A Phase 1b Study of CD40 Agonistic Monoclonal Antibody APX005M Together with Gemcitabine and nab-Paclitaxel with or without Nivolumab in Untreated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) Patients

PICI0002 (PRINCE)

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Disclosure Information
2019 AACR Annual Meeting

I have the following financial relationships to disclose:

Research support: BMS, Lilly, AstraZeneca, Celldex, KaryoPharm
Consultant: KaryoPharm, Exelixis

I will discuss the following investigational drugs in my presentation:

- APX005M
- Nivolumab

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Trial sponsored and conducted by
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In collaboration with
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Background

- 1L treatment for metastatic PDAC is composed of combination chemotherapy with modest results

Regimen	N	Response Rate	Disease Control Rate	Median PFS	Median OS
FOLFIRINOX[1]	171	32% (24.7 – 39.1)	70%	6.4 mos	11.1 mos
Gemcitabine/nab-paclitaxel[2]	431	23% (19 – 27)	48%	5.5 mos	8.5 mos

- PDAC is poorly immunogenic; limited responses to checkpoint inhibition[3,4]

- Phase I study of gemcitabine, nab-paclitaxel, and nivolumab demonstrated modest results[5]

Regimen	N	Response Rate	Disease Control Rate	Median PFS	Median OS
Gemcitabine/nab-paclitaxel/nivolumab[5]	50	18%	64%	5.5 mos	9.9 mos

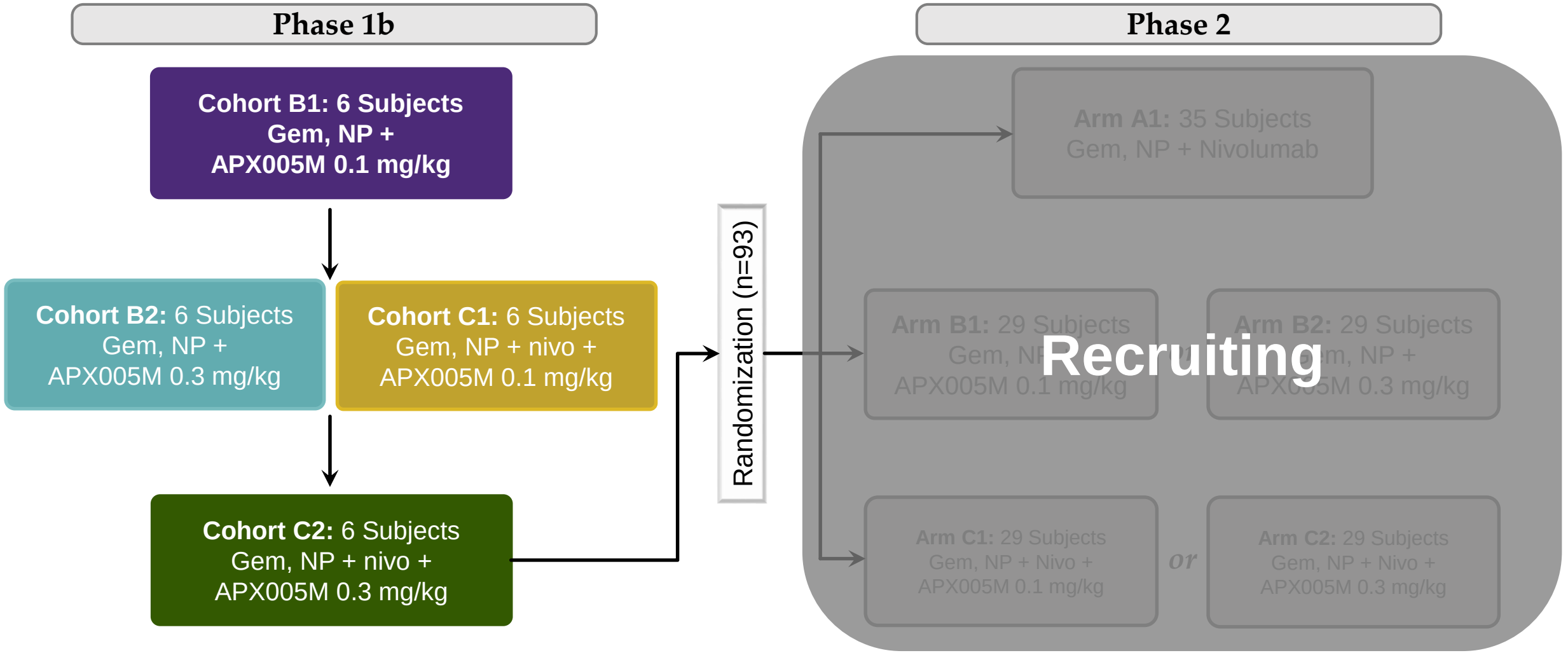
[1]Conroy T et al, 2011; [2]Von Hoff DD et al, 2013; [3]Royal RE et al, 2010; [4]Brahmer JR et al, 2012; [5]Wainberg ZA et al, 2019

Rationale for Combining Chemo/CD40/PD-1

- Chemotherapy releases tumor antigens, which are then presented on antigen presenting cells, including dendritic cells
- Engagement of CD40 primes and activates antigen presenting cells
- In preclinical pancreatic cancer models
  - Gemcitabine, nab-paclitaxel (NP) and agonist CD40 mAb synergize to drive tumor destruction in a T-cell dependent manner[1]
  - Addition of PD-1 mAb to chemo/CD40 further improves survival[2]
- Here, we present the preliminary results of a clinical trial in metastatic PDAC of CD40 agonist, APX005M, with Gem/NP ± nivolumab
  - APX005M is a humanized agonistic IgG1k monoclonal antibody against CD40 with a demonstrated safety profile as a single agent[3]

