6-6-2024

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Journal for ImmunoTherapy of Cancer

Long-term survival follow-up for tebentafusp in previously treated metastatic uveal melanoma

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To cite: Sacco JJ, Carvajal RD, Butler MO, *et al*. Long-term survival follow-up for tebentafusp in previously treated metastatic uveal melanoma. *Journal for ImmunoTherapy of Cancer* 2024;**12**:e009028. doi:10.1136/jitc-2024-009028

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2024-009028).

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Accepted 19 April 2024

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ABSTRACT

Background Tebentafusp, a bispecific (gp100×CD3) ImmTAC, significantly improved overall survival (OS) outcomes for HLA-A*02:01+ adult patients with untreated metastatic uveal melanoma (mUM) and showed promising survival in previously treated mUM with 1-year OS of 62% in the primary analysis of study IMCgp100-102. Here we report long-term outcomes from this phase 1/2 study in pretreated mUM.

Patients and methods Patients with previously treated mUM received tebentafusp weekly intravenous at 20 µg dose 1, 30 µg dose 2 and either 54, 64, 68, or 73 µg (phase 1) or 68 µg (phase 2) dose 3+. The primary objective was overall response rate. Secondary objectives included OS and safety. OS was estimated by Kaplan-Meier methods. Association between OS and baseline covariates, on-treatment Response Evaluation Criteria in Solid Tumors (RECIST) response, baseline tumor biopsy and circulating-tumor DNA (ctDNA) changes were assessed.

Results 146 patients were treated with tebentafusp: 19 in phase 1 and 127 in phase 2. With a median follow-up duration of 48.5 months, the median OS was 17.4 months (95% CI, 13.1 to 22.8), and the 1-year, 2-year, 3-year and 4-year OS rates were 62%, 40%, 23% and 14%, respectively. Improved survival was associated with lower ctDNA baseline levels and greater ctDNA reductions by week 9 on-treatment, with 100% 1-year, 73% 2-year and 45% 3-year OS rates for patients with ctDNA clearance. Baseline gp100 expression was not associated with survival, despite more RECIST responses among patients with higher expression. No new safety signals were reported with long-term dosing.

Conclusions This study represents the longest follow-up of a Tcell receptor bispecific to date and confirms the durable survival benefits achieved with tebentafusp in previously treated mUM with good tolerability long-term. A role for ctDNA reduction as an early indicator of clinical benefit was again suggested for patients treated with tebentafusp.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Metastatic uveal melanoma (mUM) is associated with poor prognosis, with median overall survival (OS) of ≤1 year historically. Tebentafusp significantly improves survival outcomes for treatment-naïve HLA-A*02:01+ patients with mUM (HR=0.51), and promising survival benefits were also observed in previously treated mUM after a median follow-up of 19.5 months in the phase 2 IMCgp100-102 trial.

WHAT THIS STUDY ADDS

⇒ This final analysis of the phase 1/2 IMCgp100-102 study of tebentafusp in previously treated mUM provides important long-term data in this population, with a median follow-up of >4 years.

⇒ The median OS and estimated OS rates continued to be approximately double that observed historically for a similar population of patients. The survival benefit was observed even in patients with a best overall response to progressive disease and in patients with poor prognostic indicators.

⇒ Lower baseline and greater on-treatment circulating-tumor DNA (ctDNA) reduction by week 9 was associated with longer OS. Deep reductions in ctDNA were observed across Response Evaluation Criteria in Solid Tumors (RECIST) response categories, even in patients with a best response to progressive disease.

INTRODUCTION

Historically, metastatic uveal melanoma (mUM) has been associated with a very poor prognosis with no recognized standard of care,[1] with a median overall survival (OS) of approximately 10–12 months,[2 3] and 7–8 months in the second-line or later-line treatment setting.[4 5] The recent introduction of tebentafusp has significantly improved survival outcomes for treatment-naïve HLA-A*02:01+ adult patients with unresectable or mUM,[6 7] and is the only therapy specifically approved for this patient population.[8] In 2023, melphalan for Injection/Hepatic Delivery System (HEPZATO KIT) became only the second therapy to be approved for this cancer and is indicated for patients with

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current analysis of tebentafusp efficacy and safety at 4 years of median follow-up represents the longest follow-up of a T cell receptor bispecific to date and confirms and expands our understanding of this drug. Tebentafusp continues to show marked survival benefits for previously treated patients alongside a predictable and manageable safety profile. The potential survival benefit of tebentafusp in patients who have the progressive disease by standard RECIST reconfirmed the need for a better response evaluation system or response biomarkers for patients treated with immunotherapies. In this regard, the measurement of ctDNA might provide supplemental information for treatment decision, particularly in patients with RECIST-defined disease progression.

unresectable mUM with hepatic metastases present in <50% of the liver and no extrahepatic disease, or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation.[9]

Tebentafusp is a first-in-class ImmTAC (Immune mobilizing monoclonal T-cell receptor Against Cancer) bispecific protein that targets gp100 and induces polyclonal T cell activation and redirected killing of melanoma cells. In the randomized phase 3 trial, tebentafusp significantly improved OS in previously untreated mUM when compared with the investigator's choice of treatment (single-agent pembrolizumab, ipilimumab or dacarbazine), with an HR for the death of 0.51 (95% CI, 0.37 to 0.71; p<0.001) and 1-year OS rate of 73% versus 59%, respectively.[7] Notably, a survival benefit was observed even in patients who had a best response of progressive disease (HR 0.43; 95% CI, 0.27 to 0.68).

Tebentafusp has also shown favorable survival outcomes in phase 1/2 studies in treatment-refractory mUM compared with historical benchmarks.[5 10] The phase 1 portion of study IMCgp100-102 in patients with previously treated mUM established the 3-week step-up dosing regimen (20–30–68 µg) that was used in subsequent phase 2 and 3 studies, and additionally provided an efficacy signal with a promising 1-year OS rate of 67% and median OS of 25.5 months.[10] In the phase 2 portion of the same study, the 1-year OS rate and median OS were 62% (95% CI, 53% to 70%) and 16.8 months (95% CI, 12.9 to 21.3), respectively, despite a modest overall response rate of 5% (95% CI, 2% to 10%).[5] Importantly, there was a strong association between OS and early reduction in circulating-tumor DNA (ctDNA) levels, suggesting benefit beyond traditional radiographic-based response criteria.[5]

The safety profile of tebentafusp has been consistent across studies reported to date, with adverse events (AEs) in the phase 2 study in previously treated patients with mUM[5] similar to those in the phase 3 study in treatment-naïve patients.[7] Consistent with the mechanism of action of tebentafusp, the most frequently reported treatment-related AEs include cytokine-mediated events and cutaneous events; most of these events occurred following the first three to four doses of tebentafusp, and decreased in frequency and severity with subsequent doses.[5 7 10]

The prior publication from the phase 2 portion of the IMCgp100-102 study reported outcome data from a median follow-up duration of 19.5 months.[5] Herein, we report the final analysis of tebentafusp efficacy and safety at 4 years of follow-up, which represents the longest follow-up of a T cell receptor (TCR) bispecific to date.

