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Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma

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Abstract

BACKGROUND—Tebentafusp, a T-cell receptor–bispecific molecule that targets glycoprotein 100 and CD3, is approved for adult patients who are positive for HLA-A*02:01 and have unresectable or metastatic uveal melanoma. The primary analysis in the present phase 3 trial supported a long-term survival benefit associated with the drug.

METHODS—We report the 3-year efficacy and safety results from our open-label, phase 3 trial in which HLA-A*02:01–positive patients with previously untreated metastatic uveal melanoma were randomly assigned in a 2:1 ratio to receive tebentafusp (tebentafusp group) or the investigator's choice of therapy with pembrolizumab, ipilimumab, or dacarbazine (control group), with randomization stratified according to the lactate dehydrogenase level. The primary end point was overall survival.

RESULTS—At a minimum follow-up of 36 months, median overall survival was 21.6 months in the tebentafusp group and 16.9 months in the control group (hazard ratio for death, 0.68; 95% confidence interval, 0.54 to 0.87). The estimated percentage of patients surviving at 3 years was 27% in the tebentafusp group and 18% in the control group. The most common treatment-related adverse events of any grade in the tebentafusp group were rash (83%), pyrexia (76%), pruritus (70%), and hypotension (38%). Most tebentafusp-related adverse events occurred early during treatment, and no new adverse events were observed with long-term administration. The percentage of patients who discontinued treatment because of adverse events continued to be low in both treatment groups (2% in the tebentafusp group and 5% in the control group). No treatment-related deaths occurred.

CONCLUSIONS—This 3-year analysis supported a continued long-term benefit of tebentafusp for overall survival among adult HLA-A*02:01–positive patients with previously untreated metastatic uveal melanoma. (Funded by Immunocore; IMCgp100–202 ClinicalTrials.gov number, NCT03070392; EudraCT number, 2015–003153-18.)

Uveal melanoma accounts for up to 5% of all melanomas.[1] Metastatic disease develops in approximately half the patients with the condition, after which the prognosis is poor, with a historical median overall survival of approximately 1 year.[2,3] The liver is the predominant site of metastasis, with secondary sites including lung, bone, and skin.[4]

Until recently, results from clinical trials showing improvements in progression-free or overall survival have been lacking.[4–6] Immune-checkpoint inhibitors, which revolutionized outcomes in cutaneous melanoma, are largely ineffective in metastatic uveal melanoma, which is a distinct disease in its genetic and biologic characteristics as well as in its clinical course.[1,7–9]

Tebentafusp, a first-in-class T-cell receptor–bispecific fusion protein (specific for glycoprotein 100 [gp100] and CD3) that redirects T cells to kill gp100-positive melanoma cells, is the only approved systemic therapy for adult HLA-A*02:01–positive patients with unresectable or metastatic uveal melanoma.[10] In the primary analysis in the pivotal phase 3 IMCgp100–202 trial, treatment with tebentafusp resulted in significantly longer overall survival than control therapy (investigator's choice of single-agent pembrolizumab, ipilimumab, or dacarbazine) among patients with previously untreated metastatic uveal melanoma, with a hazard ratio for death of 0.51 (95% confidence interval [CI], 0.37 to 0.71; P<0.001) and 73% and 59% of the patients, respectively, surviving at 1 year.[11]

Tebentafusp has shown promising results with respect to survival in phase 1–2 studies of previously treated metastatic uveal melanoma, with overall survival that was nearly double the historical benchmark values.[12,13] The radiographic response and progression-free survival for tebentafusp in these studies underestimated the survival benefit, and in the phase 3 trial, a survival benefit was found even in patients with radiographic evidence of progressive disease (hazard ratio, 0.43; 95% CI, 0.27 to 0.68).[11] These findings highlight the need for surrogate markers of benefit with tebentafusp and, in an exploratory analysis of the phase 2 study, a strong association between overall survival and early reductions in the circulating tumor DNA (ctDNA) level was found, which suggested the superiority of this measure over traditional radiographic response criteria.[12] Here, we report an updated

analysis of efficacy and safety from the phase 3 IMCgp100–202 trial after 3 years of follow-up.

METHODS

PATIENTS

A full list of the eligibility criteria used in this trial has been published previously.[11] In brief, eligible patients were 18 years of age or older, were HLA-A*02:01–positive as determined by central assay, had metastatic uveal melanoma confirmed by histologic or cytologic analysis, had received no previous systemic or liver-directed therapy for metastases, had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores reflecting greater disability), and had at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[14]

TRIAL DESIGN AND TREATMENT

In this phase 3, international, open-label trial, patients were randomly assigned in a 2:1 ratio to receive either tebentafusp (tebentafusp group) or the investigator's choice of single-agent therapy with pembrolizumab, ipilimumab, or dacarbazine (control group). Randomization was stratified according to lactate dehydrogenase (LDH) status (LDH level higher than the upper limit of the normal range or less than or equal to the upper limit of the normal range). Tebentafusp was administered intravenously in weekly doses of 68 μg after two step-up doses (20 μg on day 1 and 30 μg on day 8). Pembrolizumab was given intravenously at a dose of 2 mg per kilogram of body weight (with a maximum of 200 mg per dose) 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 given intravenously at a dose of 1000 mg per square meter of body-surface area on day 1 of each 21-day cycle.

