UPDATED RESULTS OF A PHASE 1 STUDY OF SEA-CD40, GEMCITABINE, NAB-PACLITAXEL, AND PEMBROLIZUMAB IN PATIENTS WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) (SGNS40-001)

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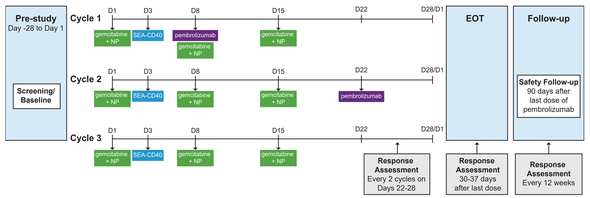
Background

- PDAC has a 5-year survival rate of <5% in patients with metastatic disease. Despite established therapy with multiagent chemotherapy, median overall survival still ranges from 9–13 months, and additional therapies are needed.[1,2]
- SEA-CD40 is an investigational, receptor-agonistic, nonfucosylated, humanized IgG1 monoclonal antibody directed to CD40, which is expressed on antigen-presenting cells.[3]
- SEA-CD40 binds with increased affinity to FcγRIIIa resulting in enhanced effector function and CD40 agonism, allowing amplification of immune stimulation and antitumor activity.[4]
- In preclinical models, the combination of SEA-CD40 and chemotherapy resulted in significant antitumor activity, which was further enhanced with anti-PD1 treatment.[4]
- SGNS40-001 is assessing SEA-CD40 as monotherapy and in combination with other agents. In preliminary results, SEA-CD40 + gemcitabine, nab-paclitaxel, and pembrolizumab showed a tolerable safety profile and evidence of immune activation in patients with PDAC. Here, we present updated clinical results for this cohort.[5,6,7]

SEA-CD40 Proposed Mechanism of Action

*SEA-CD40 is an investigational agent, and its safety and efficacy have not been established.

Study Design



- In this ongoing phase 1 study (NCT02376699), Cohort L[a] was to enroll approximately 60 efficacy-evaluable patients, including approximately 40 patients in the dose-finding cohort (20 patients at each dose level) and an additional 20 patients in the dose-expansion cohort at the recommended phase 2 dose[b]
- Key Eligibility Criteria
  - Must have histologically or cytologically confirmed metastatic PDAC for which patients did not receive previous systemic therapy in the metastatic setting
  - Previous adjuvant or neoadjuvant therapy for non-metastatic PDAC allowed if fully completed >4 months before study treatment
- Endpoints
  - Efficacy: confirmed ORR per RECIST by investigator (primary); ORR per iRECIST by investigator, DCR, DOR, PFS, OS (secondary)
  - Safety: AEs, laboratory abnormalities, DLTs (secondary)
  - PK parameter estimates and ATAs (secondary)

a Patients must be ≥18 years; have an ECOG status ≤1; adequate renal, hepatic, and hematologic function; and measurable disease per RECIST v1.1 criteria.
b Study drug administration (IV): SEA-CD40 10 or 30 µg/kg on Day 3 every 28 days; Gemcitabine 1000 mg/m² on Days 1, 8, and 15 every 28 days; Nab-paclitaxel 125 mg/m² on Days 1, 8, and 15 every 28 days; Pembrolizumab 400 mg every 6 weeks starting on Day 8 of Cycle 1. Continued treatment permitted in patients with ongoing clinical benefit. Pembrolizumab to discontinue after ~2 years (18 pembrolizumab treatments).

Patient Characteristics at Baseline

Characteristic	10 µg/kg N=40	30 µg/kg N=21	Total N=61
Age, Median Years (Range)	66.0 (40–80)	65.0 (41–76)	66.0 (40–80)
Sex, n (%)			
Male	18 (45)	11 (52)	29 (48)
Female	22 (55)	10 (48)	32 (52)
ECOG Performance Status, n (%)			
0	24 (60)	8 (38)	32 (52)
1	16 (40)	13 (62)	29 (48)
Liver Lesion, n (%)			
Yes	24 (60)	16 (76)	40 (66)
No	16 (40)	5 (24)	21 (34)
Received Radiation Therapy, n (%)			
Yes	7 (18)	3 (14)	10 (16)
No	33 (83)	18 (86)	51 (84)
Received Prior Surgery, n (%)			
Yes	9 (23)	5 (24)	14 (23)
No	31 (78)	16 (76)	47 (77)
Prior Neoadjuvant or Adjuvant Therapy, n (%)			
Yes	10 (25)	6 (29)	16 (26)
No	30 (75)	15 (71)	45 (74)