METHODS

Study design, patients, and procedures

Full details of the IMCgp100-102 study have been published.[5 10] In brief, this was a single-arm, open-label, international, phase 1/2 study (NCT02570308), which included dose escalation (phase 1) and expansion (phase 2) cohorts. The study was initiated in March 2016, and the final database lock for this analysis was October 17, 2022.

Patients were aged ≥18 years, with a histologically or cytologically confirmed diagnosis of mUM, a life expectancy of >3 months (as estimated by the investigator), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Eligible patients were required to be HLA-A*02:01 positive by central assay, and those enrolled in the expansion phase had to have measurable disease (according to Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 criteria) and have received at least one prior line of therapy (including chemotherapy, immunotherapy, or targeted therapy) in the metastatic setting. Key exclusion criteria were the presence of symptomatic or untreated central nervous system metastases; history of severe hypersensitivity reactions to other biologic drugs or monoclonal antibodies; out-of-range protocol-defined laboratory parameters; and clinically significant cardiac disease or impaired cardiac function.

Study participants received weekly tebentafusp as an intravenous infusion, with each treatment cycle defined as 28 days. A step-up dosing regimen was used with 20 µg administered on day 1 of cycle 1 and 30 µg on day 8 of cycle 1. During the dose escalation phase, the dose from day 15 of cycle 1 was either 54, 64, 68, or 73 µg; for all patients in the expansion cohort, the dose from day 15 of cycle 1 was 68 µg.

Treatment continued until confirmed disease progression as per immune-related response criteria (irRECIST), the development of unacceptable toxic effects, or a decision to withdraw by the investigator or patient. However, patients could continue with treatment beyond the time of initial RECIST-defined disease progression in the absence of signs or symptoms indicating clinically significant progressive disease which would require urgent alternative medical intervention, and providing the investigator believed that there was continuing clinical benefit.

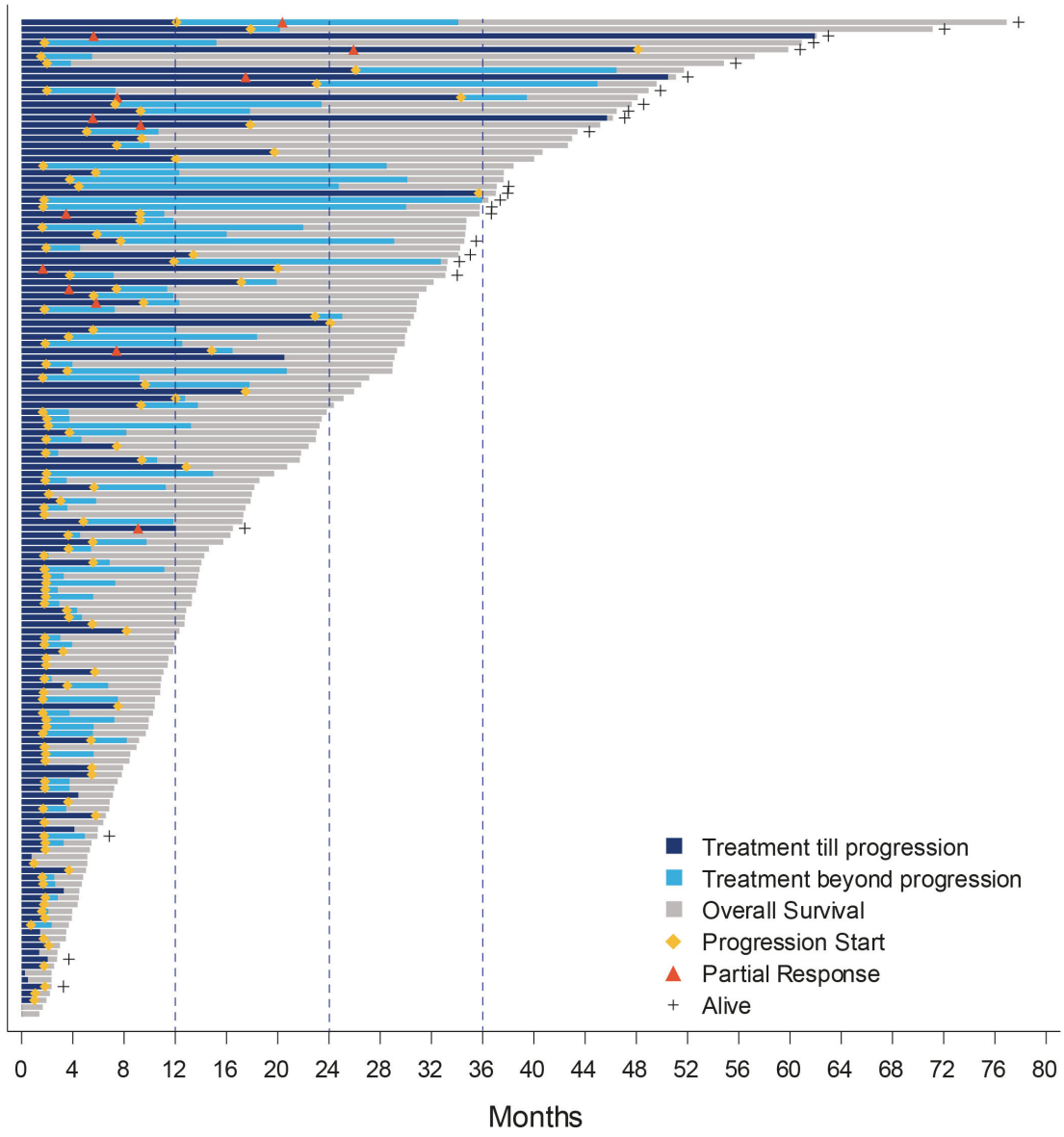

Figure 1 Overall survival and duration of treatment for tebentafusp-treated patients (N=146). The median duration of treatment beyond progression was 2.8 months (range: <1–34 months; n=97).

Study oversight

This clinical study was designed and implemented in accordance with the International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the ethical principles laid down in the Declaration of Helsinki, and all applicable local regulations. The study protocol was approved by the relevant ethics bodies at each participating site. All patients provided written informed consent before being screened for enrollment.

Study end points and assessments

The primary efficacy outcome measure, which was reported previously, was tumor response (per RECIST V.1.1 and modified irRECIST) in the phase 2 portion of the study.[5] For the current analysis, the main efficacy outcome of interest was OS (measured from the start of treatment to the time of death; patients alive at the time of the analysis were censored on the last date they were known to be alive). In addition, the duration of treatment, including treatment beyond initial radiographic progression, was calculated. OS rates according to patient characteristics were evaluated to identify potential markers for survival.

