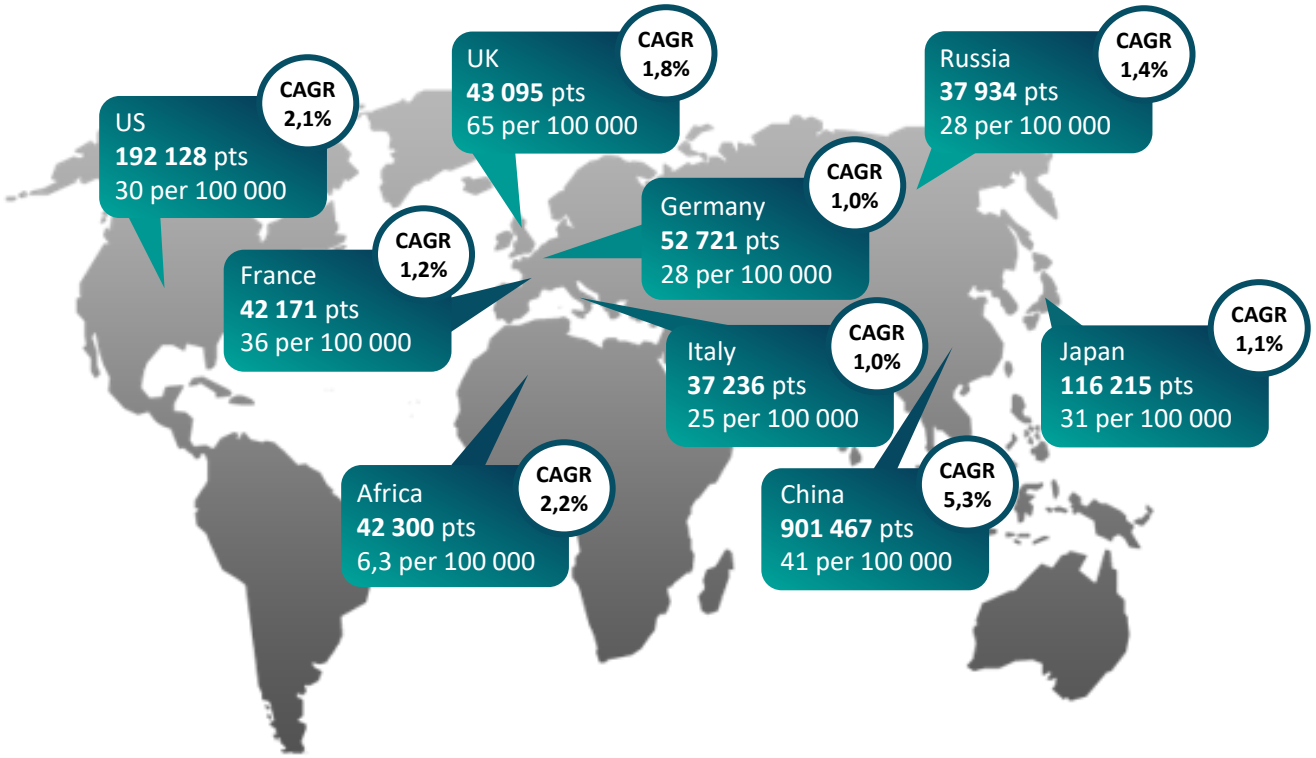
Age-specific Cases of NSCLC

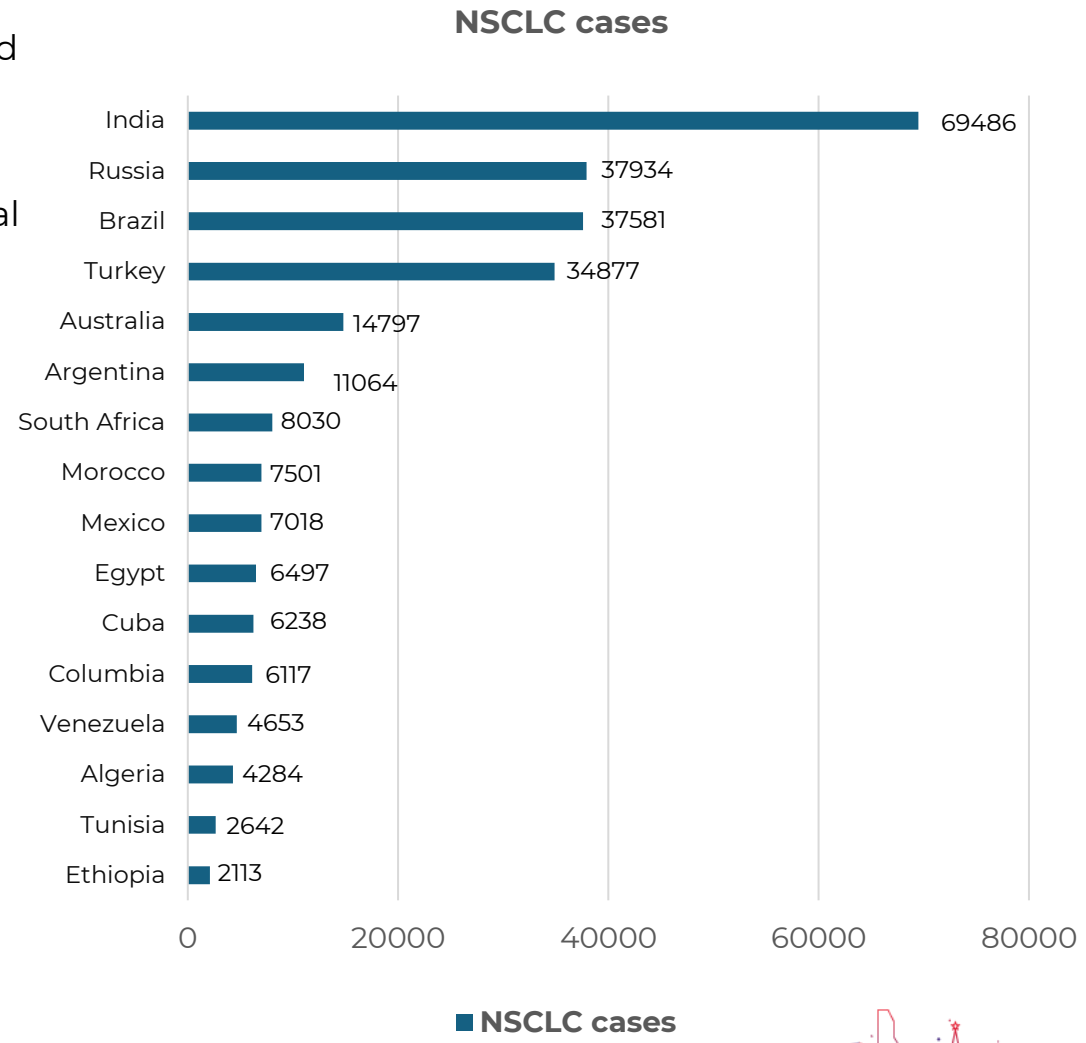


Cancer Today

INCIDENT CASES OF LUNG CANCER

- Lung cancer is the most common cancer globally
- There are two main types of lung cancer: small cell lung cancer (SCLC) and **non-SCLC (NSCLC)** which accounts for approximately **85% of all cases** of lung cancer[2].
- 70% patients with locally advanced or metastatic disease at initial diagnosis





1. Malignant neoplasms in Russia in 2023. Incidence and mortality. Edited by A.V. Kaprin, V.V. Stanrinsky, A.O. Shakhzadova; 2023 Cancer Today

CURRENT TREATMENT PARADIGM | NON-SMALL CELL LUNG CANCER (NSCLC)

NEOADJUVANT 2-4 courses **(IIA and IIIA/IIIB)**

CHEMO (Pt + pemetrexed/gemcitabine, etc.)

without EGFR /ALK mutations

- **Pembrolizumab + CHEMO**
- **Nivolumab + CHEMO**
- **Durvalumab + CHEMO**

SURGERY (IA-IIIA)

Tumour is not resectable, cancellation of the operation

Chemo-radiation therapy

ADJUVANT

Residual cancer burden	Target mutation	CT+ICI (without neo)
CHEMO (Pt combo)	**Osimertinib** (EGFR+) **Alectinib** (ALK+)	▪ **Atezolizumab** PD-L1≥50%, EGFR -, ALK- ▪ **Pembrolizumab** IPD-L1 1-49%, EGFR -, ALK

Maintenance therapy

EGFR +	EGFR- / ALK-
Osimertinib	▪ **Durvalumab** regardless PD-L1 expression

- Based on a personalized approach that takes into account disease stage, tumour molecular profile, PD-L1 status and the patient's general condition.
- Neoadjuvant therapy increases resectability by 15-20%.
- A key trend is the shift from 'chemotherapy for all' to biomarker-based therapy selection
- The use of IO contributes to an increase in ORR by up to 40-60%
- Overcoming resistance to targeted and IO therapy - is a major unresolved challenge

SYSTEMIC THERAPY

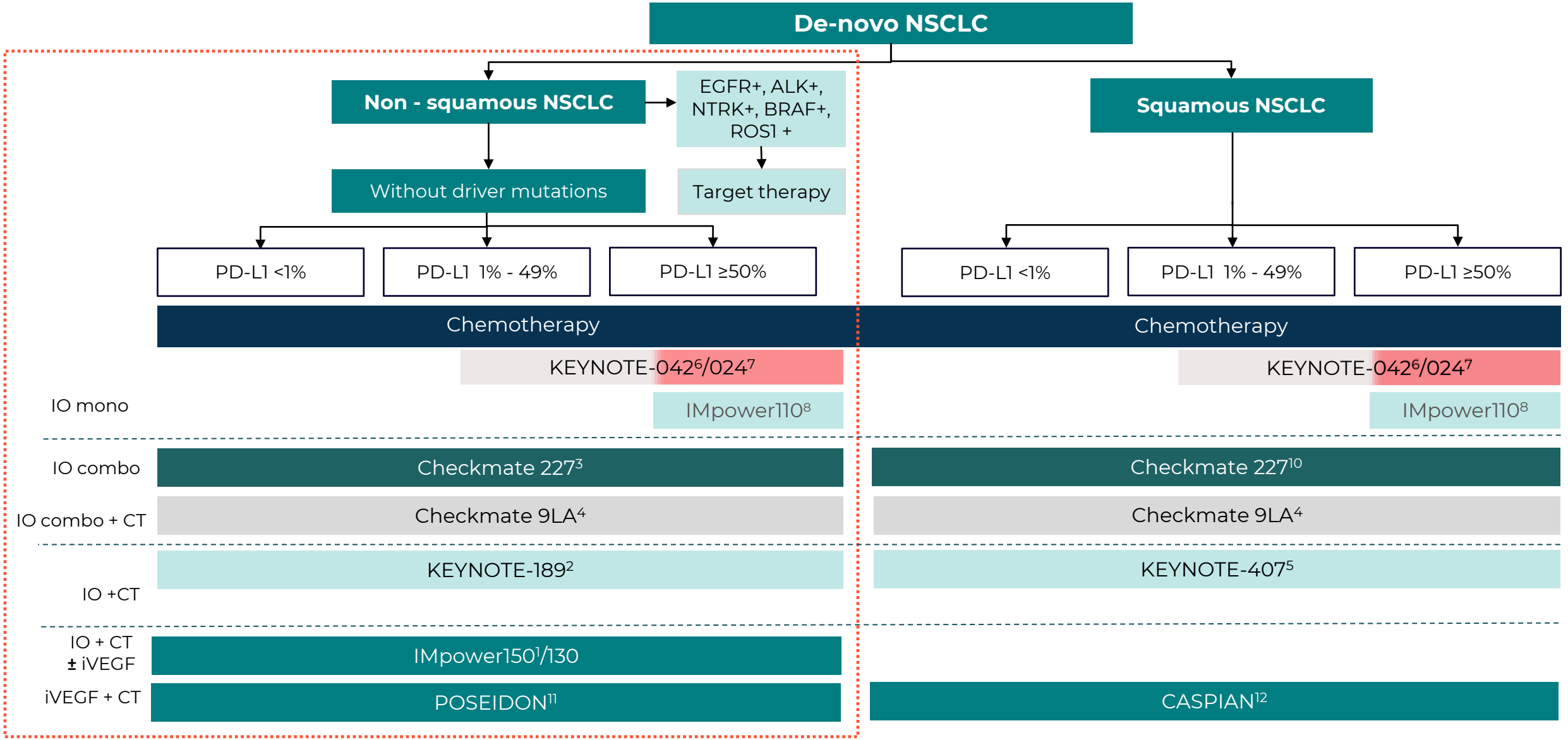
1st line

Non-squamous aNSCLC (≈46%)				*Squamous aNSCLC (≈54%)*
Without mutation EGFR, ALK, BRAF, ROS1	EGFR +	ALK+	BRAF V600E	
▪ Pt based chemotherapy± Bev ▪ Pembro /Atezo (PD-L1 ≥50) ▪ Pembro + Chem +pemetrexed ▪ Nivo + Ipi + Chem ▪ Chem mono (pemetrexed, Vin, Gem, taxans)	▪ Osimertinib ± CT ▪ Gefitinib ▪ Afatinib ▪ Erlotinib +/- ramucirumab ▪ Erlotinib +/-Bev ▪ Amivantamab + Lazertinib	▪ Crizotinib ▪ Ceritinib ▪ Alectinib	▪ Dabrafenib ▪ Trametinib	▪ Pt based chemotherapy ▪ Pembro/Atezo (PD-L1 ≥50) ▪ Pembro + Chem ▪ Nivo + Ipi + Chem ▪ Chem mono (Ven, Gem, taxans)

2nd line

▪ Pt based chemotherapy ▪ Chemotherapy +/- ramucirumab ▪ Nintedanib +pemetrexed ▪ Nivo + Ipi + Chem ▪ IO if not used in line 1st	▪ **Osimertinib** ▪ *Gefitinib* ▪ *Afatinib* ▪ *Erlotinib*	▪ Alectinib ▪ Lolratinib ▪ Ceritinib	▪ Pt based CT± Bev	▪ Pt based chemotherapy ▪ Chem mono (Ven, Gem, taxans) ▪ Anti-PD-1 / anti-PD-L1, if not used in line 1st

GENERAL ALGORITHM FOR THE NSCLC 1ST LINE THERAPY



This diagram is for demonstration purposes and does not illustrate all therapeutic approaches. Prepared on the basis of NCCN

Is the targeting of PD-L1 expression levels important in the selection of 1st - line treatment regimens?

Scheme	PD-1/PD-L1 expression level
Pembro mono KEYNOTE 024[7]	TPS PD-1 ≥ 50%
KEYNOTE 042[3]	TPS PD-1 ≥ 1% and chemotherapy intolerance
Atezo mono IMPower 110[8]	TPS PD-L1 ≥ 50% or IC ≥ 10%
Pembro + pemotrexed + Pt (CT) KeyNote-189 [2]	any
Atezo + CT + Bev IMPower 150 [1]	any
Nivo + Ipi CheckMate 227 [3]	any
Nivo + Ipi + CT CheckMate 9LA [4]	any
Durva +Treme + CT Poseidon[9]	any
Prolgo + CT Domajor [9,10]	any

CT – chemotherapy, Pembro – pembrolizumab, Pt – platinum, Atezo – atezolizumab, Bev – bevacizumab, Nivo – nivolumab, Ipi – ipilimumab, Durva – durvalumab, Treme – tremelimumab, Prolgo - prolgolimab

PROLGOLIMAB: COMPETITIVE LANDSCAPE IN NSCLC

Indication for prolgolimab in RU: in combination with pemetrexed and platinum chemotherapy for previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC) without EGFR or ALK mutations

INN	Target	Brand name	Company	Indication (in prolgolimab targeted population)	Degree of threat
Pembrolizumab	aPD1	Keytruda®	MSD	1. in combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-squamous NSCLC without EGFR or ALK mutations 2. monotherapy for the first-line treatment of metastatic NSCLC with a ≥ 50% tumor proportion score (TPS) without EGFR or ALK mutations.	HIGH
Atezolizumab	aPD-L1	Tecentriq®	Roche	1. in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of metastatic non-squamous NSCLC 2. in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of metastatic non-squamous NSCLC without EGFR or ALK mutations 3. monotherapy for the first-line treatment of metastatic NSCLC with PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) without EGFR or ALK mutations	HIGH
Nivolumab +ipilimumab	aPD1+ aCTLA-4	Opdivo®+ Yervoy®	BMS	Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCLC without EGFR or ALK mutations	MEDIUM
Durvalumab +tremelimumab	aPD-L1+ aCTLA-4	Imfinzi® +Imjudo®	AstraZeneca	Tremelimumab in combination with durvalumab and platinum-based chemotherapy for the first-line treatment of metastatic NSCLC without EGFR or ALK mutations	MEDIUM
Cemiplimab	aPD-1	Libtayo®	Sanofi	1. monotherapy is indicated for the first-line treatment of NSCLC expressing PD-L1 (in ≥ 50% tumor cells), with no EGFR, ALK or ROS1 aberrations 2. In combination with platinum-based chemotherapy for the first-line treatment of NSCLC expressing PD-L1 (in ≥ 1% of tumor cells), with no EGFR, ALK or ROS1 aberrations	MEDIUM

Competitive landscape may vary from country to country

RU – Russian Federation, PD-L1 = programmed death ligand CTLA-4 cytotoxic T-lymphocyte-associated antigen-4, NSCLC - non-small cell lung cancer

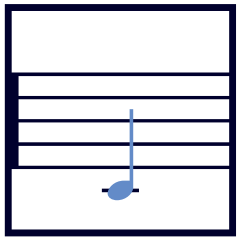
PROLGOLIMAB CLINICAL DEVELOPMENT PROGRAM

HARMONY DOMAJOR

HARMONY

HARMONY — a compre**H**ensive progr**A**m of clinical t**R**ials on the efficacy, safety, phar**M**acokinetics and immun**O**genicity of prolgolimab in o**N**colog**Y**

LUNG CANCER[9]

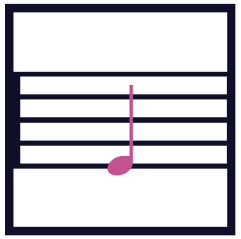


DOMAJOR

Ph III
Advanced NSCLC
Prolgolimab + CT 1L
EU **CHINA** **RUSSIA**

Status: **completed**

MELANOMA[13]



MIRACULUM

Ph II
Advanced Melanoma
Prolgolimab monotherapy
RUSSIA

Status: **completed**

BIOCAD
Biotechnology Company

HARMONY

DOMAJOR

Prolgolimab in Combination With Chemotherapy As The First-Line Therapy for Advanced nsNSCLC: Results of the Phase 3 Clinical Study DOMAJOR

DOMAJOR

An International, Multicenter, Randomized, Double-blind, Placebo-controlled Clinical Study of the Efficacy and Safety of BCD-100 in Combination with Pemetrexed + Cisplatin/Carboplatin Versus Placebo in Combination with Pemetrexed + Cisplatin/Carboplatin as First-Line Therapy in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC)[9]

Product development phase: III

Geography: Russian Federation, China, Slovakia, Hungary

Study period (years): September 2019 to May 2023

NCT03912389

Study Design

Non-Squamous NSCLC:

- Stage IV
- ECOG 0-1
- No previous treatment for advanced disease
- Measurable disease

n = 292

R 1:1

prolgolimab 3 mg/kg IV
pemetrexed 500 mg/m²
cisplatin 75 mg/m² /carboplatin AUC5
4 cycles Q3W

prolgolimab 3 mg/kg IV
pemetrexed 500 mg/m²

placebo 3 mg/kg IV
pemetrexed 500 mg/m²
cisplatin 75 mg/m² /carboplatin AUC5

placebo 3 mg/kg IV
pemetrexed 500 mg/m²

Until disease progression or unacceptable toxicity*

*not more than 36 months after initiation of study therapy

Primary endpoint:
- mOS

Secondary endpoints:
- mPFS
- ORR
- DCR
- Time to response
- Duration of response
- Safety

Stratification factors:
- *platinum drug (carboplatin or cisplatin),*
- *PD-L1 expression (TPS <1% or ≥1%),*
- *race (non-Asian or Asian).*

The secondary efficacy endpoints were progression-free survival, overall response rate (ORR), disease control rate (DCR), time to response (TTR) and duration of response (DOR) and were based on assessment performed by blinded independent central review (BICR) according to RECIST 1.1

