**Background** Immuno-oncology (IO) therapy with checkpoint inhibitors has demonstrated higher response rate, duration of response, and overall survival than chemotherapy. However, predicting which FDA approved IO therapies or pharmaceutical agents, as well as best combinations and delivery sequence, will have optimal patient response remains a significant challenge for personalized medicine. Nilogen Oncosystem’s 3D-PREDICT is a novel ex vivo therapeutic investigative platform that provides a functional model of a patient’s tumor to directly investigate susceptibility to different therapeutic approaches. Derived from core biopsies, the 3D-PREDICT model captures the tumor heterogeneity while preserving the tumor microenvironment by retaining stromal components, cell-cell and cell-extracellular matrix interactions. Here we employed the 3D-PREDICT platform to compare the efficacy of different therapeutic approaches, alone or in combination, targeting immune checkpoints in various solid tumor indications ex vivo.

**Methods** Tumoroids from 18-gauge core biopsies from a variety of solid tumors were generated using Nilogen Oncosystems’s proprietary mechanical process forgoing any enzymatic digestion or propagation whilst keeping the spatial contexture of stroma intact. Pooled tumoroids were treated ex vivo for 72 hours with various standard of care as mono or combo therapy (carboplatin, anti-programmed death-ligand 1 (PD-L1) antibody atezolizumab, anti-CD47 antibody magrolimab, anti-programmed cell death receptor-1 (PD-1) antibody nivolumab, or a combination of magrolimab and atezolizumab). Treatment-mediated immune modulation in tumor microenvironment were analyzed to predict patient response to subjected therapies.

**Results** Treatment-mediated tumor cell killing activity was evaluated using 3D high throughput confocal imaging and Nilogen Oncosystems’s proprietary algorithm for data analysis. The ex vivo response to checkpoint inhibitors were correlated with retrospective patient clinical information. Tumoroid samples treated with atezolizumab and magrolimab demonstrated enhanced tumor cell killing. Differential T-cell activation status was observed based on treatment and tumor type. Approximately 20% of tumors showed increased CD8 T-cell activation upon ex vivo treatment, correlating with proinflammatory cytokine release in conditioned media.

**Conclusions** The 3D-PREDICT ex vivo tumoroid platform provides a unique resource to predict patients’ response to treatment, potentially serving as a clinical diagnostic to guide clinical care and stratifying patient procurement into clinical trials. This would allow prospective assessment of therapeutic efficacy ex vivo to match each patient to the most effective and least toxic thereby, to improve outcomes, reduce costs, and assign therapeutics on a more rational basis.

**Ethics Approval** This study was approved by Vanderbilt University Ethics Board; approval number 031078 and Ohio State University Ethics Board: 2014J0130.

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