To assess potential predictors of the efficacy of tebentafusp, analyses were conducted by the patient subgroup with baseline characteristics as covariates. Baseline and on-treatment changes in ctDNA levels were reported previously.[5] In brief, ctDNA levels in serum were assessed at baseline and at weeks 5 and 9 on-treatment using a custom panel of mutations commonly found in uveal melanoma (Natera). ctDNA was amplified by multiplex PCR and analyzed by next-generation sequencing (performed by Natera). Variants with allele frequencies

Table 1 First subsequent anticancer therapy among patients who discontinued tebentafusp

Type of anticancer therapy, n (%)	Overall (N=146)	Best overall response to first subsequent therapy, n (%)				
		CR	PR	SD	PD	NE/missing
Any therapy	88 (60)	1 (1)	3 (3)	34 (39)	21 (24)	29 (33)
Systemic	65 (74)	1 (2)	2 (3)	16 (25)	21 (32)	25 (38)
Immunotherapy	54 (61)	1 (2)	2 (4)	14 (26)	16 (30)	21 (39)
Anti-CTLA4 monotherapy	5 (6)	0	0	2 (40)	2 (40)	1 (20)
Anti-PD1/PDL1 monotherapy	19 (22)	0	0	7 (37)	6 (32)	6 (32)
Anti-PD1+anti-CTLA4	28 (32)	1 (4)	2 (7)	4 (14)	7 (25)	14 (50)
Chemotherapy	4 (5)	0	0	0	1 (25)	3 (75)
Targeted therapy	8 (9)	0	0	2 (25)	5 (63)	1 (13)
Local	34 (39)	0	1 (3)	22 (65)	2 (6)	9 (26)
Radiotherapy	12 (14)	0	1 (8)	6 (50)	0	5 (42)
Liver-directed therapy	22 (25)	0	0	16 (73)	2 (9)	4 (18)

Patients could have received more than one subsequent therapy.
CR, complete response; CTLA4, cytotoxic T lymphocyte-associated protein 4; NE, not evaluable; PD, progressive disease; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

≤0.3% at baseline were excluded from the analysis. ctDNA levels were analyzed for association with OS. Baseline expression of glycoprotein 100 (gp100, also known as premelanosome protein (PMEL); highly expressed in melanoma cells[11] and targeted by tebentafusp[12]) was assessed by immunohistochemistry (see online supplemental methods) and quantified using the H-score. Expression was defined as low or high, corresponding to the lowest quartile and above the lowest quartile of gp100 H-scores, respectively. Subsequent therapy (after discontinuation of tebentafusp) was also evaluated.

Treatment-related AEs (TRAEs) during tebentafusp treatment were graded by the investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03. Rash was evaluated as a composite term for a list of skin toxicities of any grade, as previously reported.[5] Elevations in liver function tests (LFTs) were used to identify hepatic events.

Statistical analyses

For the current analysis, all patients enrolled in the phase 1/2 IMCgp100-102 study who received at least one full or partial dose of the study drug were evaluated for efficacy and safety. Time-to-event estimates were calculated using Kaplan-Meier methodology, with the median and 95% CIs calculated by the method of Brookmeyer and Crowley. SAS software V.9.4 (SAS Institute, Cary, North Carolina, USA) was used for data calculations. To assess the influence of baseline factors on OS a multivariate Cox proportional hazards model was fitted including categorical factors for age, sex, ECOG, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), largest liver lesion size, prior checkpoint inhibitor and time from diagnosis. For analysis of ctDNA, the percentage of patients alive at 1, 2, 3 and 4 years was derived from the Cox model plotted for patients based on their per cent reduction in ctDNA by week 9 on-treatment. For analysis of baseline gp100, survival analysis was carried out (R package survminer V.0.4.9), and the Cox likelihood ratio test was used to assess differences between the survival curves. TRAEs and subsequent therapy were summarized descriptively.

RESULTS

Study population and treatment

A total of 146 patients were treated with tebentafusp: 19 in the dose escalation phase and 127 patients in the expansion phase (online supplemental figure 1). Overall, 133 patients received a dose of 68 µg of tebentafusp from cycle 1 day 15 onwards; of the remaining patients, 3 received 54 µg, 6 received 64 µg, and 4 received 73 µg in the dose escalation phase. At the data cut-off, the median duration of follow-up was 48.5 months (range 0.9–76.4 months) for all patients and 46 months (range 0.9–59.4 months) for patients in the expansion phase.

Baseline characteristics for patients enrolled in each phase have been previously reported.[5 10] For all study patients, the median age was 61 years (range 25–88), 49% were men, 30% had an ECOG=1, 58% had baseline LDH above the upper limit of normal, and 50% had largest liver lesion ≥3 cm at baseline (online supplemental table 1). Three patients in the phase 1 escalation phase were treatment naïve; the rest (n=143/146; 98%) had received ≥1 prior anticancer therapy regimens in the metastatic setting. Greater than two-thirds of patients (n=105) received prior immunotherapy, mainly immune checkpoint inhibition (n=90), and nearly half received prior liver-directed therapy (n=69).

Tumor response

The overall response rate remained unchanged at 5% despite extended follow-up, with seven partial responses.

