ORIGINAL ARTICLE

Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma

Paul Nathan, M.D., Ph.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Jean-Francois Baurain, M.D., Ph.D., Marcus O. Butler, M.D., Max Schlaak, M.D., Ryan J. Sullivan, M.D., Sebastian Ochsenreither, M.D., Reinhard Dummer, M.D., John M. Kirkwood, M.D., Anthony M. Joshua, M.D., Ph.D., Joseph J. Sacco, M.D., Ph.D., Alexander N. Shoushtari, M.D., Marlana Orloff, M.D., Josep M. Piulats, M.D., Ph.D., Mohammed Milhem, M.D., April K.S. Salama, M.D., Brendan Curti, M.D., Lev Demidov, M.D., Lauris Gastaud, M.D., Cornelia Mauch, M.D., Ph.D., Melinda Yushak, M.D., M.P.H., Richard D. Carvajal, M.D., Omid Hamid, M.D., Shaad E. Abdullah, M.D., Chris Holland, M.S., Howard Goodall, M.D., and Sophie Piperno-Neumann, M.D., for the IMCgp100-202 Investigators*

ABSTRACT

BACKGROUND

Uveal melanoma is a disease that is distinct from cutaneous melanoma, with a low tumor mutational burden and a 1-year overall survival of approximately 50% in patients with metastatic uveal melanoma. Data showing a proven overall survival benefit with a systemic treatment are lacking. Tebentafusp is a bispecific protein consisting of an affinity-enhanced T-cell receptor fused to an anti-CD3 effector that can redirect T cells to target glycoprotein 100–positive cells.

METHODS

In this open-label, phase 3 trial, we randomly assigned previously untreated HLA-A*02:01–positive patients with metastatic uveal melanoma in a 2:1 ratio to receive tebentafusp (tebentafusp group) or the investigator's choice of therapy with single-agent pembrolizumab, ipilimumab, or dacarbazine (control group), stratified according to the lactate dehydrogenase level. The primary end point was overall survival.

RESULTS

A total of 378 patients were randomly assigned to either the tebentafusp group (252 patients) or the control group (126 patients). Overall survival at 1 year was 73% in the tebentafusp group and 59% in the control group (hazard ratio for death, 0.51; 95% confidence interval [CI], 0.37 to 0.71; P<0.001) in the intention-to-treat population. Progression-free survival was also significantly higher in the tebentafusp group than in the control group (31% vs. 19% at 6 months; hazard ratio for disease progression or death, 0.73; 95% CI, 0.58 to 0.94; P=0.01). The most common treatment-related adverse events in the tebentafusp group were cytokine-mediated events (due to T-cell activation) and skin-related events (due to glycoprotein 100–positive melanocytes), including rash (83%), pyrexia (76%), and pruritus (69%). These adverse events decreased in incidence and severity after the first three or four doses and infrequently led to discontinuation of the trial treatment (2%). No treatment-related deaths were reported.

CONCLUSIONS

Treatment with tebentafusp resulted in longer overall survival than the control therapy among previously untreated patients with metastatic uveal melanoma. (Funded by Immunocore; ClinicalTrials.gov number, NCT03070392; EudraCT number, 2015-003153-18.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Nathan at the Mount Vernon Cancer Centre, Northwood HA6 2RN, United Kingdom, or at p.nathan@nhs.net.

*A complete list of investigators in the IMCgp100-202 trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2021;385:1196-206.
DOI: 10.1056/NEJMoa2103485

Uveal melanoma, the most common intraocular cancer in adults, represents approximately 3 to 5% of all melanomas.[1] Although uveal melanoma arises from melanocytes, it is distinct from cutaneous melanoma, with different molecular drivers and metastatic patterns and a different tumor-immune microenvironment.[1-4] These differences are believed to contribute to a poor clinical response to systemic treatment, including immune checkpoint inhibition.[5,6] Up to 50% of patients with uveal melanoma will have metastases, which develop predominantly in the liver,[7-10] and the prognosis in such patients is very poor; the median overall survival is approximately 1 year.[6,11] Data showing a survival benefit with systemic therapy are lacking.

Molecules termed immune-mobilizing monoclonal T-cell receptors against cancer (ImmTAC) are a new class of T-cell–redirecting bispecific fusion proteins that use an engineered high-affinity T-cell receptor to target any protein, including intracellular antigens, that is presented as a peptide–HLA complex on the target-cell surface.[12,13] Tebentafusp (formerly IMCgp100) consists of a soluble affinity-enhanced HLA-A*02:01–restricted T-cell receptor that is specific for the glycoprotein 100 (gp100) peptide YLEPGPVTA and is fused to an anti-CD3 single-chain variable fragment. Once ImmTAC molecules are bound to their specific peptide–HLA complexes on the target-cell surface, they recruit and activate polyclonal T cells, through CD3, to release cytokines and cytolytic mediators against target cells.[12,14-16]

In a single-group, phase 2 study involving 127 patients with previously treated metastatic uveal melanoma, tebentafusp monotherapy showed more promising overall survival than historical controls.[17] Traditional responses, as defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were observed, but this surrogate end point did not sufficiently predict long-term survival benefit. Clinical benefit included indolent tumor growth and slow tumor shrinkage.[18] In this multicenter, randomized, phase 3 trial, we compared tebentafusp with the investigator's choice of treatment as first-line systemic therapy in patients with metastatic uveal melanoma.

