2022 ASCO® ANNUAL MEETING

nature medicine

Distinct biosignatures associate with survival after chemoimmunotherapy in a randomized, three-arm phase II study in patients with metastatic pancreatic cancer

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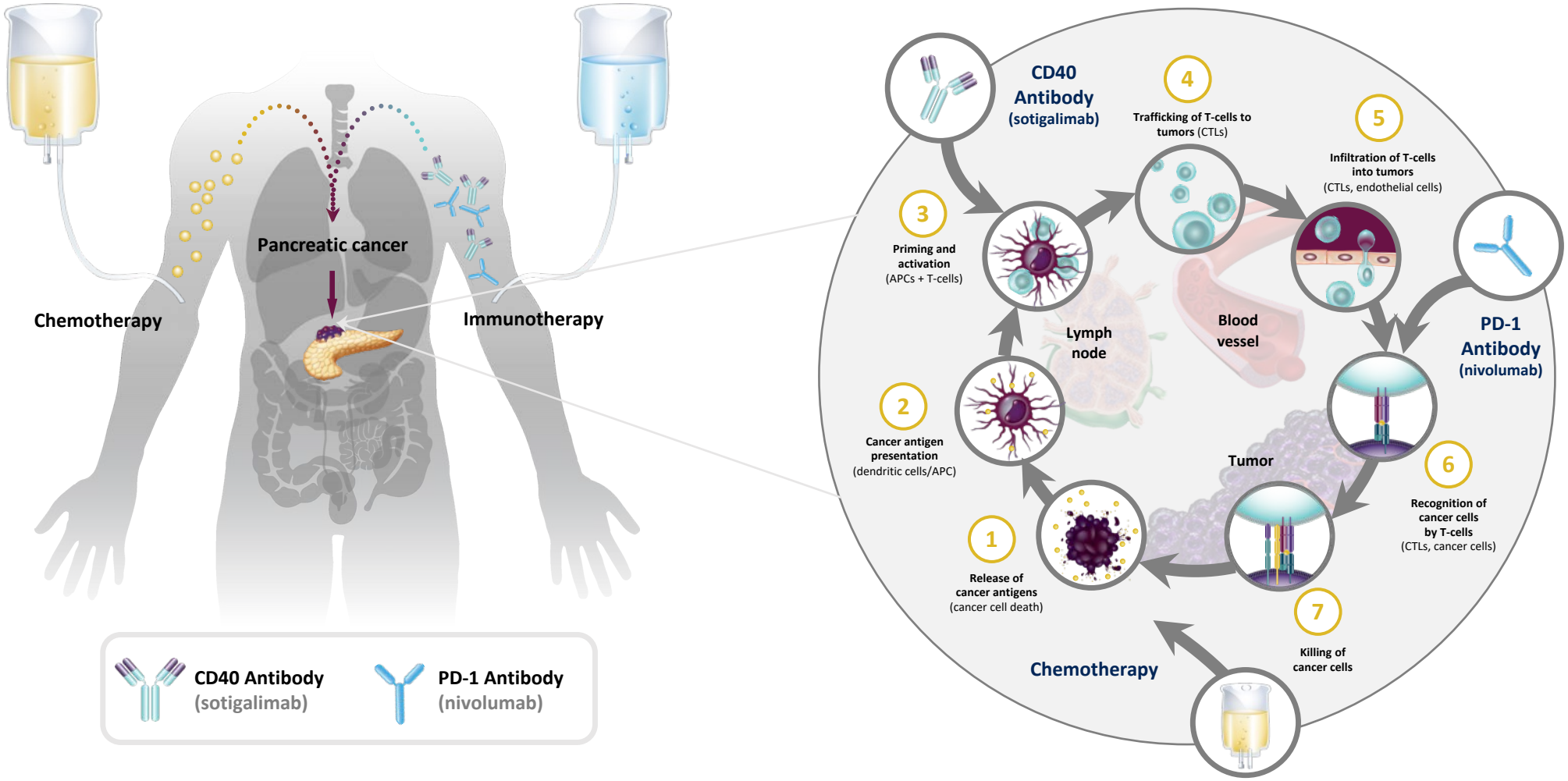
PRINCE clinical trial of chemoimmunotherapy combinations in mPDAC

Gemcitabine + nab-Paclitaxel +/- CD40 agonist (sotigalimab) +/- PD-1 blockade (nivolumab)



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PRINCE trial design

1L Metastatic PDAC *N=105*

Ph2 Randomization

- **nivo/chemo (*n=34*): gem/nab-P* + nivolumab 240 mg q2w**
- **sotiga/chemo (*n=30 + n=6 ph1b*): gem/nab-P* + sotigalimab 0.3 mg/kg q4w (D3 of each cycle)**
- **sotiga/nivo/chemo (*n=29 + n=6 ph1b*): gem/nab-P* + sotigalimab 0.3 mg/kg q4w (D3) + nivolumab 240 mg q2w**

Follow up for Progression and Survival

* gem/nab-P dosing and administration per SOC

Baseline and on-treatment tumor biopsies, stool collection and peripheral blood collection (including at PD)