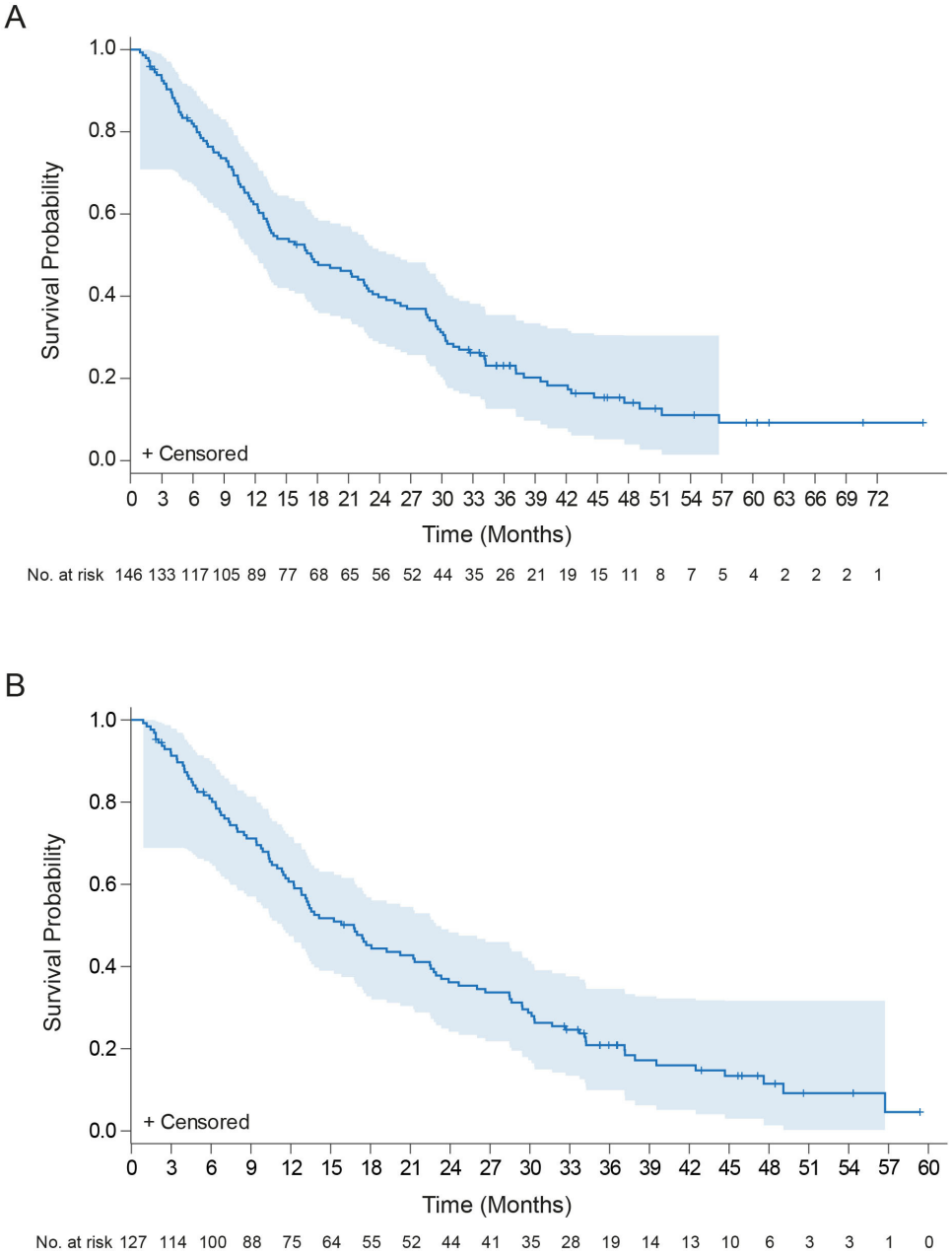

Figure 2 Kaplan-Meier plots of overall survival with 95% Hall-Wellner bands for (A) all patients treated (N=146) and (B) patients enrolled in the phase 2 cohort (n=127). Events were defined as deaths due to any cause. Patients not known to have died at the time of analysis were censored. The median overall survival for all patients was 17.4 (95% CI, 13.1 to 22.8) months with 1-year, 2-year, 3-year, and 4-year overall survival rates of 62% (95% CI, 54% to 70%), 40% (95% CI, 32% to 48%), 23% (95% CI, 17% to 30%), and 14% (95% CI, 9% to 21%).

48% (n=61) of evaluable patients (n=127) achieved any tumor shrinkage of target lesions including 10 patients with a best response of progressive disease by RECIST (online supplemental figure 2).

Two-thirds of patients (n=97; 66%) were treated beyond initial radiographic progression (defined per the investigator according to RECIST criteria); this included 14/19 patients (74%) in phase 1 and 83/127 (65%) in phase 2 (figure 1). The median duration of treatment beyond initial progression was 2.8 months (range <1–34 months).

Of the 146 study patients, 88 (60%) received subsequent treatment for mUM after discontinuation of tebentafusp (table 1). The most common first subsequent therapy was immunotherapy (61%), predominantly anti-programmed death 1 (PD1)/programmed death ligand 1 or combination anti-PD1 and anti-cytotoxic T lymphocyte-associated protein 4 (47/88; 53%), followed by liver-directed therapy (25%) and radiotherapy (14%). The overall response rate to the first subsequent therapy was 5% with one complete response and three partial responses, with three

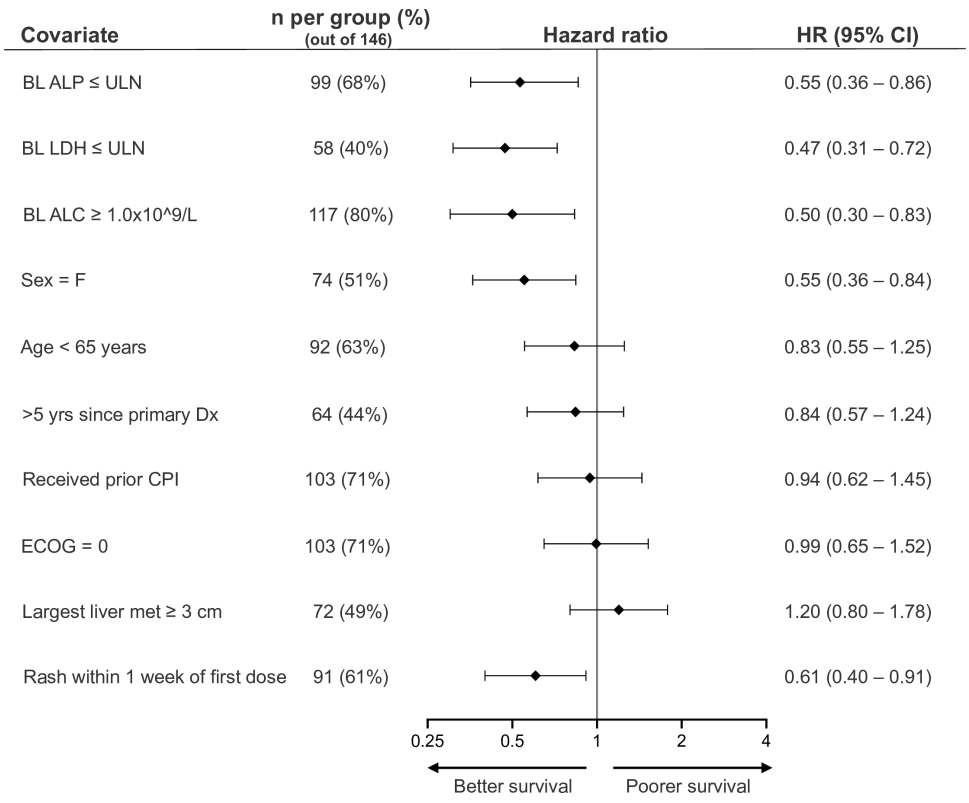

Figure 3 Survival prognosis according to patient baseline characteristics. Forest plot showing the results of the multivariate analysis of the factors associated with overall survival (N=146). ALC, absolute lymphocyte count; ALP, alkaline phosphatase; BL, baseline; CPI, checkpoint inhibitor; Dx, diagnosis; ECOG, Eastern Cooperative Oncology Group; F, female; LDH, lactate dehydrogenase; ULN, upper limit of normal.

of the four responses occurring with subsequent immunotherapy.