R – randomization; median progression-free survival (mPFS), median overall survival (mOS), IV - intravenously, Quality to be delivered every 2 weeks; Q3W - Quality to be delivered every 3 weeks.; ECOG = Eastern Cooperative Oncology Group, PD-L1 = programmed death ligand

NCT03912389

Patients characteristics[9]

Patient population in DOMAJOR reflects real clinical practice

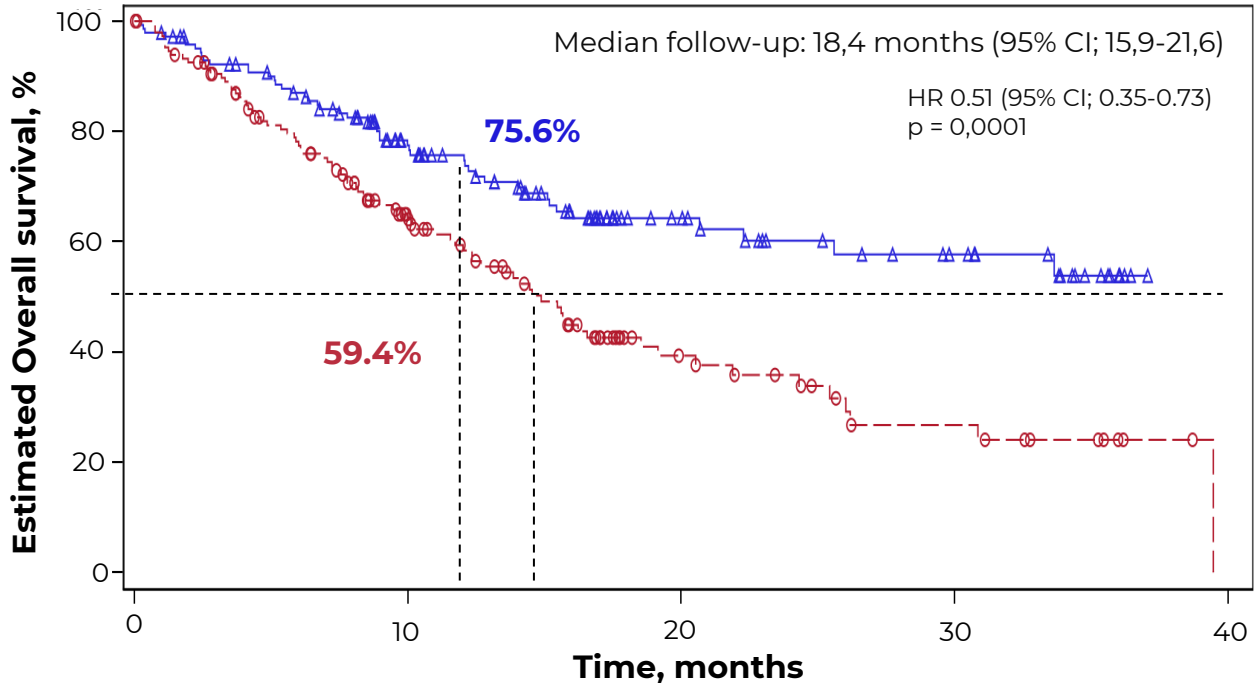
	PROLGO + CT (n = 143)	Placebo + CT (n = 149)
Age, n (%)		
>=18 to <65 years old	91 (63.6)	91 (61.1)
>=65 to <75 years	46 (32.2)	48 (32.2)
>=75 years	6 (4.2)	10 (6.7)
Sex, n (%)		
Female	48 (33.6)	42 (28.2)
Male	95 (66.4)	107 (71.8)
Race, n (%)		
Caucasian	98 (68.5)	105 (70.5)
Asian	45 (31.5)	44 (29.5)
Smoking, n (%)		
Current/history	99 (69.2)	109 (73.2)
Non-smokers	44 (30.8)	40 (26.8)
ECOG status, n (%)		
0	40 (28)	37 (24.8)
1	103 (72)	112 (75.2)
PD-L1 status, n (%)		
TPS <1%	57 (39.9)	60 (40.3)
TPS≥1%	86 (60.1)	89 (59.7)

	PROLGO + CT (n = 143)	Placebo + CT (n = 149)
Histological type of tumor, n (%)		
Adenocarcinoma	96 (97.0)	103 (98.1)
Large cell carcinoma	3 (3.0)	2 (1.9)
Presence of MTS, %	143 (100)	95 (100)
Number of organs with MTS		
Median	3	3
Minimum	1	1
Maximum	8	10
Organs with MTS, n (%)		
bones	63 (44.1)	47 (31.5)
liver	23 (16.1)	22 (14.8)
lung	90 (62.9)	106 (71.1)
brain	15 (10.5)	23 (15.4)
peritoneum	1 (1)	2 (1.3)
lymph nodes	109 (76.2)	128 (85.9)
adrenal gland	29 (20.3)	42 (28.2)
other	65 (45.5)	61 (40.9)

The population was enriched with patients with poor prognosis: ECOG = 1 (72 %), PD-1 TPS< 1 % (40 %), patients with bone and brain metastases (44 % and 11 %, respectively), patients who were never smokers (31 %), the **number of whom was higher than those enrolled in similar trials** number of whom was higher than those enrolled in similar trials.

Prolgo – prolgolimab, mts – metastasis, TPS - tumor Proportion Score

Overall survival



No. at risk					
Prolgo + CT	143	87	34	19	0
Placebo + CT	149	72	23	10	0

Parameter	PROLGO+CT n = 143	Placebo+CT n = 149
mOS (mos) [95% CI][1]	**NA** (22,3; NA)	14,6 (11,7; 19,2)
Estimated OS, 12 mos (%)	**75,6**	59,4
Estimated OS, 18 mos (%)	**64,1**	42,2

RECIST 1.1

Median OS not reached in Prolgo + CT group with a median follow-up more than 1,5 year.

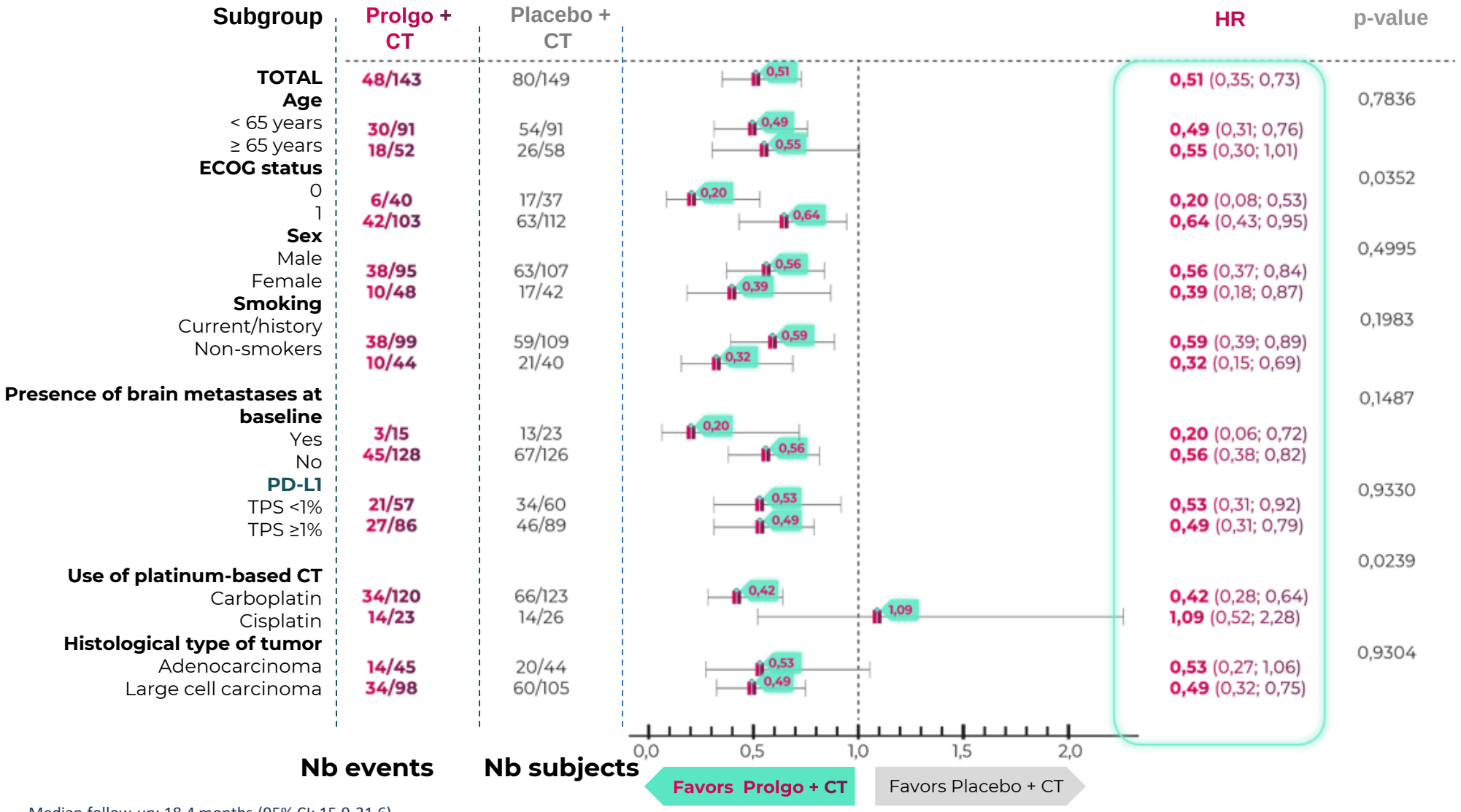
Prolgolimab combination (events: 48/143), median and 95% CI: NA (22.280; NA)

Placebo combination (events: 80/149), median and 95% CI: NA (11.730; 19.150)

OS, overall survival; CI, confidence interval; HR, hazard ratio. Stratified analysis was performed for stratification variables used in dynamic randomization based on IWRS data: use of a platinum drug (carboplatin or cisplatin),

PD-L1 expression (TPS <1% or >=1%), race (Asian or non-Asian). NA, not achieved., CT - chemotherapy

Prolgolimab benefits for different patients subgroups



The forest plot analyses demonstrated a consistent benefit of the Prolgo + CT over the placebo combination across groups, including all subgroups of PD-L1 TPS[9]

Median follow-up: 18,4 months (95% CI; 15,9-21,6)

OS, overall survival; CI, confidence interval; HR, hazard ratio. Stratified analysis was performed for stratification variables used in dynamic randomization based on IWRS data: use of a platinum drug (carboplatin or cisplatin), PD-L1 expression (TPS <1% or >=1%), race (Asian or non-Asian). NA, not achieved., CT – chemotherapy, Prolgo - prolgolimab

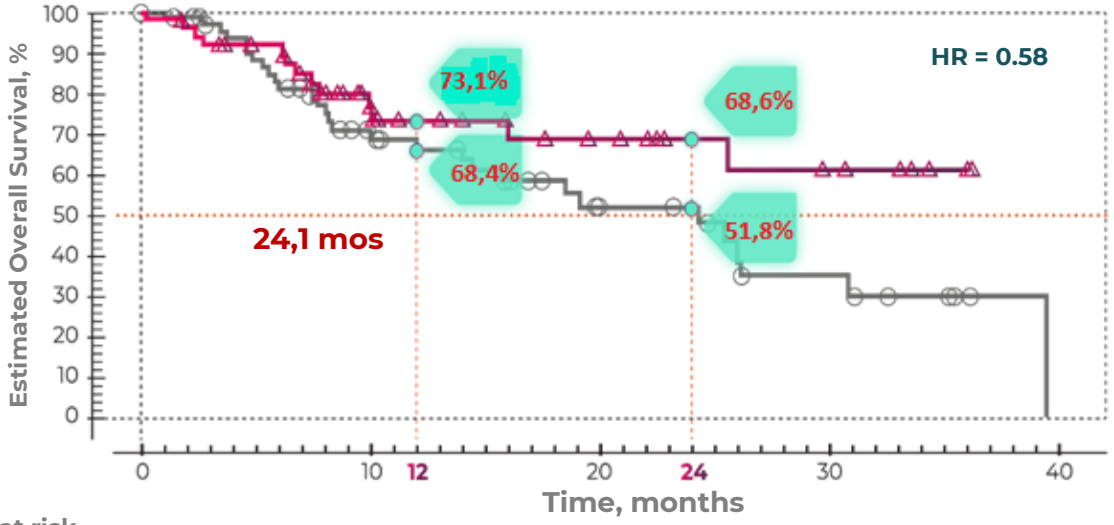
Subgroups by PD-L1 expression level (TPS%)

RECIST 1.1

PD-L1 expression level TPS ≥ 50%

No. at risk					
Prolgo + CT	38	26	15	8	0
Placebo + CT	27	9	2	1	0

PD-L1 expression level TPS ≥ 1% - 49%



No. at risk					
Prolgo + CT	48	24	15	8	0
Placebo + CT	62	30	15	7	0

OS in subgroups by PD-L1 expression level: The PD-L1 expression level is not a predictor of the Prolgolimab + CT efficacy. At the time of data analysis, the mOS had not been reached (Prolgo + CT arm)[9]

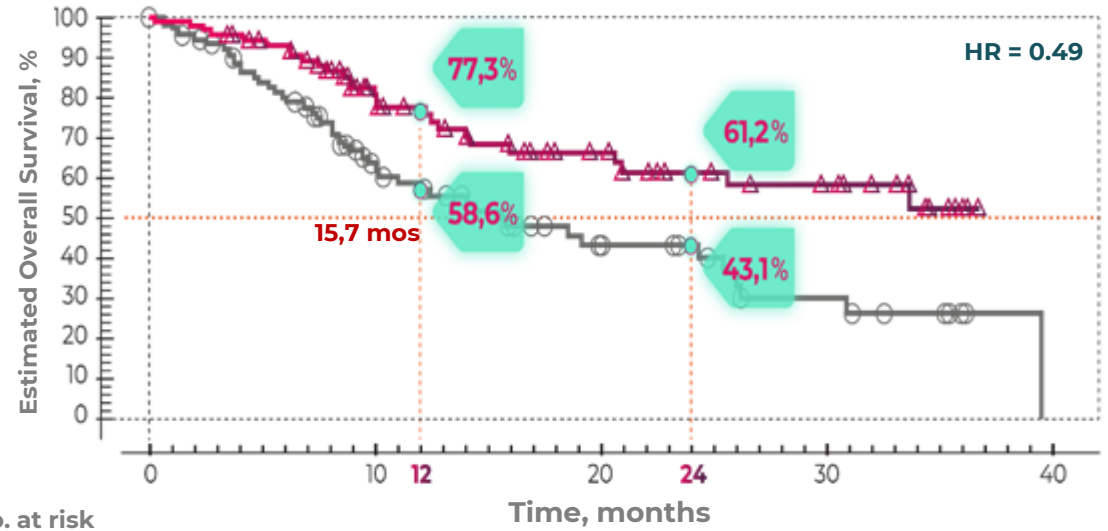
mOS, median overall survival; CI, confidence interval; HR, hazard ratio. Stratified analysis was performed for stratification variables used in dynamic randomization based on IWRS data: use of a platinum drug (carboplatin or cisplatin), PD-L1 expression (TPS <1% or >=1%), , prolgo – prolgolimab, mo – month, CT – chemotherapy,

Results of a Phase III Trial of Prolgolimab with Chemotherapy as First-Line Therapy for Patients with Advanced Non-Squamous NSCLC: DOMAJOR. Laktionov, K. et al. Journal of Thoracic Oncology, Volume 19, Issue 10, S34 - S35

Subgroups by PD-L1 expression level (TPS%)

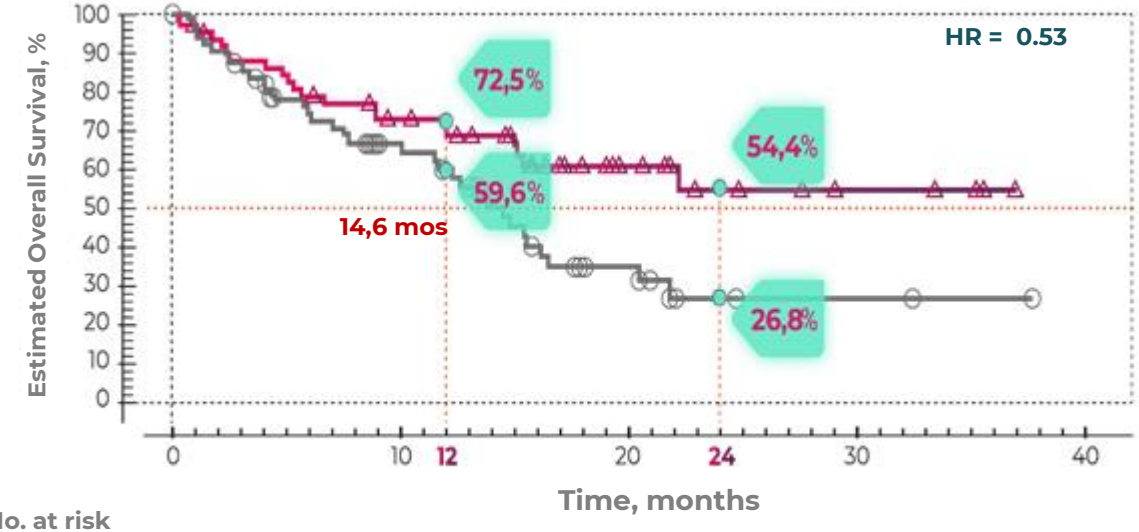
HARMONY DOMAJOR

PD-L1 expression level TPS ≥ 1%



No. at risk					
Prolgo + CT	86	50	28	15	0
Placebo + CT	89	39	17	8	0

PD-L1 expression level TPS < 1%



No. at risk					
Prolgo + CT	57	36	13	5	0
Placebo + CT	60	30	10	2	0

OS in subgroups by PD-L1 expression level: The PD-L1 expression level is not a predictor of the prolgolimab + CT efficacy. At the time of data analysis, the mOS had not been reached (Prolgo + CT arm)[9]

mOS, median overall survival; CI, confidence interval; HR, hazard ratio. Stratified analysis was performed for stratification variables used in dynamic randomization based on IWRS data: use of a platinum drug (carboplatin or cisplatin), PD-L1 expression (TPS <1% or >=1%), , prolgo – prolgolimab, mo – month, CT – chemotherapy,

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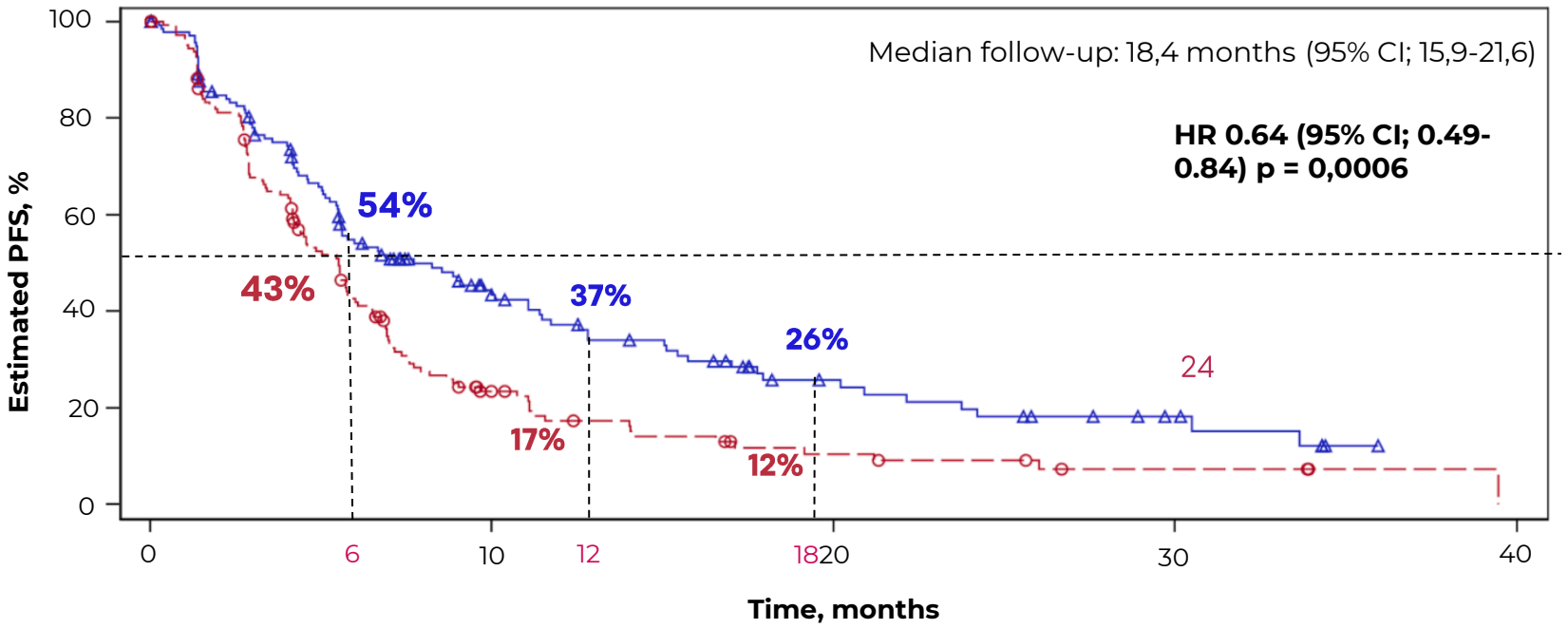
Progression Free Survival
(RECIST 1.1 assessed by BICR)



