A Phase I/IIa Open-label Dose Escalation and Expansion Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of AZD7789, an anti-PD-1 and anti-TIM-3 Bispecific Antibody, in Participants with Advanced or Metastatic Solid Tumors

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This study has been transitioned to CTIS with ID 2022-502774-17-00 check the CTIS register for the current data. Part A Dose Escalation: To assess the safety and tolerability, characterize the dose-limiting toxicities (DLTs), and determine the...

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

Summary

ID

NL-OMON56048

Source
ToetsingOnline

Brief title
D9570C00001 (study with AZD7789)

Condition

- Other condition
- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym

Metatstatic Solid Tumors, Solid tumors

Health condition

Maagdarmstelselneoplasmata benigne

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Opdrachtgever/sponsor: AstraZeneca

Intervention

Keyword: AZD7789, PD-1, Solid tumors, TIM-3

Outcome measures

Primary outcome

Part A Dose Escalation:

To assess the safety and tolerability, characterize the DLTs, and determine the

MTD or OBD and a RP2D of AZD7789 in

participants with advanced or metastatic solid tumors

Part B Expansion:

To assess the safety and tolerability of AZD7789 in participants with advanced

or metastatic solid tumors

To assess the preliminary antitumor activity of AZD7789 in participants with

advanced or metastatic solid tumors

Secondary outcome

Part A Dose Escalation

To assess the preliminary antitumor activity of AZD7789 in participants with

advanced or metastatic solid tumors

Part B Dose Expansion

To further assess the preliminary antitumor activity of AZD7789 in participants with advanced or metastatic solid tumors

Part A Dose Escalation and Part B Dose Expansion

To assess the pharmacokinetics (PK) of AZD7789 in participants with advanced or metastatic solid tumors

To assess the immunogenicity of AZD7789 in participants with advanced or metastatic solid tumors

Study description

Background summary

While PD-1/PD-L1 targeting strategies have yielded a breakthrough in cancer therapeutics, the majority of cancers progress even after initial response to anti-PD-1/PD-L1 antibody therapy suggesting that additional immune therapies are required to further improve patient outcome.

Multiple reports have identified a high correlation in PD-1 and TIM-3 expression on tumor infiltrating lymphocytes associated with diminished functionality. Additionally, recent studies suggest that TIM-3 is upregulated on T cells following PD-1 receptor blockade and acts as a compensatory inhibitory mechanism to downregulate antitumor T cell responses.

Dual targeting of PD-1 and TIM-3 has the potential to reinvigorate an immune response in participants who develop progression on prior PD-1/PD-L1 monotherapies and also may lead to more durable responses in participants who have not been previously treated with PD-1/PD-L1 checkpoint inhibitors, thereby resulting in a clinical benefit.

Study objective

This study has been transitioned to CTIS with ID 2022-502774-17-00 check the CTIS register for the current data.

Part A Dose Escalation:
To assess the safety and tolerability, characterize the dose-limiting toxicities (DLTs), and determine the maximum tolerared dose (MTD) or optimal biological dose (OBD) and a recommended phase 2 dose (RP2D) of AZD7789 in participants with advanced or metastatic solid tumors

Part B Expansion:
To assess the safety and tolerability of AZD7789 in participants with advanced or metastatic solid tumors
To assess the preliminary antitumor activity of AZD7789 in participants with advanced or metastatic solid tumors

Study design

This is a first-time-in-human (FTIH), multicenter, open-label, dose-escalation and dose-expansion study to evaluate the safety, tolerability, PK, pharmacodynamics, and antitumor activity of AZD7789 in adult participants with advanced or metastatic non-small cell lung cancer (NSCLC) and other solid tumors. The study includes 2 parts: Part A Dose Escalation and Part B Dose Expansion. Initially, participants with Stage IIIB to IV NSCLC will be enrolled in the study; additional tumor types may be explored and added in a future amendment to the clinical study protocol.

Approximately 192 participants will receive treatment with AZD7789 in the study at approximately 20 sites globally.
Part A Dose Escalation will evaluate approximately 8 dose levels of AZD7789 in approximately 41 participants with Stage IIIB to IV NSCLC with PD-L1 tumor proportion score (TPS) <1% or >=1% who have anti-PD-1/PD-L1 immune-oncology (IO) acquired resistance in order to determine a MTD or OBD and a RP2D.
Dose escalation for the first 5 dose levels of AZD7789 (2, 7, 22.5, 75, and 225 mg) is planned to follow an accelerated titration design (ATD) consisting of 5 single-participant cohorts. Dose escalation for subsequent dose levels of AZD7789 (750, 1500, and 2000 mg) will follow the modified toxicity probability interval (mTPI-2) algorithm consisting of a minimum of 3 and a maximum of 12 participants per dose level. If predefined safety criteria are met in an ATD cohort, dose escalation will switch to the mTPI-2 algorithm for all subsequent dose levels.
Intermediate dose levels (50, 150, 450, 1000, 1250, and 1750 mg) may be explored if warranted by emerging safety, PK, pharmacodynamic, biomarker, and response data. Participants will be evaluated for DLTs during a 21-day DLT-evaluation period.

