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Original Research

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

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ABSTRACT

Background: Prolgolimab is an IgG1 anti-PD-1 monoclonal antibody with the Fc-silencing 'LALA' mutation. The phase III DOMAJOR study assessed efficacy and safety of prolgolimab in combination with pemetrexed and platinum-based chemotherapy vs placebo in combination with pemetrexed and platinum-based chemotherapy as first-line treatment for advanced non-small cell lung cancer (NSCLC).

Methods: 292 patients with advanced non-squamous NSCLC were randomized 1:1 to receive 4 cycles of pemetrexed, platinum-based drug and either prolgolimab (3 mg/kg Q3W) or placebo followed by prolgolimab/placebo with pemetrexed until disease progression or toxicity (≤36 months). The primary endpoint was overall survival (OS).

Results: After a median follow-up of 18 months, the median OS was not reached (95 % CI, 22.28 – NA) in the prolgolimab-combination group vs 14.6 months (95 % CI, 11.73 – 19.15) in the placebo-combination group (HR, 0.51; 95 % CI, 0.35 – 0.73, p = 0.0001). The OS improvement was independent of PD-L1 status. Median progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) was 7.7 months in the prolgolimab-combination group and 5.5 months in the placebo-combination group (HR, 0.65; 95 % CI, 0.49 – 0.85, p = 0.0004). The only adverse events that were reported in at least 10 % of the patients that were significantly more frequent in the prolgolimab-combination group were blood creatinine increased and dyspnoea.

Conclusion: Among patients with advanced NSCLC the addition of prolgolimab to pemetrexed and a platinum-based drug increased OS and PFS, with no new safety concerns. This benefit was retained in patients with PD-L1 negative tumors. (ClinicalTrials.gov, NCT03912389)

1. Introduction

Over the last decade, immunotherapy has become a standard of care for advanced NSCLC. The advantages of adding pembrolizumab to the pemetrexed and platinum chemotherapy first have been demonstrated within KEYNOTE-189 study [1]. Prolgolimab is a fully human anti-PD-1 monoclonal antibody (IgG1 isotype) with the Fc-silencing L234A/L235A mutation which results in lower affinity to Fcγ receptors. This modification minimizes the effector properties of the antibody. Thus, prolgolimab does not bind to the FcγR receptors of macrophages, which heighten protection of the activated T lymphocytes population from possible antibody-dependent phagocytosis by macrophages and thereby enhance the antitumor effect [2].

In 2020 prolgolimab was approved for the treatment of metastatic or unresectable melanoma based on the results of the phase II/III randomized clinical trial MIRACULUM (NCT03269565) in the Russian Federation and Republic of Belarus. Currently, the indications for the prolgolimab use are expanding. In the Russian Federation, at the end of 2023, prolgolimab in combination with platinum-based chemotherapy was approved as a first-line treatment for patients with advanced non-squamous NSCLC based on the phase III DOMAJOR trial (NCT03912389). The efficacy of prolgolimab is comparable to other drugs in the PD-1 inhibitor class, and the safety profile was most favorable in an indirect comparison [3,4].

The phase III DOMAJOR study was designed to assess efficacy of prolgolimab in combination with pemetrexed and platinum-based drug vs placebo in combination with pemetrexed and platinum-based drug as first-line treatment for metastatic NSCLC.

2. Material and methods

2.1. Patients

Eligible patients were aged 18 years or older; had histologically confirmed stage IV non-squamous NSCLC; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, at least one measurable lesion according to RECIST 1.1 [5]; a life expectancy of at least 12 weeks; had provided a tumor sample for determination of PD-L1 status; and received no previous systemic therapy for metastatic disease. The exclusion criteria included presence of *EGFR* mutation or *ALK* rearrangement, previous treatment with targeted or immunotherapy drugs, radiation therapy within 14 days before the first dose of the study drug and active central nervous system metastases or carcinomatous meningitis.

2.2. Trial design and treatment

Eligible patients were randomly assigned (1:1) to receive either prolgolimab 3mg/kg or placebo, both as intravenous infusions every 3 weeks until progression or signs of unacceptable toxicity (up to 36 months after the start of study therapy). Randomization was stratified according to platinum chemotherapy (carboplatin vs cisplatin), PD-L1 expression (tumor proportion score, <1 % vs ≥1 %), and race (non-Asian vs Asian).

All the patients received four cycles of the investigator's choice of intravenously administered cisplatin (75 mg/m^2) or carboplatin (area under the concentration–time curve, 5 mg/ml×min) plus pemetrexed (500 mg/m^2), all administered intravenously every 3 weeks, followed by pemetrexed (500 mg/m^2) every 3 weeks.

For patients who experienced disease progression per RECIST 1.1, study treatment could continue until confirmation of disease progression per iRECIST [6].