Key Eligibility Criteria

- 1L metastatic (recurrent or de novo) pancreatic ductal adenocarcinoma (mPDAC)
- ECOG 0-1
- Mandatory baseline tumor tissue collection
- No active CNS metastases

Primary Endpoint

- 1-year OS compared to historical control (35%, Von Hoff 2013)

Key Secondary Endpoints

- Objective Response Rate (RECIST 1.1)
- Duration of Response
- Progression Free Survival
- Safety

Biomarker analyses

- Multi-omic, multiparameter analysis of tissue, blood and stool

Participating Institutions

- PENN
- MSK
- MDACC
- UCSF
- UCLA
- Stanford
- DFCI

Phase 1b: O'Hara et. al, *Lancet Oncology,* 2021

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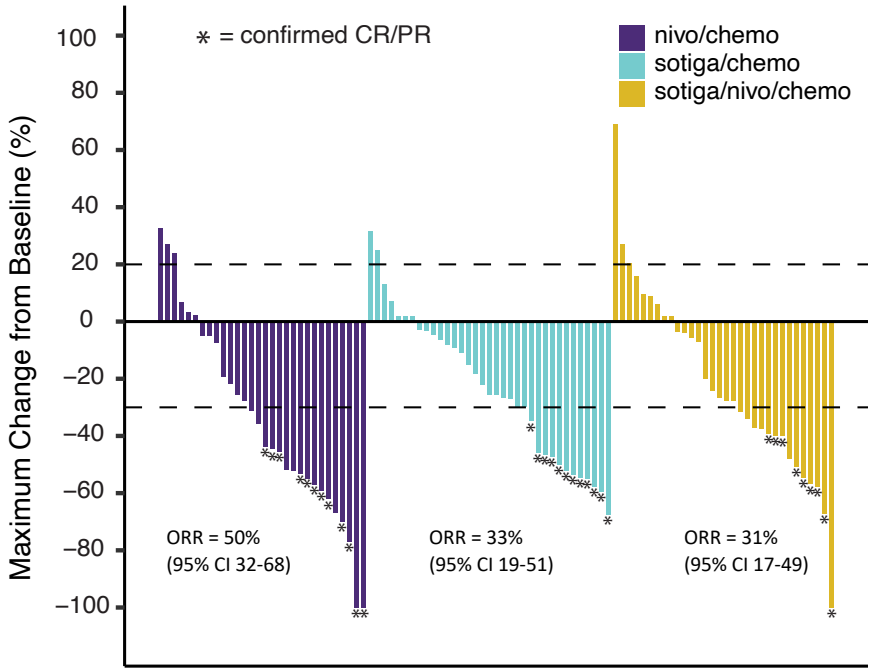
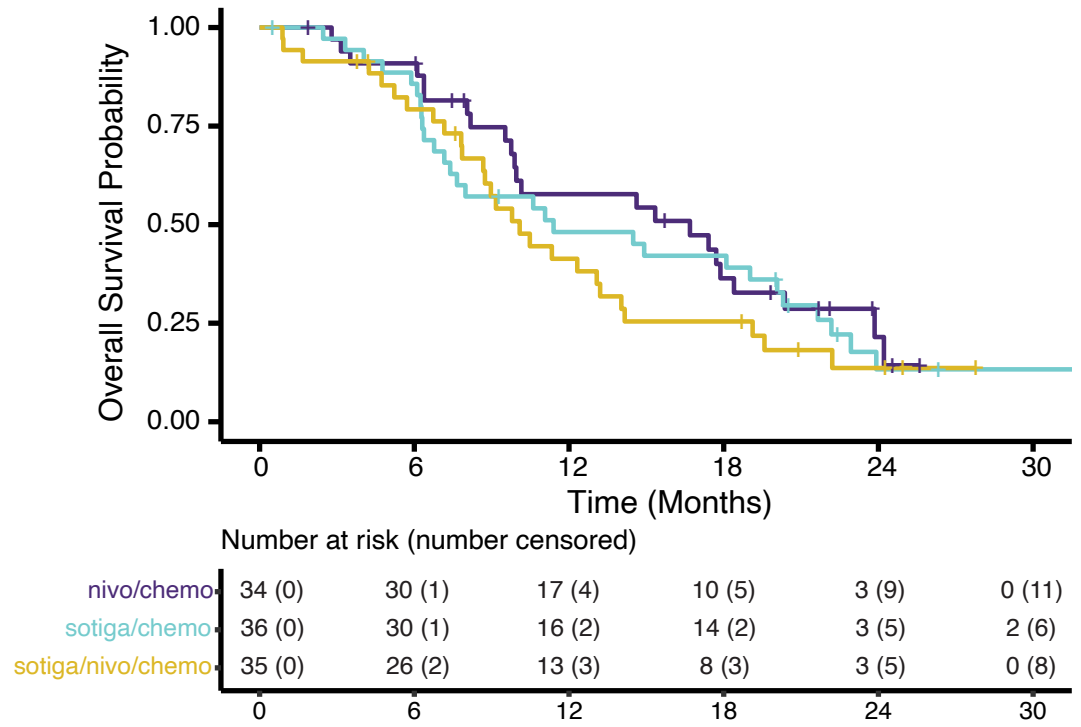
Clinical results

