Gemcitabine and nab-Paclitaxel ± Nivolumab ± CD40 Agonistic Monoclonal Antibody Sotigalimab (APX005M) in Participants with Untreated Metastatic Pancreatic Adenocarcinoma: Phase 2 Final Results

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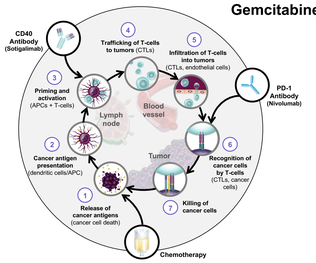
BACKGROUND



Gemcitabine + nab-Paclitaxel + CD40 mAb Sotigalimab ± PD-1 mAb Nivolumab

- Modest anti-tumor activity has been observed in small studies with gemcitabine (Gem)/nab-paclitaxel (NP) plus nivolumab and Gem plus an agonistic CD40 monoclonal antibody (mAb).[1,2]
- Phase 1b portion of this study[1] showed that sotigalimab and Gem plus NP with or without nivolumab is tolerable in metastatic pancreatic adenocarcinoma and shows clinical activity; 0.3 mg/kg of sotigalimab is the recommended phase 2 dose.
- Here we present the results from phase 2 of this randomized, open-label, multicenter study (NCT03214250).

METHODS

STUDY DESIGN

- Phase 1b was a dose-ranging study to assess safety and clinical activity and to determine the recommended phase 2 dose of sotigalimab in combination with Gem/NP ± nivolumab. The phase 1b results have been previously published.[3]
- The first 12 participants were randomized 4:1:1 to A1 (Gem+NP+Nivolumab), B2 (Gem+NP+Sotigalimab 0.3 mg/kg), or C2 (Gem+NP+Nivolumab+Sotigalimab 0.3 mg/kg). The remaining participants were randomized in a 1:1:1 allocation. The 12 dose-limiting toxicity (DLT)-evaluable participants from phase 1b (6 in B2 and 6 in C2) were included in phase 2 efficacy analyses (**Figure 1**).
- This study was not powered to compare between treatment cohorts. As this study did not enroll participants to a standard of care (Gem+NP) cohort, results were compared to historical control data.

ENDPOINTS

- *Primary:* 1-year overall survival (OS) rate compared with a 35% historical rate for Gem+NP.[4]
- *Secondary:* safety (adverse events [AEs], treatment-related adverse events [TRAEs]), objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and duration of response (DOR).
- *Exploratory:* immune pharmacodynamics, associations between immune biomarkers and clinical outcomes, and baseline and on-treatment microbiome profiles.

ENROLLMENT

Participants were eligible for enrollment if they had:

- Histological or cytological diagnosis of metastatic pancreatic adenocarcinoma and Eastern Cooperative Oncology Group (ECOG) 0, or 1; no prior treatment for metastatic disease was permitted, nor was prior CD40, PD-1, PD-L1, CTLA-4 treatment in any setting.
- The enrollment period for phase 2 was from August 30, 2018, to June 10, 2019.

DOSING SCHEDULE

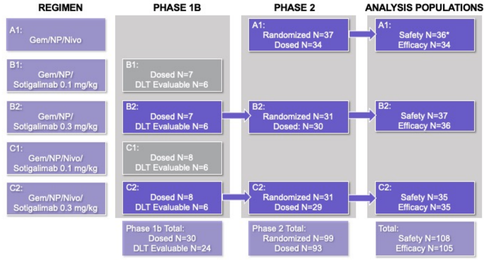
- For each 28-day cycle, on Day 1, Day 8, and Day 15 chemotherapy (Gem[1000 mg/m^2]+NP [125 mg/m^2]) was administered. Both were starting doses.
- For cohorts A1 and C2, on Day 1 and Day 15 nivolumab 240 mg was administered.
- For cohorts B2 and C2, on Day 3 sotigalimab was administered.

SAMPLE COLLECTION

- Tumor biopsies were collected at screening and Cycle 2 Day 4 (cohorts w/ sotigalimab) or Day 8 (cohort w/out sotigalimab) and end of treatment (optional).
- Baseline (Cycle 1 Day 1 or at screening) and on-treatment blood, tumor tissue, and stool samples were collected and analyzed for tumor and immune biomarkers using a variety of technologies.