Methods

Patients

Patients were eligible for enrollment if they had local histologic or cytologic confirmation of metastatic uveal melanoma, were at least 18 years of age, were HLA-A*02:01–positive (as are approximately 45% of persons in the United States and Europe), had received no previous systemic or liver-directed therapy for metastatic disease, had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability),[19] and had at least one measurable lesion, according to RECIST, version 1.1.[20] Patients were excluded if they had symptomatic central nervous system metastases, if they had active autoimmune disease for which they were receiving glucocorticoids, or if they were receiving systemic immunosuppressive treatment. Full eligibility criteria are provided in the Methods sections of the Supplementary Appendix and in the trial protocol, both of which are available with the full text of this article at NEJM.org.

A Quick Take is available at NEJM.org

Trial Design and Treatment

Patients were randomly assigned in a 2:1 ratio to receive tebentafusp (tebentafusp group) or the investigator's choice of treatment with single-agent pembrolizumab, ipilimumab, or dacarbazine (control group). Intrapatient dose escalation of tebentafusp had previously been shown to reduce toxic effects. Therefore, patients received intravenous tebentafusp at a dose of 20 μg on day 1, 30 μg on day 8, and 68 μg weekly thereafter. Patients were monitored overnight after treatment for the first 3 weeks during dose escalation. Pembrolizumab was administered intravenously at a dose of 2 mg per kilogram of body weight to a maximum of 200 mg per dose or (where approved locally) at a fixed dose of 200 mg on day 1 of each 21-day cycle. Ipilimumab was administered intravenously at a dose of 3 mg per kilogram on day 1 of each 21-day cycle for a maximum of four doses. Dacarbazine was administered intravenously at a dose of 1000 mg per square meter of body-surface area on day 1 of each 21-day cycle. Randomization was stratified according to centrally assessed lactate dehydrogenase (LDH) status (LDH level higher than

the upper limit of the normal range [ULN] or LDH level less than or equal to the ULN).

Treatment (except for ipilimumab) was continued until the occurrence of radiographic progression, the development of unacceptable toxic effects, a decision by the investigator, or withdrawal of consent by the patient. Patients who were receiving tebentafusp, pembrolizumab, or ipilimumab could continue with treatment beyond the time of initial RECIST-defined disease progression if they met prespecified criteria, as described in the Methods section in the Supplementary Appendix. Subsequent therapy was determined at the investigator's discretion. Crossover between treatment groups was not permitted during the trial, in accordance with the original design of the trial. However, on the basis of the survival benefit observed at the first interim analysis, patients in the control group were subsequently permitted to cross over to receive tebentafusp. Additional details regarding treatment decisions, including management of adverse events, are provided in the protocol.

END POINTS AND ASSESSMENTS

The primary end point was overall survival as evaluated in a time-to-event analysis. On the basis of a phase 2 study that showed an association between rash and survival,[17] we performed a prespecified analysis of overall survival in patients in the tebentafusp group in whom a rash of any grade had developed within 1 week after initiation of tebentafusp treatment, as compared with all the patients in the control group. Secondary end points included disease control (defined as complete response, partial response, or stable disease for ≥12 weeks, according to RECIST, version 1.1), objective response (defined as complete response or partial response, according to RECIST, version 1.1), and progression-free survival as evaluated in a time-to-event analysis, and safety. All the secondary end points were assessed by investigators who were aware of the treatment assignment. Adverse events were assessed by the investigator and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, with the exception of cytokine release syndrome, which was evaluated and graded post hoc according to the 2019 recommendations of the American Society for Transplantation and Cellular Therapy (ASTCT) for consensus grading for cytokine release syndrome.[21] In this trial, rash was used as a composite term for a list of skin-related adverse events of any grade (Table S2 in the Supplementary Appendix).

TRIAL OVERSIGHT

The sponsor (Immunocore) and a steering committee designed the trial and analyzed the data, with the participation of all the authors. The protocol was approved by the institutional review board or independent ethics committee at each center. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. An independent data and safety monitoring committee provided oversight of efficacy and safety. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

The primary objectives were to evaluate overall survival in the tebentafusp group as compared with the control group in two analysis populations: the intention-to-treat population and the "rash analysis population." The intention-to-treat population included all the patients who were randomly assigned to either group, and the rash analysis population included all the patients in the tebentafusp group in whom a rash had developed within the first week of treatment and all the patients in the control group. A 1-week interval for occurrence of rash was selected on the basis of previous clinical experience with tebentafusp and to limit the immortal time bias (i.e., the potential for bias in that patients must be alive to be assessed for rash). Progression-free survival and best objective response were evaluated in the intention-to-treat population only. If the intention-to-treat analysis of overall survival showed statistical significance, these secondary end points were to be tested in a hierarchical manner.

