A PHASE Ia/Ib, OPEN LABEL, MULTICENTER, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND ACTIVITY OF RO7502175 AS A SINGLE AGENT AND IN COMBINATION WITH ATEZOLIZUMAB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

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This study has been transitioned to CTIS with ID 2023-504709-35-00 check the CTIS register for the current data. This is a first-in-human Phase Ia/Ib, open-label, multicenter, dose-escalation study designed to evaluate the safety, tolerability,...

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

Summary

ID

NL-OMON56405

Source
ToetsingOnline

Brief title
GO43860 Study

Condition

- Other condition
- Metastases

Synonym
A solid tumor/cancer is an abnormal tissue mass that arises from uncontrolled growth of cells and continues to grow locally or spread to other parts of the body (metastatic).

Health condition

Locally Advanced or Metastatic Solid Tumors

Research involving
Human

Sponsors and support

Primary sponsor: Genentech Inc. c/o F. Hoffmann-La Roche Ltd
Source(s) of monetary or material Support: Genentech Inc.

Intervention

Keyword: Atezolizumab, Locally Advanced Solid Tumors, Metastatic Solid Tumors, RO7502175

Outcome measures

Primary outcome

Safety objective:

The safety objective for this study is to evaluate the safety of RO7502175 when

administered as a single agent (Phase Ia) or in combination with atezolizumab

(Phase Ib), including characterization of dose-limiting toxicities (DLTs), on

the basis of the following endpoints:

• Incidence and nature of DLTs

• Incidence and severity of adverse events, with severity determined according

to National Cancer Institute Common Terminology Criteria for Adverse Events,

Version 5.0

• Change from baseline in targeted vital signs

• Change from baseline in targeted clinical laboratory test results

• Change from baseline in ECG parameters

Secondary outcome

Pharmacokinetic objectives:

The pharmacokinetic (PK) objective for this study is to characterize the RO7502175 PK profile when administered as a single agent (Phase Ia) or in combination with atezolizumab (Phase Ib) on the basis of the following endpoint:

• Serum concentration of RO7502175 at specified timepoints

Activity objectives:

The activity objective for this study is to make a preliminary assessment of the activity of RO7502175 when administered as a single agent (Phase Ia) or in combination with atezolizumab (Phase Ib) on the basis of the following endpoints:

• Objective response rate (ORR), defined as the proportion of patients with a complete response or partial response on two consecutive occasions >= 4 weeks apart, as determined by the investigator according to RECIST v1.1

• Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1

• Progression-free survival (PFS) after enrollment, defined as the time from enrollment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to

RECIST v1.1

Immunogenicity objectives:

The immunogenicity objective for this study is to evaluate the immune response to RO7502175 when administered as a single agent (Phase Ia) or in combination with atezolizumab (Phase Ib) on the basis of the following endpoints:

• Prevalence of anti-drug antibodies (ADAs) to RO7502175 at baseline (baseline prevalence) and incidence of ADAs to RO7502175 after initiation of study treatment (post-baseline incidence)

Biomarker objective:

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to RO7502175 when administered as a single agent (Phase Ia) or in combination with atezolizumab (Phase Ib) (i.e., predictive biomarkers), can provide evidence of RO7502175 activity (i.e., pharmacodynamic [PD] biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to RO7502175, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

• Relationship between biomarkers in blood and tumor tissue and safety, PK, PD, activity, immunogenicity, or other biomarker endpoints

Additional objective:

An additional objective for this study is to identify a recommended Phase II

dose for RO7502175 on the basis of the following endpoint:

• Relationship between RO7502175 dose and safety, PK, PD, activity, and

immunogenicity endpoints

Study description

Background summary

Current treatment options for solid tumor malignancies include chemotherapy, radiation, surgery, targeted therapies, and immunotherapy. One form of immunotherapy, known as checkpoint inhibitor (CPI) therapy, works by blocking inhibitory receptors on T cells, with the goal of enhancing tumor-specific T-cell responses, resulting in anti-tumor activity. CPIs, such as PD-(L)1 inhibitors, have demonstrated clinical efficacy and are approved for the treatment of various cancers (Tecentriq; Keytruda; Opdivo). However, not all cancers respond to CPIs and many tumors progress following initial treatment, suggesting that additional immunosuppressive factors, such as regulatory T cells (Treg cells), may be present that inhibit anti-tumor responses.

RO7502175 is an afucosylated humanized IgG1 antibody that binds to human C-C motif chemokine receptor 8 (CCR8). RO7502175 binds to the N-terminus of CCR8 and does not block binding of CCR8 to its natural ligand. CCR8 is a chemokine receptor that is expressed on Treg cells. Treg cells are a subset of CD4+ T cells that are immunosuppressive and play a key role in preventing autoimmunity. RO7502175 is designed to preferentially eliminate CCR8+ Treg cells in the tumor microenvironment through antibody-dependent cell-mediated cytotoxicity (ADCC)-mediated depletion, thus reversing the suppression of CD8+ effector T cells. RO7502175 is designed to deplete intra-tumoral Treg cells, with the goal of enhancing the host immune response against cancer cells without evoking autoimmunity.

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors. These are PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells.
Atezolizumab has been shown to block PD-L1 binding, thereby enhancing tumor-specific T cell responses, resulting in improved anti-tumour activity. Atezolizumab has minimal binding to Fc receptors, eliminating detectable Fc

effector function and associated antibody-mediated clearance of activated CD8+ effector T cells. Atezolizumab is approved by some health authorities for the treatment of urothelial carcinoma (UC), NSCLC, small cell lung cancer, triple negative breast cancer (TNBC), hepatocellular carcinoma (HCC), and melanoma.