TREATMENT COHORTS AND ANALYSIS POPULATIONS

Figure 1.



*Two participants were randomized to cohort C2 but did not receive a dose of Sotigalimab and are therefore listed under cohort A1 for this figure.
Note B1/C1 are not described in this poster.

RESULTS

STUDY POPULATION

- All participants had a minimum follow-up of 15 months at the time of this data snapshot (March 2021).
- Baseline characteristics were generally balanced across arms, inclusive of tumor burden, presence of liver metastases (25 [73.5%], 28 [75.7%], 27 [73.0%] for A1, B2, and C2 respectively) and stage at initial diagnosis (stage 1-3 versus stage 4 [stage 4: 27 (79.4%), 28 (75.5%), and 27 (73.0%) for A1, B2, and C2 respectively]) (**Table 1**).
- Overall, baseline tumor and immune profiling reveal cohorts were balanced and consistent with published PDAC prevalence for tumor gene expression, tumor immune content, immune profiling, and gut microbiome abundances.

Table 1. Demographics and Baseline Characteristics. (Safety Population)

Demographics	Cohort A1 (N=34)	Cohort B2 (N=37)	Cohort C2 (N=37)	Total (N=108)
Age (yr)				
Median (IQR)	62.5 (54-67)	61.0 (55-69)	62.0 (57-69)	62.0 (55-68.5)
Sex				
Male	20 (58.8%)	24 (64.9%)	20 (54.1%)	64 (59.3%)
Race or ethnic group				
Asian	3 (8.8%)	4 (10.8%)	1 (2.7%)	8 (7.4%)
Black	0	3 (8.1%)	2 (5.4%)	5 (4.6%)
Other	2 (5.9%)	1 (2.7%)	2 (5.4%)	5 (4.6%)
White	29 (85.3%)	29 (78.4%)	32 (86.5%)	90 (83.3%)
Hispanic or Latino	1 (2.9%)	1 (2.7%)	1 (2.7%)	3 (2.8%)
ECOG Performance Score at Screening				
0	15 (44.1%)	20 (54.1%)	17 (45.9%)	52 (48.1%)
1	19 (55.9%)	17 (45.9%)	20 (54.1%)	56 (51.9%)
Pancreatic Tumor Location				
Body	12 (35.3%)	10 (27.0%)	10 (27.0%)	32 (29.6%)
Head	14 (41.2%)	17 (45.9%)	20 (54.1%)	51 (47.2%)
Tail	8 (23.5%)	10 (27.0%)	7 (18.9%)	25 (23.1%)
Neutrophil-Lymphocyte Ratio (NLR) at Screening				
<5	26 (76.5%)	23 (62.2%)	23 (62.2%)	72 (66.7%)
≥5	8 (23.5%)	14 (37.8%)	14 (37.8%)	36 (33.3%)
CA19-9 (U/mL) at Cycle 1, Day 1				
n	25	26	31	82
<100	3 (12.0%)	4 (15.4%)	3 (9.7%)	10 (12.2%)
100-1000	4 (16.0%)	7 (26.9%)	9 (29.0%)	20 (24.4%)
≥1000	18 (72.0%)	15 (57.7%)	19 (61.3%)	52 (63.4%)
Number of Evaluable Participants	23	19	20	62
KRAS Mutations				
Gly12D	9 (39.1%)	7 (36.8%)	6 (30.0%)	22 (35.5%)
Gly12V	7 (30.4%)	5 (26.3%)	5 (25.0%)	17 (27.4%)
Gly12R	2 (8.7%)	3 (15.8%)	1 (5.0%)	6 (9.7%)
Other	1 (4.4%)	3 (15.8%)	1 (5.0%)	5 (8.1%)
MSI-H	1 (4.4%)	0	0	1 (1.6%)

Note: Cohort A1: Gem+NP+Nivolumab, Cohort B2: Gem+NP+Sotigalimab, Cohort C2: Gem+NP+Nivolumab+Sotigalimab