2.3. Assessments

PD-L1 expression, *EGFR* mutations and *ALK* rearrangements were assessed at a central laboratory in formalin-fixed paraffin-embedded tumor samples obtained at screening or 42 days prior to ICF signing. PD-L1 expression was assessed by means of the PD-L1 IHC 22C3 pharmDx assay (Agilent) and categorized according to the tumor proportion score

Table 1
Baseline demographic and disease characteristics. Full analysis set.

Parameter	Prolgolimab Combination(N = 143)	Placebo Combination (N = 149)
Median (range) age, (years)	62.0 (43 – 81)	62.0 (34 – 81)
Sex, n (%)		
Female	48 (33.6)	42 (28.2)
Male	95 (66.4)	107 (71.8)
Race, n (%)		
Asian	45 (31.5)	44 (29.5)
White	98 (68.5)	105 (70.5)
Baseline ECOG performance status score, n (%)		
0	40 (28.0)	37 (24.8)
1	103 (72.0)	112 (75.2)
Status PD-L1, n (%)		
TPS < 1 %	57 (39.9)	60 (40.3)
TPS ≥ 1 %	86 (60.1)	89 (59.7)
1 % ≤ TPS < 50 %	48 (33.6)	62 (41.6)
TPS ≥ 50 %	38 (26.6)	27 (18.1)
Histological tumor type, n (%)		
Adenocarcinoma	139 (97.2)	146 (98.0)
Large cell carcinoma	4 (2.8)	3 (2.0)
Prior anti-cancer therapy for nonmetastatic disease	7 (4.9)	7 (4.7)
Prior surgical treatment, n (%)	63 (44.1)	65 (43.6)
Current/Former smoker, n (%)	99 (69.2)	109 (73.2)

(TPS). Absence of tumor activating *EGFR* mutations and *ALK* gene rearrangements was assessed by standardized method (DNA-based tests for *EGFR* and immunohistochemistry staining or a FISH analysis for *ALK*) and served as confirmation that *EGFR* or *ALK*-directed therapy was not indicated.

Adverse events (AEs) were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE 5.0).

Tumor size assessment by contrast-enhanced computed tomography / magnetic resonance imaging (CT/MRI) was scheduled for screening and weeks 7, 13, 19, 25, 31, 40, 49, 61, 73, 97, 121, 145. Tumor response was assessed according to RECIST, version 1.1 and iRECIST. Patients were contacted every 12 weeks to assess survival during follow-up.

2.4. Endpoints

The primary endpoint was overall survival. 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. Additional assessment of PFS and ORR was performed according to iRECIST. The safety endpoints include proportion of patients with AEs of any grade, severe AEs (Grade ≥3), serious AEs (SAEs), proportion of patients requiring treatment discontinuation due to AEs.

