Vibostolimab coformulated with pembrolizumab versus pembrolizumab alone as adjuvant therapy for high-risk stage IIB–IV melanoma (KEYVIBE-010): a randomised, double-blind, phase 3 study

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Summary

Background Combination therapy with vibostolimab plus pembrolizumab has previously shown promising antitumor activity in melanoma. We aimed to evaluate the efficacy and safety of vibostolimab coformulated with pembrolizumab as adjuvant therapy for high-risk resected melanoma.

Methods This randomised, double-blind, phase 3 study was done at 205 global sites (hospitals and cancer centres). Participants aged 12 years or older with surgically resected, stage IIB–IV cutaneous melanoma per the American Joint Committee on Cancer Cancer Staging Manual 2017 (8th edition), with no evidence of metastatic disease after resection, were randomly assigned (1:1) to receive vibostolimab 200 mg coformulated with pembrolizumab 200 mg or pembrolizumab 200 mg alone intravenously every 3 weeks. Randomisation was done using an interactive response technology system and was stratified by risk-based staging and geographical region. Participants, investigators, and site staff were masked to group assignment. The primary endpoint was recurrence-free survival assessed in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of the study treatment. The protocol-prespecified first interim analysis was an event-driven nonbinding futility analysis of recurrence-free survival that was planned for when 111 events had occurred (futility bar of observed HR 0·95). This study is registered with ClinicalTrials.gov (NCT05665595), and is closed to recruitment.

Findings Between Jan 19, 2023, and March 6, 2024, 1402 participants were randomly assigned to receive coformulated vibostolimab–pembrolizumab (n=701) or pembrolizumab (n=701). At the first interim analysis, median study follow-up, defined as time from randomisation to data cutoff, was 4·2 months (IQR 1·9–6·7). The median age was 61·0 years (IQR 51·0–70·0), 829 (59%) of 1402 participants were male and 573 (41%) were female. 1107 (79%) of participants were White, 273 (19%) were Asian, and 22 (2%) were of other race or race was missing. At the time of the first interim analysis, a total of 119 (8%) of 1402 participants had had a recurrence-free survival event, including 67 (10%) of 701 in the vibostolimab–pembrolizumab group and 52 (7%) of 701 in the pembrolizumab alone group. The median recurrence-free survival was not reached in either group; the hazard ratio for recurrence-free survival in the vibostolimab–pembrolizumab group versus pembrolizumab alone group was 1·25 (95% CI 0·9–1·8). The most common (occurred in more than five participants) grade 3 or higher treatment-related adverse events were adrenal insufficiency in 13 (2%) participants, hepatitis in 11 (2%) participants, rash in 9 (1%) participants, maculopapular rash in 7 (1%) participants, and pruritus in 6 (1%) participants in the vibostolimab–pembrolizumab group and increased alanine aminotransferase in 7 (1%) participants in the pembrolizumab alone group. Treatment-related serious adverse events occurred in 74 (11%) participants and 30 (4%) participants, respectively. Treatment-related adverse events led to death in two (<1%) participants in the vibostolimab–pembrolizumab group (myasthenia gravis and myocarditis) and one participant (<1%) in the pembrolizumab group (myositis). The external data monitoring committee decided to discontinue the study according to prespecified futility criteria.

Interpretation Vibostolimab coformulated with pembrolizumab did not provide additional clinical benefit versus pembrolizumab as adjuvant therapy in participants with resected stage IIB–IV melanoma. Pembrolizumab monotherapy remains a standard of care for resected high-risk melanoma.

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Research in context

Evidence before this study

We searched PubMed from database inception to March 11, 2025, for reports published in English using the search terms "(PD-1) OR (PD-L1)" AND "TIGIT" filtered by clinical trial article type. We identified six relevant clinical studies. These studies generally reported manageable safety and some indicated antitumor activity when anti-TIGIT antibodies were used in combination with anti-PD-1 or anti-PD-L1 antibodies, although not all reported significant improvements in efficacy. A first-in-human, phase 1 study reported manageable safety and promising antitumor activity with the anti-TIGIT antibody vibostolimab in combination with the anti-PD-1 antibody pembrolizumab, with an objective response rate (ORR) of 7% reported for patients with solid tumours and an ORR of 26% reported for patients with anti-PD-1-naive or anti-PD-L1-naive non-small cell lung cancer. Substudy 02C of the global, rolling group, phase 1/2 adaptive design KEYMAKER-U02 trial reported manageable safety and similar efficacy for neoadjuvant pembrolizumab plus vibostolimab versus pembrolizumab alone followed by adjuvant pembrolizumab in participants with resectable stage IIIB–IIID melanoma, with pathological complete response rates of 38% versus 40%, respectively. A first-in-human, phase 1a/b study of the anti-TIGIT antibody etigilimab in combination with the anti-PD-1 antibody nivolumab reported an acceptable safety profile and preliminary evidence of clinical benefit, with one (10%) of ten patients reaching a partial response (ovarian cancer) and with one (10%) patient having stable disease (gastric cancer). The phase 2 CITYSCAPE study reported that combination therapy with the anti-TIGIT antibody tiragolumab plus the anti-PD-L1 antibody atezolizumab was well tolerated and provided a clinically meaningful improvement in ORR (31·3% *vs* 16·2%) and progression-free survival (median 5·4 *vs* 3·6 months) compared with placebo plus atezolizumab in patients with chemotherapy-naive PD-L1–positive recurrent or metastatic non-small cell lung cancer. Results of the phase 3 SKYSCRAPER-02 study showed that the addition of tiragolumab to atezolizumab plus carboplatin and etoposide did not provide additional benefit in previously untreated extensive-stage non-small cell lung cancer. The phase 2 SKYSCRAPER-04 study reported a higher ORR with tiragolumab plus atezolizumab versus a historical reference in patients with PD-L1-positive persistent or recurrent cervical cancer, but this did not reach statistical significance. Although the results of these studies are mixed, combining anti-TIGIT and anti-PD-1 or anti-PD-L1 antibodies warrants further investigation.

Added value of this study

In this randomised, double-blind, phase 3 study, the coformulation of vibostolimab with pembrolizumab did not provide additional clinical benefit when compared with pembrolizumab alone as adjuvant therapy in participants with resected stage IIB–IV melanoma. This adds to the body of evidence from clinical trials that suggests that anti-TIGIT antibodies might have limited added efficacy when combined with anti-PD-1 or anti-PD-L1 antibodies in this setting.

