An Open-Label Phase 1 Study to Investigate SGNCEACAM5C/SAR445953 in Adults With Advanced Solid Tumors (SGNCEA5C-001)

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Objective

- This is a first-in-human study designed to characterize the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity of CEACAM5C:PF-08046050/SAR445953 (hereafter CEACAM5C) in adults with select advanced solid tumors.

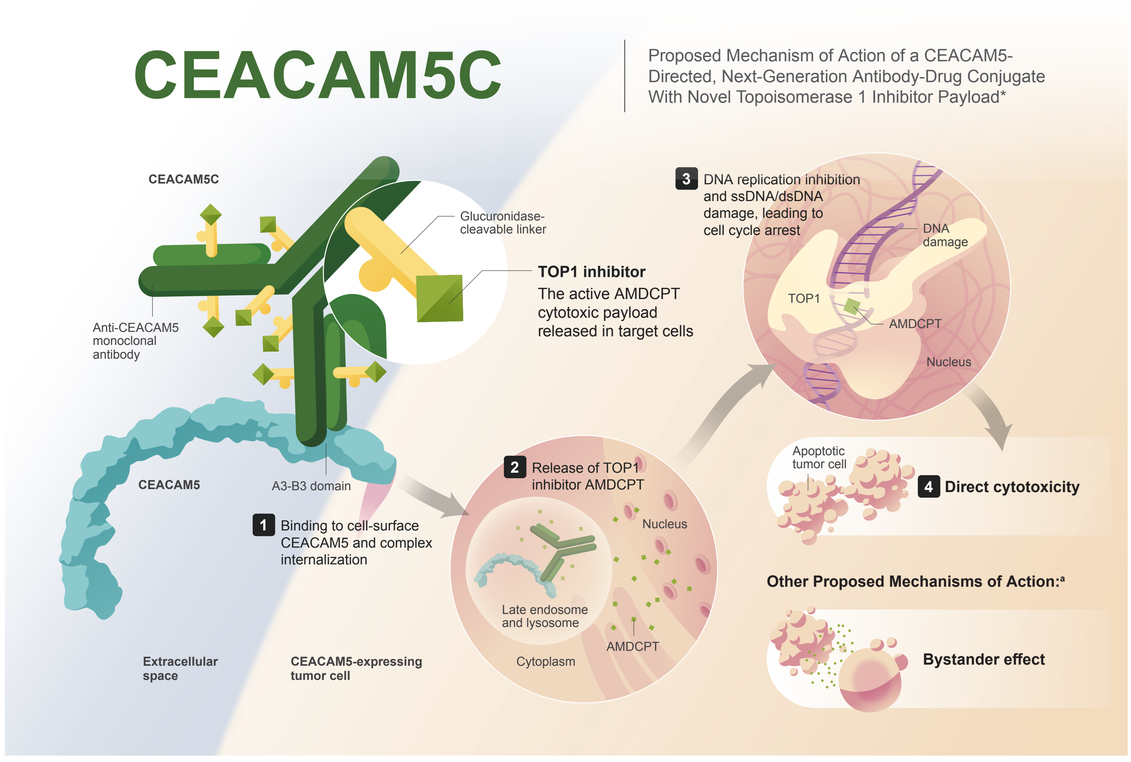
Conclusion

- Recruitment is ongoing for Part A in North America. Additional sites in Europe are planned.

Background

- CEACAM5 is a member of the CEACAM sub-group of a family of glycoproteins involved in cell adhesion.[1]
  - It is expressed in several tumors of epithelial origin such as CRC, PDAC, GC, and NSCLC, while expression in normal tissue is restricted.[1-3]
- CEACAM5C is an investigational ADC that is directed to CEACAM5 and is composed of the humanized IgG1 anti-CEACAM5 mAb tusamitamab chemically conjugated to 8 molecules of the TOP1 inhibitor AMDCPT.
  - AMDCPT is not subject to efflux and is highly permeable, giving rise to bystander activity.[4-7]
- CEACAM5C selectively binds CEACAM5 present on the cell surface and is internalized via the endo-lysosomal pathway, with subsequent release of the payload through enzymatic cleavage. Release of the cytotoxic payload induces DNA damage, cell cycle arrest in S phase, and apoptosis (**Figure 1**).

