OVERALL SURVIVAL ON TEBENTAFUSP IN METASTATIC UVEAL MELANOMA (MUM) ACROSS THE RANGE OF TUMOR GP100 EXPRESSION LEVELS

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Background Tebentafusp is a TCR–anti-CD3 bispecific fusion protein that targets melanoma-expressed gp100 antigen and has shown survival benefit in a randomized phase 3 trial in 1L patients with metastatic uveal melanoma.^{1 2} In phase 2 and 3 trials (NCT02570308, NCT03070392) enrolling late-stage mUM patients, we explored associations between gp100 expression in the tumor and pharmacodynamic response and clinical outcomes on tebentafusp.

Methods 2L+ (NCT02570308) or 1L (NCT03070392) HLA-A*02:01+ mUM patients were treated weekly with 68mcg tebentafusp after intra-patient dose escalation. Archival or fresh tumor biopsies were obtained prior to dosing. Expression of baseline gp100 was determined by immunohistochemistry (IHC) and RNAseq analysis (2L+ only) in up to 118 (2L+) and 187 (1L) samples. RNAseq analysis was used to evaluate association between baseline mRNA levels of gp100 and T cell infiltration and activation after 3 doses of tebentafusp (n=35). Serum samples (n=118, 2L+ only) collected at baseline and on-treatment were analyzed for ctDNA. An H-Score quantified tumoral gp100 protein expression. gp100 H score or mRNA levels were cut at the lowest quartile to identify gp100 low patients.

Results Distribution of gp100 protein by IHC was similar in both studies with median H-Scores of 170 (IQR 60–260) (2L+) and 155 (IQR 68–229) (1L). Over 70% of samples had ≥ 50% gp100+ tumor cells at any intensity. gp100 H-scores were similar in archival and fresh tumor biopsies. High baseline gp100 mRNA levels were associated with ~2-fold increased CD3 and CD8 cell infiltration on tebentafusp compared to little or no change in the gp100 low group. There was greater T cell activation in the gp100 mRNA high group as demonstrated by induction of IFN α (fold change in gp100 high=2.5 p=0.00005), IFN γ signatures (FC in gp100 high=5.7 p=0.00004) and cytotoxic genes GZMB (FC high=4.6 p=0.000006) and PRF1 (FC high=2.4 p=0.00051) compared to little or no activation in the gp100 mRNA low group. Tumor shrinkage (TS) and overall survival (OS) > 12 months were observed in low and high gp100 H-score subgroups (table 1), and a RECIST partial response was observed at very low gp100 (H-score 11). ctDNA reduction on tebentafusp was also observed across the range of gp100 expression levels.

OS and ctDNA reduction—were observed across the range of gp100 expression levels.

Trial Registration NCT02570308, NCT03070392

REFERENCES

1. 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 Can Res* 2020;**26**:5869–5878.
2. Sacco JJ, Carvajal R, Butler MO, *et al.* 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-S1143.

Ethics Approval The institutional review board or independent ethics committee at each center approved the trial. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

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Abstract 868 Table 1 TS and OS in gp100 high and gp100 low patient groups

Clinical Trial	gp100 Group (H score IHC)	TS (% with tumor reduction)	OS (% survival >12 months)
1L (NCT03070392)	gp100 high	38%	49%
	gp100 low	43%	50%
2L+ (NCT02570308)	gp100 high	48%	58%
	gp100 low	32%	61%

*P>0.05 for all high vs low (lowest quartile H score) comparisons within each trial.

Conclusions High gp100 expression was associated with the acute pharmacodynamic response to tebentafusp including greater T cell infiltration and activation in the tumor microenvironment. However, clinical outcomes on tebentafusp—TS,