Treatment (except for ipilimumab) was continued until the occurrence of disease progression, the development of unacceptable toxic effects, a decision by the investigator, or withdrawal of consent by the patient. Treatment beyond the time of initial RECIST-defined disease progression was permitted for patients who were receiving tebentafusp, pembrolizumab, or ipilimumab if they met prespecified criteria.[11] After the first interim analysis showed an overall survival benefit for tebentafusp, the trial protocol was amended to allow eligible patients in the control group to crossover to receive tebentafusp.

END POINTS AND ASSESSMENTS

Results for the primary end point of overall survival and the hierarchical secondary end point of progression-free survival at the time of the primary analysis have been reported previously.[11] A subsequent planned analysis of best overall response did not meet the criteria for significance. At the 3-year minimum follow-up, exploratory analyses included updated data on efficacy and safety outcomes in the intention-to-treat and safety populations, respectively. The dual end-point analysis of overall survival in the "rash analysis population" was not reassessed in this update, since rash within 1 week was not an independent predictor

of overall survival.[11] Overall survival and progression-free survival were evaluated in a time-to-event analysis. Tumor response was assessed according to RECIST, version 1.1. Disease control is defined as complete response, partial response, or stable disease for at least 12 weeks, and objective response is defined as complete response or partial response. Adverse events were graded by the investigator with the use of the National Cancer institute Common Terminology Criteria for Adverse Events, version 4.03. Cytokine release syndrome was evaluated and graded post hoc according to the 2019 recommendations of the American Society for Transplantation and Cellular Therapy (ASTCT).[15]

A full description of the methods used in the exploratory analyses of tumor mutational burden and ctDNA levels is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The protocol and statistical analysis plan are also available at NEJM.org.

TRIAL OVERSIGHT

The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent before enrollment. The sponsor (Immunocore) and a steering committee designed the trial and analyzed the data with the participation of the authors. The trial protocol and amendments were reviewed and approved by the institutional review board or independent ethics committee at each trial center. An independent data and safety monitoring committee provided oversight of efficacy and safety. Access to tebentafusp was made available by the committee to eligible patients enrolled in the control group after the results for the primary end point of overall survival were found to be significant. The authors attest that the trial was conducted in accordance with the protocol and vouch for the accuracy and completeness of the data.

STATISTICAL ANALYSIS

Full information on the primary analyses and end points have been published previously.[11] In brief, we calculated that a sample of 369 patients and the occurrence of 250 deaths would be required 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. Secondary end points were to be tested in a hierarchical manner only if the primary end point met the criteria for significance.

At the prespecified first interim analysis (data cutoff, October 13, 2020), 150 deaths had occurred. This analysis crossed the prespecified boundary for overall survival, statistically confirming an overall survival benefit for tebentafusp as compared with control in the intention-to-treat population, and thus became the primary analysis in the trial. Hierarchical testing of progression-free survival also showed a significant benefit for tebentafusp as compared with control. The present analysis includes a descriptive update of efficacy end points reported at the 95% confidence level after a minimum follow-up of 36 months. Confidence intervals were not corrected for multiplicity and therefore should not be used to imply statistical significance.

Efficacy end points were assessed in the intention-to-treat population, which included all patients who had undergone randomization. Patients who had received at least one dose of investigational product were included in analyses of safety. Time-to-event estimates of overall survival and progression-free survival were calculated with the use of Kaplan–Meier methods. Treatment effects were characterized by the hazard ratio derived from a stratified Cox proportional hazards regression model, which was stratified according to the LDH status — but only if the proportional hazards assumption, which was tested as proposed by Lin et al.,[16] was met, which was the case for all primary and secondary end points. The best overall response was compared between the treatment groups with the use of an odds ratio and its associated 95% confidence interval from a stratified Cochran–Mantel–Haenszel test with adjustment for the baseline LDH status. Additional statistical methods are described in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT

Patients were enrolled from March 2017 through June 2020. Of the 378 eligible HLA-A*02:01–positive patients, 252 were randomly assigned to the tebentafusp group and 126 to the control group; of the patients in the control group, 103 (82%), 16 (13%), and 7 (6%) were assigned to receive pembrolizumab, ipilimumab, and dacarbazine, respectively (Fig. S1 in the Supplementary Appendix). Seven patients who were assigned to the tebentafusp group and 15 patients who were assigned to the control group did not receive treatment.