Percent Change in Sum of Target Lesions



- No updates to clinical data presented at ASCO 2021
- Baseline characteristics were generally balanced across arms
- Treatment regimens were tolerable with manageable safety profiles
- 1-Year OS rates were compared to 35% historical control (Von Hoff, 2013)

Overall Survival



	N	1-yr OS rate (95% lower CI)	P-value vs. 35% control	Median OS (95% CI)
nivo/chemo	34	57.7% (41.7%)	0.006	16.7 months (9.8 – 18.4)
sotiga/chemo	36	48.1% (33.7%)	0.062	11.4 months (7.2 – 20.1)
sotiga/nivo/chemo	35	41.3% (27.0%)	0.233	10.1 months (7.9 – 13.2)

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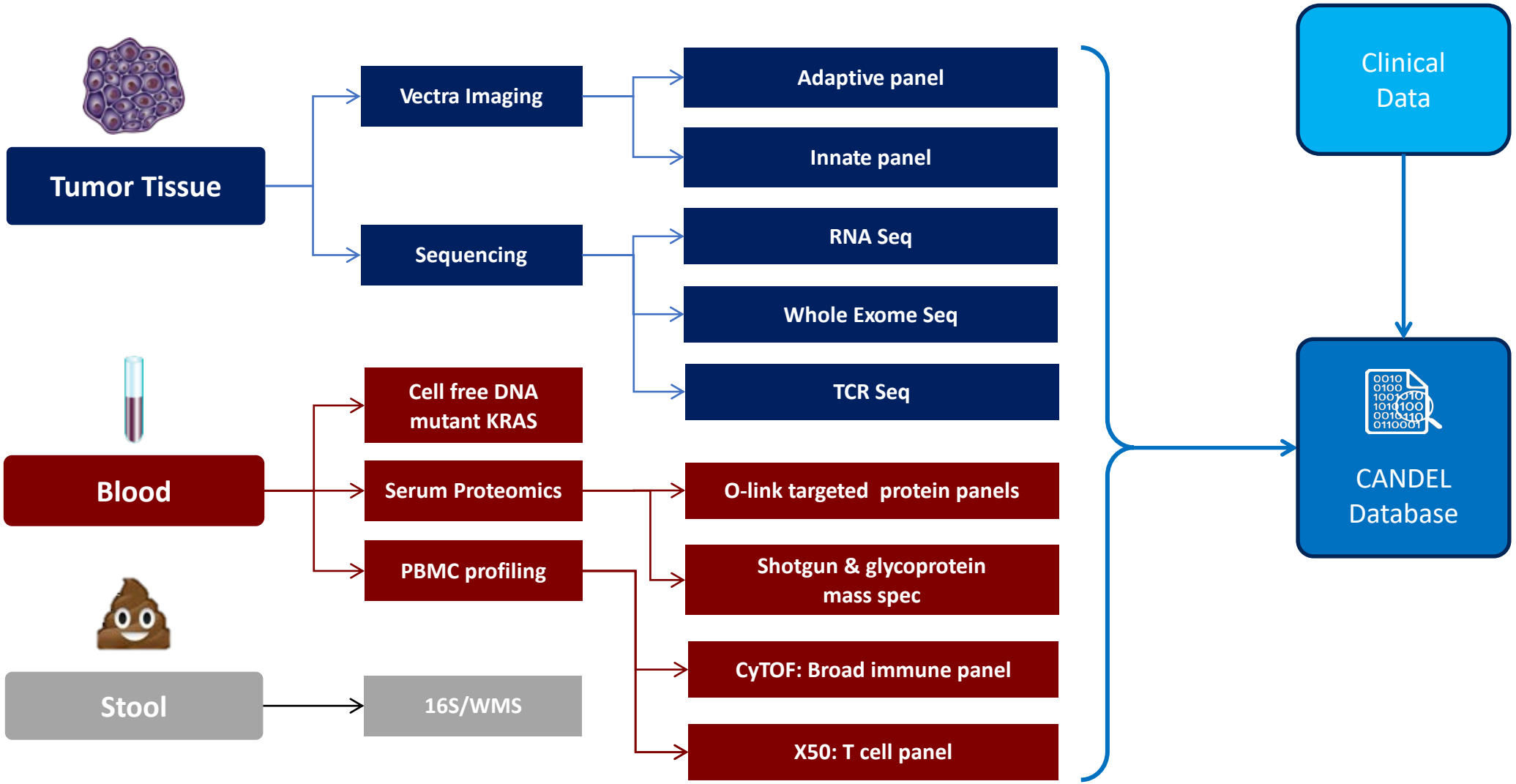
PRINCE translational profiling



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CANDEL: Our software platform for multi-omic data analysis

