A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI*PD-L1 ANTIBODY) COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL BLADDER CANCER AFTER FAILURE WITH PLATINUM-CONTAINING CHEMOTHERAPY

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This is a phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti PDL1 antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after...

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

Summary

ID

NL-OMON45200

Source
ToetsingOnline

Brief title
GO29294

Condition

- Other condition

Synonym
bladder cancer, locally advanced or metastatic urothelial bladder cancer

Health condition

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Research involving
Human

Sponsors and support

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

Intervention

Keyword: Anti-PD-L1 Antibody, Atezolizumab, Phase III, Urothelial Bladder Cancer

Outcome measures

Primary outcome

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of atezolizumab treatment compared with

chemotherapy treatment with respect to overall survival (OS) in patients with

locally advanced or metastatic urothelial bladder cancer (UBC) who have

progressed during or following a platinum-containing regimen

Secondary outcome

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab compared with chemotherapy with

respect to anti-tumor effects as measured by objective response rate (ORR) per

investigator with use of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by progression-free survival (PFS) per investigator with use of RECIST v1.1

- To evaluate the efficacy of atezolizumab compared with chemotherapy with respect to anti-tumor effects as measured by duration of objective response (DOR) per RECIST v1.1

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab compared with chemotherapy

- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

atezolizumab *F. Hoffmann-La Roche Ltd

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Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the pharmacokinetics of MPDL32820A in patients with locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen

Patient-Reported Outcome Objectives

The patient-reported outcome (PRO) objective for this study is as follows:

- To evaluate and compare PROs of patient health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30)

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab with respect to anti-tumor effects as measured by PFS, ORR, and DOR per modified Response Evaluation Criteria in Solid Tumors (RECIST)
- To evaluate and compare disease control rate (DCR) between the two treatment arms
- To evaluate the relationship between tumor tissue programmed death*ligand 1 (PD-L1) expression and measures of 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 assess health status as measured using the EuroQol 5-Dimension, 3-level version (EQ-5D [3L]) questionnaire for health economic modeling

Study description

Background summary

Atezolizumab is a human IgG1 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 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.

For more background of the study see page 25-29 in the protocol

Study objective

This is a phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti PDL1 antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy

Study design

This is a Phase III, global, multicenter, open-label, two-arm, randomized, controlled study designed to evaluate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen. The selection of the specific chemotherapy for patients who are randomized to the chemotherapy arm will be per investigator*s choice.
Male and female patients aged > 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who have histologically or cytologically proven, locally advanced or metastatic UBC and who have experienced disease progression during or following treatment for advanced disease consisting of platinum-based therapy are eligible.
Patients who experience disease progression during or within 12 months following completion of a platinum-based adjuvant or neoadjuvant regimen will also be eligible for enrollment into the study.
Patients must have received at least one platinum containing regimen (e.g., gemcitabine and cisplatin [GC], methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], carboplatin and gemcitabine [CarboGem], etc.) for locally advanced or metastatic UBC. The maximum number of prior therapies in the locally advanced or metastatic setting is restricted to two.
Tumor specimens from eligible patients will be prospectively tested for PD-L1

expression by a central laboratory. Both patients and investigators will be blind to the PD-L1 expression status. The study will enroll all patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.
This study will enroll approximately 767 patients, including a minimum of 230 patients with PD-L1 immunohistochemistry (IHC) 2/3 (enrollment of all patients will continue to reach the minimum requirement of patients with PD-L1 IHC 2/3). Patients will be randomized in a 1:1 ratio to receive either atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel):
- Arm A (experimental arm): atezolizumab 1200 mg every 3 weeks (q3w)
Arm B (control arm): Vinflunine 320 mg/m2 q3w, paclitaxel 175 mg/m2 q3w, or docetaxel 75 mg/m2 q3w

Intervention

Test product

Atezolizumab is administered at a dose of 1200 mg by IV infusion on Day 1 of each 21-day cycle.

Comparators

Vinflunine is administered at a dose of 320 mg/m2 by IV infusion on Day 1 of each 21-day cycle.
Paclitaxel is administered at a dose of 175 mg/m2 over 3 hours by continuous IV infusion on Day 1 of each 21-day cycle.
Docetaxel is administered at a dose of 75 mg/m2 on Day 1 of each 21-day cycle.