Implications of all the available evidence

Our results suggest that vibostolimab–pembrolizumab did not provide any additional benefit compared with pembrolizumab alone when used as adjuvant therapy for melanoma. This suggests that PD-1 inhibitors should remain the standard of care for patients with high-risk resected melanoma. There continues to be a need to further optimise treatment in this setting. Based on the finding of this study, and other trials in the KEYVIBE programme, the clinical development of vibostolimab has been discontinued.

Introduction

Programmed cell death protein 1 (PD-1) is an immune checkpoint protein expressed on T cells that has a major role in immune resistance within the tumour microenvironment.[1] Inhibition of the PD-1 pathway has been shown to significantly improve survival outcomes across various malignancies, including melanoma.[1] Adjuvant therapy with the PD-1 inhibitors pembrolizumab or nivolumab is now considered a standard of care for patients with resected stage IIB to IV melanoma.[2]

Pembrolizumab initially showed antitumour activity as adjuvant therapy in the phase 3 EORTC1325/KEYNOTE-054 study, significantly prolonging recurrence-free survival compared with placebo in participants with stage III melanoma (hazard ratio [HR] 0·57 [98·4% CI 0·43–0·74]; p <0·001).[3] At the 7-year follow-up of EORTC1325/KEYNOTE-054, pembrolizumab showed a sustained benefit, with 7-year recurrence-free survival rates of 50% with pembrolizumab versus 36% with placebo, 7-year distant metastasis-free survival rates of 54% versus 42%, and 7-year progression-free or recurrence-free survival 2 rates of 61% versus 53%.[4] Adjuvant pembrolizumab has also shown efficacy in resected stage IIB and IIC melanoma, significantly improving recurrence-free survival and distant metastasis-free survival compared with placebo in the phase 3 KEYNOTE-716 study.[5,6] After a median follow-up of over 3 years, the 36-month recurrence-free survival rate in KEYNOTE-716 was 76·2% in the pembrolizumab group compared with 63·4% in the placebo group, and the 36-month distant metastasis-free survival rates were 84·4% and 74·7%, respectively.[7] The results of these studies established pembrolizumab as an adjuvant treatment option for stage IIB, IIC, or III resectable melanoma. However, there remains an opportunity to further improve clinical outcomes in this setting.

T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (TIGIT) is an inhibitory checkpoint receptor expressed on effector CD4 and CD8 T cells, regulatory

T cells, and natural killer cells.[8] TIGIT competes with the stimulatory CD226 receptor to bind its ligands CD155 and CD112, thereby attenuating the immune response by inhibiting host T-cell activation and proliferation.[8] Anti-TIGIT antibodies block the interaction of TIGIT with these ligands, allowing CD226 to bind them, thereby activating T cells and leading to antitumour activity.[8] Anti-TIGIT antibodies with functional Fc domains also activate myeloid cells via FCγ receptor engagement, leading to the production of cytokines and chemokines necessary for the antitumour response.[9] In contrast to TIGIT, PD-1 inhibits the phosphorylation of CD226 via its ITIM-containing intracellular domain, suggesting a mechanistic rationale for dual PD-1 and TIGIT blockade.[10]

Vibostolimab is a humanised IgG1 anti-TIGIT antibody that blocks TIGIT from interacting with CD112 and CD155 and engages the FCγ receptors on myeloid cells.[11] In the first-in-human phase 1 KEYVIBE-001 study, the combination of vibostolimab plus pembrolizumab showed antitumour activity and manageable safety in participants with advanced solid tumours.[12] Promising antitumour activity reflected by a high major pathological response was also observed with neoadjuvant pembrolizumab plus vibostolimab followed by adjuvant pembrolizumab in participants with resectable stage IIIB–IIID melanoma in the phase 1/2 KEYMAKER-U02 substudy 02C.[13] Here, we report results from the phase 3 KEYVIBE-010 study, which was designed to evaluate the efficacy and safety of vibostolimab coformulated with pembrolizumab (vibostolimab–pembrolizumab) as adjuvant therapy for resected stage IIB to IV melanoma.

Methods

Study design and participants

The randomised, double-blind, phase 3 KEYVIBE-010 study was done at 205 global sites (hospitals and cancer centres; appendix pp 2–6). Eligible participants were aged 12 years or older, and had surgically resected, histologically or pathologically confirmed stage IIB, IIC, III, or IV cutaneous melanoma per the American Joint Committee on Cancer 2017, 8th edition, with no evidence of metastatic disease after resection, and adequate organ function. Complete lymph node dissection or sentinel lymph node biopsy were not required. Participants could not have received previous systemic therapy for melanoma. An adequate performance status was required: a Lansky Play-Performance Scale (LPS) score of 70 or more for participants aged 16 years or younger, a Karnofsky Performance Scale (KPS) score of 70 or more for participants aged between 16 and 18 years, or an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 for participants aged 18 years or older. Participants with a known additional malignancy that was progressing or had required active treatment within the past 3 years; a history of CNS metastases or carcinomatous meningitis; or ocular, mucosal, or conjunctival melanoma were excluded. Full eligibility criteria are provided in the protocol. This study is registered with ClinicalTrials.gov (NCT05665595), and is closed to recruitment.

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies (appendix pp 7–47). No cancer survivors or patient representatives were involved in the study design. All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1) to receive vibostolimab–pembrolizumab or pembrolizumab alone. A role-based, validated, proprietary system, Clinical Schedule Generation System, was used to generate and store the randomisation schedule for this study. Treatment assignments were obtained using a Randomization and Trial Supply Management system (version 4.3; Signant Health, PA, USA). Randomisation was stratified by risk-based staging (IIB–IIIB *vs* IIIC–IV) and region (Asia *vs* rest of the world). Masking was allocated by an interactive response technology system. At each centre, the study coordinator, data coordinator, and pharmacist were masked to treatment. The clinical scientist, clinical data manager, site monitors, site monitor back-up, site monitor manager, trip report reviewer, statistician, and statistical programmer were also masked to treatment. At the site, clinical supplies were shipped to and stored in the pharmacy in a locked unit. Study drug preparation was completed by the pharmacist before it was given to the masked staff. Masking was controlled systematically in the interactive response technology system and using an emergency unmasked call centre. There was no visual unmasking difference in size, volume, or colour between the study drugs at the time of infusion.