We estimated that a sample of 367 patients and the occurrence of 250 deaths would provide the trial with 89% power to show a significant survival advantage for tebentafusp in the intention-to-treat population, assuming a hazard ratio for death of 0.645 and using a two-sided alpha

level of 0.045. The survival distribution was assumed to be exponential, with a median time to death of 12 months in the control group,[6] and it was anticipated that 10% of the patients overall would withdraw from the trial. For the overall survival analysis in the rash analysis population, a two-sided alpha level of 0.005 was considered to be sufficient to provide the trial with 89% power to show an overall survival benefit, with the assumption that a rash would develop in 50% of the patients in the tebentafusp group during week 1 and that the hazard ratio for death would be 0.53.

We planned to perform two interim analyses after the occurrence of approximately 150 deaths and 200 deaths (60% and 80% of the anticipated deaths) in the intention-to-treat population. We used a Lan–DeMets alpha-spending function to calculate the O'Brien–Fleming stopping boundary in order to adjust for variability in the actual number of events relative to the target number of events at the time of the interim analyses.[22,23] The timing of the interim analyses of overall survival in the rash analysis population coincided with the timing of the interim analyses of overall survival in the intention-to-treat population, and the Lan–DeMets alpha-spending function was again used to determine the stopping boundaries. For the first interim analysis of overall survival, the analysis in the rash analysis population was to be performed first. If the results were found to be significant, then the full alpha from that analysis (0.005) could be carried over to the analysis in the intention-to-treat population, which would result in an alpha level of 0.05 for the intention-to-treat analysis. Taken together, the overall two-sided, experiment-wise type I error rate was preserved at 5% with the use of a combination of alpha splitting, hierarchical testing, group-sequential design methods, and, if necessary, the Maurer–Bretz graphical approach.[24]

Sensitivity analyses of efficacy and safety end points were performed in the safety population, which consisted of all the patients who had received at least one dose of tebentafusp or the control treatment. Time-to-event estimates of overall survival and progression-free survival were calculated by the Kaplan–Meier method. The treatment groups were formally compared with the use of a log-rank test, stratified according to LDH status. Proportional-hazards assumptions were tested as proposed by Lin et al.[25] If an assumption was met, then treatment effects were characterized according to the hazard ratio derived from a stratified Cox proportional-hazards regression model. In an ad hoc analysis of overall survival that evaluated the best response of stable disease and progressive disease according to treatment group, a landmark approach was used to address the immortal time bias, whereby overall survival was measured starting from day 100 and patients were categorized on the basis of their best response by that time. Confidence intervals were not adjusted for multiplicity and therefore cannot be used to infer effects.

RESULTS

PATIENTS AND TREATMENT

From March 2017 through June 2020, a total of 442 HLA-A*02:01–positive patients were screened; of these patients, 378 were randomly assigned to either the tebentafusp group (252 patients) or the control group (126 patients) (Fig. S1). Among the 64 patients who were screened but did not undergo randomization, a majority (51) did not meet all the inclusion criteria or met at least one exclusion criterion. Among the patients in the control group, 103 (82%) received pembrolizumab, 16 (13%) received ipilimumab, and 7 (6%) received dacarbazine. Demographic and clinical characteristics of the two groups were well balanced at baseline (Table 1).

Among all the patients who had undergone randomization, 36% had an LDH level above the ULN, 5% had extrahepatic disease only, and the median time since the primary diagnosis was 2.8 years, with no substantial difference between the groups in any of these variables. At the time of the clinical data cutoff for the first interim analysis (October 13, 2020), the median duration of follow-up was 14.1 months.

OVERALL SURVIVAL

At the data cutoff for the first interim analysis, 150 deaths had occurred in the intention-to-treat population: 87 in the tebentafusp group and 63 in the control group. The estimated overall survival at 1 year was 73% (95% confidence interval [CI], 66 to 79) in the tebentafusp group and 59% (95% CI, 48 to 67) in the control group; the estimated median duration of overall survival was

Table 1. Demographic and Disease Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Tebentafusp Group (N=252)	Control Group (N=126)
Median age (range) — yr	64 (23–92)	66 (25–88)
Male sex — no. (%)	128 (51)	62 (49)
Median time since primary diagnosis (range) — yr	3.0 (0.1–25)	2.4 (0.1–36)
ECOG performance-status score — no. (%)†		
0	192 (76)	85 (67)
1	49 (19)	31 (25)
2	0	1 (1)
Data missing	11 (4)	9 (7)
Lactate dehydrogenase >ULN — no. (%)	90 (36)	46 (37)
Largest metastatic lesion — no. (%)‡		
≤3.0 cm, stage M1a	139 (55)	70 (56)
3.1 to 8.0 cm, stage M1b	92 (37)	46 (37)
≥8.1 cm, stage M1c	21 (8)	10 (8)
Location of metastasis — no. (%)		
Hepatic only	131 (52)	59 (47)
Extrahepatic only	9 (4)	10 (8)
Hepatic and extrahepatic	111 (44)	55 (44)
Data missing	1 (<1)	2 (2)
Previous surgical therapy for metastatic disease — no. (%)	24 (10)	9 (7)

* ULN denotes the upper limit of the normal range. Percentages may not sum to 100 because of rounding.
† The Eastern Cooperative Oncology Group (ECOG) performance-status scale ranges from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates no symptoms, 1 mild symptoms, and 2 moderate symptoms.
‡ Lesions were assessed with the use of the seventh edition of the Cancer Staging Manual of the American Joint Committee on Cancer.