[1] Byrne and Vonderheide, 2016; [2] Winograd R et al, 2015; [3] Vonderheide RH et al, 2017

Study Design



ClinicalTrials.gov Identifier: NCT03214250

Phase 1b Objectives

Primary

- To determine the feasibility, safety and dose-limiting toxicities (DLT) of each treatment cohort
- To determine the recommended Phase 2 dose (RP2D) of APX005M when combined with NP/Gem
- To determine the RP2D of APX005M when combined with nivolumab/NP/Gem

Secondary

- To determine objective response rate (ORR) and duration of response of each treatment cohort

Exploratory

- To assess the pharmacokinetics (PK) of APX005M in Cycles 1 to 4
- To assess immune pharmacodynamic effects of each treatment cohort, in both blood and tumor tissue

Key Inclusion and Exclusion Criteria

Inclusion

- Metastatic pancreatic adenocarcinoma
- Measurable disease per RECIST 1.1
- Age ≥ 18
- ECOG status 0 or 1
- Baseline tissue mandatory
- Adequate hematologic, hepatic and renal function

Exclusion

- Previous systemic therapy in the metastatic setting
- Symptomatic CNS metastases
- Concurrent active invasive malignancy
- History of autoimmune disorders
- Concomitant use of immunosuppressive agent within 14 days of first dose

Enrollment Timelines and Minimum Follow-Up

Cohort B1: Gem/NP/APX005M 0.1 mg/kg

Enrollment
08/2017 – 11/2017

Minimum Follow-Up **15 Months**

Cohort B2: Gem/NP/APX005M 0.3 mg/kg
Cohort C1: Gem/NP/APX005M 0.1 mg/kg + nivo

Concurrent Enrollment
01/2018 – 03/2018

Minimum Follow-Up **11 Months**

Cohort C2: Gem/NP/APX005M 0.3 mg/kg + nivo

Enrollment
04/2018 – 07/2018

Minimum Follow-Up **7 Months**

Baseline Subject Characteristics

Safety-evaluable population (N=30): received ≥ 1 dose of any study drug

	Cohort B1 Gem/NP/ APX005M 0.1 mg/kg (N=7)	Cohort B2 Gem/NP/ APX005M 0.3 mg/kg (N=7)	Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=8)	Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=8)	Total (N=30)
Age (yr)					
Median	66	64	69	61	66
Min-Max	52-73	54-76	61-79	39-71	39-79
Sex					
Female	5 (71.4%)	2 (28.6%)	3 (37.5%)	4 (50.0%)	14 (46.7%)
Male	2 (28.6%)	5 (71.4%)	5 (62.5%)	4 (50.0%)	16 (53.3%)
Race					
Asian	0	0	1 (12.5%)	1 (12.5%)	2 (6.7%)
Black/African American	0	1 (14.3%)	0	1 (12.5%)	2 (6.7%)
White	7 (100%)	6 (85.7%)	7 (87.5%)	6 (75.0%)	26 (86.7%)
ECOG Performance Score					
0	3 (42.9%)	1 (14.3%)	5 (62.5%)	4 (50.0%)	13 (43.3%)
1	4 (57.1%)	6 (85.7%)	3 (37.5%)	4 (50.0%)	17 (56.7%)

Time on Treatment

	Cohort B1 Gem/NP/ APX005M 0.1 mg/kg (N=7)	Cohort B2 Gem/NP/ APX005M 0.3 mg/kg (N=7)	Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=8)	Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=8)	Total (N=30)
Time on Treatment					
Median (Weeks)	30.3	39.1	19.6	NR	30.3
Min-Max (Weeks)	2.1 – 59.1+	0.4 – 50.3+	0.4 – 45.1	0.4 – 38.1+	0.4 – 59.1+
Current # subjects on treatment	1 (14%)	2 (29%)	0	5 (63%)	8 (27%)
Median # Gem Doses	22	22	9	14.5	15
Median # NP Doses	19	19	12.5	14.5	16

NR = Not Reached
+ = subject still on treatment/study

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Patient Populations

Safety-evaluable population (N=30)

- Received ≥ 1 dose of any study drug

DLT-evaluable population (N=24)

- Enrolled in Phase 1b
- Received at least 2 doses of Gem/NP and 1 dose of APX005M during Cycle 1
- Completed the DLT observation period (Cycle 1) or experienced a DLT event

Dose-Limiting Toxicities and Deaths

- 2 DLTs were observed, unrelated to APX005M or nivolumab

Cohort	Treatment	Severity	Event	SAE?	Recovered?
B2	Gem/NP/APX005M 0.3 mg/kg	Grade 3	Febrile neutropenia	Yes	Yes
C1	Gem/NP/APX005M 0.1 mg/kg + nivo	Grade 4	Febrile neutropenia	No	Yes

- 1 treatment-related death
  - Grade 4 sepsis, starting day 220
  - Cohort B1 (Gem/NP/APX005M 0.1 mg/kg)
  - Unrelated to APX005M or nivolumab