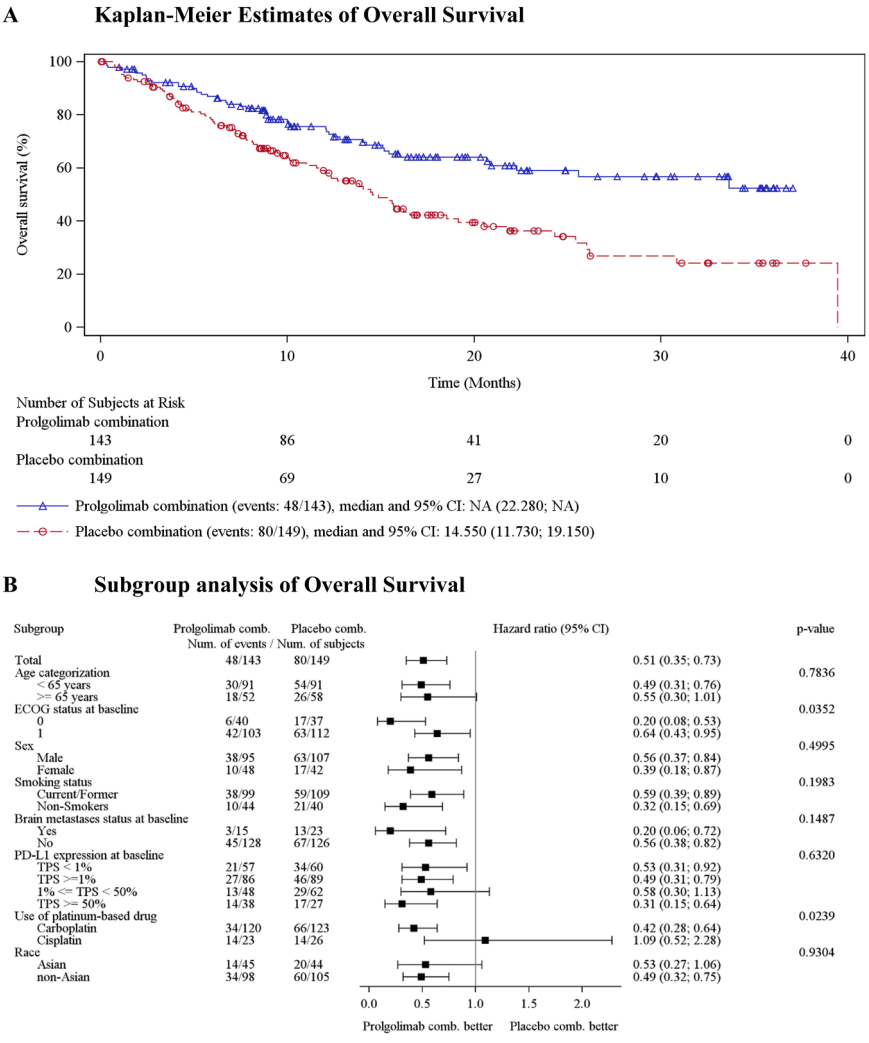


Fig. 1. Overall survival. Full Analysis Set. A Kaplan-Meier Estimates of Overall Survival. B Subgroup analysis of Overall Survival.

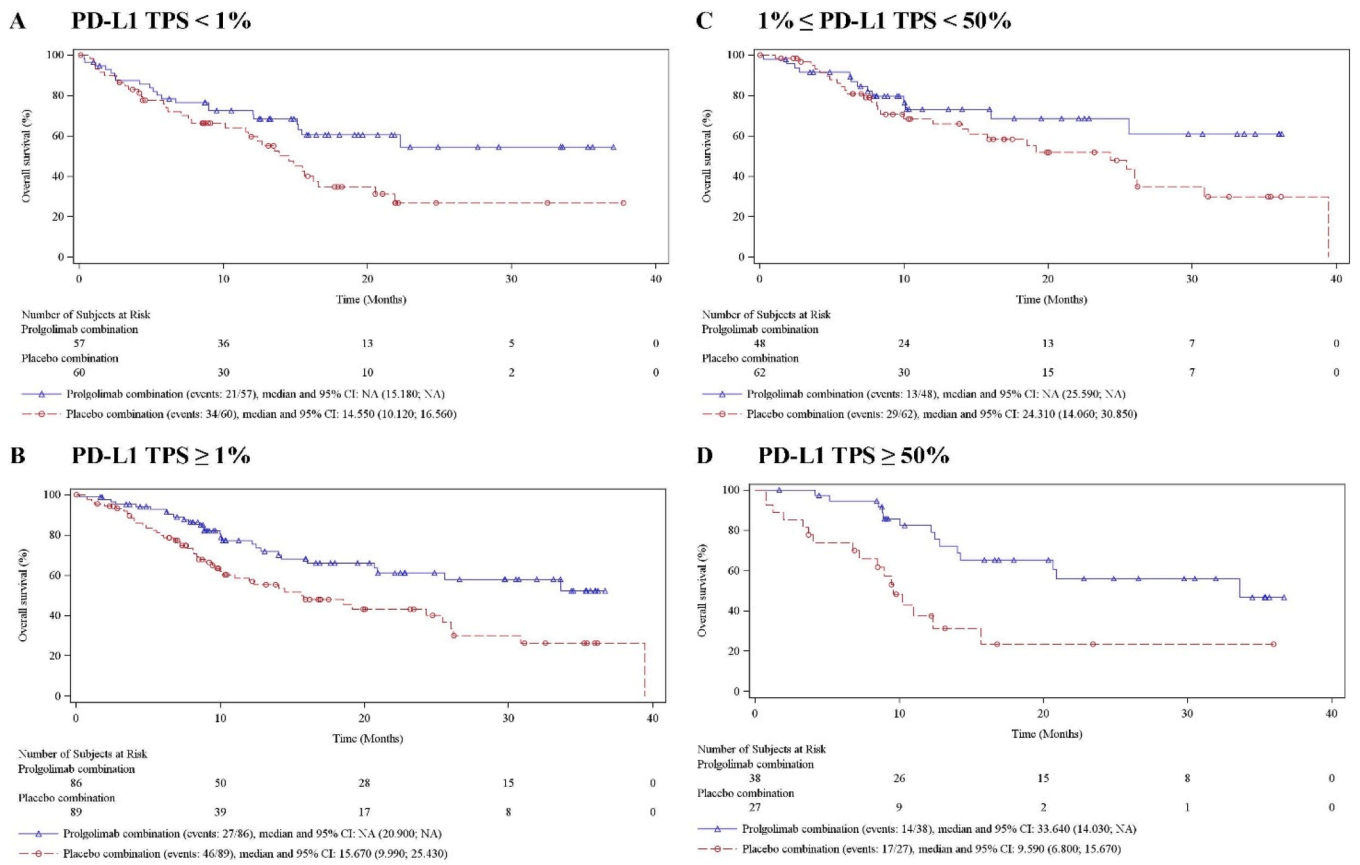


Fig. 2. Overall Survival, According to PD-L1 TPS. Full Analysis Set.