RESULTS

EFFICACY

- Median time on treatment was 5.2, 5.1, and 4.7 months for Cohort A1, B2, and C2 respectively.
- 1-year OS rate was 57.3% (1-sided p=0.007, 95% lower CI bound=41%) for A1, 48.1% (p=0.062, 95% lower CI bound=34%) for B2, and 41.3% (p=0.236, 95% lower CI bound=27%) for C2 vs 35% historical rate.
- The single MSI-H patient in A1 had an OS of 249 days and therefore does not meaningfully impact interpretation of the primary endpoint.
- Median OS and secondary endpoints are listed in **Table 2**.
- **Figure 2** shows the percent changes in the sum of target lesions, and **Figure 3** shows OS.

Table 2. Overall Survival and Secondary Endpoints for Efficacy Population.

% (n) [95% CI]	A1 (n=34)	B2 (n=36)	C2 (n=35)
ORR*	50 (17) [32-68]	33 (12) [19-51]	31 (11) [17-49]
ORR (confirmed)*	35 (12) [20-54]	33 (12) [19-51]	26 (9) [13-43]
DCR	74 (25) [56-87]	78 (28) [61-90]	69 (24) [51-83]
Median DOR, mos	7.3 [2.1-NE]	5.5 [3.7-7.9]	7.9 [1.9-NE]
Median PFS, mos	6.3 [5.2-8.8]	7.2 [5.3-9.2]	6.7 [4.1-9.8]
Median OS, mos	16.7 [9.8-18.4]	11.4 [7.2-20.1]	10.1 [7.9-13.2]
1-year OS, % [p]	57.3 [0.007]	48.1 [0.062]	41.3 [0.236]

*1 CR observed in A1; NE=not estimable.

Figure 2. Percent Changes in Sum of Target Lesions.

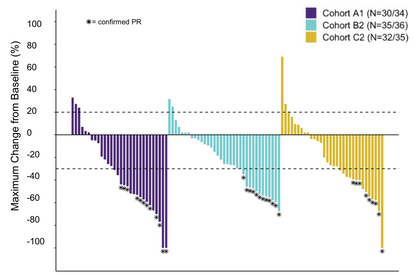
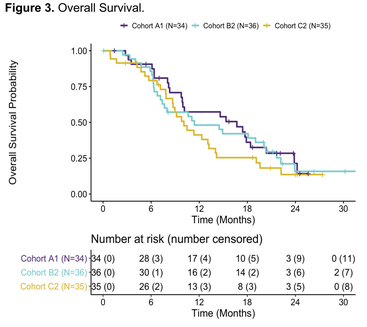


Figure 3. Overall Survival.



SAFETY

- Rates of TRAEs were overall similar and consistent across cohorts and with phase 1b portion of the study.
- 8 (7%) participants experienced an AE leading to treatment discontinuation of which 6 were from A1 (peripheral neuropathy, myocarditis, pneumonitis, thrombotic microangiography (2), and hyperbilirubinemia), 1 from B2 (pneumonitis), 1 from C2 (pyrexia).
- 98.1% of participants experienced a TRAE, with at least 1 having a Grade 3 or 4 event (66.7%, 86.5%, 80.0% for A1, B2, C2 respectively). The top 5 TRAEs occurring in 10% or more of participants by preferred term are shown in **Table 3**.
- 39 (36%) participants experienced a serious TRAE (13, 15, 11 in A1, B2, C2 respectively) and 2 participants died due to TRAEs; 1 each in B2 (acute hepatic failure possibly related to all study drugs) and C2 (intracranial hemorrhage possibly related to all study drugs).
- Cytokine release syndrome occurred in 0, 9 (24.3%), and 12 (34.3%) participants in A1, B2, and C2 respectively, with 0, 3 (8.1%), and 2 (5.7%) participants at Grade 3-4 in A1, B2, and C2 respectively.

Table 3. Most Frequent TRAEs by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term.

