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Sabatolimab in combination with spartalizumab in patients with non-small cell lung cancer or melanoma who received prior treatment with anti-PD-1/PD-L1 therapy: a phase 2 multicentre study

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ABSTRACT

Objective This study evaluates the safety/efficacy of sabatolimab plus spartalizumab in patients with melanoma or non-small cell lung cancer (NSCLC).

Design, setting and participants This is a phase 1–1b/2, open-label, multinational, multicentre study of patients with advanced/metastatic melanoma or NSCLC with ≥1 measurable lesion.

Interventions Patients were given sabatolimab 800 mg every 4 weeks plus spartalizumab 400 mg every 4 weeks until unacceptable toxicity, disease progression and/or treatment discontinuation.

Outcome measures The phase 2 primary outcome measure was overall response rate and secondary objectives included evaluation of the safety, tolerability, efficacy and pharmacokinetics of sabatolimab in combination with spartalizumab.

Results 33 patients (melanoma n=16, NSCLC n=17) received sabatolimab plus spartalizumab. 31 (94%) experienced ≥1 adverse event (AE); 15 (46%) experienced grade 3/4 events. The most frequent grade ≥3 AEs for NSCLC were anaemia, dyspnoea and pneumonia (each n=2, 12%); for patients with melanoma, the most frequent grade ≥3 AEs were physical health deterioration, hypokalaemia, hypophosphataemia, pathological fracture and tumour invasion (each n=1; 6%). One (3%) patient discontinued treatment due to AE. Stable disease was seen in three patients with melanoma (19%) and six patients with NSCLC (35%). Median progression-free survival was 1.8 (90% CI 1.7 to 1.9) and 1.7 (90% CI 1.1 to 3.4) months for patients with melanoma and NSCLC, respectively. Patients with stable disease had higher expression levels of CD8, LAG3, programmed death-ligand 1 and anti-T-cell immunoglobulin and mucin-domain containing-3 at baseline. The pharmacokinetics profile of sabatolimab was consistent with the phase 1 study.

Conclusions Sabatolimab plus spartalizumab was well tolerated in patients with advanced/metastatic melanoma or NSCLC who had progressed following antiprogrammed death-1/antiprogrammed death-ligand 1 treatment. Limited antitumour activity was observed. The tolerability of sabatolimab administration supports the potential to explore treatment with sabatolimab in various combination regimens and across a spectrum of tumour types.

Trial registration number NCT02608268.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A first-in-human, single-arm, multicentre, multi-country, open-label study to assess the safety and efficacy of the combination of sabatolimab and spartalizumab in patients with advanced malignancies.
⇒ Limited biomarker data are available to be able to identify an association between biomarkers and response to treatment.
⇒ The study was terminated early due to the study sponsor's decision.

INTRODUCTION

In both solid tumours and haematological malignancies, immune dysfunction results in impaired antitumour immune responses, leading to tumour immune escape.[1 2] Programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) blockade therapy has shown sustained survival benefits in multiple malignancies.[3] However, only a minority of patients respond to PD-1/PD-L1 blockade therapy, and these patients are at risk of primary or acquired resistance.[3] Therefore, it is important to investigate new strategies to improve response rates and

prolong the duration of response (DOR) to immune-based therapy.

T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) is an inhibitory cell surface receptor expressed on multiple immune cell types, including dysfunctional and regulatory T cells, natural killer cells, macrophages/monocytes and dendritic cells.[4] TIM-3 is often coexpressed with PD-1 and may also contribute to the resistance to PD-1 blockade.[5 6] Additionally, in animal models, concurrent blockade of TIM-3 and PD-1 restored T-cell function and suppressed tumour growth more effectively than targeting either pathway alone, providing further rationale for dual targeting of TIM-3 and PD-1 for more effective cancer immunotherapy.[7 8]

Sabatolimab (MBG453) is a high-affinity, humanised, anti-TIM-3 IgG4 (S228P) monoclonal antibody that blocks binding of TIM-3 to phosphatidylserine and partially blocks the binding of TIM-3 to galectin-9.[9] Preliminary findings from a phase 1 study of sabatolimab plus hypomethylating agents (HMAs) demonstrate encouraging safety and durable responses with sabatolimab in patients with haematological malignancies, providing support for the use of sabatolimab in situations wherein combination therapy is needed without introducing additional safety concerns.[10] Spartalizumab (PDR001) is a humanised IgG4 (S228P) monoclonal antibody that binds PD-1 and blocks its interaction with PD-L1/2, which has demonstrated preliminary clinical activity in patients with non-small cell lung cancer (NSCLC) or melanoma, with a manageable safety profile.[9 11]

A subset of patients with melanoma or NSCLC do not respond to anti-PD-1/anti-PD-L1 blockade, and upregulation of TIM-3 has been observed in clinical cases of resistance to anti-PD-1 therapy.[5] Therefore, sabatolimab in combination with checkpoint inhibition may show clinical activity in these patients. In a phase 1 dose-escalation study, sabatolimab plus spartalizumab was safe and well tolerated, with preliminary antitumour activity in advanced solid tumours, including in patients with prior anti-PD-1/PD-L1 therapy.[9] Here, we report data from the phase 2 part of the study—sabatolimab in combination with spartalizumab for patients with melanoma or NSCLC who had progressive disease (PD) on or after prior anti-PD-1/PD-L1 therapy.