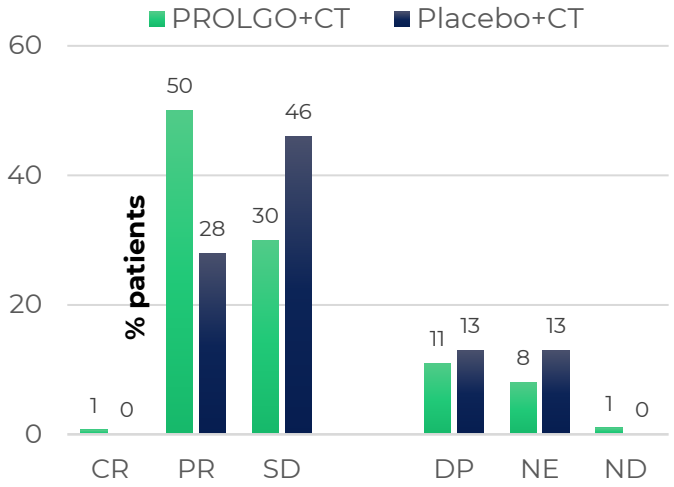
Parameter	PROLGO+CT n = 143	Placebo+CT n = 149
mPFS (mos) [95% CI]	**7,7** (5,6; 11)	5,5 (4,170; 6,510)
Estimated PFS, 6 mos (%)	**54**	43
Estimated PFS, 12 mos (%)	**37,2**	17
Estimated PFS, 18 mos (%)	**25,7**	11,7

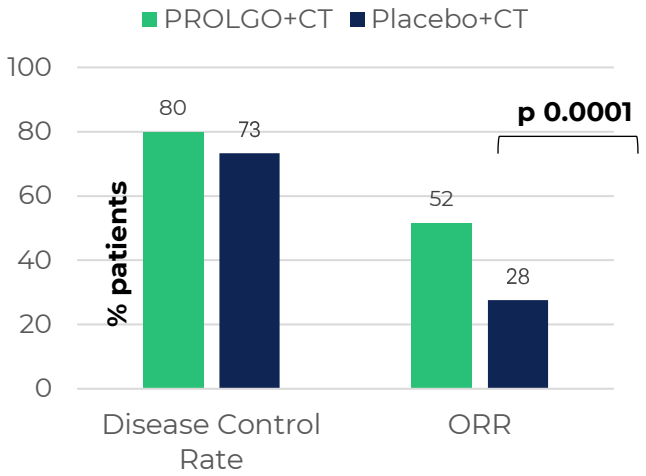
	PROLGO+ CT	PLACEBO + CT	HR
mPFS, mos (95%CI)			
TPS≥1%	9.1	5.6	0.58
• ≥1-49%	10.0	5.8	0.65
• ≥50%	8.9	5.5	0.35
TPS<1%	5.6	4.4	0.73

PD-L1-negative patients progress faster, but the expression level does not affect overall survival

Results of a Phase III Trial of Prolgolimab with Chemotherapy as First-Line Therapy for Patients with Advanced Non-Squamous NSCLC: DOMAJOR. Laktionov, K. et al. Journal of Thoracic Oncology, Volume 19, Issue 10, S34 - S35

Greater disease control was achieved in the Prolgolimab + CT group





	PROLGOLIMAB + CT	PLACEBO + CT
Best overall response (95% CI)		
CR (%)	0.7	0
PR (%)	49.7	27.5
SD (%)	30.1	46.3
Non-CR / Non-PD (%)	0	0.7
PD (%)	11.2	12.8
NE (%)	7.7	12.8
ND (%)	0.7	0
DCR (%)	80.4	73.8
mDoR, months (95% CI)	12.5 (8.4; 15.0)	5.6 (3.5; 8.6)
mTTR, months (95% CI)	2.3 (1.6; 2.8)	2.8 (1.6; 2.9)

- The ORR in the PROLGOLIMAB + CT arm was 51,4% vs 27,5% in the CT arm
- Response duration was also longer in PROLGOLIMAB + CT arm

CR-complete response, PR – partial response, SD - stable disease, DP – progression disease, Disease Control Rate (CR+PR+SD), ORR – overall response rate (CR+PR), mDoR – median Duration of Response, mTTR – median Time To Response

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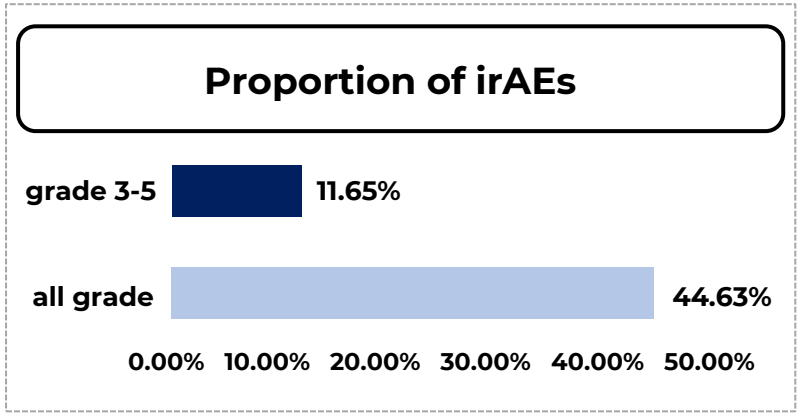
Prolgolimab Safety Analysis

Proportion of patients	PROLGO + CT n = 143, (%)	PLACEBO + CT n = 149, (%)
AE (all grades)	**139** (97,2)	**132** (89,2)
AE (grades 3-4)	**81** (56,6)	**55** (37,2)
TRAE (all grades)	**92** (64,3)	**74** (50,0)
TRAE(grades 3-4)	**29** (20,3)	**12** (8,1)
irAE (all grades)	**49** (34,3)	**22** (14,9)
irAE (grades 3-4)	**12** (8,4)	**4** (2,7)
Treatment discontinuation due to AE	**14** (9,8)	**12** (8,1)
Serious TRAE	**12** (8,4)	**4** (2,7)
AE (grade 5)	**12** (8,4)	**16** (10,8)
TRAE (grade 5)	**1** (0.7)	**0**

The assessment was carried out using the CTCAE v.5.0



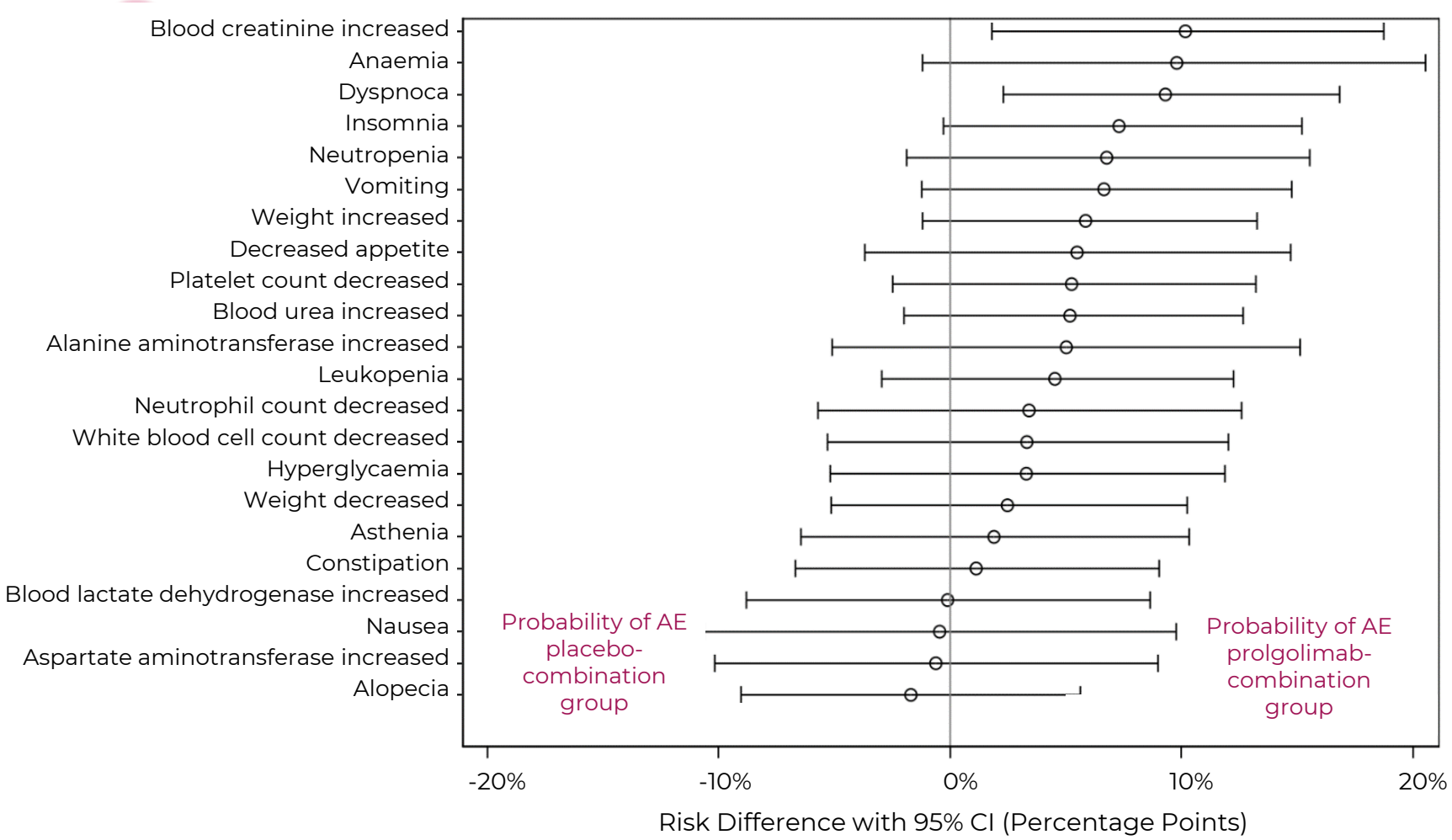
Zhou, Yixin, et al. *European Journal of Cancer* (2024): 114203.

The proportion of AEs 3-4 grade was higher in the PROLGOLIMAB + CT group due to the additional immune component of the therapy. This did not increase the incidence of treatment-related discontinuation.

AE, adverse event due to any cause; TRAE, treatment-related adverse event; irAE, immune-related adverse event

Results of a Phase III Trial of Prolgolimab with Chemotherapy as First-Line Therapy for Patients with Advanced Non-Squamous NSCLC: DOMAJOR. Laktionov, K. et al. Journal of Thoracic Oncology, Volume 19, Issue 10, S34 - S35

Forest plot for the most frequent AE (reported in ≥ 10% of patients).
Safety Analysis Set



The only AEs were more frequent in the prolgolimab-containing group:

- blood creatinine increased
- dyspnoea

The reported AEs were typical for IO class of drug

Results of a Phase III Trial of Prolgolimab with Chemotherapy as First-Line Therapy for Patients with Advanced Non-Squamous NSCLC: DOMAJOR. Laktionov, K. et al. Journal of Thoracic Oncology, Volume 19, Issue 10, S34 - S35

RESULTS OF DOMAJOR TRIAL PRESENTED ON WCLC 2024

2024 World Conference on Lung Cancer | SEPTEMBER 7-10, 2024 SAN DIEGO, CA USA | #WCLC24 wclc2024.iaslc.org

Results of a phase III trial of prolgolimab with chemotherapy as first-line therapy for patients with advanced non-squamous NSCLC: DOMAJOR

D. Stroyakovskiy[1], K. Laktionov[2], A. Smolin[3], V. Moiseenko[4], M. Dvorkin[5], T. Andabekov[6], Y. Cheng[7], B. Liu[8], V. Kozlov[9], S. Odintsova[10], S. Dvoretsky[11], A. Mochalova[12], M. Urda[13], T. Yi[14], X. Li[15], U. László[16], V. Müller[17], K. Bogos[18], N. Fadeeva[19], G. Musaev[20], Q. Liu[21], D. Kirtbaya[22], J. Shi[23], O. Gladkov[24], M. Narimanov[25], T. Semiglazova[26], A. Khasanova[27], J. Chovanec[28], I. Andrašina[29], A. Szabová[30], O. Rosinská[31], D. Sudekova[32], P-S. Zsolt[33], F. Ran[34], M. Sun[35], O. Jiang[36], R. Chen[37], E. Zhao[38], C. Liu[39], W. Tan[40], A. Pirmagomedov[41], E. Poddubskaya[42], N. Kislov[43], I. Shumskaya[44], A. Zinkina-Orikhan[45], Y. Linkova[45], D. Liaptseva[45], A. Siliutina[45], I. Sorokina[45-46], F. Kryukov[45]

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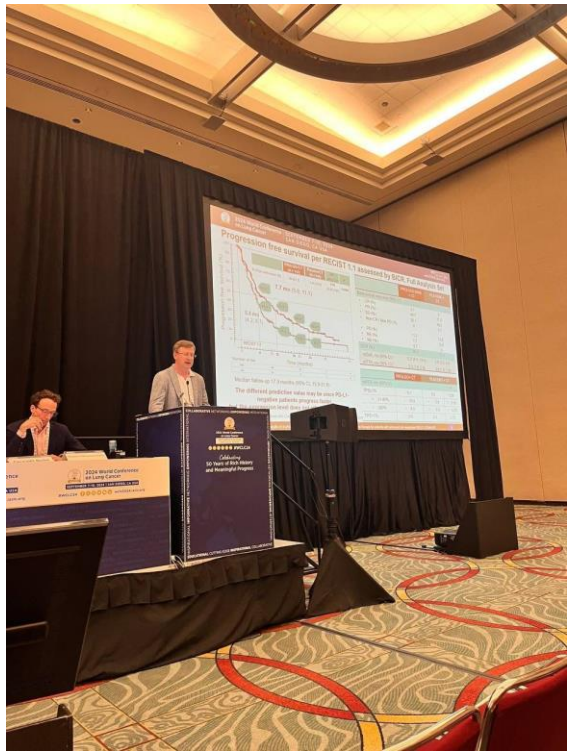
OA11 SHIFTING THE BAR IN THE FRONT LINE IMMUNOTHERAPY SETTING, MONDAY, SEPTEMBER 9, 2024 - 14:00 - 15:15 · Volume 19, Issue 10, Supplement , S34-S35, October 2024

OA11.05 Results of a Phase III Trial of Prolgolimab with Chemotherapy as First-Line Therapy for Patients with Advanced Non-Squamous NSCLC: DOMAJOR

K. Laktionov [1] · A. Smolin [2] · D. Stroyakovsky [3] · V. Moiseenko [4] · M. Dvorkin [5] · T. Andabekov [6] · Y. Cheng [7] · B. Liu [8] · V. Kozlov [9] · S. Odintsova [10] · S. Dvoretsky [11] · A. Mochalova [12] · M. Urda [13] · T. Yi [14] · X. Li [15] · U. László [16] · V. Müller [17] · K. Bogos [18] · N. Fadeeva [19] · G. Musaev [20] · Q. Liu [21] · D. Kirtbaya [22] · J. Shi [23] · O. Gladkov [24] · M. Narimanov [25] · T. Semiglazova [26] · A. Khasanova [27] · J. Chovanec [28] · I. Andrašina [29] · A. Szabová [30] · O. Rosinská [31] · D. Sudekova [32] · P.-S. Zsolt [33] · F. Ran [34] · M. Sun [35] · O. Jiang [36] · R. Chen [37] · E. Zhao [38] · C. Liu [39] · W. Tan [40] · A. Pirmagomedov [41] · E. Poddubskaya [42] · N. Kislov [43] · I. Shumskaya [44] · A. Zinkina-Orikhan [45] · Y. Linkova [45] · D. Liaptseva [45] · A. Siljutina [45] · I. Sorokina [46] · F. Kryukov [45] Show less



- DOMAJOR clinical trial results were presented at the World Conference on Lung Cancer (WCLC) in 2024 in the scientific part
- Abstract of oral session from WCLC 2024 is published in Journal of Thoracic Oncology
- Results of DOMAJOR trial are accepted for publication in European Journal of Cancer, published paper is expected Q1 2025
- Prolgolimab showed high efficacy both in PD-L1-positive and PD-L1-negative populations and favorable safety profile

ELSEVIER

European Journal of Cancer

Volume 217, 25 February 2025, 115255

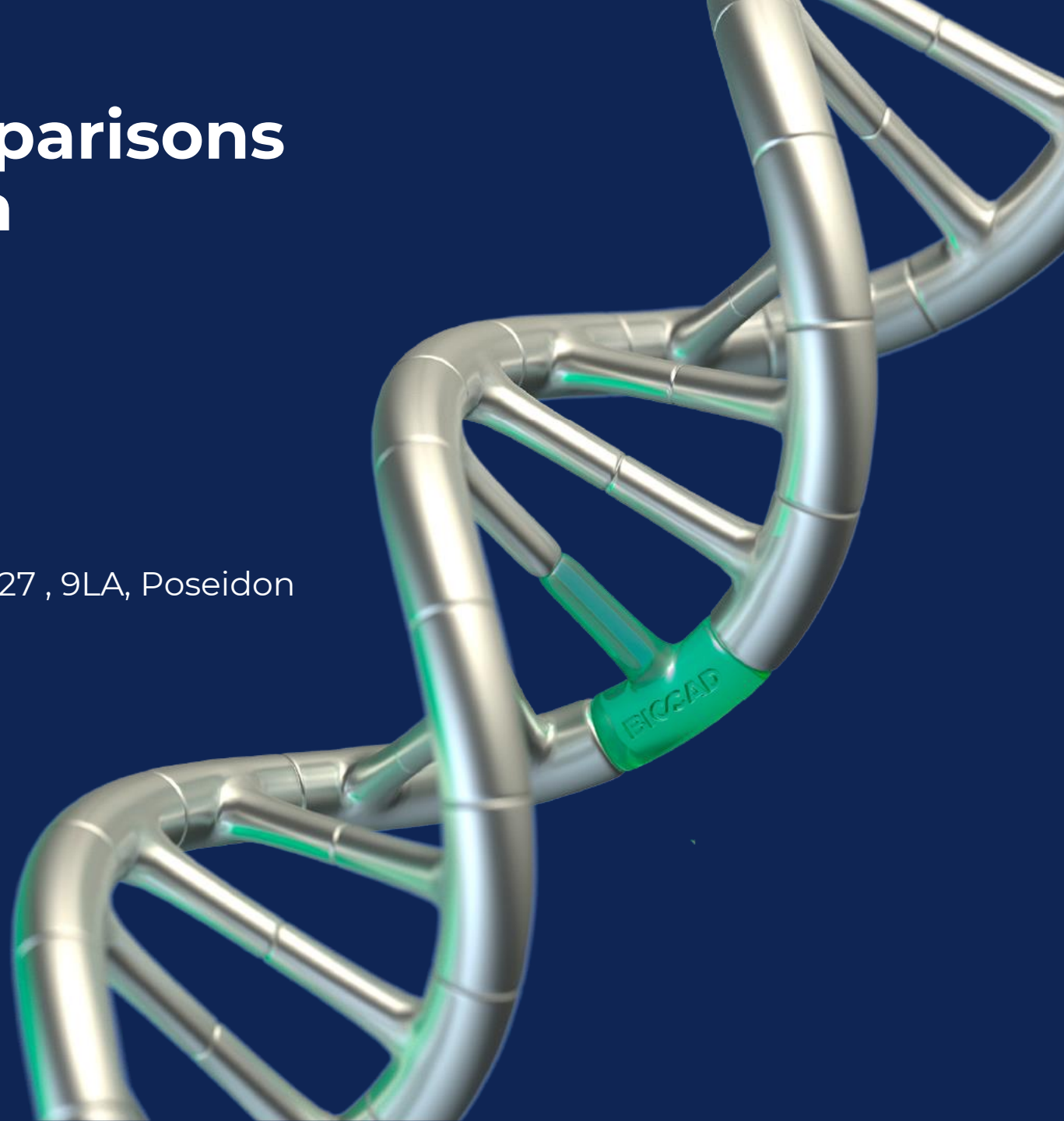
Original Research

Prolgolimab with chemotherapy as first-line treatment for advanced non-squamous non-small-cell lung cancer