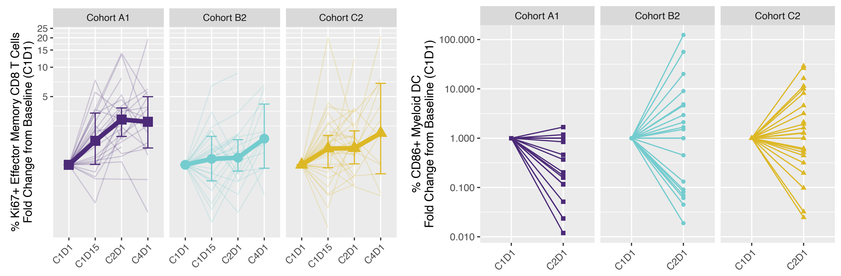
	Cohort A1 (N=36)		Cohort B2 (N=37)		Cohort C2 (N=35)	
MedDRA Preferred Term	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Nausea	25 (69.4%)	0	32 (86.5%)	0	28 (80.0%)	0
Fatigue	25 (69.4%)	9 (25.0%)	27 (73.0%)	5 (13.5%)	27 (77.1%)	5 (14.3%)
Pyrexia	11 (30.6%)	0	28 (75.7%)	1 (2.7%)	24 (68.6%)	1 (2.9%)
Aspartate aminotransferase increased	18 (50.0%)	7 (19.4%)	24 (64.9%)	14 (37.8%)	20 (57.1%)	9 (25.7%)
Chills	3 (8.3%)	0	30 (81.1%)	3 (8.1%)	27 (77.1%)	0

Note: Cohort A1: Gem+NP+Nivolumab, Cohort B2: Gem+NP+Sotigalimab, Cohort C2: Gem+NP+Nivolumab+Sotigalimab

PHARMACODYNAMIC EFFECTS

- Immune pharmacodynamic effects consistent with the immunotherapy mechanism of action were observed with the treatment in blood, tumor, and stool (**Figures 4** and **5**).
- All 3 cohorts showed an increase in activated effector memory (EM) T cells (Ki67+CD8+ cells [**Figure 4** left panel]/CD4+ EM cells [data not shown]), with nivolumab+chemotherapy (cohort A1) inducing the most pronounced effect.
- An increase in activated myeloid dendritic cells (CD86+ mDC) occurred in the majority of participants in cohort B2 (sotigalimab+chemotherapy) and frequently in cohort C2 (nivolumab+sotigalimab+chemotherapy) as an expected pharmacodynamic effect of sotigalimab, whereas nivolumab+chemotherapy (A1) treatment predominantly resulted in a decrease (**Figure 4**, right panel).

Figure 4. Immune Profiling of PBMCs (Flow or Mass Cytometry).



RESULTS

- A decrease in the percentage of tumor cells expressing PD-L1 was observed in response to treatment with nivolumab (A1, n=5 and C2, n=6) in most tumors, whereas sotigalimab+chemotherapy (B2, n=3) shows mixed changes in PD-L1 expression (**Figure 5**, left panel).
- Sotigalimab+chemotherapy (B2, n=2) treatment increased in tumoral CD80+ M1 macrophages, whereas nivolumab-containing treatments decreased (A1, n=2 and C2, n=1) (**Figure 5**, right panel).
- Nivolumab+chemotherapy (A1) treatment increased bacteroidia and decreased clostridia, whereas sotigalimab+chemotherapy (B2) showed the opposite effect. All 3 treatment arms displayed increases in gammaproteobacteria consistent with a chemotherapy effect (**Figure 6**).

Figure 5. Tumor Multiplex IHC Analysis.

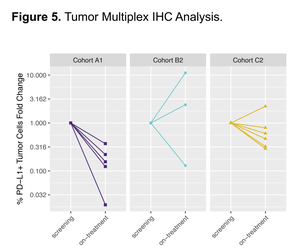
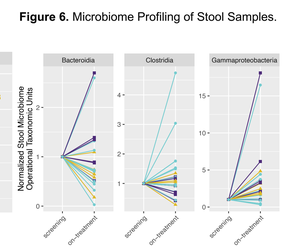


Figure 6. Microbiome Profiling of Stool Samples.



