A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab (SAR650984) in combination with atezolizumab or isatuximab alone in patients with advanced malignancies

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Phase1: To characterize the safety and tolerability of isatuximab in combination with atezolizumab in participants with unresectable hepatocellular carcinoma (HCC), platinum-refractory recurrent/metastatic squamous cell carcinoma of the head and...

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46722

Source
ToetsingOnline

Brief title
ACT15377

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Sanofi

Intervention

Keyword: anti PD-1/PD-L1 mAb, anti-CD38 mAb, cancer, solid tumors

Outcome measures

Primary outcome

Phase 1:

- Dose limiting toxicities (DLTs) (in Cycle 1)

- Adverse events (AEs)/serious adverse events (SAEs),

- Laboratory abnormalities and the recommended Phase 2 dose (RP2D) defined as

the dose selected for the Phase 2 portion.

Phase 2 :

- RR defined as the proportion of patients with complete response and partial

response as best overall response (assessed by Investigators using RECIST

criteria 1.1 for patients with HCC, SCCHN and EOC;

- PFS-6 defined as the PFS rate at 6 months assessed by Investigators using

RANO criteria for GBM.

Secondary outcome

Phase 2:

- Adverse events (AE)/serious AEs and laboratory abnormalities;

- Incidence rate of anti-drug antibodies development (ADA: anti-isatuximab and

anti-atezolizumab antibodies)

- PK assessed from concentrations of isatuximab (non-compartmental analysis and population PK approach) and atezolizumab (population PK approach).

- Best percent-change from baseline in tumor burden change, disease control rate (DCR) defined as the sum of the complete response, partial response and stable disease rates, duration of response (DoR), progression free survival (PFS) (HCC, SCCHN, EOC per RECIST 1.1 and GBM per RANO criteria), RR (GBM only, per RANO criteria).

Study description

Background summary

Monoclonal antibodies that block the PD-1/PD-L1 axis have changed the landscape of cancer therapy. Despite the success of PD-1/PD-L1 blockers, optimal outcomes for many patients will require combination therapies. In solid tumors, CD38 is found expressed on the tumor cells of treatment naïve prostate adenocarcinoma and glioblastoma biopsies. A recent report has shown that the combination of anti-PD-L1 and CD38 antibodies induces a greater anti-tumor immune response than anti-PD-L1 in a mouse lung cancer model.
Isatuximab can induce different immuno-modulatory mechanisms that can contribute to reshape the tumor microenvironment and enhance the anti-tumor activity of anti-PD-1 antibodies. Isatuximab has shown clinical response in relapsed/refractory MM patients as a single agent and in combination with immunomodulatory agents. Although isatuximab has not been tested yet in solid tumors, we hypothesize, based on the immunomodulatory activities described above, that isatuximab may contribute to reshaping the tumor immune-environment and will enhance the activity of anti-PD-L1 therapy.

The current study (ACT15377) will evaluate the safety, tolerability, and RRs of isatuximab in combination with atezolizumab as primary objective in patients with solid tumors; unresectable HCC, recurrent/metastatic SCCHN, platinum-resistant/refractory recurrent EOC and recurrent GBM. In HCC, SSCHN, EOC the presence of PD-1 expressing lymphocytes support the use of PD-1/PD-L1 immune checkpoint blockade as a therapeutic strategy. In GBM the PD-1/PD-L1 pathway is recognized as a therapeutic strategy, CD38 expression is observed in GBM which suggest the addition of a anti CD38 therapy to anti PD-1/PD-L1 may

potentiate tumor-specific immune reponse.

Study objective

Phase1: To characterize the safety and tolerability of isatuximab in combination with atezolizumab in participants with unresectable hepatocellular carcinoma (HCC), platinum-refractory recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN), platinumresistant/refractory epithelial ovarian cancer (EOC), or recurrent glioblastoma multiforme (GBM), and to determine the recommended Phase 2 dose (RP2D).

Phase2:
- To assess response rate (RR) of isatuximab in combination with atezolizumab in participants with HCC or SCCHN or EOC.
- To assess the progression free survival rate at 6 months (PFS-6) of isatuximab in combination with atezolizumab, or as a single agent in participants with GBM.

Study design

This is a Phase 1/2 open-label, non-randomized, multi-center, safety, preliminary efficacy, and PK study of isatuximab in combination with atezolizumab, or isatuximab alone in participants with advanced malignancies. The study will be conducted in 2 phases.
Phase 1 is the safety run-in for the determination of the maximum tolerated dose and RP2D for the isatuximab and atezolizumab combination.
Phase 2 investigates the efficacy of the RP2D isatuximab and atezolizumab combination with a 2-stage design. Enrollment in Cohort A, B, C and D-1 will be performed in parallel. Then enrollment in Cohort D-2 and E will be performed sequentially at the end of each respective Stage 2 of previous cohorts depending on results observed.

Intervention

Phase 1: patients receive 1200 mg once every 3 weeks (Q3W) for atezolizumab with isatuximab given 10 mg/kg or 5 mg/kg once weekly for 3 weeks followed by Q3W.
Phase 2: patients receive 1200 mg once every 3 weeks for atezolizumab with isatuximab given dose based on results from phase 1 once weekly for 3 weeks followed by Q3W.

Study burden and risks

The risks are related to the blood samples and the possible side effects of the study medication.
The burden on the patient will be the frequency of visits to the research

center.

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

- Patients must have a known diagnosis of either unresectable hepatocellular carcinoma (HCC), platinum-refractory recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN), platinum-resistant/refractory epithelial ovarian cancer (EOC) with evidence of measurable disease;or recurrent glioblastoma multiforme (GBM).;- *18 years of age.;-For patients with HCC: Documentation of progressive disease (PD) during or after treatment with either sorafenib or lenvatinib, or intolerance to the therapy.;-For patients with SCCHN: Received and failed up to 2 lines of prior systemic anti-cancer therapy with documentation of tumor recurrence or PD within 6 months of last platinum-based therapy in primary, recurrent, or metastatic setting.;-For patients with EOC: Received and failed up to 3 lines of prior

platinum-containing therapy when the disease was platinum-sensitive, and the patients should not have received any systemic therapy for platinum-resistant/refractory disease.;-For patients with GBM: Documentation of PD or first recurrence during or after temozolomide maintenance therapy for newly diagnosed GBM treated with 1st line radiotherapy plus concurrent temozolomide.

Exclusion criteria

- Prior exposure to agent that blocks CD38 or participation in clinical studies with isatuximab;- For patients with HCC, SCCHN, EOC or GBM prior exposure to any agent (approved or investigational) that blocks the PD-1/PD-L1 pathway.;- Evidence of other immune related disease /conditions.;- History of non-infectious pneumonitis requiring steroids or current pneumonitis; history of the thoracic radiation.;- Has received a live-virus vaccination within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.;- Prior solid organ or bone marrow transplantation.;- Eastern Cooperative Oncology Group performance status (PS) *2 for patients with HCC, SCCHN or EOC or Karnofsky performance score * 70 for patients with GBM;- Poor bone marrow reserve.;- Poor organ function.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-08-2018
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	Isatuximab
Product type:	Medicine
Brand name:	Tecentriq
Generic name:	atezolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-06-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	05-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EudraCT	EUCTR2018-000390-67-NL
CCMO	NL65453.078.18
Other	U1111-1202-0839

Study results

Date completed: 20-08-2020

Results posted: 21-11-2022

First publication
10-09-2021