Integration of patient-derived tumor organoids and patient clinical multimodal data to investigate the role of organoids in predicting treatment response

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INTRODUCTION

Patient-derived organoids (PDOs) enable the *ex vivo* study of intertumoral heterogeneity and its effect on response to treatment. Our previous work demonstrated that our robust pan-cancer organoid platform shows genetic and transcriptomic concordance with clinical tumor samples and can be deployed for high-throughput drug response screening (Larsen et al., 2021, Cell Reports). Here, we ran a standard of care (SOC) panel on PDOs with paired de-identified clinical response data to enable a comparison of patient response to the same drugs, and *ex vivo* exploration of potentially more effective treatment alternatives.

METHODS

Patient tumor tissue samples were cultured into tumor organoids in extracellular matrix + chemically defined media. PDOs were identified as Hoechst-positive cell clusters and the number of live and dead cells for each PDO was individually determined using fluorescent viability stains. Drug screens were run with 3 doses per compound and the inverse area under the curve of TO-PRO-3 live cell measurements was calculated to quantify response. Tempus xT and whole transcriptome assays were used to perform NGS on organoids and paired patient tumors (where available). The resulting data was processed through our standard pipeline to identify targetable mutations, neoantigens, CNVs and fusions.

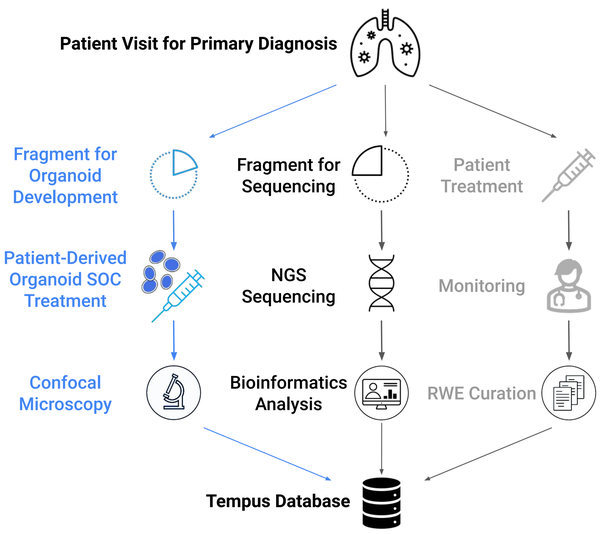

Figure 1. The data used throughout this study were generated through three parallel paths: (left) Generation of a patient derived organoid from a tumor fragment, sequenced, and treated with a panel of standard of care drugs; (middle) Sequencing of the biopsy taken directly from the patient; and (right) curated patient records up to the time of the biopsy

SUMMARY

- Across the full PDO cohort with multiple tumor types, we observed a range of responses to SOC therapies, providing a platform to better understand biomarkers and mechanisms of response.
- For the majority of patients with progressive disease recorded after treatment, the corresponding organoids showed limited response to the same treatment. However, all three patients with progression-free survival of over a year and complete/stable clinical response had corresponding organoids highly sensitive to the same SOC drugs.
- These results suggest that PDOs may serve as a powerful tool for predicting patient response to treatment and aiding the development of new therapies.

RESULTS

PDO Response to Standard of Care Therapies

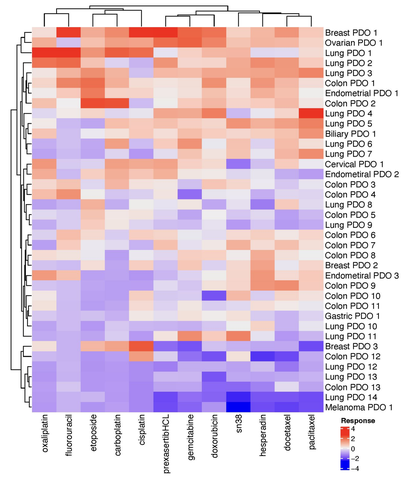

Figure 2. TO-PRO-3 live cell inverse area under the curve measurements for 38 organoids with paired patient data. The heatmap represents a diverse group of indications and responses to standard of care therapies. The SoC therapies cluster by shared mechanism of action, indicating that PDOs will show similar responses to related treatment types

Comparison of Standard of Care Panel Results to Patient Treatment Response

Treatment	rwPFS (days)	OR
Carboplatin + Paclitaxel	419	CR
Cisplatin + gemcitabine	957	SD
Fluorouracil + Leucovorin + oxaliplatin	1316	CR
Fluorouracil + Leucovorin + oxaliplatin + panitumumab	400	PR
Carboplatin + Paclitaxel	130	PR
Cyclophosphamide + docetaxel	83	*NA*
Carboplatin + Paclitaxel	130	PD
Fluorouracil + Leucovorin + oxaliplatin	686	PD
Fluorouracil + Leucovorin + oxaliplatin	77	PR
Cyclophosphamide + Doxorubicin + Paclitaxel	185	*NA*
Carboplatin + pemetrexed + Radiotherapy	794	*NA*
Fluorouracil + Leucovorin + oxaliplatin	249	PD
Antineoplastic Agents	674	*NA*
Carboplatin + Fluorouracil	1248	*NA*
Antineoplastic Agents + Radiotherapy	700	*NA*
Paclitaxel	83	*NA*
Carboplatin + pemetrexed	101	PD