2.5. Trial oversight

The study was designed and sponsored by BIOCAD. The protocol and all its amendments were approved by the ethics committee at each study site. An independent data monitoring committee reviewed interim data during the study. The study was conducted in accordance with the principles of Declaration of Helsinki and the Good Clinical Practice guidelines. All the patients provided written informed consent before enrollment.

Representatives of the sponsor prepared the manuscript. All authors approved the final version.

2.6. Statistical analysis

The sample size for superiority hypothesis was estimated such that 113 events of death would provide the trial with 80 % power to detect a hazard ratio of 0.59 (with assumption about 12 month-accrual period and 18 month-follow-up period) for the comparison between the prolgolimab-combination group and the placebo-combination group at a one-sided alpha of 0.025. The planned enrollment was 292 patients of which up to 30 % (88 patients) were from People's Republic of China.

Efficacy, subject disposition, demographics and baseline characteristics were assessed in the Full Analysis Set (FAS) included all randomized patients «as randomized» . Safety was assessed in the Safety Analysis Set included all patients who received at least one dose of prolgolimab or placebo «as treated» .

OS (defined as the time from randomization to death from any cause) was estimated by means of the Kaplan–Meier method. The magnitude of the treatment effect (i.e., hazard ratio and corresponding two-sided 95 % confidence interval) was calculated with the use of a Cox proportional hazard model adjusting for covariates. The stratification factors used for randomization were applied as covariates. Between-group differences were assessed with the use of the stratified log-rank test. Median follow-up was estimated by reverse Kaplan-Meier method.

PFS (defined as the time from the date of randomization until the date of disease progression per RECIST 1.1 or death) and TTR (defined as the time from the date of randomization until the date of response per RECIST 1.1) were analyzed similarly to the primary endpoint.

DOR (defined as the time from the date of response until the date of disease progression per RECIST 1.1 criteria or death) was assessed by Kaplan-Meier method for responders.

Between-group comparisons of the ORR (defined as the proportion of patients achieving a complete response or partial response) and DCR (defined as the proportion of patients achieving complete response, partial response or stable disease) according to RECIST 1.1 and iRECIST criteria were performed with the use of the stratified Miettinen and Nurminen method and Cochran-Mantel-Haenszel test.

The stratification factors at randomization (as entered in the IWRS) were applied to all the stratified analyses.

At the time of the data cutoff (May 25, 2023), the median duration of follow-up was 17.9 months, 128 deaths had been registered.

3. Results

3.1. Patients and treatment

Between September 13, 2019, and November 30, 2022, 605 patients were screened, of whom 292 were randomly assigned to the prolgolimab-combination group or the placebo-combination group (Fig. S1 in the Supplementary Appendix). The baseline demographic and disease characteristics were generally well balanced between the groups (Table 1).

At the data cutoff 183 patients were withdrawn from the study, the main reason for withdrawal was death (126 patients).

Table 2
Secondary efficacy endpoints per RECIST 1.1 assessed by BICR. Full analysis set.

Parameter	ProlgolimabCombination (N = 143)	PlaceboCombination **(N = 149)**
Progression-free survival		
Median PFS, months (95 % CI)[a]	7.720 (5.550; 11.070)	5.520 (4.210; 6.010)
HR (95 % CI)[b]	0.65 (0.49; 0.85)	
p-value[c]	0.0004	
Best overall response		
Complete response (CR), n (%)	1 (0.7)	0
Partial response (PR), n (%)	71 (49.7)	41 (27.5)
Stable disease (SD), n (%)	43 (30.1)	69 (46.3)
Non-complete response / Non-progressive disease (Non-CR / Non-PD), n (%)*	0	1 (0.7)
Progressive disease (PD), n (%)	16 (11.2)	19 (12.8)
Not evaluable (NE), n (%)	11 (7.7)	19 (12.8)
No disease (ND), n (%)* *	1 (0.7)	0
Disease control rate (CR+PR+SD), n (%) (95 % CI[d])	115 (80.4)(73.0; 86.6)	110 (73.8)(66.0; 80.7)
Risk difference (95 % CI)[e]	0.05 (−0.04; 0.15)	
p-value[f]	0.2673	
Overall response rate (CR+PR), n (%)(95 % CI[d])	72 (50.3)(41.9; 58.8)	41 (27.5)(20.5; 35.4)
Risk difference (95 % CI)[e]	0.21 (0.11; 0.32)	
p-value[f]	0.0001	
Duration of response (DOR)		
Median DOR, months (95 % CI)[a]	12.450 (8.380; 14.980)	5.590 (3.480; 8.610)
Range, months	0.72; 32.85	1.25; 33.94
p-value[c]	0.0289	
Time to response (TTR)		
Median TTR, months (95 % CI)[a]	2.300 (1.610; 2.760)	2.790 (1.580; 2.860)
HR (95 % CI)[g]	1.56(1.02; 2.40)	
p-value[c]	0.0164	