Molecular data

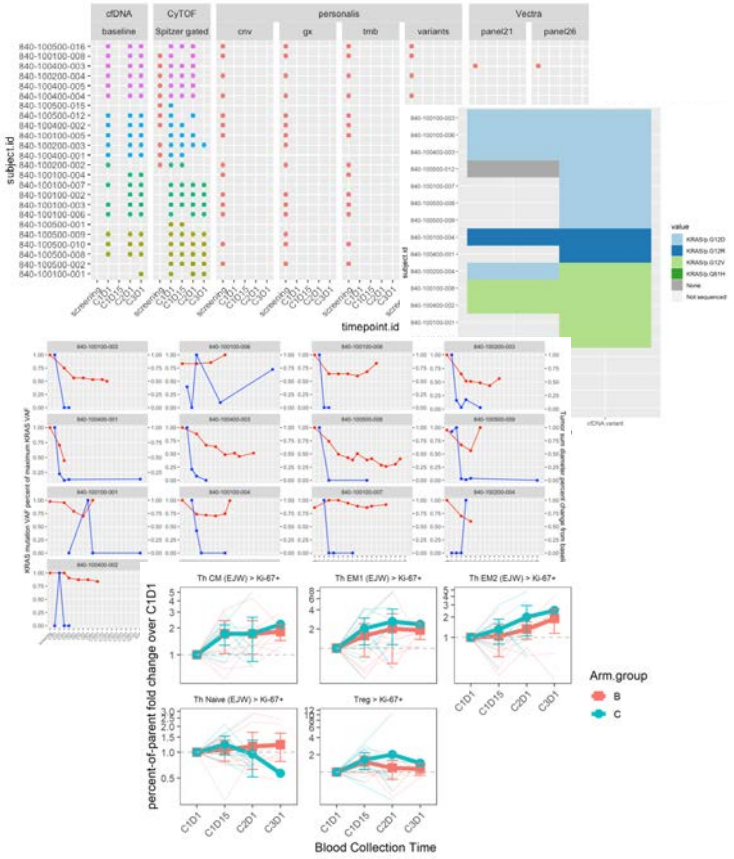
- Tumor sequencing
- Gene expression
- Immune profiling
- High-dimensional imaging
- Cell Free DNA

Clinical data

- Treatment information
- Efficacy data
- Safety data
- Lab values

CANDEL

Informatics and Translational Teams



- Biomarkers of response
- Machine learning to predict outcomes
- Insights into resistance

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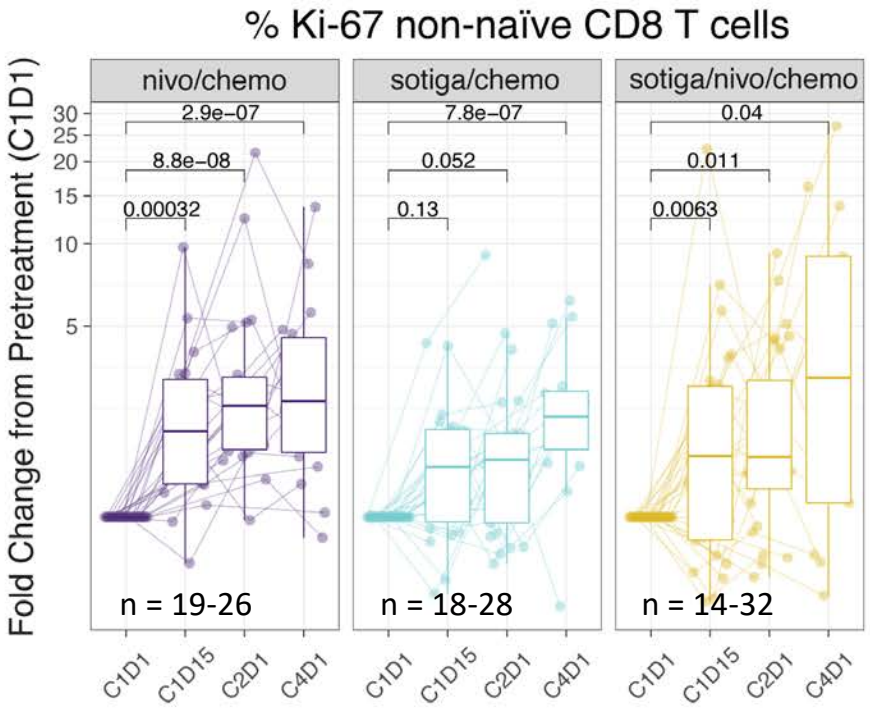
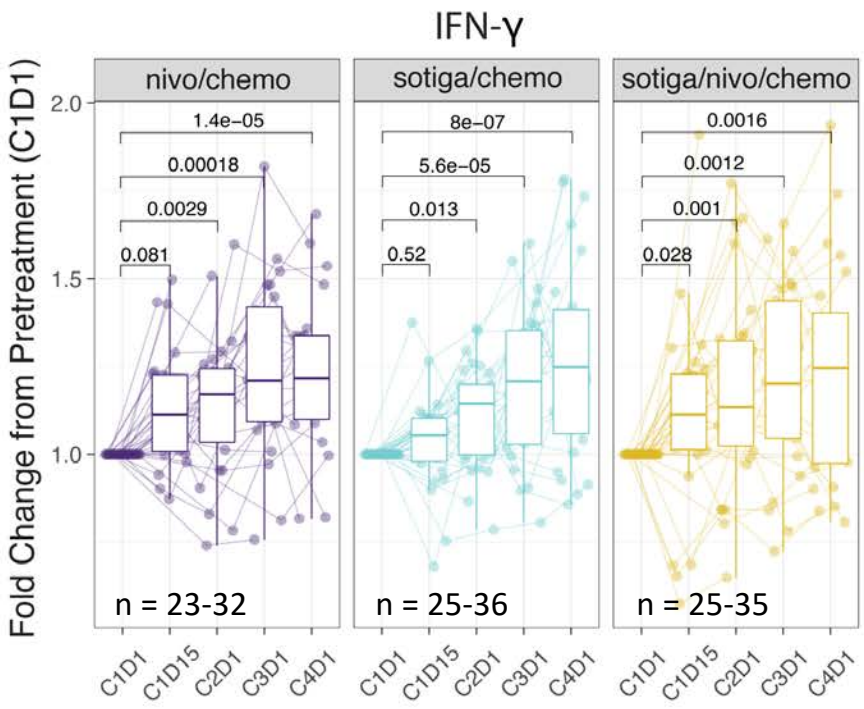
Pharmacodynamic effects of immunotherapies

