A Phase IIB, Open Label, Study of Zirconium Zr 89 Crefmirlimab Berdoxam PET-CT in Subjects with Selected Advanced or Metastatic Malignancies including Melanoma, Merkel Cell, Renal Cell and Non-Small Cell Lung Cancers, Scheduled to Receive Standard-of-Care Immunotherapy (IOT) as a Single Agent or Combination, to Predict Response to Therapy

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Primary objective: evaluate the performance of zirconium Zr 89 crefmirlimab berdoxam PET-CT for predicting patient response to immunotherapy. Secondary objectives: - evaluate the performance of zirconium Zr 89 crefmirlimab berdoxam PET-CT for...

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

Summary

ID

NL-OMON54060

Source
ToetsingOnline

Brief title
iPREDICT

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Respiratory tract neoplasms
- Skin neoplasms malignant and unspecified

Synonym
melanoma (skin cancer), non-small cell lung cancer (lung cancer), renal cell cancer (renal cell cancer)

Research involving
Human

Sponsors and support

Primary sponsor: ImaginAb, Inc.
Source(s) of monetary or material Support: industry

Intervention

Keyword: Immunotherapy, Melanoma, Non-small cell lung cancer, Renal Cell Cancer, Zirconium Zr 89 Crefmirlimab Berdoxam PET-CT

Outcome measures

Primary outcome

Best Overall Response (BOR) assessed by conventional imaging CT and/or MRI

using RECIST 1.1 from three (or up to three) consecutive standard of care

imaging assessments (CT and/or MRI) following onset of IOT treatment.

For iTOX:

• Analysis of zirconium Zr 89 crefmirlimab berdoxam PET/CT of irAE affected

organs

• Phenotypic and functional characterization of mucosal and circulating immune

cells before and during irAEs

• Differences and changes in relative abundance of immune cell populations as

determined by flow cytometry

• Differences and changes in cytokine response patterns of circulating immune cells against different microbial stimulations between patients experiencing IOT-related colitis and colitis-free patients.

• RNA expression analysis determined by RNAseq from sigmoidal biopsies pre- and post-treatment.

• Multiplex immunohistochemistry staining of sigmoidal biopsy tissue.

• Gut microbiome composition in fecal samples and in situ in colon biopsies.

Secondary outcome

Largest measured difference from baseline in the lesion major axis from three (or up to three) consecutive standard of care imaging assessments (CT and/or MRI) following onset of IOT treatment.

Assessments:

- Incidence and severity of infusion/injection reactions occurring during or shortly after infusion/injection of the investigational product.

- Incidence of treatment emergent adverse events probably or definitely related to zirconium Zr 89 crefmirlimab berdoxam, coded per CTCAE v5.0 TEAEs.

- Incidence of withdrawals from scanning protocol due to zirconium Zr 89 crefmirlimab berdoxam-related AEs.

- Laboratory results and clinically significant changes in laboratory test results over the study course.

- Changes in 12-lead electrocardiogram (ECG) related to zirconium Zr 89 crefmirlimab berdoxam.

- Anti-Drug Antibodies (ADA)

Study description

Background summary

Immuno-oncology therapy (IOT) has altered the treatment options in subjects with selected solid tumors and lymphoma. Despite tremendous advances, not all subjects benefit from this type of therapy, and many develop immune-related toxicities. The presence of CD8+ Tumor Infiltrating Lymphocytes (TILs) in the tumor microenvironment is critical for the establishment of an IOT response. Current methods for determining CD8+ TILs require invasive procedures which suffer from sampling errors due to tumor heterogeneity.
Zirkonium-Zr-89-crefmirlimab-berdoxam is a promising novel radiotracer that can provide whole body PET assessments of the CD8+ cell distribution in tumor lesions and other tissues.
It is not known whether pre-treatment CD8+ assessment or the change from pre-treatment to on-treatment CD8+ assessment would be more clinically valuable. In the former case CD8+ assessment may perform better to select patients for standard IOT and identify those patients who may not benefit. This last group can be preferentially enrolled in clinical trials. In the latter case it may provide mechanistic insights of the working mechanism of IOT. Also it is studied if it performs better than standard assessments to represent response or progression on IOT.
In this protocol, ImaginAb will evaluate the performance of zirkonium-Zr-89-crefmirlimab-berdoxam PET-CT (pre-treatment and on treatment) for predicting subsequent RECIST 1.1 responses in subjects with selected solid malignancies treated with IOT (as single or combination IOT agents).

For iTOX:
With this study we want to further explore one of the exploratory objectives of the iPREDICT study: to evaluate the predictive value of the zirconium Zr 89 crefmirlimab berdoxam PET/CT scans. The results of the additional analyzes in the iTOX can make an important contribution to understanding and predicting toxicity reactions after immunotherapy. Characterizing the immune cells during immune checkpoint inhibitor induced toxicity can contribute to early recognition of these side effects and to identify patients who are more likely to develop toxicity. It is also a stepping stone to future intervention studies focusing on the underlying mechanism of immuno-toxicity.