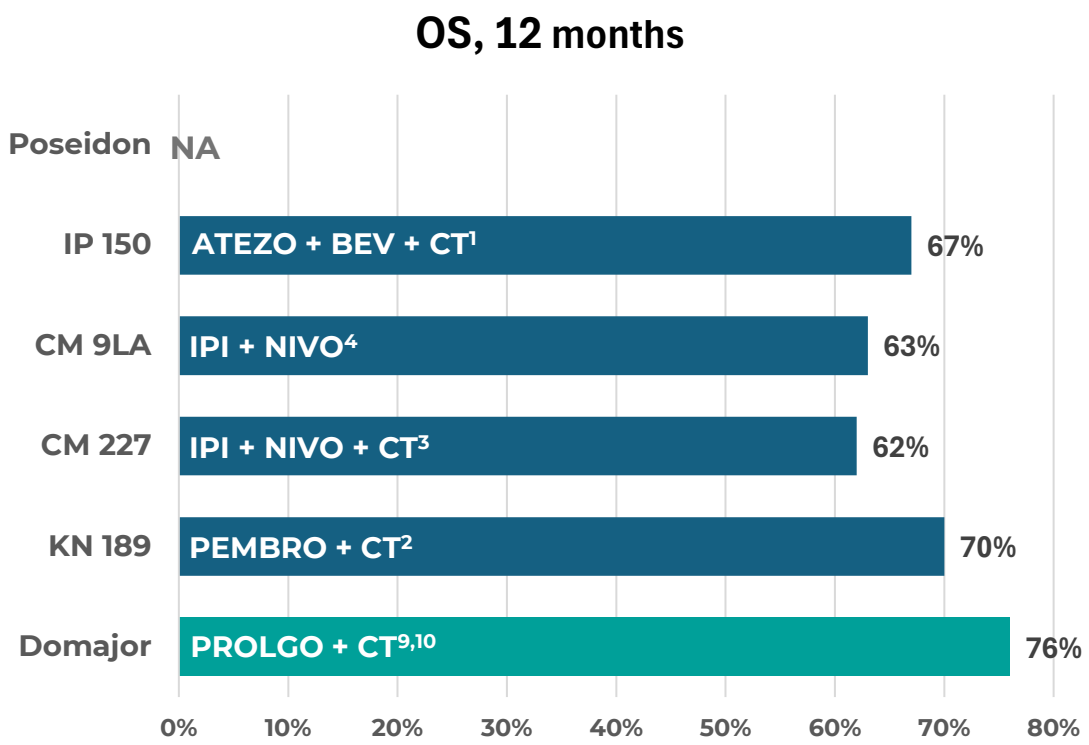
K. Laktionov [a], A. Smolin [b], D. Stroyakovskiy [c], V. Moiseenko [d], M. Dvorkin [e], T. Andabekov [f], Y. Cheng [g], B. Liu [h], V. Kozlov [i], S. Odintsova [j], S. Dvoretsky [k], A. Mochalova [l], M. Urda [m], T. Yi [n], X. Li [o], U. László [p], V. Müller [q], K. Bogos [r], N. Fadeeva [s], G. Musaev [t]...F. Kryukov [as]

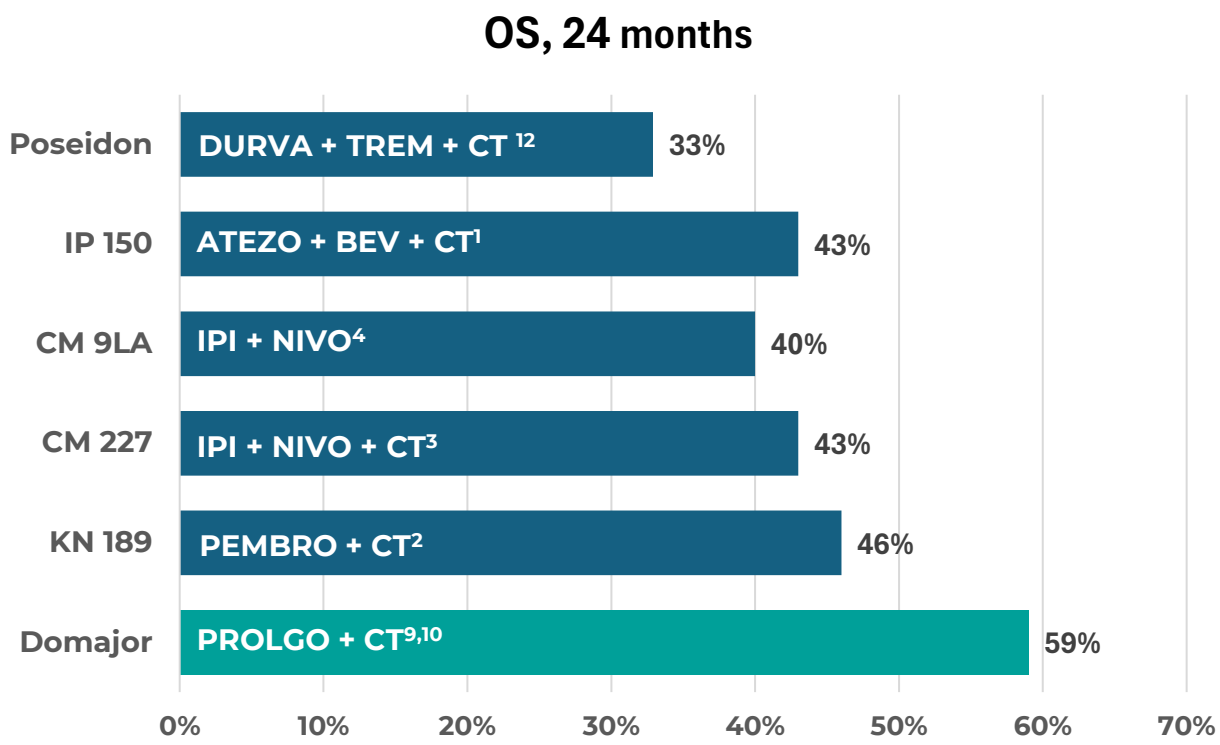
DOMAJOR: indirect comparisons clinical trials results data

DOMAJOR, Keynote 189 , Impower 150, Checkmate 227 , 9LA, Poseidon



Overall survival (OS) in the PROLGOLIMAB group compared with other CHEMO + IMMUNOTHERAPY results



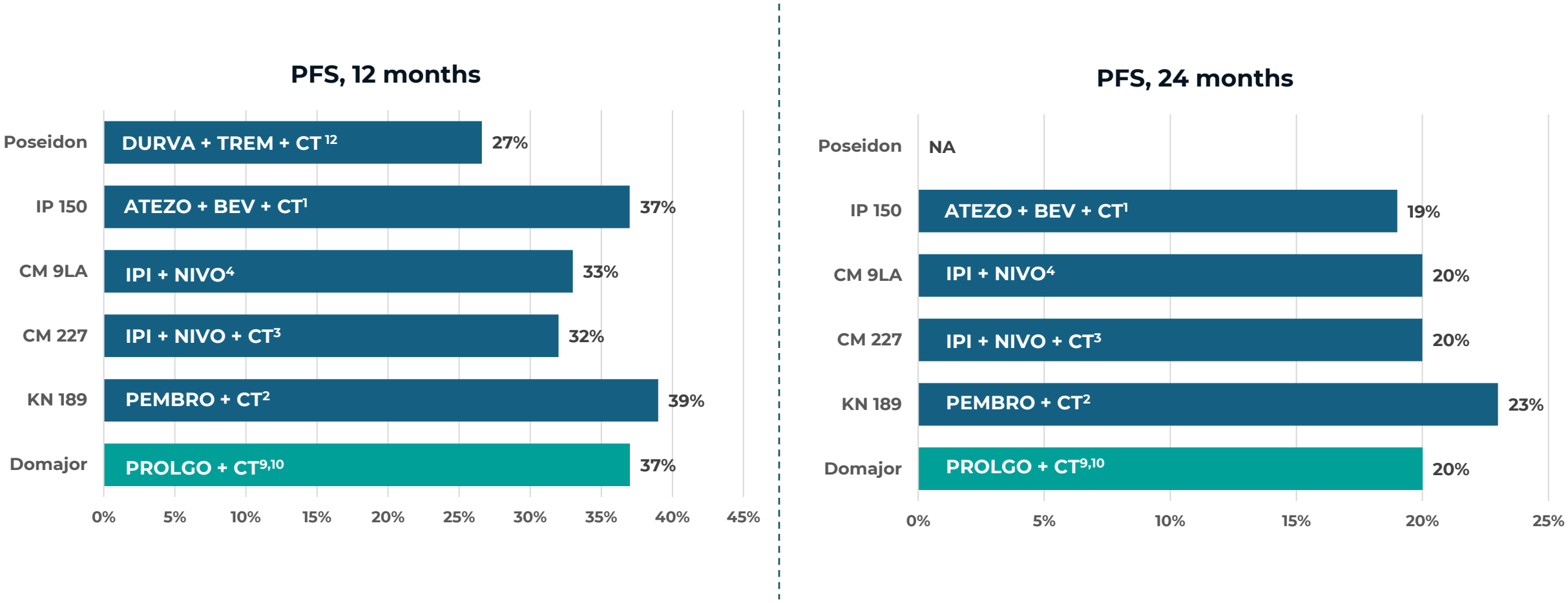


Indirect comparison

mOS, median overall survival; CI, confidence interval; HR, hazard ratio. Stratified analysis was performed for stratification variables used in dynamic randomization based on IWRS data: use of a platinum drug (carboplatin or cisplatin), PD-L1 expression (TPS <1% or >=1%), , prolgo – prolgolimab, mo – month, CT – chemotherapy, CT – chemotherapy, Pembro – pembrolizumab, Pt – platinum, Atezo – atezolizumab, Bev – bevacizumab, Nivo – nivolumab, Ipi – ipilimumab, Durva – durvalumab, Treme – tremelimumab, Prolgo - prolgolimab

Overall survival (PFS) in the PROLGOLIMAB group compared with other CHEMO + IMMUNOTHERAPY results

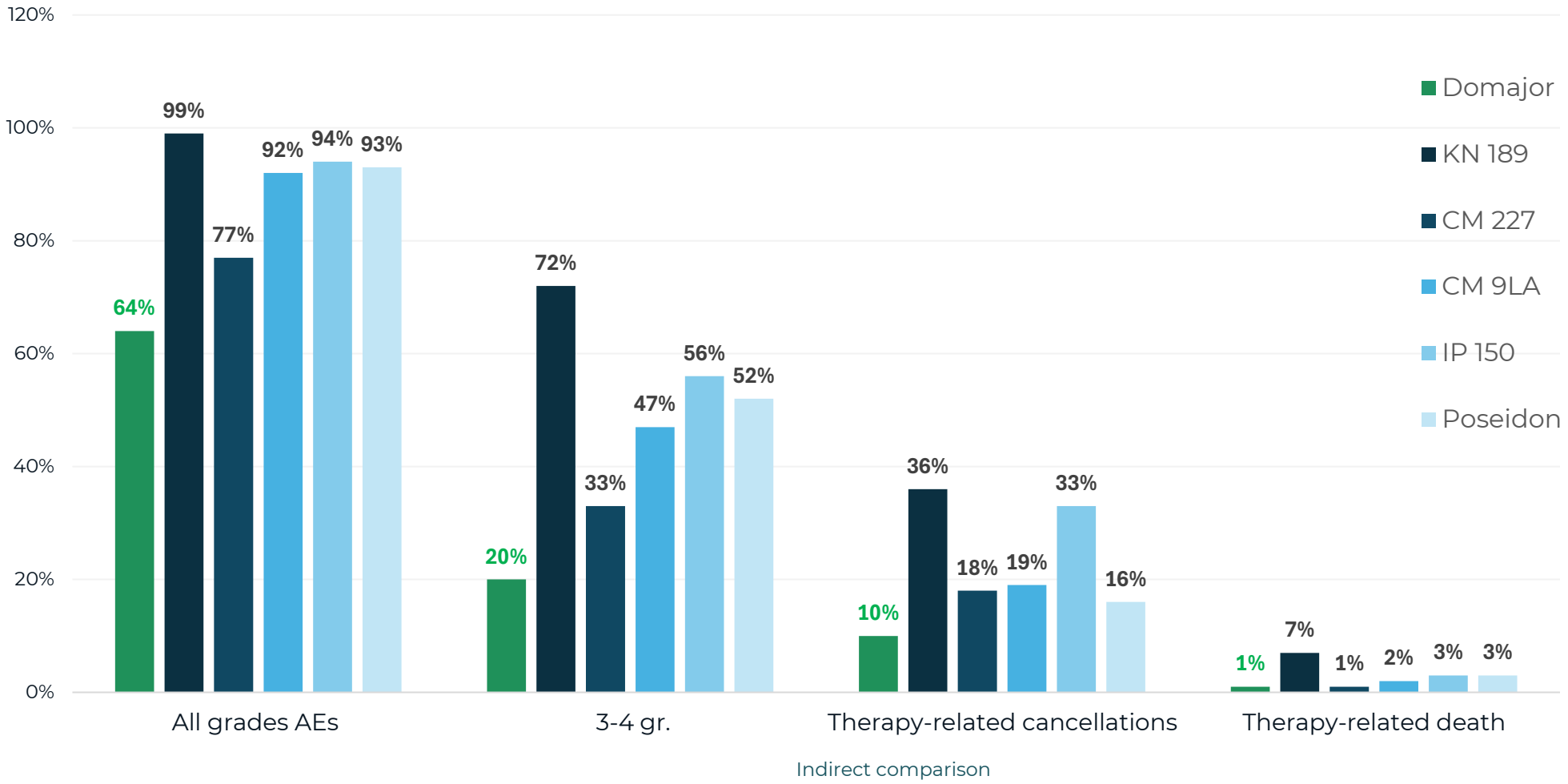
HARMONY DOMAJOR



Indirect comparison

PFS, progression free survival; CT – chemotherapy, IP – IMPowre, CM – Checkmate, KN – Keynote, NA – not availible

PROLGOLIMAB shows the most favourable profile among other CHEMO + IMMUNOTHERAPY regimens



Indirect comparison

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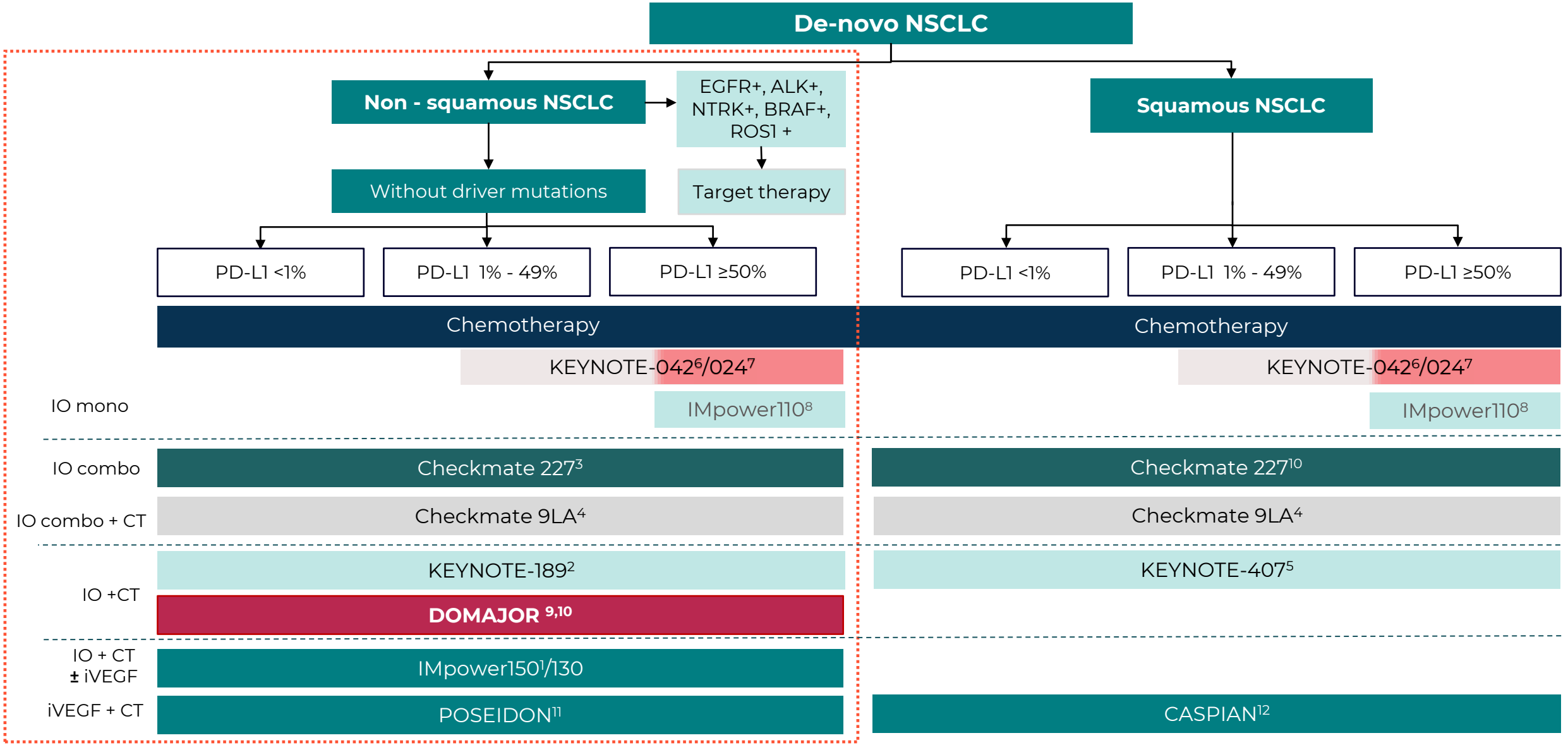
General algorithm for the NSCLC 1st line therapy

Prolgolimab + CT - 1st -line treatment of NSCLC regardless of the level of PD-L1 expression in patients with advanced disease



DOMAJOR: conclusions

- The superiority of prolgolimab 3 mg/kg Q3W in combination chemotherapy vs placebo in combination with chemotherapy was demonstrated.
- Prolgolimab + CT combination in 1st line NSCLC has significant advantage vs CT in terms of OS, PFS and response rates.
- Prolgolimab + CT regimens in 1st line NSCLC are effective in patients regardless of tumour PD-L1 expression level
- The safety profile of prolgolimab + CT in the study was favourable: the rate of discontinuation due to HP was less than 10% and did not differ from the rate in patients receiving CT alone
- Prolgolimab + CT option had comparable efficacy and a more favourable safety profile in an indirect comparison with available combination regimens in 1st line NSCLC

CT – chemotherapy

NSCLC patient profile (example)

Prolgolimab

- Adenocarcinoma
- 1st line of therapy
- Without activating mutations (EGFR, ALK)
- Regardless of PD-L1 expression
- Scheduled chemotherapy: **pemetrexed 500 mg/m^2 + carboplatin/cisplatin**
- Patient (ECOG-1) for whom it is particularly important to reduce the toxicity of combination therapy

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2. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Non-squamous Non-Small-Cell Lung Cancer. Shirish Gadgeel, J Clin Oncol . 2020 May 10;38(14):1505-1517. doi: 10.1200/JCO.19.03136.

