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Early reduction in ctDNA, regardless of best RECIST response, is associated with overall survival (OS) on tebentafusp in previously treated metastatic uveal melanoma (mUM) patients

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Background

Tebentafusp (tebe), an investigational TCR–anti-CD3 bispecific fusion protein that targets gp100 and activates T cells, has shown OS benefit in 1st line mUM. OS was improved in patients (pts) regardless of RECISTv1.1 best response, suggesting better surrogate efficacy endpoints are needed.

Methods

2L+ HLA-A*02:01+ mUM pts were treated weekly with 68mcg tebe after intra-patient dose escalation (NCT02570308). RECISTv1.1 was assessed by an independent radiographic committee. Serum samples (N=118) collected at baseline (BL) and at weeks (wks) 5, 9 on tebe were analyzed for ctDNA using a targeted mPCR-NGS assay for mutations in 15 genes including mUM oncogenes GNAQ, GNA11, SF3B1, CYSLTR2, PLCB4 and EIF1AX. 0.1-3 log reductions in mean tumour molecules (MTM) per ml of serum observed on treatment were tested for association with OS.

Results

109/118 (92%) of pts had detectable ctDNA. MTM at BL was correlated with tumor burden as assessed by sum of longest diameters (Spearman's r=0.61, P=10^{-10}). By wk 9, in 99 pts with BL and on-treatment MTM measurements, any (>0) ctDNA reduction was observed in 69 (70%). In 97 pts that were evaluable by RECISTv1.1, any ctDNA reduction was observed in 31/48 with progressive disease (PD), 34/45 with stable disease (SD) and 2/4 with partial response (PR). Magnitude of ctDNA reduction by wk 9 was strongly associated with improvement in OS (R^2=0.87, P<0.0001): 0.1 log reduction hazard ratio HR 0.8; 0.5 log reduction HR 0.5; 1 log reduction HR 0.4; 2 log reduction HR 0.3, 3 log reduction HR 0.2 and undetectable ctDNA (clearance) HR 0.1. 1 yr OS was 100% in pts with ctDNA clearance (N=14) vs 57% in those with increased ctDNA (N=30). Best overall response among those with ctDNA clearance was PD in 4 (29%), SD in 8 (57%) and PR in 1 (7%).

Conclusions

ctDNA was detected in most mUM pts, associated with tumor burden at BL and reduced in 70% of pts on tebe, despite a RECIST response rate of <10%. ctDNA reduction as early as 9 wks on tebe was strongly associated with improved OS, even in pts with RECIST PD or SD. Early ctDNA reduction may be a better surrogate of tebe efficacy than RECIST objective response in mUM.

Clinical trial identification

NCT02570308.

Legal entity responsible for the study

Immunocore Ltd.

Funding

Immunocore Ltd.

Disclosure

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