Procedures

Participants were randomly assigned to receive vibostolimab 200 mg coformulated with pembrolizumab 200 mg or pembrolizumab 200 mg alone (2 mg/kg up to 200 mg for participants younger than 18 years) intravenously every 3 weeks. Treatment continued for up to 17 cycles or until recurrence or disease progression, unacceptable toxicity, prolonged interruption of treatment, a medical condition that put the participant at unnecessary risk, a confirmed positive serum pregnancy test, use of a prohibited medication, initiation of new anticancer treatment, or withdrawal of consent. Dose reductions were not permitted. Treatment could be interrupted or withdrawn to manage immune-related adverse events.

Sex, race, and ethnicity were self-reported. Imaging by CT or MRI was done every 12 weeks for the first 2 years, then every 6 months up to year 4, and once at year 5. Participants who completed study intervention or who

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See **Online** for appendix

discontinued study treatment for reasons other than disease recurrence, continued with imaging assessment every 12 weeks during follow-up until disease recurrence, withdrawal of consent, death, or the end of the study, whichever occurred first. Tumour response was assessed per RECIST (version 1.1) by the investigator review. Adverse events, including serious adverse events, were monitored throughout treatment and for 90 days thereafter or 30 days if new anticancer therapy was initiated. Adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Treatment-related adverse events were determined by investigator to be related to study treatment. Immune-mediated adverse events and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and vibostolimab and were considered regardless of attribution to study treatment by the investigator. Survival status was monitored every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurred first.

Laboratory testing including for pregnancy, haematological parameters (eg, platelet count, red blood cell count, haemoglobin, and haematocrit) and chemistry (eg, blood urea nitrogen, albumin, creatinine, creatinine clearance, glomerular filtration rate, and glucose), urine analyses, thyroid function, lactate dehydrogenase, coagulation (eg, prothrombin time to international normalised ratio and activated partial thromboplastin time [PTT]/PTT), and serology (eg, HIV antibody, hepatitis B surface antigen or hepatitis B virus DNA, and anti-hepatitis C virus antibody or hepatitis C virus RNA) were done at screening and periodically during the study as described in the protocol (appendix pp 75–235).

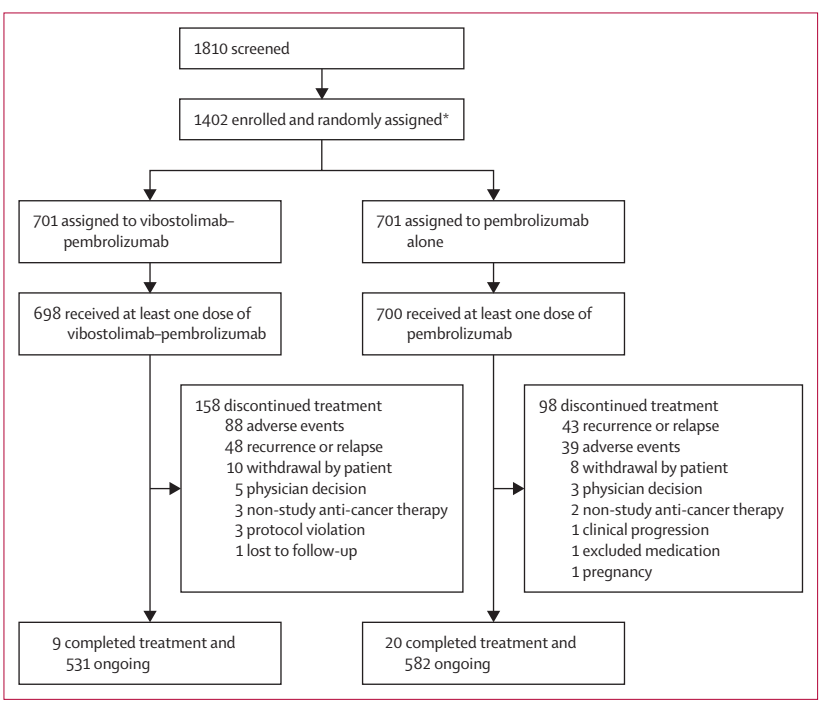

Figure 1: **Trial profile**
*306 participants were excluded because they did not meet eligibility criteria; 102 participants were randomly assigned to treatment, but after the data cutoff date for this analysis (March 6, 2024).

Outcomes

The primary endpoint was recurrence-free survival, defined as the time from randomisation to any recurrence (local, locoregional, regional, or distant) assessed per RECIST, or death from any cause, whichever occurred first. Secondary endpoints included distant metastasis-free survival, defined as the time from randomisation to appearance of a distant metastasis per RECIST, or death from any cause, whichever occurred first; overall survival, defined as the time from randomisation to death from any cause; and safety. Change from baseline in health-related quality of life, as measured using the EORTC QLQ-C30 (global health status and quality of life score [items 29 and 30], physical functioning score [items 1–5], and role functioning score [items 6 and 7]), was also a secondary endpoint; however, patient-reported outcome data were not available at the first interim analysis. Per protocol, distant metastasis-free survival and overall survival were not analysed at the first interim analysis.

Statistical analysis

Efficacy was assessed in all participants randomly assigned to treatment (intention-to-treat population). Safety was assessed in all randomly assigned participants who received at least one dose of study treatment. The study planned to enrol 1560 participants, which would provide 91% power to detect a HR for recurrence of 0·7 or better after 451 recurrence-free survival events at a one-sided α of 2·5% at final analysis. The protocol specified five interim analyses and a final analysis; an external data monitoring committee reviewed results of the interim analyses. The graphical method of Maurer and Bretz was used to control the family-wise type I error rate at a one-sided α level of 2·5% for multiple hypotheses as well as interim analyses. The prespecified first interim analysis was an event-driven nonbinding futility analysis of recurrence-free survival that was planned for when 111 events (25% information fraction) occurred; the stopping rule was set at an HR >0·95 for the recurrence-free survival endpoint (ie, the trial was stopped if the Cox model-estimated HR for recurrence-free survival was above 0·95).

