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Original Research

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

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Abstract ***Background:*** Prolgolimab is an IgG1 anti–PD-1 (programmed cell death protein 1) monoclonal antibody containing the Fc-silencing 'LALA' mutation. We assessed the efficacy and safety of two dosing regimens of prolgolimab in patients with advanced melanoma in a multicenter open-label parallel-arm phase II trial (MIRACULUM). We present the final analysis after 1 year of follow-up and additional efficacy results from 2 years of follow-up.
Methods: Patients with advanced cutaneous or non-cutaneous melanoma, including stable brain metastasis, without autoimmune disease and who underwent no prior targeted therapy, anti–PD-(L)1 or anti–CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) therapy were randomly assigned (1:1) to receive prolgolimab in 2 dosing regimens, 1 mg/kg every 2 weeks

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(arm 1) or 3 mg/kg every 3 weeks (arm 2), until disease progression or intolerable toxicity. Randomisation was stratified based on performance status (Eastern Cooperative Oncology Group 0 or 1), lactate dehydrogenase levels (elevated or normal) and prior systemic therapy (naive or previously treated). The primary outcome was the objective response rate, assessed as per immune-related Response Evaluation Criteria in Solid Tumours by independent central review. The hypothesis that each dosing regimen of prolgolimab has an overall response rate >28% was tested independently for each study arm comprising all patients who received at least one dose of prolgolimab. Exploratory assessment of efficacy, including subgroup analysis, at 2 years of follow-up was not specified in the protocol. This study is registered withClinicalTrials.gov(NCT03269565).

Results: Between August 2017 and March 2018, 126 patients with advanced melanoma were enrolled. At main 1-year data cut-off, the median follow-up was 13.8 and 14.5 months in arm 1 and 2, respectively. An objective response was observed in 38.1% of patients (arm 1) and in 28.6% (arm 2). Grade III–IV treatment-related adverse events occurred in 12.7% and 3.2% of patients in arm 1 and 2, respectively. For exploratory efficacy analysis, the median follow-up was 25.4 and 25.7 months in arm 1 and 2, respectively. The 2-year progression-free survival was 33.3% in arm 1 and 30.2% in arm 2, and the 2-year overall survival was 57.1% and 46.0%, respectively.

Conclusions: The MIRACULUM study met its primary end-point in both the study arms. Prolgolimab showed significant antitumour activity and a manageable safety profile in patients with advanced melanoma.

1. Introduction

Melanoma remains the deadliest type of skin cancer, with a worldwide annual increase in incidence [1]. Immune checkpoint blockade (e.g. anti–PD-1/L1) represents a significant achievement in melanoma care. For instance, anti–PD-1 therapeutic antibodies, including pembrolizumab and nivolumab, dramatically improve prognosis in patients with advanced melanoma [2–5]. In treatment-naive patients with advanced melanoma, pembrolizumab monotherapy or nivolumab monotherapy resulted in an objective response rate (ORR) of 39.4% and 40.0%, respectively [2,6]. Long-term follow-up demonstrated that approximately 40% of patients will survive for 5 years and more [7,8].

Based on the results mentioned previously, both anti–PD-1 therapies have become the standard of care for patients with advanced melanoma.

The variable region of the monoclonal antibodies (mAbs) that target immune checkpoints is critical for primary functional activities. However, the antibody effector functions mediated through interaction of the crystallisable fragment (Fc) with Fcg receptors [9] are also important for improving clinical outcomes [10]. Most anti–PD-1 mAbs, including nivolumab and pembrolizumab, have an IgG4S228P heavy chain, which retains effector-binding functions similar to that of wild-type human IgG4 [11]. Human IgG4 has low affinity to FcgRIIIa and low antibody-dependent cellular cytotoxicity (ADCC) induction [12] and has high affinity to FcγRI, which can have an impact on the efficacy of therapy [13,14]. IgG4 can bind to FcγRIIb, leading to reduced antitumour efficacy probably through induction of a more immunosuppressive environment [13,15]. FcγRI binding is substantially reduced in the IgG1 mAbs with the 'LALA' mutation (L234A/L235A), compared with IgG4S228P mAbs [16]. Moreover, the LALA mutation eliminated binding to FcγRI, IIa and IIIa for both IgG1 and IgG4 [17]. Another study showed the double mutant did not bind either FcγR or C1q and abolished both ADCC and complement-dependent cytotoxicity functions [18]. Therefore, an anti–PD-1 antibody with LALA mutations potentially may have additional benefits in anti–PD-1 therapy.

