Phase 1 Study of SEA-CD40, Gemcitabine, Nab-Paclitaxel, and Pembrolizumab in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (Trial in Progress)

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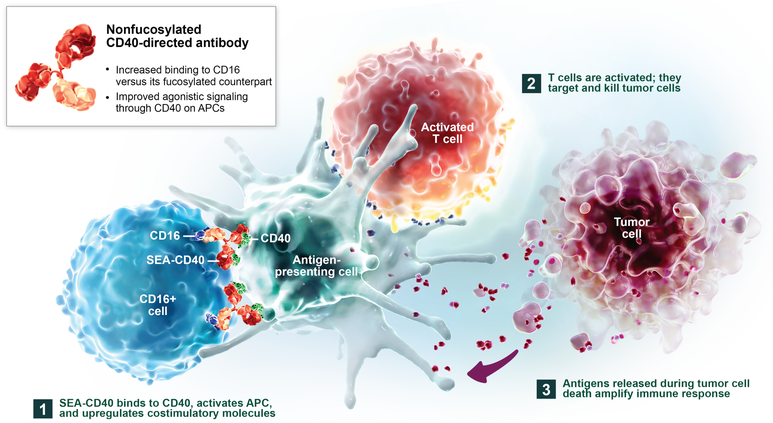
CD40 and Tumor Immunity

- CD40 is a costimulatory receptor of the tumor necrosis factor receptor superfamily expressed on antigen presenting cells (APCs).[1]
- Antibodies targeting CD40 may have therapeutic benefit via multiple mechanisms, including innate immune activation that can support generation of antigen-specific antitumor T cell responses and binding to CD40-expressing cancer cells leading to antibody-mediated killing of target cells.[2]
- The combination of CD40 stimulation with chemotherapy could enhance antigen uptake and presentation and, therefore, could initiate de novo immune responses.[3]

Description: SEA-CD40

- SEA-CD40 is an investigational agonistic, nonfucosylated, humanized IgG1 monoclonal antibody directed against CD40.
- SEA-CD40 has enhanced FcγRIIIa binding (~10x greater than parent IgG1 antibody) that drives increased effector function, resulting in more potent immune stimulatory activity than antibodies with muted or selective FcγR binding.[2]
- The enhanced effector function of SEA-CD40 may confer greater immune stimulation and antitumor activity relative to other CD40-directed therapeutics.[2]
- SEA-CD40 demonstrates enhanced activity compared to other CD40-targeted antibodies in vitro and in vivo, suggesting that enhanced effector function enables optimal immune cell agonism.[2]

SEA-CD40 Proposed Mechanism of Action



SEA-CD40 is an investigational agent, and its safety and efficacy have not been established. ©2021 Seagen Inc. All rights reserved.

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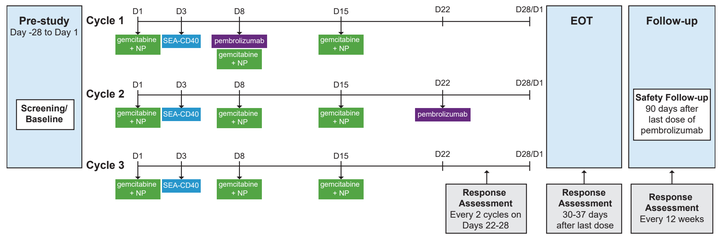
- **SEA-CD40 is an investigational differentiated CD40 agonist that potently activates the innate immune system**
- **In preclinical models, the combination of a CD40 agonist and chemotherapy can initiate a de novo antitumor immune response**
- **Cohort L of the SGNS40-001 study is assessing SEA-CD40, gemcitabine, nab-paclitaxel, and pembrolizumab in patients with metastatic pancreatic adenocarcinoma**

Study Design

- This ongoing, phase 1 study (NCT02376699) will 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.
- Study drug administration (IV):
  - SEA-CD40 10 or 30 mcg/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 42 days starting on Day 8 of Cycle 1
- Continued treatment permitted in patients with ongoing clinical benefit. Pembrolizumab to be discontinued after approximately 2 years of treatment (18 pembrolizumab treatments).



Study Objectives

Primary
- To evaluate the antitumor activity of SEA-CD40 combined with gemcitabine, nab-paclitaxel, and pembrolizumab in patients with previously untreated metastatic exocrine ductal pancreatic cancer

Secondary
- To evaluate the safety and tolerability of SEA-CD40 in combination with gemcitabine, nab-paclitaxel, and pembrolizumab
- To evaluate the pharmacokinetic (PK) parameters of SEA-CD40 and pembrolizumab and incidence of antitherapeutic antibodies (ATA) against SEA-CD40 and pembrolizumab when SEA-CD40 is given in combination with gemcitabine, nab-paclitaxel, and pembrolizumab

Endpoints

Efficacy Endpoints
- ORR, confirmed per Response Evaluation Criteria in Solid Tumors (RECIST) by investigator assessment (primary)
- ORR, confirmed per immune-based RECIST (iRECIST) by investigator assessment
- Disease control rate per iRECIST and RECIST v1.1
- Duration of response per iRECIST and RECIST v1.1
- Progression-free survival per iRECIST and RECIST v1.1
- Overall survival

Safety Endpoints
- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Type, incidence, and severity of laboratory abnormalities
- Incidence of dose-limiting toxicity

Pharmacokinetics
- Estimates of selected PK parameters
- Incidence of ATAs

Eligibility

Key Inclusion Criteria
- Histologically or cytologically confirmed metastatic exocrine ductal adenocarcinoma of the pancreas not amenable to curative therapy
- No prior systemic therapy, including chemotherapy, biological therapy, or targeted therapy, permitted for metastatic pancreatic adenocarcinoma
  - Patients who have received prior therapy for non-metastatic pancreatic adenocarcinoma are eligible if therapy was fully completed more than 4 months before start of study treatment
- Measurable disease per RECIST v1.1
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Adequate baseline hematologic, renal, and hepatic function
- Recovery to Grade 1 of any clinically significant toxicity attributed to prior anticancer therapy before the start of study drug administration
- Age 18 years and older

Key Exclusion Criteria
- History of radiation pneumonitis
- Neuropathy Grade ≥2
- Prior treatment with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another stimulatory or co-inhibitory T cell receptor
- Recent or ongoing serious infection within 2 weeks
- Received allogenic tissue/solid organ transplant
- Active autoimmune or autoinflammatory ocular disease within 6 months
- Known or suspected active organ-threatening autoimmune disease
- Active central nervous system tumor or metastases
- History of severe immune-mediated adverse reactions or severe hypersensitivity to pembrolizumab

Assessments

Safety Assessments
- Surveillance and recording of AEs and serious AEs
- Recording of concomitant medication
- Measurements of protocol-specified physical examination findings and ocular examination findings
- Measurements of protocol-specified laboratory tests

Response Assessments
- Antitumor activity assessed after every 2 cycles (28-day cycles) of treatment
- Responses determined using iRECIST and RECIST v1.1 criteria
- After disease progression or initiation of a new anticancer treatment, patients will remain in follow-up for survival until death or study closure, whichever comes first

Study Sites and Completion Dates

- 12 sites in the United States are recruiting patients
- First patient enrolled in November 2019

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