BASELINE IMMUNE AND TUMOR BIOMARKERS ASSOCIATED WITH CLINICAL OUTCOMES

- Baseline blood, tumor, and stool biomarkers defined different subsets of PDAC participants that were associated with improved overall survival with nivolumab/chemotherapy and/or sotigalimab/chemotherapy treatment but not the immunotherapy combination.
- Higher baseline levels of CXCR5+ EM CD8+ T cells (**Figure 7**, left panel) are associated with improved survival in response to nivolumab+chemotherapy (A1) treatment, whereas lower baseline levels are associated with improved survival with sotigalimab+chemotherapy (B2) but not the nivolumab+sotigalimab combination (C2).
- Lower baseline levels of exhausted (CD244+) EM CD4+ T cells are associated with improved survival in response to sotigalimab+chemotherapy (B2) treatment, but no difference in survival outcomes was observed in the cohorts containing nivolumab treatment (**Figure 7**, right panel).
- Lower baseline levels of inflammatory gene signature (TNFα) were associated with improved survival in response to nivolumab+chemotherapy (A1, n=17) treatment, but no difference in survival outcomes was observed in the sotigalimab-containing arms (B2, n=12; C2, n=12) (**Figure 8**, left panel).
- Lower levels of MYC (**Figure 8**, right panel) gene signatures were associated with improved survival in response to sotigalimab+chemotherapy (B2, n=12) treatment, but no difference in survival outcomes was observed in the nivolumab-containing arms (A1, n=17; C2, n=12).

Figure 7. Baseline Immune Profiling of CXCR5+ Effector Memory CD8+ T Cells (Left) and CD244+ Effector Memory CD4+ T Cells (Right).

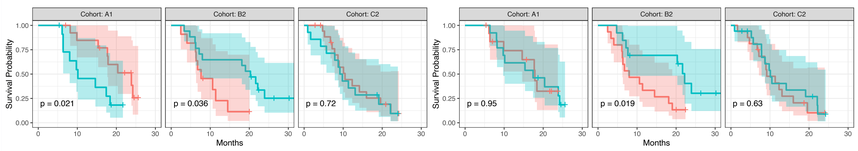
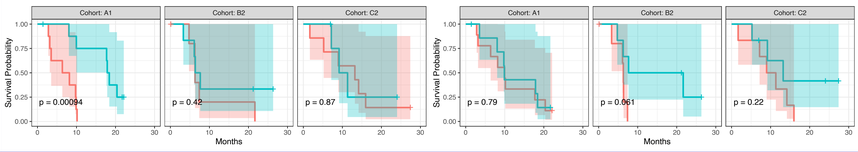


Figure 8. Baseline Tumor Gene Expression Profiling from RNA Seq Analysis: TNFα (Left) and MYC (Right) Signatures.



CONCLUSIONS

- The primary endpoint of 1-year OS rate >35% was met in A1 (nivolumab+chemotherapy) in contrast with previously reported data in this setting.[3] The primary endpoint was not met in B2 or C2, although moderate clinical activity was observed in B2 (sotigalimab+chemotherapy).
- Safety profiles for the IO+chemotherapy treatments across the 3 cohorts were manageable and consistent with previously reported phase 1b data.
- Comprehensive multi-omic analyses of pre- and on-treatment blood, tissue, and stool samples revealed expected pharmacodynamic effects and immune activation in A1 and B2.
- Moreover, biomarker signatures that associate with patient subsets with clinical benefit in response to nivolumab+chemotherapy (A1) do not overlap with signatures associated with benefit to sotigalimab+chemotherapy (B2). Such signatures were associated with use of immunotherapy but not chemotherapy.
- The combination of sotigalimab, nivolumab, and chemotherapy treatment (C2) exhibited mixed pharmacodynamic effects and did not have a clear biomarker subset that showed benefit, raising the potential hypothesis of IO-IO drug antagonism in this setting.
- Given observed clinical activity and hypothesis-generating biomarker results, further exploration and prospective testing of baseline biomarkers is warranted to improve clinical precision of IO+chemotherapy in PDAC, and a platform study (REVOLUTION, NCT04787991), has been initiated to build on these data.

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