The demographic and baseline clinical characteristics of the patients were generally well balanced between the treatment groups (Table S1). Among all the patients enrolled, 36% had LDH levels above the upper limit of the normal range, 45% had a largest metastatic lesion that was greater than 3 cm in the longest diameter, and 50% had extrahepatic disease involvement.

At the time of the database lock on July 3, 2023, all the patients had the opportunity to have been followed for a minimum of 36 months. The median follow-up was 43.3 months. More than half the patients who received treatment in the tebentafusp group (139 of 245 [57%]) were treated beyond initial radiographic progression, as compared with a quarter of the patients in the control group (28 of 111 [25%]). Sixteen patients in the control group crossed over to receive tebentafusp after the primary analysis (Table S2). The median time between ending control treatment and starting crossover treatment was more than 1 year. The median duration of crossover treatment was 4.3 months.

A similar percentage of patients in the tebentafusp group and the control group (59% and 58%, respectively) received at least one subsequent line of systemic therapy after discontinuation of treatment (Table S3). The median time from the last dose of randomly assigned therapy to the first subsequent therapy was similar in the two treatment groups, at approximately 1 month. Immunotherapy, particularly immune checkpoint inhibitors, was the most common systemic therapy given after discontinuation of either tebentafusp (52%) or control therapy (46%).

OVERALL SURVIVAL

In this 3-year analysis, the overall survival benefit continued to favor tebentafusp, with a stratified hazard ratio for death of 0.68 (95% CI, 0.54 to 0.87) (Fig. 1A). Median overall survival was 21.6 months (95% CI, 19.0 to 24.3) in the tebentafusp group and 16.9 months (95% CI, 12.9 to 19.5) in the control group. The percentage of patients who were surviving at 1, 2, and 3 years among those treated with tebentafusp was 72%, 45%, and 27%, respectively, as compared with 60%, 30%, and 18% among the patients in the control group (Fig. 1A and Table S4). When this analysis was repeated with data from patients who crossed over to the tebentafusp group censored at the start of treatment with tebentafusp, the effect on the hazard ratio for death was minimal (0.70; 95% CI, 0.54 to 0.90).

The baseline factors that were most associated with longer overall survival during treatment with tebentafusp included an ECOG performance-status score of 0, levels of LDH and alkaline phosphatase in the normal range, a largest metastatic lesion that was less than 8 cm in diameter, and a longer time since primary diagnosis (Table S5). Because high tumor mutational burden can be associated with better outcomes in patients with diverse tumors treated with immune checkpoint inhibitors,[17] we examined the association between tumor mutational burden and overall survival among patients with available biopsies. Tumor mutational burden was low in these patients (median, 0.46 mutations per megabase) and was not associated with overall survival in either the tebentafusp group or the control group (Fig. S3A), findings that were consistent with those reported in the literature[18]; overall survival was superior in the tebentafusp group, regardless of whether the tumor mutational burden was high or low (Fig. S3B). Among the patients who crossed over to receive tebentafusp after the primary analysis, median overall survival from the start of tebentafusp treatment was 14.2 months (95% CI, 4.4 to 16.6) with a median follow-up of 24.4 months (Fig. S4).

PROGRESSION-FREE SURVIVAL AND TUMOR RESPONSE

With extended follow-up, the percentage of patients who had an objective response continued to be higher in the tebentafusp group than in the control group (11% vs. 5%), with five additional patients in the tebentafusp group having a partial response since the previous analysis (Table 1 and Fig. S5). The median time to response was 2.9 months (range, 1.2 to 22.2) in the tebentafusp group and 4.1 months (range, 2.0 to 11.8) in the control group. The median duration of response was 11.1 months in the tebentafusp group and 9.7 months in the control group. By 18 months after the first response, no patients in the control group had a continuing response, whereas a third of the patients (9 patients) in the tebentafusp group continued to have a response. Median progression-free survival was 3.4 months (95% CI, 3.0 to 5.4) in the tebentafusp group and 2.9 months (95% CI, 2.8 to 3.0) in the control group (stratified hazard ratio for progression or death, 0.76; 95% CI, 0.60 to 0.97) (Fig. 1B and Table S4).

A greater percentage of the patients in the tebentafusp group than in the control group had any tumor shrinkage (40% vs. 24%) (Fig. S7). In a 100-day landmark analysis involving the patients who had a best overall response of progressive disease by day 100 after randomization, postlandmark overall survival was longer in the tebentafusp group than in

the control group (Fig. 2, Table S6, and Figs. S8 and S9). The hazard ratio for death in this analysis was 0.62 (95% CI, 0.44 to 0.89) in favor of tebentafusp.