*This category of overall tumor assessment was used when target lesions did not exist at baseline and the non-target lesion assessment was Non-CR / Non-PD according to RECIST 1.1 criteria, provided the criteria for PD or NE are not met.
* *This category of overall tumor assessment was used when a subject has no disease at baseline, provided the criteria for PD or NE are not met.
[a] Kaplan-Meier estimate,
[b] Cox model adjusted for covariates,
[c] Stratified log-rank test,
[d] Confidence interval by exact Clopper-Pearson method,
[e] Stratified confidence intervals by Miettinen-Nurminen method,
[f] Cochran-Mantel-Haenszel test,
[g] Stratified Cox model. Stratified analysis was performed on the stratification variables used in dynamic randomization based on IWRS data: use of platinum-based drug (carboplatin or cisplatin), PD-L1 expression (TPS <1 % or >=1 %), race (Asian or non-Asian).

3.2. Overall survival

After a median follow-up of 17.9 months, with 128 deaths in the FAS, the estimated 12-months OS was 75.6 % in the prolgolimab-combination group and 59.0 % in the placebo-combination group. The median OS was not reached (95 % CI, 22.3 – NA) in the prolgolimab-combination group and was 14.6 months (95 % CI, 11.7 – 19.2) in the placebo-combination group (HR, 0.51; 95 % CI, 0.35–0.73; p = 0.0001) (Figs. 1A and 2). The forest plot analyses demonstrated a consistent benefit of the prolgolimab combination over the placebo combination across groups, including all subgroups of PD-L1 TPS and the subgroup with Asian patients (Fig. 1B). The number of patients received cisplatin as a platinum-based drug (<20 %) makes analysis less reliable in this subgroup. PD-L1 status was not also a statistically significant predictor in both multi- and univariate Cox models (p > 0.3). AUC of the time-dependent ROC-curve (AUC=0.6) suggests that level of PD-L1 expression did not predict survival probability (Fig. S3 in the Supplementary Appendix).

3.3. Progression free survival

With 215 events of progression or death, the median of PFS was significantly higher in the prolgolimab-combination group (Table 2, Fig. 3A). The estimated proportion of patients who were alive and progression free at 12, 18 and 24 months was 2-fold higher in the prolgolimab-combination group. The results were similar when progression was assessed according to iRECIST (Table S1 in the Supplementary Appendix). The HR for PFS was less than 1.00 across all subgroups that were analyzed (Fig. 3B).

3.4. Tumor response

The prolgolimab-combination group had a significantly higher ORR compared with the placebo-combination group. The median DOR and median TTR were also significantly higher in the prolgolimab-combination group (Table 2). The results were similar when response was assessed according to iRECIST (Table S1 in the Supplementary Appendix). Overall response results were consistent across all subgroups (Fig. S2 in the Supplementary Appendix).

3.5. Adverse events

The overall incidence of AEs of any cause and regardless of attribution to treatment by the investigator was slightly higher in the prolgolimab-combination group as compared to the placebo-combination group, but the incidence of SAEs was comparable between groups (Table 3 and Table S2 in the Supplementary Appendix).

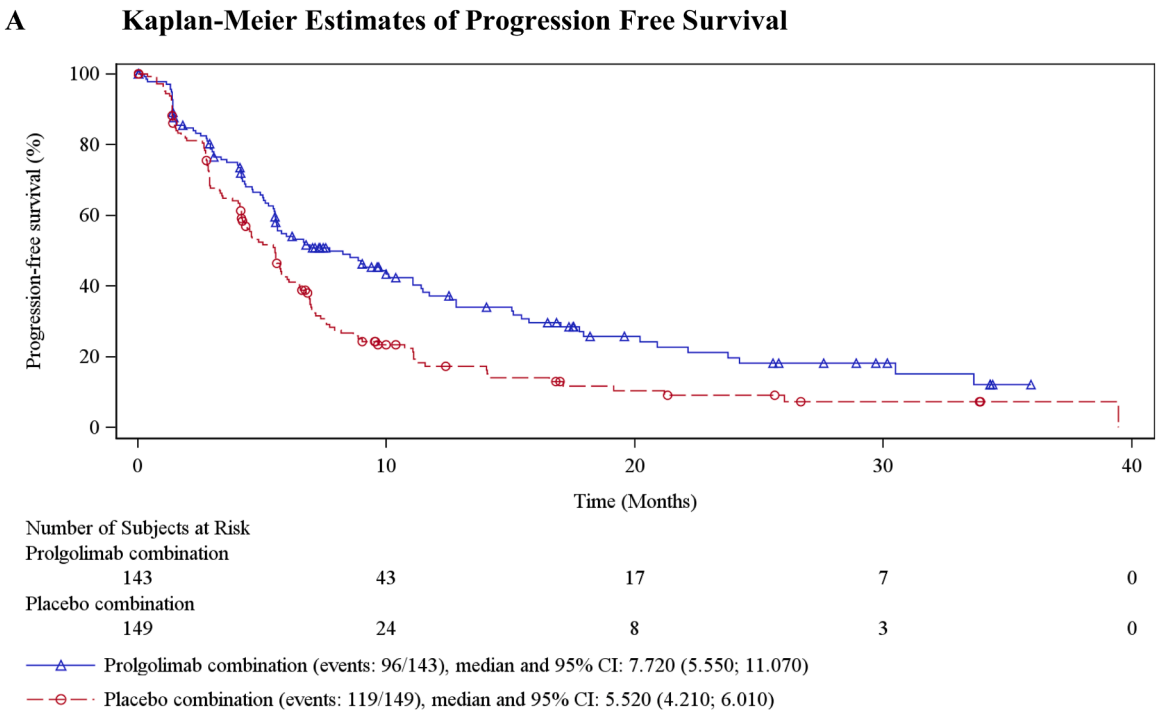
The only adverse events that were reported in at least 10 % of the patients that were significantly more frequent in the prolgolimab-combination group were blood creatinine increased and dyspnoea (Fig. 4).