MATERIALS AND METHODS

Clinical study design and oversight

This first-in-human, multicentre, open-label, phase 1-1b/2 study consists of a phase 1 dose escalation part of sabatolimab as a single agent and a phase 1b dose escalation part of sabatolimab in combination with spartalizumab in patients with advanced solid tumours.[9] An additional phase 2 part investigated sabatolimab in combination with spartalizumab (at the recommended phase 2 dose (RP2D) from phase 1/1b) in patients with advanced/metastatic melanoma or NSCLC. The study design of the phase 1/1b part of the study has been previously described.[9] In the phase 2 part, sabatolimab 800 mg every 4 weeks was administered in combination with spartalizumab at 400 mg every 4 weeks (RP2D) until unacceptable toxicity, PD per immune-related response criteria (irRC) and/or treatment discontinuation due to patient/physician decision. Patients did not discontinue treatment based on PD per Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1 unless clinical deterioration or an increase in tumour markers were observed.

Patient and public involvement

Patients were not involved in the design and recruitment of the study, assessing the burden of the intervention or plans to disseminate the study results to participants and relevant wider patient communities.

Study objectives

The primary objective for the phase 2 part of the study was to assess the antitumour activity of sabatolimab in combination with spartalizumab in advanced/metastatic melanoma or NSCLC. The primary endpoint was the overall response rate (ORR) per RECIST V.1.1. Secondary objectives included an evaluation of the safety, tolerability, efficacy, pharmacokinetics (PK) and pharmacodynamics of sabatolimab in combination with spartalizumab. Secondary endpoints included the incidence and severity of adverse events (AEs) and serious AEs (SAEs), vital signs and ECG assessments, the number of dose interruptions and reductions, dose intensity, serum PK parameters and concentration vs time profiles, as well as best overall response (BOR), progression-free survival (PFS), overall survival (OS) and DOR per RECIST V.1.1, and ORR and PFS per irRC.

Patients

Patients with advanced/metastatic melanoma or NSCLC with at least one measurable lesion as determined by RECIST V.1.1 were eligible. All enrolled patients had progressed on anti-PD-1/PD-L1 therapy. Patients were aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, with the site of disease amenable to biopsy.

Key exclusion criteria included patients with symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that required local CNS-directed therapy or increasing doses of corticosteroids within 2 weeks of study start, impaired cardiac function or clinically significant cardiac disease and/or active or a history of autoimmune disease.

Safety and response assessments

Regular safety assessments included physical examination, vital signs, ECOG performance status, laboratory parameters and cardiac evaluations. AEs were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03 and were assessed at every visit. Efficacy was evaluated by the local investigator's assessment using RECIST V.1.1[12] at baseline, starting on cycle (C) 3 days (D) 1, every two cycles until C11D1,

and then every three cycles until progression of disease per irRC or patient withdrawal. Durable clinical benefit (DCB) on prior anti-PD-1/PD-L1 therapy was defined as a best response of complete response (CR) or partial response (PR), or stable disease (SD) for ≥6 months; non-durable clinical benefit (NDCB) on prior anti-PD-1/PD-L1 therapy was defined as a best response of PD or SD for <6 months.

Biomarker assessments

Biomarker analyses were performed to explore potential predictive markers and a possible relationship between biomarkers with exposure and/or clinical outcomes. Tumour samples were obtained at screening and during treatment (any time during C3D1 and at the end of treatment). These samples were analysed by RNA expression analysis and immunohistochemistry for immune-related markers (including PD-L1, CD8 and FoxP3) and pathways associated with TIM-3.

PK assessments

Serum samples were collected for PK profiling at the following time points: preinfusion and 1, 24, 168, 240 and 336 hours postinfusion during C1 and C3; preinfusion during C4; preinfusion and 1-hour postinfusion during C5 and C6; and at the end of treatment. PK parameters included maximum concentration, exposure and half-life. Samples were also analysed for soluble TIM-3 (sTIM-3) using a validated ELISA. PK data were described using non-compartmental analysis.

Pharmacodynamic assessments

Tumour biopsies were collected at screening. Expression of CD8 (Ventana, clone CD8/144B), PD-L1 (Dako, 22C3 pharmaDx), CD163 (Ventana, clone MRQ-26), lymphocyte-activation gene 3 (LAG-3; Ventana, clone 17B4, R1231) and TIM-3 (Ventana, clone D5D5R, R1262) was evaluated by immunohistochemistry. Immunohistochemistry data are expressed as a percentage of the total marker area, except PD-L1, which is expressed as a percentage of positive tumour cells. Tumour biopsies were also analysed using RNA sequencing; analyses focused on 28 genes and 7 gene signatures related to immune cell infiltration/function or pathways associated with TIM-3.