In an exploratory analysis, 202 of the 252 patients in the tebentafusp group had baseline and week 9 serum samples that were obtained during treatment and were available for ctDNA analysis; 123 of the patients with a sample (61%) had at least one detectable uveal mutation at baseline. The characteristics of the patients and overall survival in these populations were similar to those in the overall intention-to-treat population (Table S1 and Fig. S10), whereas patients with undetectable ctDNA at baseline were more likely to have normal LDH levels and smaller lesions. Most of the 123 patients with detectable baseline ctDNA (108 [88%]) had a reduction in ctDNA levels by week 9 during treatment, and 45 (37%) had ctDNA clearance (Fig. 3A).

Baseline ctDNA levels were prognostic; patients with undetectable ctDNA at baseline had longer overall survival than those with detectable ctDNA (Figs. S11 and S12). Likewise, patients who had clearance of ctDNA by week 9 had longer overall survival than those without clearance (median overall survival, 29.6 months vs. 10.2 months) (Fig. 3B). Overall survival among the 99 patients who had a reduction of at least 50% in the ctDNA level was longer than that among the 24 patients who had a reduction of less than 50%, no change, or an increase in the ctDNA level (hazard ratio for death, 0.41; 95% CI, 0.25 to 0.67) (Fig. 3C).

SAFETY AND ADVERSE EVENTS

The safety profile remained consistent with that in the primary analysis, with no new types of adverse events with long-term administration. The most common treatment-related adverse events of interest of any grade in the tebentafusp group were rash (83%), pyrexia (76%), pruritus (70%), and hypotension (38%) (Tables S7, S8, and S9). Grade 3 or 4 treatment-related adverse events occurred in 116 patients (47%); the most common were rash (19%) and an elevation in the aspartate aminotransferase level (6%). Most tebentafusp-related adverse events occurred within the first 4 weeks of treatment during administration of step-up doses and decreased in frequency and severity with subsequent doses (Fig. 4). According to ASTCT grading criteria,[15] cytokine release syndrome, which was graded post hoc, occurred in 89% of tebentafusp-treated patients and was most frequent in the first 4 weeks of treatment.[11] Most of the patients who had cytokine release syndrome (88%) had grade 1 (12%) or 2 (76%) as the maximum grade, although some patients (1%) had a grade 3 event. The grade 3 or 4 treatment-related adverse events that occurred after the initial 6 months of treatment were primarily laboratory abnormalities (e.g., increases in the aspartate aminotransferase level) that were temporally associated with disease progression.

No new treatment-related discontinuations were reported: during the trial, 2% of the patients in the tebentafusp group and 5% of those in the control group discontinued treatment because of adverse events that were related to treatment. No treatment-related deaths occurred during the trial.

The treatment-related adverse events of any grade that were reported most often in the control group were rash (27%), fatigue (25%), and pruritus (23%). Adverse events that occurred during treatment in the crossover group were consistent with initial tebentafusp

use: pruritus (75%), pyrexia (56%), chills (50%), and rash (50%) were the most common events (Table S10).

The development of anti-tebentafusp antibodies in 29% of the patients, including neutralizing antibodies (in 19% of the patients), did not affect the safety or efficacy of tebentafusp. These findings are consistent with those in the primary analysis.

DISCUSSION

In the primary analysis in this trial, tebentafusp showed an overall survival benefit in patients with metastatic uveal melanoma. This updated analysis confirms that the overall survival benefit with tebentafusp, as compared with the investigator's choice of single-agent pembrolizumab, ipilimumab, or dacarbazine, persisted after a follow-up of at least 3 years. An estimated 27% of the patients who were randomly assigned to receive tebentafusp were alive at the 3-year landmark, as compared with 18% of patients who were assigned to the control group. The event rate in the Kaplan–Meier overall survival curve (Fig. 1A) decreased with time, but because of the censoring of data beyond 3 years, it was still too early at the time of this report to know whether a stable plateau will emerge.

Before tebentafusp, programmed cell death 1 (PD-1) inhibitors with or without ipilimumab were used to treat metastatic uveal melanoma on the basis of its efficacy for the treatment of metastatic cutaneous melanoma; however, only the monotherapies (pembrolizumab or ipilimumab) were assessed in the control group of the current trial. The 1-year overall survival percentages of 52% and 56% in two single-group phase 2 studies of ipilimumab plus nivolumab as first-line treatment (GEM-1402)[19] and as mixed-line treatment[20] for metastatic uveal melanoma were similar to the 1-year percentage of 60% in the control group in our current trial, in which the predominant treatment was single-agent pembrolizumab (in 82% of the patients), and both are lower than the 1-year percentage of 72% with tebentafusp. Cross-trial comparisons are imprecise at best, but these data suggest that the availability of combination ipilimumab plus nivolumab may not have altered the overall survival benefit seen in the current trial.

