Background Tebentafusp, a TCR bispecific (gp100xCD3) fusion protein (ImmTAC) that targets gp100 in the context of HLA-A*02:01 and activates T cells to kill tumor cells, was approved for the treatment of unresectable or metastatic uveal melanoma (mUM), with many patients demonstrating OS benefit despite radiographic progression.1,2 We explored molecular features of the tumor and its micro-environment at clinically confirmed progression, and their association with OS on tebentafusp.

Methods NCT02570308 was conducted in HLA-A*02:01 2L+ patients with advanced mUM. Tumor biopsies (N=14) collected soon after progression on tebentafusp were analyzed by immunohistochemistry (IHC) and RNAseq. Presence of HLA-A and B2M on tumor cells was analyzed by IHC with expression at any intensity quantified. Presence of necrosis was determined by hematoxylin and eosin staining, and CD163+ melanophages by IHC. K-M analysis landmarked to 90 days from initiation of treatment was used for OS.

Results Median OS in the 14 pts with biopsies collected at the time of progression was 22 months, and patients were treated with tebentafusp for 1 day-22 months beyond progression.

Expression of PMEL (gp100) was high at the time of progression and not associated with OS. The degree of necrosis or presence of melanophages in the tumor microenvironment was also not associated with OS.

RNAseq analysis revealed that higher levels of the antigen presentation machinery, presence of PRDM1 expressing effector CD3 T cells, expression of genes required in the necroptosis and apoptosis pathways, and the IFN-inducible transcription factor IRF1 were associated with long OS. In contrast, higher expression of the cell cycle gene CDC45 and the tumor metabolism gene HPDL were associated with short OS. (table 1).

Membrane bound HLA-A was strongly correlated with B2M expression on tumor cells (R-squared = 0.68, p = 2.8e-9), consistent with the requirement of B2M for stability of cell surface HLA. Lack of membrane-bound HLA-A and B2M was associated with short OS, consistent with the requirement of cell surface HLA for antigen presentation.

Conclusions Tebentafusp has demonstrated OS benefit even in patients with progressive disease. Based on tumor biopsies at time of progression, long OS was associated with higher levels of antigen presentation machinery, expression of apoptosis and necroptosis pathways, presence of effector memory T cells and activation of the interferon pathway. These observations provide mechanistic insight into how some patients can derive benefit from tebentafusp despite radiographic progression.

Trial Registration NCT02570308

REFERENCES

Ethics Approval Written informed consent was provided by all study participants. The study was approved by each site’s Institutional Review Board. An independent data monitoring committee (IDMC) was also established to provide oversight of safety and efficacy considerations and give advice and recommendations regarding steps to ensure both patient safety and the ethical integrity of the study.