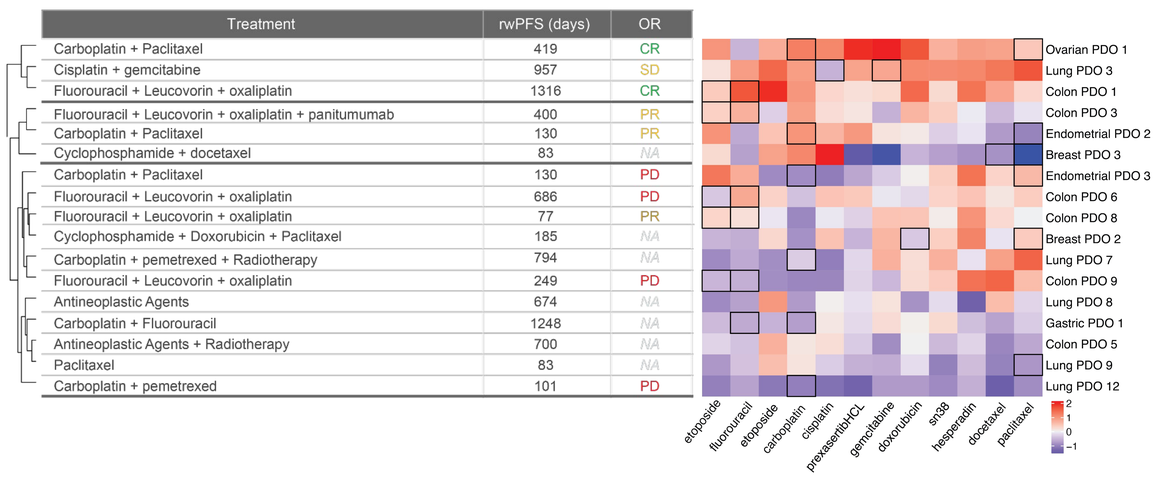

Figure 3. Paired patient response to SOC following biopsy extraction (left) and the inverse area under the curve TO-PRO-3 live cell response to corresponding treatment of organoids (right). In the three patients with progression-free survival of over a year and outcomes of either complete response or stable disease, strong responses to the corresponding drugs in the SOC panel were observed in the PDO. For the majority of patients with progressive disease recorded after treatment, the corresponding organoids cluster showed limited response to treatment.

PDO Response to Targeted Therapies

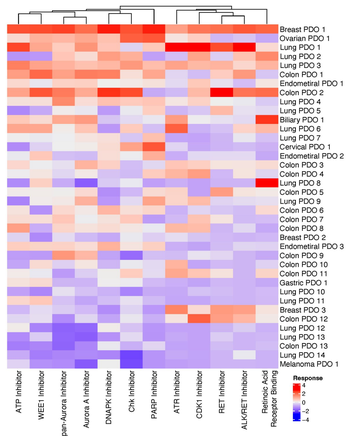

Figure 4. The SOC panel includes several targeted therapies, enabling assessment of patient treatment responses beyond chemotherapy. Presented in the same sample order as Figure 2, the heatmap highlights multiple PDOs that have improved response to targeted therapies compared to chemotherapy.

Organoid and Patient Response to ER-Targeted Therapy

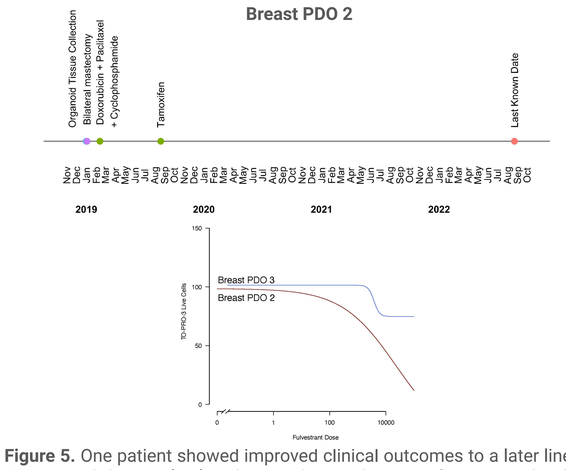

Figure 5. One patient showed improved clinical outcomes to a later line of ER-targeted therapy (top) with a similar mechanism of action to the drug that showed response in the organoid (bottom). The dose response curve shows the superior anti-tumor activity of fulvestrant in Breast PDO 2 compared to another ER+ PDO.

Response to KRAS Inhibitors in Lung Cancer Patients

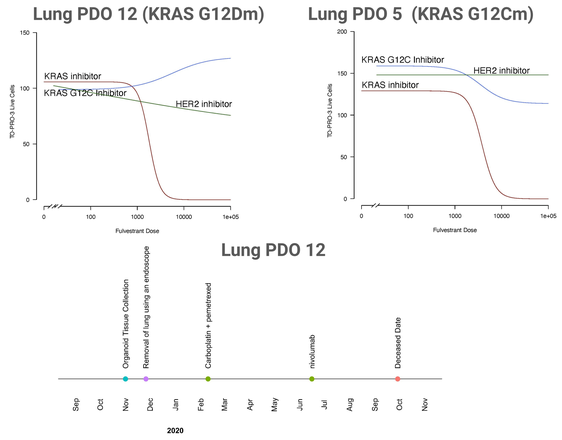

Figure 6. Two PDOs with KRAS hotspot mutations, were screened with pan-KRAS and KRAS mutant specific inhibitors: KRAS G12D (top left) and KRAS G12C (top right). Notably, one patient with matching treatment history (bottom) had disease progression on other classes of therapies, suggesting potential benefit from KRAS-targeted therapy.

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