calling, CNA and tumour purity analyses were performed, predictive variables were included in logistic regression.

Results: Incorporating MHC-II neoantigen load, CNAs and tumour purity, our multivariate model predicted response with AUC 0.86 Responders were associated with a higher number of predicted clonal neoantigens (p=0.0029), driven by MHC-II neoantigens (p=2e-04), and were more statistically significant biomarkers than TMB (p=0.016). A higher total neoantigen burden (p=0.02) and MHC-II neoantigen burden (p=0.06), but not higher TMB, were associated with superior OS. Independently, low tumour purity was associated with response (p=0.005) and superior OS (p=0.04) Non-responders harboured CNAs in key melanoma driver genes, including *CDKN2A* loss of function (p=0.04), and *TERT* gain (p=0.03) which was associated with inferior TTF (p=0.02) Genomic imprinting has established links to cancer pathogenesis, most notably at 11p15.5. In our cohort, loss of heterozygosity (LOH) at 11p.15.5 was associated with response (p=0.007), superior TTF (p=0.05), and higher MHC-II neoantigen load (p=0.04), while non-LOH loss at the same loci was associated with non-response (p=0.003), inferior TTF (p=0.007) and OS (p=0.02), highlighting that different classes of loss can lead to opposing biological sequelae. LOH with loss of the active allele and persistence of the imprinted allele will lead to non-expression of the oncogene. External validation with matched WGS and RNA will be presented at the conference.

Conclusions: In our cohort, 1L ICI response in melanoma was driven by MHC-II neoantigens, CNAs and tumour purity.

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2237P Avelumab (AVE), cetuximab (CET) and irinotecan (IRI) for treatment refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC): Translational analyses of the AVETUXIRI phase II trial

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Background: This trial explores the clinical efficacy and safety of AVE, CET and IRI for treatment refractory MSS mCRC. We aim at characterizing the immune response for biomarker discovery through associated translational research.

Methods: MSS, chemorefractory (anti-EGFR refractory if RAS wt) mCRC patients (pts) were enrolled (RAS wt: 28 pts, RAS mut: 27 pts) and treated with CET and IRI from week 1(W1) and AVE from W3. Clinical objectives (safety, tumor response, disease control rate (DCR), PFS and OS) were presented separately. Exploratory endpoints include predictive efficacy biomarkers (immunoscore (IS), immune tumor microenvironment, gene expression profile (GEP), ctDNA) and modification overtime. Multiplex immunofluorescence (MIF), RNAseq and ctDNA analyses were done (sequential metastasis biopsies and plasma samples at W0, W3, W11). CD3, CD8, CD45RO, PD1, PD-L1cells densities were quantified. RNA-seq data were used to perform several analyses (DESeq2, GSEA, deconvolution, gene ontology). OncoSELECT panel (58 genes) was used to follow ctDNA variation over time (mean variant allele frequency).

Results: Among 55 treated pts, 95 biopsies (W0: 39, W3: 29, W11: 27) were available for MIF (table: W0 results). On 23 pts (1st stage), upregulation of adaptive immune response signature was associated with tumor shrinkage, PFS>6 and OS>12 months (p. adj= 0.00). Few modifications of immune cells and GEP were observed overtime (W0, W3, W11). ctDNA decrease (>10%) was associated with tumor response (p=0.04) and PFS (6.6 vs 3.4 months, p=0.08).

Table: 2237P

Characteristics	IS (CD3/CD8) high	CD3/PD1 high	CD3/CD8/CD45RO/ PD1 high
High/others:pts	10/29	10/29	8/31
RAS-wt/RAS-mut:OR, p-v	1.39, p=0.73	0.82, p=0.99	0.83, p=0.99
Tumor shrinkage: OR, p-v	8.32, p=0.00	4.50, p=0.05	9.54, p=0.00
DCR:OR, p-v	8.02, p=0.05	3.16, p=0.26	5.55, p=0.12
PFS:HR, p-v	0.29, p=0.00	0.28, p=0.00	0.43, p=0.03
OS:HR, p-v	0.62, p=0.19	0.26, p=0.00	0.47, p=0.06

Conclusions: Independently of RAS mutation, existing adaptive immune response within metastases is associated with treatment benefit. ctDNA decrease is associated with tumor response.

Clinical trial identification: NCT03608046.

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2238P Tebentafusp reprograms immunosuppressive tumor-associated M2 macrophages towards anti-tumoral M1 macrophages

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Background: Tebentafusp, a gp100-directed ImmTAC bispecific (gp100 x CD3), is the first TCR therapeutic to demonstrate survival benefit and is approved for the treatment of HLA-A*02:01+ adults with unresectable or metastatic uveal melanoma (mUM)[1]. High $CD3^+$ T cell: $CD163^+$ M2 macrophage ratio was associated with therapeutic benefit from tebentafusp despite the immunosuppressive effects of M2 macrophages[2]. Here we explored the effects of ImmTAC-redirected T cell activation on macrophage reprogramming in vitro and in vivo.