A Phase 1 Study of SGN-PDL1V in Advanced Solid Tumors

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This study has been transitioned to CTIS with ID 2023-506604-18-00 check the CTIS register for the current data. Primary:- To evaluate the safety and tolerability of SGN-PDL1V in subjects with advanced solid tumors.- To identify the maximum...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51357

Source
ToetsingOnline

Brief title
A study of SGN-PDL1V in Advanced Solid Tumors

Condition

- Other condition
- Metastases

Synonym
cancer of head and neck, cancer of the esophagus (gullet), cancer of the ovaries, melanoma, non-small cell lung cancer, triple negative breast cancer

Health condition

squamous cell carcinoma of head and neck, non-small cell lung cancer, oesophageal squamous cell carcinoma, malignant melanoma, ovarian cancer, triple negative breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Seagen Inc.
Source(s) of monetary or material Support: Seagen Inc.

Intervention

Keyword: advanced solid tumors, first-in-human, refractory, relapsed

Outcome measures

Primary outcome

Safety assessments will include the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs), recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

Primary endpoints will be

- type, incidence, severity, seriousness, and relatedness of AEs and type, incidence, and severity of laboratory abnormalities
- incidence of dose-limiting toxicities (DLTs) and incidence of DLTs and cumulative safety by dose level

Secondary outcome

Antitumor activity will be assessed by radiographic imaging at protocol-specified time points.

Corresponding endpoints are objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as assessed by the investigator, duration of objective response per RECIST v1.1 as assessed by the investigator, progression-free survival (PFS) per RECIST v1.1 as assessed by the investigator, and overall survival (OS)

Pharmacokinetic and Immunogenicity Assessments: blood samples for PK and immunogenicity assessments will be collected at protocol-defined time points. PK parameters to be estimated may include, but are not limited to, area under the concentration-time curve (AUC), maximum concentration (Cmax), time to maximum concentration (Tmax), apparent terminal halflife (t*), and trough concentration (Ctrough). Additional analytes may be evaluated as necessary. Immunogenicity will be assessed based on the incidence of anti-drug antibodies (ADAs).

Pharmacodynamic and Biomarker Assessments: tumor tissue is required for enrollment.

Exploratory, predictive, and prognostic biomarkers associated with response, resistance, or safety observations will be monitored before and during treatment with SGN-PDL1V. Pharmacodynamic assessments may include disease burden monitoring (tumor mutational burden [TMB] from ctDNA or tumor antigens), changes to target expression, gene expression related to MOA, changes to tumor microenvironment, immune cell profiling, immune activation, receptor occupancy (RO), other biomarkers.
To characterize the malignancy and immune response, biomarker assessments in peripheral blood may include next generation sequencing of whole blood/circulating tumor DNA (ctDNA), proteomic methodologies, immunoassays as a marker of tumor response or therapy resistance, and markers of immune function, includingabundance of immune cell subsets and cytokines, gene expression,

cytogenetics, genetic polymorphisms,

somatic mutations associated with cancer and circulating immune function, and disease markers. SGN-PDL1Vinteractions with peripheral blood cells and tissues may also be monitored. Methods of analysis may include immunohistochemistry (IHC), next generation sequencing of RNA and DNA, and immunoassays such as flow cytometry and enzyme-linked immunosorbent assays (ELISA).

To characterize the malignancy and response to study treatment, biomarker assessments in tumor biospecimensmay include measurements of SGN-PDL1V and its potential metabolites as well as characterization of the tumor microenvironment, drug target(s), tumor subtyping, profiling of somatic mutations and/or gene expression. Assays may include IHC, proteomics and next generation sequencing of RNA and DNA.