Figure 1: Proposed mechanism of action



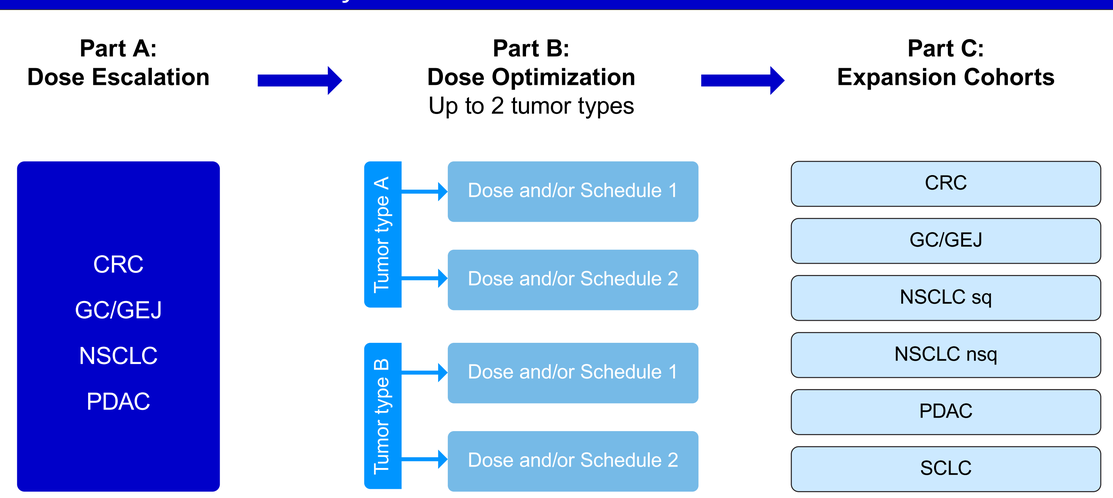
[a]Additional mechanisms of action and their potential to complement the direct cytotoxicity of some camptothecin-based antibody-drug conjugates are currently under investigation.
AMDCPT=7-aminomethyl-10,11-methylenedioxycamptothecin; CEACAM5=carcinoembryonic antigen cell adhesion molecule 5; dsDNA=double-stranded DNA; ssDNA=single-stranded DNA; TOP1=topoisomerase 1
***CEACAM5C is an investigational agent, and its safety and efficacy have not been established. CEACAM5C is developed in partnership with Sanofi.**

  - CEACAM5C is highly active in multiple patient-derived xenograft models, including CRC, GC, and NSCLC, across various levels of CEACAM5 expression.[6,7]
  - Based on the evidence of preclinical effectiveness to date, CEACAM5C has the potential to be a new therapeutic option for patients with advanced solid tumors.

Methods

- SGNCEA5C-001 (NCT06131840) is an open-label, multicenter, phase 1, dose escalation, dose and schedule optimization, and dose expansion study evaluating CEACAM5C in adults with select advanced solid tumors (**Figure 2**).
- The dose escalation portion of this study (Part A) will be conducted using the BOIN design.[8,9]

Figure 2: SGNCEA5C-001 study schema



Approximately 410 patients may be enrolled and treated in this study.

PATIENT ELIGIBILITY

- Patients must have relapsed, refractory, or progressive disease and no appropriate standard therapy available.
- In dose and schedule optimization (Part B) and dose expansion (Part C), patients with NSCLC with sq or nsq histology or SCLC must have tumors that express CEACAM5, in ≥1% of tumor cells at an intensity of ≥2+ by central IHC testing.
- Patients must have measurable disease per RECIST v1.1, an ECOG performance status of 0 or 1, and adequate organ function.
- Patients will receive CEACAM5C as an intravenous infusion.

Study Objectives and Endpoints

- **Primary objectives:** safety and tolerability, maximum tolerated dose or maximum administered dose, and recommended dose and schedule.
- **Secondary objectives:** pharmacokinetics, immunogenicity, and anti-tumor activity.
- **Exploratory objectives:** tumor samples will be analyzed for exploratory biomarkers.

Abbreviations: ADC=antibody-drug conjugate; AMDCPT=7-aminomethyl-10,11-methylenedioxycamptothecin; BOIN=Bayesian Optimal Interval; CEACAM5=carcinoembryonic antigen-related cell adhesion molecule 5; CRC=colorectal cancer; ECOG=Eastern Cooperative Oncology Group; GC=gastric adenocarcinoma; GEJ=gastroesophageal junction adenocarcinoma; IgG1=immunoglobulin G1; IHC=immunohistochemistry; mAb=monoclonal antibody; NSCLC=non–small cell lung cancer; nsq=non-squamous; PDAC=pancreatic ductal adenocarcinoma; SCLC=small cell lung cancer; sq=squamous; TOP1=topoisomerase 1

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