The median study follow-up was defined as time from randomisation to the data cutoff. Median recurrence-free survival, recurrence-free survival at the 3-month and 6-month timepoints, and corresponding 95% CIs were estimated using the Kaplan–Meier method. The difference in recurrence-free survival between treatment groups was assessed using a stratified log-rank test and the magnitude of difference (ie, HR) was estimated using a stratified Cox proportional hazards model with the

Efron method for handling ties. The stratification factors used for randomisation were applied to both the stratified log-rank test and the stratified Cox proportional hazards model. For the primary recurrence-free survival analysis, participants with missing disease assessment data were censored either at the last assessment date or at the last date the participant was known to be alive (appendix p 48). Participants who were alive and did not have a recurrence event were censored at the last disease assessment date before new anticancer therapy, if any, was initiated. To determine whether the treatment effect was consistent across various subgroups, the estimates of the between-group treatment effect (with a nominal 95% CI) for recurrence-free survival was estimated and plotted within each subgroup, as prespecified in the protocol. The protocol-specified subgroups were age (<65 years *vs* ≥65 years), sex (male *vs* female), race (White *vs* all others), ECOG performance status (0 *vs* 1; or equivalent in KPS or LPS [70 or 80 *vs* 90 or 100]), region (Asia *vs* rest of world), and risk-based stage (IIB–IIIB *vs* IIIC–IV). Recurrence-free survival was analysed in these subgroups using an unstratified Cox proportional hazards model. Statistical analyses were done with SAS (version 9.4). For the proportional hazard assumption (for treatment), a Supremum test (using statement of "assess ph" in SAS PROC PHREG) was performed, and the assumption was not violated. As the prespecified futility criterion for the trial was met, no p values were reported.

Role of the funding source

The funder of the study participated in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Jan 19, 2023, and March 6, 2024, 1810 participants were screened for enrolment, of whom 1402 met the eligibility criteria and were randomly assigned to the vibostolimab–pembrolizumab coformulation group (n=701) or the pembrolizumab alone group (n=701; efficacy analysis population; figure 1). Baseline demographics and disease characteristics were balanced between treatment groups (table 1). The median age was 61·0 years (IQR 51·0–70·0); no paediatric participants younger than 18 years were enrolled. 829 (59%) of 1402 participants were male and 573 (41%) were female, 1175 (84%) had an ECOG performance status of 0, 847 (60%) had stage IIB–IIIB disease, and 552 (39%) had stage IIIC–IV disease. Of 701 participants assigned to the vibostolimab–pembrolizumab group, 698 received at least one dose of study treatment; of 701 participants assigned to the pembrolizumab alone group, 700 received at least one dose of study treatment (safety analysis population; figure 1). At the first interim analysis, the median study follow-up, defined as time from randomisation to the data cutoff (March 6, 2024), was 4·2 months (IQR 1·9–6·7). The median duration of treatment in the vibostolimab–pembrolizumab group was 85·0 days (IQR 42·0–147·0), with 393 (56%) of 698 participants who received at least one dose of treatment having received less than 3 months of therapy (appendix p 49). The median duration of treatment in the pembrolizumab alone group was 87·5 days (IQR 43·0–168·0), with 357 (51%) of 700 participants who received at least one dose of treatment having received less than 3 months of therapy. 27 (4%) of 701 participants in the vibostolimab–pembrolizumab group and 22 (3%) of 701 in the pembrolizumab alone

	Vibostolimab–pembrolizumab group (n=701)	Pembrolizumab group (n=701)
Age, years*	61·0 (51·0–69·0)	61·0 (50·0–70·0)
<65	419 (60%)	427 (61%)
≥65	282 (40%)	274 (39%)
Sex		
Male	419 (60%)	410 (58%)
Female	282 (40%)	291 (42%)
Race		
White	553 (79%)	554 (79%)
Asian	134 (19%)	139 (20%)
Other	12 (2%)	7 (1%)
Data missing	2 (<1%)	1 (<1%)
Ethnicity		
Hispanic or Latino	84 (12%)	73 (10%)
Not Hispanic or Latino	585 (83%)	586 (84%)
Not reported or unknown	32 (5%)	42 (6%)
Region		
Asia	133 (19%)	135 (19%)
Rest of world	568 (81%)	566 (81%)
ECOG performance status		
0	585 (83%)	590 (84%)
1	116 (17%)	111 (16%)
Overall cancer stage		
IIB	118 (17%)	111 (16%)
IIC	85 (12%)	87 (12%)
IIIA	77 (11%)	69 (10%)
IIIB	141 (20%)	159 (23%)
IIIC	223 (32%)	222 (32%)
IIID	19 (3%)	15 (2%)
IV	37 (5%)	36 (5%)
Data missing	1 (<1%)	2 (<1%)
Stratification risk-based stage		
IIB/IIC/clinical IIB and IIC/IIIA/IIIB	427 (61%)	427 (61%)
IIIC/IIID/IV	274 (39%)	274 (39%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *No paediatric participants were enrolled; the youngest participant enrolled was age 21 years.

Table 1: **Baseline demographics and clinical characteristics**

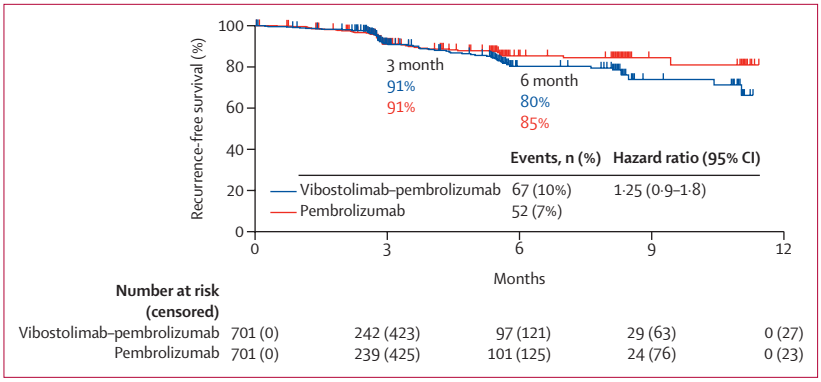

Figure 2: **Kaplan–Meier estimate of recurrence-free survival per RECIST by investigator review**

