A PHASE II, MULTICENTER, SINGLE-ARM STUDY OF ATEZOLIZUMAB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER

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For the primary and secondary efficacy objectives, analyses will be performed in patients in different patient subpopulations according to programmed death*ligand 1 (PD-L1) expression in tumor tissue as evaluated by immunohistochemistry (IHC). The...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44787

Source
ToetsingOnline

Brief title
GO29293

Condition

- Other condition

Synonym
bladder cancer, locally advanced or metastatic urothelial bladder cancer

Health condition

lokaal gevorderd of gemetastaseerde urotheliale blaaskanker

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Atezolizumab, PD-L1-POSITIVE, Phase 2, Urothelial Bladder Cancer

Outcome measures

Primary outcome

The primary efficacy outcome measures are as follows:

• IRF-assessed objective response according to RECIST v1.1

• Investigator-assessed objective response according to modified RECIST (this is applicable only to Cohort 2)

An objective response is defined as a confirmed PR or CR. Modified RECIST outcomes, which incorporate the measurement of new lesions, are described in detail in Appendix 3. The ORR is defined as the proportion

Secondary outcome

The secondary efficacy outcome measures are as follows:

•DOR, defined as the time from the first occurrence of a documented PR or CR (whicheveroccurs first) to the time of first radiographic progression as determined by an IRF perRECIST v1.1 or death due to any cause on study

•Investigator-assessed ORR per RECIST v1.1 is defined as the proportion of

patients whoseoverall response is either confirmed PR or CR assessed by the investigator according toRECIST v1.1

•DOR will also be measured as the time from the first occurrence of a documented PR or CR (whichever occurs first) to the time of first radiographic progression as assessed byinvestigator per RECIST v1.1 or death due to any cause on study

•DOR per modified RECIST, defined as the time from the first occurrence of a documentedPR or CR (whichever occurs first) to the time of first confirmed radiographic progression asassessed by investigator per modified RECIST or death due to any cause on study, this isapplicable only to Cohort 2

•PFS per the IRF is defined as the time from the first dose of atezolizumab to the time of firstradiographic progression as determined by IRF per RECIST v1.1 or death from any causeon study

•PFS per investigator is defined as the time from the first dose of atezolizumab to the time offirst radiographic progression as determined by investigator per RECIST v1.1 or death fromany cause on study

•PFS per modified RECIST (applicable only to Cohort 2) is defined as the time fromrandomization to disease progression as determined by the investigator per modifiedRECIST or death from any cause, whichever comes first. A patient is considered to havedisease progression by modified RECIST if either of the following conditions are met:

a)Modified RECIST criteria for progression were met at a tumor assessment and nosubsequent tumor assessment was performed

b)Modified RECIST criteria for progression were met at a tumor assessment and

atthe subsequent tumor assessment the criteria for confirmed progression bymodified RECIST were also met

For patients who meet criterion a), the date of progression is the date of the tumor assessment that met the criteria for modified RECIST. For patients who meet criterion b), the date of progression is the date of the tumor assessment at which the modified RECIST criteria for progression were first met. Patients who do not meet either of the above criteria are not considered to have had disease progression by modified RECIST.

•OS, defined as the time from the first dose of atezolizumab to the time of death from anycause on study

•Landmark outcome: 1-year OS

Study description

Background summary

Atezolizumab is a human Ig G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy atezolizumab*F. Hoffmann-La Roche Ltd Protocol GO29293, Version 3 (EU Countries Only) 38 chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human programmed death*ligand 1 (PD-L1) and inhibits its interaction with its receptors, programmed death*1 (PD-1) and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells. Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

Study objective

For the primary and secondary efficacy objectives, analyses will be performed in patients in different patient subpopulations according to programmed

death*ligand 1 (PD-L1) expression in tumor tissue as evaluated by immunohistochemistry (IHC). The IHC assay will be used to evaluate PD-L1 expression on tumor-infiltrating immune cells (ICs) and will have three scoring categories (IC0, IC1, and IC2/3).

Primary Objectives
The primary objective for this study is to evaluate the efficacy of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer (UBC), as measured by:
• Independent Review Facility (IRF)*assessed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
• Investigator-assessed ORR according to modified RECIST (this is applicable only to Cohort 2)
The efficacy analysis for each cohort will follow a hierarchical fixed-sequence procedure.

