Results: All Luminex biomarkers showed difference between the R and NR groups 14 days after Y90 treatment (P<0.05). The higher increment of IL-18, IL-12p70, and CCL24 after Y90 treatment related to better treatment response and 3-year OS. CXCL9+ and CXCR3+ CD8 clusters differed between R and NR on the 21st and 35th day after Y90-RE, respectively. IL-18 and IL-12p70 were significantly associated with CXCL9+ and CXCR3+ CD8 clusters in the Rs, but not NRs.

Conclusions: IL-18, IL-12p70, and CCL24 were potential predictors for treatment response as well as 3-year OS for HCC patients treated by Y90-Nivo.

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227P Biomarkers for novel NK checkpoint inhibitor anti LLT1 antibody, ZM008: Patient transcriptome analysis

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Background: C-type lectin superfamily protein LLT1 interacts with CD161 on NK cells and facilitates tumor immune escape. Disruption of LLT1-CD161 with anti LLT1 antibody, ZM008 activates immune cells and kills cancer cells. This study aims to identify new biomarkers to classify specific patient population in ZM008 clinical studies.

Methods: TCGA transcriptome data was used to understand expression of LLT1 in 33 cancers. Correlation analysis was performed to compare LLT1 expression with immune gene signatures. Genomic cancer markers (TMB, MATH, MMR and MSI) status were determined using “Maftools” and “MSI sensor”. Univariate Cox proportional hazard regression analysis (SURVIVAL) was used to measure patient survival.

Results: High expression of LLT1 was found in 11 different cancers. CIBERSORT analysis revealed significant immune cell infiltration (activated NK or CD8+ T) in TME. However, LLT1 expression in multiple cancers is negatively correlated with proinflammatory gene signatures (IL-2, IL-6, EOMES, and LAMP1 etc.), positively correlated with immune exhaustion markers PD1, LAG3, TIM3, TIGIT, ICOS and immune suppressive signals (high Treg cells and CD33+ MDSC; $p < 0.05$). These data suggest immune suppressive “Cold tumor” phenotype associated with LLT1 expressing cancers. Further, immune check point predictors analysis in LLT1 positive tumors suggests positive correlation with high TMB score in COAD, UCEC and KICH; MSI score is elevated in PRAD and COAD; MMR genes expression is negatively correlated in COAD, KICH, BRCA, HNSC, KIRC, LUAD and PRAD; lastly, MATH score is correlated for GBM patients only ($p < 0.05$). Subsequently, significant hazard ratios of 1.115, 2.114 and 1.067 were observed only for COAD, KICH and KIRC, respectively ($p < 0.05$).

Conclusions: The transcriptome data analysis revealed LLT1 expression is associated with immune repressive TME in multiple cancers, suggesting therapeutic significance of ZM008. Multiple anti-inflammatory gene signatures could be useful in stratifying patients for ZM008 treatment. In addition, TMB & MSI scores and MMR gene expression could be monitored as potential biomarkers in phase I clinical trials with ZM008.

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228P Biomarker discovery via meta-analysis of immunotherapy clinical trials in cancer

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Background: Clinical profiling studies have shed light on molecular features and mechanisms that modulate response or resistance to immunotherapy but their predictive value remains largely unclear. We (Bareche et al., Annals of Oncology 2022) and others (Litchfield et al., Cell 2021) have recently curated a compendium of public datasets of DNA, RNA and clinical profiles of patients treated with immunotherapy.

Methods: Leveraging our compendium of immunotherapy clinical datasets, we developed, PredictIO, an open-source meta-analysis pipeline to assess the predictive value of molecular predictors. We first used PredictIO to compute the association between immunotherapy response and established biomarkers, such as tumor mutation burden (TNB) or CD8 gene expression, and a collection of 91 molecular signatures curated from the literature. Second, we used PredictIO for de novo RNA signature discovery pipeline to build a new predictor of immunotherapy response.

Results: Using molecular and clinical profiles of ∼3600 patients across 12 tumor types, our meta-analysis pipeline revealed thatTMB and ∼50% of the gene signatures were significantly predictive of immunotherapy response across tumor types, although their predictive value were strongly dependent on specific tumour types. We next developed a de novo gene expression signature from our pan-cancer analysis and demonstrated its superior predictive value over other biomarkers. To identify novel targets, we computed the T-cell dysfunction score for each gene within PredictIO and their ability to predict dual PD-1/CTLA-4 blockade in mice. Two genes, F2RL1 and RBFOX2, were concurrently associated with worse ICB clinical outcomes, T-cell dysfunction in ICB-naive patients and resistance to dual PD-1/CTLA-4 blockade in preclinical models.

Conclusions: Our study highlights the potential of large-scale meta-analyses in identifying novel biomarkers and potential therapeutic targets for cancer immunotherapy. These initial results, while promising, suffer from severe limitations in terms of data availability for specific cancer types and the lack of frameworks to develop and validate multi-omics predictors of immunotherapy response in a collaborative and scalable way.

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229P Leucine zipper 4 (LUZP4) IgG as a novel biomarker for testicular germ cell tumors

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Late withdrawal