Prolgolimab (formerly, BCD-100) is an IgG1 anti–PD-1 mAb that contains the Fc-silencing LALA mutation, which provides an immunopotentiating advantage by abolishing the interaction between the Fc-region of the antibody and FcγR expressed on various immune cells, thus blocking the possible effector functions of the antibody [10]. Anti–PD-1 mAbs with $IgG4_{S228P}$ retain high-affinity binding to FcγRI and mediate cross-linking of PD-1 and FcγRI, which brings PD-1+ T cells and $Fc\gamma RI^{+}$ macrophages together. The cross-linking induces the inhibition of PD-1+ T-cell functions via antibody-dependent cellular phagocytosis (ADCP) and macrophage-mediated IL-10 secretion [19].

During a phase I study, prolgolimab demonstrated a favourable safety profile and objective tumour responses in heavily pretreated patients with advanced solid tumours, including melanoma [20]. Two dosing regimens of prolgolimab (1 mg/kg every 2 weeks [Q2W] and 3 mg/

kg every 3 weeks [Q3W]) were chosen based on the results of phase I study and pharmacokinetic modelling. Herein, we report the final analysis of prolgolimab treatment in patients with advanced melanoma in a multicentre open-label parallel-arm (MIRACULUM) study. In addition, we provide updated efficacy results after 2 years of follow-up. This trial is the first to our knowledge to evaluate prolgolimab, a novel IgG1 anti–PD-1 antibody with the Fc-silencing 'LALA' mutation, in patients with advanced melanoma.

2. Methods

2.1. Patients

The inclusion criteria included adult patients (≥18 years old) with stage II–IV unresectable or metastatic melanoma; who were treatment-naive or previously treated (≤2 lines of systemic chemotherapy); who had never received targeted therapy, anti–PD-1 or anti–CTLA-4 therapy; with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and without autoimmune disease. The enrolment of patients previously treated for advanced disease was limited to 30%. Patients with stable brain metastases and patients with non-cutaneous melanoma were eligible. $BRAF^{V600E/K}$ mutation status and programmed death ligand 1 (PD-L1) expression were not considered exclusion criteria. The prior targeted therapy (BRAF/MEK inhibitors and other tyrosine kinase inhibitors) was an exclusion criterion.

2.2. Trial design and treatment

In this multicenter open-label parallel-arm phase II trial, the patients were randomly assigned in a 1:1 ratio to receive one of the following regimens: prolgolimab at a dose of 1 mg per kilogram of body weight Q2W or prolgolimab at a dose of 3 mg per kilogram Q3W. Randomisation was stratified based on performance status (ECOG score of 0 or 1), lactate dehydrogenase (LDH) levels (elevated or normal) and prior therapy for advanced disease (naive or previously treated). Treatment was continued until disease progression, intolerable toxicity or withdrawal of consent. Immune-related response criteria (immune-related Response Evaluation Criteria in Solid Tumours [irRECIST]) were used to assess tumour progression [21]. The prolgolimab therapy was continued for up to one year after the administration of the first dose until unacceptable toxicity, progressive disease (irRECIST), death or withdrawal of consent. Patients with clinical benefit and no signs of unacceptable toxicity could continue treatment after one year according to the investigator's discretion in the extension study.

2.3. Assessments

Tumour response was assessed by a blinded independent central review as per irRECIST. The assessment was conducted once every 8 weeks for the first 6 months and then once every 12 weeks for up to one year from the start of the therapy or until progression or discontinuation of treatment. Survival was assessed using the pooled data available, including data from the follow-up visits and phone calls with dropouts until death, loss to follow-up or withdrawal from the trial. PD-L1 expression was examined retrospectively in a central laboratory by immunohistochemistry (BIOCAD's in-house immunohistochemistry PD-L1 test system) using the combined positive score (CPS) [22]. $BRAF^{V600E/K}$ mutation status was determined following local laboratories' standards. Safety parameters were assessed as per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [23]. Immunogenicity was studied in patients who had assessable samples at the screening and at least one another sampling time point.

2.4. Trial oversight

The protocol and amendments were approved by the ethics boards and committees at each trial site. The trial was conducted as per the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonisation. All the patients were provided with written informed consent before initiation of any study procedures. The sponsor, BIOCAD, designed the trial. Data were collected and analysed by the sponsor. The article was submitted for publication after all the authors contributed to subsequent drafts and provided final approval.

2.5. Statistical analysis

For each study arm, there was an independent primary end-point of ORR (as per irRECIST). The secondary efficacy parameters were progression-free survival (PFS), overall survival (OS), disease control rate (DCR), time to response (TTR) and duration of response (DOR).

Efficacy end-points were analysed in the modified intent-to-treat population (patients who had received at least one dose of prolgolimab). The sample size was estimated for each study arm using different hypotheses (for two different dosing regimens) [24]. The statistical hypothesis that prolgolimab has a significant antitumour effect (an ORR more than 28% doubled the efficacy of dacarbazine monotherapy [2]) was tested for each study arm with a type I error (a rate of 5% [$\alpha = 0.05$]), a type II error (a rate of 20% [$\beta = 0.2$]) and 80% power. The enrolment of approximately 57 patients

would be required for the analysis of the primary end-point in each study arm.