21.7 months (95% CI, 18.6 to 28.6) and 16.0 months (95% CI, 9.7 to 18.4), respectively (Fig. 1A). The stratified hazard ratio for death was 0.51 (95% CI, 0.37 to 0.71; P<0.001) in favor of the tebentafusp group, and this treatment effect was generally observed across the prespecified subgroups (Fig. S2). For all results in which a hazard ratio is reported, the proportional-hazards assumption was tested and verified.

PROGRESSION-FREE SURVIVAL AND TUMOR RESPONSE

Treatment with tebentafusp resulted in a significant progression-free survival benefit in the intention-to-treat population; at 6 months, the estimated progression-free survival was 31%, as compared with 19% in the control group (stratified hazard ratio for disease progression or death, 0.73; 95% CI, 0.58 to 0.94; P=0.01) (Fig. 1B and Table S3). The percentage of patients who had an objective response was 9% (95% CI, 6 to 13) in the tebentafusp group and 5% (95% CI, 2 to 10) in the control group (Table S4). The median duration of response was similar in the two groups: 9.9 months in the tebentafusp group and 9.7 months in the control group. The percentage of patients who had disease control (complete response, partial response, or stable disease for ≥12 weeks) was higher in the tebentafusp group (46%; 95% CI, 39 to 52) than in the control group (27%; 95% CI, 20 to 36).

In a landmark-based analysis, among patients who had disease progression as the best response before day 100, tebentafusp was associated with an estimated median duration of overall survival of 15.3 months (95% CI, 12.0 to not reached), as compared with 6.5 months (95% CI, 4.9 to 13.4) in the control group (hazard ratio for death, 0.43; 95% CI, 0.27 to 0.68) (Fig. 2). This benefit appeared to be independent of prog-