Grade 3/4 Treatment-Related AEs

Occurring in ≥ 20% of N=30 Subjects

MedDRA Preferred Term	Cohort B1 Gem/NP/ APX005M 0.1 mg/kg (N=7)	Cohort B2 Gem/NP/ APX005M 0.3 mg/kg (N=7)	Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=8)	Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=8)	Total (N=30)
Lymphocyte count decreased	5 (71.4%)	6 (85.7%)	5 (62.5%)	4 (50.0%)	20 (66.7%)
Neutropenia	3 (42.9%)	5 (71.4%)	1 (12.5%)	3 (37.5%)	12 (40.0%)
Anemia	2 (28.6%)	3 (42.9%)	4 (50.0%)	1 (12.5%)	10 (33.3%)
Fatigue	3 (42.9%)	2 (28.6%)	3 (37.5%)	0	8 (26.7%)
Aspartate aminotransferase increased	0	4 (57.1%)	0	3 (37.5%)	7 (23.3%)
Leukopenia	0	4 (57.1%)	1 (12.5%)	1 (12.5%)	6 (20.0%)

- No grade 3/4 cytokine release syndrome was noted

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Best Overall Response

Determined by RECIST 1.1 in DLT-Evaluable Population

	Cohort B1 Gem/NP/ APX005M 0.1 mg/kg (N=6)	Cohort B2 Gem/NP/ APX005M 0.3 mg/kg (N=6)	Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=6)	Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=6)	Totals (N=24)
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	3 (50%)	2 (33%)	4 (67%)	4 (67%)	13 (54%)
Confirmed PR	2	2	3	4	11
Unconfirmed PR	1	0	1	0	2
Stable Disease (SD)	3 (50%)	3 (50%)	1 (17%)	2 (33%)	9 (38%)
Progressive Disease (PD)	0	1 (17%)	0	0	1 (4%)
Not Evaluable / No Scan	0	0	1 (17%)*	0	1 (4%)*

*Death prior to on-study tumor assessment.

DLT-evaluable Population (N=24)

ORR = 54.2% (95% exact CI: 32.8 – 74.4)

- *Phase 1b Secondary Objective*
- *DCR = 92%*

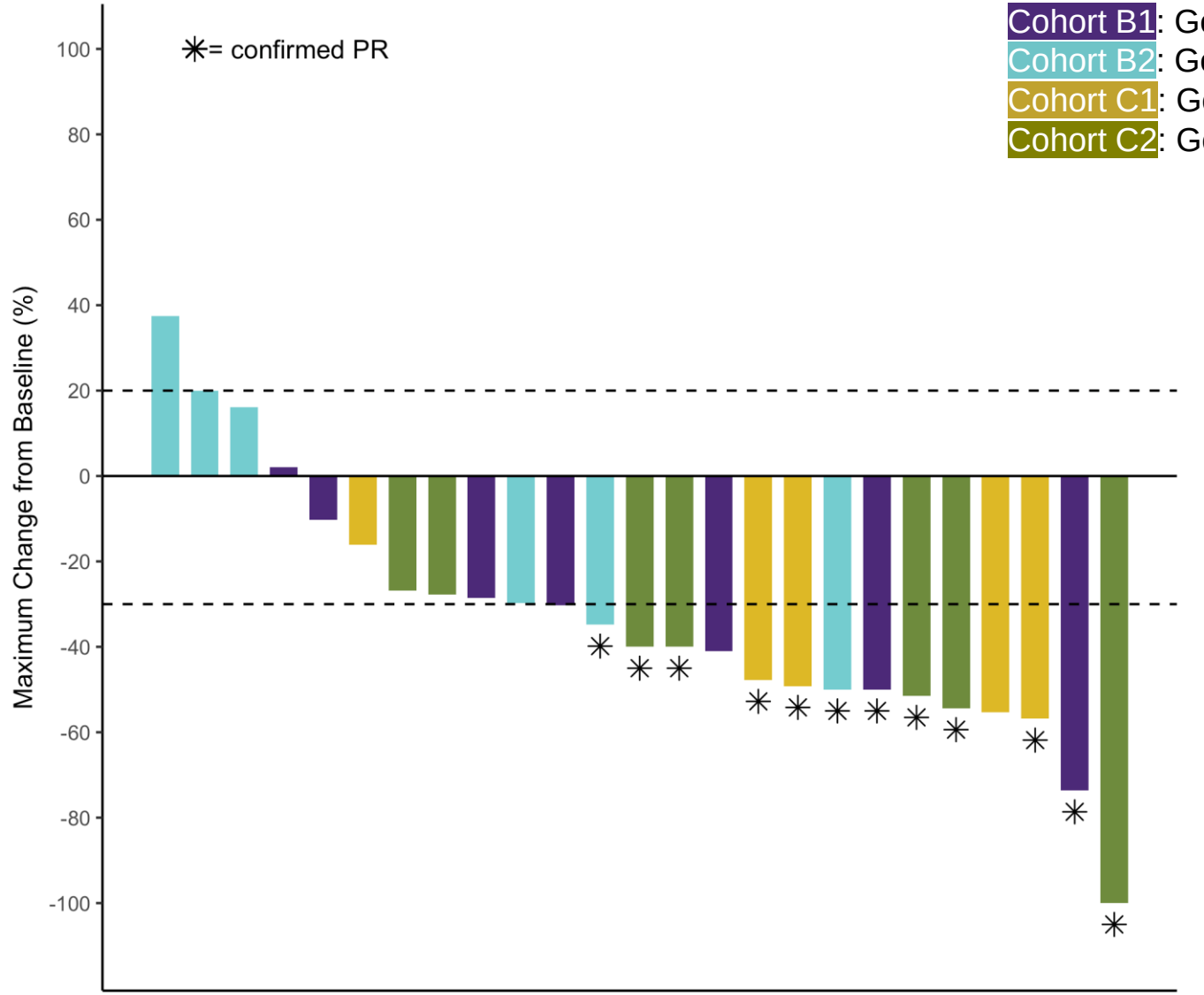
Safety-evaluable Population (N=30)

