A PHASE 3, MULTINATIONAL, RANDOMIZED, OPEN-LABEL, PARALLEL-ARM STUDY OF AVELUMAb (MSB0010718C) IN COMBINATION WITH AXITINIB (INLYTA®) VERSUS SUNITINIB (SUTENT®)) MONOTHERAPY IN THE FIRST-LINE TREATMENT OF PATIENTS WITH ADVANCED RENAL CELL CARCINOMA

Published: 07-03-2016
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Primary ObjectiveTo demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging PFS or OS in the first-line treatment of PD-L1 positive patients with aRCC.Secondary Objectives* To demonstrate that...

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50769

Source
ToetsingOnline

Brief title
B9991003

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Advanced Kidney Cancer, Grawitz tumor

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pharmaceutische industrie

Intervention

Keyword: ADVANCED RENAL CELL CARCINOMA, AVELUMAB, AXITINIB, SUNITINIB

Outcome measures

Primary outcome

Progression-Free Survival (PFS) or overall survival (OS) based on Blinded

Independent Central Review (BICR) assessment per RECIST v.1.1. for DP-L1

positive patients.

Overall Survival for PD-L1 patients.

Secondary outcome

*Progression-Free Survival (PFS) by (BICR) assessment per RECIST v.1.1. for

patients unselected PD-L1 expression

Overall Survival (OS) for patients unselected PD-L1 expression

* Objective Response (OR), Disease Control (DC), Time to Tumor Response (TTR)

and Duration of Response (DR) based on BICR assessment and based on Investigator

assessment, per RECIST v.1.1.

* Progression-Free Survival (PFS) based on Investigator assessment per RECIST

v.1.1.

*Progression-Free Survival on next-line therapy (PFS2)

* Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 6); vital signs (blood pressure, pulse rate).

*Time to treatment discontinuation/failure due to toxicity

*Treatment discontinuation due to toxicity

* PK parameters including trough concentrations (Ctrough) of avelumab and trough concentrations (Ctrough) and maximum concentrations (Cmax) of axitinib

* Tumor tissue biomarker status (ie, positive or negative; based on, for example, PD-L1 expression and/or quantitation of tumor infiltrating CD8+ T lymphocytes as assessed by immunohistochemistry [IHC]).

* Measures of clinical outcome (PFS, OS, OR, DC, TTR, and DR) in biomarker-positive and biomarker-negative subgroups.

* Anti-drug antibodies (ADAs; nAbs) of avelumab when in combination with axitinib.

* Patient-Reported Outcomes (PRO): FACT-Kidney Symptom Index (FKSI-19), EuroQol 5 Dimension (EQ 5D).

Study description

Background summary

Overall, the observed benefit-risk profile supports the further investigation of avelumab in combination with axitinib in the patient population chosen for this study. The proposed Phase 3 clinical trial seeks to evaluate the efficacy and safety of avelumab in combination with axitinib and demonstrate superior PFS of this combination versus sunitinib monotherapy in the first-line treatment of patients with aRCC.
See for more information protocol background/rationale.

Study objective

Primary Objective
To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging PFS or OS in the first-line treatment of PD-L1 positive patients with aRCC.

Secondary Objectives
* To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in proloning PFS in first line treatment of PD-L1 positivepatients with aRCC unselected for PD-l1 expression
* To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in proloning OS in first line treatment of PD-L1 positivepatients with aRCC unselected for PD-l1 expression
* To evaluate other measures of efficacy of avelumab in combination with axitinib and
sunitinib monotherapy in the first-line treatment of aRCC patients.
* To evaluate PFS on next-line of therapy (PFS2);
* To evaluate the overall safety profile of the IMPs in combination with axitinib and
sunitinib monotherapy in the first-line treatment of aRCC patients.
* To evaluate the population pharmacokinetics of avelumab and axitinib when administered in combination.
* To evaluate the time to treatment discontinuation/failure due to toxicity and the proportion of patients who discontinued treatment due to toxicity
* To evaluate candidate predictive biomarkers in pre-treatment tumor tissue that may
aid in the identification of a patient subpopulation most likely to benefit from treatment with avelumab in combination with axitinib and sunitinib monotherapy.
* To assess the immunogenicity of avelumab combined with axitinib.
* To evaluate the effects of avelumab in combination with axitinib and sunitinib monotherapy on patient-reported outcomes.