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4. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial Luis Paz-Ares. Lancet Oncol . 2021 Feb;22(2):198-211. doi: 10.1016/S1470-2045(20)30641-0.

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6. Associations of tissue tumor mutational burden and mutational status with clinical outcomes in KEYNOTE-042: pembrolizumab versus chemotherapy for advanced PD-L1-positive NSCLC T S K Mok. Ann Oncol . 2023 Apr;34(4):377-388. doi: 10.1016/j.annonc.2023.01.011

7. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater Martin Reck J Clin Oncol . 2019 Mar 1;37(7):537-546. doi: 10.1200/JCO.18.00149.

8. Updated Overall Survival Analysis From IMpower110: Atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1-Selected NSCLC Jacek Jassem . J Thorac Oncol . 2021 Nov;16(11):1872-1882. doi: 10.1016/j.jtho.2021.06.019.

9. Prolgolimab with chemotherapy as first-line treatment for advanced non-squamous non-small-cell lung cancer. K Laktionov, Eur J Cancer . 2025 Feb 25:217:115255. doi: 10.1016/j.ejca.2025.115255.

10 . MC-CN-12392

11. Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial Jonathan W Goldman, MD. The Lancet Volume 22, Issue 1p51-65January 2021

12. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study, Melissa L. Johnson, MD https://orcid.org/0000-0001-9874-1314

BIOCAD

PROLGOLIMAB

Unresectable and metastatic melanoma

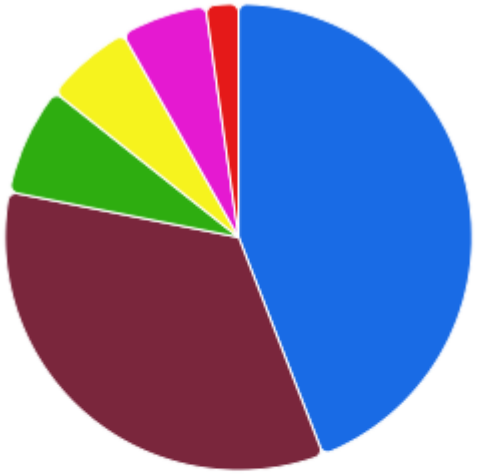
Global Medical Affairs Lead Onco1

BIOCAD

Melanoma represents a critical public health challenge, driven by its rising global incidence and mortality.

World data

Incidence



Continent	Cases	Percent
Europe	146 321	44.1%
Northern America	112 807	34.0%
Asia	25 003	7.5%
Latin America and the Caribbean	20 291	6.1%
Oceania	19 823	6.0%
Africa	7 477	2.3%

Incidence, both sexes

Mortality

Continent	Deaths	Percent
Europe	26 180	44.6%
Asia	13 147	22.4%
Northern America	8 737	14.9%
Latin America and the Caribbean	5 842	10.0%
Africa	2 859	4.9%
Oceania	1 902	3.2%

Mortality, both sexes

Incidence

Rank	Cases	ASR (World)
17	331 722	3.2

Mortality

Rank	Deaths	ASR (World)
22	58 667	0.53

Cancer Today

BICCAD

Current treatment paradigm | Melanoma skin cancer

METASTIC OR UNRESECTABLE MELANOMA

	BRAF+		BRAF -	KIT-
	Pts not eligible for IO*	Pts eligible for both BRAF/MEK inhibitors AND IO		
1st line		**IMMUNONCOLOGY:** Prolgolimab ± nurulimab/Nivolumab ± {ipilimumab/relatlimab}/Pembrolizumab		**Imatinib**
	iBRAF/iMEK: vemurafenib ± cobimetinib ± atezolizumab/ dabrafenib ± trametinib ± pembrolizumab** encorafenib + binimetinib			
	CHEMOTHERAPY			
2nd line	**IMMUNOTHERAPY IF WERE NOT USED BEFORE:** nivolumab + ipilimumab/prolgolimab/Pembrolizumab/Nivolumab/Ipilimumab		**IMMUNOTHERAPY:** ipilimumab ± nivolumab IF WEREN`T USED BEFORE	
		iBRAF/iMEK OR IPILIMUMAB IF WERE NOT USED BEFORE: vemurafenib + cobimetinib/ dabrafenib + trametinib encorafenib + binimetinib	**CHEMOTHERAPY/Pembrolizumab + Lenvatinib****	
Subsequent lines	**CHEMOTHERAPY/Pembrolizumab + Lenvatinib****			

Area of competition between BRAF/MEK inhibitors and Immunotherapy

This diagram is for demonstration purposes and does not illustrate all therapeutic approaches. Prepared on the basis of NCCN

BICCAD

*because of visceral disease or high tumor burden;
**off-label: dabrafenib+trametinib±pembrolizumab combination did not show statistical significance in terms of efficacy; IO – immunoncology therapy

PROLGOLIMAB CLINICAL DEVELOPMENT PROGRAM

PROLGOLIMAB CLINICAL DEVELOPMENT PROGRAM

HARMONY

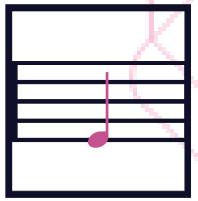
HARMONY — a compre**H**ensive progr**A**m of clinical t**R**ials on the efficacy, safety, phar**M**acokinetics and immun**O**genicity of prolgolimab in o**N**colog**Y**

MELANOMA

NEOMIMAJOR

Ph III
Advanced Melanoma
Neoadjuvant treatment
Prolgolimab monotherapy
RUSSIA **BELARUS** **KAZAKHSTAN**
Status: **active, ongoing**

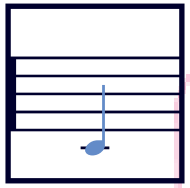
MELANOMA[13]



MIRACULUM

Ph II
Advanced Melanoma
Prolgolimab monotherapy
RUSSIA
Status: **completed**

MELANOMA



OCTAVA

Ph III
Advanced Melanoma
Prolgolimab vs Prolgolimab+Nurulimab
RUSSIA **BELARUS** **INDIA**
Status: **completed**

MIRACULUM

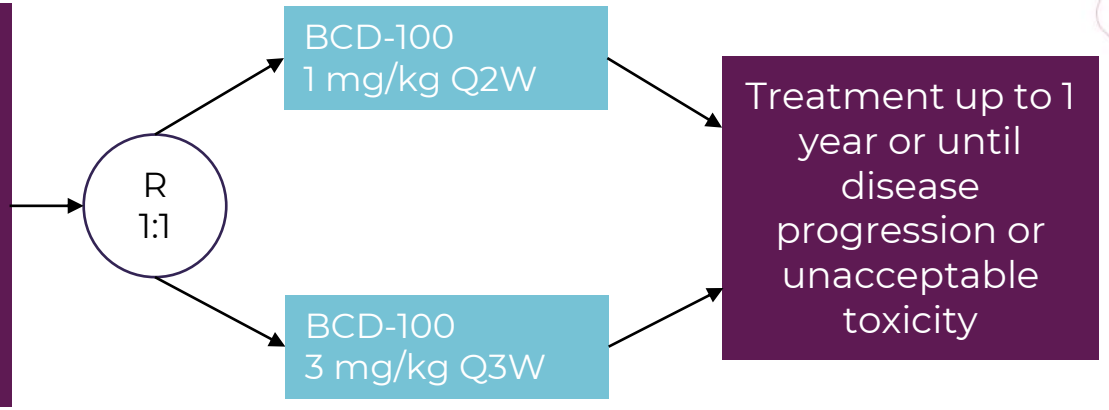
MIRACULUM

Phase II study of prolgolimab (BCD-100) in patients with metastatic or unresectable melanoma

MIRACULUM TRIAL DESIGN

Patients with unresectable or metastatic melanoma regardless of BRAF status

Previously untreated patients or patients treated without targeted agents (PD-1/PD-L1, CTLA-4, BRAF, MEK) who have progressed after or during prior therapy



Stratification factors:
- ECOG 0-1
- LDH (normal/above normal)
- Prior therapy (yes/no)

Primary Endpoints:
- ORR per irRECIST*

Secondary Endpoints:
- PFS, OS, DCR
- TTR, DoR
- Safety
- Pharmacokinetics
- Immunogenicity

***IrRECIST** - Immune-related Response Evaluation Criteria In Solid Tumors
mITT population = modified intent-to-treat population, patients who had received at least one dose of BCD-100 (prolgolimab), R – randomization

progression-free survival (PFS), overall survival (OS), disease control rate (DCR), time to response (TTR) and duration of response (DOR) Quality to be delivered every 2 weeks; Q3W - Quality to be delivered every 3 weeks.; PD – disease progression, ORR – overall response rate, LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group

Patient characteristics

The demographic and baseline disease characteristics of the patients were well balanced about prognostic factors and mutation status

	Prolgolimab 1 mg/kg, Q2W n = 63	Prolgolimab 3 mg/kg, Q3W n = 63
Age, years		
Mediana	57 (27-83)	57 (24-82)
Sex, n (%)		
Female	34 (54.0)	35 (55.6)
Male	29 (46.0)	28 (44.4)
Metastasis stage (A)CC, 7th edition, n %		
M1a	6 (9.5)	8 (12.7)
M1b	13 (20.6)	44 (12.7)
M1c	44 (69.8)	40 (74.6)
ECOG status, n (%)		
0	34 (54.0)	36 (57.1)
1	29 (46.0)	27 (42.9)
PD-L1 expression* , n %		
Positive	33 (52.4)	31 (49.2)
Negative	12 (19.1)	14 (22.2)
Unknown	18 (28,6)	18 (28,6)

	Prolgolimab 1 mg/kg, Q2W n = 63	Prolgolimab 3 mg/kg, Q3W n = 63
Non-cutaneous melanoma, n (%)		
Uveal	3 (4.8)	5 (7.9)
Mucosal	1 (1.6)	0 (0,0)
Baseline tumour size, median, mm	71.0	97.0
Lines of previous systemic therapy		
0	46 (73.0)	47 (74.6)
1	15 (23.8)	8 (12.7)
2	2 (3.2)	8 (12.7)
Brain metastases, n %		
Yes	63 (44.1)	47 (31.5)
Now	23 (16.1)	22 (14.8)
LDH		
Normal	42 (66.7)	41 (74.6)
Elevated	21 (33.3)	22 (34.9)
BRAF$^{V600E/K}$ status		
Wild-type	25 (39.7)	22 (34.9)
Mutant	21 (33.3)	14 (38.1)
Unknown	17 (27.0)	17 (27.0)

The population was enriched with patients with poor prognosis: ECOG = 1 (46 %), patients with brain metastases (44 %), patients with BRAF V600E/K mutation (33%)

LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death ligand 1; CPS = combined positive score.
* Defined as a CPS ≥1 as assessed by immunohistochemistry using BIOCAD in-house anti–PD-L1 antibody. M0 = no distant metastasis; M1a = metastasis to skin, subcutaneous tissues or distant lymph nodes; M1b = metastasis to lung; M1c = metastasis to all other visceral sites or distant metastases at any site associated with elevated serum concentrations of LDH. Quality to be delivered every 2 weeks; Q3W - Quality to be delivered every 3 weeks

MIRACULUM

Patient population in prolgolimab group in MIRACULUM trial is more unfavourable vs pembrolizumab and nivolumab studied patient populations

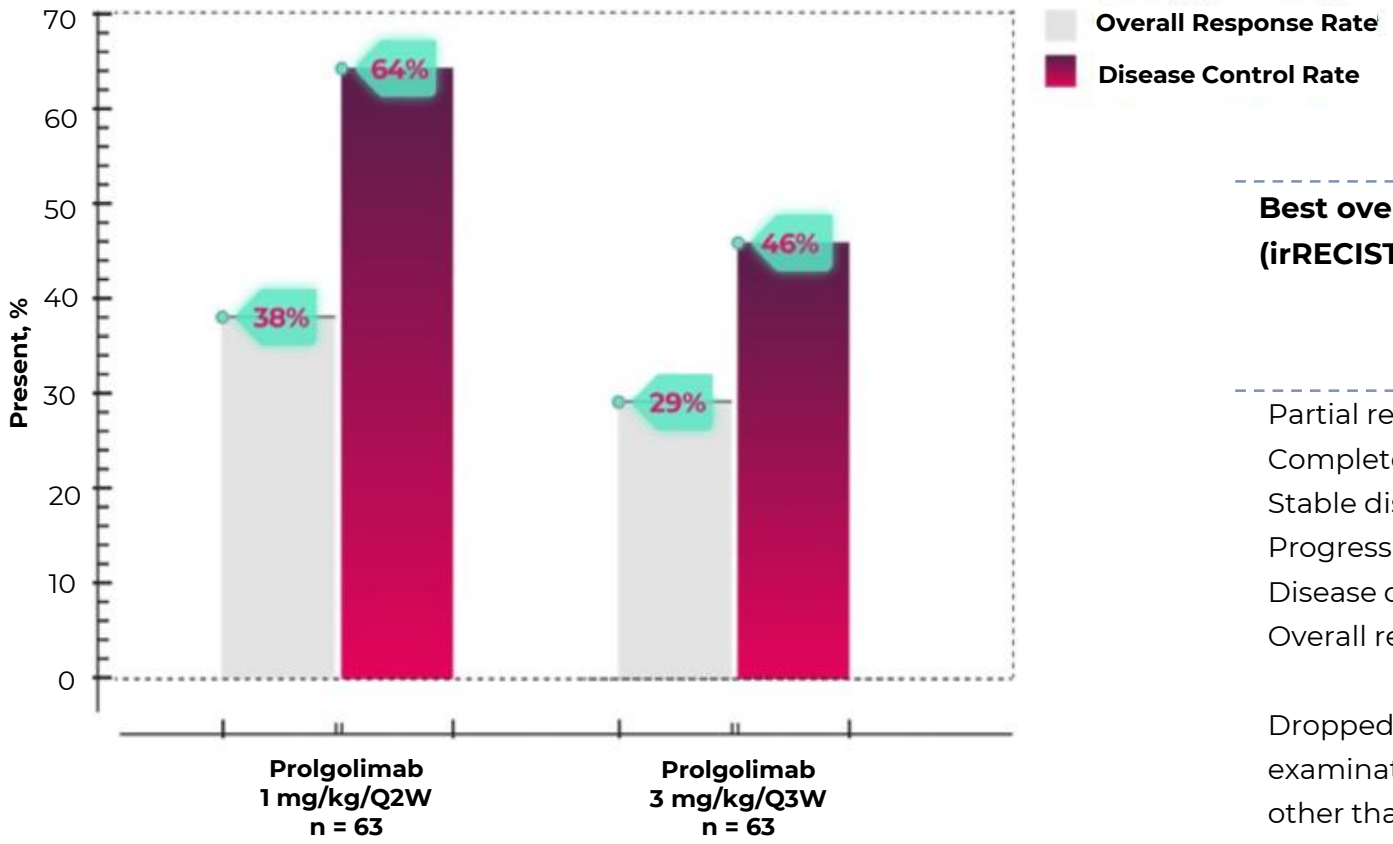
MIRACULUM study patient population reflects that in real clinical practice

	MIRACULUM[4,5] (prolgolimab)	KEYNOTE-006[1,3] (pembrolizumab Q2W)	CheckMate 067[2] (nivolumab)
ECOG > 0, %	44	30	25
LDH elevated, %	34	29	35
>1st and sequence therapy,%	8	0	0
Brain metastasis,%	21	9	2
Non-cutaneous melanoma,%	7	0	0
Baseline tumour size (median, mm)	84 41% > 100	58.5	54 25%> 97
≥3 metastasis site, %	52.3	NA	NA

LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death ligand 1; CPS = combined positive score.

Indirect comparision

The primary endpoint (ORR) reached in both groups. Prolgolimab showed anti-tumour activity in the study dose regimens[5]



Response to treatment

Best overall response (irRECIST)	Prolgolimab, 1 mg/kg, Q2W n = 63		Prolgolimab, 3 mg/kg, Q3W n = 63	
	n	%	n	%
Partial response	19	30.2	16	25.4
Complete response	5	7.9	2	3.2
Stable disease	16	25.4	11	17.5
Progressive disease (PD)	22	34.9	31	49.2
Disease control rate	40	63.5	29	46.0
Overall response rate (ORR)	24	38.1 I, 95% CI, [26.4-51.2]	18	28.6 95% CI,[18.2-41.5]
Dropped out before CT examination for reasons other than PD	1	1.6	3	4.8

CT - computed tomography; CI - confidence interval; irRECIST immune-related Response Evaluation Criteria in Solid Tumours; Q2W - every 2 weeks; Q3W - every 3 weeks

Based on this ORR data, dosing regimen 1 mg/kg was selected

Tumour response was assessed by a blinded independent central review as per irRECIST.

ORR – overall response rate, Q2W - Quality to be delivered every 2 weeks; Q3W - Quality to be delivered every 3 weeks

*IrRECIST - Immune-related Response Evaluation Criteria In Solid Tumors

MIRACULUM

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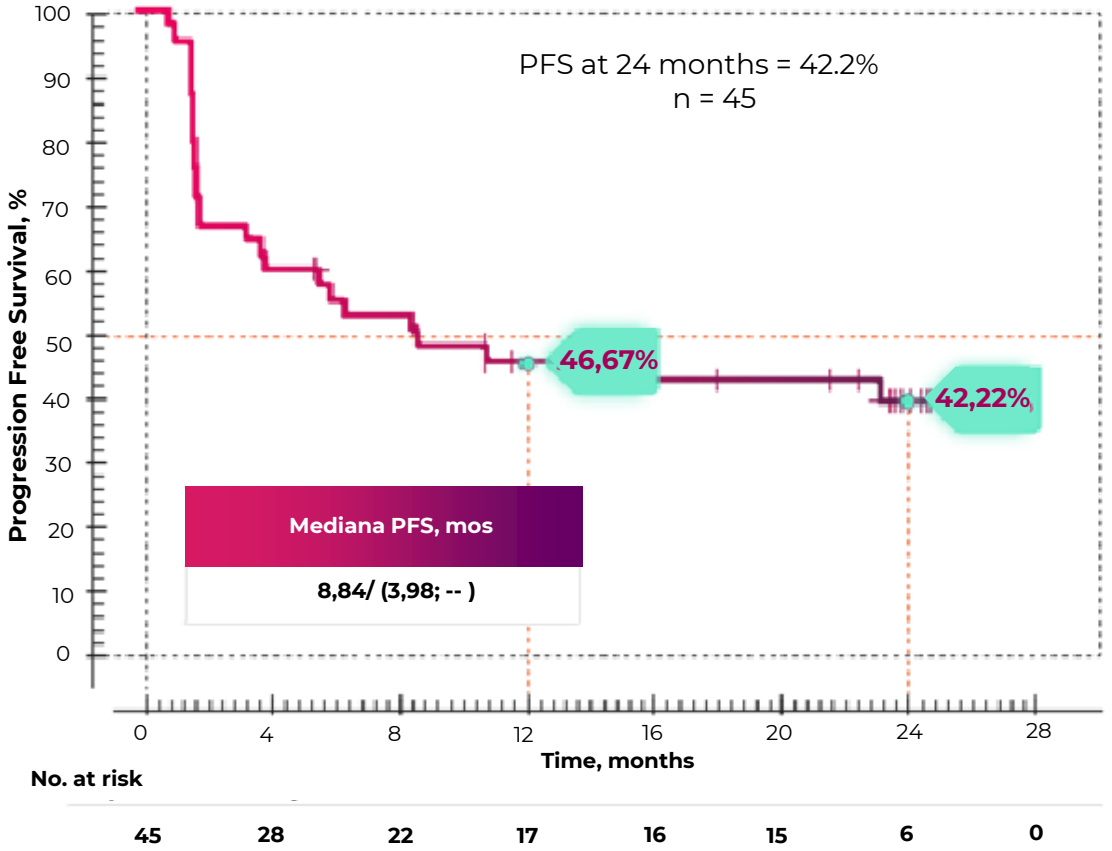
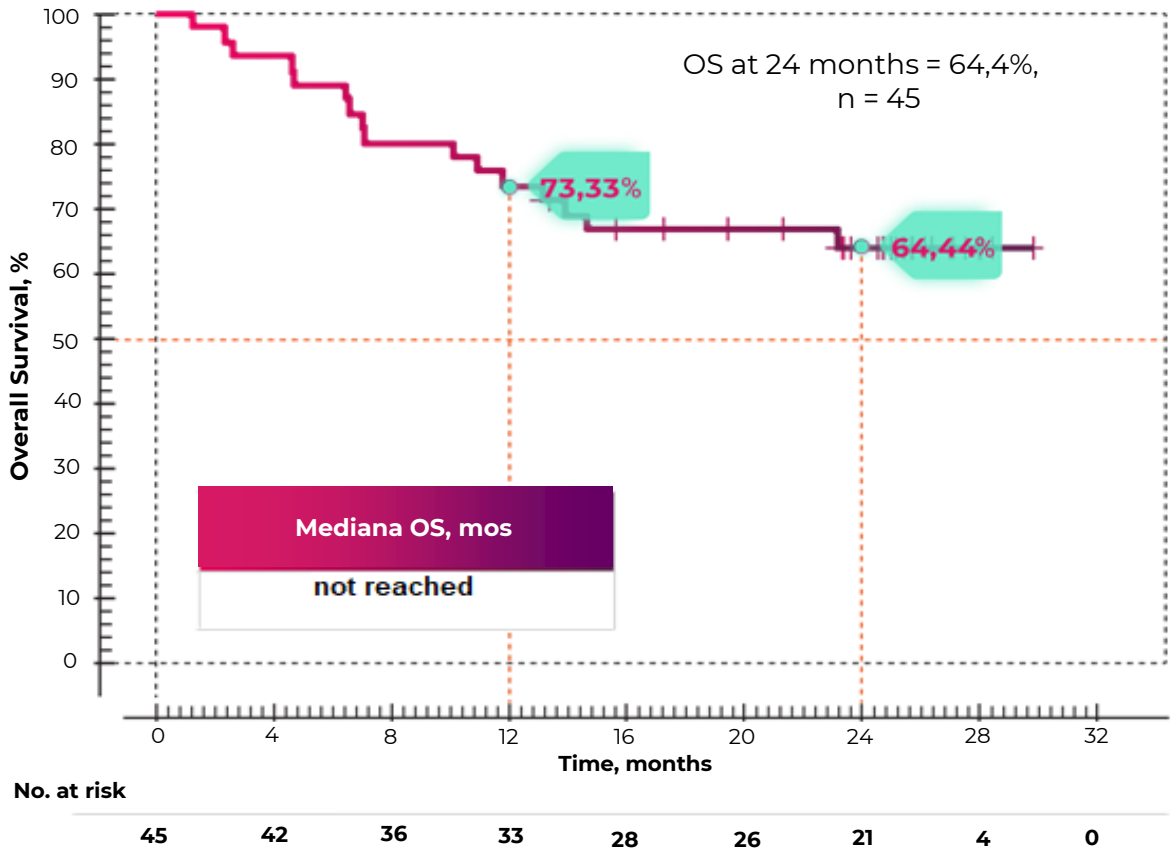
1st line Prolgolimab efficacy in cutaneous melanoma patients[5]