Immune relatedness of AEs was assessed by the investigator. The overall incidence of immune-related AEs (irAEs) in the placebo-combination group do not exceed incidence of placebo-reported irAE in other randomized controlled trials [7]. Each irAE was reported for less than 5 % of the patients. Most cases were grade 1–2. The majority of severe reported irAE in the prolgolimab-combination group were laboratory abnormalities. Two irAE (pneumonitis and immune-mediated myocarditis) led to death in the prolgolimab-combination group, however after the database lock the investigator reassessed the relatedness of the reported fatal pneumonitis to the study drug to “unrelated”.

4. Discussion

DOMAJOR phase III trial was conducted to access the efficacy and safety of prolgolimab in combination with pemetrexed and platinum-based drug vs placebo in combination with pemetrexed and platinum-based drug as first-line treatment for metastatic non-squamous NSCLC. This trial was initiated at a time when chemotherapy was considered the standard first-line option for this population.

In the DOMAJOR trial the eligibility criteria were designed to be more inclusive and reflect the real-world patient population undergoing first-line treatment for advanced NSCLC. The eligibility criteria did not restrict participation of patients with previously treated and clinically stable CNS metastases (without immunosuppressive doses of steroids, and without mandatory radiological evidence of response to treatment), and with known controlled viral infections. 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



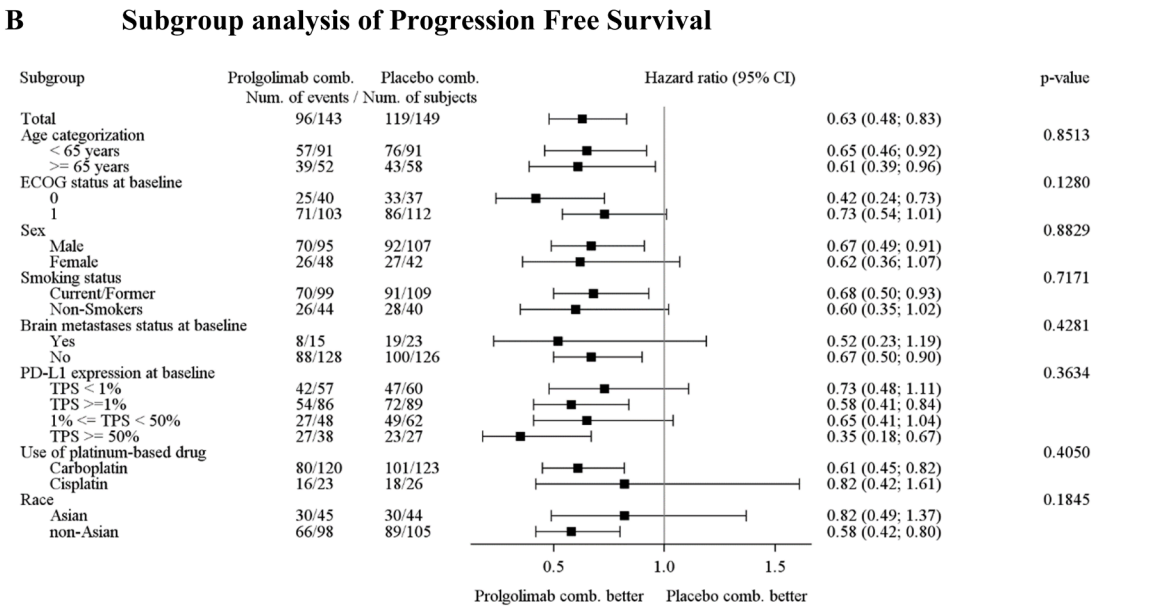


Fig. 3. Progression free survival per RECIST 1.1 assessed by BICR. Full Analysis Set. A Kaplan-Meier Estimates of Progression Free Survival. B Subgroup analysis of Progression Free Survival.

number of whom was higher than those enrolled in similar trials [1]. Most patients were enrolled in Eastern Europe and China, where smoking is the most prevalent, especially among men [8–11]. As a result, the number of men enrolled was higher than women, consistent with the men-to-women ratio (2:1) of lung cancer incidence in Eastern Europe [11–13]. Despite differing geographic areas of enrollment, patient characteristics were similar, and obtained results were consistent.