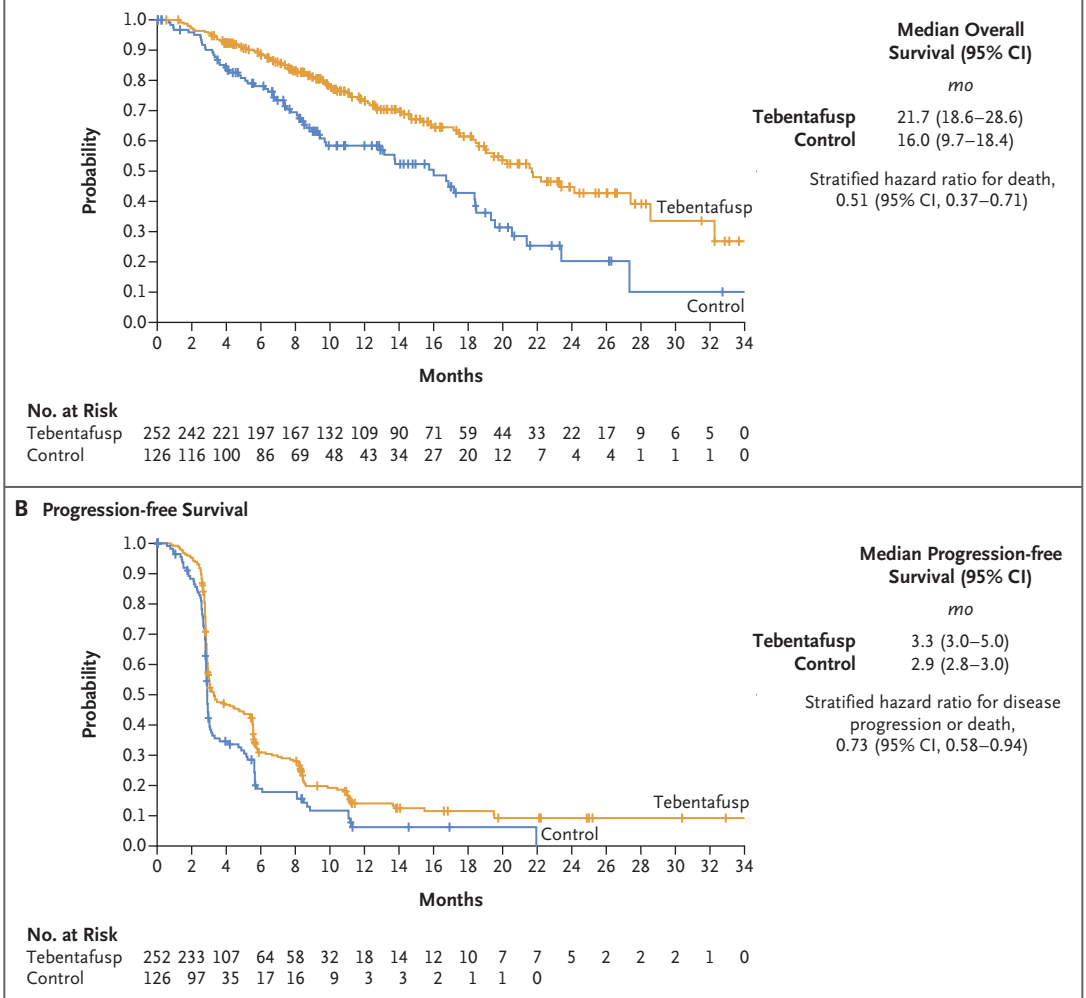


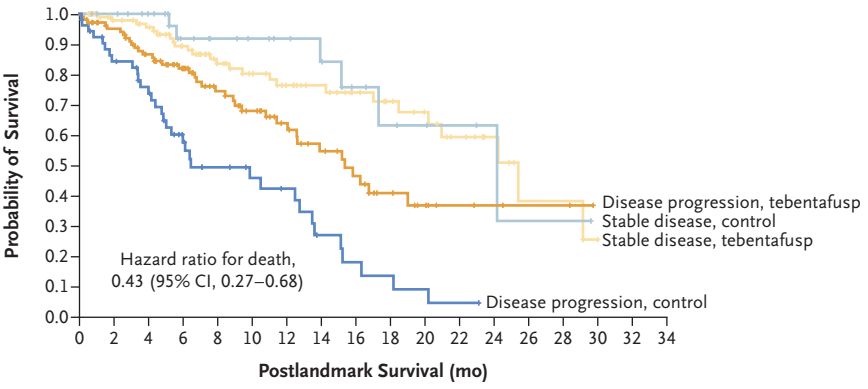
Figure 1. Overall Survival and Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of overall survival (Panel A) and of progression-free survival (Panel B), according to treatment group. Tick marks indicate censored data.

nostic variables at baseline. Some patients had regression of some target lesions despite having a best response of disease progression; however, the overall survival benefit was also observed among patients who had no tumor shrinkage and only tumor growth as their best change while they were receiving treatment (Fig. S4). In addition, more patients in the tebentafusp group than in the control group had tumor regression that did not meet the RECIST criteria for partial response (Fig. S3). In both groups, tumor regression was associated with longer overall survival.

SAFETY

The most common treatment-related adverse events of any grade in the tebentafusp group were cytokine-related adverse events, such as pyrexia (76%), chills (47%), and hypotension (38%), and skin-related adverse events, such as rash (83%), pruritus (69%), and erythema (23%). Treatment-related adverse events of grade 3 or 4 were reported in 109 patients (44%) in the tebentafusp group and in 19 patients (17%) in the control group (Table 2 and Tables S5 and S6). No treatment-related deaths were reported in either group.



No. at Risk

Stable disease, tebentafusp	101	89	82	67	53	45	37	32	26	21	17	12	7	3	3	0
Stable disease, control	34	32	29	20	17	15	13	10	7	5	4	3	2	1	1	0
Disease progression, tebentafusp	105	92	78	62	47	38	29	22	17	11	6	4	3	2	2	0
Disease progression, control	53	42	35	23	16	13	11	6	4	3	2	1	0			

Figure 2. Postlandmark Overall Survival in Patients with Best Overall Response of Stable Disease or Disease Progression.

Shown are Kaplan–Meier estimates of overall survival in patients who had stable disease or disease progression as the best overall response before the landmark time point (day 100). The hazard ratio for death among patients who had disease progression as the best overall response is shown. Tick marks indicate censored data.

In a majority of the patients in the tebentafusp group (57%), the treatment-related adverse events occurred in the first 4 weeks of treatment during intrapatient dose escalation; the incidence and severity of such events decreased with repeated dosing (Fig. 3). After 3 weeks of treatment, most of the patients transitioned to receive tebentafusp on an outpatient basis with no unacceptable toxic effects. Treatment-related adverse events of any grade in the control group reflected expected adverse effects of the therapies used. The percentage of patients who permanently discontinued the trial treatment owing to treatment-related adverse events was low in both groups: 2% in the tebentafusp group and 5% in the control group.

Cytokine release syndrome, as defined according to the 2019 ASTCT criteria,[21] occurred in 89% of the patients in the tebentafusp group (Table 2). Cytokine release syndrome, which was identified on the basis of the presence of pyrexia, hypotension, and hypoxia, usually occurred within a few hours after the first three doses were administered. In most of the patients who were identified as having cytokine release syndrome, the maximum grade of this event was either grade 1 (12%) or grade 2 (76%). Few patients (1%) had grade 3 cytokine release syndrome, and no patient had cytokine release syndrome of grade 4 or 5. Although prophylactic glucocorticoids or other premedications were not mandated, patients who had cytokine release syndrome during the trial were usually treated with antipyretic agents, intravenous fluids, glucocorticoids, or a combination of these therapies.

The prespecified analysis of overall survival in the rash analysis population included 149 patients in the tebentafusp group in whom a rash of any grade had developed within 1 week of tebentafusp treatment, as compared with all 126 patients in the control group. The estimated median overall survival was 27.4 months (95% CI, 20.2 to not reached) in the tebentafusp group and 16.0 months (95% CI, 9.7 to 18.4) in the control group ($P<0.001$). However, the presence of a rash during week 1 was found not to be an independent predictor of overall survival benefit, based on a multivariate Cox model that included patients who were randomly assigned to tebentafusp and that included known baseline prognostic factors (Table S7).

