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Bispecific Fusion Protein Tebentafusp Significantly Improves Overall Survival in Patients With Metastatic Uveal Melanoma

PHILADELPHIA – Compared with available standard therapies, including immune checkpoint inhibitors, treatment with the bispecific fusion protein tebentafusp nearly halved the risk of death among patients with metastatic uveal melanoma, according to results of a phase III clinical trial presented during Week 1 of the virtual AACR Annual Meeting 2021, held April 10-15.

"Even though uveal melanoma is rare overall, it is the most common eye cancer in adults, and represents approximately 3-5 percent of all melanomas," said Jessica Hassel, MD, associate professor and section head of DermatoOncology in the Department of Dermatology and the National Center for Tumor Diseases at the University Hospital Heidelberg in Germany. "Prognosis for uveal melanoma is very poor with a median survival after metastasis of less than one year, and there are currently no standard-of-care treatments for this aggressive cancer," she said.

Tebentafusp is a bispecific fusion protein that recognizes two targets, with one target present on melanoma cells, and the second target present on T cells. "Tebentafusp builds a bridge between the tumor and the immune cells, enabling the immune cells to attack the tumor," Hassel explained. One end of tebentafusp recognizes a part of the gp100 protein expressed in melanoma cells. This recognition occurs through a high-affinity T-cell receptor (TCR) binding domain that targets the gp100 antigen, which is presented by the tumor cells using a specific HLA (for human leukocyte antigen) type, known as HLA-A*02:01. The other end of tebentafusp binds, activates, and redirects T cells to attack the gp100-expressing melanoma cells, explained Hassel.

Because the TCR binding domain only recognizes a specific gp100-derived peptide presented on HLA-A*02:01, tebentafusp can only be used to treat patients with this HLA type, Hassel said. However, this HLA type is frequently observed in Caucasians, the population most affected by uveal melanoma, with roughly 50 percent of Caucasians expressing this HLA type, she noted.

Hassel and colleagues compared tebentafusp with investigator's choice as first-line therapy in 378 previously untreated HLA-A*02:01-positive patients with metastatic uveal melanoma. Patients were randomly assigned 2:1 to receive tebentafusp (252 patients) or investigator's choice, which included the checkpoint inhibitors pembrolizumab (Keytruda; 103 patients) and ipilimumab (Yervoy; 16 patients) or the chemotherapeutic dacarbazine (seven patients). A primary endpoint of the trial was overall survival (OS) between the randomized arms.

After a median follow-up of 14.1 months, compared with patients randomly assigned to investigator's choice, patients randomized to tebentafusp had almost half the risk of death. Further, the estimated one-year OS rate was 73.2 percent among patients in the tebentafusp arm, compared with 58.5 percent in the investigator's choice arm. The difference in progression-free survival (HR 0.73) was statistically significant between the two treatment arms, but much less compared to overall survival. Response rates according to RECIST were 9 percent with tebentafusp (one complete response, 22 partial responses) and 5 percent with investigator's choice. The disease control rate including patients with stable disease at 12 weeks was 46 percent and 27 percent, respectively.

Patients who do not have either a partial response or stable disease but experience disease progression, called best response of progressive disease, are generally not considered to be benefiting from a therapy. “However, surprisingly, in a landmark Day 100 analysis limited to patients who had a best response of progressive disease, tebentafusp still conferred a better overall survival compared to the investigator’s choice,” Hassel noted.

While immune checkpoint inhibitors are commonly used treatments for metastatic uveal melanoma, benefit is very limited, in contrast to cutaneous melanoma. This difference may, in part, be explained by the fact that uveal melanoma belongs to the cancers with a low mutational burden, which can lead to impaired T-cell recognition, Hassel explained. “Tebentafusp redirects any T cell to target cells expressing gp100 and thereby has the chance to activate the immune response against the gp100-expressing uveal melanoma,” she added.

Adverse events associated with tebentafusp treatment were predictable and manageable, Hassel noted, and the rate of treatment discontinuation was lower in the tebentafusp arm compared with the investigator’s choice arm (2 percent versus 4.5 percent, respectively).