Blood

Increases in activated and proliferating T cells



Increases in soluble proteins indicating immune activation



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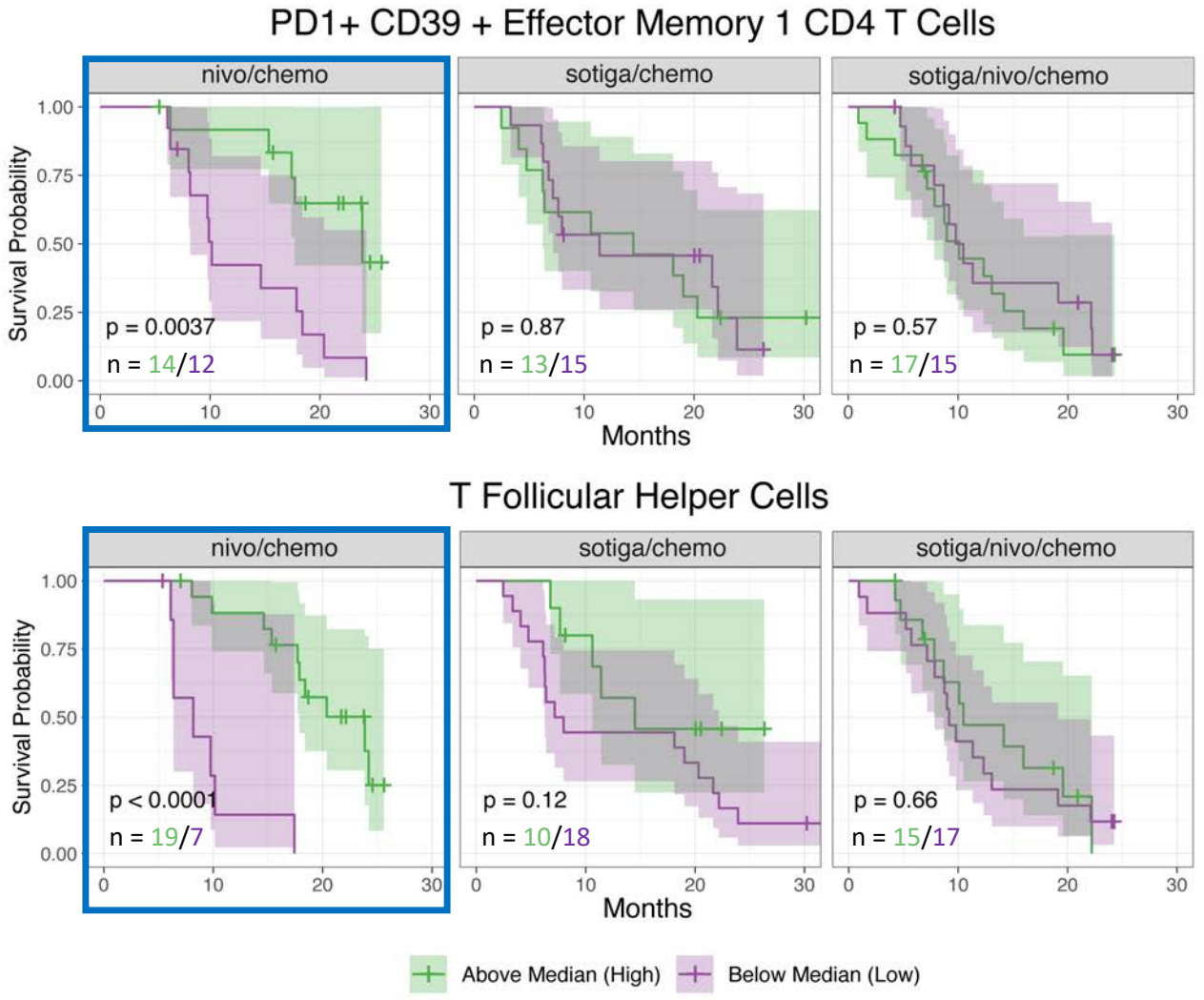
Circulating biomarkers of survival following nivo/chemo