Study description

Background summary

PD-L1 is expressed in numerous human adenocarcinomas, including, but not limited to ovarian, NSCLC, gastric cancer and gastroesophageal junction carcinoma, esophageal, endometrial, breast, bladder, cervical, colon, and pancreatic. Additionally, PD-L1 is expressed disproportionally high in cancers with mucinous histologies regardless of the tumor type. The high expression of PD-L1 on tumor cells is associated with tumorigenesis, metastatic potential, immune suppression, chemoresistance, and poor prognosis. Targeting PD-L1 with the ADC SGN-PDL1V has been studied in a series of preclinical disease models in vitro and in vivo. In vitro models have shown effective target binding and internalization of the ADC into cells as
well as cellular toxicity. In vivo, SGN-PDL1V demonstrated tumor growth-delay and tumor regression in a series of relevant tumor models.
Based on the evidence of preclinical effectiveness to date, SGN-PDL1V can be a new therapeutic option with the potential of delaying the development of new metastatic lesions and/or controlling or reducing disease burden. Subjects may also derive other benefits from participating in this phase 1 trial because of

the regimented routine that subjects undergo such as routine physical examinations, laboratory draws, and radiological examinations.

Study objective

This study has been transitioned to CTIS with ID 2023-506604-18-00 check the CTIS register for the current data.

Primary:
- To evaluate the safety and tolerability of SGN-PDL1V in subjects with advanced solid tumors.
- To identify the maximum tolerated dose (MTD) of SGN-PDL1V in subjects with advanced solid tumors.
- To identify a recommended dose and schedule for SGN-PDL1V.

Secondary:
- To assess the antitumor activity of SGN-PDL1V.
- To assess the pharmacokinetics (PK) of SGN-PDL1V.
- To assess the immunogenicity of SGN-PDL1V.

Exploratory:
- To characterize the pharmacodynamics of SGN-PDL1V.
- To assess the pharmacokinetic/pharmacodynamic (PK/PD) relationships of SGN-PDL1V.
- To assess exploratory markers of clinical outcomes, PK, and pharmacodynamics.
- To assess patient reported outcomes (PRO) for quality of life (QoL) per validated tools (Part C in head and neck squamous cell carcinoma (HNSCC) subjects only).

Study design

This is a phase 1, open-label, multicenter study designed to evaluate the safety, tolerability, PK, and antitumor activity of SGN-PDL1V in adults with select advanced solid tumors. The study will include multiple tumor types for the dose escalation (Part A), followed by cohorts for dose and schedule optimization (Part B, optional), and disease-specific cohorts in dose expansion (Part C).

The study will include dose escalation (Part A) enrolling subjects with HNSCC, non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC) or esophageal squamous cell carcinoma (SCC) who have programmed death -ligand 1 (PD-L1) expression >=1 by combined positive score (CPS), tumor proportion score (TPS), or immune cell score (%IC) based on historical testing. The initial dosing schedule to be tested will be Day 1 and Day 8 of a 21-day cycle (2Q3W). The initial dose level to be evaluated in the 2Q3W schedule is 0.5 mg/kg. Dose escalation will proceed by increments of 0.25

mg/kg, up to the dose level of 2.5 mg/kg, if tolerated. At any time, an alternative dosing schedule (eg, Day 1, Day 8, and Day 15 of a 28-day cycle [3Q4W], or Day 1 and Day 15 of a 28-day cycle [2Q4W], or Day 1 of a 21-day cycle [Q3W]) may be activated with additional subjects. The initial dose for the alternative dosing schedule will be the same as the dose cleared in the initial dosing schedule (ie, 2Q3W) as long as the dose intensity is the same or lower. The modified toxicity probability interval (mTPI) dose escalation rule will be applied separately to each dosing schedule. Not all alternative dosing schedules will necessarily be evaluated.