ORR = 46.7% (14/30) (95% exact CI: 28.3 – 65.7)

- *DCR = 80%*

Clinical Snapshot date: 05MAR19

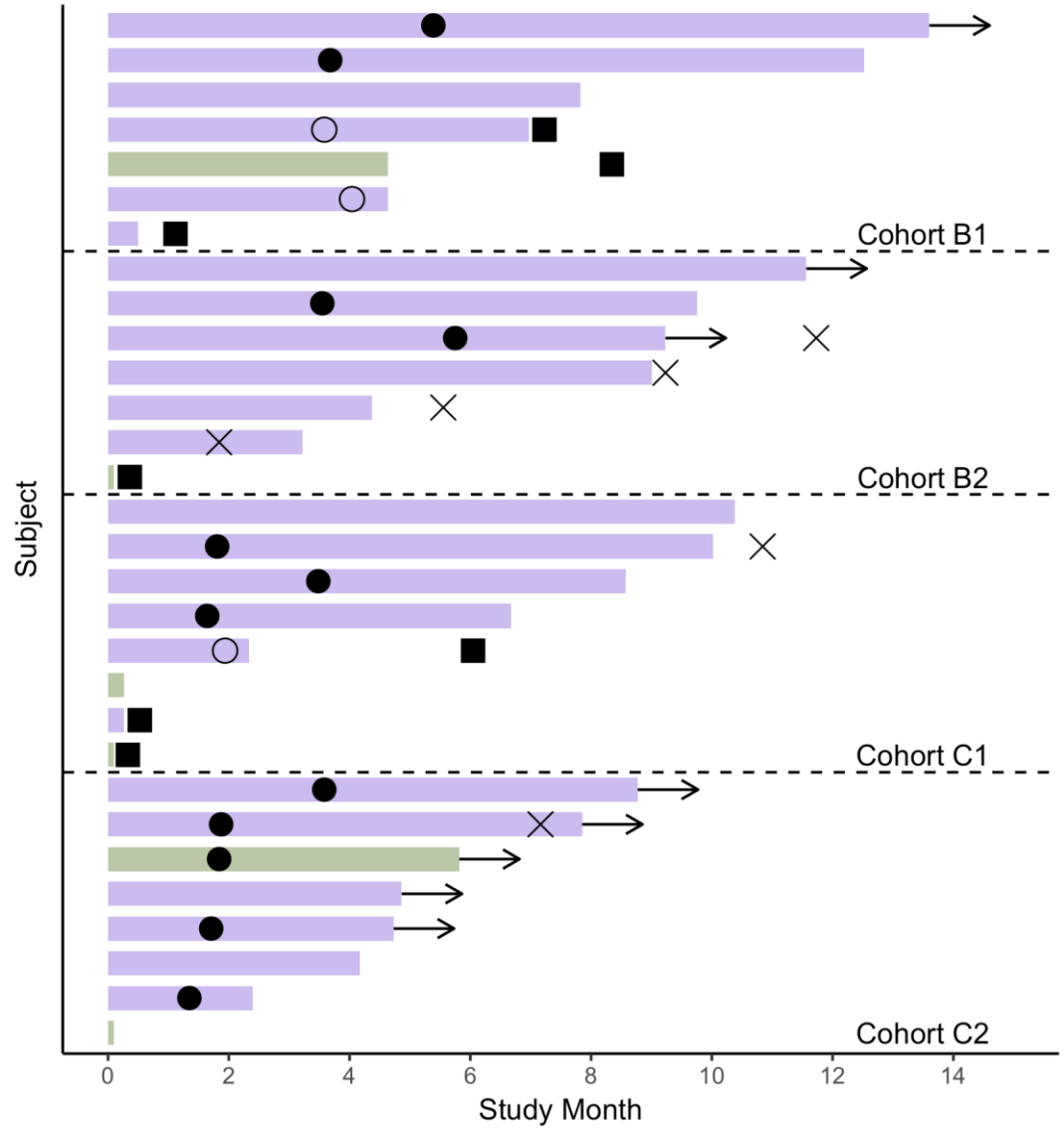
Percent Change in Sum of Target Lesions (Best Response)



Cohort B1: Gem/NP/APX005M 0.1 mg/kg
Cohort B2: Gem/NP/APX005M 0.3 mg/kg
Cohort C1: Gem/NP/APX005M 0.1 mg/kg + nivo
Cohort C2: Gem/NP/APX005M 0.3 mg/kg + nivo

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Time on Treatment and Time to First Response



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Cohort C1: Gem/NP/APX005M 0.1 mg/kg + nivo
Cohort C2: Gem/NP/APX005M 0.3 mg/kg + nivo

