Context-based drug positioning and multimodal characterization for OKN4395

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Background

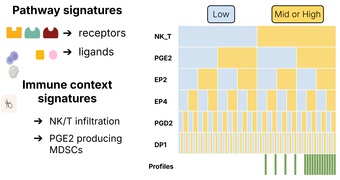
→ The **prostaglandin pathway** is associated with **immune evasion** and **poor outcome** in patients under **immune checkpoint blockade**.

→ **OKN4395**, a **triple antagonist** of prostaglandin receptors **EP2/EP4/DP1**, is currently in a Ph1 trial (NCT06789172) in solid tumors, both as a **monotherapy** and in **combination with pembrolizumab**.

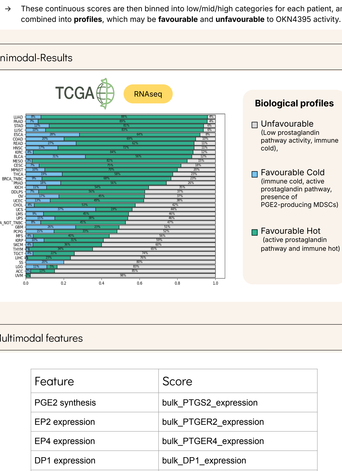
→ **Selecting patients** that maximize the drug-enabling context of OKN4395 is a key component of clinical development.

→ **Advanced multimodal biomedical data** and **AI** may help to identify the appropriate patient populations across cancer types.

Objectives



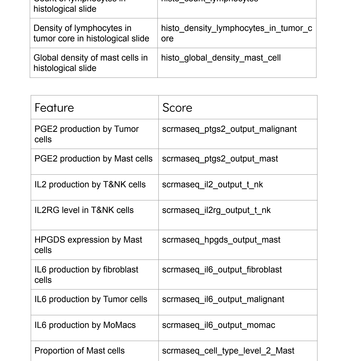
Unimodal context features



→ Using bulk RNAseq, we first derived **drug-enabling scores** based on literature, expert knowledge and wetlab data. These scores are used as proxy to infer the **prostaglandin pathway activity** (presence of receptor and ligand) and the **immune context** (NK/T cell infiltration, PGE2-producing MDSCs etc...)

→ These continuous scores are then binned into low/mid/high categories for each patient, and combined into **profiles**, which may be **favourable** and **unfavourable** to OKN4395 activity.

Unimodal-Results



Multimodal features

Feature	Score
PGE2 synthesis	bulk_PTGS2_expression
EP2 expression	bulk_PTGER2_expression
EP4 expression	bulk_PTGER4_expression
DP1 expression	bulk_DP1_expression
NK/T infiltration	bulk_nk_t_genes
PGE2-expressing MDSCs	bulk_mdsc_ptgs2
Anti-PD(L)1 response prediction	bulk_anti_PD(L)1_response
Proportion of Malignant spots colocalized with T_NK cells, producing PGE2 and PDL1	spatial_Malignant+/T_NK+/PTGS2+/CD274+
Proportion of Malignant spots colocalized with T_NK cells, producing PGE2 and IL6	spatial_Malignant+/T_NK+/PTGS2+/IL6+
Bearing a PIK3CA mutation	wes_pik3ca_mutated
Bearing a TP53 mutation	wes_tp53_mutated
Count of lymphocytes in histological slide	histo_count_lymphocytes
Density of lymphocytes in tumor core in histological slide	histo_density_lymphocytes_in_tumor_core
Global density of mast cells in histological slide	histo_global_density_mast_cell

Feature	Score
PGE2 production by Tumor cells	scrmaseq_ptgs2_output_malignant
PGE2 production by Mast cells	scrmaseq_ptgs2_output_mast
IL2 production by T&NK cells	scrmaseq_il2_output_t_nk
IL2RG level in T&NK cells	scrmaseq_il2rg_output_t_nk
HPGDS expression by Mast cells	scrmaseq_hpgds_output_mast
IL6 production by fibroblast cells	scrmaseq_il6_output_fibroblast
IL6 production by Tumor cells	scrmaseq_il6_output_malignant
IL6 production by MoMacs	scrmaseq_il6_output_momac
Proportion of Mast cells	scrmaseq_cell_type_level_2_Mast
Proportion of T&NK	scrmaseq_cell_type_level_2_T_NK

→ Normalized **multimodal features** derived from **bulk RNAseq**, interpretable features derived from **histology AI-models, spatialTx** and **scRNAseq**

Multimodal features

→ Beyond prostaglandin-related features in bulk, predicted responders are enriched in **IL6 expression**, but not in TP53 or PIK3CA mutations. Interestingly, some but not all are predicted responders to **anti-PD(L1)**, suggesting an independent drug action.

→ Histology AI models reveal a **continuous mast cells** presence in Favourable Cold, despite the lack of T and NK cells globally and in the tumor core.

→ This pattern is consistent with scRNAseq, which suggests **PTGS2/HPGDS expression by Mast** cells in predicted responders, and a specific **IL6 expression from fibroblast and MoMacs**.

→ SpatialTx reveals that a significant amount of **PTGS2+ Malignant&T_NK-containing spots are CD274-**, which suggests complementarity between OKN4395 and pembrolizumab

→ These features enrich our understanding of OKN4395 biology and will help **orient subsequent distillation** into clinically actionable biomarkers.

Conclusions

→ We developed a context-aware drug positioning pipeline using multimodal omics data

→ This work supports our Phase1b clinical trial in solid tumors NCT06789172

→ Similar data is being generated during the clinical trial, combining multimodal data and response readouts.