At the completion of dose escalation, dose and schedule optimization (Part B) may be activated to additionally evaluate up to two of the SGN-PDL1V dosing schedules recommended from Part A in 2 different tumor types. This part will allow optimization of the dose and schedule that will be recommended for expansion. The choice of which schedule(s) to open for enrollment will be made by the sponsor in consultation with the Safety Monitoring Committee (SMC), on the basis of available data on safety, dose-limiting toxicity (DLT), PK, and initial antitumor activity. Subjects as described in Part A will be enrolled in Part B. Up to 2 dosing schedules in 2 different tumor types may be evaluated in parallel cohorts with up to 10 subjects per schedule per tumor type. Subjects participating in Part B will be randomized to allocate to different dose and schedules with equal probability for a specific tumor type. If, following Part A, there is sufficient evidence to support bringing a dosing schedule forward for SGN-PDL1V, Part B may be omitted, provided at least 6 subjects have been dosed at the recommended dose and schedule. The optimal recommended dose and schedule for further evaluation in the Part C disease-specific expansion cohorts will be determined on the basis of safety, PK, preliminary antitumor activity, and relevant pharmacodynamic and biomarker data.

Dose expansion (Part C) in HNSCC with PD-L1 expression >=20 by TPS or CPS and NSCLC with PD-L1 expression >=50 by TPS will be activated by the sponsor in consultation with the SMC using the dose and schedule identified by Part A and/or Part B. Two additional disease-specific cohorts for HNSCC and NSCLC with PD-L1 expression <20 and <50, respectively, by TPS or CPS may be activated. An additional signal-seeking cohort in subjects with melanoma, ovarian cancer, TNBC, or esophageal SCC may be activated. A biology cohort including HNSCC, NSCLC, TNBC, esophageal SCC, melanoma or ovarian cancer may also be activated. The recommended dose and schedule for Part C will be determined in Parts A or B.

Dose escalation (Part A):
* Approximately 45 subjects will be treated to evaluate the safety, tolerability, and PK of SGN-PDL1V, and to identify the MTD and recommended dose and schedule. The dose-escalation portion of the trial will be conducted using the modified toxicity probability interval (mTPI) design (Ji 2010) to evaluate safety and tolerability, and to identify the MTD of SGN-PDL1V. If the MTD is not reached, safety, PK, pharmacodynamics, and biomarker analyses, as well as preliminary antitumor activity, will be used to determine a recommended dose

and schedule. Decisions on dose escalation, dose level modification, and subsequent cohort size will be made by the sponsor in consultation with the SMC. Note: For each new dose escalation cohort recommended for initiation by the SMC, no more than 1 subject should receive treatment within a 24 hour period. De-escalation to a lower dose level may be performed at any time by the sponsor in consultation with the SMC. At any time, an additional alternate dosing schedule for dose escalation (3Q4W, 2Q4W or Q3W) may be activated by the sponsor in consultation with the SMC. The initial dose for an alternate dosing schedule will be the same as the highest dose cleared in the original dosing schedule as long as the dose intensity will be the same or lower. The mTPI dose escalation rules will be applied separately to each dosing schedule. Not all alternative schedules will necessarily be evaluated.
* Dose-limiting toxicities (DLTs) will be evaluated during dose escalation. The DLT evaluation period will be the first cycle. A DLT is defined as any of the below criteria related to SGN-PDL1V treatment during the DLT evaluation period, excluding toxicities clearly related to disease progression or intercurrent illness. Grading will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

Dose and schedule optimization (Part B):
o Approximately 40 subjects with HNSCC, NSCLC, TNBC, or esophageal SCC who have PD-L1 expression >=1 by CPS, TPS, or %IC based on historical testing may be enrolled (up to 10 subjects per tumor type per schedule) to evaluate up to 2 different dosing schedules to optimize the dose and schedule for SGN-PDL1V. Subjects participating in Part B will be randomized to allocate to different dose and schedules with equal probability for a specific tumor type.
o If there is sufficient evidence to support bringing a dose and schedule forward for SGN-PDL1V based on dose escalation (Part A), Part B may be omitted.