Blood

- Baseline levels of T cell populations in circulation predict survival following nivo/chemo
- Many predictive T cell populations show an activated, antigen-experienced phenotype
- Biomarkers predict survival after controlling for clinical covariates



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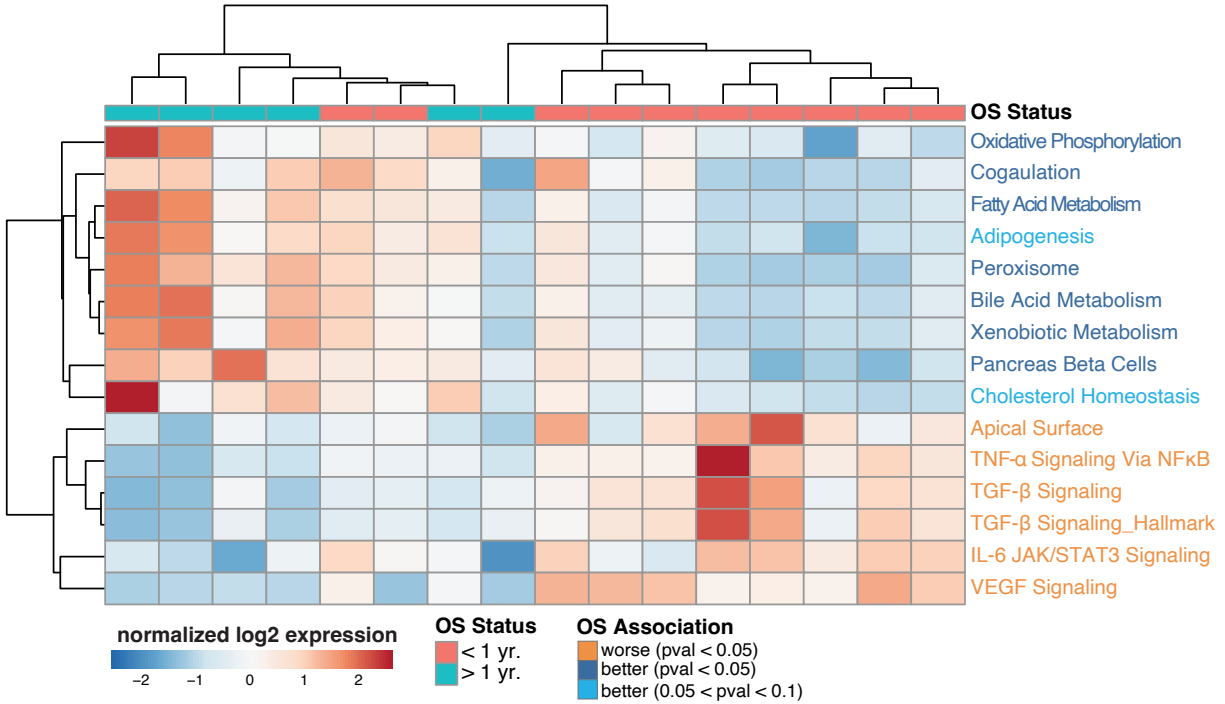
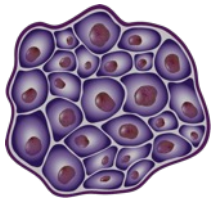
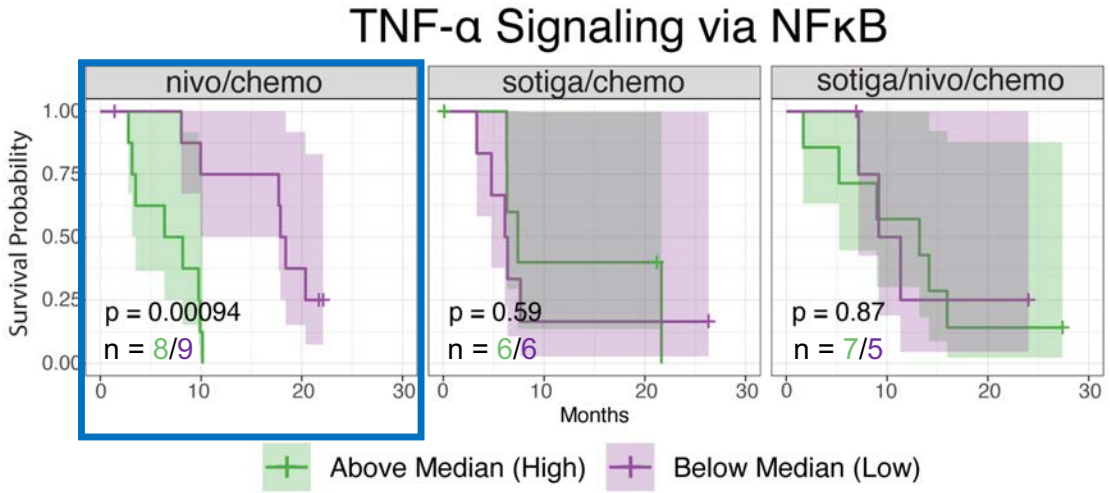
Tumor biomarkers of survival following nivo/chemo