Statistical analyses

Data were summarised using descriptive statistics (mean, SD, median, minimum and maximum), contingency tables (frequencies and percentages) and inferential analyses. The ORR was summarised primarily using Bayesian analysis for each indication. As a supportive analysis, the estimation of ORR and the corresponding 90% exact CI was performed using the exact Clopper-Pearson method for each indication. PFS and OS were estimated using the Kaplan-Meier method, summarised with their median and their corresponding 90% CI, assessed for each indication. SAS V.9.4 and R were used for analysis and the Kaplan-Meier curves.

RESULTS

Patient disposition baseline demographic and disease characteristics

33 patients were enrolled: 16 with melanoma and 17 with NSCLC. All patients received sabatolimab (800 mg every 4 weeks) plus spartalizumab (400 mg every 4 weeks). As of the data cut-off date of 9 March 2020, of the 16 patients with melanoma, 14 had discontinued the study treatment; 13 discontinuations were due to disease progression (81%) and 1 was due to physician decision (6%). All 17 patients with NSCLC had discontinued study treatment due to disease progression (n=10; 59%), death (n=4; 24%), physician/patient/guardian decision (n=2; 12%), or AEs (n=1; 6%, not related to the study drug). Patient demographics and baseline characteristics are shown in online supplemental table S2. The median age was 64 years (range, 42–78) and 69 (range, 46–78) for patients with melanoma and NSCLC, respectively. Sex and race were equally represented for patients with melanoma; for patients with NSCLC, the majority were male (82%) and Caucasian (65%). An ECOG performance status of 0 or 1 was evident in all patients with melanoma and in 88% of patients with NSCLC. For patients with melanoma, the primary site of cancer was cutaneous (88%), non-cutaneous (6%) and uveal (6%). For patients with NSCLC, 59% had adenocarcinoma, and 41% had squamous cell carcinoma.

Immediate prior anti-PD-1/PD-L1 therapy was administered in 63% of patients with melanoma and 65% of patients with NSCLC. Durable clinical benefit (DCB) of prior anti-PD-1/PD-L1 therapy was reported in six (37.5%) patients with melanoma and seven (41.2%) with NSCLC. NDCB of prior anti-PD-1/PD-L1 therapy was reported in 10 (63%) patients with melanoma and nine (53%) with NSCLC. One patient with NSCLC had the unknown clinical benefit of prior anti-PD-1/PD-L1 therapy.

Efficacy

The median duration of exposure to sabatolimab plus spartalizumab was 11.9 weeks (range, 4.0–88.1 weeks) for patients with melanoma and 8 weeks (range, 1.6–34.1 weeks) for patients with NSCLC. ORR and BOR are summarised in table 1. Among patients with melanoma, SD was the BOR in three patients (19%); two of these three patients had DCB to prior anti-PD-1/PD-L1 treatment and one had NDCB. Also, two of these three patients remained in SD for >12 months. 12 (75%) patients with melanoma had a BOR of PD. Among patients with NSCLC, six (35%) had a BOR of SD; among these six patients, the response on prior anti-PD-1/PD-L1 was DCB in three patients, NDCB in two patients and unknown in one patient. Also, five of the six patients remained in SD for >3 months. BOR was unknown in one (6%) and six (35%) patients with melanoma and NSCLC, respectively.

PFS is shown in figure 1. Among patients with melanoma, the median PFS was 1.8 months (90% CI 1.7 to 1.9) and PFS rate was 13.3% (90% CI 3.2% to 30.8%) at

Table 1 Best overall response by indication (investigator assessed according to RECIST V.1.1)

Characteristic	Melanoma				NSCLC			
	Clinical benefit of prior anti-PD-1/PD-L1 therapy				Clinical benefit of prior anti-PD-1/PD-L1 therapy			
Best overall response, n (%)	DCB (N=6)	NDCB (N=10)	Unknown (N=0)	All (N=16)	DCB (N=7)	NDCB (N=9)	Unknown (N=1)	All (N=17)
Stable disease (SD)	2 (33.3)	1 (10.0)	–	3 (18.8)	3 (42.9)	2 (22.2)	1 (100.0)	6 (35.3)
Progressive disease (PD)	4 (66.7)	8 (80.0)	–	12 (75.0)	3 (42.9)	2 (22.2)	0	5 (29.4)
Unknown	0	1 (10)	–	1 (6.3)	1 (14.3)	5 (55.6)	0	6 (35.3)
Overall response rate, %*	0	0	–	0	0	0	0	0
Disease control rate, % (90% CI)†	33.3 (6.3 to 72.9)	10.0 (0.5 to 39.4)	–	18.8 (5.3 to 41.7)	42.9 (12.9 to 77.5)	22.2 (4.1 to 55.0)	100.0 (5.0 to 100.0)	35.3 (16.6 to 58.0)

*CR or PR.
†CR or PR or SD or NCRNPD.
CR, complete response; DCB, durable clinical benefit; NCRNPD, neither CR nor PD; NDCB, non-DCB; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours.

6 months and 12 months (figure 1A). In patients with NSCLC, median PFS was 1.7 months (90% CI 1.1 to 3.4) and PFS rate was 6.3% (90% CI 0.7% to 21.0%) at 6 months and not estimable at 12 months (figure 1B).