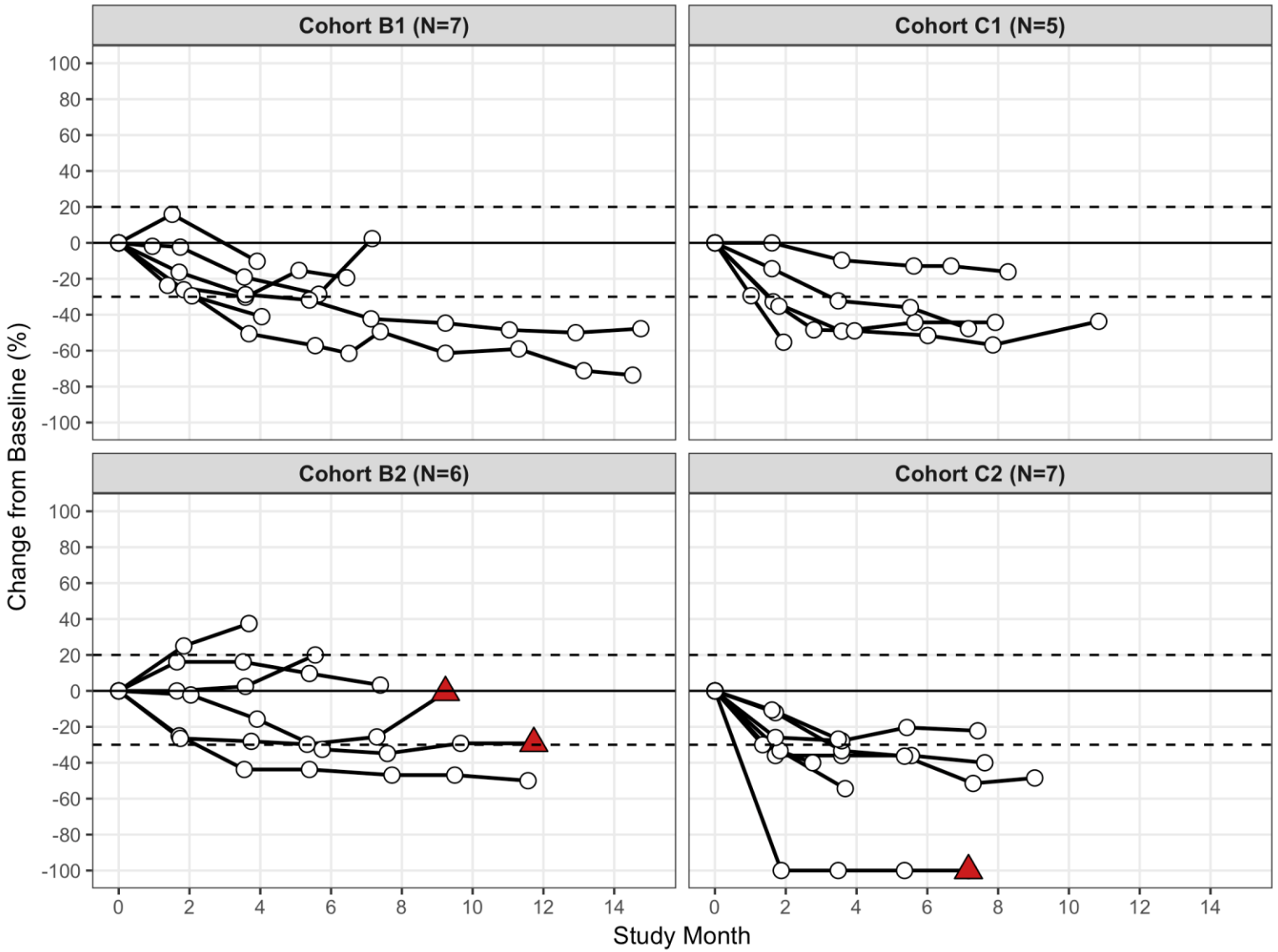
DLT-evaluable
- No
- Yes

Event
- Confirmed PR
- Unconfirmed PR
- Death
- Radiologic PD

→ Treatment ongoing

Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Percent Change in Sum of Target Lesions



Cohort B1: Gem/NP/APX005M 0.1 mg/kg
Cohort B2: Gem/NP/APX005M 0.3 mg/kg
Cohort C1: Gem/NP/APX005M 0.1 mg/kg + nivo
Cohort C2: Gem/NP/APX005M 0.3 mg/kg + nivo

▲ = New lesion

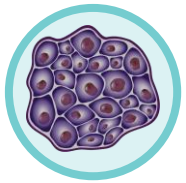
Clinical Snapshot date: 05MAR19
Safety-evaluable Population

Deep Immune Profiling

Harmonized methods of collection and processing at a central biorepository

Biomarker Samples

Patient Samples



Tumor

Blood

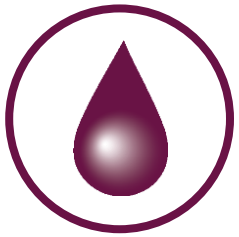
Clinical Metadata

- **Germline WES**
- **Tumor WES**
- **RNAseq** (tumor & blood)
- **Multiparameter Imaging**
- **Immune Profile CyTOF/Flow**
- **ctDNA: Mutant KRAS**
- **Cytokine** (serum)

- **HLA Determination** (MHC Class I and II)
- **Neo-epitope Prediction**
- **TME Gene Expression Signature**
- **Tumor Genome/TMB**