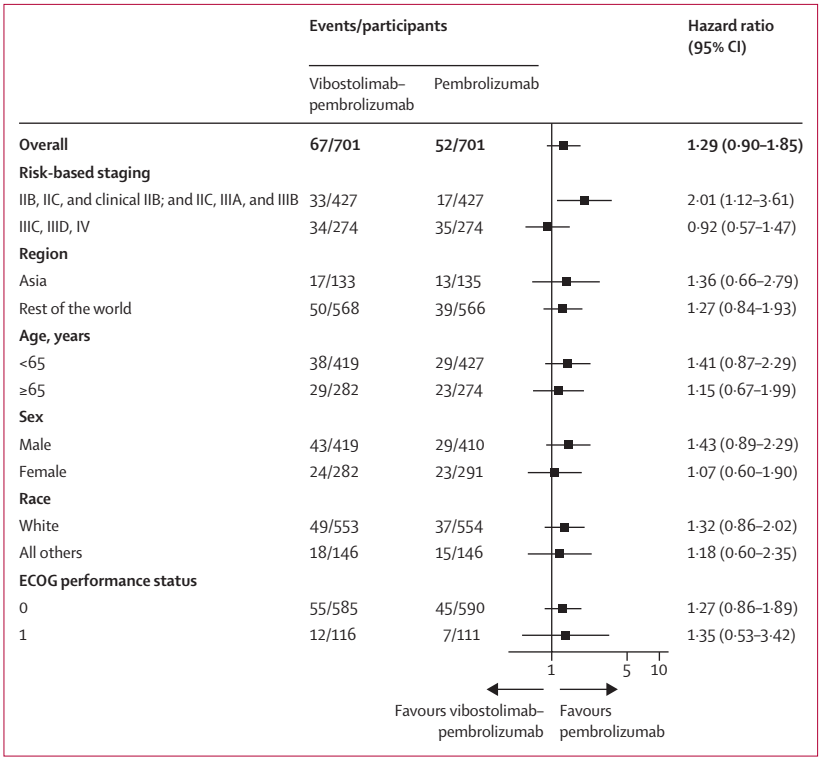

Figure 3: **Recurrence-free survival per RECIST by investigator review in participant subgroups**
ECOG=Eastern Cooperative Oncology Group.

group received at least one subsequent anticancer therapy (appendix pp 50–51).

At the time of the first interim analysis, a total of 119 (8%) of 1402 participants had experienced a recurrence-free survival event, including 67 (10%) of 701 in the vibostolimab–pembrolizumab group and 52 (7%) of 701 in the pembrolizumab alone group (figure 2). The most common types of recurrence-free survival events (≥10 participants) were distant (22 [3%]), local (15 [2%]), and regional (14 [2%]) in the vibostolimab–pembrolizumab group, and distant (19 [3%]) and local (15 [2%]) in the pembrolizumab alone group (appendix p 52). The median recurrence-free survival was not reached in either group (HR 1·25 [95% CI 0·9–1·8]). The 6-month recurrence-free survival rates were 80% (95% CI 75–85) in the vibostolimab–pembrolizumab group and 85% (81–89) in the pembrolizumab alone group. Vibostolimab–pembrolizumab did not provide a recurrence-free survival benefit over pembrolizumab alone across subgroups (figure 3). When the external data monitoring committee reviewed the results of the first interim analysis (after 119 events), it was determined that the primary endpoint of recurrence-free survival had met the prespecified futility criterion. The study was unmasked, and participants receiving vibostolimab–pembrolizumab were offered the option of switching to pembrolizumab monotherapy.

All-cause adverse events occurred in 574 (82%) of 698 participants in the vibostolimab–pembrolizumab group and 558 (80%) of 700 participants in the pembrolizumab alone group (appendix pp 53–65); grade 3 or higher adverse events occurred in 153 (22%) and 76 (11%) participants in each group, respectively. All-cause adverse events led to deaths in three (<1%) participants in the vibostolimab–pembrolizumab group (myasthenia gravis [n=1], myocarditis [n=1], and septic shock [n=1]), and in one (<1%) participant in the pembrolizumab alone group (myositis). Treatment-related adverse events occurred in 517 (74%) of 698 participants in the vibostolimab–pembrolizumab group, most commonly (≥15%) pruritus (166 [24%]), rash (162 [23%]), and fatigue (111 [16%]; table 2). Treatment-related adverse events occurred in 462 (66%) of 700 participants in the pembrolizumab alone group, the most common of which (≥15%) was fatigue (116 [17%]; table 2). Grade 3–5 treatment-related adverse events occurred in 111 (16%) of 698 participants in the vibostolimab–pembrolizumab group, with adrenal insufficiency (13 [2%]), hepatitis (11 [2%]), rash (9 [1%]), maculopapular rash (7 [1%]), pruritus (6 [1%]), colitis (4 [1%]), hypophysitis (4 [1%]), and type 1 diabetes (4 [1%]), the only events to occur in ≥1% of participants. Grade 3–5 treatment-related adverse events occurred in 48 (7%) of 700 participants in the pembrolizumab alone group, with increased alanine aminotransferase (7 [1%]), increased aspartate aminotransferase (4 [1%]), and hepatitis (4 [1%]), the only events to occur in ≥1% of participants. Treatment-related adverse events led to discontinuation of treatment in 87 (12%) of 698 participants in the vibostolimab–pembrolizumab group, most commonly (≥1%) hepatitis (10 [1%]), rash (9 [1%]), myocarditis (5 [1%]), pneumonitis (4 [1%]), and maculopapular rash (4 [1%]). Treatment-related adverse events led to discontinuation of treatment in 44 (6%) of 700 participants in the pembrolizumab alone group, most commonly (≥1%) hepatitis (5 [1%]) and pneumonitis (4 [1%]). Treatment-related serious adverse events occurred in 74 (11%) participants in the vibostolimab–pembrolizumab group and 30 (4%) participants in the pembrolizumab alone group