Our results show greater disease control and more durable responses in the tebentafusp group than in the control group, and the results for progression-free survival remained in favor of tebentafusp, with an estimated 8% of the patients in the tebentafusp group progression-free at 2 years, as compared with 3% of the patients in the control group. However, the results for radiographic response and progression-free survival underestimated the overall survival benefit with tebentafusp. In contrast, the degree of the reduction in ctDNA levels at 9 weeks, which in most cases occurred before the response as defined by RECIST was apparent, was strongly associated with overall survival in patients who were receiving tebentafusp as first-line therapy. This association between the reduction in ctDNA levels and overall survival replicates the association observed in previously treated patients in the phase 2 trial of tebentafusp.[12] These findings support additional exploration of the association between an early reduction in ctDNA levels and the activity of tebentafusp.

The safety profile of tebentafusp has been established[11,12] and is consistent with its mechanism of action, with most adverse events being either cytokine-mediated, caused by T-cell activation, or skin-related (because of the targeting of gp100-expressing melanocytes). Most adverse events occurred early during treatment, primarily during the administration of step-up doses, and decreased in frequency and severity with continued administration. With longer follow-up, no new safety signals or new treatment-related discontinuations occurred (percentage of patients who discontinued in the tebentafusp group, 2% overall). Autoimmune adverse events requiring long-term management, as seen with immune checkpoint inhibitors (e.g., colitis and thyroiditis),[21] were not observed among the patients treated with tebentafusp. Although neutralizing antibodies were found in 19% of the patients treated with tebentafusp, the efficacy and safety of the drug did not appear to be affected.

This 3-year analysis confirms a long-term survival benefit of tebentafusp in HLA-A*02:01–positive adults with previously untreated metastatic uveal melanoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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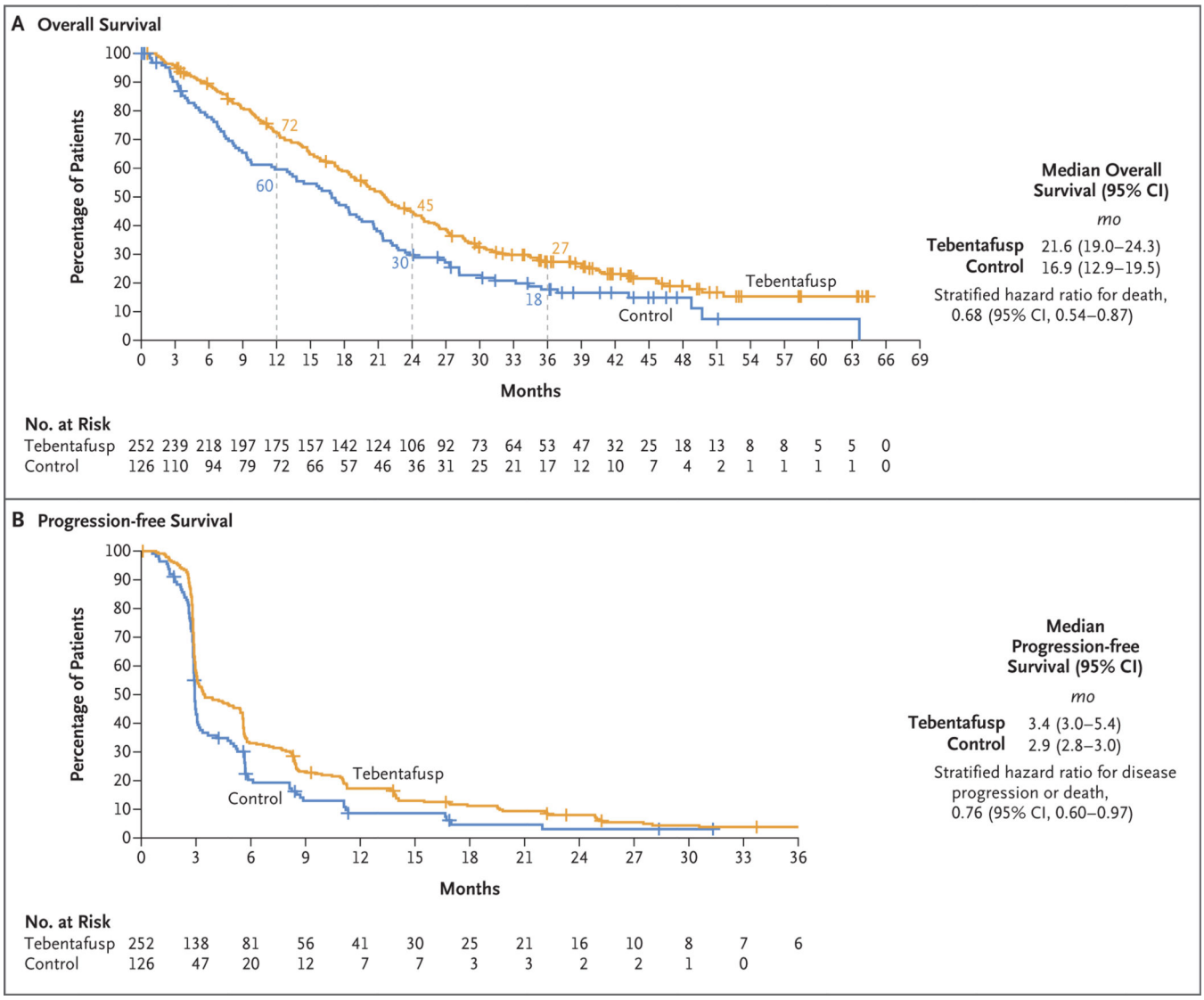