- Several baseline tumoral gene expression signatures correlate with survival following nivo/chemo
- Signatures reflect biology of a tumor low in immune suppression and in a favorable oxidative lipogenic metabolic state







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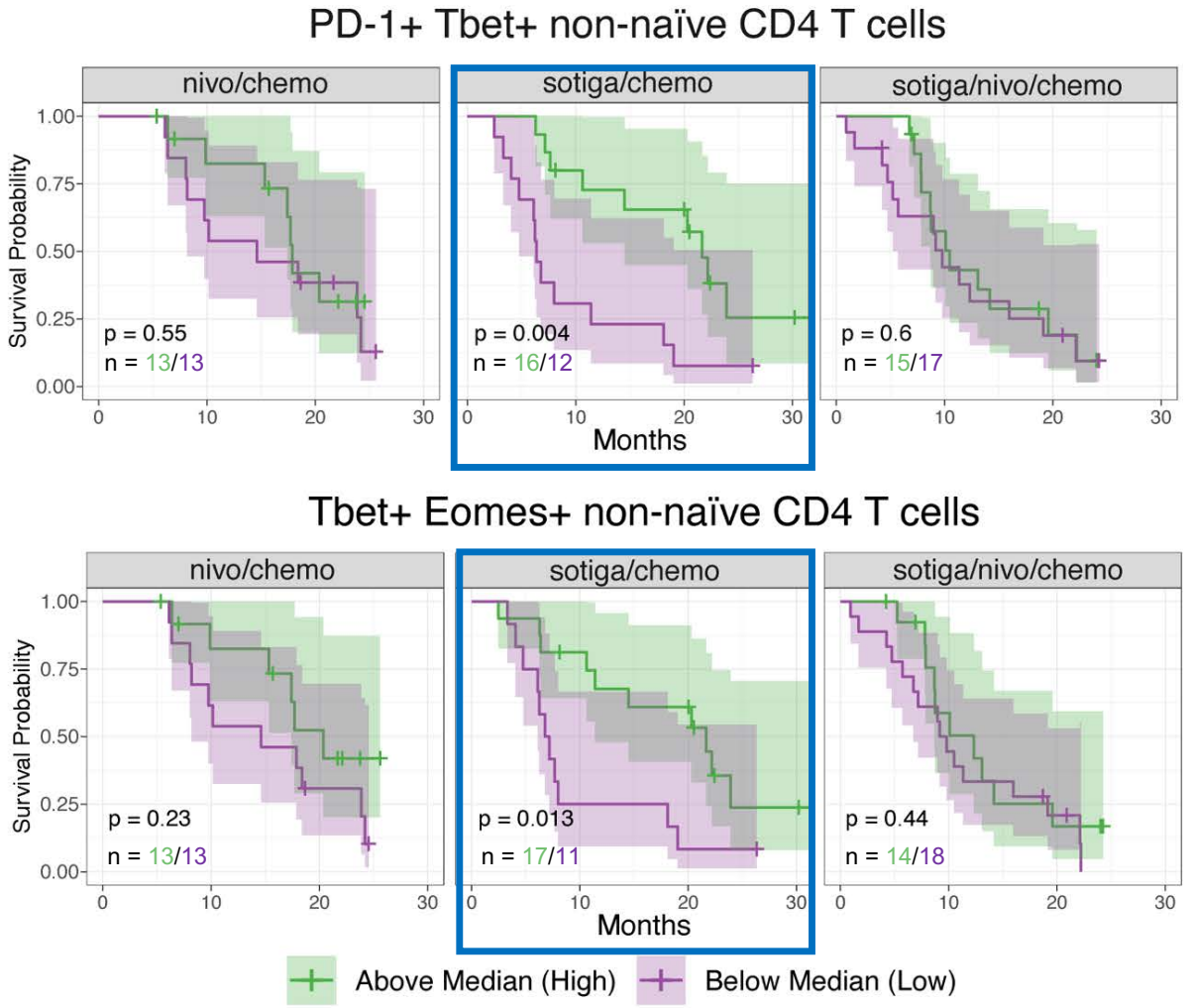
Circulating biomarkers of survival following sotiga/chemo

Blood

- Pretreatment levels of CD4 T cell, B cell, and dendritic cell subsets predict survival benefit
- Predictive cell populations reflect the mechanism of action of agonistic CD40 therapy
- Biomarkers predict survival after controlling for clinical covariates