Overall survival

The median OS for all patients was 17.4 months (95% CI, 13.1 to 22.8 months); estimated 1-year, 2-year, 3-year, and 4-year OS rates were 62%, 40%, 23%, and 14%, respectively (figure 2). For patients in the expansion phase, median OS was 16.8 months (95% CI, 12.3 to 21.3 months) with 1-year, 2-year, 3-year, and 4-year OS rates of 61%, 36%, 21%, and 11%, respectively, which are approximately double those observed for previously treated patients from a recent meta-analysis (37%, 15% and 9% 1, 2 and 3-year OS rates),[4] yielding an unadjusted HR of 0.54 (95% CI, 0.42 to 0.69) in favor of tebentafusp (online supplemental figure 3).

At primary analysis, longer survival was associated with any tumor shrinkage, including partial responses by RECIST.[5] With longer follow-up, six of the seven patients who achieved a partial response lived >2 years with four of the seven patients living beyond 3 years (online supplemental table 2). All but one patient (10/11; 91%) with a minor response (defined as a 10–29% reduction in the sum of the longest diameters of target lesions) lived at least 2 years. Notably, however, a proportion of patients with best overall response (BOR) of progressive disease (PD) had extended survival, with 25 (40%) having OS ≥1 year, 9 (14%) having OS ≥2 years and 3 (5%) lived at least 3 years.

In a multivariate analysis, patients with longer OS were more likely to be women (HR 0.55; 95% CI, 0.36 to 0.84), have baseline LDH (HR 0.47; 95% CI, 0.31 to 0.72) and ALP (HR 0.55; 95% CI, 0.36 to 0.86) in the normal range, and have an absolute lymphocyte count ≥1.0×10^9/L at baseline (HR 0.50; 95% CI, 0.0 to 0.83; figure 3). Patients who experienced rash within 1 week of their first tebentafusp dose also had longer OS. Other factors including the size of the largest liver lesion at baseline, and time from diagnosis were not independently associated with survival. Importantly, estimated survival rates in the current study were longer in all predefined subgroups, including those associated with poor prognosis (online supplemental figure 4), when compared with historical controls from a previously reported meta-analysis.[3] OS at 1, 2 and 3 years was 54%, 35% and 27% for patients ≥65 years of age on tebentafusp resulting in an unadjusted HR of 0.62 (95% CI, 0.44 to 0.87) versus historical controls, 46%, 25% and 12% for patients with elevated LDH at baseline (unadjusted HR 0.61; 95% CI, 0.47 to 0.79) and 52%, 26% and 15% for patients with baseline largest target liver lesion ≥3 cm (unadjusted HR 0.61; 95% CI, 0.46 to 0.81) (online supplemental table 3).

Low or undetectable ctDNA levels at baseline, which were previously shown to be associated with a lower

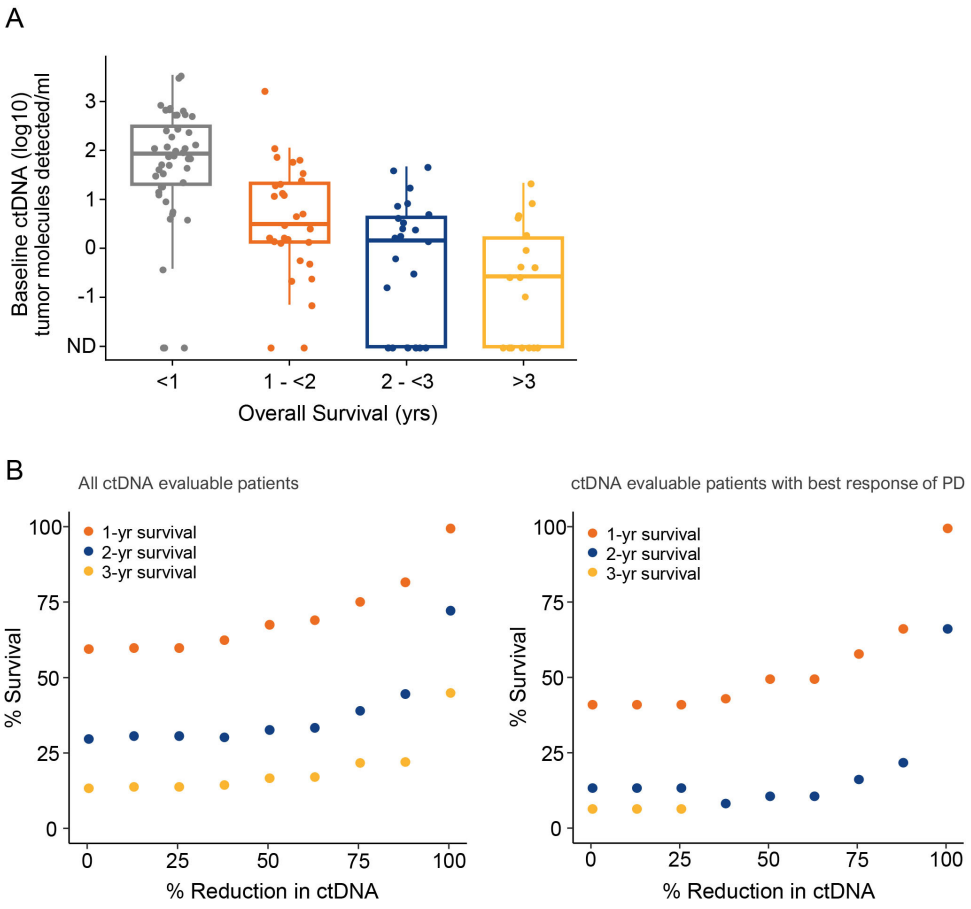

Figure 4 Circulating-tumor DNA (ctDNA) levels at baseline and on-treatment were associated with overall survival. (A) The level of ctDNA at baseline was plotted for patients with overall survival <1 year (n=45), 1 to <2 years (n=29), 2 to <3 years (n=25) and >3 years (n=18). ND, not detected. (B) The percentage of patients alive at 1 year (orange), 2 years (green) and 3 years (blue) was plotted for all ctDNA evaluable patients (left panel) and those with a best response of progressive disease (PD; right panel) based on their per cent reduction in ctDNA by week 9 on-treatment.

tumor burden at baseline,[5] were associated with longer OS (figure 4A). Greater reductions in ctDNA levels by week 9 on-treatment were also associated with longer OS (figure 4B). Specifically, ctDNA clearance by week 9, noted in 12 patients, was associated with 100% 1-year, 73% 2-year, 45% 3-year and 23% 4-year survival rates. Deep reductions in ctDNA were observed across RECIST responses, even among patients with a best response of PD. Greater reductions in ctDNA were associated with longer survival, including three PD patients who cleared their ctDNA by week 9 (figure 4B, online supplemental figure 4). ctDNA reductions were also observed regardless of baseline tumor burden, LDH levels, disease location, or ECOG status (online supplemental table 4).