The final analysis of PFS and OS occurred after all the patients had at least 12 months of follow-up. Exploratory assessment of efficacy, including subgroup analysis, at 2-year follow-up was not specified in the protocol. The efficacy data characterising survival were analysed using the log-rank test, Kaplan-Meier method and survival tables. The trial design was not powered for a comparison between the two dosing regimens.

3. Results

3.1. Patients and treatment

The trial was conducted at 21 study sites from August 21, 2017, through February 22, 2019. In total, 126 patients (63 in each arm) received at least one intravenous dose of prolgolimab: 1 mg/kg Q2W (arm 1) or 3 mg/kg Q3W (arm 2). The demographic and baseline disease characteristics of the patients were well balanced (Table 1). At baseline, 69.8% of patients in the Q2W arm and 74.6% of patients in the Q3W arm had stage IV-M1c disease (American Joint Committee on Cancer, 7th edition) [25], 33.3% and 34.9% had elevated LDH levels, 27.0%, and 14.3% had stable brain metastases, 6.4%, and 7.9% had non-cutaneous melanoma (uveal or mucosal), 33.3% and 38.1% had a $BRAF^{V600\ E/K}$ mutation and 52.4% and 49.2% were PD-L1 positive (CPS $\geq$1), respectively. The proportion of treatment-naive and previously treated patients included in the study was 73.0% and 27.0% in arm 1 and 74.6%, and 25.4% in arm 2, respectively. A significant difference in baseline tumour size (BTS) was noted between the groups (Table 1).

The database for final study analysis was locked at February 22, 2019, the median follow-up was 13.8 months (95% confidence interval [CI], 13.2–14.7) in arm 1 and 14.5 months (95% CI, 13.9–15.2) in arm 2. The data cut-off for 2-year efficacy analysis was March 1, 2020, and the median follow-up was 25.4 months (95% CI, 24.8–27.0) in arm 1 and 25.7 months (95% CI, 24.6–27.2) in arm 2. The number of patients who completed one year of therapy in accordance with the protocol and extended their treatment was 21 patients in the Q2W arm and 17 patients in the Q3W arm (Fig. 1).

3.2. Efficacy

In the prolgolimab Q2W arm, 5 complete and 19 partial responses were registered, with an ORR of 38% and DCR of 63.5%. In the prolgolimab Q3W arm, 2 complete and 16 partial responses were observed, with an ORR of 28.6% and a DCR of 46% (Table 2). Both dosing regimens exceeded the 28% predefined ORR; therefore, the study met its primary end-point.

At 1-year data cut-off, the median TTR was 3.7 months (95% CI, 1.8 to 4.0) and 3.7 months (95% CI, 1.8 to 5.6) in the Q2W and Q3W arms, respectively. The median DOR has not been reached in either study arm. After 2 years of follow-up, 75% of all responses were ongoing.

Objective response was registered in subpopulations of patients with unfavourable prognostic factors such as brain metastases. Objective response was observed in 29.1% of patients with brain metastases in arm 1 and in 33.3% of patients with brain metastases in arm 2.

Table 1
Patient characteristics.

Characteristics	Prolgolimab, 1 mg/kg, Q2W (n = 63)	Prolgolimab, 3 mg/kg, Q3W (n = 63)
Age, median, years	57 (27–83)	57 (24–82)
Sex		
Male	29 (46.0%)	28 (44.4%)
Female	34 (54.0%)	35 (55.6%)
ECOG performance status score		
0	34 (54.0%)	36 (57.1%)
1	29 (46.0%)	27 (42.9%)
Metastasis stage (AJCC, 7th edition)		
M1a	6 (9.5%)	8 (12.7%)
M1b	13 (20.6%)	8 (12.7%)
M1c	44 (69.8%)	47 (74.6%)
Brain metastases		
Yes	17 (27.0%)	9 (14.3%)
No	46 (73.0%)	54 (85.7%)
LDH		
Normal	42 (66.7%)	41 (65.1%)
Elevated	21 (33.3%)	22 (34.9%)
Baseline tumour size, median[b]	71 mm	97 mm
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%)
Non-cutaneous melanoma		
Uveal	3 (4.8%)	5 (7.9%)
Mucosal	1 (1.6%)	0
PD-L1 expression[a]		
Positive	33 (52.4%)	31 (49.2%)
Negative	12 (19.1%)	14 (22.2%)
Unknown	18 (28.6%)	18 (28.6%)
$BRAF^{V600E/K}$ status		
Wild-type	25 (39.7%)	22 (34.9%)
Mutant	21 (33.3%)	24 (38.1%)
Unknown	17 (27.0%)	17 (27.0%)

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

[a] Defined as a CPS $\geq$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.

[b] $p < 0.05$.