	Vibostolimab–pembrolizumab (n=698)				Pembrolizumab (n=700)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Pruritus	160 (23%)	6 (1%)	0	0	86 (12%)	0	0	0
Rash	153 (22%)	9 (1%)	0	0	65 (9%)	0	0	0
Fatigue	111 (16%)	0	0	0	114 (16%)	2 (<1%)	0	0
Hyperthyroidism	85 (12%)	0	0	0	78 (11%)	0	0	0
Hypothyroidism	62 (9%)	1 (<1%)	0	0	60 (9%)	0	0	0
Aspartate aminotransferase increased	51 (7%)	2 (<1%)	0	0	36 (5%)	4 (<1%)	0	0
Alanine aminotransferase increased	48 (7%)	2 (<1%)	1 (<1%)	0	48 (7%)	7 (1%)	0	0
Rash maculo-papular	37 (5%)	7 (1%)	0	0	22 (3%)	0	0	0
Diarrhoea	34 (5%)	1 (<1%)	0	0	31 (4%)	3 (<1%)	0	0
Asthenia	31 (4%)	1 (<1%)	0	0	12 (2%)	1 (<1%)	0	0
Nausea	29 (4%)	2 (<1%)	0	0	35 (5%)	0	0	0
Myalgia	25 (4%)	1 (<1%)	0	0	20 (3%)	1 (<1%)	0	0
Pyrexia	19 (3%)	1 (<1%)	0	0	3 (<1%)	0	0	0
Eczema	16 (2%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Blood bilirubin increased	14 (2%)	1 (<1%)	0	0	14 (2%)	0	0	0
Dermatitis	14 (2%)	2 (<1%)	0	0	6 (1%)	0	0	0
Decreased appetite	13 (2%)	2 (<1%)	0	0	9 (1%)	1 (<1%)	0	0
Gamma-glutamyltransferase increased	13 (2%)	1 (<1%)	0	0	7 (1%)	1 (<1%)	0	0
Eosinophilia	12 (2%)	1 (<1%)	0	0	6 (1%)	0	0	0
Rash pruritic	11 (2%)	3 (<1%)	0	0	2 (<1%)	0	0	0
Adrenal insufficiency	9 (1%)	11 (2%)	2 (<1%)	0	5 (1%)	2 (<1%)	0	0
Anaemia	9 (1%)	0	1 (<1%)	0	7 (1%)	0	0	0
Blood alkaline phosphatase increased	9 (1%)	0	0	0	3 (<1%)	1 (<1%)	0	0
Blood creatine phosphokinase increased	9 (1%)	2 (<1%)	0	0	9 (1%)	0	0	0
Lymphocyte count decreased	9 (1%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	0	0
Hyperglycaemia	7 (1%)	3 (<1%)	0	0	9 (1%)	0	0	0
Arthritis	6 (1%)	3 (<1%)	0	0	11 (2%)	0	0	0
Hypophysitis	6 (1%)	4 (1%)	0	0	2 (<1%)	0	0	0
Pneumonitis	6 (1%)	1 (<1%)	0	0	6 (1%)	1 (<1%)	0	0
White blood cell decreased	6 (1%)	1 (<1%)	0	0	4 (1%)	0	0	0
Erythema	5 (1%)	1 (<1%)	0	0	4 (1%)	0	0	0
Hyponatraemia	5 (1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Rash papular	5 (1%)	1 (<1%)	0	0	0	0	0	0
Hypertriglyceridaemia	4 (1%)	0	0	0	6 (1%)	1 (<1%)	0	0
Cortisol decreased	3 (<1%)	1 (<1%)	0	0	0	0	0	0
Myocarditis	3 (<1%)	0	2 (<1%)	1 (<1%)	0	0	1 (<1%)	0
Psoriasis	3 (<1%)	1 (<1%)	0	0	6 (1%)	0	0	0
Amylase increased	2 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Dermatitis acneiform	2 (<1%)	1 (<1%)	0	0	2 (<1%)	1 (<1%)	0	0
Hepatitis	2 (<1%)	8 (1%)	3 (<1%)	0	2 (<1%)	3 (<1%)	1 (<1%)	0
Immune-mediated dermatitis	2 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Immune-mediated enterocolitis	2 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Lipase increased	2 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Neutropenia	2 (<1%)	0	1 (<1%)	0	2 (<1%)	0	0	0
Proteinuria	2 (<1%)	0	0	0	4 (1%)	1 (<1%)	0	0
Cardiac failure	1 (<1%)	0	0	0	0	0	1 (<1%)	0
Colitis	1 (<1%)	4 (1%)	0	0	5 (1%)	1 (<1%)	0	0
Diabetes	1 (<1%)	0	1 (<1%)	0	0	0	0	0
Dyspnoea	1 (<1%)	1 (<1%)	0	0	4 (1%)	0	0	0
Hypertension	1 (<1%)	0	0	0	3 (<1%)	2 (<1%)	0	0
Hypertransaminasaemia	1 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0

(Table 2 continues on next page)

	Vibostolimab–pembrolizumab (n=698)				Pembrolizumab (n=700)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Hypokalaemia	1 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Immune-mediated hypophysitis	1 (<1%)	2 (<1%)	0	0	0	0	0	0
Immune-mediated hypothyroidism	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Leukopenia	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Lichenoid keratosis	1 (<1%)	2 (<1%)	0	0	1 (<1%)	0	0	0
Migraine	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Polymyalgia rheumatica	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Uveitis	1 (<1%)	2 (<1%)	0	0	1 (<1%)	0	0	0
Type 1 diabetes	0	3 (<1%)	1 (<1%)	0	1 (<1%)	3 (<1%)	0	0
Encephalopathy	0	2 (<1%)	1 (<1%)	0	0	0	0	0
Meningitis aseptic	0	2 (<1%)	0	0	0	0	0	0
Muscular weakness	0	2 (<1%)	0	0	1 (<1%)	0	0	0
Arrhythmia	0	1 (<1%)	0	0	0	0	0	0
Costochondritis	0	1 (<1%)	0	0	0	0	0	0
Device related infection	0	1 (<1%)	0	0	0	0	0	0
Drug reaction with eosinophilia and systemic symptoms	0	1 (<1%)	0	0	0	0	0	0
Dysphagia	0	1 (<1%)	0	0	0	0	0	0
Encephalitis autoimmune	0	1 (<1%)	0	0	0	0	0	0
Febrile neutropenia	0	1 (<1%)	0	0	0	0	0	0
General physical health deterioration	0	1 (<1%)	0	0	0	0	0	0
Guillain–Barre syndrome	0	1 (<1%)	0	0	0	0	0	0
Hypoxia	0	1 (<1%)	0	0	0	0	0	0
Immune-mediated hepatitis	0	1 (<1%)	0	0	2 (<1%)	2 (<1%)	0	0
Immune-mediated myositis	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Iridocyclitis	0	1 (<1%)	0	0	0	0	0	0
Meningitis	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Myelitis transverse	0	1 (<1%)	0	0	0	0	0	0
Myositis	0	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
Syncope	0	1 (<1%)	0	0	0	0	0	0
Systemic inflammatory response syndrome	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Transaminases increased	0	1 (<1%)	0	0	2 (<1%)	0	0	0
Vasculitis	0	1 (<1%)	0	0	0	0	0	0
Visual impairment	0	1 (<1%)	0	0	0	0	0	0
Autoimmune haemolytic anaemia	0	0	1 (<1%)	0	0	0	0	0
Diabetic ketoacidosis	0	0	1 (<1%)	0	0	1 (<1%)	0	0
Immune thrombocytopenia	0	0	1 (<1%)	0	0	0	0	0
Myasthenia gravis	0	0	0	1 (<1%)	0	0	0	0
Neutrophil count decreased	0	0	0	0	2 (<1%)	1 (<1%)	0	0
Atrial fibrillation	0	0	0	0	1 (<1%)	1 (<1%)	0	0
Immune-mediated myocarditis	0	0	0	0	0	3 (<1%)	0	0
Tubulointerstitial nephritis	0	0	0	0	0	2 (<1%)	0	0
Gastritis erosive	0	0	0	0	0	1 (<1%)	0	0
Hepatitis C	0	0	0	0	0	1 (<1%)	0	0
Optic neuropathy	0	0	0	0	0	1 (<1%)	0	0
Persistent postural-perceptual dizziness	0	0	0	0	0	1 (<1%)	0	0
Vogt–Koyanagi–Harada disease	0	0	0	0	0	1 (<1%)	0	0