For all phase 2 patients, the median (range) H-score of gp100 expression at baseline was 169 (0–300). No differences in OS rates at <1, 1 to <2, 2 to <3, or ≥3 years according to baseline gp100 H-scores were observed, although RECIST partial responses were observed more frequently at high gp100 H-score (five of the six immunohistochemistry evaluable patients with partial responses had H-score >180; four of which were >270 of a maximum of 300) (online supplemental figure 5A). There was also no difference in median OS according to whether gp100 expression at baseline was classified as low (median (range) H-score: 6 (0–50); n=28) or high (204 (60–300); n=84) (online supplemental figure 5B).

Long-term safety and adverse events

Consistent with the prior analyses of phase 1 and phase 2 portions of IMCgp100-102, most TRAEs occurred early during the course of treatment (figure 5). No new safety concerns or treatment-related discontinuations were reported. All treatment-related discontinuations (n=4) occurred in expansion patients in the first cycle of treatment.[5] Moreover, the severity of the rash, fever, hypotension and LFT elevations decreased with prolonged exposure with only seven Grade 3 or 4 events in three (7%) patients beyond 12 months of treatment (figure 5); all were temporally related to tumor progression, and the majority involved laboratory abnormalities. Episodes of rash, a common tebentafusp-related AE early on-treatment, were infrequent after 6 months, with no Grade 3 or 4 events. As AE symptoms related to cytokine release syndrome (CRS) (ie, fever, hypotension) were uncommon during weeks 3–7 and rare after week 8,

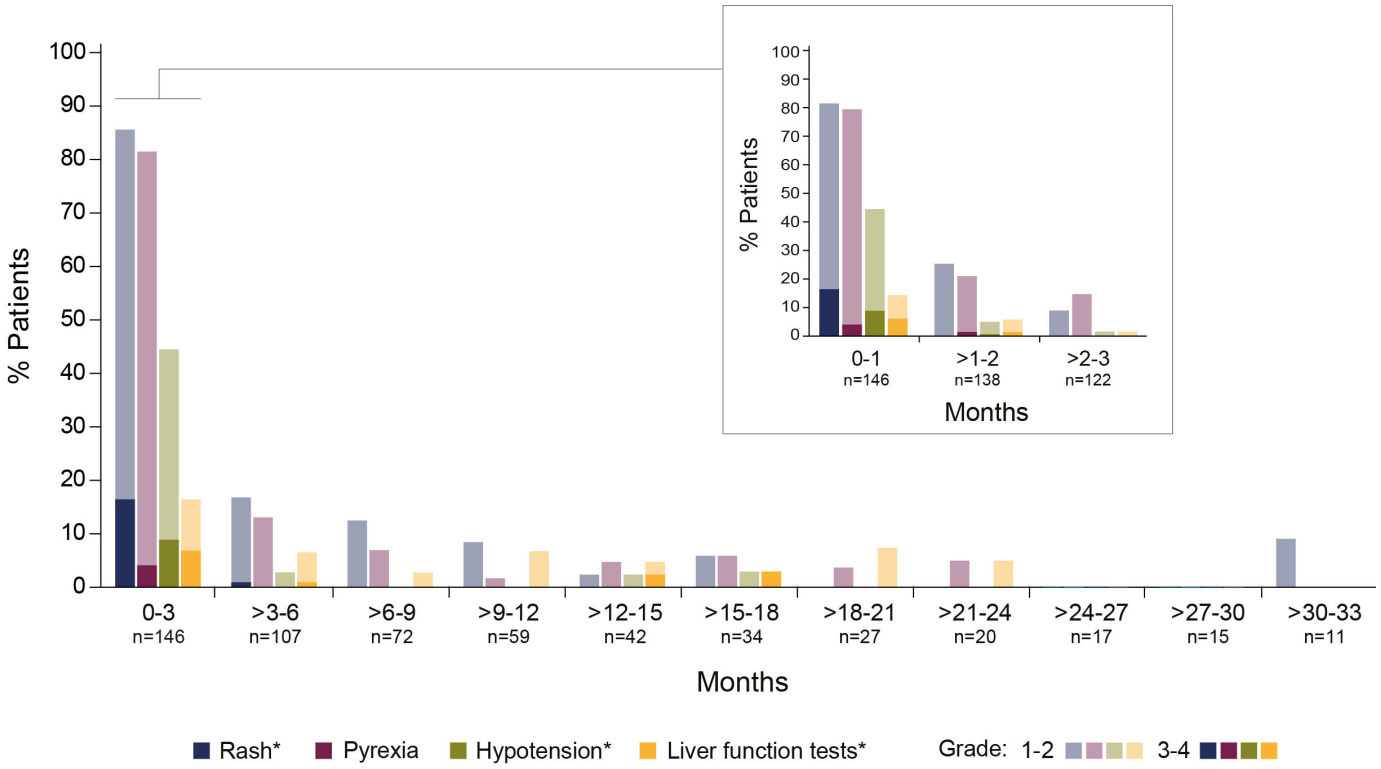

Figure 5 Select treatment-related adverse events (TRAEs) over time with tebentafusp treatment. The percentage of patients experiencing Grade 1–2 (light bars) and Grade 3–4 (dark bars) rash (blue), fever (magenta), hypotension (green) and elevations in liver function tests (yellow) are plotted in 3-month intervals during the course of treatment. Inset includes the percentage of patients experiencing these select TRAEs in the first 3 months of treatment. The number of patients at risk are denoted for each time interval. Rash and liver function tests are composite terms for a list of related adverse events of any grade (online supplemental table 5).

post hoc adjudication of CRS events according to American Society for Transplantation and Cellular Therapy (ASTCT) criteria was not performed on later data cuts.

DISCUSSION

This report, of the final OS analysis from the phase 1/2 IMCgp100-102 study of tebentafusp, represents the longest follow-up of a TCR bispecific to date, and confirms the promising OS benefit from the primary analysis[5] in this cohort of previously treated patients with mUM.