Dose expansion (Part C): Subjects with PD-L1 expression >=20 and >=50, HNSCC and NSCLC, respectively, by TPS or CPS (approximately 40 subjects with HNSCC and NSCLC each) will be enrolled. Additional disease-specific expansion cohorts in subjects who have PD-L1 expression <20 and <50, for HNSCC and NSCLC, respectively, by TPS or CPS (approximately 40 subjects with HNSCC and NSCLC each) will be enrolled. A signal-seeking cohort in subjects with melanoma, ovarian cancer, TNBC or esophageal SCC (approximately 40 subjects total) may also start enrollment. A biology cohort (approximately 30 subjects with HNSCC, NSCLC, esophageal SCC, melanoma, TNBC or ovarian cancer) may be activated based on the data generated in Parts A and B of the study. Subjects in the biology cohort will be gated based on data generated from other expansion cohorts and must have accessible tumors to provide additional tissue for multiple (up to 3) biopsies to enable biomarker studies of SGN-PDL1V, comparing pre- and post-treatment tumor samples to characterize the clinical mechanism of action (MOA) and correlates of sensitivity/resistance at the MTD or recommended dose. Note: Part C will be initiated in France and Germany following submission of data from Parts A and B to the appropriate regulatory authorities.

An SMC consisting of site investigators, the study medical monitor, drug safety representative, and the study biostatistician will monitor the safety of subjects and make dosing recommendations throughout dose escalation and dose expansion. The SMC may recommend further evaluation of safety at a given dose (ie, enro

Intervention

SGN-PDL1V, referred to as the investigational product, is comprised of a human antibody which targets the PD-L1 inhibitory molecule (a member of the B7 family of immune checkpoint molecules) conjugated to the tubulin-disrupting antimitotic agent, monomethylauristatin E (MMAE) via a cleavable peptide linker. SGN-PDL1V will be administered intravenously.

Study burden and risks

This study is not very different from standard care. The tests and procedures that will be performed during this study mostly replace the ones the subject would have as part of standard care. Blood samples will be taken for safety and research tests and to check on the subject's disease. These are extra blood samples just for the study but there will also be blood draws for normal medical care.

Contacts

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Scientific
Seagen Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Parts A and B:
• Participants must have one of the following histologically- or cytologically-confirmed metastatic or unresectable solid tumor types
o Non-small cell lung cancer (NSCLC)
o Head and neck squamous cell carcinoma (HNSCC)
o Triple negative breast cancer (TNBC)
o Esophageal squamous cell carcinoma (SCC)
• Participants must have disease that is relapsed or refractory, that has progressed on approved therapies, be intolerant to or refused such therapies, or such and therapies are contraindicated and in the judgement of the investigator, should have no appropriate SoC therapeutic option
- Part C:
• Participants must have disease that is relapsed or refractory or be intolerant to SoC therapies and must have one of the following tumor types
o HNSCC
- Participants with HNSCC must have histologically or cytologically-confirmed SCC of the head and neck
o NSCLC
o Esophageal SCC
o TNBC
o Ovarian cancer
o Melanoma
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
- Measurable disease per RECIST v1.1 at baseline

Exclusion criteria

- History of another malignancy within 3 years of first dose of study treatment or any evidence of residual disease from a previously diagnosed malignancy.
- Known active central nervous system metastases. Participants with

previously-treated brain metastases may participate provided they:
• Are clinically stable for at least 4 weeks prior to study entry after brain metastasis treatment
• Have no new or enlarging brain metastases
• And are off of corticosteroids prescribed for symptoms associate with brain metastases for at least 7 days prior to first dose of study treatment
- Lepto-meningeal disease
- Prior treatment with an anti-PD-L1 agent within less than 5 half-lives.
- Previous receipt of an monomethylauristatin E (MMAE)-containing agent.
- Pre-existing neuropathy >=Grade 2 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2022
Enrollment:	13
Type:	Anticipated

Ethics review

Approved WMO Date:	04-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-06-2022
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-07-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-506604-18-00
EudraCT	EUCTR2021-003517-19-NL
ClinicalTrials.gov	NCT05208762
CCMO	NL80527.031.22