A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI*PD-L1 ANTIBODY) AS MONOTHERAPY AND IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA

Published: 16-02-2017
Last updated: 04-01-2025

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus gemcitabine/carboplatin or cisplatin compared with placebo plus gemcitabine/carboplatin or cisplatin on the basis of the following endpoints:- Co-primary…

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

Summary

ID

NL-OMON45493

Source
ToetsingOnline

Brief title
WO30070/ IMVIGOR130

Condition

- Other condition

Synonym
cancer, urothelial cancer

Health condition

urotheel kanker

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Roche

Intervention

Keyword: Atezolizumab, Efficacy study, randomized placebo controlled, Urothelial cancer

Outcome measures

Primary outcome

Treatment with atezolizumab, both as a single-agent and in combination with

platinum-based chemotherapy offers the potential for clinical benefit in

previously untreated patients with metastatic urothelial carcinoma

See section K: Objective and protocol paragraph 1.3 and 2.1 pages 76-78.

Secondary outcome

The exploratory efficacy objectives for this study are to evaluate the efficacy

of atezolizumab given

as either monotherapy or in combination with platinum-based chemotherapy

compared with

placebo in combination with platinum-based chemotherapy on the basis of the following endpoints:

• Disease control rate (DCR), defined as the proportion of patients with confirmed CR or PR as best response, or stable disease maintained for >= 6 months, per RECIST v1.1

• Relationship between tumor tissue PD-L1 expression and measures of efficacy

• Predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment

• Disease and treatment burden as measured by the symptom (e.g., pain, fatigue) and function scores from the QLQ C30

An additional exploratory objective is to characterize patients who are able to continue treatment past progression by RECIST v1.1 as permitted per protocol and to describe clinical outcomes by treatment arm using modified RECIST, such as ORR, DOR, DCR, and PFS

The PK objective for this study is to characterize the pharmacokinetics of atezolizumab when administered as monotherapy or in combination with platinum-based chemotherapy in patients who are treatment-naive:

• PK parameters for atezolizumab include maximum serum concentration (Cmax) and minimum serum concentration (Cmin) when appropriate, as data allow.

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab as monotherapy and in combination with platinum-based

chemotherapy on the basis of the following endpoint:

• Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of detectable ATAs on the basis of the following endpoint:

• Correlation between ATA status and efficacy, safety, and PK endpoints

Health Economics Objective:

Health status will be measured using the EuroQol 5-Dimension, 5-Level version (EQ-5D-5L; EuroQol Group 1990) questionnaire to be included in health economic modeling. As such, data from the EQ-5D-5L will not be reported in the Clinical Study Report (CSR).

See also section K: Objective and protocol paragraph 2.1 pages 79-80.

Study description

Background summary

Urothelial carcinoma (UC, also termed transitional cell carcinoma [TCC], urothelial bladder cancer or urothelial cell carcinoma [UCC] of the urinary tract) is the most common cancer of the urinary system worldwide with urothelial carcinoma of the bladder being the predominant histologic type and location. The overall 5-year survival rate for metastatic urothelial carcinoma is approximately 5.4%
Approximately 5% of patients present with metastatic disease at diagnosis. Despite the low frequency of de novo disease, approximately half of the patients with locally advanced urothelial carcinoma progress to metastatic disease within two years of cystectomy.

Platinum-based combination chemotherapy is the preferred regimen in the first-line setting, and single agent chemotherapy is typically reserved for the second-line setting.
There is a significant medical need for efficacious and more tolerable regimens. Overall survival for this patient population is low.

No targeted agents, such as Atezolizumab, currently have a role in the treatment of urothelial carcinoma.

See also protocol Chapter 1 page 71-78.

Study objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus gemcitabine/carboplatin or cisplatin compared with placebo plus gemcitabine/carboplatin or cisplatin on the basis of the following endpoints:
- Co-primary endpoints of progression-free survival (PFS) and overall survival (OS) for arms A and C
- Primary endpoint of overall survival for arm B

The secondary efficacy objectives for this study are to evaluate the efficacy of atezolizumab monotherapy and in combination with platinum based therapy compared with placebo plus platinum based therapy on the basis of the following endpoints:
Objective response rate (ORR).
Duration of response (DOR).
PFS assessed by Independent Review Facility (IRF).
OS rate at 1 year.
PFS rate at 1 year
Time to deterioration in global health status as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ C30).
Time to deterioration in physical function as measured by the EORTC QLQ-C30

Safety objective:
evaluate the safety and tolerability of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy on the basis of the following: • Incidence, nature, and severity of adverse events graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 • Changes in vital signs, and clinical laboratory results,

Next to this the there is a Pharmacokinetic, Immunogenicity, Exploratory Efficacy and Health Economics Objective

See also protocol Chapter 2 page 78-80.

Study design

Tumor specimens from eligible patients will be prospectively tested for PD-L1 immunohistochemistry (IHC) expression by a central laboratory prior to randomization. The IHC scores will have two categories (tumor-infiltrating immune cell [IC] 0/1, IC2/3). Both patients and investigators will be blind to the PD-L1 expression status but the Sponsor will be able to view aggregate PD-L1 expression data. The study will enroll all eligible patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.
This study will enroll approximately 1215 patients at approximately 200 sites
Patients will be randomized in a 1:1:1 ratio to receive one of the following:
• Arm A (experimental arm): blinded atezolizumab in combination with gemcitabine/carboplatin or gemcitabine/cisplatin
• Arm B (experimental arm): open-label atezolizumab monotherapy
• Arm C (control arm): blinded placebo in combination with gemcitabine/carboplatin or gemcitabine/cisplatin
Investigators will determine whether their patient is eligible or ineligible to receive cisplatin-based chemotherapy. Those patients considered eligible to receive cisplatin and who are randomized to Arm A or Arm C will receive gemcitabine/cisplatin. Those patients determined as cisplatin ineligible (see Inclusion Criteria) and who are randomized to Arm A or Arm C will receive gemcitabine/carboplatin. The Sponsor anticipates a 60:40 ratio of cisplatin-eligible to cisplatin-ineligible patients for Arms A-C, based on treatment patterns and data from real world data studies.