“As there are currently no standard treatments for patients with metastatic uveal melanoma, tebentafusp has the potential to become a practice-changing therapy for patients with this disease,” Hassel said.

The major limitation of tebentafusp is that it can only be used in patients who have a specific HLA type, Hassel said. “There still remains an unmet need for patients who do not have this particular surface protein,” she noted.

This study was sponsored by Immunocore.

Hassel is a consultant for Pierre Fabre, Sanofi, Sun Pharma, Merck Sharp & Dohme Corp., Immunocore, Bristol Myers Squibb, and Novartis. She has received payment for talks from Bristol Myers Squibb, Merck Sharp & Dohme Corp., Roche, Novartis, Pfizer, Sanofi, and Almirall. Hassel has received research funding from Bristol Myers Squibb, Immunocore, Roche, Novartis, BioNTech, Regeneron, Merck, Genentech, 4SC, and Philogen.

Abstract

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Abstract Body:

Background: Metastatic uveal melanoma (mUM) has a poor prognosis. No systemic treatment has shown an OS benefit; the 1-yr OS rate is 52%. Tebentafusp (tebe), a bispecific consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target gp100+ cells, has shown promising activity in previously treated mUM pts. Here, we report the primary analysis in the intention-to-treat population (ITT) of a Ph3 trial of tebe vs. investigator's choice (IC) as first line therapy in HLA-A*02:01-positive adult pts with mUM [NCT03070392].

Materials and Methods: In this randomized, open-label, Ph3 trial, first line HLA-A*02:01+ pts with mUM were randomized in a 2:1 ratio to receive tebe or IC of pembrolizumab, ipilimumab or dacarbazine, stratified by LDH. The two co-primary endpoints were overall survival (OS) in all randomized pts (ITT) and OS in tebe-randomized pts who develop rash during week 1. Secondary endpoints included safety and RECIST-defined overall response rate (ORR), progression free survival (PFS) and disease control rate (DCR). The study was unblinded by an independent data monitoring committee at the first pre-specified interim analysis. ORR data are immature and will be reported in a subsequent analysis.

Results: 378 pts were randomized to tebe (252) or IC, including pembrolizumab (103), ipilimumab (15) or dacarbazine (7). After a median follow-up of 13.7 mo (range X-X), tebe significantly prolonged OS compared to IC (HR 0.51; 95% CI 0.36-0.71; P<0.0001) in the ITT population, with estimated 1-yr OS rate of 73.2% (95% CI 66.3-78.9) vs 57.5% (95% CI 47.0-66.6), respectively. The OS benefit of tebe was observed in pre-specified subgroups, including vs. pembrolizumab IC (HR 0.52; 95% CI 0.34-0.78) and by stratification variable of LDH>ULN (HR 0.73; CI 0.47-1.13). The DCR was 45.2% (95% CI 39-51.6) for tebe and 27.8% (95% CI 20.2-36.5) for IC and the PFS HR was 0.8 (95% CI 0.62, 1.03) in favor of tebe. In a post-hoc landmark OS analysis of pts with best response of disease progression (PD), tebe had OS benefit HR of 0.399 (95% CI 0.248-0.642). Most common TRAEs were target-mediated (gp100+ melanocytes) or cytokine-mediated (T cell activation) and included pyrexia (75%), pruritus (66%), and rash (49%); these AEs decreased in frequency and severity after the first 3-4 doses and were generally manageable with standard interventions. The rate of treatment discontinuation due to related AEs was lower in the tebe arm (X% vs Y%). There were no treatment related deaths in the tebe arm.

Conclusions: In first line systemic mUM pts, tebe monotherapy significantly improved OS compared to IC; the first investigational therapy to improve OS in pts with mUM. Tebe had a predictable and manageable AE profile with low rate of related discontinuation. An OS benefit of tebe in pts with PD suggests that RECIST-based radiologic endpoints may underestimate benefit from TCR bispecifics.

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