Study objective

Primary objective: evaluate the performance of zirconium Zr 89 crefmirlimab berdoxam PET-CT for predicting patient response to immunotherapy.

Secondary objectives:
- evaluate the performance of zirconium Zr 89 crefmirlimab berdoxam PET-CT for predicting lesion response to immunotherapy.
-to assess safety of the repeat zirconium Zr 89 crefmirlimab berdoxam infusions/injections.

Exploratory objectives:
- Evaluate zirconium Zr 89 crefmirlimab berdoxam PET-CT as a discriminator of pseudo-progression.
- Evaluate zirconium Zr 89 crefmirlimab berdoxam PET-CT in subjects who develop clinical and/or radiographic progression to explore mechanisms for treatment resistance.
- Evaluate zirconium Zr 89 crefmirlimab berdoxam PET-CT as a predictor or surrogate for immunotherapy immune related AEs.
- Correlate zirconium Zr 89 crefmirlimab berdoxam PET uptake with CD8 expression and PD-1/PD-L1 expression as determined by immunohistochemistry
- Evaluate zirconium Zr 89 crefmirlimab berdoxam PET-CT as a predictor of Progression Free Survival (PFS) and Duration of Response (DoR).

For iTOX:
- To deepen exploratory objective 3 of iPREDICT, which is to evaluate zirconium Zr 89 crefmirlimab berdoxam PET/CT as a predictor for immune-oncology therapy (IOT) immune related adverse events (irAEs)
- To understand the irAE zirconium Zr 89 crefmirlimab berdoxam PET/CT results by integration with additional immunological parameters. iTOX specific endpoints will be correlated with occurrence of irAEs and zirconium Zr 89 crefmirlimab berdoxam PET/CT scan data.

Study design

Eligible subjects who meet Inclusion/Exclusion criteria will receive up to 3 zirconium Zr 89 crefmirlimab berdoxam PET-CT scans as an IV infusion/injection as follows:
- first scan within 14 days prior to the onset of immunotherapy,
- second scan 4 to 6 weeks after start of immunotherapy.
The second zirkonium-Zr-89-crefmirlimab-berdoxam infusion/injection and scan should be completed prior to the start of the third cycle of IOT. Subjects who are determined by the treating physician to have progressive disease (PD) on immunotherapy can receive the optional third zirkonium-Zr-89-crefmirlimab-berdoxamPET scan at the PI*s discretion. All PET-CT scans will be obtained at 24 ± 3 hours after each infusion/injection of zirconium Zr 89 crefmirlimab berdoxam.

Conventional contrast enhanced CT Chest, Abdomen and Pelvis (including Neck, Brain and Extremities, if applicable) or MRI will be performed within 30 days prior to 1st infusion/injection of zirconium Zr 89 crefmirlimab berdoxam.

Whole Body 18FDG-PET scan within 30 days prior to 1st infusion/injection of zirconium Zr 89 crefmirlimab berdoxam at sites where Whole Body 18FDG-PET is a SOC scan. 18FDG-PET scans will not be a required assessment to enroll patients onto the study or determine eligibility.

Anti-drug antibody (ADA) blood samples will be collected at the following time points:
- baseline, prior to receiving zirconium Zr 89 crefmirlimab berdoxam infusion/injection.
- at Visit 2, 5, and 7: the days on which the PET-CT scan are being made

End of Study Visit: 48 weeks after the start of immunotherapy or following confirmation of progressive disease and/or treatment discontinuation, whichever occurs first.

Follow up Standard of Care (SOC) imaging should be performed in coordination with the subjects treatment schedule. It is anticipated that subjects who receive IOT every 2 or 4 weeks will undergo SOC imaging every 8 weeks ± 3 days while subjects who receive IOT every 3 weeks will undergo SOC imaging every 9 week ± 3 days. SOC images will be requested by ImaginAb for up to 48 weeks after the start of immunotherapy or following confirmation of progressive disease and/or treatment discontinuation, whichever occurs first.

For iTOX:
Patients will be taking part in the iPREDICT. When an immunotherapy related event occurs, the patients will come for an additional zirconium Zr 89 crefmirlimab berdoxam PET-CT scan. Therefore 2 extra visits, iTOX1 and iTOX2 are needed, one for administration of the IP, one for the PET-CT scan. These visits are similar to visits 1 and 2 respectively. For iTOX some extra tests will be added to Visit 1 and Visit 4 and are also in Visit iTOX-1: a blood sample, a stool sample and a sigmoid biopsy.