OS is shown in figure 2. For patients with melanoma, median OS was 6.0 months (90% CI 4.9 to 10.3) and OS rate was 53.3% (90% CI 30.6% to 71.6%) at 6 months, 26.7% (90% CI 10.5% to 46.0%) at 12 months and 10.0% (90% CI 1.4% to 29.2%) at 18 months (figure 2A). For patients with NSCLC, median PFS was 6.6 months (90% CI 1.1 to 9.0) and OS rate was 58.8% (90% CI 37.0% to 75.4%) at 6 months, 29.4% (90% CI 13.2% to 47.8%) at 12 months and 5.9% (90% CI 0.7% to 19.9%) at 18 months (figure 2B).

Postbaseline tumour assessments were performed in 15 patients with melanoma and 11 patients with NSCLC. The best percentage change from baseline in the sum of diameters of target lesions is shown in online supplemental figure S1. Percentage change from baseline in the sum of diameters of target lesions across time is presented for patients with melanoma and NSCLC in online supplemental figure S2. The best percentage change from baseline of target lesions for patients with melanoma and NSCLC is presented by response to prior anti-PD-1/PD-L1 therapy in online supplemental figure S3. Overall, the majority of patients who had postbaseline tumour assessments had tumour growth of target lesions. For patients with melanoma, 11 (73.3%) had tumour growth and 6 (40%) developed new lesions. A best percentage target decrease of >0% was observed in four (26.7%) patients. For patients with NSCLC, nine (81.8%) had tumour growth, three (27.3%) developed new lesions and a best percentage target decrease of >0% was observed in one (9.1%) patient.

Safety

Overall, 31 (94%) patients experienced at least one AE regardless of relationship to study treatment: 15 (94%) patients with melanoma and 16 (94%) patients with NSCLC (online supplemental table S3). Clinically significant AEs regardless of relationship to study treatment are seen in table 2. 15 (46%) patients experienced grade 3/4 AEs: 5 (31%) patients with melanoma and 10 (59%) with NSCLC. The most frequent grade ≥3 AEs reported for NSCLC were anaemia, dyspnoea and pneumonia (each n=2; 12%). The most frequent grade ≥3 AEs in patients with melanoma were physical health deterioration, hypokalaemia, hypophosphataemia, pathological fracture and tumour invasion (each n=1; 6%). Only two (6.1%) patients (both with NSCLC) experienced grade ≥3 AEs that were suspected to be related to study treatment, with one report each of pruritus, increase of alanine aminotransferase, increase of amylase and increase of lipase (online supplemental table S4). No patient with melanoma and four (24%) patients with NSCLC experienced AEs leading to dose adjustment or interruption. AEs leading to discontinuation occurred in one (6%) patient with melanoma (tumour invasion) and two (12%)