The frequency of anti-tebentafusp antibodies was 29% (63 of 220 patients), and 6% of patients (13 of 220) had a decrease in the tebentafusp serum concentration. The development of anti-

Table 2. Treatment-Related Adverse Events (Safety Population).*

Event	Tebentafusp Group (N=245)		Control Group (N=111)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any treatment-related adverse event	243 (99)	109 (44)	91 (82)	19 (17)
Cytokine release syndrome†	217 (89)	2 (1)	3 (3)	0
Rash‡	203 (83)	45 (18)	27 (24)	0
Pyrexia	185 (76)	9 (4)	3 (3)	0
Pruritus	169 (69)	11 (4)	23 (21)	0
Chills	114 (47)	1 (<1)	3 (3)	0
Nausea	105 (43)	2 (1)	21 (19)	0
Fatigue	101 (41)	7 (3)	29 (26)	1 (1)
Hypotension	93 (38)	8 (3)	0	0
Dry skin	72 (29)	0	4 (4)	0
Vomiting	64 (26)	1 (<1)	7 (6)	0
Erythema	56 (23)	0	1 (1)	0
Headache	53 (22)	1 (<1)	3 (3)	1 (1)
Aspartate aminotransferase increased	47 (19)	11 (4)	9 (8)	0
Alanine aminotransferase increased	43 (18)	7 (3)	8 (7)	2 (2)
Lipase increased	32 (13)	9 (4)	7 (6)	6 (5)
Diarrhea	31 (13)	2 (1)	16 (14)	3 (3)
Lymphopenia	22 (9)	6 (2)	2 (2)	0
Hyperbilirubinemia	21 (9)	5 (2)	2 (2)	0
Hypophosphatemia	19 (8)	7 (3)	1 (1)	0
Hypertension	15 (6)	9 (4)	2 (2)	1 (1)

* Shown are treatment-related adverse event that were reported in at least 20% of patients (any grade) or in at least 2% of patients (grade ≥3) in either group.
† Cytokine release syndrome was graded according to the 2019 recommendations of the American Society for Transplantation and Cellular Therapy for consensus grading for cytokine release syndrome.[21]
‡ Rash is a composite term for a list of skin-related adverse events of any grade (see Table S2).

tebentafusp antibodies had no effect on overall survival and was not associated with an increased risk of hypersensitivity reactions (Fig. S5 and Table S8).

DISCUSSION

In this randomized, controlled, phase 3 trial involving HLA-A*02:01–positive patients with previously untreated metastatic uveal melanoma, treatment with tebentafusp resulted in significantly longer overall survival than the investigator's choice of treatment with pembrolizumab, ipilimumab, or dacarbazine. At the data cutoff for the first prespecified interim analysis, treatment with tebentafusp had resulted in a relative risk of death that was 49% lower than that with the control therapy.

The decision to use the investigator's choice of therapy for the control group reflects the fact that, to date, a proven standard treatment has not been established. Melanoma is generally refractory to chemotherapy.[11] In contrast to cutaneous melanoma, uveal melanoma has low tumor mutational burden, which may partially explain the low sensitivity of uveal melanoma to checkpoint inhibitors.[26] Recent single-group, phase 2 studies involving patients with uveal melanoma who were treated with ipilimumab plus nivolumab showed a 1-year survival of 52%[27]

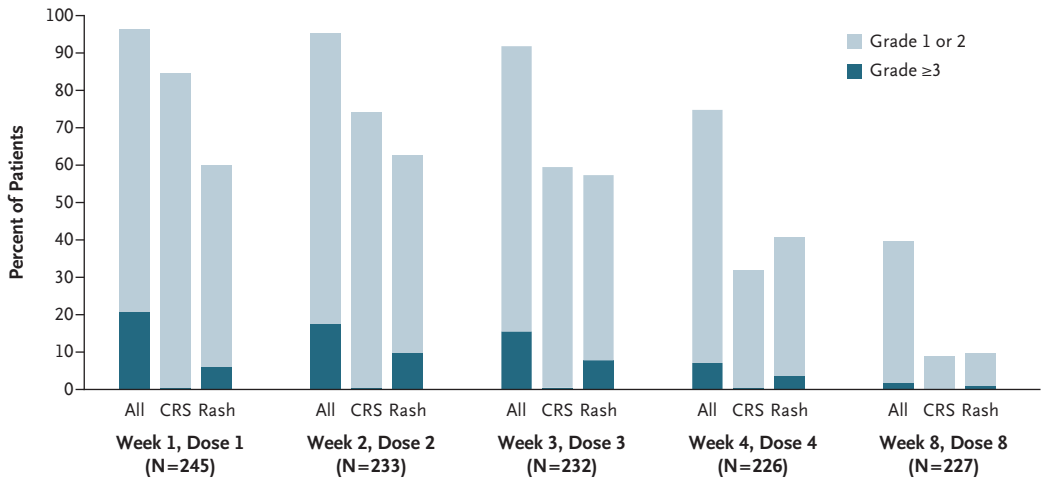


Figure 3. Incidence and Severity of Treatment-Related Adverse Events after Initial Doses of Tebentafusp.