In a randomized phase 3 study in previously untreated mUM, tebentafusp improved median OS by~50% compared with the control arm (HR 0.51),[7] and this survival benefit persisted after a minimum follow-up of 3 years (HR 0.68).[13] Although differences in study designs and patient characteristics preclude direct comparisons across studies, the median OS and 1, 2, and 3-year OS rates in this analysis (17.4 months and 62%, 40%, and 23%, respectively) were approximately double those historically reported for patients with mUM in the second-line or later-line treatment setting (7–8 months and 37%, 15% and 9%, respectively).[4 5] The 3-year OS rate of 23% is notable in this population given that the average historical median survival is generally 1 year or less for patients with mUM.[2 3] Survival benefits were also observed across a range of patient subgroups, including known poor prognostic indicators such as elevated LDH at baseline or liver lesions ≥3 cm.[3 14 15]

A combination of nivolumab plus ipilimumab is often used as a standard of care in mUM based on evidence in cutaneous melanoma, despite a lack of randomized data in mUM. Furthermore, retrospective analyses of this combination in mUM using real-world evidence have not demonstrated clear survival benefits for patients with mUM.[16–19] The only prospective single-arm, phase 2 studies of the ipilimumab plus nivolumab combination in the first-line,[20] or first-line or later-line settings,[21] reported respective 1-year OS rates of 52% and 56% with much higher significant toxicity rates. In the absence of a head-to-head trial, a recent weighted propensity score analysis using patient-level data from the phase 3 tebentafusp trial[7] and the single-arm first-line phase 2 GEM-1402 study[20] of ipilimumab plus nivolumab demonstrated an OS benefit in favor of tebentafusp, with an HR of 0.43 (95% CI, 0.29 to 0.64).[22] This finding was replicated in a recent population-level matching-adjusted indirect comparison.[23] While the Pelster *et al* phase 2 study of ipilimumab plus nivolumab included second line plus patients,[21] there were insufficient numbers to make any meaningful comparison with the population in this phase 1/2 study. Furthermore, no significant difference in OS

was found between single-agent pembrolizumab (in the 202 control arm) versus combination ipilimumab and nivolumab (HR 0.76; 95% CI, 0.49 to 1.16) in a similar propensity score weighted analysis.[22] In this regard, tebentafusp may be a more attractive approach, relative to dual checkpoint blockade, for maintaining the quality of life in eligible patients with mUM.

As in the primary analysis, the overall response rate (the primary end point for the IMCgp100-102 study) underestimated the survival benefit obtained from tebentafusp treatment.[5] Indeed, a high proportion (40%) of patients with a best response to PD were alive ≥1 year and 14% of these patients survived more than 2 years. This is consistent with the phase 3 trial in treatment-naïve patients, where survival benefit with tebentafusp versus the investigator's choice of immune checkpoint inhibitors (mostly single-agent pembrolizumab) was observed in patients with PD in a post hoc analysis.[24]

The results of the current analysis also support the earlier finding linking baseline ctDNA level and early on treatment reduction with survival.[5] Importantly, ctDNA performed better than RECIST assessment in identifying patients with longer survival, especially in patients considered to be PD by RECIST. Interestingly, expression of the tumor target for tebentafusp, gp100, did not appear to influence OS despite the enrichment of RECIST responses among patients with higher gp100 expression. However, we acknowledge that the inferences that can be drawn from this single-arm, phase 2 study are limited, and further investigation of the predictive ability of ctDNA and gp100 expression levels in tebentafusp-treated mUM is warranted.

Reassuringly, the long-term follow-up period did not result in the identification of any new safety signals. The discontinuation rate due to TRAEs was low, and there were no treatment-related deaths. More than half of patients with advanced melanoma treated with nivolumab plus ipilimumab develop Grade 3 or 4 immune related TRAEs (irTRAEs)[25]; similarly, patients with mUM treated with ipilimumab plus nivolumab combination therapy have reported chronic irAEs, some of which required study drug discontinuation and medium to long-term systemic steroids,[21] and including some which persisted beyond the study follow-up period.[20] In contrast, there were no long-term irTRAEs associated with tebentafusp, likely due to its high specificity for the tumor cells and a decreased occurrence of off-target effects.[12]

As noted above, the main limitation of this study was the lack of a comparator arm, and the ability to conduct only indirect comparisons with historical studies.

In conclusion, this long-term follow-up of patients with mUM treated with tebentafusp confirms and expands our understanding of this drug, with tebentafusp continuing to provide survival benefits for previously treated patients alongside a predictable and manageable safety profile. The potential survival benefit of tebentafusp in patients who have PD by standard RECIST reconfirmed the need for a better response evaluation system or response biomarkers for patients treated with immunotherapies. In this regard, the measurement of ctDNA might provide supplemental information for treatment decision, particularly in patients with RECIST-defined disease progression.

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Acknowledgements We thank the patients and their families and caregivers for participating in the study, as well as the study teams at participating sites for their support of this trial and the following employees of Immunocore: Ramakrishna Edukulla for statistical analysis support; Michelle L McCully for assistance with preparation of the manuscript; David Berman, Mohammed Dar and Connie Pfeiffer for critical review of the manuscript. Medical writing assistance with the first draft of this manuscript was provided by Sally-Anne Mitchell, PhD, on behalf of Ashfield MedComms, an Inizio company, with funding provided by Immunocore.

Contributors All authors listed have actively participated in the production of this manuscript through trial conception/design, data acquisition, analysis, and/or interpretation. All authors contributed to the drafting or review of the manuscript and approved the final version. JJS accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This study was funded by Immunocore Ltd (no grant number).

Competing interests JJS discloses PI on clinical trial: Amgen, AstraZeneca, Bristol-Myers Squibb, Delcath Systems, Merck, Replimune, Transgene; Research Grant/Contract: AstraZeneca, Bristol-Myers Squibb, Immunocore; Consultant/Advisory Board: Bristol-Myers Squibb, Delcath Systems, Immunocore, Merck; Congress attendance: Bristol-Myers Squibb, Merck. RDC discloses Consultant: Aura Biosciences, Castle Biosciences, Chimeron, Immunocore, InxMed, Iovance, Merck, Oncosec, Pierre Fabre Pharmaceuticals Inc., PureTech Health, Regeneron Pharmaceuticals, Rgenix, Sanofi Genzyme, Sorrento Therapeutics, TriSalus; Stock Option: Aura Biosciences, Chimeron, Rgenix. MOB discloses Consultant/Advisory Board: Adaptimmune, Bristol-Myers Squibb Canada, GlaxoSmithKline, Immunocore, Instil Bio, Iovance Biotherapeutics, Merck, Novartis, Pfizer, Sanofi Pasteur Inc., Sun Pharma, IDEAYA Bio, Medison, Regeneron and Iovance.; Safety Review Committee: GlaxoSmithKline, Adaptimmune; Research Funding: Merck,