Combination therapies that address resistance to anti-PD-L1/PD-1 therapies are needed. Treg cells are believed to contribute to the resistance of tumors to cancer immunotherapy, and selective Treg cell depletion may provide a mechanism to overcome this resistance. Through the targeting of CCR8, RO7502175 is designed to specifically deplete intra-tumoral Treg cells, with the goal of enhancing the host immune response against cancer cells without evoking significant autoimmunity.

More information can be found in section 1 of the research protocol.

Study objective

This study has been transitioned to CTIS with ID 2023-504709-35-00 check the CTIS register for the current data.

This is a first-in-human Phase Ia/Ib, open-label, multicenter, dose-escalation study designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary anti-tumor activity of RO7502175 as a single agent (Phase Ia) or in combination with atezolizumab (Phase Ib) and to identify a recommended Phase II dose for RO7502175 in patients with locally advanced, recurrent, or metastatic incurable solid tumor malignancies.

Study design

Both the Phase Ia and Ib portions of the study consist of a screening period, a treatment period, a follow-up period, and a survival follow-up. In each phase, patients are admitted into two phases: a dose-escalation phase and an expansion phase.

In the escalation phases, the maximum tolerated dose (MTD) or maximum dose administered (MAD) of R07502175 as monotherapy (Phase Ia) or in combination with atezolizumab (Phase Ib) is determined. In the expansion phases, patients will be treated at or below the maximum tolerated dose (MTD) or maximum dose administered (MAD) of R07502175 as monotherapy (Phase Ia) or in combination with atezolizumab (Phase Ib).

Patients in the Phase Ia portion of the study may be transferred to the Phase Ib portion and treated with RO7502175 in combination with atezolizumab, provided they meet crossover criteria.

Intervention

The investigational medicinal products for this study are RO7502175 (Phase Ia and Ib) and atezolizumab (Phase Ib only). RO7502175 will be administered on Day 1 of every 21-day cycle by IV infusion in the Phase Ia and Phase Ib portions of this study. The starting dose of RO7502175 is 2 mg. Atezolizumab (Phase Ib) will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle in combination with RO7502175. Atezolizumab will be administered after RO7502175 and the subsequent observation period.

Study burden and risks

Because this is a first-in-human study of RO7502175, the clinical benefit and risks are unknown. However, the available nonclinical data showing the anti-tumor effects of antiCCR8 as a single agent, and the synergistic anti-tumor effects in combination with antiPD-L1, provide a strong rationale for evaluating RO7502175 in cancer patients.

General risks
• Infusion-Related Reactions (IRR) directed against introduced recombinant antibodies. RO7502175 is expected to have a low risk of cytokine release syndrome. This antibody binds to CCR8 outside the ligand binding site (does not inhibit the function of CCR8)
• Immunogenicity - ADAs (anti-drug antibodies) may develop which may affect drug safety through allergic response and immune complex-mediated disease.
• Immune-mediated adverse events (irAEs) can involve virtually all organ systems

Risks related to treatment with atezolizumab are largely already known. These include: rash, flu-like symptoms, endocrinopathies, hepatitis, transaminitis, pneumonitis, colitis, and myasthenia gravis.

Risks related to treatment with RO7502175 are still largely unknown, let alone those that could occur in combination treatment with atezolizumab.

Tregs play a critical role in immune homeostasis and skin homeostasis. A large portion of the Tregs reside in the skin, where they are involved in hair follicle generation, wound healing, and immune tolerance to commensal microbes. Therefore, depletion of Tregs with RO7502175 is expected to cause a disruption of skin homeostasis with implications for hair development, wound healing, and tolerance to the commensal skin microbiome.

Dermatologic toxicity and rash are identified risks for other partial Treg depletion agents, including anti-CCR4 (mogamulizumab) and anti-CD25 (RO7296682). However, skin toxicity was not observed in toxicity studies in cynomolgus monkeys

Risk of mild neutropenia and thrombocytopenia

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

- Age >= 18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Life expectancy >= 12 weeks
- Adequate hematologic and end-organ function
- Histologically confirmed locally advanced, recurrent, or metastatic incurable solid tumor malignancy
- Availability of representative tumor specimens
- Measurable disease per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating sperm

Exclusion criteria

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of study treatment
- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases
- History of leptomeningeal disease
- Significant cardiovascular disease within 3 months prior to initiation of study treatment
- History of malignancy other than disease under study within 3 years prior to screening
- Any immune-mediated adverse events related to prior cancer immunotherapy that have not resolved completely to baseline
- Active or history of autoimmune disease or immune deficiency
- Active tuberculosis, hepatitis B or acute or chronic active EBV infection
- Positive test for human immunodeficiency virus (HIV) infection
- Positive hepatitis C virus (HCV) antibody test
- Known infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Major surgical procedure or significant traumatic injury within 28 days prior to first study drug infusion
- Prior allogeneic stem cell or organ transplantation

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	30-09-2023
Enrollment:	62
Type:	Anticipated

Medical products/devices used

Generic name:	VENTANA PD-L1 (SP142) Assay and VENTANA PD-L1 (SP263) Assay
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	RO7502175
Generic name:	-
Product type:	Medicine
Brand name:	RO7502175 Diluent
Generic name:	-
Product type:	Medicine
Brand name:	Tecentriq®
Generic name:	Atezolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-11-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-06-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	19-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	CTIS2023-504709-35-00
EudraCT	EUCTR2021-006708-34-NL
ClinicalTrials.gov	NCT05581004
CCMO	NL82332.042.23