Study design

This is a Phase 3, multinational, multicenter, randomized, open-label, parallel

2-arm study in which approximately 583 patients including a minimum of 830 PD-L1 positive patients sare planned to be randomized in a 1:1 ratio to receive either avelumab in combination with axitinib or sunitinib monotherapy.

Intervention

In Arm A, patients will receive:
* Avelumab as a 1-hour IV infusion Q2W in a 6-week cycle.
* Axitinib PO BID, with or without food, on a continuous dosing schedule.
In Arm B, patients will receive:
* Sunitinib PO 50 mg QD on a schedule of 4 weeks on treatment followed by 2 weeks
off treatment (Schedule 4/2 in 6-week cycles).

Study burden and risks

The following side effects have been observed among 1738 subjects treated with avelumab according to the results from two oncology clinical studies in patients with various solid tumors

Side effects observed in 10 or more out of 100 subjects
• General signs or symptoms: Tiredness; Nausea; Loose or watery stools (diarrhea); Constipation; Reduced appetite; Decrease in weight; Vomiting; Low number of red blood cells (anemia); Belly pain; Cough; Fever; Shortness of breath; Swelling of feet and legs; Back pain; Joint pain.

Reactions that occur during or following the infusion:
may include chills or shaking, fever, flushing, back pain, belly pain,, shortness of breath or wheezing, decrease in blood pressure, hives. These infusion reactions are mostly mild or moderate and generally resolve with a slowdown or discontinuation of the infusion and administration of medications such as anti-allergic and pain-killer drugs.

Risks Associated with the Combination of Avelumab plus Axitinib:
observed among 55 subjects treated in an ongoing study of avelumab in combination with axitinib in subjects with metastatic renal cancer.

Observed in 10 or more out of 100 subjects
Decreased appetite, decreased thyroid function, disturbance of taste, high blood pressure, hoarseness, increased blood levels of liver enzymes (liver function blood tests) such as alanine aminotransferase and aspartate aminotransferase, increased blood levels of pancreatic enzymes (pancreatic function blood tests) such as amylase and lipase, inflammation of the skin (including skin rash, itchy skin, redness or blisters in the skin), loose or watery stools (diarrhea), mucosal inflammation, muscle pain, nausea, reactions that occur during or following the infusion (symptoms may include chills,

fever, muscle pain, shortness of breath, low or high blood pressure), pain in joints, proteins in urine, pruritus (itch), redness and/or pain in hands and feet, shortness of breath, soreness or swelling of the mouth, tiredness, vomiting, weight decreased.

Immune side effects observed in at least >= 10% of subjects: decreased function of the thyroid gland, inflammation of the skin (including skin rash, itchy skin, redness or blisters in the skin).

Other side effects (less often) for avelumab as well as side effects for avelumab plus axitinib, axitinib and sunitinib are described in informed consent for patients. Besides, side effects can occur as a consequence of study procedures.

Contacts

Public
Pfizer

East 42nd Street 235
New York, NY 10017
US
Scientific
Pfizer

East 42nd Street 235
New York, NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

1. Diagnosis:
Histologically or cytologically confirmed advanced or metastatic renal cell carcinoma with a clear cell component. A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from a de novo tumor biopsy during screening will be required. Alternatively, a recently obtained archival FFPE tumor tissue block (not cut slides) from a primary tumor resection or biopsy can be provided. If an FFPE tissue block cannot be provided as per documented regulations then 15 unstained slides will be acceptable. Availability of an archival FFPE tumor tissue block from primary diagnosis specimen (or 15 unstained slides). At least one measurable lesion defined by RECIST that has not been previously irradiated;
2. Evidence of a personally signed and dated informed consent document indicating that
the patient (or a legally acceptable representative, as allowed by local guideline/practice) has been informed of all pertinent aspects of the study.
3. Patients who are willing and able to comply with scheduled visits, treatment plans,
laboratory tests, and other study procedures.
4. Age *18 years (*20 years in Japan).
5. Estimated life expectancy of at least 3 months.
6. ECOG PS 0 or 1.
7. No evidence of uncontrolled hypertension as documented by 2 baseline blood pressure (BP) readings taken at least 1 hour apart. The baseline systolic BP readings
must be *140 mm Hg, and the baseline diastolic BP readings must be *90 mm Hg. Use of antihypertensive medications to control BP is allowed.
8. Adequate bone marrow function, including:
a. Absolute Neutrophil Count (ANC) *1,500/mm3 or *1.5 x 109/L;
b. Platelets *100,000/mm3 or *100 x 109/L;
c. Hemoglobin *9 g/dL (may have been transfused).
9. Adequate renal function, including:
a. Estimated creatinine clearance >=50 mL/min as calculated using the Cockcroft-Gault (CG) equation.
b. Urinary protein <2+ by urine dipstick. If dipstick is *2+, then 24-hour urinary
protein <2 g per 24 hours.
10. Adequate liver function, including:
a. Total serum bilirubin *1.5 x ULN;
b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) *2.5 x ULN.
11. Left ventricular ejection fraction (LVEF) >= lower limit of normal (LLN) as assessed
by either multigated acquisition (MUGA) scan or echocardiogram (ECHO).