The DOMAJOR clinical trial showed PFS, OS, and depth of response benefits of adding prolgolimab to standard chemotherapy with pemetrexed and a platinum-based drug in patients with untreated metastatic non-squamous NSCLC without sensitizing *EGFR* mutations or *ALK* rearrangements. The survival benefit associated with prolgolimab combination was consistent across all subgroups of PD-L1 TPS, including patients with PD-L1-negative cancers, a population for which PD-1 and PD-L1 inhibitors both as monotherapy and in combination with other drugs demonstrate lower clinical activity [1,14–19]. The efficacy of prolgolimab-combination therapy across all PD-L1 expression levels was also shown previously in the international randomized double-blind phase II CAESURA study for treatment patients with advanced cervical cancer despite limited sample size [20].

It is not unlikely that described efficacy in the PD-L1-negative cancers is associated with prolgolimab structure: it was designed as a recombinant IgG1 antibody carries a LALA (L234A/L235A) mutation, which reduces its binding to FcγR and has been described as one of the most potent modifications reducing the antibody effector functions [4,21]. These effector functions may negatively affect the efficacy of

Table 3
Safety parameters. Safety analysis set.

Parameter	Prolgolimab Combination (N = 143)n (%)	Placebo Combination (N = 148)n (%)	Total(N = 291) n (%)	CI for difference (%)[h]
Proportion of patients with AEs	139 (97.2)	132 (89.2)	271 (93.1)	2.4–14.4
Proportion of patients with grade 3 or 4 AEs	81 (56.6)	55 (37.2)	136 (46.7)	8.0–30.4
Proportion of patients with immune-related AEs[i]	49 (34.3)	22 (14.9)	71 (24.4)	9.6–29.0
Proportion of patients requiring all study therapy discontinuation due to AEs	14 (9.8)	12 (8.1)	26 (8.9)	−5.1–8.6
Proportion of patients requiring discontinuation (withdrawal) of study drug (Prolgolimab/Placebo) due to AEs	14 (9.8)	13 (8.8)	27 (9.3)	−5.9–8.0
Proportion of patients requiring discontinuation (withdrawal) of pemetrexed due to AEs	22 (15.4)	16 (10.8)	38 (13.1)	−3.3–12.6
Proportion of patients requiring discontinuation (withdrawal) of platinum-based drug due to AEs	3 (2.1)	6 (4.1)	9 (3.1)	−6.7–2.4
Proportion of patients requiring temporary discontinuation (interruption) of study drug (Prolgolimab/Placebo) due to AEs	89 (62.2)	67 (45.3)	156 (53.6)	5.5–28.0
Proportion of patients with SAEs	35 (24.5)	34 (23.0)	69 (23.7)	−8.3–11.3
Proportion of patients with grade 5 AEs	12 (8.4)	16 (10.8)	28 (9.6)	−9.5–4.6
Proportion of patients with grade 5 ARs	2 (1.4)[j]	0	2 (0.7)	−1.2–5.0

[h] two-sided 95 % CI for the percentage difference between the Prolgolimab-combination and Placebo-combination groups according to the method of Miettinen-Nurminen.

[i] Immune relatedness of AEs was assessed by the investigator

[j] After the database lock the investigator reassessed the relatedness of one of the two reported fatal ARs to the study drug to "unrelated"