Study burden and risks

Side effects from the drugs or procedures used in this study may be experienced. Side effects can vary from mild to very serious and may vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, Roche, the study doctor, and other doctors do not know all of the side effects that could occur. The study doctors may give drugs to help lessen side effects. Many side effects go away soon after you stop what is causing them. In some cases, side effects can be serious and may be long lasting or may never go away. There also is a rare risk of death. The doctor will evaluate the subject for any symptoms during your study visits.
One of the drugs the subjects may be randomized to is called docetaxel. This drug contains alcohol, which may cause the experience of intoxication or feel drunk during and after treatment. If this is a concern, or if alcohol needs to be avoided or the exposure to alcohol should be kept to a minimum, this should be discussed with the doctor prior to participating in the study.

SIDE EFFECTS ASSOCIATED WITH ATEZOLIZUMAB TREATMENT
Some or all of these same side effects can be experienced. It is also possible that side effects are experienced that are unknown at this time. As is true for any experimental drug, there may be unknown and potentially serious or life threatening side effects that could occur with atezolizumab . Once the drug is stopped it is not known how long the side effect of the drug will last.
The following events are those considered associated with atezolizumab
* Colitis (inflammation of the intestines); symptoms may include diarrhea, blood in stool, and stomach pain.
* Flu-like illness (symptoms include fever, fatigue, asthenia [lack of energy], chills, myalgia [muscle pain], arthralgia [joint pain], and headache).
* Inflammation of the thyroid and adrenal glands (hypothyroidism, hyperthyroidism, or adrenal insufficiency); symptoms may include headaches, tiredness, weight loss, weight gain, change in mood, hair loss, constipation, and dizziness.
* Hepatitis (inflammation of the liver); symptoms may include yellowing of skin, nausea, vomiting, bleeding or bruising, dark urine, and stomach pain.
* Meningitis (inflammation of the membrane around the spinal cord and brain); symptoms may include neck stiffness, headache, fever, chills, vomiting, and eye sensitivity to light).
* Neuropathies (damage to the nerves); symptoms may include muscle weakness and numbness and tingling in hands and feet.
* Pneumonitis (inflammation of the lungs); symptoms may include new or worsening cough, shortness of breath, and chest pain.
* Reactions associated with infusion (events occurring during or within 1 day following infusion and include fever, chills, shortness of breath, and flushing)
* Skin reactions (rash, itching, dry skin, redness, and changes in skin pigmentation)

Immune Related Side Effects
Atezolizumab is designed to increase the number of immune system cells that can fight cancer. These cells may cause inflammation within the tumor, as well as with normal tissue. Therefore, by taking atezolizumab you may develop a condition where there is inflammation against a part of your own body (an autoimmune disease). These events are rare and are listed in the table above.

Allergic Reactions
Allergic reactions may occur with atezolizumab and typically occur while it is being given into your vein or shortly after it is given. No events of allergic reactions to atezolizumab have been reported. Symptoms could include nausea, vomiting, skin reactions (hives or rash), difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability. If you experience these symptoms, your study doctor will interrupt or even stop the delivery of atezolizumab into your vein. Your study doctor may also give you some drugs to treat these symptoms.

Other Medications
If a vaccination is required, it is required to receive it at least 4 weeks before receiving treatment with atezolizumab . The patient must agree not to receive live, attenuated vaccines during treatment or within 90 days following the last dose of atezolizumab. Atezolizumab may have some side effects that may overlap with some of the side effects caused by other medications that also stimulate the immune system. It may be dangerous to take both of these drugs at the same time. It is important to tell the doctor the last time any medication stimulating the immune system has been taken. It is also important that you do no other drugs that may alter your immune system (immunomodulatory drugs) are taken for 10 weeks after your last dose of atezolizumab .
Once the drug is stopped, it is not known how long the side effect(s) of the drug will last.

For risks of chemotherapeutics and other risks, see page 82 to 96 of the protocol and the informed consent form

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

*Histologically or cytologically documented locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, urethra);*Representative tumor specimens as specified by the protocol;*Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;*Life expectancy <= > 12 weeks;*Measurable disease, as defined by RECIST v1.1

Exclusion criteria

* Any approved anti-cancer 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;*Pregnant and lactating women;*History of autoimmune disease

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-06-2015
Enrollment:	52

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Atezolizumab
Generic name:	MPDL3280A
Product type:	Medicine
Brand name:	Taxol
Generic name:	Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxotere
Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vinflunine
Generic name:	Vinflunine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-01-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-04-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	21-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-07-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-07-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-05-2017

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-12-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2014-003231-19-NL
ClinicalTrials.gov	NCT02302807
CCMO	NL50564.100.15