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A 30 PDX PANEL OF 3D IN VITRO TUMOR MODELS IDENTIFIES RESPONDERS TO PEMBROLIZUMAB AND SOLITOMAB

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Background Immunotherapies are emerging as a novel approach to combat cancer. Among them, checkpoint inhibitor treatment has found success in a subset of cancer patients by reversing T cell dysfunction and unleashing their cytolytic potential in the immunosuppressive tumor microenvironment (TME).¹ Nevertheless, many tumors which constitutively express these targets fail to respond to checkpoint inhibitors due to a range of issues – lack of T cell infiltrate, alternative dysfunction pathways, exhaustion and others.² Thus, there is a critical need to assay antitumor effects of novel immunotherapies or combinations across a range of target expression status and tumor indications. Here, we describe a 3D Tumor Panel of 30 patient-derived xenograft (PDX) in vitro models for rapid and scalable screening of immunotherapy. The models incorporate tumor cells, fibroblasts, and peripheral blood monocytes (PBMCs) in a hydrogel matrix to recreate the complex TME and are screened for antitumor effects using high content image analysis.

Methods Thirty PDX-derived tumor cell lines and human dermal fibroblasts (HDF) were grown in a hydrogel matrix³ in 96-well plates. The PDX histotypes included lung, renal, colon, gastric, breast, head and neck, liver, uterus, pancreatic, pleura-mesothelioma, sarcoma, melanoma, and ovary. PBMCs along with test compounds – Pembrolizumab (anti-PD-1) and Solitomab (EpCAM/CD3 bispecific antibody) – were later added to wells in a six-dose, serially diluted fashion. Response was detected at day four endpoint using high content image analysis of tumor size (Hoechst nuclear stain) and killing (DRAQ7 cell death and Caspase 3/7 apoptosis markers).

Results A subset of tumors responded to Pembrolizumab after four days of treatment, where the strongest responders resided in colon, lung and renal cancer. Interestingly, Solitomab responded in pancreatic tumors where Pembrolizumab failed to respond, however, oppositely, Solitomab did not respond in 75% of renal tumors on the Panel. In both compounds, anti-tumor effect was principally observed by tumor size and total tumor area reduction.

Conclusions A robust and diverse 3D PDX tumor panel comprising various solid tumor indications was developed in a hydrogel matrix platform. The PDX cells were grown along with fibroblasts and PBMCs to mimic the tumor, stromal and immune compartments of the TME. Endpoints including tumor size and killing highlighted PDX responders to both Pembrolizumab and Solitomab. These data highlight the ability to screen various immunotherapy compounds in a standardized 3D PDX in vitro panel for determining antitumor effect in drug discovery and translational research to enhance patient outcomes.

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