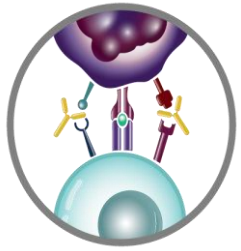
Extensive Computational Analysis

Collaboration Enables Cutting-Edge Science



Biomarker Sample Collection

High-Dimensional Tissue Imaging



Tumor & Immune Monitoring

Bioinformatics and Data Science

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UCSF

Stanford MEDICINE

University of Pennsylvania Abramson Cancer Center

UCLA

The University of Texas MD Anderson Cancer Center

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

OHSU

Multiplex IHC panels and imaging

University of Pennsylvania Abramson Cancer Center

Stanford MEDICINE

UCSF

FACS Symphony flow panel *ctDNA-mutant KRAS* *CyTOF panels*

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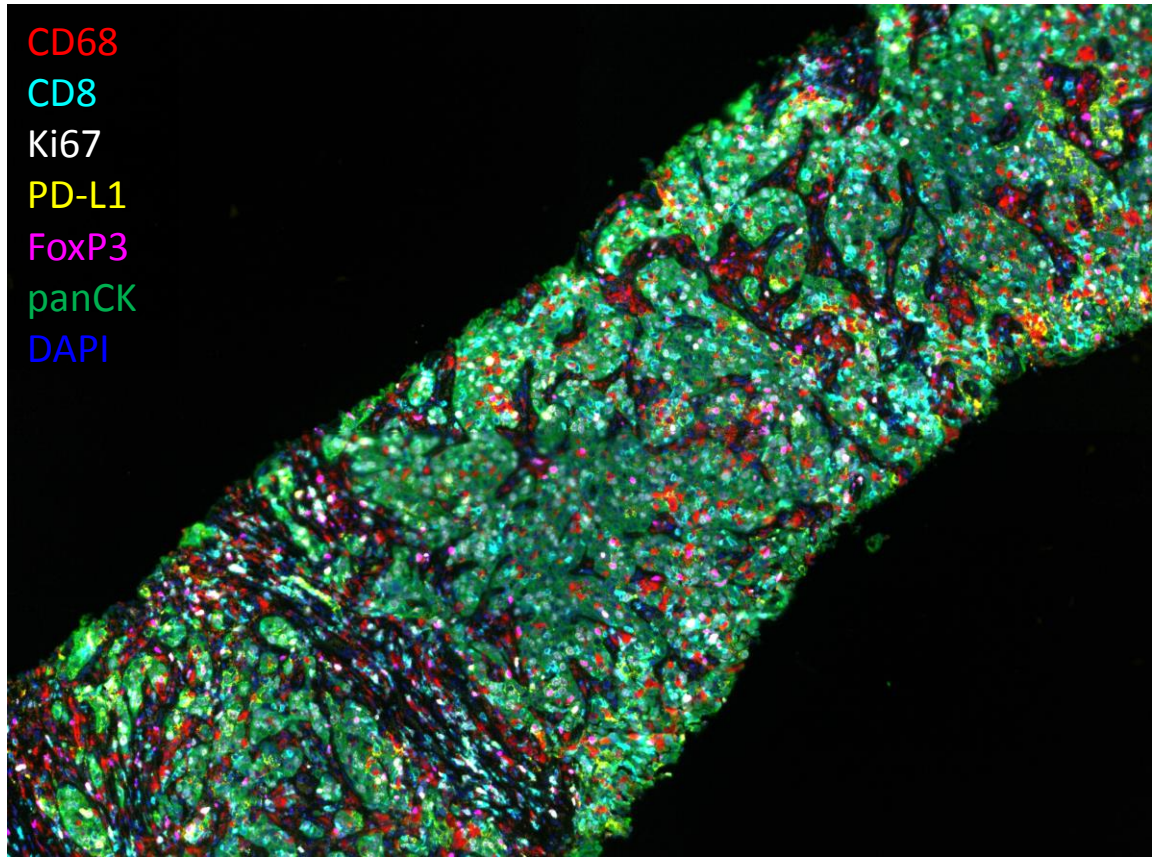
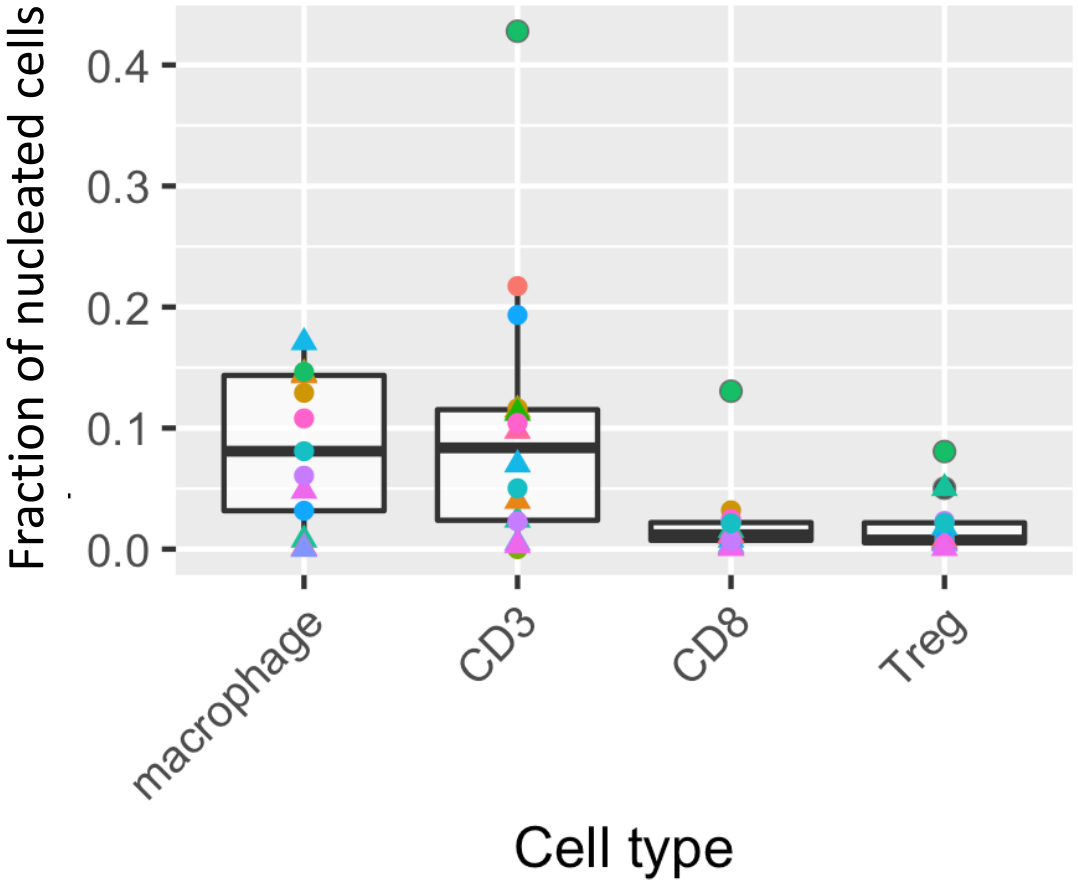
Tumor Immune Profiling with High-Dimensional Imaging