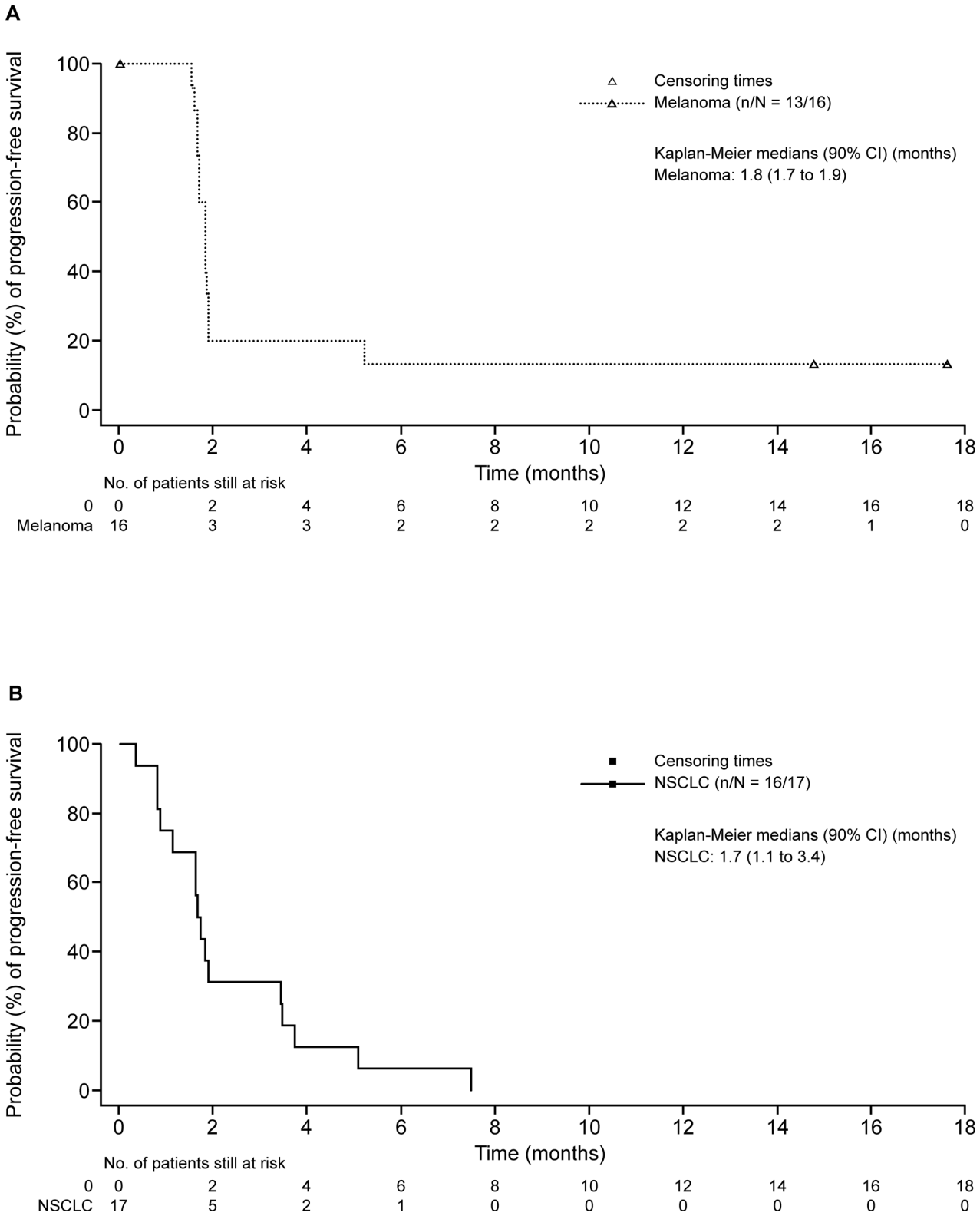

Figure 1 Progression-free survival among patients with (A) melanoma and (B) NSCLC. NSCLC, non-small cell lung cancer.

patients with NSCLC (general physical health deterioration and superior vena cava syndrome).

11 (33%) patients experienced at least 1 SAE regardless of relationship to study treatment: 2 (13%) patients with melanoma and 9 (53%) with NSCLC. 10 (30%) patients experienced grade 3/4 events: 2 (13%) patients with melanoma and 8 (47%) with NSCLC. The most frequent grade ≥3 SAE (≥10% of patients) reported for NSCLC was dyspnoea. No grade ≥3 SAEs occurred in ≥10% of patients with melanoma. There were no SAEs considered by the investigator to be related to the study treatment for either indication.