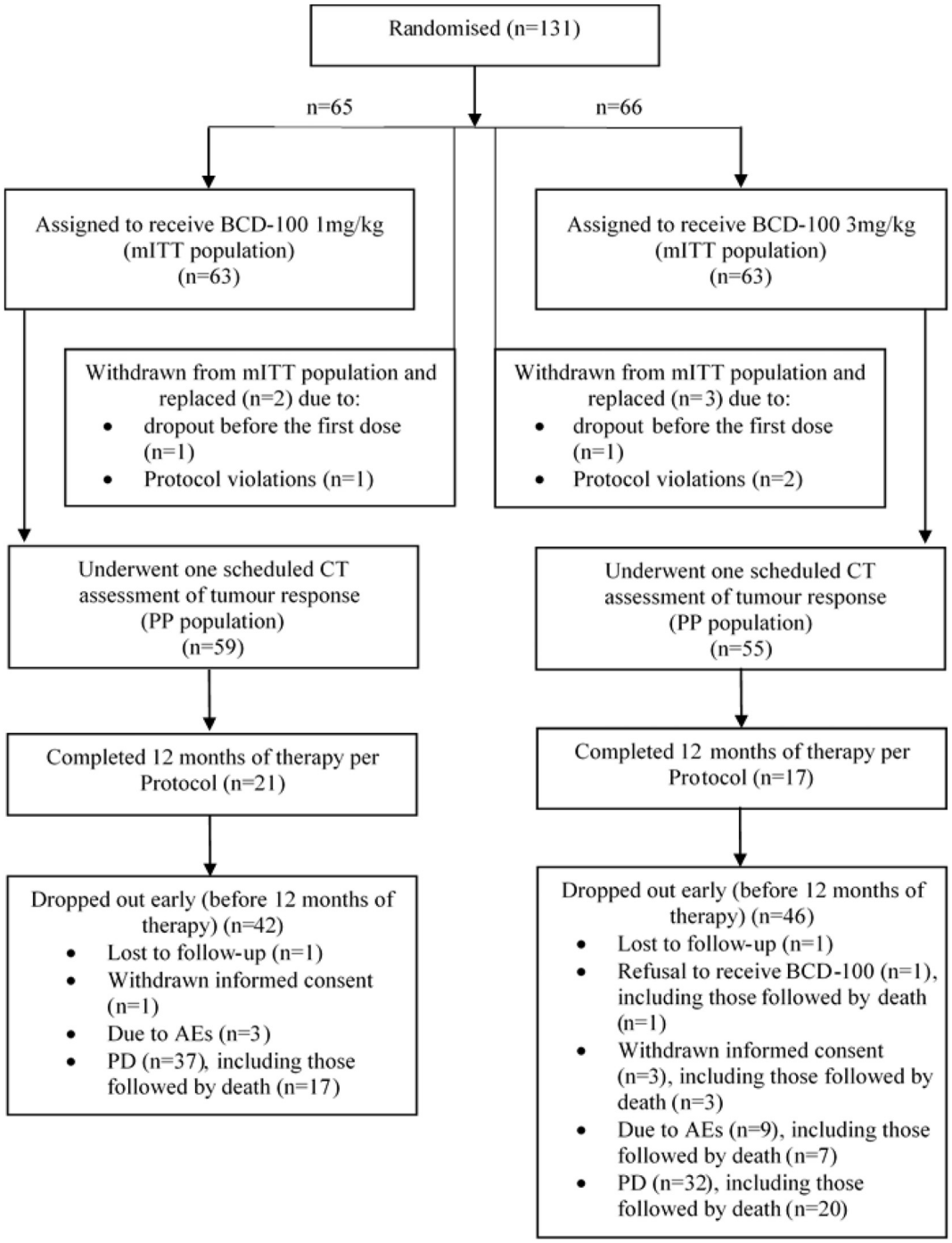


Fig. 1. Trial CONSORT diagram. mITT population = a modified intent-to-treat population, patients who had received at least one dose of BCD-100; PP population = a per-protocol population, patients who had received at least one dose of BCD-100 and who had undergone at least one scheduled CT examination to assess the dynamics of tumour response (apart from the baseline); CT = computed tomography; AEs = adverse events; PD = progressive disease.

After 2 years of follow-up, the median OS was not reached (NR) in the prolgolimab 1-mg/kg Q2W arm, and 15.0 months (95% CI, 10.2 to NR) in the 3-mg/kg Q3W arm (Fig. 2). The OS at 2-year follow-up was 57.1% and 46.0% in the Q2W and Q3W arms, respectively. The median PFS was 6.6 months (95% CI, 3.9 to 13.9) in the Q2W arm and was 3.7 months (95% CI, 2.1 to 8.5) in the Q3W arm (Fig. 3). Two-year PFS was achieved in 33.3% of patients in the Q2W arm and in 30.2% of patients in the Q3W arm.