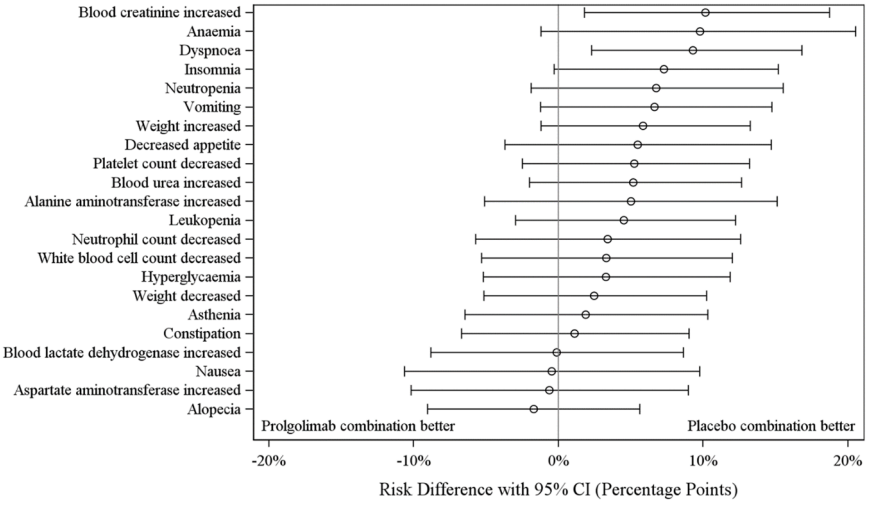


Fig. 4. Forest plot for the most frequent (reported in ≥ 10 % of patients) adverse events. Safety Analysis Set.

antitumor therapy by eliminating PD-1^{+} T-cells via ADCC, ADCP and CDC [22]. Nevertheless, this statement deserves further evaluation in the non-clinical research.

The observed OS benefit was consistent across other studied subgroups, except for patients receiving cisplatin which may be explained by the relatively small number of participants in this treatment group that was underpowered for efficacy assessment. As expected in the era of immunotherapy, the survival curves in the prolgolimab-group seemed to be reaching a plateau at the time of this analysis.

Superior treatment efficacy was observed across all secondary efficacy endpoints. The 24-month PFS was 20 % in the immunotherapy group compared with 9 % in the chemotherapy-only group, which is consistent with data from similar studies. ORR rate as a correlation factor of long-term success of immunotherapy for patients with NSCLC was about 2 times higher in the prolgolimab group vs chemotherapy group.

The safety profile of the prolgolimab-combination group was favorable that is in line with previous studies of this drug. No unexpected safety concerns occurred for this prolgolimab-based therapy. The addition of prolgolimab did not appear to increase the frequency of AEs that are commonly associated with pemetrexed-platinum chemotherapy. The incidence of immune-mediated AEs was not higher than that previously observed with prolgolimab monotherapy [3,4,23]. The frequency of severe AEs and therapy discontinuation due to AEs were lower with indirect comparison with others similar trials [18,19,24–26].

5. Conclusion

The DOMAJOR data demonstrated that addition of prolgolimab to standard chemotherapy with pemetrexed and platinum drug conferred a significant benefit with respect to overall survival, progression-free survival and response rate among patients with metastatic non-squamous NSCLC without sensitizing *EGFR* mutations or ALK rearrangements. The survival benefit for prolgolimab combination therapy was observed across all categories of PD-L1 expression. The safety profile is favorable.

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CRediT authorship contribution statement

K. Laktionov: Investigation, Conceptualization, Supervision. **A. Smolin:** Investigation, Conceptualization, Supervision. **D.Stroyakovskiy:** Investigation, Conceptualization, Supervision. **V. Moiseenko**: Investigation. **M. Dvorkin:** Investigation. **T. Andabekov**: Investigation. **Y. Cheng:** Investigation. **B. Liu:** Investigation. **V. Kozlov**: Investigation. **S. Odintsova**: Investigation. **S. Dvoretsky**: Investigation. **A. Mochalova**: Investigation. **M. Urda**: Investigation. **T. Yi**: Investigation. **X. Li:** Investigation. **U. László**: Investigation. **V. Müller:** Investigation. **K. Bogos**: Investigation. **N. Fadeeva**: Investigation. **G. Musaev**: Investigation. **Q. Liu:** Investigation. **D. Kirtbaya:** Investigation. **J. Shi**: Investigation. **O. Gladkov**: Investigation. **M. Narimanov**: Investigation. **T. Semiglazova**: Investigation. **A. Khasanova:** Investigation. **J. Chovanec**: Investigation. **I. Andrašina**: Investigation. **A. Szabová:** Investigation. **O. Rosinská:** Investigation. **D. Sudekova:** Investigation. **P.-S. Zsolt**: Investigation. **F. Ran:** Investigation. **M. Sun:** Investigation. **O. Jiang:** Investigation. **R. Chen:** Investigation. **E. Zhao:** Investigation. **C. Liu:** Investigation. **W. Tan:** Investigation. **A. Pirmagomedov:** Investigation. **E. Poddubskaya**: Investigation. **N. Kislov**: Investigation. **I. Shumskaya:** Investigation. **I. Sorokina**: Writing – review & editing, Validation, Methodology, Data curation. **A. Zinkina-Orikhan**: Supervision, Review and editing. **Yu. Linkova:** Supervision, Review and editing. **S. Fogt:** Supervision, Review and editing. **D. Liaptseva**: Writing – review & editing, Validation, Methodology, Data curation. **A. Siliutina:** Writing – review & editing, Validation, Methodology, Data curation. **O. Basova**: Formal analysis. **F. Kryukov**: Conceptualization, Validation, Methodology, Review and editing, Supervision.

Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115255.

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