## 30 MOLECULAR FEATURES ASSOCIATED WITH LONG SURVIVAL ON TEBENTAFUSP IN PREVIOUSLY UNTREATED METASTATIC UVEAL MELANOMA IN A PHASE 3 TRIAL

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**Background** Metastatic uveal melanoma(mUM), a rare cancer with poor prognosis, has a historical 1-yr overall survival (OS) rate of 52%. Tebentafusp, a bispecific (gp100 x CD3) ImmTAC, is approved for adult HLA-A*02:01+ patients (pts) with unresectable or mUM. In the primary analysis of the Ph3 IMCgp100–202 study in previously untreated mUM [NCT03070392], tebentafusp significantly improved OS compared to investigator's choice (IC) [HR 0.51]. We explored molecular features in tumor biopsies and serum as predictors of long OS (≥3 years) on tebentafusp in the Ph3 study.

**Methods** In this randomized, open-label, Ph3 trial, 1L HLA-A*02:01+ mUM pts were randomized 2:1 to receive tebentafusp or IC, stratified by LDH. Primary endpoint was OS. This analysis is based on OS Nov 2022 data cutoff. Serum cytokines were measured using a multiplex panel of 11 immune markers in 226 patients on tebentafusp and 76 on IC. Tumor biopsies were available from 176 pts on tebentafusp and 72 on IC. Biopsies were analyzed by immunohistochemistry using antibodies to gp100, CD3 and CD163 and assessed by a pathologist or quantified using digital image analysis. Sera (N=202) collected at baseline and week 9 on tebentafusp were analyzed for ctDNA using targeted mPCR-NGS assay for mutations in 15 genes including GNAQ, GNA11, SF3B1, CYSLTR2, PLCB4 and EIF1AX.

**Results** 378 pts were randomized to tebentafusp (245) or IC, including pembrolizumab (77), ipilimumab (11) or dacarbazine (7). After a median follow-up of 22 months, the estimated 3-year OS on tebentafusp was 27% (95% CI 22–34) vs IC of 13% (95% CI 7–23).

At baseline, gp100 expression in the tumor was not associated with long OS in the tebentafusp arm. Lower CD163:CD3 ratio in tumor biopsies or lower serum levels of IL6, IL10, CXCL10, CXCL11, MCP1 cytokines were associated with long OS on tebentafusp but not IC. Combination of low tumor CD163:CD3 ratio and low serum IL10 levels was most strongly associated with long OS (table 1). This subset also had long OS in the Ph2 IMCgp100–102 study enrolling 2L+ treated mUM patients (3 yr OS 46% (95% C.I. 28–74)).

In the tebentafusp arm, 13/18 (72%) ctDNA evaluable pts with survival ≥3 years cleared their ctDNA at week 9 after initiation of tebentafusp, and 5/18 pts had ≥50% reduction in ctDNA.

**Conclusions** A low immunosuppressive tumor microenvironment, low serum levels of inflammatory cytokines and ctDNA reduction by week 9 are associated with OS ≥3 years on tebentafusp in previously untreated mUM.

**Trial Registration** NCT03070392: A Phase II Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared With Investigator Choice in HLA-A*0201 Positive Patients With Previously Untreated Advanced Uveal Melanoma

**Ethics Approval** Institutional review board approval was obtained and all participants gave informed consent prior to enrolement.

**Abstract 30 Table 1**

| Biomarker | Subgroup | Tebentafusp arm | | Investigator choice arm | |
|---|---|---|---|---|---|
| | | 3-year % OS (95% C.I.) | N | 3-year % OS (95% C.I.) | N |
| CD163:CD3 | Low | 41 (28-60) | 45 | 17 (6-47) | 18 |
| | High | 21 (15-30) | 131 | 8 (3-22) | 54 |
| Serum IL10 | Low | 32 (25-41) | 162 | 10 (4-24) | 61 |
| | High | 21 (12-35) | 64 | 29 (13-66) | 15 |
| CD163:CD3 & serum IL10 | Low/low | 53 (37-77) | 31 | 14 (4-52) | 14 |
| | High/high | 20 (10-41) | 32 | 20 (6-69) | 10 |

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0030