Figure 1. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival in the Intention-to-Treat Population.

Patients in the control group received the investigator's choice of single-agent therapy with pembrolizumab, ipilimumab, or dacarbazine. Tick marks indicate censored data.

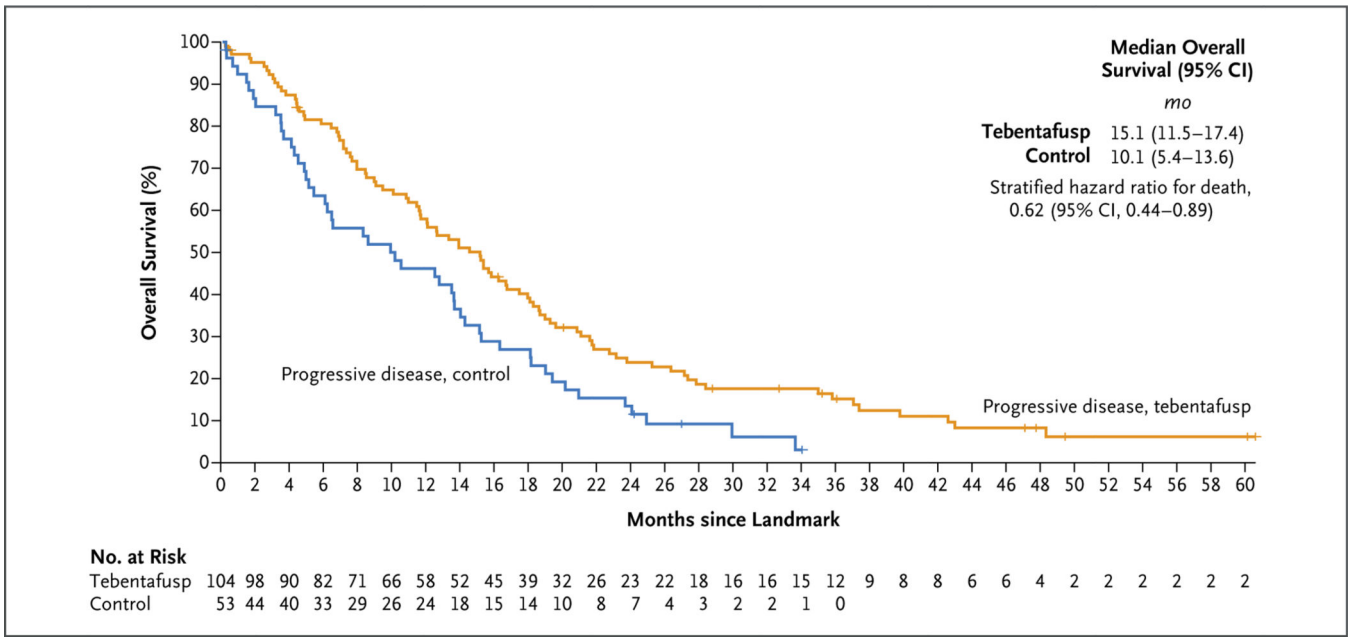

Figure 2. Kaplan–Meier Estimates of Postlandmark Overall Survival among Patients with Best Overall Response of Disease Progression.

Shown is overall survival after the landmark (day 100 after randomization) among the patients with a best overall response of progressive disease before the landmark, with progressive disease defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Tick marks indicate censored data.