In a protocol, non-specified subgroup analysis of prolgolimab monotherapy resulted in durable responses in patients with poor prognostic factors, including ECOG Performance Status of 1, elevated LDH levels,

Table 2
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 (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.

PD-L1 CPS of <1, BTS ≥100 mm, brain metastasis, and previous systemic therapy (Table S1, Supplementary Appendix). Numerically better efficacy results, including ORR, PFS and OS, were observed in treatment-naive patients with cutaneous melanoma (Table 3). None of the patients with non-cutaneous melanoma responded. The best response to treatment in 8 patients was stable disease in 2 of 8 patients with uveal melanoma.

3.3. Safety

A total of 126 patients received at least one dose of study treatment and were included in the safety analysis population. No statistically significant difference was found between the study arms in any safety parameter. The majority of adverse events (63.9%) during 1-year follow-up were reported in the first 3 months of treatment.

The incidence of any-grade treatment-related adverse events was similar in the 1-mg/kg Q2W and 3-mg/kg Q3W arms, 55.6% and 54.0%, respectively. Treatment-related adverse events of grade III or higher were reported in 12.7% and 3.2% of patients in the Q2W and Q3W arms, respectively (Table 4).

Treatment-related toxicity resulted in discontinuation of treatment in 2 patients in the 1-mg/kg Q2W arm and 1 patient in the 3-mg/kg Q3W arm—treatment-related adverse events leading to discontinuation comprised pneumonitis. Two cases of treatment-related serious adverse events were reported in the prolgolimab 1-mg/kg group: grade III hypersensitivity pneumonitis and grade IV pneumonitis. No deaths were deemed related to prolgolimab toxicity.

Immune-related adverse events (irAEs) were registered in 36.5% and 34.9% of patients in the Q2W arm and Q3W arm, respectively. Most of the irAEs were of grade I or II. Most of the irAEs comprising endocrine and cutaneous toxicities including irAEs of grade III or higher were reported in 5 patients in the Q2W arm (7.9%) and 1 patient in the Q3W arm (1.6%) (Table 5).

Immunogenicity analysis did not reveal anti-prolgolimab antibodies in patients who had assessable samples at the screening and at least one another sampling time point (n = 121).

4. Discussion

To our knowledge, MIRACULUM, is the first phase II trial of an IgG1 PD-1 inhibitor with the silenced Fc-region. At 1-year data cut-off, the primary end-point was met in both the study arms, showing that prolgolimab monotherapy resulted in objective response in 42 of 126 patients with advanced melanoma who received at least one dose of treatment.

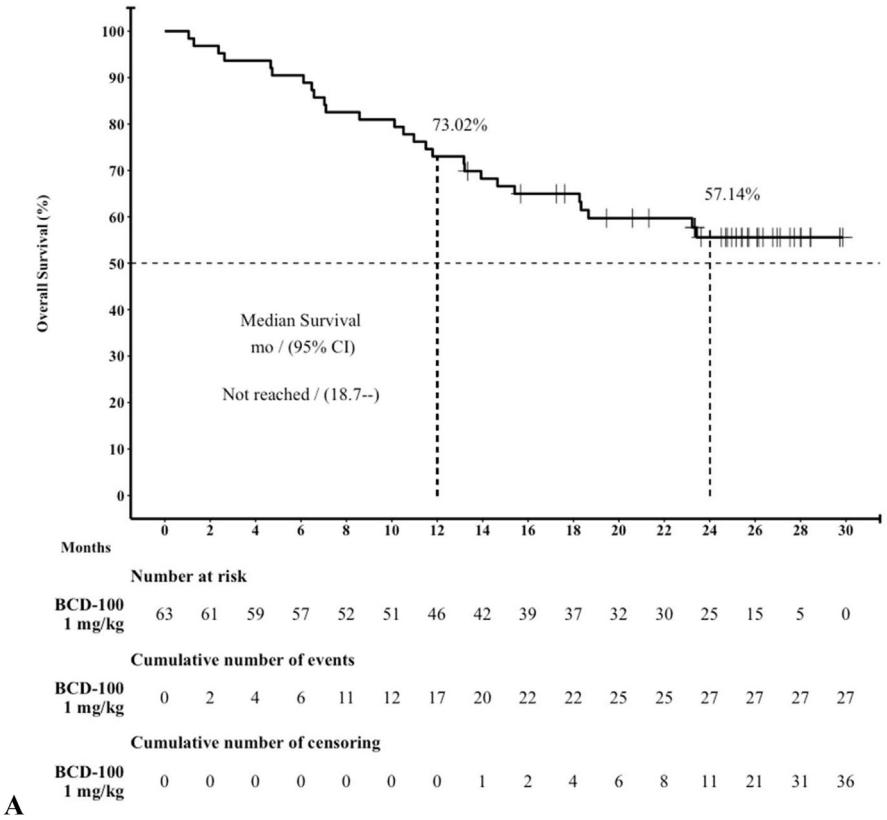
Overall, patients included in MIRACULUM had a poor prognosis. Almost half of the patients had an ECOG PS of 1, more than one-third had elevated LDH levels, one fourth had ≥1 line of previous systemic therapy for advanced disease and one-fifth had brain metastases. This study included 8 patients with uveal melanoma, which is known to be almost irresponsive to any kind of systemic treatment [26,27]. As expected, prolgolimab demonstrated observably better efficacy in treatment-naive patients with cutaneous melanoma.