Shown are the percentages of patients in the tebentafusp group who had treatment-related adverse events of grade 1 or 2 or of grade 3 or higher after the initial doses of tebentafusp. CRS denotes cytokine release syndrome.

and 56%.[28] These overall survival results overlap with those observed in the control group of the current trial (58%) as well as in recent meta-analyses (52 to 56%)[6,11]; these findings confirm that the 1-year survival associated with ipilimumab plus nivolumab is no better than that with the investigator's choice of treatment used in the current trial. The 1-year overall survival with tebentafusp was 73% — a result that was higher than that reported for the combination of ipilimumab and nivolumab.[27,28]

Tebentafusp is a bispecific protein that consists of a soluble T-cell receptor fused to an anti-CD3 single-chain variable fragment–activating domain. The high-affinity, high-specificity T-cell receptor targets a nine-amino-acid peptide that is derived from proteasomal degradation of the intracellular gp100 protein and that is presented by HLA molecules on the surface of target cells, including skin melanocytes and tumors derived from melanocytes.[13] By targeting a specific shared tumor-associated antigen, these T-cell receptor bispecific molecules (in which one end binds cells bearing tumor peptide and the other end binds and activates T cells) can recruit T cells to target tumors independent of the presence of tumor antigen-specific T cells or of the tumor mutational status.

The progression-free survival benefit and the tumor response (as defined according to RECIST) of tebentafusp were both low in comparison with the magnitude of the survival benefit. However, patients who received tebentafusp and had disease progression as the best response had longer survival than patients who had disease progression as the best response in the control group. This finding implies a clinically meaningful effect on outcomes for patients, even if a patient had no radiographically significant decrease in tumor size. Although follow-up with respect to subsequent therapy remains immature, the percentage of patients who received any subsequent therapy, including immunotherapy, was generally similar in the two groups.

Further investigation will be needed to understand the decoupling of RECIST-based radiographic assessment and overall survival. Whether this observation is more broadly applicable to T-cell receptor bispecifics in other solid-tumor indications is unknown and also warrants further study.

The safety profile of tebentafusp can be categorized into two major types of adverse events: cytokine-mediated events and skin-related events. Cytokine-mediated adverse events due to T-cell activation were reported in most of the patients, but a majority of the events were mild to moderate in severity and were managed symptomati-

cally with standard treatment interventions. These events occurred in the hours after the first few doses; therefore, overnight monitoring of all the patients after the first three infusions was required. After this induction period, cytokine-mediated adverse events decreased in incidence and severity, and the extension of overnight monitoring beyond that required by the protocol was uncommon.

The occurrence of skin-related adverse events, which were presumably due to the recognition of gp100-expressing melanocytes by tebentafusp, was also generally limited to the hours after administration of the first few doses. The onset of rash in the first week of treatment appeared to be associated with longer survival, which suggests that the skin inflammation may be a surrogate of activity against the tumor. However, the use of rash for clinical management decisions is not appropriate, since rash is not an independent predictor of overall survival; most patients will have a rash at some point during treatment with tebentafusp, and some patients without a rash may also benefit. Overall, few patients discontinued treatment with tebentafusp owing to treatment-related adverse events, and no tebentafusp-related deaths were reported during the trial.

Anti-tebentafusp antibodies developed in some patients, with minimal effect on the tebentafusp concentration and no apparent effect on either overall survival or the risk of hypersensitivity reactions. Whether the antibodies neutralize the effect of tebentafusp has not yet been determined.

In this randomized, phase 3 trial, treatment with tebentafusp, a soluble T-cell receptor and CD3-directed bispecific fusion protein, was associated with longer overall survival than the investigator's choice of therapy in HLA-A*02:01–positive patients with metastatic uveal melanoma.

Supported by Immunocore.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families and caregivers; the trial teams at the participating sites; Manuel Rodrigues, M.D., Ph.D., Christophe Le Tourneau, M.D., Ph.D., Heather Shaw, M.D., Antje Blank, M.D., Monika Dudzisz-Sledz, M.D., Ph.D., Frank Cornélis, M.D., Filomena Mazzeo, M.D., David Hogg, M.D., Anna Spreafico, M.D., Ph.D., and Sam Saibil, M.D., Ph.D., for the provision of trial materials, referral of patients, patient care, or a combination of these; Igor Puzanov, M.D., Serge Leyvraz, M.D., Takami Sato, M.D., Ph.D., and Mark R. Middleton, M.D., Ph.D., for their insights and guidance regarding the tebentafusp development program; Ramakrishna Edukulla, Ph.D., of Immunocore, for statistical analysis support; Michelle L. McCully, Ph.D., of Immunocore, for writing and editorial assistance; and David Berman, M.D., Ph.D., and Mohammed Dar, M.D., both of Immunocore, for their leadership and critical review of an earlier version of the manuscript.