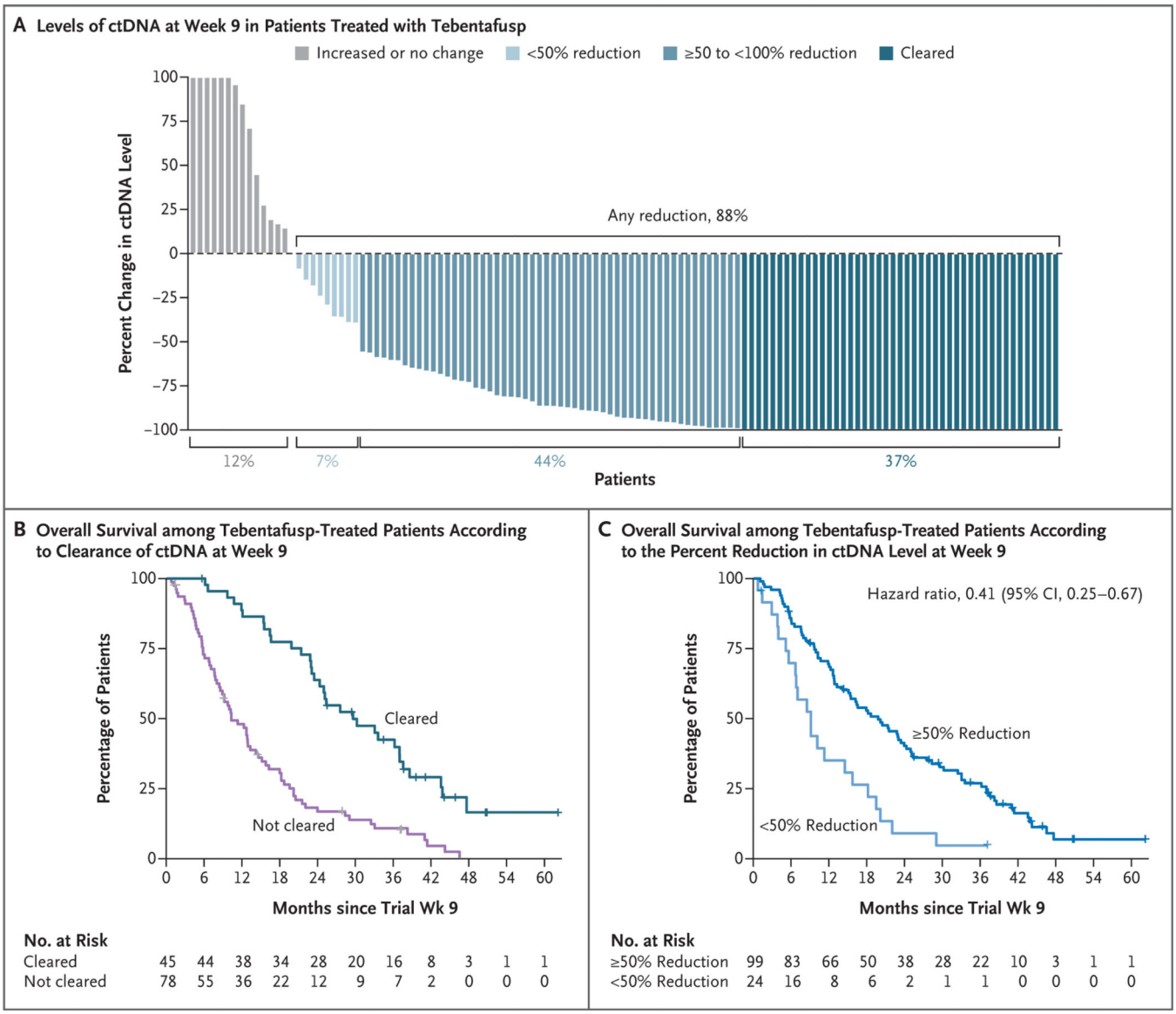

Figure 3. Dynamics of Circulating Tumor DNA and Association with Overall Survival in Patients Treated with Tebentafusp.

Panel A shows a waterfall plot of percent changes in the circulating tumor DNA (ctDNA) level at week 9 during treatment in all 123 tebentafusp-treated patients with evaluable data. Panel B shows Kaplan–Meier estimates of overall survival from week 9 among tebentafusp-treated patients who had ctDNA clearance as compared with those who did not have ctDNA clearance at week 9. Panel C shows K aplan–Meier estimates of overall survival from week 9 among tebentafusp-treated patients who had a reduction of at least 50% in the ctDNA level as compared with those who had a reduction of less than 50%, no change, or an increase at week 9. Tick marks in Panels B and C indicate censored data.