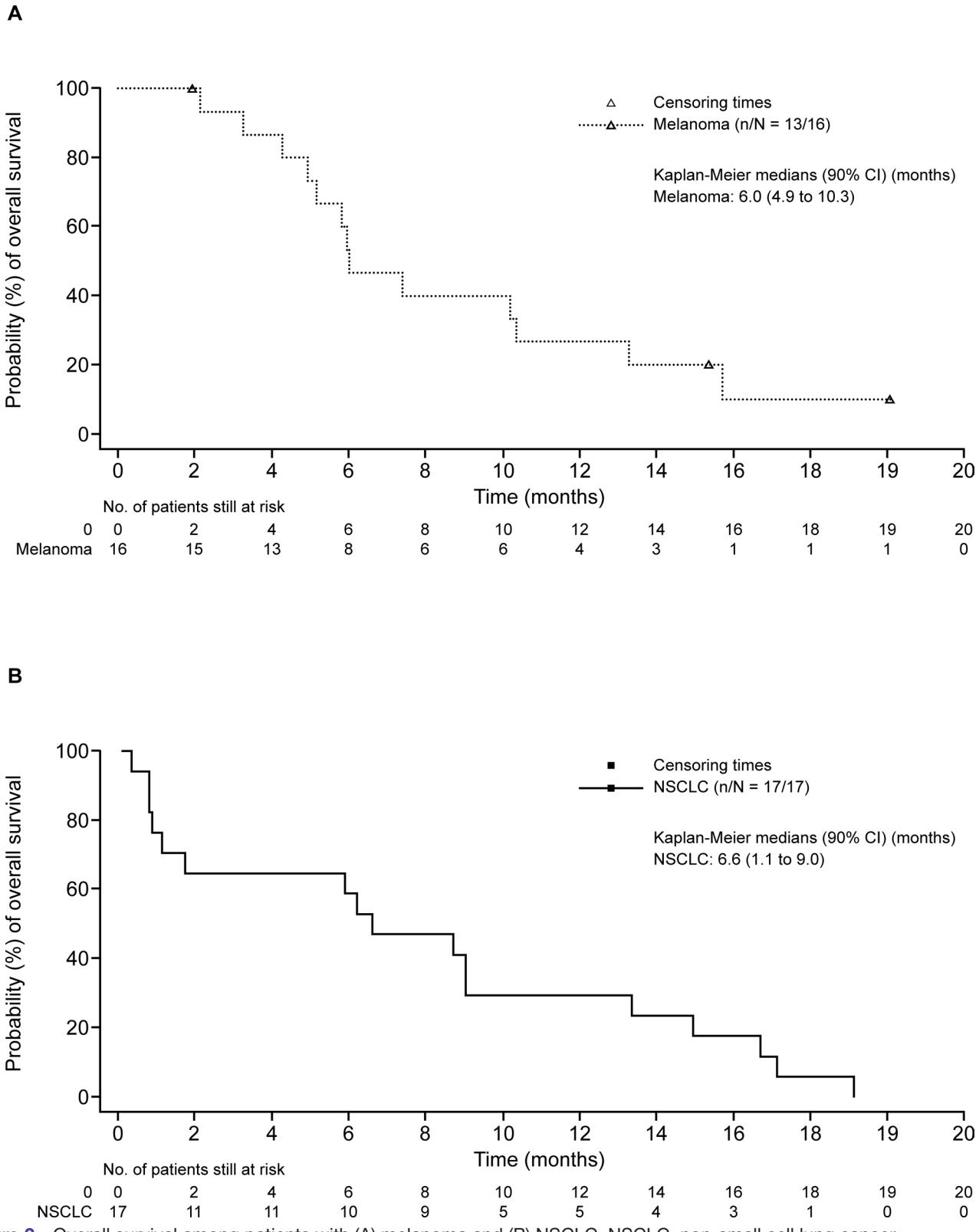

Figure 2 Overall survival among patients with (A) melanoma and (B) NSCLC. NSCLC, non-small cell lung cancer.

There were 30 deaths in the study: 13 (81%) patients with melanoma and 17 (100%) with NSCLC. The primary reason for death was cancer for the majority of patients in both indications; one NSCLC patient had an unknown cause of death.

Biomarker analysis

The association of expression of potential biomarkers at screening with response (PD/SD) is shown in figure 3. Overall, patients who achieved SD appeared to have a trend towards higher expression levels of CD8, LAG-3,

Table 2 Grade ≥3 adverse events regardless of study treatment relationship (≥5% of patients)

Preferred term	Melanoma (N=16) Grade ≥3 n (%)	NSCLC (N=17) Grade ≥3 n (%)	All patients (N=33) Grade ≥3 n (%)
Number of patients with at least one event	5 (31.3)	10 (58.8)	15 (45.5)
Fatigue	0	1 (5.9)	1 (3.0)
Anaemia	0	2 (11.8)	2 (6.1)
Dyspnoea	0	2 (11.8)	2 (6.1)
Abdominal pain	0	1 (5.9)	1 (3.0)
Alanine aminotransferase increased	0	1 (5.9)	1 (3.0)
Asthenia	0	1 (5.9)	1 (3.0)
Pruritus	0	1 (5.9)	1 (3.0)
General physical health deterioration	1 (6.3)	1 (5.9)	2 (6.1)
Hypokalaemia	1 (6.3)	0	1 (3.0)
Hypophosphataemia	1 (6.3)	0	1 (3.0)
Pneumonia	0	2 (11.8)	2 (6.1)
Stomatitis	0	1 (5.9)	1 (3.0)
Amylase increased	0	1 (5.9)	1 (3.0)
Aspartate aminotransferase	0	1 (5.9)	1 (3.0)
Bronchial obstruction	0	1 (5.9)	1 (3.0)
Chronic obstructive pulmonary disease	0	1 (5.9)	1 (3.0)
Colitis	0	1 (5.9)	1 (3.0)
Diabetes mellitus	0	1 (5.9)	1 (3.0)
Lipase increased	0	1 (5.9)	1 (3.0)
Pathological fracture	1 (6.3)	0	1 (3.0)
Skin infection	0	1 (5.9)	1 (3.0)
Superior vena cava syndrome	0	1 (5.9)	1 (3.0)
Tumour invasion	1 (6.3)	0	1 (3.0)

NSCLC, non-small cell lung cancer.

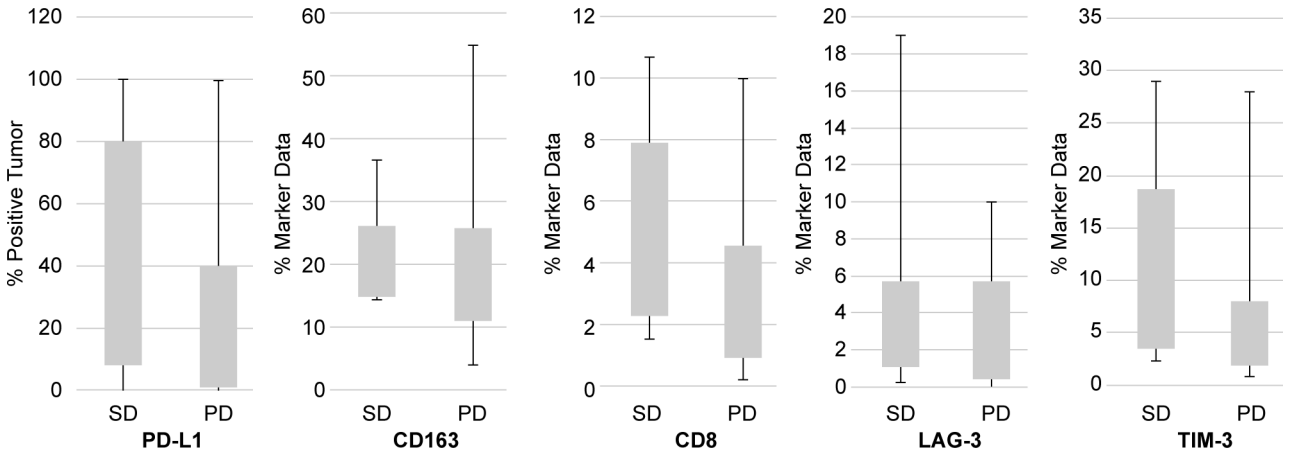

Figure 3 Association of expression of potential biomarkers at screening with response for patients with melanoma and NSCLC. CD, cluster of differentiation; LAG-3, lymphocyte-activation gene 3; NSCLC, non-small cell lung cancer, PD, progressive disease; PD-L1, programmed death ligand 1; SD, stable disease; TIM-3, T-cell immunoglobulin and mucin-domain containing-3.

