First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1047 in subjects with malignant solid tumors

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This study has been transitioned to CTIS with ID 2024-510722-10-00 check the CTIS register for the current data. • Evaluate antitumor activity based on response assessment criteria (RECIST v1.1)• Determine RP2D (unless determined in the Escalation...

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

Summary

ID

NL-OMON56075

Source
ToetsingOnline

Brief title
GEN1047 for Solid Tumors - FIH Trial

Condition

- Other condition

Synonym
cancer, Solid tumor

Health condition

breast, uterine, ovarian and squamous non-small cell lung cancer (NSCLC-SCC)

Research involving

Human

Sponsors and support

Primary sponsor: Genmab
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: First-in-human, Solid Tumors

Outcome measures

Primary outcome

Dose Expansion Part:

• Objective response rate (ORR) based on RECIST v1.1 as assessed by the

independent review committee (IRC)

Secondary outcome

Dose Expansion Part:

• Antitumor activity, based on RECIST v1.1 as assessed by the IRC: DOR, TTR, DCR

• Progression-free survival (PFS) based on RECIST v1.1 as assessed by the IRC;

Overall Survival (OS)

• AEs and safety laboratory parameters

• PK parameters (clearance; volume of distribution; AUClast; AUCinf; Cmax;

Tmax; Ctrough; t1/2)

• ADA response

Study description

Background summary

There is a strong unmet medical need to develop new efficacious therapies for

patients with advanced solid cancers whose disease no longer responds to currently available therapies. GEN1047 (DuoBody®-CD3×B7H4) is a bispecific antibody (bsAb) that induces T-cell mediated cytotoxicity of B7H4-positive cells by crosslinking cluster of differentiation (CD)3 on T cells with B7H4 expressed on target cells. The immune regulatory molecule B7H4 is expressed on various solid cancers. This is a first-in-human (FIH), open-label, multinational, phase 1/2a trial to evaluate the safety, preliminary efficacy, pharmacokinetics (PK), and pharmacodynamics of GEN1047. GEN1047 will be administered as an intravenous (IV) infusion to a population of patients with various malignant solid tumors known to express B7H4.

Study objective

This study has been transitioned to CTIS with ID 2024-510722-10-00 check the CTIS register for the current data.

• Evaluate antitumor activity based on response assessment criteria (RECIST v1.1)
• Determine RP2D (unless determined in the Escalation part)

Study design

This is an FIH, open-label, multinational, multicenter phase 1/2a trial to evaluate the safety, PK, pharmacodynamics, and preliminary efficacy of GEN1047.

The trial consists of 2 consecutive parts: a Dose Escalation (phase 1) and an Expansion (phase 2a). In the Dose Escalation, subjects will receive escalating doses of GEN1047. The incidence of dose-limiting toxicities (DLTs) will be monitored to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose(s) (RP2D). In the Expansion, preliminary efficacy of GEN1047 at the RP2D will be assessed together with safety, tolerability, PK, pharmacodynamics, and biomarkers.

Netherlands participation is for the Expansion (phase 2a) only.

Intervention

GEN1047 will be administered as an IV infusion to a mixed population of subjects with solid tumors.

Study burden and risks

Potential Benefit: The tumor-associated antigen B7H4 is expressed in a variety of solid cancers with unmet medical need, while expression on normal cells is limited. GEN1047 (DuoBody-CD3×B7H4) is a bsAb that induces T-cell mediated cytotoxicity of B7H4-positive tumor cells, associated with CD4+ and CD8+ T-cell

activation and cytokine production, by crosslinking CD3* on T cells and B7H4 on tumor cells. Crosslinking of CD3* and B7H4 by GEN1047 may have therapeutic benefits in patients with selected solid tumors in advanced stages who have very limited treatment options beyond palliative intent.