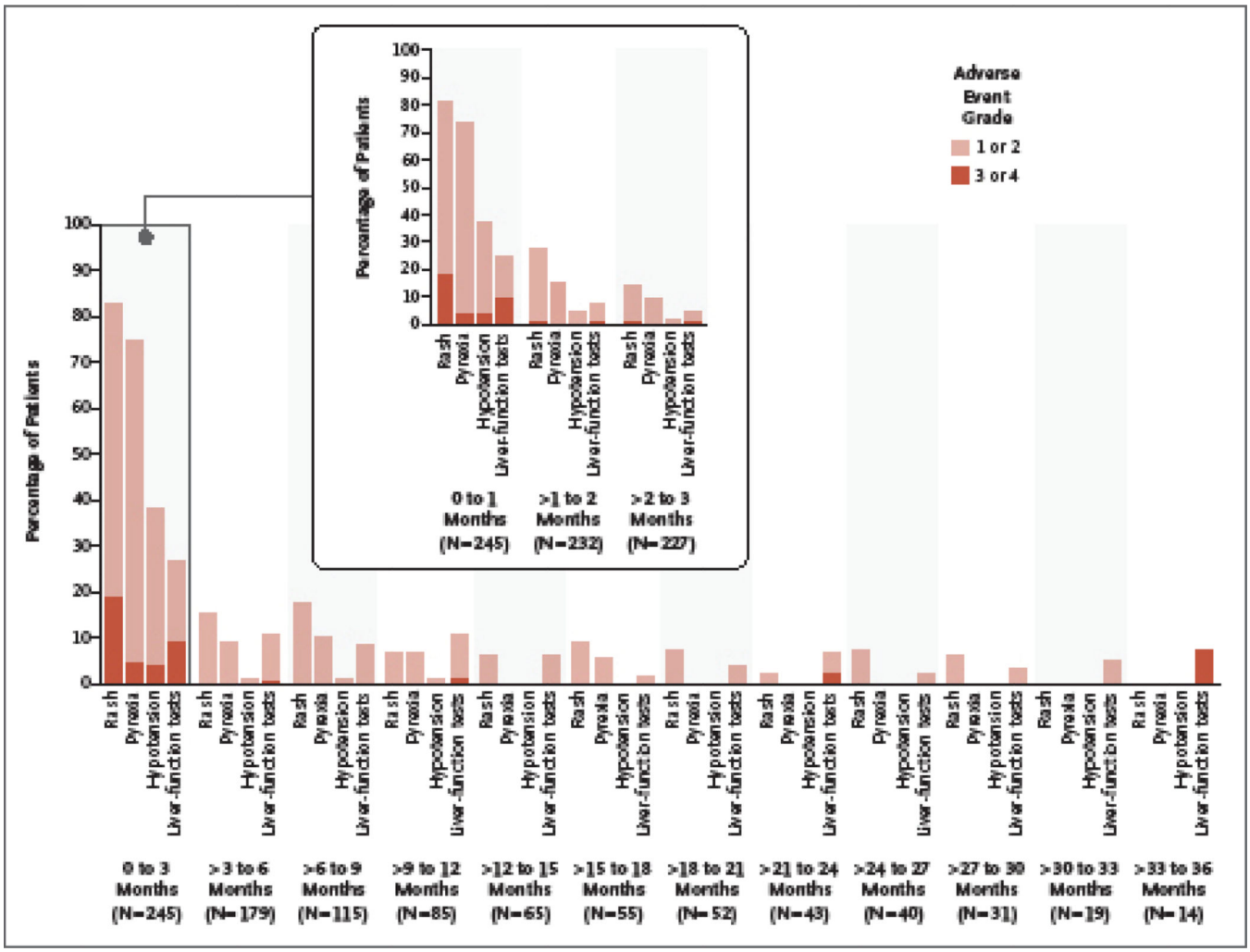

Figure 4. Long-term Frequency and Severity of Selected Treatment-Related Adverse Events with Tebentafusp.

The numbers of patients at risk for each time interval are indicated. Rash, hypotension, and liver-function tests (i.e., elevated liver-function values) are composite terms for a list of related adverse events of any grade (Table S11).

Table 1.

Tumor Response.

Response	Tebentafusp (N = 252)	Control (N = 126)*
Best overall response — no. of patients (%)		
Complete response	1 (<1)	0
Partial response	27 (11)	6 (5)
Stable disease	87 (35)	28 (22)
Progressive disease	132 (52)	82 (65)
Not evaluable or not applicable	5 (2)	10 (8)
Objective response — no. of patients (%)	28 (11)	6 (5)
Stratified odds ratio for objective response, tebentafusp vs. control (95% CI)†	2.46 (1.00–6.06)	Reference
Disease control at 12 wk — no. of patients (%)‡	115 (46)	34 (27)
Stratified odds ratio for disease control, tebentafusp vs. control (95% CI)§	2.34 (1.45–3.76)	Reference

*Patients in the control group received the investigator's choice of single-agent therapy with pembrolizumab, ipilimumab, or dacarbazine.

†The 95% confidence intervals were calculated with the use of the exact Clopper–Pearson method.

‡Disease control was defined as a complete response, a partial response, or stable disease that persisted for at least 12 weeks.

§The odds ratio and 95% confidence interval were calculated with a Stratified Cochran–Mantel–Haenszel test, with stratification according to lactate dehydrogenase (LDH) status (i.e., LDH level higher than the upper limit of the normal range or less than or equal to the upper limit of the normal range).