SGN228-001: A Phase 1 Open-label Dose Escalation and Expansion Study of SGN-CD228A in Select Advanced Solid Tumors (Trial in Progress)

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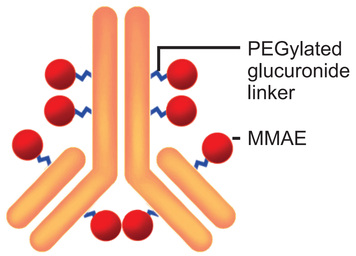
SGN-CD228A

- SGN-CD228A is an investigational ADC that combines an IgG1 humanized anti-CD228 mAb, a cleavable glucuronide linker, and the highly potent microtubule-disrupting agent, MMAE.
- SGN-CD228 is directed towards CD228, a protein which has low expression in normal tissue but high expression in multiple types of carcinomas including melanoma, mesothelioma, NSCLC, and HER2-negative breast, pancreatic, and colorectal cancers.

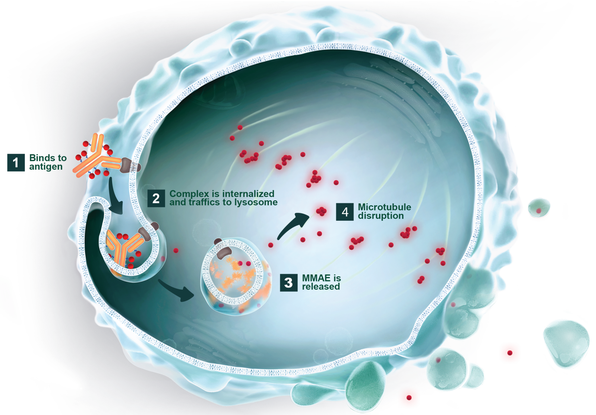
Anti-CD228 mAb (hL49)



- SGN-CD228A has demonstrated *in vivo* activity in melanoma, NSCLC, and triple-negative breast cancer xenograft models, even in tumors with low CD228 expression.[1]

SGN-CD228A Proposed Mechanism of Action

- The proposed MOA for SGN-CD228A involves binding to CD228 on the cell surface, internalization of the ADC, and trafficking to lysosomes. MMAE is subsequently released through β-glucuronidase-mediated cleavage of the glucuronide-MMAE linker. This allows MMAE to bind to tubulin, which disrupts microtubule networks and causes cell cycle arrest followed by apoptosis.



Study Treatment and Sample Size

- SGN-CD228A will be administered IV once every 21 days; 5 dose levels are planned. Up to 240 subjects will be enrolled, with up to approximately 30 subjects each in a dose escalation cohort, in the 6 disease-specific dose expansion cohorts, and in a biology cohort (to evaluate exploratory biomarkers).

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SGN228-001 (NCT04042480) is a phase 1 open-label, multicenter, dose-escalation and cohort expansion, first-in-human study of SGN-CD228A in subjects with advanced cutaneous melanoma, HER2-negative BC, NSCLC, CRC, PDAC, or MPM

Study Objectives and Endpoints

Primary Objectives

- Evaluate safety and tolerability of SGN-CD228A
- Identify MTD and recommended dose of SGN-CD228A

Secondary Objectives

- Assess antitumor activity at the recommended dose
- Assess the PK
- Assess immunogenicity

Primary Endpoints

- Type, incidence, severity, seriousness, and relatedness of AEs, and type, incidence, and severity of laboratory abnormalities

Secondary Endpoints

- Best response, ORR, PFS, overall survival, and duration of response and complete response
- Selected PK parameters for plasma SGN-CD228A antibody, antibody-conjugated MMAE, and released MMAE concentrations
- Incidence of ATA

Eligibility

Key Inclusion Criteria

- Histologically or cytologically confirmed disease that is relapsed, refractory, or progressive, without available standard therapy
  - Dose escalation cohort: advanced cutaneous melanoma, HER2-negative BC, NSCLC, CRC, PDAC, or MPM
  - Expansion cohorts: MPM, advanced or metastatic cutaneous melanoma (excluding acral or mucosal varieties) or HER2–negative BC, locally advanced or metastatic EGFR wild type NSCLC or CRC, unresectable or advanced PDAC
- ≥18 years of age
- Measurable disease per RECIST v1.1
- ECOG performance status ≤1
- Adequate renal, hepatic, and hematologic function

Key Exclusion Criteria

- Pre-existing neuropathy Grade ≥2
- Retinal or macular disease requiring treatment or ongoing active monitoring
- CNS lesions, including leptomeningeal metastasis, unless definitively treated

Dose Escalation Cohort

- Dose escalation will be conducted using the modified toxicity probability interval method[2] to evaluate the safety of SGN-CD228A and identify the MTD.
- DLTs will be evaluated in the first cycle during dose escalation. The MTD will be estimated based on data from all subjects across all evaluated dose levels.

Response and Safety Assessments

- Response assessments will be every 6 weeks per RECIST v1.1; MPM will also be assessed per modified RECIST.[3]
- All subjects will be followed for safety; AEs, vital signs, and laboratory assessments (metabolic panel, CBC with differential and reticulocyte count, eGFR, and coagulation panel) will be evaluated.
- The first 30 subjects enrolled will undergo triplicate 12-lead ECGs on Cycle 1 and 2, Days 1, 2, 3, 4, 8, and 15.

PK and Biomarker Assessments

- Dense PK sampling will be undertaken during Cycle 1 and additional samples in subsequent cycles. Antibody-conjugated MMAE, total antibody, and free MMAE concentrations in serum or plasma will be determined. Levels of ATA against SGN-CD228A in serum will be sampled at each cycle.
- Exploratory biomarker assessments may include assessments of peripheral blood and the tumor microenvironment, including retrospective evaluation of CD228 levels in tumor tissue.

Study Status

- The first subject was enrolled in Sep 2019; the study will continue until approximately 3 years after last subject has discontinued study treatment (estimated to be May 2022).
- The study has multiple sites in the US, UK, France, Spain, and Italy.
- Evaluation of multiple dose levels is ongoing.

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Abbreviations

ADC=antibody-drug conjugate; AE=adverse event; ATA=antitherapeutic antibodies; BC=breast cancer; CBC=complete blood count; CNS=central nervous system; CRC=colorectal cancer; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eGFR=estimated glomerular filtration rate; EGFR=epidermal growth factor receptor; HER=human epidermal growth factor receptor; IgG1=immunoglobulin G1; IV=intravenous; mAb=monoclonal antibody; MMAE=monomethyl auristatin E; MOA=mechanism of action; MPM=malignant pleural mesothelioma; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PDAC=pancreatic ductal adenocarcinoma; PK=pharmacokinetics; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

References

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Disclosures

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