A Phase 2, Multicenter, Randomized, Open-Label Trial of GEN1046 as Monotherapy and in Combination With Pembrolizumab in Subjects With Relapsed/Refractory Metastatic Non-Small Cell Lung Cancer After Treatment With Standard of Care Therapy With an Immune Checkpoint Inhibitor

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This study has been transitioned to CTIS with ID 2024-513770-22-00 check the CTIS register for the current data. Primary objective:• Evaluate the anti-tumor activity of GEN1046 as monotherapy and in combination with pembrolizumab in subjects with…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms benign (excl mesotheliomas)
Study type	Interventional

Summary

ID

NL-OMON54259

Source
ToetsingOnline

Brief title
GEN1046 as mono and combination therapy in recurrent NSCLC (phase 2)

Condition

- Respiratory and mediastinal neoplasms benign (excl mesotheliomas)

- Respiratory tract neoplasms

Synonym
NSCLC, Relapsed/Refractory Metastatic Non-Small Cell Lung Cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: GEN1046, Non-Small Cell Lung Cancer (NSCLC), Pembrolizumab

Outcome measures

Primary outcome

Primary Endpoint:

• Objective response rate (ORR) per Response Evaluation Criteria in Solid

Tumors (RECIST) v1.1 as assessed by investigator

Secondary outcome

Secondary Endpoints:

• Duration of response (DOR) per RECIST v1.1

• Time to response (TTR) per RECIST v1.1

• Progression-free survival (PFS) per RECIST v1.1

• Overall survival (OS)

• Incidence and severity of adverse events (AEs)

• Incidence and severity of laboratory abnormalities

Study description

Background summary

GEN1046 (DuoBody®-PD-L1×4-1BB) is a PD-L1×4-1BB bispecific antibody that induces activation of T cells by simultaneously blocking an inhibitory signal via the programmed cell death protein 1 (PD 1)/ programmed death-ligand 1 (PD-L1) axis and conditionally inducing a stimulatory signal via 4-1BB. The Fc domain of GEN1046 was engineered to silence interactions with FcγR and the complement factor C1q. GEN1046 mediated signaling of 4 1BB on activated T cells is strictly dependent on simultaneous binding of the PD L1 arm. In addition, the PD L1 specific arm of GEN1046 functions as a classical immune checkpoint inhibitor (CPI) by blocking the PD-1/PD-L1 axis when 4-1BB binding is absent. The hypothesis is that by simultaneous binding of PD-L1 on tumor cells or antigen-presenting cells and 4-1BB on tumor-specific T cells, GEN1046 will induce efficacious T cell activation in the tumor or in tumor-draining lymph nodes, thereby enhancing antitumor immunity.

Although anti-PD-1/PD-L1 inhibitors as monotherapy or in combination with other systemic therapy have been approved for non-small cell lung cancer (NSCLC) as first line therapy, durable clinical responses are observed only in a minority of patients and resistance to these therapies remains a major challenge. Therefore, there is a strong unmet medical need to develop new efficacious therapies for the patients who no longer respond to standard of care (SOC) therapy. Thus, the dual-targeted approach by GEN1046 on both 4-1BB and PD-L1 receptors may improve the clinical benefits of anti-PD-1/anti PD-L1 inhibitors in patients with NSCLC after treatment with anti-PD-1/anti-PD-L1-containing therapies.
The objectives of the GCT1046-04 trial are to investigate the safety and efficacy of GEN1046 as monotherapy in a sequential activation regimen and in combination therapy with pembrolizumab in adult subjects with relapsed/refractory metastatic NSCLC after treatment with CPI containing therapy.

Study objective

This study has been transitioned to CTIS with ID 2024-513770-22-00 check the CTIS register for the current data.

Primary objective:
• Evaluate the anti-tumor activity of GEN1046 as monotherapy and in combination with pembrolizumab in subjects with relapsed/refractory metastatic NSCLC

Secondary objectives:
• Evaluate time to onset and durability of the anti tumor response of GEN1046 as monotherapy and in combination with pembrolizumab in subjects with relapsed/refractory metastatic NSCLC
• Evaluate the clinical benefit of GEN1046 as monotherapy and in combination

with pembrolizumab
• Assess safety and tolerability of GEN1046 as monotherapy and in combination with pembrolizumab

Study design

This is a phase 2, multicenter, randomized, open-label trial evaluating the safety and efficacy of GEN1046 as monotherapy and in combination with pembrolizumab in adult subjects with relapsed/refractory metastatic NSCLC after treatment with CPI-containing therapy.