Although not directly comparable owing to trial design, both dosing regimens of prolgolimab (1 mg/kg Q2W and 3 mg/kg Q3W) demonstrated similar efficacies to other anti–PD-1 antibodies in patients with advanced melanoma [2,3]. Most responses were durable and ongoing at the time of data cut-off, including 2-year follow-up, regardless of the treatment group. The current analysis provides clinically meaningful data on disease control in patients with advanced melanoma.

In our study, there was a trend to worse ORR and OS rates in the 3-mg/kg group, which is potentially due to the significant difference in BTS between the groups. It has been shown that BTS is an independent prognostic factor for OS in patients with melanoma treated with pembrolizumab. Moreover, it negatively and significantly affects ORR [28].

In our trial, there were no new safety concerns compared with previous reports of other anti–PD-1 agents [2–4]. Most of the treatment-related adverse events observed were of grade I or II, emphasising an acceptable safety profile of prolgolimab in patients with advanced melanoma. Notably, only 2 patients discontinued the treatment owing to a treatment-related adverse event.

The key limitations to this study are a small number of patients and the absence of a comparator arm. Longer follow-up results with comparator arms will be available in the ongoing phase III trials in patients with advanced non–small cell lung cancer [29] and cervical cancer [30] and will further characterise clinical activity



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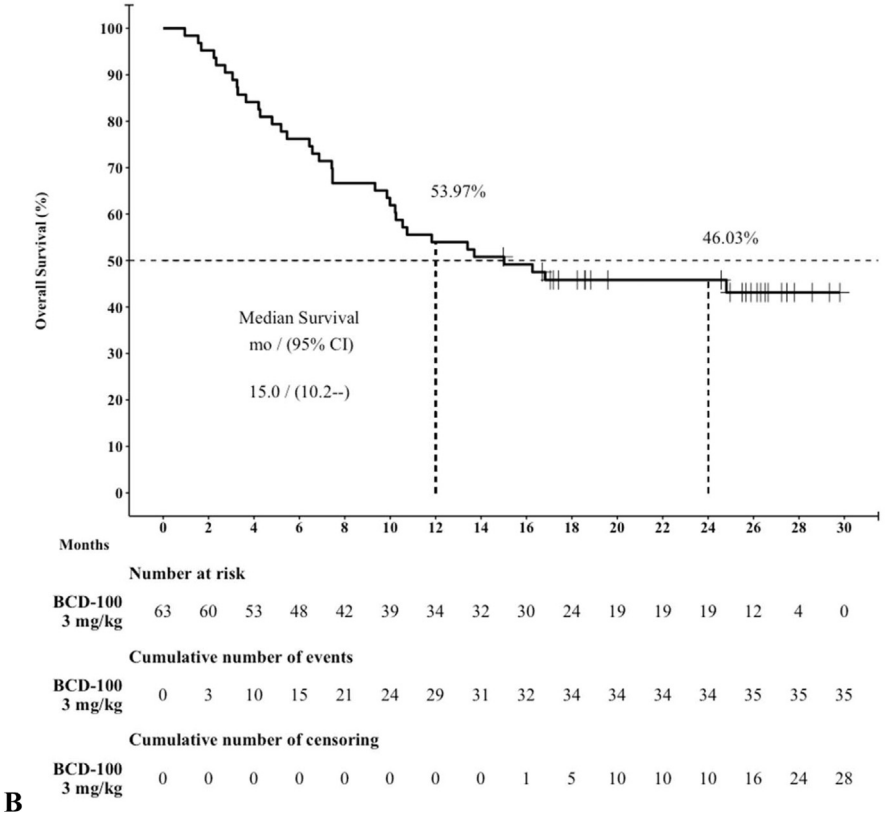

B

Fig. 2. (A–B) Kaplan-Meier plots of overall survival. (A) Prolgolimab, 1 mg/kg, every 2 weeks; (B) prolgolimab, 3 mg/kg, every 3 weeks. CI = confidence interval.