APPENDIX

The authors' affiliations are as follows: Mount Vernon Cancer Centre, Northwood (P.N.), the Clatterbridge Cancer Centre NHS Foundation Trust, Wirral (J.J.S.), the University of Liverpool, Liverpool (J.J.S.), and Immunocore, Abingdon (S.E.A., C.H., H.G.) — all in the United Kingdom; the Department of Dermatology and the National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg (J.C.H.), the Department of Dermatology and Allergy, University Hospital, Ludwig Maximilian University of Munich, Munich (M.S.), the Department of Hematology and Oncology, Charité–Comprehensive Cancer Center (S.O.), Berlin, and the Department of Dermatology and the Center for Integrated Oncology, University Hospital Cologne, Cologne (C.M.) — all in Germany; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland (P.R.); Institut Roi Albert II des Cliniques Universitaires Saint-Luc and Université Catholique de Louvain, Brussels (J.-F.B.); Princess Margaret Cancer Centre, Toronto (M.O.B.); Massachusetts General Hospital Cancer Center, Boston (R.J.S.); the Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland (R.D.); Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh (J.M.K.); Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia (M.O.); Kinghorn Cancer Centre, Saint Vincent's Hospital, Darlinghurst, NSW, Australia (A.M.J.); Memorial Sloan Kettering Cancer Center (A.N.S.) and Irving Medical Center, Columbia University (R.D.C.) — both in New York; Institut d'Investigació Biomèdica de Bellvitge–Centro de Investigación Biomédica en Red de Oncología, Institut Català d'Oncologia, Barcelona (J.M.P.); University of Iowa Hospitals and Clinics, Iowa City (M.M.); Duke University, Durham, NC (A.K.S.S.); Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR (B.C.); N.N. Blokhin Cancer Research Center, Moscow (L.D.); Centre Antoine Lacassagne, Nice (L.G.) and Institut Curie, Paris Sciences and Letters Research University, Paris (S.P.-N.) — both in France; Winship Cancer Institute, Emory University, Atlanta (M.Y.); and the Angeles Clinic and Research Institute, a Cedars–Sinai Affiliate, Los Angeles (O.H.).

REFERENCES

1. Jager MJ, Shields CL, Cebulla CM, et al. Uveal melanoma. Nat Rev Dis Primers 2020;6:24.
2. Coupland SE, Lake SL, Zeschnigk M, Damato BE. Molecular pathology of uveal melanoma. Eye (Lond) 2013;27:230-42.
3. Milam RW, Daniels AB. Uveal melanoma. In: Riker AI, ed. Melanoma: a modern multidisciplinary approach. Copenhagen: Springer International Publishing, 2018:273-312.
4. van der Kooij MK, Speetjens FM, van der Burg SH, Kapiteijn E. Uveal versus cutaneous melanoma: same origin, very distinct tumor types. Cancers (Basel) 2019;11:845.
5. Buder K, Gesierich A, Gelbrich G, Goebeler M. Systemic treatment of metastatic uveal melanoma: review of litera-

ture and future perspectives. Cancer Med 2013;2:674-86.
6. Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. Melanoma Res 2019;29:561-8.
7. Carvajal RD, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic disease from uveal melanoma: treatment options and future prospects. Br J Ophthalmol 2017;101:38-44.
8. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci 2003;44:4651-9.
9. Lorenzo D, Piulats JM, Ochoa M, et al. Clinical predictors of survival in metastatic uveal melanoma. Jpn J Ophthalmol 2019;63:197-209.
10. Weis E, Salopek TG, McKinnon JG, et al. Management of uveal melanoma: a consensus-based provincial clinical practice guideline. Curr Oncol 2016;23(1):e57-e64.
11. Khoja L, Atenafu EG, Suciu S, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. Ann Oncol 2019;30:1370-80.
12. Liddy N, Bossi G, Adams KJ, et al. Monoclonal TCR-redirected tumor cell killing. Nat Med 2012;18:980-7.
13. Lowe KL, Cole D, Kenefeck R, OKelly I, Lepore M, Jakobsen BK. Novel TCR-based biologics: mobilising T cells to warm 'cold' tumours. Cancer Treat Rev 2019;77:35-43.
14. Bossi G, Buisson S, Oates J, Jakobsen BK, Hassan NJ. ImmTAC-redirected tumour cell killing induces and potentiates antigen cross-presentation by dendritic cells. Cancer Immunol Immunother 2014;63:437-48.
15. Boudousquie C, Bossi G, Hurst JM, Rygiel KA, Jakobsen BK, Hassan NJ. Polyfunctional response by ImmTAC (IMCgp100) redirected $CD8^+$ and $CD4^+$ T cells. Immunology 2017;152:425-38.
16. Middleton MR, McAlpine C, Woodcock VK, et al. Tebentafusp, a TCR/Anti-CD3 bispecific fusion protein targeting gp100, potently activated antitumor immune responses in patients with metastatic melanoma. Clin Cancer Res 2020;26:5869-78.
17. Sacco JJ, Carvajal R, Butler MO, et al. 64MO A phase (ph) II, multi-center study of the safety and efficacy of tebentafusp (tebe) (IMCgp100) in patients (pts) with metastatic uveal melanoma (mUM). Ann Oncol 2020;31:S1442-S1443.
18. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.
19. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
20. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
21. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-38.
22. Gordon Lan KK, Demets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.
23. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
24. Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5:311-20.
25. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika 1993;80:557-72.
26. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med 2017;377:2500-1.
27. Piulats JM, Espinosa E, de la Cruz Merino L, et al. Nivolumab plus ipilimumab for treatment-naïve metastatic uveal melanoma: an open-label, multicenter, phase II trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). J Clin Oncol 2021;39:586-98.
28. Pelster MS, Gruschkus SK, Bassett R, et al. Nivolumab and ipilimumab in metastatic uveal melanoma: results from a single-arm phase II study. J Clin Oncol 2021;39:599-607.