

## 619 TEBENTAFUSP INDUCED T AND B CELL EPITOPE SPREAD IN PATIENTS WITH ADVANCED MELANOMA

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**Background** ImmTAC<sup>®</sup> molecules are TCR-CD3 bispecific fusion proteins that can redirect and activate polyclonal T cells to kill tumors. Tebentafusp, which targets gp100 (gp100 × CD3), is the first ImmTAC to demonstrate overall survival benefit and is approved for the treatment of metastatic uveal melanoma<sup>1</sup> in HLA-A\*02:01+ patients. We explored whether tebentafusp can induce new T and B cell responses to tumor antigens other than gp100, a phenomenon termed epitope spread.

**Methods** TCRseq was performed on pre- and post-treatment PBMC samples from tebentafusp-treated patients with advanced malignant melanoma (N=10 from NCT01211262). T cell repertoire breadth was assessed using Simpson clonality index (SCI). A proteome array with 22,976 human proteins was used to assess changes in serum antibody profiles on tebentafusp treatment (N=29 from NCT02570308). Immunohistochemistry (N=36) and RNAseq (N=35) were used to analyze paired baseline and on-treatment tumor biopsies.

**Results** Substantial T cell clonal expansion and diversification were observed upon treatment with tebentafusp. A median of 56 (range 11-216) T cell clones per patient were expanded after 5-8 doses of tebentafusp, of which 25 (range 0-46) were new clones undetected at baseline. Patients with greater than 1 year overall survival (OS, N = 4) exhibited a focused T cell repertoire at baseline (median SCI=0.08) compared to patients with shorter than 6 months OS (N = 6, median SCI=0.02, p=0.009), which increased in diversity on tebentafusp in patients with long OS but not short OS (median 44% on-treatment decrease in SCI from baseline in patients with long OS compared to a median of 15% on-treatment increase in SCI in patients with short OS, p=0.038).

B cell responses were also induced upon treatment with tebentafusp. B cells were recruited to the tumor microenvironment after 3 doses of tebentafusp, with evidence of new tertiary lymphoid structures. On-treatment B cell levels in biopsies correlated with better OS (hazard ratio HR=0.3, p=0.016) and tumor shrinkage (odds ratio OR=0.06, p=0.007). Serum IgG repertoire profiling showed a median of 42 auto-antibody specificities (range 16-114) per patient at baseline, which increased to 106 (range 32-261) after 4 doses of tebentafusp. Tebentafusp induced antibodies against multiple proteins including p53, the uveal melanoma driver CYSLTR2 and numerous cancer testis antigens. Antibodies were also induced against novel somatic mutants in 2 patients.

**Conclusions** By inducing T cell repertoire expansion and diversification and antibodies against multiple tumor antigens, tebentafusp is the first TCR-CD3 bispecific to demonstrate T and B cell epitope spread.

**Trial Registration** A Study of the Intra-Patient Escalation Dosing Regimen With IMCgp100 in Patients With Advanced Uveal Melanoma

ClinicalTrials.gov Identifier: NCT02570308

Study to Assess the Tolerability of a Bispecific Targeted Biologic IMCgp100 in Malignant Melanoma

IMCgp100-01 study: NCT01211262

### REFERENCE

1. Nathan P *et al.* *N Engl J Med.* 2021;1196–1206.

**Ethics Approval** 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.

**Consent** Written informed consent was provided by all study participants.

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