Progression Free Survival, n = 45



Overall Survival, n = 45



Subgroup analysis of efficacy Prolgo 1 mg/kg Q2W arm in treatment-naive patients with cutaneous melanoma

mo – month, mPFS – median progression free survival, mOS – median overall survival, quality to be delivered every 2 weeks – Q2W

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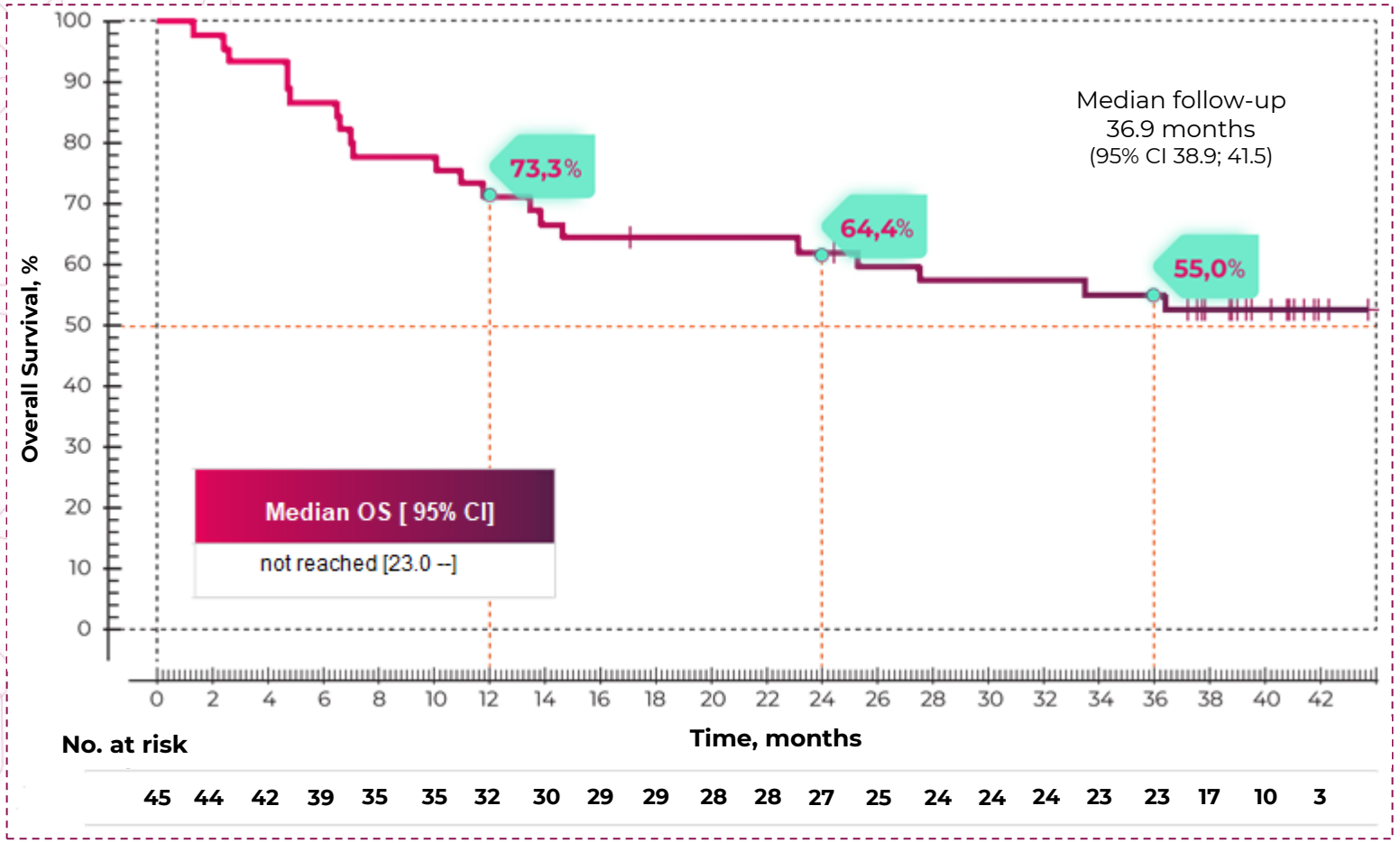
1st line Prolgolimab efficacy in cutaneous melanoma patients: results remains stable[7]



Median OS not reached by 36 months of follow-up

More than 50% of patients still alive after 3 years of prolgolimab therapy

Prolgolimab has shown high efficacy in a prognostically unfavorable patient population

Subgroup analysis of efficacy Prolgo 1 mg/kg Q2W arm in treatment-naive patients with cutaneous melanoma

OS – overall survival

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Efficacy of anti-PD-1 drugs in patients with metastatic skin melanoma in 1st line therapy

	MIRACULUM[5,7] (prolgolimab)	KEYNOTE-006[1,3] (pembrolizumab (Q2W)	CheckMate 067[2] (nivolumab)
Overall Response Rate	49%	37%	44%
24 months - Progression Free Survival	42%	31%	NA
24 months - Overall Survival	64%	55%	59%
36 months - Overall Survival	55%	51%	52%

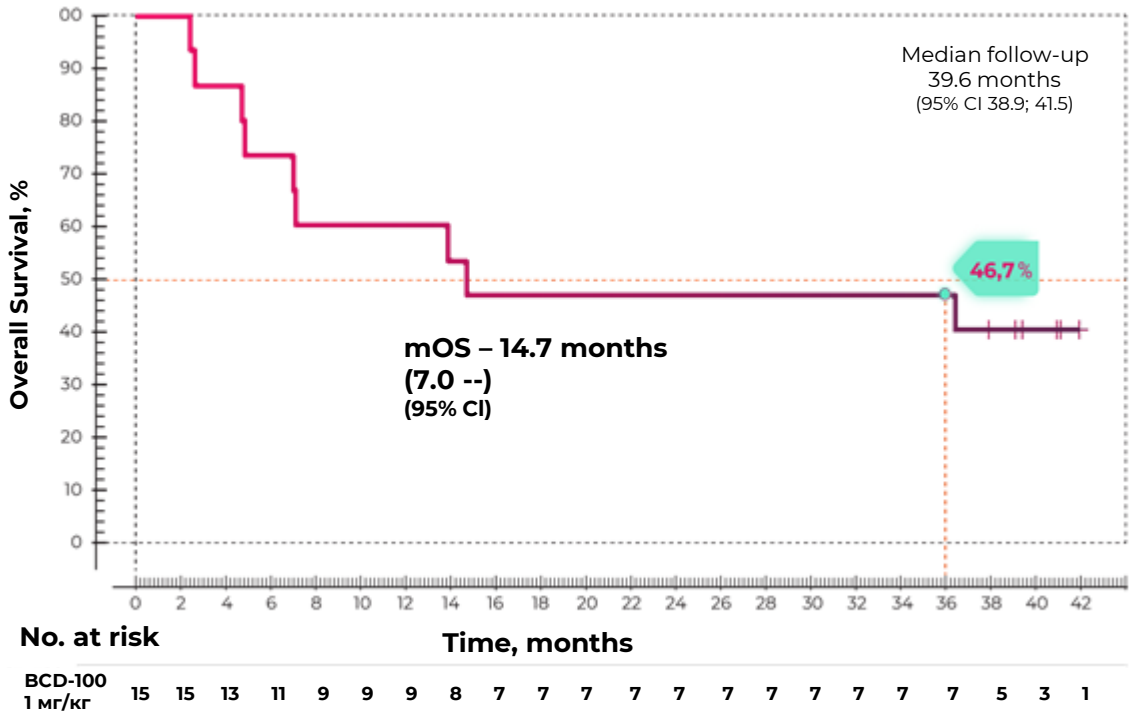
Prolgolimab had comparable result in its class in indirect comparison

Indirect comparison

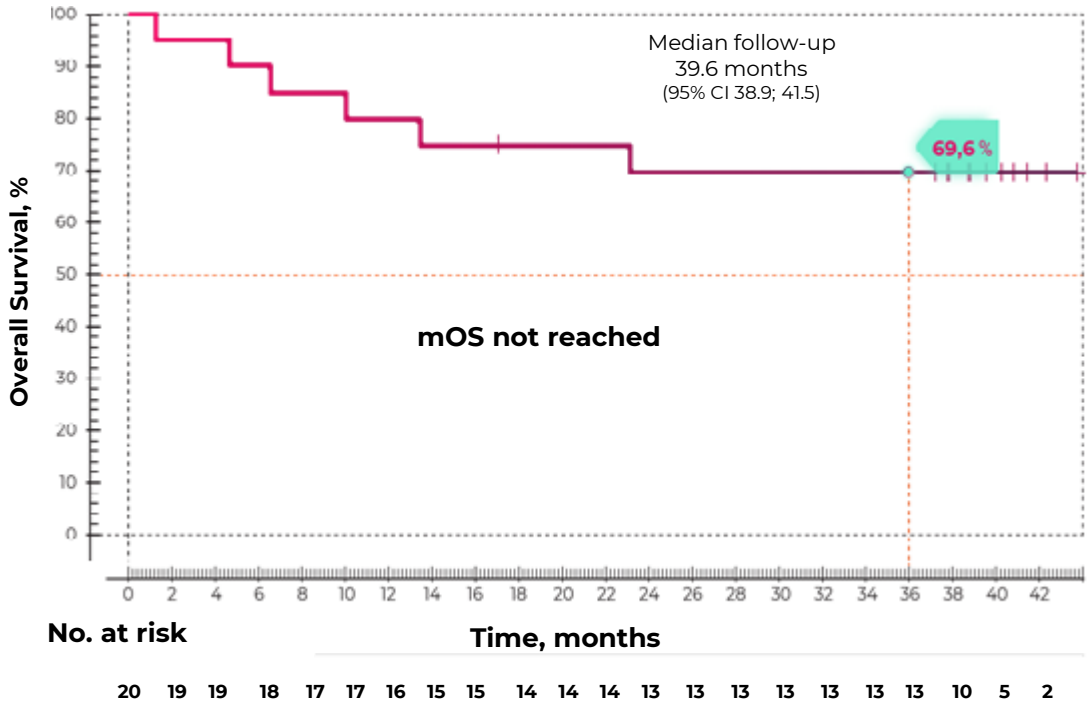
Prolgolimab is effective 1st line therapy option of metastatic melanoma regardless of BRAF mutation profile[7]

Overall Survival (OS)

OS in group with BRAF (+)



OS in group without BRAF (-)



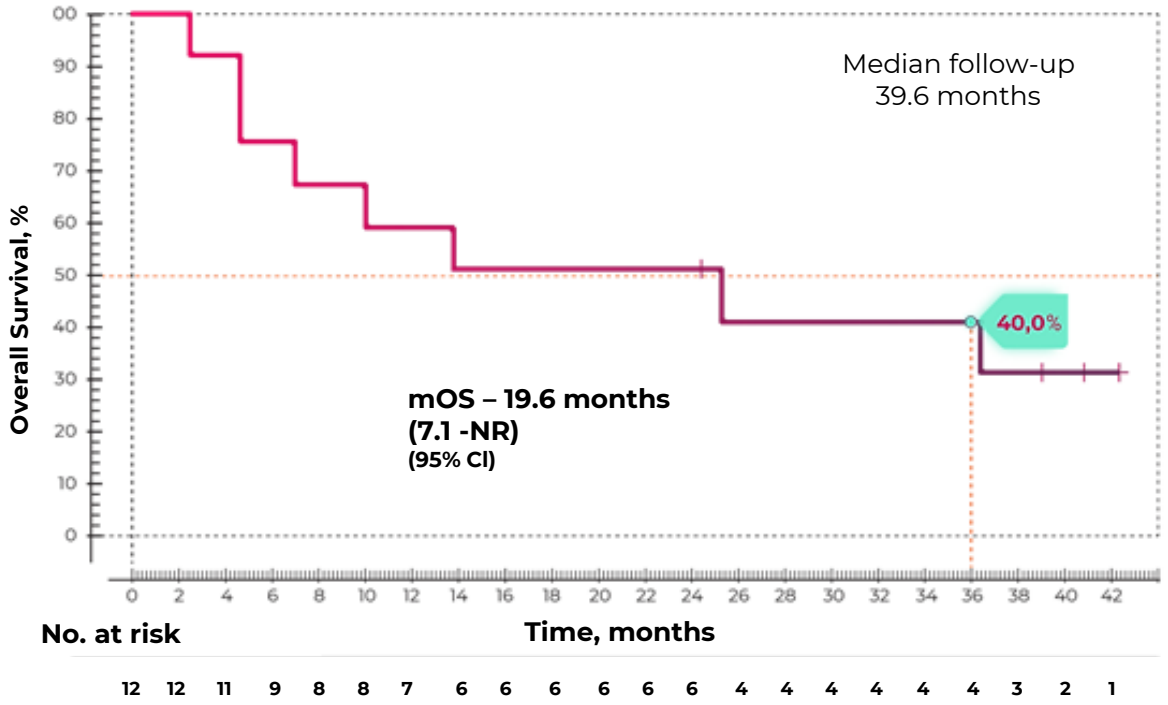
mOS – median overall survival

Kaplan-Meier OS over 3 years of follow-up

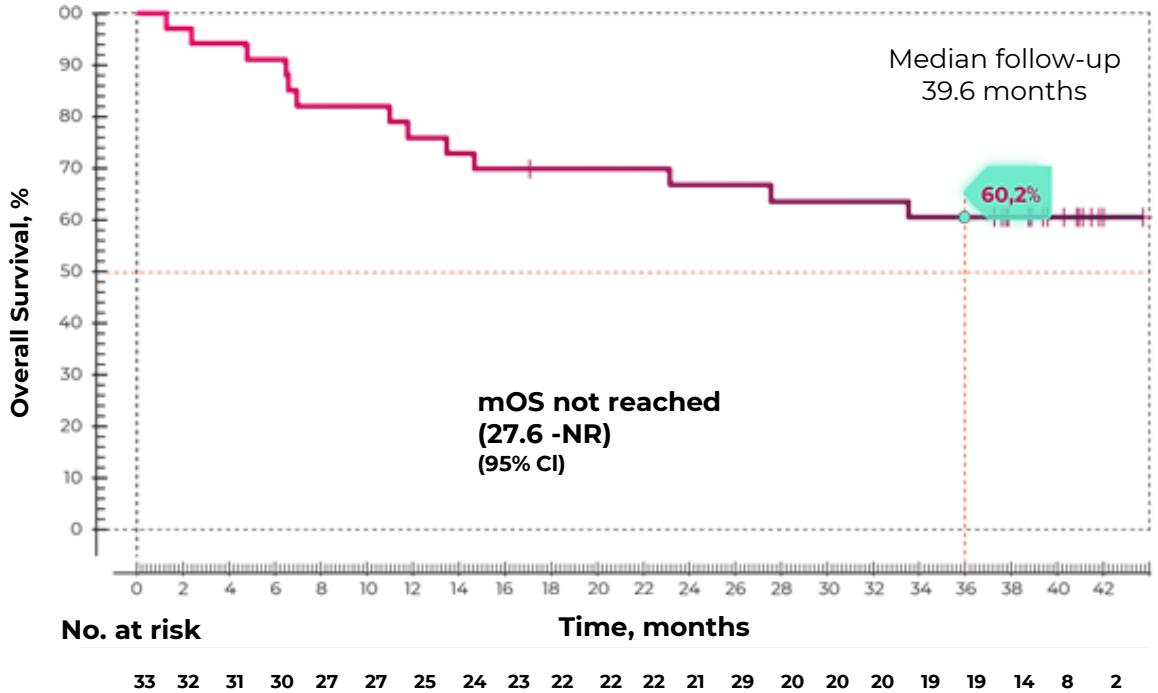
Prolgolimab is 1st line therapy option for patients with/without brain metastases[7]

Overall Survival (OS)

OS in group with brain mts



OS in group without brain mts



Prolgolimab structural features (IgG1)
designed to help cross the blood-brain barrier

mOS – median overall survival; NR – not reached; mts - metastases

Kaplan-Meier OS over 3 years of follow-up

Safety profile of anti-PD-1 inhibitors: clinical trial data

	MIRACULUM[5,7] (prolgolimab)	KEYNOTE-006[1] (pembrolizumab)	CheckMate 067[2] (nivolumab)
AEs (all grades), %	55.6	82	86
AEs (grades 3-4),%	12.7	17	21
Serious AEs, %	3.2	12	12
Treatment discontinuation due to AEs, %	3.2	7	12
Median follow-up, mos	14,2	22,9	36,0

The assessment was carried out using the CTCAE v.5.0

Prolgolimab has the best safety profile in its class according to indirect comparison

- AEs rate did not exceed 13%
- Incidence of involuntary treatment-related withdrawal was low - 3.2%
- Immunogenicity study confirmed no binding antibodies to prolgolimab formed in all patients

Indirect comparison

AE, adverse event ; mos - months

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Prolgolimab Safety profile: immune-related adverse events