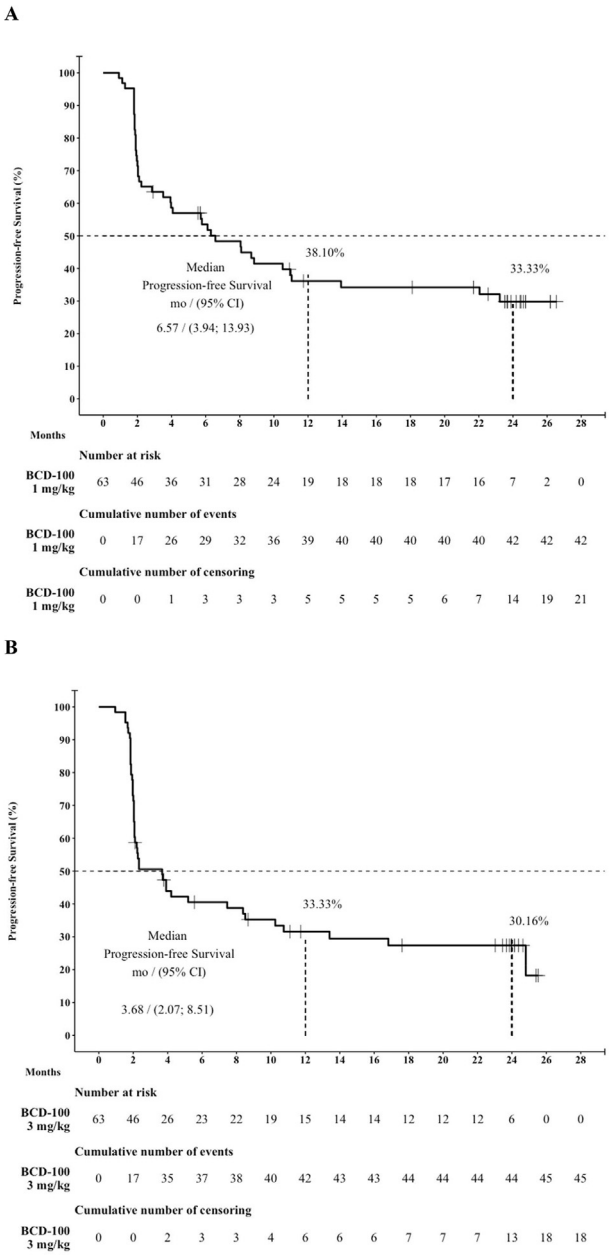

Fig. 3. (A–B) Kaplan-Meier plots of progression-free survival. (A) Prolgolimab, 1 mg/kg, every 2 weeks; (B) prolgolimab, 3 mg/kg, every 3 weeks. CI = confidence interval.

Table 3
Subgroup analysis of efficacy in treatment-naive patients with cutaneous melanoma.

Efficacy parameters	Prolgolimab, 1 mg/kg, every 2 weeks (n = 45)	Prolgolimab, 3 mg/kg, every 3 weeks (n = 44)
Objective response rate, %	48.9	31.8
Overall survival at 24 months, %	64.4	47.7
Median overall survival, months (95% CI)	Not reached (NR; NR)	16.5 (10.0; NR)
Progression-free survival at 24 months, %	42.2	29.5
Median progression-free survival, months (95% CI)	8.84 (4.0; NR)	3.91 (2.2; 13.4)

CI = confidence interval; NR = not reached.

Table 4
General safety data of prolgolimab.

Safety parameters	Prolgolimab, 1 mg/kg, every 2 weeks (n = 63)		Prolgolimab, 3 mg/kg, every 3 weeks (n = 63)	
	n	%	n	%
Treatment-related AEs	35	55.6	34	54.0
Grade ≥3 treatment-related AEs	8	12.7	2	3.2
Treatment-related SAEs	2	3.2	0	0.00
Immune-related AEs	23	36.5	22	34.9
Grade ≥III irAEs	5	7.9	1	1.6
Treatment discontinuation due to TRAEs	2	3.2	1	1.6

AE, adverse event; TRAE, treatment-related adverse event; SAE - serious adverse event; irAE, immune-related adverse event.

and durability of therapeutic effect of prolgolimab in patients with advanced solid tumours.

Another limitation of this study is the use of a non-survival primary end-point. However, ORR is the most common primary end-point in phase II trials of immune checkpoint inhibitors, including anti–PD-1 antibodies [31]. Finally, while the sample sizes for the post hoc subgroup analyses of efficacy were small, objective responses were observed in all groups.

Regardless of these limitations, prolgolimab showed clinical activity in two dosing regimens in a patient group that has a poor prognosis. Moreover, objective responses were registered in patients with brain metastases (8 of 26 patients) and in patients with PD-L1–negative tumours (4 of 26 patients).

