

## Poster 20 Ex vivo 3D micro-tumor testing platform to guide patient stratification for clinical development of ADCs

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### Background

Most newly developed oncology drugs fail before entering the clinic, primarily due to lack of efficacy that was not identified by poorly translational pre-clinical models. Ex vivo 3D micro-tumor testing offers near clinical efficacy evaluation of multiple drug classes, including antibody-drug conjugates (ADCs), bi-specifics and cell therapies and is clinically predictive for platinum-based therapy. This study aims to evaluate ex vivo sensitivity to the ADC mirvetuximab soravtansine (MIRV) for ovarian cancer patients in relation to the patients' ex vivo platinum sensitivity. Pre-clinical evaluation of patient sensitivity to next-generation biotherapeutics can guide clinical development and patient selection of promising treatment options in ovarian cancer with a high unmet need.

### Materials and Methods

Feasibility of ex vivo evaluation of patient specific responses to ADCs was established by testing MIRV in 25 samples from ovarian cancer patients (24x ascites, 1x pleural fluid) (TUMOVCA trial IRB P18.032). Tumor tissue was processed within 48 hours. Enriched tumor clusters with native tumor microenvironment (TME) were embedded in a protein-rich hydrogel and exposed to MIRV and standard of care chemotherapy. Screening plates were fixed, stained and imaged and phenotypical features were extracted after image analysis. Drug responses were correlated based on AUC of fitted dose-response curves. Target protein expression profiling was performed by immunofluorescence staining of untreated micro-tumors and quantification of 1) mean intensity per micro-tumor, 2) % of micro-tumors positive for the target protein and 3) mean intensity of positive micro-tumors.

### Results

Patient specific ex vivo ADC efficacy for MIRV was observed: 32% (8/25) of the patients demonstrated strong sensitivity ( $E_{max} < 50\%$ ), 48% (12/25) of the patients demonstrated intermediate sensitivity ( $E_{max} 50-90\%$ ) and 20% of the patients (5/25) demonstrated complete MIRV resistance ( $E_{max} > 90\%$ ). A strong correlation was observed between MIRV and paclitaxel sensitivity ( $R = 0.86$ ), that both target tubulin. A reduced correlation was observed for MIRV and carboplatin ( $R = 0.59$ ), that acts by crosslinking DNA. Target protein expression profiling revealed inter and intra-tumor heterogeneity. Some patients demonstrate low target protein expression in all micro-tumors, while others demonstrate high expression in a small percentage of micro-tumors.

## **Conclusions**

While MIRV is introduced into the clinical practice for platinum-resistant ovarian cancer this study shows ex vivo efficacy in newly diagnosed patients. Ex vivo 3D micro-tumor testing is a tool to facilitate near clinical evaluation of patients' response to novel compounds and benchmarking against standard of care treatment options. Highly quality controlled evaluation of target expression in relation to the anti-tumor effects of ADCs in fresh heterogeneous patient samples could further increase the success rate of the drugs in clinical trials.