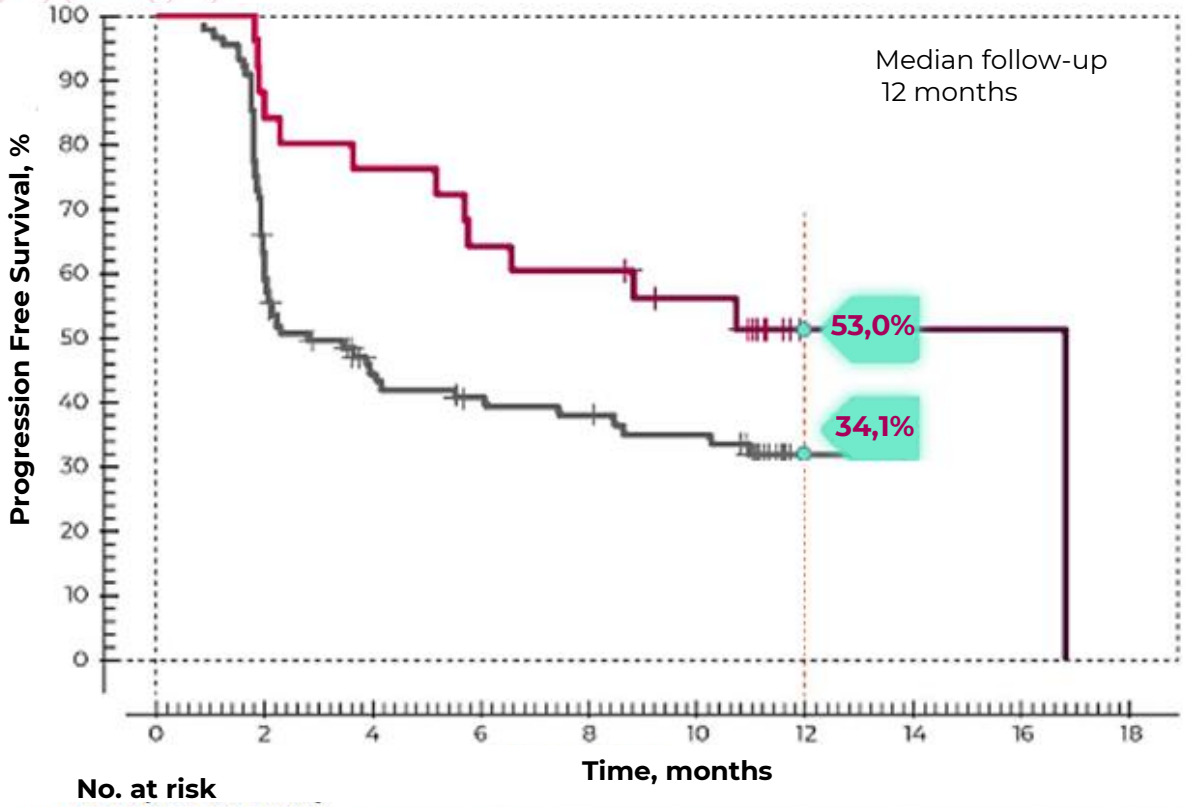
Type of AEs	AEs (all grades), n (%)	AEs (grades 3-4), n (%)
All	23 (36,5%)	5 (7,9%)
Treatment discontinuation due to AEs	1 (1,6%)	-
Endocrine system disorders		
All	13 (20,7%)	12%
Thyroiditis	1 (1,6%)	0 (0%)
Hypothyroidism	9 (14,3%)	0 (0%)
Hyperthyroidism	10 (15,9%)	0 (0%)
Skin and subcutaneous tissue disorders		
Rash	5 (7,9%)	2 (3,2%)
Skin itching	1 (1,6%)	1 (1,6%)
Respiratory system disorders		
Pneumonitis	2 (3,2%)	1 (1,6%)

- 44% of patients had irAEs 1-2 grade
- Thyroid dysfunction was most common
- 94% of irAEs were reported in the first 6 months[4,5,10]

AE, adverse event ; irAE, immune-related adverse event

The occurrence of endocrine irAEs was associated with increased PFS rates[10]

Progression Free Survival, n = 117



No. at risk

Pts with ioAEs	26	23	20	17	16	13	1	1	1	0
Pts with other AEs	91	60	37	31	29	26	1	0	0	0

	Death and disease progression	mPFS	ORR
Patients with irAEs	**13/26**	**16.8% (5,7- -)**	**53.6%**
Patients without irAEs	57/91	3.7% (2.07-8.67)	27.6%

The occurrence of endocrine irAEs can be considered as a predictor of prolgolimab efficacy

Protsenko, S. A., 'Safety of the drug prolgolimab - expected and unexpected' - plenary report VI St. Petersburg International Cancer Forum 'White Nights', 25-28 June 2020

mPFS – median Progression Free Survival, ORR – Overall Response Rate, irAE – immune-related adverse event

Prolgolimab monotherapy has the most favourable safety profile among other therapeutic options

	MIRACULUM[4,5,10] (prolgolimab)	Anti-PD-1 monotherapy (nivo group)[2]	CheckMate 067[2] (nivo+ipi group)	BRAF inhibitors monotherapy[9]	BRAF + MEK inhibitors[9]
AEs (grades 3-4)	**12.7%**	21%	59%	52%	60%
Serious AEs	**3.2%**	12%	30%	28%	37%
Treatment discontinuation due to AEs	**3.2%**	12%	39%	11%	14%
The most frequently occurring AEs	Rash, pruritus, hypothyroidism, arthralgia, colitis and diarrhea (especially combination with ipilimumab), etc.			Rash, arthralgia, photosensitivity, squamous cell skin cancer, diarrhea, weakness, etc.	

Prolgolimab had the best safety profile in its class in IO clinical trials data indirect comparison

Indirect comparison

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AE, adverse event ; TRAE, treatment-related adverse event; irAEs – immune-related adverse events, nivo – nivolumab, ipi - ipilimumab

Conclusions

- Prolgolimab demonstrates high efficacy in unfavorable patients population with inoperable or metastatic melanoma

- Prolgolimab efficacy was shown in all subgroups of MIRACULUM study:
  - BRAF (+) and BRAF (-),
  - patients with and without CNS metastases

- Prolgolimab in 1st line skin melanoma therapy in dosing regimen of 1 mg/kg Q2W achieved a 3-year OS = 55%

- The safety profile of prolgolimab is favorable and well manageable among other therapeutic options, including nivolumab and pembrolizumab

- The occurrence of endocrine irAEs during prolgolimab treatment was associated with PFS

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Q2W - every 2 weeks, irAEs - immune-related adverse events , CNS – central nervous system, OS – overall survival, PFS – progression free survival, CNS - central nervous system

Original article

European Journal of Cancer 149 (2021) 222–232

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Novel PD-1 inhibitor prolgolimab: expanding non-resectable/metastatic melanoma therapy choice

https://pubmed.ncbi.nlm.nih.gov/33872982/

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5. *Tjulandin S, Demidov L, Moiseyenko V et al. Novel PD-1 inhibitor prolgolimab: expanding non-resectable/metastatic melanoma therapy choice. European Journal of Cancer 149 (2021), p. 222-232*
6. *Strojakovsky, D.L., 'Efficacy of the drug prolgolimab - what do we know?'. - plenary report. VI St. Petersburg International Oncology Forum 'White Nights', 25-28 June 2020*
7. *Stroyakovsky D.L., 'MIRACULUM clinical trial: results of prolgolimab efficacy in metastatic melanoma during 3 years of follow-up'. St. Petersburg International Oncological Forum 'White Nights', 2021*
8. *Ascierto, P.A., et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. The Lancet. Oncology 17, 1248-1260 (2016).*
9. *Protsenko, S. A., 'Safety of the drug prolgolimab - expected and unexpected' - plenary report VI St. Petersburg International Cancer Forum 'White Nights', 25-28 June 2020*

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A multicenter observational program to evaluate the safety and efficacy of prolgolimab in patients with metastatic or unresectable melanoma (RWE)

FOR/.

The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials

Common eligibility criteria for immunotherapy trials may exclude over 50% of the patients diagnosed with metastatic melanoma[1].

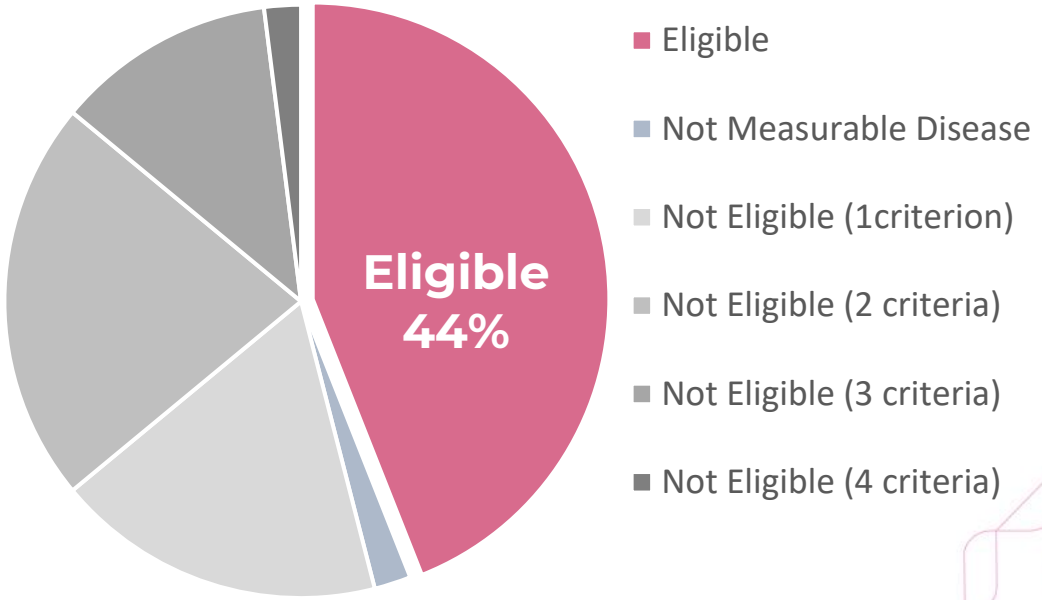
MDX010-20[3,4] Ipilimumab with or without gp100 vaccine in previously treated MM

CA184024[5] Ipilimumab with dacarbazine in previously untreated MM

CA209066[6] Nivolumab in previously untreated MM

Keynote-006[7] Pembrolizumab versus ipilimumab in untreated or previously treated MM

CA209067[8] Ipilimumab with nivolumab or monotherapy in untreated MM



The proportion of 'eligible' patients as well as 'not eligible' patients, because they do not meet one, two or more pre-defined inclusion criteria is shown[1].

FORA – FOrteca® (Prolgolimab) Real Practice Assessment

MIRACULUM

A multicenter observational program to evaluate the prolgolimab safety and efficacy in patients with **metastatic** or **unresectable melanoma in Russia**[2]

Which patients are included in the FORA study?

All patients with morphologically confirmed metastatic and/or locally advanced unresectable melanoma who were prescribed prolgolimab therapy and received at least one dose of the product as part of routine clinical practice in the Russian Federation

Exclusion criteria:

Participation in any interventional clinical study

- The study was approved in October 14, 2020, registered on clinicaltrials.gov - NCT05120024 NCT05120024
- More than 60 centers and 85 investigators involved, in the Russian Federation
- The ITT** population included 693 patients in the efficacy analysis and the PP* population included 559 patients in the efficacy analysis
- The 3rd interim analysis was presented at the conference MELANOMA AND SKIN TUMORS organized by Association Melanoma.PRO in 2022

Purposes of the study:

1. To describe the safety of prolgolimab in the standard dosing regimen of 1 mg/kg every 2 weeks in patients with metastatic or unresectable melanoma in routine practice.

2. To evaluate the PFS, OS, ORR, DCR in all patients and in separate subgroups.

From October 2020 through October 2022, the study includes 700 patients with NMM receiving prolgolimab within the framework of real clinical practice on the territory of the Russian Federation of which 7 people were excluded from the analysis during the monitoring 7 people were subsequently excluded from the analysis (blank, duplicates, which corresponded to the numbers in the study)

PFS – Progression Free Survival, OS – Overall Survival, ORR – Overall Response Rate, DCR – Disease Control Rate; *PP – per protocol population, **ITT - Intention-to-treat

FORA

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Patients characteristics

The demographic and baseline disease characteristics

Parameter	n (%)
Sex, n (%)	
Female	374 (54.4)
Male	316 (45.6)
Age, years	
Mediana	62 (18-93)
ECOG status, n (%)	
0	277 (40.0)
1	374 (54.0)
2	40 (5.8)
No data	2 (0.3)
LDH, n (%)	
Normal	306 (44.2)
≥ 2 ULN	130 (18.8)
≤ 2 ULN	33 (4.8)
No data	224 (32.2)

Parameter	n (%)
Tumour localisation, n (%)	
Cutaneous melanoma	529 (76.3)
MUP	99 (14.3)
Mucosal	33 (4.8)
Uveal	32 (4.6)
Comorbidities, n (%)	
Yes	241 (34.8)
No	452 (65.2)
Number of previous therapy lines, n %	
Untreated	457 (65.9)
1	169 (24.4)
2	35 (5.1)
3	17 (2.5)
4	6 (0.9)
≥5	9 (1.3)

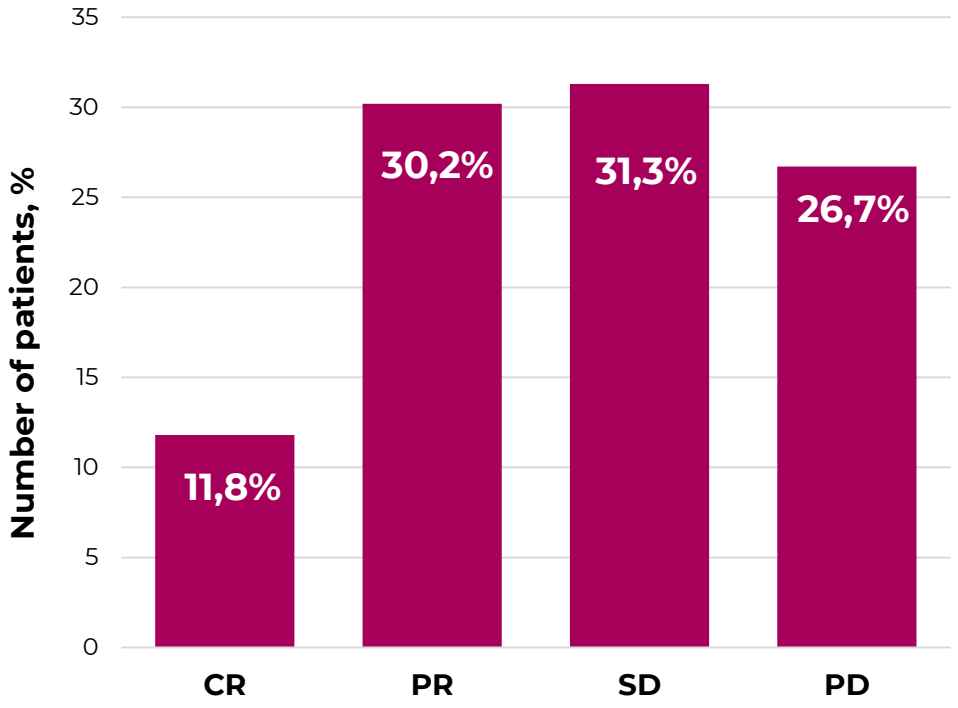
Parameter	n (%)
PD-L1 expression, n (%)	
Positive	15 (2.2)
Negative	12 (1.7)
Unknown	666 (96,1)
BRAF mutation, n (%)	
Positive	389 (56.1)
Negative	210 (30.3)
Unknown	94 (13.6)
c-KIT, n (%)	
Positive	118 (13.6)
Negative	3 (0.4)
Unknown	572 (82.5)
NRAS mutation, n (%)	
Positive	53 (7.6)
Negative	12 (1.7)
Unknown	628 (90.6)

N.B. In same cases, the necessary information was not available in medical history

LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death ligand 1; ULN - upper limit of normal, MUP- melanoma of unknown primary

Efficacy analysis of prolgolimab therapy

Analysis of the efficacy of prolgolimab therapy in PPP*,
n = 559



Prolgolimab efficacy by line of therapy in PPP*
n = 559, p = 0,074

	CR + PR, n (%)	SD, n (%)	PD, n (%)
Prolgo in 1st line	159 (43,2)	105 (28,5)	104 (28,3)
Prolgo in 2nd line	59 (42,4)	53 (38,1)	27 (19,5)
Prolgo in 3rd and subsequent lines	17 (32,7)	17 (32,7)	18 (34,6)

- Prolgolimab therapy in real clinical practice allowed to **achieve disease control in 73.3%** of umM patients **regardless of the therapy line[2].**
- Prolgolimab is effective in pretreated patients

Prolgo – prolgolimab, CR – complete response, PR – partial response PD - disease progression SD - stable disease. umM - metastatic or unresectable melanoma , PPP – per protocol population

Prolgolimab efficacy has been confirmed in real clinical practice.

Median follow-up - 12 months
(95% CI 0-36), ITT population, n = 693

Fig.1. Progression free survival (PFS) for all included patients, regardless of line of therapy.

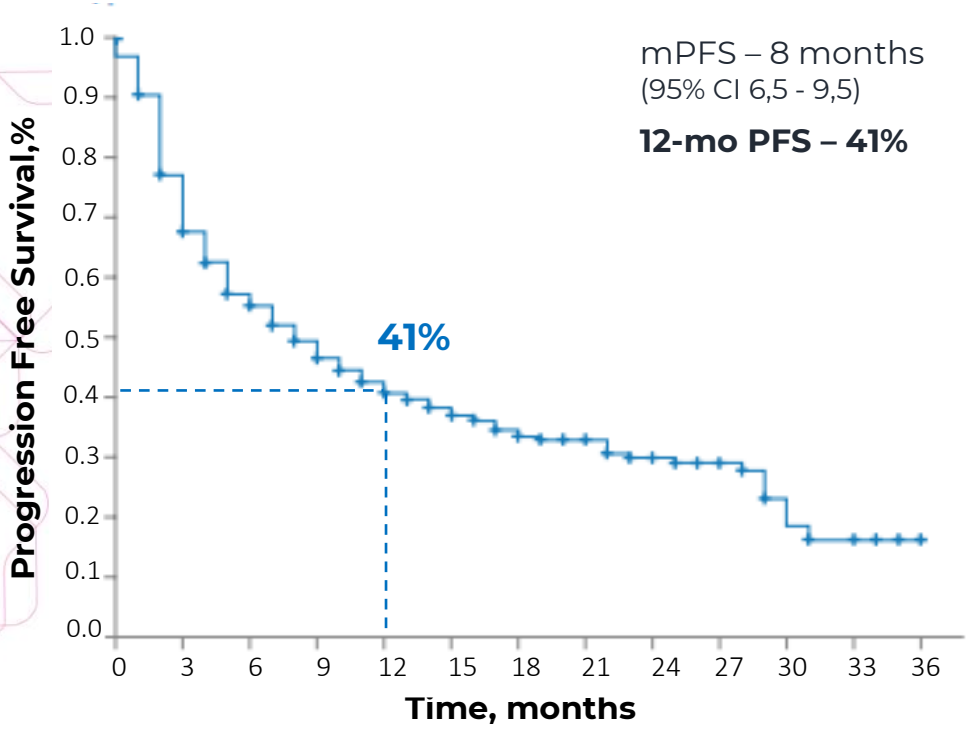
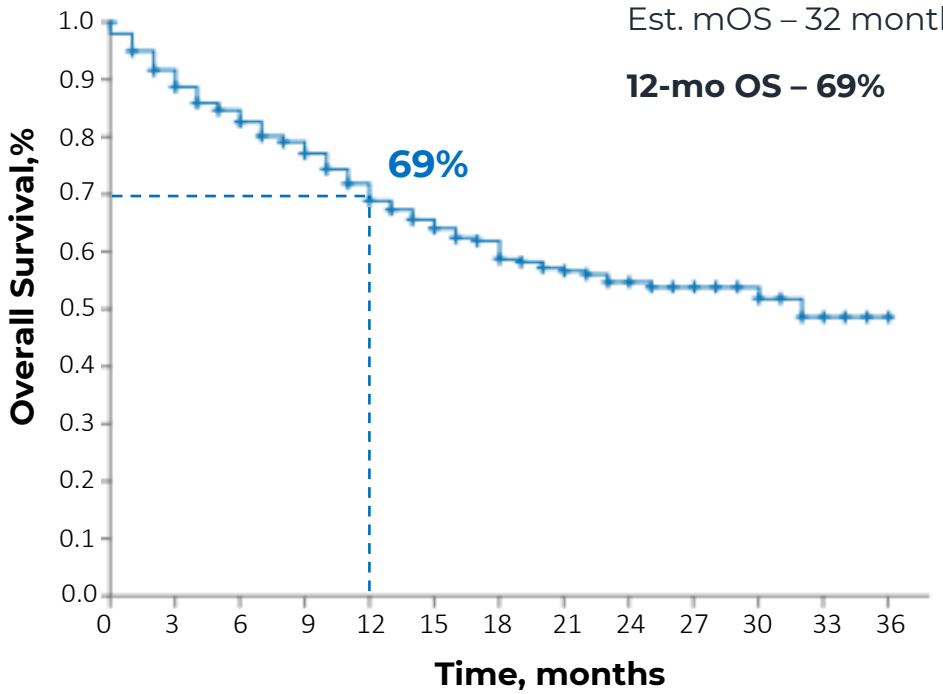