Up to 24 subjects who are PD-L1 positive by local or central testing, are planned for enrollment in the safety run-in part of the trial. Up to 12 subjects can be enrolled in Arms B and C. Thereafter, enrollment in the randomized part of the trial will continue until at least 40 subjects, who are PD-L1 positive by central testing, have been randomized in each arm. It is expected that in total, approximately 160 subjects will be enrolled in the trial. Randomization will be stratified by PD-L1 expression (>=50% vs 1% to 49% PD-L1 positive tumor cells) and histology (squamous vs non-squamous).

a. GEN1046 100 mg Q3W for the first 2 cycles followed by GEN1046 500 mg Q6W for the subsequent cycles
b. GEN1046 100 mg Q3W in combination with pembrolizumab 200 mg Q3W
c. GEN1046 100 mg Q6W in combination with pembrolizumab 400 mg Q6W

During a preliminary safety run-in to assess tolerability of Arms B and C, an adapted *3+3* design will be utilized with up to 12 subjects (up to 6 subjects per arm) to be enrolled in Arms B and C in the following sequence. Three subjects from Arm C will be treated and closely monitored for 1 treatment cycle. If no subject experiences a DLT, no more subjects will be evaluated for DLTs in the safety run-in for Arm C. If at least one subject experiences a DLT, an additional 3 subjects will be treated in the safety run-in for Arm C. However, if two or three subjects experience a DLT of a similar nature, no more subjects will be treated in the safety run-in for Arm C unless endorsed by the Safety Committee. Upon the completion of 3 DLT-evaluable subjects in the safety run-in for Arm C, the same process will be followed for Arm B.

To better understand the safety, tolerability, PK, pharmacodynamic, or anti-tumor activity, up to 6 additional subjects may be allocated to Arms B and C in the safety run-in if the Safety Committee considers it appropriate. After completion of the safety run-in for Arms B and C, the collective data (including, but not limited to, all relevant safety and clinical data) will be evaluated. After this review, if the combination regimens do not pose significant safety concerns, randomization for Arms A, B, and C will begin.

Disease status will be evaluated per RECIST v1.1. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) will be obtained at

baseline before the first dose and 6, 12, 18, and 24 weeks (±7 days) after the first dose of trial medication, and thereafter, every 9 weeks (±7 days). CT or MRI will continue to be obtained until disease progression (as assessed by the investigator), start of subsequent anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. In Germany, the preferred imaging modality for all radiologic assessments should be MRI, unless the investigator deems this option is contraindicated for this trial.

Safety, including AEs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status (PS), vital signs, electrocardiograms, and laboratory values, will be monitored throughout the trial.

Blood samples will be drawn from all subjects to assess PK, pharmacodynamics, immunogenicity status, and other exploratory biomarkers. Subjects must provide fresh and/or archival tumor tissue for determination of PD-L1 expression in the tumors.

Changes in quality of life will be assessed via patient-reported outcomes questionnaires.

To explore the potential of including decentralized clinical trial (DCT) components in future studies in order to increase subject participation and retention, this trial includes an optional DCT part. The DCT part consists of remote visits conducted in the subject*s home or an agreed upon location by a dedicated DCT nurse and completion of questionnaires.

Intervention

All components of trial treatment are administered via IV infusion.
• Arm A: GEN1046 100 mg Q3W for the first 2 cycles followed by GEN1046 500 mg Q6W for the subsequent cycles
• Arm B: GEN1046 100 mg Q3W in combination with pembrolizumab 200 mg Q3W
• Arm C: GEN1046 100 mg Q6W in combination with pembrolizumab 400 mg Q6W

Study burden and risks

A subject will undergo extra examinations and tests which make the visits last longer than the subject is used to. Additionally, participation in this study may affect the subject's eligibility for receiving subsequent treatment for NSCLC.

For the complete study, a subject will need to visit the hospital approximately 53 times over 31 months. One visit will last approximately 4 hours. In total, approximately 3540 ml of blood will be collected over 31 months. For sites using CT scans, a subject will receive approximately 85 mSV of radiation in 31 months.