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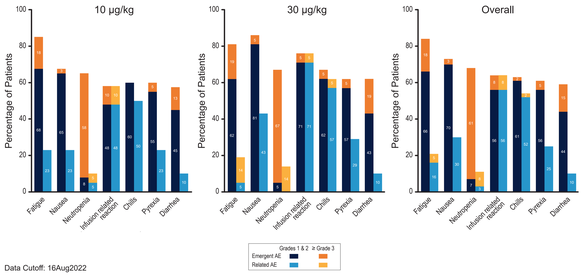
Overall AEs and AEs Related to SEA-CD40



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- IRRs were the most common AEs considered related to SEA-CD40 and were generally ≤ Grade 2
  - All patients received mandatory pre-medication with H1 + H2 antihistamines, acetaminophen, ibuprofen, and anti-emetic of investigator's choice, as well as a controlled infusion rate
- There was a trend toward better tolerability at 10 µg/kg
- AEs leading to treatment discontinuation:
  - SEA-CD40 10 µg/kg: immune-mediated lung disease, n=3 (8%); septic shock, n=1 (3%)
  - SEA-CD40 30 µg/kg: colitis, n=1 (5%); portal vein thrombosis, n=1 (5%)

Abbreviations

AE: adverse event; APC: antigen-presenting cell; ATA: antitherapeutic antibody; C: cycle; CD: cluster of differentiation; CI: confidence interval; CR: complete response; D: day; DCR: disease control rate; DLT: dose limiting toxicity; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FcγRIII: a receptor on macrophages, natural killer cells, and neutrophils; H1 + H2: histamine receptor 1 and 2; IgG: immunoglobulin G; IP-10 (CXCL10): interferon gamma-induced protein 10; iRECIST: immune Response Evaluation Criteria in Solid Tumours; IRR: infusion-related reaction; IV: intravenous; MCP-1: monocyte chemoattractant protein-1; MIG (CXCL9): monokine induced by interferon-gamma; MIP-1beta: macrophage inflammatory protein-1 beta; NE: not evaluable; NK: natural killer (cell); NP: nab-paclitaxel; ORR: objective response rate; OS: overall survival; PD: progressive disease; PD-1: programmed cell death protein 1; PDAC: pancreatic ductal adenocarcinoma; PFS: progression-free survival; PK: pharmacokinetic; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease; Treg: T regulatory cells.

References

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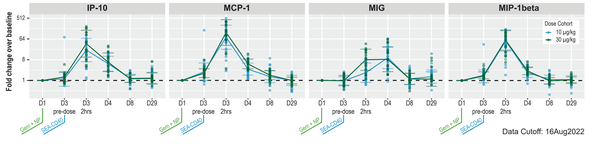
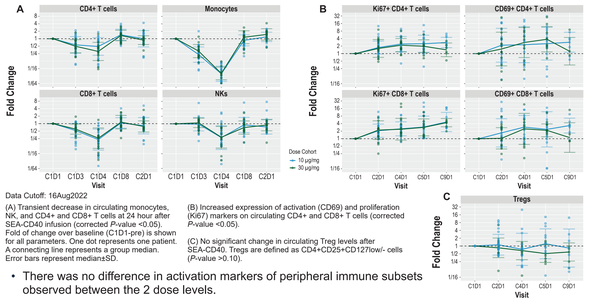
Transient Increase in Circulating Cytokines and Chemokines in Peripheral Blood Associated With Immune Activation and Trafficking After Treatment



Fold of change over baseline (C1D1-pre) for each cytokine is shown. One dot represents 1 patient. A connecting line represents a group median. Error bars represent median±SD. Corrected *P*-value <0.001 between peak induction and baseline.