12. Serum pregnancy test (for females of childbearing potential) negative at screening.
13. Male patients able to father children and female patients of childbearing potential and
at risk for pregnancy must agree to use 2 highly effective methods of contraception
(see Section 4.3.1) throughout the study and for at least 90 days after the last dose of
assigned treatment.

Exclusion criteria

1. The following prior therapies are excluded:
* Prior systemic therapy directed at advanced or metastatic RCC.
* Prior adjuvant or neoadjuvant therapy for RCC if disease progression or relapse
has occurred during or within 12 months after the last dose of treatment, immunotherapy, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
* Prior therapy with axitinib and/or sunitinib as well as any prior therapies with
other VEGF pathway inhibitors.
2. Participation in other therapeutic studies within 4 weeks prior to randomization.
3. Patients with newley diagnosed brainmetastases or patients with known symptomatic brain metastases requiring steroids.
4. Major surgery within 4 weeks or major radiation therapy within 2 weeks prior to study entry
5. Persisting toxicity related to prior therapy NCI CTCAE v4.0 Grade >1;
6. Current or prior use of immunosuppressive medication within 7 days prior to study entry.
8. Known prior or suspected hypersensitivity to study drugs or any component in their
formulations.
9. Diagnosis of any other malignancy within 5 years prior to randomization, except for
adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the
breast or of the cervix, or low-grade (Gleason 6 or below) prostate cancer on surveillance.
10. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents.
11. Gastrointestinal :
12. Active infection requiring systemic therapy.
13. Diagnosis of prior immunodeficiency or organ transplant requiring

immunosuppressive therapy
Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
14. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or
chronic infection.
15. Vaccination within 4 weeks of the first dose of avelumab and while on trial is
prohibited except for administration of inactivated vaccines (for example, inactivated
influenza vaccines).
16. Requirement of anticoagulant therapy with oral vitamin K antagonists.
17. Evidence of inadequate wound healing.
18. Grade 3 hemorrhage within 4 weeks of patient randomization.
19. Any of the following in the previous 12 months: myocardial infarction, severe/unstable
angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, LVEF less than LLN, clinically significant pericardial effusion, cerebrovascular accident, transient ischemic attack
20. Any of the following in the previous 6 months prior to study entry:
deep vein thrombosis or symptomatic pulmonary embolism;
21. Evidence of tumor involvement of the myocardium or pericardium or
tumor thrombus extending to the heart;
22. Ongoing cardiac dysrhythmias of NCI CTCAE Grade >= 2 or
prolongation of the QTc interval to > 500 msec;
23. Current use or anticipated need for treatment with drugs or foods that are known
strong CYP3A4/5 inhibitors, including their administration within 10 days prior to
study entry
24. Current use or anticipated need for drugs that are known strong CYP3A4/5 inducers,
including their administration within 10 days prior to patient randomization.
25. Patients who are investigational site staff members directly involved in the conduct of
the trial and their family members, site staff members otherwise supervised by the
investigator, or patients who are Pfizer employees directly involved in the conduct of
the study.
26. Pregnant female patients; breastfeeding female patients.
27. Other severe acute or chronic medical conditions including colitis, inflammatory
bowel disease, uncontrolled asthma, and pneumonitis or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may
increase the risk associated with study participation or investigational product

administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

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:	Completed
Start date (anticipated):	25-11-2016
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avelumab
Generic name:	Avelumab
Product type:	Medicine
Brand name:	Inlyta®
Generic name:	Axitinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sutent®
Generic name:	Sunitinib

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-03-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-08-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	28-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	21-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-10-2022
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2015-002429-20-NL
ClinicalTrials.gov	NCT02684006
CCMO	NL55968.031.16