Secondary Objectives
The secondary objectives for this study are as follows:
• To evaluate progression-free survival (PFS) and duration of response (DOR) according to RECIST v1.1 as assessed by an IRF
• To evaluate PFS and DOR according to modified RECIST as assessed by the investigator (this is applicable only to Cohort 2)
• To evaluate ORR, DOR, and PFS according to RECIST v1.1 as assessed by the investigator
• To evaluate overall survival (OS) and 1-year OS
• To evaluate the safety and tolerability of atezolizumab
• To characterize the pharmacokinetics of atezolizumab
• To evaluate the incidence and titers of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

Exploratory Objectives
The exploratory objectives for this study are as follows:
• To further evaluate anti-tumor activity by IHC categories
• To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, programmed death*1 [PD-1], and others), as defined by IHC and efficacy
• To assess 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
• To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor immune infiltration) from true disease progression
• To evaluate investigator-assessed time in response (TIR) per RECIST v1.1
• To evaluate investigator-assessed TIR per modified RECIST

• To evaluate investigator-assessed disease control rate (DCR)

Study design

This is a Phase II, global, multicenter, single-arm trial designed to evaluate the efficacy and safety of atezolizumab in patients with locally advanced or metastatic UBC.

For more detailed information, please see section 3.1 of the study protocol.

Intervention

Eligible patients will be placed in Cohort 1 or 2, depending on their medical history.

A fixed dose of 1200 mg IV atezolizumab will be administered on Day 1 of each 21-day cycle.

During treatment, patients in Cohort 2 will be permitted to continue atezolizumab treatment after RECIST v1.1 criteria for progressive disease are met and if they meet all of the following criteria:
• Evidence of clinical benefit as assessed by the investigator
• Absence of symptoms and signs indicating unequivocal progression of disease (including worsening of laboratory values [e.g., new or worsening hypercalcemia])
• No decline in ECOG performance status that can be attributed to disease progression
• Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Cohort 2 patients treated with atezolizumab for whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above.

For more information, see also section 3.1 of the study protocol.

Study burden and risks

For more information, please see the answer on question number E9.

Contacts

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Roche Nederland B.V.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Histologically or cytologically documented locally advanced (T4b, any N; or any T, N 2*3) or metastatic (M1, Stage IV) TCC (also termed urothelial cell carcinoma) of the urothelium (including renal pelvis, ureters, urinary bladder, 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 have sufficient viable tumor content prior to study enrollment; tumor specimens will be evaluated for PD-L1 expression; patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with Medical Monitor.
• Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 Patients with ECOG 2 are allowed in Cohort 1.
• Measurable disease, as defined by RECIST v1.1 Previously irradiated lesions should not be

counted as target lesions.;Cohort 1-Specific Inclusion Criteria
• No prior chemotherapy for inoperable locally advanced or metastatic or recurrent UBC
• Ineligible (*unfit*) for cisplatin-based chemotherapy as defined by any one of the following criteria:
- Impaired renal function (glomerular filtration rate [GFR] > 30 but < 60 mL/min). GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
- A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies
- Grade 2 or greater peripheral neuropathy (i.e., sensory alteration or parasthesis including tingling)
- ECOG performance score of 2;Cohort 2-Specific Inclusion Criteria
• Disease progression during or following treatment with at least one platinum-containing regimen (e.g., gemcitabine and cisplatin [GC], methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], CarboGem, etc.) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence

Exclusion criteria

Cancer Specific Exclusion Criteria
• Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment
• Active or untreated central nervous system (CNS) metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments
• Leptomeningeal disease;Medication-Related Exclusion Criteria:
• Prior treatment with CD137 agonists or immune checkpoint blockade therapies,
• Treatment with systemic immunostimulatory agents within 6 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 within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-09-2014
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Atezolizumab

Ethics review

Approved WMO Date:	10-07-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-08-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-12-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-01-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-03-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-12-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-11-2016
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-12-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date: 29-11-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 17-12-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 11-01-2019

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 21-02-2019

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 15-03-2019

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 08-08-2019

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 03-09-2019

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 11-10-2019

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2013-005486-39-NL
ClinicalTrials.gov	NCT02108652
CCMO	NL48550.031.14