- Patients had transient increases in circulating cytokines and chemokines associated with immune activation and trafficking, as well as increases in markers of activation on peripheral NK cells and T cells
- Similar cytokine induction was observed after SEA-CD40 monotherapy, 4 hours after SEA-CD40 infusion (data not shown)

Changes in Immune Subsets in Peripheral Blood After Treatment Indicates Immune Activation and No Induction of Tregs



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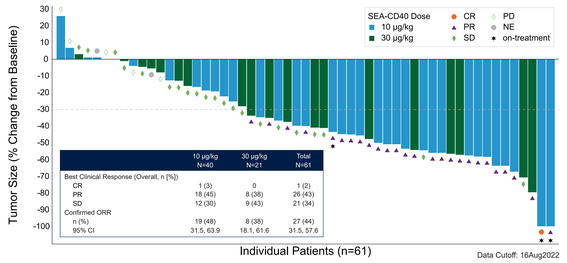
(A) Transient decrease in circulating monocytes, NK, and CD4+ and CD8+ T cells at 24 hour after SEA-CD40 infusion (corrected *P*-value <0.05). Fold of change over baseline (C1D1-pre) is shown for all parameters. One dot represents one patient. A connecting line represents a group median. Error bars represent median±SD.

(B) Increased expression of activation (CD69) and proliferation (Ki67) markers on circulating CD4+ and CD8+ T cells (corrected *P*-value <0.05).

(C) No significant change in circulating Treg levels after SEA-CD40. Tregs are defined as CD4+CD25+CD127low/- cells (*P*-value >0.10).

- There was no difference in activation markers of peripheral immune subsets observed between the 2 dose levels.

Best Percent Change in Tumor Size From Baseline per RECIST v1.1 and Confirmed Objective Response Rate



	10 µg/kg N=40	30 µg/kg N=21	Total N=61
Best Clinical Response (Overall, n [%])			
CR	1 (3)	0	1 (2)
PR	18 (45)	8 (38)	26 (43)
SD	12 (30)	9 (43)	21 (34)
Confirmed ORR			
n (%)	19 (48)	8 (38)	27 (44)
95% CI	31.5, 63.9	18.1, 61.6	31.5, 57.6

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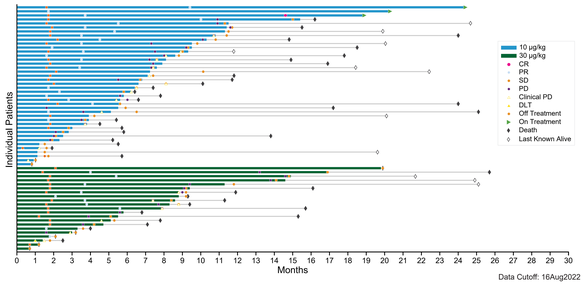
- There were comparable response rates observed at both dose levels

Duration of Treatment



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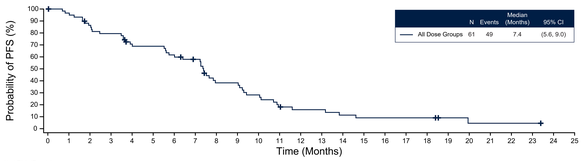
Progression-Free Survival



Median follow-up (months): 10 µg/kg, 6.7 (range: 0–23.4); 30 µg/kg, 7.4 (0.7–19.9); total, 6.9 (0–23.4)

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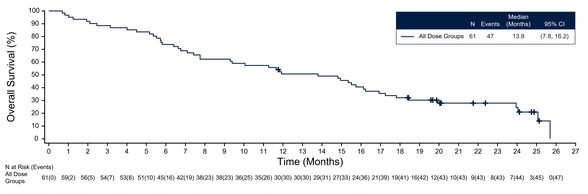
Overall Survival



Median follow-up (months): 10 µg/kg, 14.9 (range: 0.8–25.1); 30 µg/kg, 9.4 (0.7–25.7); total, 11.9 (0.7–25.7)

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Conclusions

- SEA-CD40 is an investigational, nonfucosylated, CD40-receptor agonist that potently activates the innate immune system.
- SEA-CD40 in combination with gemcitabine, nab-paclitaxel, and pembrolizumab has an acceptable safety profile.
- Evidence of immune activation in this study was consistent with the proposed SEA-CD40 mechanism of action.
- The combination of SEA-CD40 with gemcitabine, nab-paclitaxel, and pembrolizumab, in the context of a single arm trial, demonstrates evidence of antitumor activity in patients with PDAC that compares somewhat favorably to historical chemotherapy outcomes.

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