Randomization will be stratified by the following factors:
• PD-L1 status (IC0/1 vs. IC2/3)
• Investigator*s choice of chemotherapy (gemcitabine/carboplatin vs. gemcitabine/cisplatin)
• Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or liver metastasis)

Patients will undergo scheduled tumor assessment at baseline and every 9 weeks thereafter for 54 weeks after randomization. After 54 weeks, patients will undergo tumor assessment every 12 weeks until disease progression per RECIST v1.1, death, study termination by the Sponsor, or withdrawal of consent, whichever occurs first. Patients must discontinue treatment at the first occurrence of radiographic progression, per RECIST v1.1, with the certain exceptions, see protocol page 83.

See also protocol Chapter 3 page 80-87 (rationale for study design on pages 86-87) .

Intervention

Patients will be randomized in a 1:1:1 ratio to receive one of the following:
• Arm A (experimental arm): blinded atezolizumab in combination with gemcitabine/carboplatin or gemcitabine/cisplatin: via IV infusion
• Arm B (experimental arm): open-label atezolizumab monotherapy: via IV infusion
• Arm C (control arm): blinded placebo in combination with gemcitabine/carboplatin or gemcitabine/cisplatin: via IV infusion

Next to this there is bloodsampling and biopties are being taken.
See protocol Chapter 4.5 pages 111- 119.

Study burden and risks

As described in the patient information sheet there are risks and burden associated with participation as the chemotherapeutic agents as well as Atezolizumab might cause side effects as well as the treatment of these patients in general (e.g. blood sampling, radiographic assessments, biopties).

Atezolizumab has been/ is being investigated in phase 1, 2 and 3 studies. Response is being seen and the Treatment combination with chemotherapy have been generally well tolerated as seen in an ongoing phase 1B study.

Atezolizumab (TECENTRIQ*) is approved in the United States for use in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy, or whose disease has worsened within 12 months of receiving platinum-based chemotherapy before surgery (neoadjuvant) or after surgery (adjuvant).
See protocol page 74.

See protocol paragraph 1.2 pages 73-76.

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

Inclusion Criteria
• Signed Informed Consent Form
• Age * 18 years
• Eastern Cooperative Oncology Group (ECOG) performance status of * 2
• Able to comply with the study protocol, in the investigator*s judgment
• Histologically documented, locally advanced (T4b, any N; or any T, N 2*3) or metastatic urothelial carcinoma (mUC) (M1, Stage IV) (also termed Transitional cell carcinoma (TCC), also called urothelial cell carcinoma (UCC) of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)
• Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment; patients who have fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with the Medical Monitor.
• No prior chemotherapy for inoperable locally advanced or mUC
• Patients eligible for platinum based therapy. To define a patient as ineligible (*unfit*) for cisplatin-based therapy the following criteria (based on Galsky et al. 2011) can be used:
• Measurable disease, as defined by RECIST v1.1
• Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to the first study treatment:
• For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of * 1% per year during the treatment period and for at least 6 months after the last dose of cisplatin, carboplatin or gemcitabine or for 5 months after the last dose of atezolizumab

• For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:;The inclusion criteria are described more into detail in the protocol page 94-97.

Exclusion criteria

Exclusion Criteria
Patients who meet any of the following criteria will be excluded from study entry:
Cancer-Specific Exclusions
• Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:
• Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to enrollment
• Active or untreated CNS metastases as determined by computed tomography or magnetic resonance imaging evaluation during screening and prior radiographic assessments
• Leptomeningeal disease
• Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
• Uncontrolled tumor-related pain
• Uncontrolled hypercalcemia defined as any one or more of the following criteria:
• Malignancies other than urothelial carcinoma within 5 years prior to Cycle 1, Day 1;General Medical Exclusions
• Life expectancy of * 12 weeks
• Pregnant or lactating, or intending to become pregnant during the study
• Serum albumin * 2.5 g/dL ;Exclusion Criteria Related to Atezolizumab
• History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
• Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
• History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener*s granulomatosis, Sjögren*s syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
• Patients with prior allogeneic stem cell or solid organ transplantation
• History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
• Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class III or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
• Known left ventricular ejection fraction (LVEF) * 40%
• Positive test for HIV
• Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

• Active tuberculosis
• Severe infections within 4 weeks prior to randomization including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
• Therapeutic oral or IV antibiotics within 2 weeks prior to randomization
• Major surgical procedure within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis.
• Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1
• Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
• Prior treatment with CD137 agonists, anti*CTLA-4, anti*programmed death-1 (PD-1), or anti*PD-L1 therapeutic antibody or pathway targeting agents
• Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1.
• Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti*tumor necrosis factor [TNF] agents) within 2 weeks prior to Cycle 1, Day 1 or anticipated requirement for systemic immunosuppressive medications during the study;The exclusion criteria are described more into detail in the protocol page 97-101.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-08-2017

Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin-GRY
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabine Actavis
Generic name:	Gemcitabine Actavis
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tecentriq
Generic name:	Atezolizumab

Ethics review

Approved WMO Date:	16-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-09-2017
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	21-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2022

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
EudraCT	EUCTR201600025035-NL
ClinicalTrials.gov	NCT02807636
CCMO	NL60663.056.17

Study results

Date completed:	07-03-2023
Results posted:	16-08-2024

First publication
13-08-2024