To our knowledge, this is the first prospective study of a novel $IgG1_{LALA}$ anti–PD-1 therapeutic antibody prolgolimab in patients with advanced melanoma. Zhang et al [19] clearly demonstrated a better anti-tumour efficacy of the anti–PD-1 mAb with no binding to FcγRI compared with $IgG4_{S228}$. Further clinical studies needed to elucidate whether anti–PD-1 therapeutic antibodies with silenced effector functions, including FcγRI cross-link–mediated ADCP, have clinical advantage over conventional $IgG4_{S228}$, such as pembrolizumab and nivolumab.

The actual clinical development programme of prolgolimab included trials in melanoma, non-small cell lung cancer and cervical cancer. And numerous tumour types are under discussion for further clinical development of prolgolimab in immuno-oncological combinations.

Table 5
Immune-related adverse events.

Immune-related adverse events	Prolgolimab, 1 mg/kg (n = 63)		Prolgolimab, 3 mg/kg (n = 63)		p-value
	n	%	n	%	
Endocrine disorders					
Endocrine disorders (total)	13[a]	20.7	16[b]	25.4	0.671[c]
Thyroiditis	1	1.6	4	6.4	0.365[d]
Grade I	0	0	2	3.2	0.496[d]
Grade II	1	1.6	1	1.6	1.000[d]
Grade III	0	0	1	1.6	1.000[d]
Hypothyroidism	9	14.3	8	12.7	1.000[c]
Grade I	3	4.8	3	4.8	1.000[d]
Grade II	6	9.5	5	7.9	1.000[d]
Hyperthyroidism	10	15.9	7	11.1	0.603[c]
Grade I	6	9.5	2	3.2	0.273[d]
Grade II	4	6.4	5	7.9	1.000[d]
Skin and subcutaneous tissue disorders					
Rash	5	7.9	1	1.6	0.207[d]
Grade I	1	1.6	1	1.6	1.000[d]
Grade II	2	3.2	0	0	0.496[d]
Grade III	2	3.2	0	0	0.496[d]
Pruritus	1	1.6	1	1.6	1.000[d]
Grade II	0	0	1	1.6	1.000[d]
Grade III	1	1.6	0	0	1.000[d]
Vitiligo (grade I)	1	1.6	1	1.6	1.000[d]
Respiratory, thoracic and mediastinal disorders					
Pneumonitis	2	3.2	4	6.4	0.680[d]
Grade I	0	0	1	1.6	1.000[d]
Grade II	1	1.6	2	3.2	1.000[d]
Grade III	1	1.6	0	0	1.000[d]
Grade IV	0	0	1	1.6	1.000[d]
Blood and lymphatic system disorders					
Lymphocyte count decreased (grade II)	0	0	2	3.2	0.496[d]
Lymphocyte count increased (grade II)	0	0	1	1.6	1.000[d]
Vascular disorders					
Tumour haemorrhage (grade II)	1	1.6	0	0	1.000[d]
Eye disorders					
Uveitis (grade II)	0	0	1	1.6	1.000[d]
Musculoskeletal and connective tissue disorders					
Myositis	2	3.2	0	0	0.496[d]
Grade II	1	1.6	0	0	1.000[d]
Grade III	1	1.6	0	0	1.000[d]
Nervous system disorders					
Neuropathy (grade II)	1	1.6	0	0	1.000[d]

[a] Six patients experienced hyperthyroidism followed by hypothyroidism during the study; one patient experienced both hyperthyroidism and thyroiditis.
[b] Three patients experienced hyperthyroidism followed by hypothyroidism during the study.
[c] Pearson's χ^2 test with Yates correction.
[d] Two-tailed Fisher's exact test.

In conclusion, this study demonstrated antitumour activity and an acceptable safety profile of prolgolimab in patients with advanced melanoma and a poor prognosis. Both dosing regimens of prolgolimab were well tolerated and reached the primary efficacy end-point; therefore, they can be selected for further clinical development.

Author contributions

Sergey Tjulandin: investigation, conceptualisation, validation, supervision, draft. Lev Demidov: investigation, conceptualisation, validation, draft. Vladimir Moiseyenko: investigation, conceptualisation, validation, draft. Svetlana Protsenko: investigation. Tatiana Semiglazova: investigation. Svetlana Odintsova: investigation. Ruslan Zukov: investigation. Sergey Lazarev: investigation. Yuliya Makarova: investigation. Marina Nechaeva: investigation. Dina Sakaeva: investigation. Aleksey Andreev: investigation. Anna Tarasova: investigation. Natalya Fadeyeva: investigation. Mariia Shustova: writing, review and Editing, methodology, draft. Kuryshev Ivan: writing, review and editing, visualisation, methodology.

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Conflict of interest statement

M.N., N.F., R.Z., S.L., S.T., S.O., S.P., T.S., V.M., Y.M., A.T., D.S., L.D. and A.A. report clinical trial investigator's fee (MIRACULUM) and honoraria from BIOCAD for participation as a speaker at scientific and educational meetings. M.S. and K.I. are BIOCAD employees.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.02.030.

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