Part B Dose Expansion may be initiated once the MTD or OBD and a RP2D is established in Part A Dose Escalation and will evaluate the safety,

tolerability, PK, pharmacodynamics, and antitumor activity of AZD7789 at the RP2D determined during Part A Dose Escalation in 3 cohorts (Cohorts B1, B2 and B3) described below.

Cohort B1: Approximately 20 participants with Stage IIIB to IV NSCLC with PD-L1 expression >= 1% who have received at least 1 prior line of treatment and have anti-PD-1/PD-L1 IO acquired resistance.

Cohort B2: Approximately 20 participants with Stage IIIB to IV NSCLC with PD-L1 expression >= 50% who have received no prior therapy including IO therapy (ie, IO naïve).

Cohort B3: Approximately 20 participants with Stage IIIB to IV NSCLC with PD-L1 expression >= 1% who have received at least 1 prior line of treatment and have anti-PD-1/PD-L1 IO acquired resistance. Cohort B3 and B1 are the same, only dosing differs.

Cohort B4: Approximately 20 participants with advanced or metastatic gastric and GEJC who must have received at least one but no more than two prior lines of systemic therapy in the advanced/metastatic setting, of which only one prior line of therapy contained an approved anti-PD-1/PD-L1 therapy.

Intervention

Part A Dose Escalation:
Ascending dose levels of AZD7789 (2, 7, 22.5, 75, 225, 750, 1500, and 2000 mg) will be given IV every 3 weeks

Part B Dose Expansion:
The recommended phase II dose will be given IV every 3 weeks

Study burden and risks

Patients have to visit the hospital more often and the visits take longer. On several days during the study, patients will undergo the following assessments:
- Anamnesis (inclusive medical history)
- ECHO/MUGA scan (LVEF)
- ECG
- Vital signs (blood pressure, heart rate, body temperature, respiratory rate, SpO2)
- Length and weight
- ECOG performance status
- Physical examination
- Blood and urine examination
- Pregnancy test (if applicable)
- AE/SAE

- CT/MRI at screening and during the first 54 weeks of the study every 6 weeks and every 12 weeks thereafter
- MRI brain (at screening and if applicable thereafter)
- Bone scan (at screening and if applicable thereafter)
- Admission of study medication
- Tumour Biopsy at screening and at cycle 3 day 1 (mandatory for patients at part A: dose escalation backfill cohorts)
- Tumour Biopsy (optional tumour biopsy at progression)

The risks of AZD7789 are not fully known at this time. Using information available about drugs that work in a similar way to AZD7789 and information from studies of AZD7789 given to animals, the Sponsor has determined the following side effects that could occur when AZD7789 is administered in patients.

Immune-mediated side effects that may occur include, but are not limited to:
• Skin disorders causing rash, pruritus (itching), raised patchy skin lesions, or skin blisters.
• Colitis
• Endocrine abnormalities: thyroiditis, adrenal insufficiency, or type 1 diabetes mellitus
• Hepatitis
• Pneumonitis
• Myositis
• Increased pancreatic enzymes (including amylase and lipase)
• Nephritis
• Myocarditis
• Encephalitis
Other side effects include:
• Infusion-related reactions, these reactions include fever, chills, myalgia, nausea, vomiting, pruritus, rash, headache, flushing, sweating, increased heart rate, difficulty breathing, decreased blood pressure, dizziness, or light-headedness.
• Anaphylaxis
• Immune complex disease
• Cytokine release syndrome
• Cytokine storm syndrome
• Tumor Lysis Syndrome

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

General Inclusion Criteria for all cohorts:
• Must be >= 18 years of age
• Part A, B1, B2 and B3: Histologically or cytologically documented Stage IIIB to IV non-small cell lung carcinoma (NSCLC) not amenable to curative surgery or radiation
• Part B4: Histologically or cytologically documented advanced or metastatic gastric and GEJC not amendable to curative surgery
• Must have at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
• Provision of fresh tumor tissue sample and consent to undergo mandatory on-treatment biopsy for participants enrolled in Part A Dose-escalation participants
• Provision of archival tumor tissue sample or fresh tissue sample for Part B Dose-expansion participants
• Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
• Non-pregnant women and willingness of female participants to avoid pregnancy or male participants willing to avoid fathering children through highly effective methods of contraception