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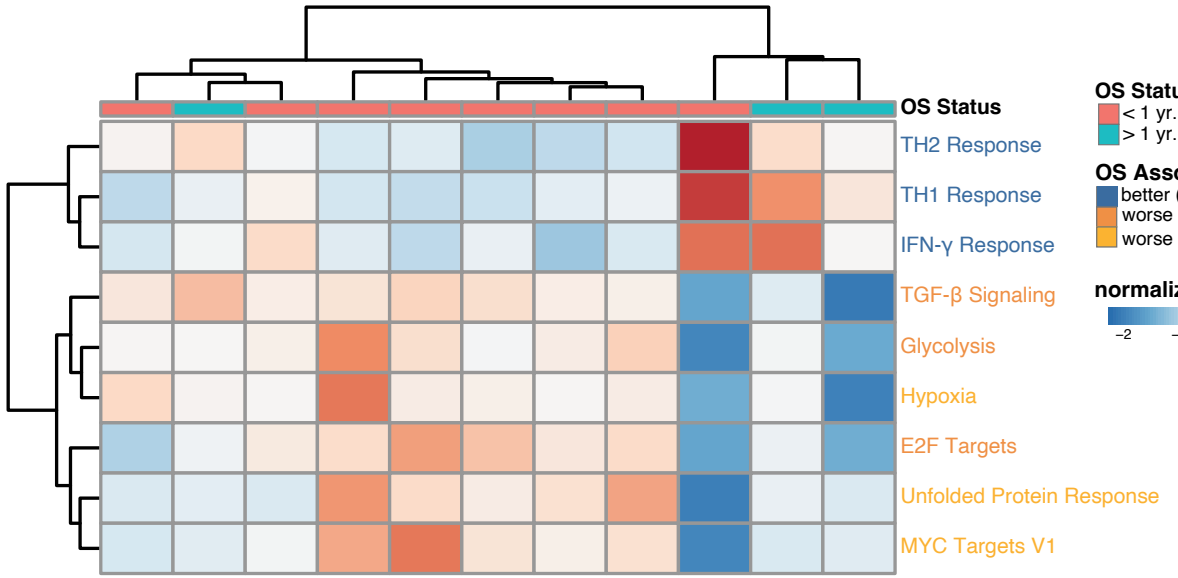
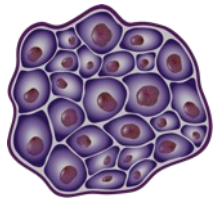
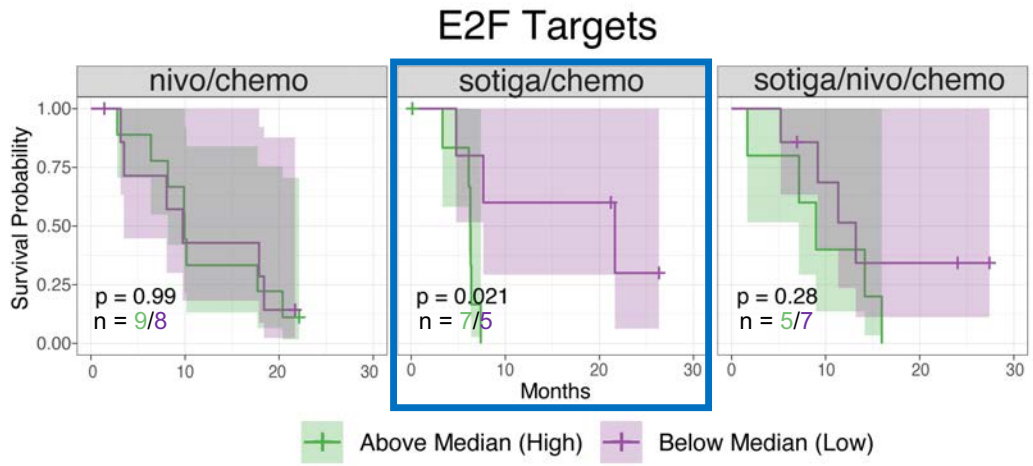
Tumoral biomarkers of survival following sotiga/chemo

- Pretreatment tumoral gene expression signatures and immune cell populations correlate with survival benefit
- Longer surviving patients have tumors higher in non-proliferating helper CD4 T cell infiltration and lower in E2F and Myc signaling







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Biomarkers of survival following sotiga/nivo/chemo

- Few factors in the tumor or circulation predicted survival benefit
- Relevant biomarkers from other arms were not predictive of survival benefit
- Hyperactivation may be leading to a dysfunctional immune state

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Conclusions

- **Immuno-pharmacodynamic effects were observed in each arm**
- **Novel circulating and tumoral biomarkers predict overall survival following treatment with nivo/chemo or sotiga/chemo**
- **Prospective studies are warranted to test the validity of blood-based predictive biomarkers of response to nivo/chemo or sotiga/chemo**
- **Proof of principle for engagement of the PICI network to conduct multi-cohort, multi-center bench-to-bedside translational and informatic studies**
- **Established a framework for REVOLUTION platform in 1L mPDAC (NCT04787991)**

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Acknowledgments

Patients & their families

Sean Parker

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PICI Central: Sultan Nawabi, Justin Fairchild, Jingying Xu, Joyson Karakunnel, Lisa Butterfield, Ramy Ibrahim, Ute Dugan, Christine Spencer, Mike Travers, Robin Kageyama, Diane Da Silva

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