Takara Bio, Novartis. ANS discloses Grant/Contract: Bristol-Myers Squibb, Immunocore, Novartis, Targovax, Pfizer, Alkermes, Checkmate Pharmaceuticals, Foghorn Therapeutics, Linnaeus Therapeutics, Prelude Therapeutics, Iovance Biotherapeutics, Bristol-Myers Squibb, Immunocore, Novartis, Pfizer, Polaris, Xcovery. JCH discloses Speaker: Amgen, Bristol-Myers Squibb, GSK, Immunocore, Merck Sharp and Dohme, Novartis Pharma, Pierre Fabre, Sanofi-Aventis U.S. LLC; Sunpharma; Research grant/contract: Bristol-Myers Squibb, Sanofi, Sunpharma; Consultant/Advisory Board: Bristol-Myers Squibb, GSK, Immunocore, Merck Sharp and Dohme, Novartis Pharma, Pierre Fabre Pharmaceuticals Inc., Philogen, Onkowissen, Sanofi-Aventis U.S. LLC, Sun Pharmaeutical Industries Inc. AI discloses Research Funding to Institution: Dynavax, GSK/Sarah Cannon, Immunocore, Merck, Neon Therapeutics/Sarah Cannon, Checkmate Pharmaceuticals. LH-A discloses Advisory/Consulting: BMS, Castle Bioscience; Research Funding to Institution: BMS, AstraZeneca, Merck, Amgen, Roche, Regeneron, Novartis, Immunocore, Merck-EMD, Corvus, Polynoma, Genentech, Foghorn. PN discloses Data and Safety Monitoring: 4SC, Achilles; Consultant/Advisory Board: 4SC, Bristol-Myers Squibb, Immunocore, Merck, Merck Sharp and Dohme, Novartis, Pfizer; Research Grant/Contract: Immunocore. OH discloses Contract: Aduro biotech, Akeso biotech, Amgen Inc., Beigene Ltd, Bioatla, Bristol-Myers Squibb, Genentech USA, Inc., GlaxoSmithKline, Idera Pharmaceuticals, Immunocore, Incyte Corporation, Janssen Global Services, LLC, Merck, Next Cure Inc., Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, Seattle Genetics, Tempus, Zelluna Immunotherapy; Contracted Research for Institution: Aduro biotech, Akeso biotech, Amgen Inc., Arcus Biosciences, Bioatla, Bristol-Myers Squibb, CytomX Therapeutics, Exelixis Inc., Genentech, GlaxoSmithKline, Idera Pharmaceuticals, Immunocore, Incyte Corporation, Iovance Biotherapeutics, Merck, Merck Serono, Moderna, NextCure Inc., Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Seattle Genetics, Torque Pharma, Zelluna Immunotherapy; Speakers Bureau: Bristol-Myers Squibb, Novartis, Pfizer. MR discloses employment and stock ownership in Syapse Inc. DBJ discloses Advisory Boards/Consultant: Bristol-Myers Squibb, Catalyst Biopharma, Iovance, Jansen, Mallinckrodt, Merck, Mosaic ImmunoEngineering, Novartis, Oncosec, Pfizer, Targovax, and Teiko; Research Funding: Bristol-Myers Squibb, Incyte. JJL discloses DSMB: AbbVie, Agenus, Amgen, Immutep, Evaxion; Scientific Advisory Board: (no stock) 7 Hills, Affivant, Bright Peak, Exo, Fstar, Inzen, RefleXion, Xilio (stock) Actym, Alphamab Oncology, Arch Oncology, Duke Street Bio, Kanaph, Mavu, NeoTx, Onc.AI, OncoNano, physIQ, Pyxis, Saros, STipe, Tempest; Consultancy with compensation: AbbVie, Agenus, Alnylam, Atomwise, Bayer, Bristol-Myers Squibb, Castle, Checkmate, Codiak, Crown, Cugene, Curadev, Day One, Eisai, EMD Serono, Endeavor, Flame, G1 Therapeutics, Genentech, Gilead, Glenmark, HotSpot, Kadmon, KSQ, Janssen, Ikena, Inzen, Immatics, Immunocore, Incyte, Instil, IO Biotech, Macrogenics, Merck, Mersana, Nektar, Novartis, Partner, Pfizer, Pioneering Medicines, PsiOxus, Regeneron, Replimmune, Ribon, Roivant, Servier, STINGthera, Synlogic, Synthekine; Research Support: (all to institution for clinical trials unless noted) AbbVie, Astellas, AstraZeneca, Bristol-Myers Squibb, Corvus, Day One, EMD Serono, Fstar, Genmab, Ikena, Immatics, Incyte, Kadmon, KAHR, Macrogenics, Merck, Moderna, Nektar, Next Cure, Numab, Palleon, Pfizer, Replimmune, Rubius, Servier, Scholar Rock, Synlogic, Takeda, Trishula, Tizona, Xencor; Patents: (both provisional) Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof). EE discloses Advisory Boards/Consultant: Immunocore. SL discloses Consulting: Bayer, Immunocore; Expenses: Bayer. LC discloses Employment and Stock: Immunocore. CH discloses Stock: Amgen Inc., Macrogenics; Employment: Immunocore. TS discloses advisory/consulting: Immunocore, Castle Biosciences; research funding to institution (clinical trials): Immunocore, Verastem, IDEAYA, TriSalus, and BMS.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by each site's Institutional Review Board: Princess Margaret Cancer Centre, Toronto, Canada; Charite Universitaetsmedizin Berlin – Campus Benjamin Franklin, Berlin, Germany; Universitaetsklinikum Heidelberg, Heidelberg, Germany; Institut Catala d'Oncologia (ICO) l'Hospitalet, Hospital Duran i Reynals, Barcelona, Spain; Hospital Universitario Virgen Macarena, Sevilla, Spain; Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain/ Hospital Universitario La Paz, Madrid, Spain; Hospital General Universitario de Valencia, Valencia, Spain; The Clatterbridge Cancer Centre, Wirral, UK; Mount Vernon Cancer Centre, Northwood, UK; Columbia University Medical Center, New York, USA; Washington University School of Medicine, St Louis, USA; Thomas Jefferson University Hospital, Philadelphia, USA; Vanderbilt University Medical Center, Nashville, USA; Memorial Sloan-Kettering Cancer Center, New York, USA; University of Colorado Cancer Center, Aurora, USA; The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, USA; H. Lee Moffitt Cancer Center and Research Institute, Inc. Tampa, USA; University of California San Diego Moores Cancer Center, La Jolla, USA; California Pacific Medical Center, San Francisco, USA; Baylor Scott Dean A. Mcgee Eye Institute, University of Oklahoma, Oklahoma City, USA; Georgetown University - Lombardi Comprehensive Cancer Center, Washington, USA; University of Miami Hospital Clinics/Sylvester Comprehensive Cancer Center, USA; The University of Chicago Medical Center, Chicago, USA; Roswell Park Cancer Institute, Buffalo, USA; Providence Portland Medical Center, Portland, USA. There are no reference IDs. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Access to pre-existing summary outputs (tables or figures) of trial-level data may be granted to qualified academic researchers in the field upon request and approval by the study management committee and subject to appropriate data sharing and transfer agreements. Requesters should submit a proposal including purpose, data format (eg, sas files), hypothesis and specific rationale to info@immunocore.com.

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