• Adequate organ and bone marrow function measured within 28*days prior to first dose.
Part A Dose Escalation Additional Inclusion Criteria:
• May have squamous or non-squamous NSCLC
• Must have received at least one prior line of systemic therapy, of which at least one prior line of therapy contained approved anti-PD-1/PD-L1
• Must have had immune-oncology (IO) acquired resistance
• PD-L1 <1% of >1% documented
Part B Dose Expansion Cohort B1 and B3 Additional Inclusion Criteria:
• May have squamous or non-squamous NSCLC
• Must have received at least one prior line of systemic therapy, of which only one prior line of therapy contained approved anti-PD-1/PD-L1
• Must have had IO acquired resistance
• PD- L1 expression >= 1% as determined by IHC
Part B Dose Expansion Cohort B2 Additional Inclusion Criteria:
• May have squamous or non-squamous NSCLC
• Must not have received prior systemic therapy including IO therapy in the first-line setting
• PD-L1 expression >= 50% as determined by IHC
Part B Dose Expansion Cohort B4 Additional Inclusion Criteria:
• Must not have received at least one but no more than two prior lines of systemic therapy in the advanced/metastatic setting, of which only one prior line of therapy contained an approved anti-PD-1/PD-L1 therapy
• Must have had IO acquired resistance
• There are no PD-L1 status requirements for this cohort

Exclusion criteria

• Patients with sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) fusions
• Documented test result for any other known genomic alteration for which a targeted first line therapy is approved per local standard of care (SoC)
• Part B dose-expansion Cohort B4: documented HER2 amplification (unless an SoC including an anti-HER2 therapy has been received)
• Unresolved toxicities of >= Grade 2 from prior therapy
• Any prior >= Grade 3 immune-mediated adverse event (imAE) while receiving immunotherapy or any unresolved imAE >= Grade 2
• Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy
• Symptomatic central nervous system (CNS) metastasis or leptomeningeal disease
• History of symptomatic and objectively confirmed arterial (including myocardial infarction) or venous thromboembolic event within 6 months prior to study drug dosing, unless participant is on treatment with adequate antithrombotic medication and is considered to be stable by the investigator.
• History of organ transplant or allogenic hematopoietic stem cell transplant.

• Infectious disease exclusions: Active infection including TB, HIV, hepatitis A, chronic or active hepatitis B, chronic or active hepatitis C, active COVID-19 infection
• History of clinically significant arrhythmia as judged by the Investigator.
• Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, cardiomyopathy of any etiology, symptomatic congestive heart failure, uncontrolled hypertension, uncontrolled diabetes mellitus, unstable angina pectoris, history of myocardial infarction within the past 6 months, serious chronic gastrointestinal conditions associated with diarrhea, active non infectious skin disease. For Part B Dose-expansion Cohort B4, medication-resistant ascites requiring drainage in the last 28 days prior the start of AZD7789 and/or the occurrence of active gastro-intestinal bleeding, as judged by the Investigator.
• Active or prior documented autoimmune or inflammatory disorders, including inflammatory bowel disease (eg, colitis or Crohn's disease), diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis, Hypophysitis, uveitis, etc.. Some exceptions have been specified in the protocol.
• Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD
• Major surgical procedure within 28 days prior to the first dose of study intervention or still recovering from prior surgery
• Other invasive malignancy within 2 years prior to screening
• Congenital long QT syndrome or history of QT prolongation associated with other medications that cannot be changed or discontinued based on a cardiologist assessment
• Any previous treatment with anti-TIM-3 therapy in any setting is not permitted. For Part A, B1 and B3: treatment with investigational therapy prior to initiation of study treatment except where the most recent line of therapy was investigational agents added to approved anti-PD-1/PD-L1 as part of standard of care. Investigational agents may be given as prior lines of therapy (other than the most recent line) and as a monotherapy, they must be given in combination with approved anti-PD-1/PD-L1. For Part B4: investigational agents, other than investigational immune checkpoint inhibitors or other IO agents, may be given as any prior lines of
therapy
• Current or prior use of immunosuppressive medication within 14 days prior to the first dose of study intervention
• Any concurrent chemotherapy, radiotherapy, investigational, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for noncancer-related conditions is acceptable.
• Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Participants should not receive live vaccine while receiving study intervention and up to 30 days after the last dose of study intervention

• Radiotherapy treatment to the lung within <= 4 weeks of the first dose of AZD7789. Palliative bone radiotherapy is allowed if >= 2 weeks prior to the first dose of AZD7789.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2022
Enrollment:	14
Type:	Actual

Ethics review

Approved WMO Date:	29-04-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-05-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	03-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	18-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-11-2023
Application type:	Amendment
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Approved WMO Date:	08-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-03-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-03-2024
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	CTIS2022-502774-17-00
EudraCT	EUCTR2021-000036-57-NL
ClinicalTrials.gov	NCTnummernognietbekend
CCMO	NL77084.031.21