Potential Risks: GEN1047 is an investigational drug with safety data only available from nonclinical studies; no information is available regarding the adverse effects of GEN1047 in humans. Based upon the information to date, potential safety risks are based on the known MOA of GEN1047 in addition to nonclinical findings. Available clinical safety data from other compounds that engage with T cells suggest that cytokine release syndrome (CRS) is a frequent (>50%) adverse event (AE). CRS results in a defined constellation of symptoms including but not limited to chills, fever, hypoxia, and hypotension. Furthermore, the onset of this syndrome is acute (when administered IV). Immune effector cell-associated neurotoxicity syndrome (ICANS) is distinct manifestation of the same pathophysiology associated with activated T cell mediated cytokine release. It usually occurs concurrently with or after CRS onset and may temporarily affect cognitive function, speech, and level of consciousness (Lee et al., 2019). CRS and ICANS can be mitigated by 1) premedications including antipyretics, corticosteroids, and antihistamines and 2) a priming dose, defined as a dose of the compound of interest less than the *full* or subsequent doses. Mandatory short-term hospitalizations will further allow close observation of subjects treated with GEN1047 during the time period during which CRS may arise. Management of CRS and ICANS includes IV hydration, oxygen, corticosteroids, and interleukin (IL)-6 signaling pathway antagonist tocilizumab. Identification of potential risks and the risk mitigation strategies are detailed for GEN1047 in Table 2-2 of the protocol.

In addition to the above mitigation strategies against the potential risk of CRS and ICANS, multiple independent safety groups ie, the Dose Escalation Committee (DEC), and the sponsor Safety Committee will be reviewing data from this trial. The potential for enhanced benefit with manageable toxicity indicates that GEN1047 should be administered in patients of high unmet need including patients with solid malignancies who have progressed on all available SOC therapies and are therefore ineligible to receive these. All patients enrolled in this trial will be monitored by qualified health care professional(s) who will provide care and evaluate the patient's response to GEN1047, in terms of its safety and efficacy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Criteria - Escalation Part:
• Subject must have histologically or cytologically confirmed solid tumor(s) in any of the following selected indications for which there is no further available standard therapy likely to confer clinical benefit (or subject is not a candidate or has previously refused such earlier available therapy), and for whom, in the opinion of the investigator, experimental therapy with GEN1047 may be beneficial (breast cancer, endometrial cancer, ovarian cancer, squamous non-small-cell lung cancer [NSCLC-SCC]).
• Subjects with ovarian cancer must have documented progressive disease (PD) on or after last prior treatment and within 60 days of Screening.
• Must be at least 18 years of age (or the legal age of consent in the jurisdiction in which the trial is taking place) on the day of signing informed consent.
• Must have either recurrence after, or progression on or lack of response to available relevant standard of care (SoC) anticancer therapies; or are deemed intolerant to or ineligible for, standard curative therapy in the recurrent setting.
• Must have at least 1 measurable lesion per RECIST v1.1. The measurable

lesion(s) must be outside the field of radiation therapy (RT) if there was prior treatment with RT.
• Must have an Eastern Cooperative Oncology Group performance status (ECOGPS) score of 0 to 1 at Screening and on C1D1 pretreatment.
• Should provide a tumor tissue sample during the Screening period and prior to C1D1.
• Provide all tumor-assessing pre-trial CT scans since failure of last prior therapy.

Criteria - Expansion Part:
• Subjects must have documented PD according to RECIST v1.1 on or after last prior treatment with latest scan performed a maximum of 28 days prior to the first dose.
• Subject must have advanced (unresectable) or metastatic, histologically confirmed diagnosis (breast cancer, endometrial cancer, ovarian cancer, squamous non-small cell lung cancer [NSCLC-SCC]).
• Must be a female and at least 18 years of age (or the legal age of consent in the jurisdiction in which the trial is taking place) at the time of consent.
• Must have at least 1 measurable lesion per RECIST v1.1 as assessed by local investigator.
• Must have an ECOG- PS score of 0 to 1 at Screening and on Cycle 1 Day 1 (C1D1) pretreatment.
• Should provide a tumor tissue sample during the Screening period and prior to C1D1.
• Provide all tumor-assessing pre-trial CT scans since failure of last prior therapy.

Exclusion criteria

• Significant cardiovascular impairment within 6 months of the first dose of trial drug.
• Subject with new or progressive brain metastases or spinal cord compression.
• Subject has a history of bowel obstruction related to underlying disease.
• Subject has been exposed to any prior therapy with a compound targeting CD3 and/or B7H4 or cell based therapies.
• Current pneumonitis (any grade) including any radiological change of ongoing pneumonitis at baseline or history of non-infectious drug-, immune-, or radiation-related pneumonitis that required steroid.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	30-06-2023
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	N/A
Generic name:	DuoBody®-CD3×B7H4

Ethics review

Approved WMO Date:	08-02-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2023
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	CTIS2024-510722-10-00
EudraCT	EUCTR2021-001790-23-NL
ClinicalTrials.gov	NCT05180474
CCMO	NL82658.056.23