Imaging of baseline tumors with two technologies:

- Vectra and 30-marker
- OHSU mIHC

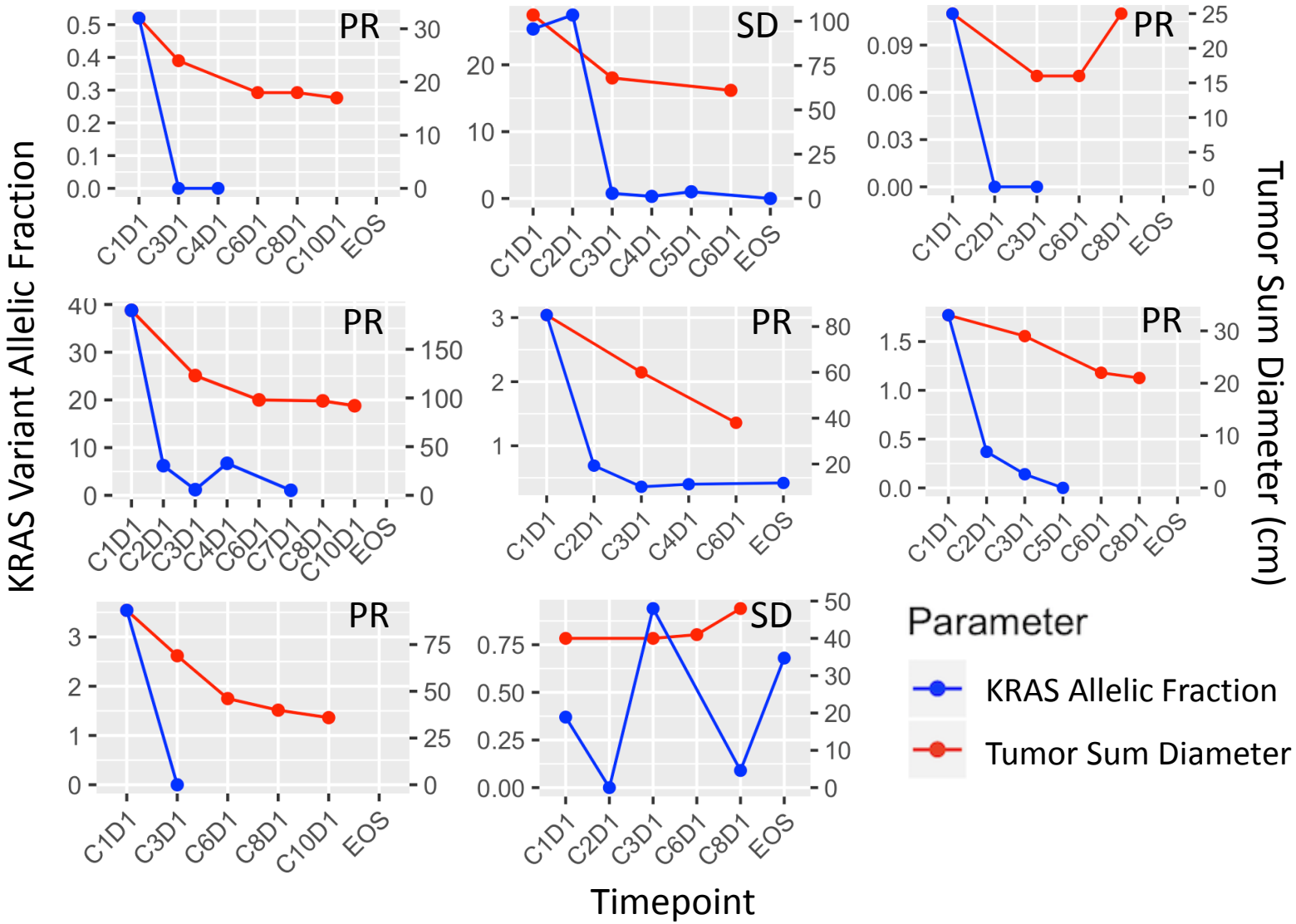
- Low overall immune infiltrate
- High macrophages and low CD8 T Cells