Treatment with GEN1046, whether or not combined with Pembrolizumab, may involve risks to humans not yet known, including potential life-threatening side effects. The study doctor will monitor a subject closely and treat side effects if needed. If needed, extra blood sampling or testing will be performed.

Furthermore, study procedures like blood draws, biopsies, MRI/CT and ECGs also carry potential risks.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Subject must be at least 18 years of age.
• Subject has histologically or cytologically confirmed diagnosis of stage 4 NSCLC with at least 1 prior line of systemic therapy containing an

anti-PD-1/PD-L1 monoclonal antibody (mAb). Subjects must have demonstrated disease progression (PD) as defined by RECIST v1.1. For the subjects whose most recent anti-cancer therapy contained an anti-PD-1/PD-L1 mAb, their recent evidence of PD must be confirmed by a second assessment no less than 4 weeks from the date of the initial documented PD.
Note: Subject must have received at least 2 doses of an approved anti PD-1/PD-L1 mAb approved in NSCLC.

o Subject has progressed during or after treatment with 1 anti-PD-1/PD-L1 mAb administered either as monotherapy, or as SOC combination (subjects who have received only anti-PD-1/PD-L1 mAb monotherapy as first-line therapy, are eligible for this study if the investigator determines treatment with platinum-containing chemotherapy is not appropriate, in line with local treatment guidelines) or;
o Subject has progressed during or after platinum doublet chemotherapy following an anti-PD-1/PD-L1 mAb or;
o Subject has progressed during or after an anti-PD-1/PD-L1 following platinum doublet chemotherapy.

• Subject must have a tumor PD-L1 expression result available prior to C1D1 demonstrating PD-L1 expression in >=1% of tumor cells as assessed by a sponsor designated central laboratory using the Dako PD-L1 IHC 22C3 pharmDx assay (TPS>=1%), or per site local assessment with the Dako PD-L1 IHC 22C3 pharmDx assay (TPS>=1%) or the VENTANA PD-L1 (SP263) assay (TC >=1%) adhering to the manufacturer*s instructions.
Note: Local PD-L1 result needs to be performed on fresh tumor tissue (obtained within 3 months prior to enrollment and after failure/stop of last prior treatment) or, if not feasible, archival tissue (obtained within 12 months prior to enrollment).
• Subject must have measurable disease per RECIST v1.1 as assessed by the investigator.
• Subject must have ECOG PS <=1.
• Subject must have life expectancy of at least 3 months.
• Subject must have adequate organ and bone marrow function as described in the protocol.

Exclusion criteria

• Documentation of known EGFR sensitizing mutations, KRAS, RET, ROS1, BRAF mutations, NTRK gene infusions, RET rearrangement, ALK gene rearrangements, high level
MET amplification, or METex 14 skipping. If documentation of mutation status is not available, for subjects with non-squamous histology or a mixed histology of non-squamous and squamous, a formalin-fixed, paraffin-embedded tumor tissue should be tested for biomarker panel analysis (which may include, but is not

limited to, EGFR, ALK, ROS1, BRAF, KRAS mutations, RET rearrangement, or NTRK gene infusions, etc.). Subjects must not be randomized until biomarker status is available in source
documentation at the site.
Note: Subjects with tumors harboring such targetable mutations, gene rearrangements, or gene amplifications as described above may enroll in the trial, if such subjects have also received an approved targeted therapy for this indication assuming satisfactory fulfilment of all other eligibility criteria (especially, at least 1 prior line of systemic therapy containing an anti-PD-1/PD-L1 mAb for metastatic NSCLC disease).

• Subject has been exposed to any of the following prior therapies:
o Prior treatment with docetaxel for NSCLC.
o Prior treatment with a 4-1BB (CD137) targeted agent, any type of antitumor vaccine, or autologous cell immunotherapy.
o Treatment with an anti-cancer agent within 28 days prior to GEN1046 administration.
• Subject discontinued treatment due to disease progression within the first 6 weeks of a CPI-containing treatment.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-02-2023
Enrollment:	25
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	GEN1046
Generic name:	GEN1046
Product type:	Medicine
Brand name:	Keytruda
Generic name:	pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-01-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	25-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2023

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2024
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	CTIS2024-513770-22-00
EudraCT	EUCTR2021-001928-17-NL
ClinicalTrials.gov	NCT05117242
CCMO	NL79351.056.21