PD-L1 and TIM-3 at baseline, as determined by IHC of tumour samples collected at screening.

Two patients with melanoma had ongoing SD at the time of data cut-off. One patient was in their 50s and had an ECOG performance status of 1 at screening. This patient achieved a BOR of SD to prior anti-PD-1 therapy and had a modest level of PD-L1 (0.5%, percentage positive tumour) at screening. The other patient was in their 70s, had an ECOG performance status of 1 at screening and achieved SD on both prior immunotherapies (anti-PD-1 and anti-LAG-3 therapy). This patient's biomarker/immunohistochemistry data at screening were unavailable.

PK and pharmacodynamics

Sabatolimab mean concentration-time profiles for sabatolimab in combination with spartalizumab in C1 and C3 are shown in online supplemental figure S4. PK parameters, including area under the plasma concentration-time curve for a dosing interval, maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}) and half-life ($T_{1/2}$), are shown in online supplemental table S5. Overall, sabatolimab exposure was comparable for both indications (online supplemental figure S4 and table S5).

The average 4-weekly doses were comparable between the two indications, whereas patients with melanoma had a higher cumulative dose compared with patients with NSCLC for both sabatolimab and spartalizumab (online supplemental table S6). The dose intensity and relative dose intensity were comparable between the two indications for both sabatolimab and spartalizumab.

DISCUSSION

Sabatolimab (800 mg every 4 weeks) in combination with spartalizumab (400 mg every 4 weeks) was safe and well tolerated in patients with melanoma and NSCLC. Incidence of grade ≥3 AEs was low and primarily consisted of anaemia, dyspnoea and pneumonia. These findings are consistent with the phase 1/1b part of this study,[9] as well as those observed for single-agent spartalizumab in solid tumours[13] and other anti-TIM-3/-PD-1 combination studies.[14 15]

The PK profile of sabatolimab is well understood from investigations across several indications. As reported here, accumulation of sabatolimab, mean half-life and other PK parameters were consistent with the phase 1 part of the study.[9] In addition to advanced solid tumours, melanoma and NSCLC, sabatolimab PK has been evaluated in patients with haematological malignancies.[16] A recent study showed that sabatolimab 400 mg every 2 weeks and 800 mg every 4 weeks provided similarly high levels of TIM-3 engagement based on analysis of sTIM-3 concentration and receptor occupancy modelling, which helped validate the selection of the 400 mg every 2 weeks and 800 mg every 4 weeks dosing regimens for ongoing and future studies with sabatolimab.[16]

The efficacy findings from the current report are consistent with preliminary data for other anti-TIM-3/anti-PD-1 combination therapies in solid tumours. Limited objective responses were reported in a phase 1A/B study of the anti-TIM-3 antibody LY3321367 in combination with an anti-PD-L1 antibody in treatment-refractory advanced solid tumours.[15] Additionally, in a phase 1 study of TSR-022 (anti-TIM-3 antibody) in combination with TSR-042 (anti-PD-1 antibody) in patients with NSCLC who had progressed following anti-PD-1 treatment, only 4 of 39 patients had PR (3 responses ongoing) and 6 had SD[14] (NCT02817633). Consistent with these findings, in another phase 1 study of Sym023 (anti-TIM-3 antibody) in combination with Sym021 (anti-PD-1 antibody) in patients with solid tumours, only 2 of 27 patients had PR (1 patient evolved to CR). As such, anti-TIM-3 and anti-PD-1 combination therapies have failed to achieve adequate responses in solid tumours in early-phase clinical trials.[17] As of data cut-off, two patients with melanoma had ongoing SD. Both patients had an ECOG performance status of 1 at screening, and both had SD to prior immunotherapies. Clinical benefit of prior anti-PD-1/PD-L1 had no effect on the response rate in patients treated with sabatolimab+spartalizumab. With limited biomarker data available, it was not possible to identify a relationship between potential biomarkers and response to treatment. As of time of print, however, this study was terminated due to the study sponsor's decision.

Although anti-TIM-3 therapy has shown limited efficacy in solid tumours, the expression of TIM-3 on leukaemic stem cells and blasts, but not normal haematopoietic stem cells, makes it a promising therapeutic target in haematological malignancies.[10] More recently, available data from a phase 1b study show the promise of sabatolimab therapy in myeloid malignancies, whereby encouraging preliminary response rates with emerging durability was observed in higher-risk myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and chronic myelomonocytic leukaemia (CMML), including those patients with cytogenetic poor or very poor risk MDS and those with *TP53/RUNX1/ASXL1* mutation (AML/MDS).[10] Consistent with the good safety profile in solid tumours, sabatolimab was generally safe and well tolerated in patients with higher-risk MDS, AML and CMML who are unfit for intensive chemotherapy, with most common treatment-emergent AEs consistent with those experienced with HMA alone.[10] Discontinuation due to an AE was infrequent, and the incidence of possible immune-mediated AEs related to treatment was low and predominantly low grade.[10] Treatment of sabatolimab in combination with spartalizumab had limited antitumour activity in patients with advanced/metastatic melanoma or NSCLC who had progressed following anti-PD-1/PD-L1. However, the low treatment-related discontinuation rate supports the potential that sabatolimab treatment can be investigated in various combination regimens across a spectrum of tumour types.