Circulating Tumor DNA: Mutant KRAS

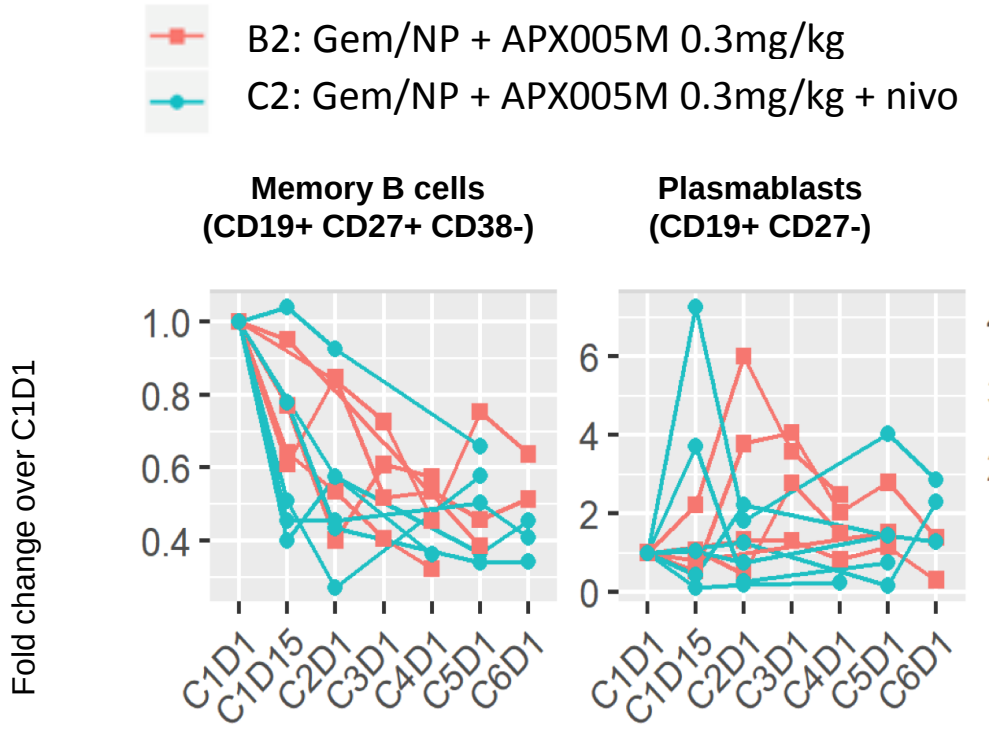
KRAS G12V, D, R mutations

- Digital droplet PCR assay to detect KRAS mutations in cell-free DNA from plasma
- KRAS variant allelic fraction decrease is associated with tumor shrinkage



High-Dimensional Cytometry for Profiling of Immune Dynamics in Blood

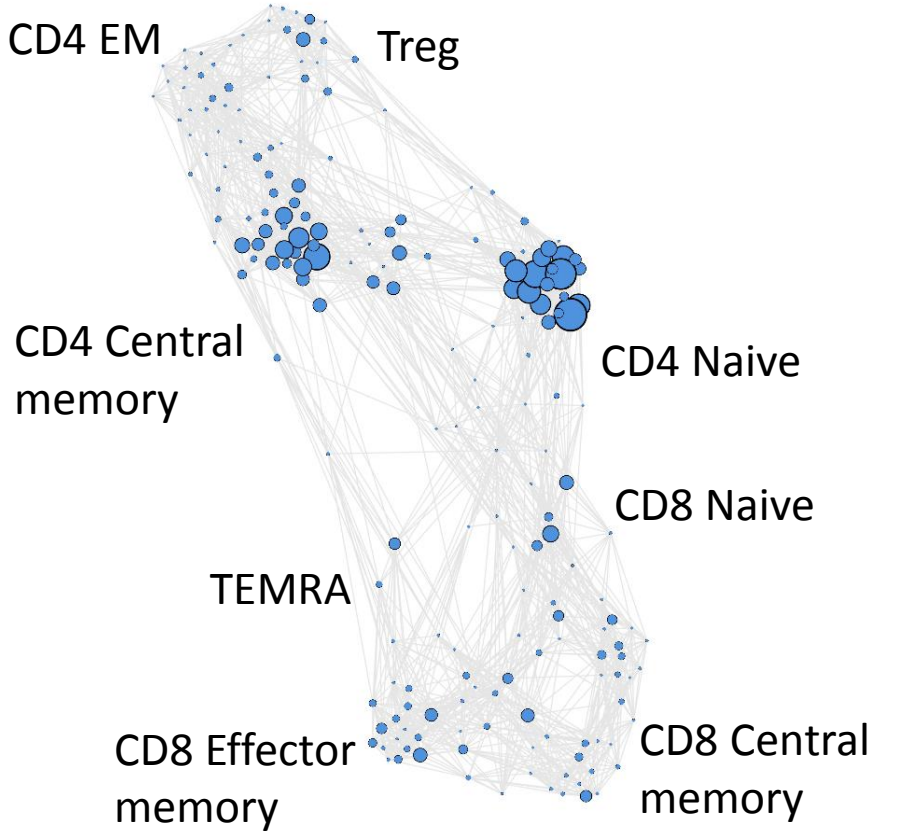
CyTOF
Immune phenotyping (37 markers)



Early observations of immune changes with treatment:

- Activation of B cells during the course of therapy

FACS Symphony
T cell panel (28 markers)



Current work: Unbiased clustering analysis of cellular population dynamics

Summary

- Gem/NP/APX005M (0.1 or 0.3 mg/kg) ± nivolumab combination is manageable
  - APX005M 0.3 mg/kg was selected for Phase 2 portion
- Preliminary results demonstrate encouraging clinical activity, across cohorts in 1L metastatic PDAC
- State-of-the-art deep immune profiling is feasible
- Randomized, Phase 2 portion of the study is ongoing at all 7 member institutions of the Parker Institute for Cancer Immunotherapy

Acknowledgements

We thank the patients, their families and our research teams for making this trial happen!

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