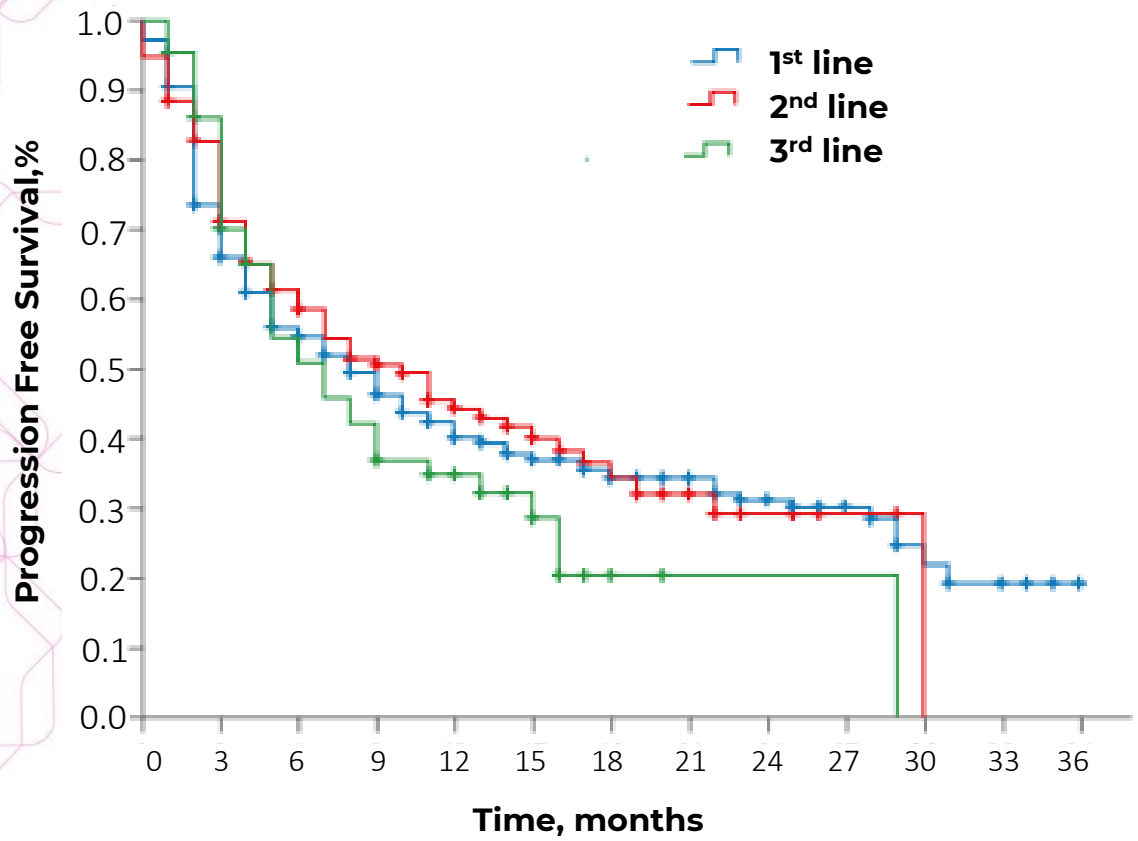
Fig.3. Overall survival (OS) for all included patients regardless of line of therapy.



mPFS – median Progression Free Survival, mo – month; est. mOS – estimated median Overall Survival ITT – intention-o-treat

Prolgolimab efficacy has been confirmed in real clinical practice. mPFS corresponds to that in MIRACULUM clinical trial[9,14]

Fig.2. PFS for all included patients by line of therapy.

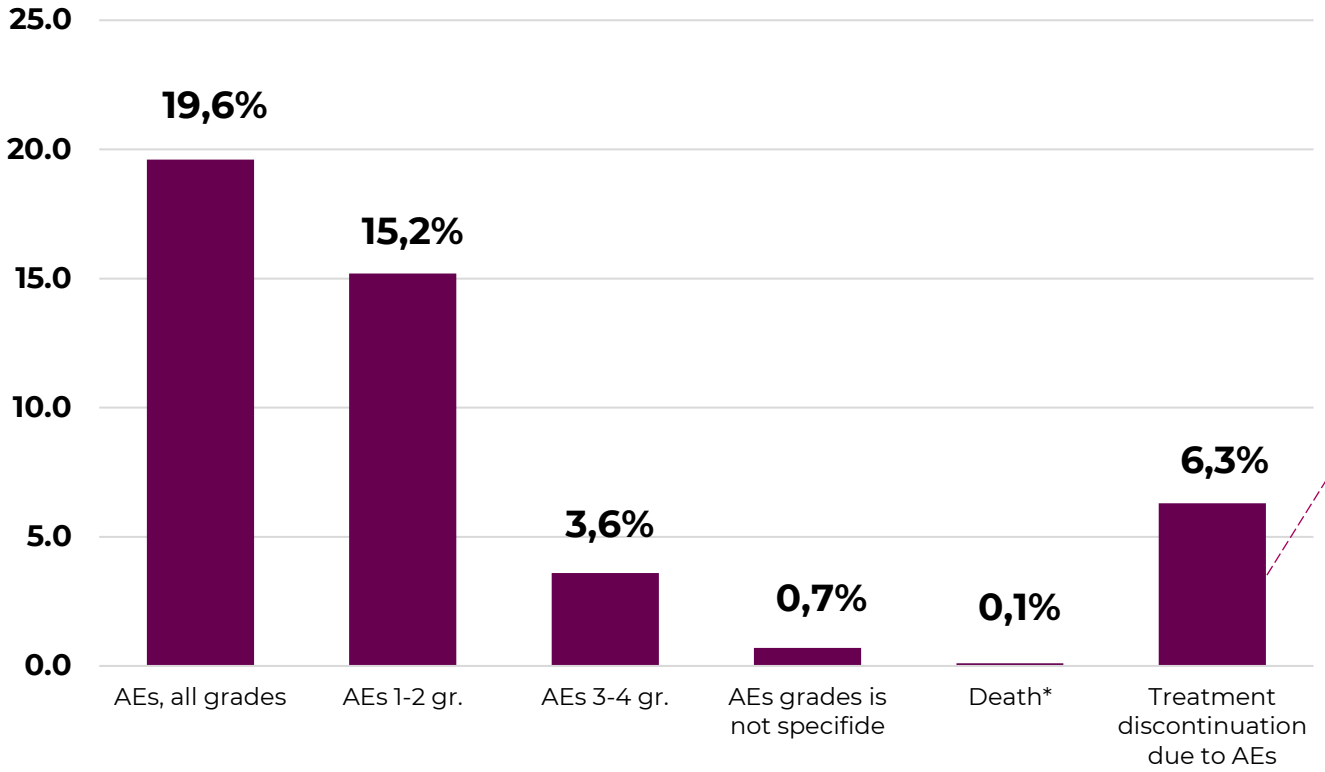


Line	mPFS (95% CI)	mOS (95% CI)
1st line	8 (6.0 – 10.0)	NR
2nd line	10 (6.6 – 13.4)	30 (16.0 – 43.9)
3rd + lines	7 (6.5 – 9.5)	22 (14.3 – 29.7)
p	0.486	0.736

- mPFS according to the line of therapy were not statistically significantly different[2]
- Prolgolimab therapy is optimal as the 1st /2nd lines of therapy.

mPFS – median Progression Free Survival, mOS –median Overall Survival

Prolgolimab safety profile remained favorable under clinical routine practice



Treatment discontinuation due to AEs	n = 44 (6.3%)
AEs (grades 1-2)	19 (2.7)
AEs (grades 3-4)	21 (3.0)
Death	1 (0.1)
Degree is not specified	3 (0.4) Toxic encephalopathy; dysphagia; arthritis

*1 death (0.1%) from thromboembolism (vascular center) with questionable association with prolgolimab (investigator's opinion[2]).

AEs- adverse events, gr - grates

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MIRACULUM phase II study results and final analyses of prolgolimab efficacy in the FORA study

	MIRACULUM[9,14]	FORA[2]
Number of patients	63	700
ORR, %	38	42
Disease Control Rate, %	63.5	73.3
mPFS, month	8.8 [95%CI 4.0 – NR]	8.0 [95%CI 6.5-9.5]
mOS, month	NR	32 (estimated)

Prolgolimab efficacy results, as reported in FORA[2] observational study, are consistent with previously published data on the prolgolimab therapy efficacy in MIRACULUN clinical trial[9]

	MIRACULUM[9,14]	FORA[2]
Number of patients	63	700
AEs (all grades), %	36.5	19.6
AEs (grades 3-4),%	7.9	3.6
Treatment discontinuation due to AEs, %	1.6	6.3

The assessment was carried out using the CTCAE v.5.0

Prolgolimab safety profile remains favorable despite treating patients with comorbidity

ORR – Overall Response Rate; mPFS – median Progression Free Survival, mOS –median Overall Survival, AE- adverse event

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The results of prolgolimab therapy (efficacy and safety) in melanoma patients were consistent with those in worldwide observational studies of real-world clinical practice of CPIs monotherapies

	Orlova K. FORA[2] (prolgolimab)	J.Kirkwood[10] (nivo/pembro)	J. Kuzmanovszki[11] (nivo/pembro)	P. Mohr[12] (pembro) ADOregister	S. Monestler[13] (nivolumab)
Number of patients	700	147	119 (cutaneous melanoma)	664	400
BRAF mutation (+), %	30	38	33	26	32
Follow-up period, mos	12 (0 - 36)	46.6 (39.8 – 57.5)	10.4 (4 – 20.7)	36.1 (33.5 – 38.3)	mDoT – 9.9
mPFS, mos	8 (6.5 - 9.5)	NA	12.6 (4.6 – 20.7)	3.9 (3.5 – 4.9)	3.3 (3 – 4.2)
mOS, mos	32 (estimated)	35.7 (23.3 – NR)	29.9 (18.7 – 41.3)	30.5 (25 – 35.4)	14.1 (11.9 – 17.9)

mPFS – median Progression Free Survival, mOS –median Overall Survival, mDoT – median Duration Of Treatment; nivo – nivolumab, pembro – pembrolizumab

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FORA conclusions

- Prolgolimab is effective in routine clinical practice in patients with melanoma: 42% achieved an response, more than a quarter of responses were complete.
- Prolgolimab in different lines of therapy provides a mPFS = 8 months, which is consistent with the data of the registration study MIRACULUM
- The safety profile of prolgolimab remains favorable in patients with comorbidities
- FORA data are consistent with data from other global real-world) trials of immunotherapy (mono) in clinical practice

ORIGINAL ARTICLE

Final data on the efficacy of the FORA study (FOrteca Real practice Assessment): a multicenter prospective observational study on the real-world efficacy of prolgolimab in patients with metastatic melanoma in Russia

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OCTAVA

Phase III Double-Blind, Placebo-Controlled, Comparative, Randomized Study of the Efficacy and Safety of Therapy with Nurulimab + Prolgolimab Followed by Therapy with Prolgolimab as Compared to Prolgolimab Monotherapy as First-Line Therapy in Patients with Unresectable or Metastatic Melanoma

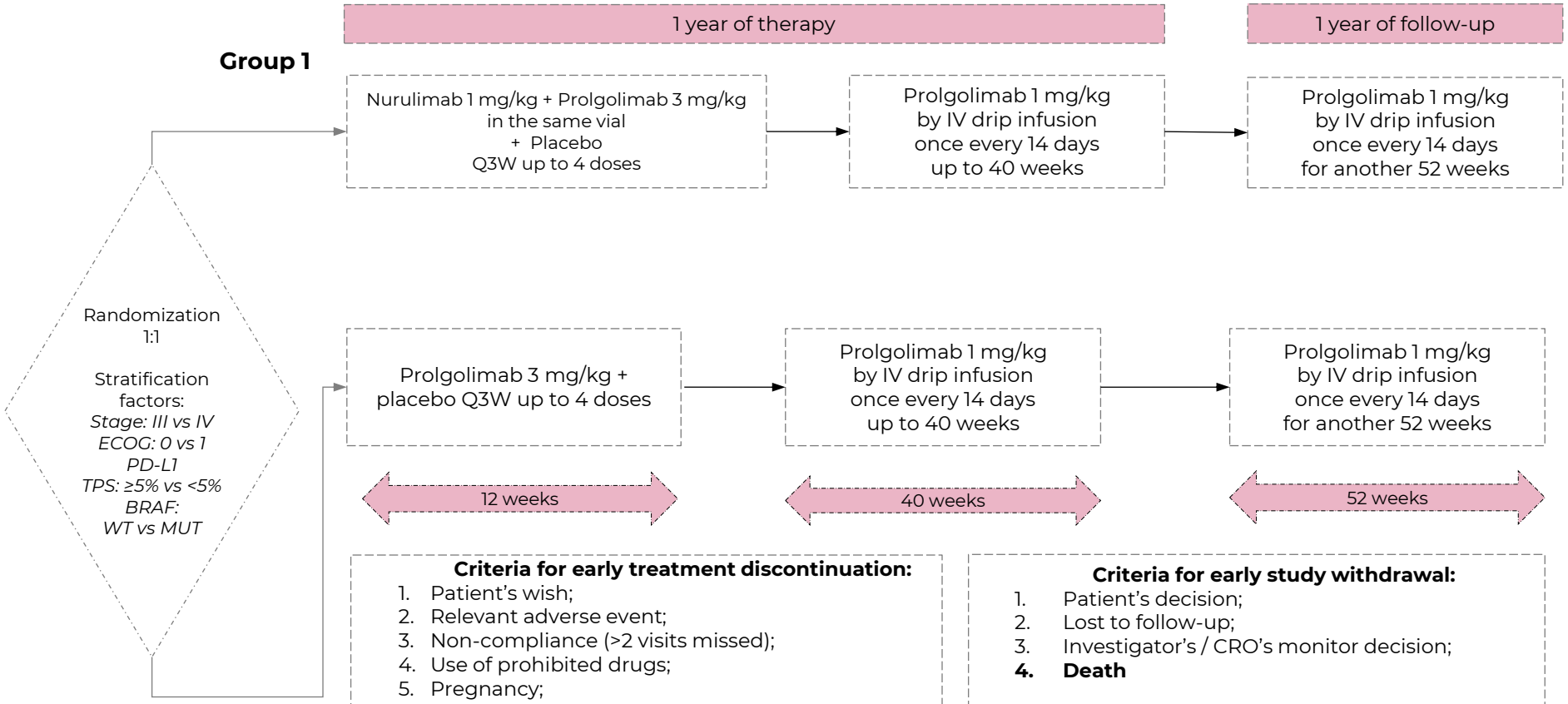
OCTAVA trial design

Population, key criteria

1. >18 years old;
2. Cutaneous melanoma **IIIC/D-IVM1c**;
3. First-line setting;
4. Tumor burden **<200 mm**;
5. Any known BRAF and PDL status;
6. Any LDH level

Ineligible patients:

1. **With noncutaneous melanoma**, including melanoma of unknown primary;
2. **With CNS metastases**;
3. **Previously treated with aPD1 or aCTLA4** (including adjuvant or neoadjuvant);
4. **Previously treated with BRAFi ± MEKi** (including adjuvant or neoadjuvant);
5. With a history of atopic bronchial asthma or angioedema;
6. With autoimmune diseases;
7. With active hepatitis B, active hepatitis C (PCR-proven), active syphilis, HIV infection, including a history thereof



Criteria for early treatment discontinuation:

1. Patient's wish;
2. Relevant adverse event;
3. Non-compliance (>2 visits missed);
4. Use of prohibited drugs;
5. Pregnancy;
6. **Progressive disease**

Criteria for early study withdrawal:

1. Patient's decision;
2. Lost to follow-up;
3. Investigator's / CRO's monitor decision;
4. **Death**

Primary endpoint:

- Progression-free survival

If the RECIST 1.1 and iRECIST scores differ, the iRECIST scores will take priority.

Secondary endpoints:

- OS
- Direct efficacy (ORR, DCR, CR, PR, stable disease)
- Time to response
- Duration of response
- Safety

IV- intravenously; wt -wild type; mut – mutation, CNS – central nervous system, LDH - LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death ligand 1; TPS = Tumor Proportion Score; PD-L1 - programmed death-ligand ; Q2W -

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Patients characteristics

The demographic and baseline disease characteristics of the patients were well balanced about prognostic factors and mutation status

Parameter	Nurdati® n = 135	Prolgolimab n = 136
Age, years		
Mediana	63.5 (57-71)	62.4 (54.5-72)
Sex, n (%)		
Female	70 (51.9)	83 (61.0)
Male	65 (48.1)	53 (39.0)
Metastasis stage, AJCC, 8th edition, n (%)		
III	18 (13.3)	16 (11.8)
IV	117 (86.7)	120 (88.2)
M0	19 (14.1)	16 (11.8)
M1	2 (1.5)	0
M1a	23 (17.0)	26 (19.1)
M1b	33 (24.4)	35 (25.7)
M1c	58 (43.0)	58 (42.6)
M1d	0	1 (0.7)
ECOG status, n (%)		
0	72 (53.3)	72 (52.9)
1	63 (46.7)	64 (47.1)

Parameter	Nurdati® n = 135	Prolgolimab n = 136
PD-L1 expression* , n %		
TPS ≥5%	44 (32.6)	45 (33.1)
TPS <5%	91 (67.4)	91 (66.9)
Metastases, n (%)		
Number of subjects with distant metastases	116 (85.9)	120 (88.2)
Number of organs with distant metastases, median (min-max)	1.9 (0–8)	2.0 (0–10)
LDH level, n (%)		
Elevated	38 (28.1)	36 (26.5)
Normal	97 (71.9)	100 (73.5)
$BRAF^{V600E/K}$ status , n (%)		
Wild-type	76 (56.3)	71 (52.2)
Mutant	59 (43.7)	65 (47.8)

* A Dako 22C3 test system

LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death ligand 1; TPS = Tumor Proportion Score; M0 = no distant metastasis; M1a = metastasis to skin, subcutaneous tissues or distant lymph nodes; M1b = metastasis to lung; M1c = metastasis to all other visceral sites or distant metastases at any site associated with elevated serum concentrations of LDH, PD – L1 - programmed death-ligand 1, AJCC - American Joint Committee on Cancer

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Prolgolimab monotherapy has comparable efficacy to other PD-1 inhibitors

	Phase	mF-up, month	ORR	DCR	mPFS, month	12-month PFS	AEs 3-4 grade	Therapy discontinuation
OCTAVA[1] Prolgolimab group*	III	17,3	**44,1%**	**61,8%**	**7,4**	**45,9%**	**14%**	**4,4%**
KEYNOTE 006[2] pembrolizumab vs ipilimumab	III	22,9	36% (Q3W) 37% (Q2W)	52% (Q3W) 52% (Q2W)	4,1 (Q3W) 5,6 (Q2W) (HR 0.68/0.69)	NA	17%(Q2W) 17% (Q3W)	7% (Q3W) 11% (Q2W)
CHECKMATE 067[3] nivolumab vs ipilimumab	III	36,0	44%	54	6,9 (HR 0,57)	NA	12%	12%
RELATIVITY 047[4] (nivo group)	III	19,3	32,6%	49%	4,6 (HR 0,78)	36,9%	11,1%	7,2%

assessed by RECIST 1.1

Indirect comparison

* All endpoints assessed according to iRECIST by blinded independent central review; mPFS – median Progression Free Survival, mOS –median Overall Survival, mDoT – median Duration Of Treatment; DCR – Disease Control Rate, ORR – Overall Response Rate, mF-up – median follow-up, AEs – Adverse Events; Q2W – Quality to be delivered every 2 weeks; Q3W - Quality to be delivered every 3 weeks, NA – not available

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