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Competing interests NM is the founder of and owns shares in MaxiVAX SA and is the CSO at MaxiVAX. C-CL reports an advisory role for AbbVie, Bayer, Blueprint Medicines, Bristol Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo, Novartis and PharmaEngine; honoraria from Lilly, Novartis and Roche; and travel support from BeiGene, Daiichi Sankyo and Lilly. GC reports research funding from Merck and fees for advisory board from BMS, Merck, AstraZeneca, Novartis, Lilly, Pfizer, Roche, Exact Science, Daiichi Sankyo, GSK, Sanofi and Seagen. AS reports serving on an advisory board for BMS, Servier, Gilead, Pfizer, Eisai, Bayer and MSD (Merck Sharp & Dohme); consultancy for Arqule, Sanofi and Incyte; and participating in speaker's bureaus for Takeda, BMS, Roche, AbbVie, Amgen, Celgene, Servier, Gilead, AstraZeneca, Pfizer, Arqule, Lilly, Sandoz, Eisai, Novartis, Bayer and MSD. D-WK reports research funding to his institution from Alpha Biopharma, Amgen, AstraZeneca/Medimmune, Boehringer-Ingelheim, Daiichi-Sankyo, Hanmi, Janssen, Merus, Mirati Therapeutics, MSD, Novartis, ONO Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, Yuhan, Chong Keun Dang, Bridge BioTherapeutics, and GSK; and travel and accommodation support for advisory board meeting attendance from Amgen and Daiichi-Sankyo. DT reports payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from Ipsen, Eisai and BMS; and consulting fees from Novartis, BMS and MSD. FSH reports receiving personal fees for serving on an advisory board for Surface, Compass Therapeutics, Apricity, Pionyr, 7 Hills Pharma, Torque, Bicara, Checkpoint Therapeutics, Bioentre, Iovance, Trillium, Amgen and Rheos; consultancy for Bristol-Myers Squibb, Merck, EMD Serono, Novartis, Sanofi, Pieris, Genentech/Roche, Catalym, Immunocore, Kairos, Eisai and Zumutor; serving as an advisor consultant for Aduro; and receiving other personal fees from Gossamer. FSH reports receiving grant support to institution from Bristol-Myers Squibb and Novartis; and having equity in Apricity, Pionyr, Torque, Bicara and Checkpoint Therapeutics. FSH holds issued patents #7250291, #9402905, #10279021 and #10106611 and pending patents #20100111973 (with royalties), #20170248603, #20160340407, #20160046716, #20140004112, #20170022275, #20170008962 and #20170343552, as well as a pending patent for Methods of Using Pembrolizumab and Trebananib. SW reports serving on an advisory board for Eisai, Bristol-Myers Squibb and Pierre Fabre (paid to institution). TD reports receiving grant support to institution from Lilly, MSD, Daiichi-Sankyo, Sumitomo Dainippon, Taiho, Novartis, Merck Biopharma, Janssen Pharma, Pfizer, BMS, AbbVie, Eisai, IQVIA, Chugai Pharma; consulting fees from Sumitomo Dainippon, Taiho, Takeda, Chugai Pharma, AbbVie, Bayer, Rakuten Medical, Otsuka Pharma, KAKEN Pharma, KYOWA KIRIN, SHIONOGI, PRA Health Science; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from BMS, Rakuten Medical, Ono Pharma, Daiichi-Sankyo, AstraZeneca; participation on a Data Safety Monitoring Board or Advisory Board for MSD, Daiichi-Sankyo, Amgen, Novartis, Boehringer Ingelheim, Janssen Pharma, AbbVie, Bayer, Astellas Pharma. CS-P was an employee of Novartis Institutes for BioMedical Research and holds patents on TIM-3 through Harvard/BWH and CoStim/Novartis. CS-P is employed by and has options in Larkspur Biosciences. SS is an employee of Novartis Institutes for BioMedical Research. SC is an NIBR employee and holds NVS stocks. AX has nothing to disclose. SG is an employee of Novartis Institutes for BioMedical Research. AP is an employee of Novartis Institutes for BioMedical Research.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Ethics approval This study involves human participants and the study was sponsored by Novartis and was performed in compliance with Good Clinical Practice. The study protocol was approved by an independent ethics committee or institutional review board for each centre and was conducted according to the principles of the Declaration of Helsinki. We have added online supplemental table to include the ethics approval details. Written informed consent was obtained from each patient. The first patient was enrolled on 23 November 2015; the data cut-off date was 9 March 2020. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who participated in the trial, in line with applicable laws and regulations. The data of these trials are made available according to the criteria and process described on www.clinicalstudydatarequest.com.

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