(Table 2 continues on next page)

	Vibostolimab–pembrolizumab (n=698)				Pembrolizumab (n=700)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Immune-mediated nephritis	0	0	0	0	0	0	1 (<1%)	0
Neuritis	0	0	0	0	0	0	1 (<1%)	0
Polymyositis	0	0	0	0	0	0	1 (<1%)	0
Septic shock	0	0	0	0	0	0	1 (<1%)	0

Data are n (%). Treatment-related adverse events included grade 1 or 2 treatment-related adverse events that occurred in ≥10% of participants, and all grade 3, 4, or 5 treatment-related adverse events.

Table 2: **Treatment-related adverse events**

(appendix pp 66–71). Treatment-related adverse events led to deaths in two (<1%) of 698 participants in the vibostolimab–pembrolizumab group (myasthenia gravis [n=1] and myocarditis [n=1]) and one (<1%) of 700 participants in the pembrolizumab alone group (myositis; table 2).

Immune-mediated adverse events and infusion reactions occurred in 212 (30%) of 698 participants in the vibostolimab–pembrolizumab group and 168 (24%) of 700 participants in the pembrolizumab alone group (appendix pp 72–74); the most common (≥5%) in both treatment groups were hyperthyroidism (88 [13%] and 81 [12%], respectively) and hypothyroidism (69 [10%] and 65 [9%], respectively). Grade 3 or higher immune-mediated adverse events and infusion reactions occurred in 83 (12%) of 698 participants in the vibostolimab–pembrolizumab group and 26 (4%) of 700 participants in the pembrolizumab alone group (appendix pp 72–74). Immune-mediated adverse events led to deaths in two (<1%) of 698 participants in the vibostolimab–pembrolizumab group (myasthenia gravis [n=1] and myocarditis [n=1]) and one (<1%) of 700 participants in the pembrolizumab alone group (myositis). Of 325 episodes of immune-mediated adverse events or infusion reactions that occurred in the vibostolimab–pembrolizumab group, 107 (33%) required treatment with corticosteroids (61 [19%] high dose [≥40 mg per day prednisone equivalent]); of 230 episodes in the pembrolizumab alone group, 47 (20%) required treatment with corticosteroids (35 [15%] high dose).

Discussion

The results of the first interim analysis of KEYVIBE-010 showed that adjuvant vibostolimab coformulated with pembrolizumab provided no benefit compared with pembrolizumab alone in participants with resected stage IIB to IV melanoma. The recurrence-free survival HR was 1·25 (95% CI 0·9–1·8), and the 6-month recurrence-free survival rates were 80% (95% CI 75–85) in the vibostolimab–pembrolizumab group versus 85% (81–89) in the pembrolizumab alone group. On reviewing these results, the external data monitoring committee determined that the primary endpoint of recurrence-free survival met the prespecified futility criteria, and treatment with vibostolimab–pembrolizumab was halted; participants in the group were offered treatment with pembrolizumab monotherapy. No benefit was observed in key subgroups with vibostolimab–pembrolizumab.

There were no new safety signals for vibostolimab–pembrolizumab in the current study compared with what was observed with vibostolimab plus pembrolizumab in KEYVIBE-001.[12] A higher rate of treatment-related adverse events, including grade 3 or higher treatment-related adverse events (16% *vs* 7%), were observed in the vibostolimab–pembrolizumab group compared with the pembrolizumab alone group; although, three participants died in the vibostolimab–pembrolizumab group and one participant died in the pembrolizumab alone group. More participants in the vibostolimab–pembrolizumab group versus the pembrolizumab alone group discontinued treatment because of treatment-related adverse events (12% *vs* 6%); however, the median duration of therapy between groups was similar (85·0 days [IQR 42·0–147·0] *vs* 87·5 days [43·0–168·0]), suggesting that the lack of an efficacy benefit with vibostolimab–pembrolizumab was not because of a higher rate of treatment discontinuation. The incidence of immune-mediated adverse events and infusion reactions was higher in the vibostolimab–pembrolizumab group compared with the pembrolizumab alone group (30% *vs* 24%), which is not unexpected given the combination of two immunotherapies with different mechanisms of action.

The combination of vibostolimab and pembrolizumab has been evaluated with variable results in several tumour types. In KEYMAKER-U02 substudy 02C, neoadjuvant pembrolizumab plus vibostolimab followed by adjuvant pembrolizumab showed promising anti-tumour activity in participants with stage IIIB–IIID melanoma; the pathological complete response rate in participants treated with the combination was 38%, the 18-month recurrence-free survival rate was 90%, the 18-month event-free survival rate was 81%, and the objective response rate was 50%.[13] Longer follow-up will provide more clarity on efficacy in this setting. In the KEYVIBE-001 study, the combination of vibostolimab

and pembrolizumab showed antitumour activity in participants with advanced solid tumours, with notable efficacy in participants with anti-PD-1-naive or anti-PD-L1-naive non-small cell lung cancer (objective response rate 26%).[12] Promising antitumour activity was observed with vibostolimab–pembrolizumab in the multicohort, phase 2, KEYVIBE-005 study, which included participants with previously untreated advanced oesophageal cancer,[14] previously treated advanced mismatch repair-deficient endometrial cancer,[15] and head and neck squamous cell carcinoma with PD-L1 combined positive score ≥1.[16] Notably, efficacy outcomes with the coformulation were not superior to those with pembrolizumab alone in participants with previously treated PD-L1-positive cervical cancer.[17] Results of the subsequent KEYVIBE-002 and KEYVIBE-008 studies were not able to show improved efficacy with vibostolimab coformulated with pembrolizumab compared with standard of care in participants with metastatic non-small cell lung cancer or extensive-stage small cell lung cancer, respectively.[18,19]

Several anti-TIGIT IgG1 antibodies are being investigated in combination with anti-PD-1 or anti-PD-L1 agents, and while some antitumour activity has been observed, several phase 3 studies were not successful in reaching their primary efficacy endpoints. The anti-TIGIT antibody tiragolumab initially showed manageable safety and clinically meaningful efficacy in combination with atezolizumab in patients with non-small cell lung cancer in the phase 2 CITYSCAPE study.[20] However, the subsequent phase 3 SKYSCRAPER-01 and SKYSCRAPER-02 trials failed to show any additional benefit with the addition of tiragolumab to atezolizumab in non-small cell lung cancer or extensive-stage small-cell lung cancer.[21,22] In the phase 2 SKYSCRAPER-04 trial, an objective response rate of 19·0% was reported with tiragolumab plus atezolizumab compared with 14·6% for a historical reference, and 15·6% for atezolizumab alone in participants with PD-L1-positive persistent or recurrent cervical cancer.[23] The anti-TIGIT antibodies etigilimab and ociperlimab also had manageable safety and evidence of clinical benefit in combination with PD-1 inhibitors in patients with advanced solid tumours.[24–26] Several trials are underway evaluating the anti-TIGIT antibody domvanalimab in combination with the anti-PD-1 antibody zimberelimab, with encouraging antitumour activity observed in indications including anti-PD-1 or anti-PD-L1 refractory hepatocellular carcinoma,[27] advanced non-small cell lung cancer,[28] and with chemotherapy in gastroesophageal cancer.[29]

Adjuvant immunotherapy, including nivolumab and pembrolizumab, showed significant improvement in recurrence-free survival and distant metastasis-free survival among patients with stage IIB, IIC, and III melanoma.[30,31] Nevertheless, the overall survival benefit with these agents remains inconclusive, pending the maturation of data from pivotal trials, most notably KEYNOTE-716 and KEYNOTE-054.[4,5,7] Several clinical trials are underway to evaluate novel immunotherapy combinations as adjuvant therapy for participants with high-risk stage II–IV cutaneous melanoma, including the phase 3 trial of the lymphocyte-activation gene 3 inhibitor fianlimab in combination with the anti-PD-1 antibody cemiplimab (NCT05608291) and the phase 3 INTerpath-001 trial (NCT05933577) of pembrolizumab plus the individualised neoantigen therapy intismeran autogene.[32,33] Although these trials are ongoing and have not produced conclusive efficacy data, they include promising research approaches that could transform the future of adjuvant immunotherapy.

Furthermore, neoadjuvant immunotherapy is increasingly recognised as a promising strategy for patients with high-risk, surgically resectable melanoma, with the potential to augment systemic antitumour immunity and improve long-term disease control.[34] However, neoadjuvant therapy is not routinely feasible for most patients with stage IIB–III melanoma with micrometastases; therefore, necessitating high-level clinical evidence to establish the definitive role of adjuvant immunotherapy in this patient population.[31] There is also a need to optimise neoadjuvant therapeutic regimens and to elucidate the necessity and scope of adjuvant immunotherapy after neoadjuvant intervention for management of patients with high-risk resectable melanoma.

The primary limitation of this analysis was that not all patients had a recurrence-free survival assessment as required by the protocol at the time of data cutoff, as they had discontinued from the study because of an adverse event, withdrawn consent, or locoregional recurrence. However, the number of patients without a recent disease assessment were small and well balanced between the two treatment groups and therefore, this problem is expected to have little or no effect on the recurrence-free survival comparison. The results of KEYVIBE-010 showed that vibostolimab coformulated with pembrolizumab did not provide benefit compared with pembrolizumab alone as adjuvant therapy in participants with resected stage IIB to IV melanoma. Adjuvant therapy with pembrolizumab remains a standard of care for participants with high-risk resected melanoma. There remains an opportunity to further optimise treatment in this adjuvant setting.

Contributors

RD contributed to data generation, trial design, and manuscript writing and approval. JG contributed to conceptualisation, data curation, and writing–review and editing. JJL contributed to study design, data collection, data analysis, data interpretation, and writing. MSC contributed to conceptualisation, data curation, investigation, methodology, project administration, resources, supervision, writing–original draft, and writing–review and editing. DS contributed to data curation, project administration, resources, writing–original draft, and writing–review and editing. MAK contributed to conceptualisation, data curation, validation, writing–original draft, and writing–review and editing. AH contributed to data collection and writing–review and editing. PAA contributed to data curation, investigation, supervision, writing–original draft, and writing–review and editing. YC, SJS, and JC

contributed to data collection. PR contributed to data collection and interpretation, and the final manuscript. ZL contributed to the investigation: their team conducted the research for KEYVIBE-010 and the investigation process, specifically performing the experiments, or data and evidence collection. GR contributed to data curation, investigation, writing–original draft, and writing–review and editing. CCo contributed to investigation. AR contributed to protocol development, patient accrual, data interpretation, and the manuscript. KM contributed to investigation. GM contributed to data curation, investigation, resources, writing–original draft, and writing–review and editing. RUV contributed to data curation, investigation, writing–original draft, and writing–reviewing and editing. OD contributed to data curation, investigation, methodology, supervision, validation, writing–original draft, and writing–review and editing. CCa contributed to the investigation, project administration, resources, and writing–reviewing and editing. DG contributed to conceptualisation, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualisation, writing–original draft, and writing–review and editing. KD contributed to data curation, formal analysis, methodology, validation, visualisation, writing–original draft, writing–reviewing and editing. CK contributed to the study design, data collection, data analysis, data interpretation, and critical review of the manuscript. GVL contributed to the study design, data collection, data interpretation, investigation, project administration, resources, writing original draft, and writing–reviewing and editing. RD and GVL had full access to and verified the raw data in the study. All authors had full access to all the data in the study and approved the decision to submit the manuscript for publication.

Declaration of interests

RD reports intermittent, project focused consulting or advisory relationships with Novartis, Merck Sharp & Dohme (MSD), Bristol Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, T3 Pharma, MaxiVAX SA, Pfizer, and Simcere, outside the submitted work, and is a senior medical advisor for Oncobit. JG reports consulting fees from MSD, Roche, Bayer, Novartis, Simcere Pharmaceutical Group, Shanghai Junshi Biosciences, and Oriengene. 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MSD, a subsidiary of Merck & Co is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (https://externaldatasharing-msd.com/) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that might prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either do the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can do the proposed analyses.

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