Intervention

Subjects will receive up to 3 PET-CT scans with the tracer zirconium Zr 89 crefmirlimab berdoxam (up to 1.0 mCi +/- 20% at 1.5 mg API per scan, for a total of up to 3.0 mCi +/- 20% and 4.5 mg API) as an IV infusion or injection as follows:
- first scan within 14 days prior to the onset of standard of care immunotherapy,
- second (scan 4 to 6 weeks after start of standard of care immunotherapy. The second zirconium Zr 89 crefmirlimab berdoxam infusion or injection and scan should be completed prior to the start of the third cycle of IOT.
- subjects who are determined by the treating physician to have progressive disease (PD) on immunotherapy can receive the optional third zirconium Zr 89 crefmirlimab berdoxam PET scan.

Fresh tumor biopsies are optional. Archival tumor tissue or on treatment biopsy material, if available, will be requested for correlation of CD8+ cells by IHC with zirconium Zr 89 crefmirlimab berdoxam uptake. Samples collected during the study will be correlated to the CD8 PET-CT scan results.
A maximum of 2 or 3 biopsies will be done, for which separate consent will be requested.

Extra for iTOX:
In case of irAEs grade >=2 subjects will have an extra PET-CT scan with zirconium Zr 89 crefmirlimab berdoxam. iTOX patients will have a sigmoid biopsy at visit 1, and visit 4. The sigmoid biopsy at the moment of the irAE is done per Standard of Care. Furthermore a blood test and a stool sample will be taken at these visits.

Study burden and risks

Patients will visit the hospital up to 8 times for this study. Each visit will take 1-2 hours.
First there is a screening visit with the following assessments: an Informed Consent procedure, medical history, demography, physical examination including ECOG, vital signs, blood tests (safety and Anti Drug Antibody sampling) and review of concomitant medications. CT/MRI is expected to be done as standard of care. If FDG-PET scan is available the results will be used, but the test is not needed for inclusion.

After inclusion patient will come for visit 1, with vital signs, ECG, Safety labs, urine pregnancy test, adverse event assessment and concomitant medication. During this visit the IP zirconium Zr 89 crefmirlimab berdoxam will be infused.

The next day patients will come for visit 2, with safety labs, blood sample for Anti Drug Antibody analyses, an optional tumor biopsy and the zirconium Zr 89 crefmirlimab berdoxam scan.

After this their standard of care immunotherapy will start at visit 3. Details of the administration of immunotherapy will be recorded

After 2 cycles of immunotherapy they will have visits 5 and 6, which are similar to visits 1 and 2.

The results of the immunotherapy will be followed with standard of care CT imaging. After disease progression there are again 2 visits visit 6 and 7, with the same assessments. These are visits optional.

48 weeks after the start of the immunotherapy, or following confirmation of progressive disease and/or treatment discontinuation, whichever occurs first,

an End of Study visit will take place. During this visit physical examination including ECOG, vital signs, safety labs, urine pregnancy test. adverse event review and concomitant medication review will be done.

The patients themselves will not have benefits from the study.

For iTOX:
On top of the above the patients will visit the hospital 2 extra times when the experience their first irAE.
On visit 1, visit 4 and one of these iTOX visits a blood sample, a stool sample and a sigmoid sample will be taken.
Per standard of care patients will visit the hospital when experiencing an irAE as well, and they would have a sigmoid sample being taken as well on that occasion.

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

1. Subjects must meet either 1a,1b or 1c:
1a. For enrollment into Cohort A: Subjects with histologically confirmed advanced or metastatic non-uveal/non-mucosal melanoma or Merkel cell carcinoma (MCPyV positive and negative) who are not amenable to surgical cure and are candidates to receive single- or combined IOT alone (not to include cytotoxic chemotherapy) as first or second line treatment as per the local label/prescribing information at the physicians discretion.
1b. For enrollment into Cohort B: Subjects with histologically confirmed advanced or metastatic clear cell Renal Cell Carcinoma or Renal Cell Carcinoma with sarcomatoid features (regardless of subtype) as defined on pathologic examination by a component of clear cell or sarcomatoid, who are not amenable to surgical cure and are candidates to receive single- or combined IOT alone or IOT in combination with VEGFR-directed or tyrosine kinase inhibitor (not to include cytotoxic chemotherapy) as first or second line treatment as per the local label/prescribing information at the physicians discretion.
c. For enrollment into Cohort C: Subjects with histologically confirmed advanced or metastatic non-small cell lung cancer without non-smokers/driver mutations who are not amenable to surgical cure, and are candidates to receive single- or combined IOT alone (not to include cytotoxic chemotherapy) as first or second line treatment as per the label/prescribing information at the physicians discretion.
i. Patients with driver mutations that are expected to show significant benefit from first line checkpoint inhibiter treatment (such as KRAS G12C mutations) are eligible if all other I/E criteria are met.

2. At least 1 RECIST 1.1-measurable, non-irradiated, non-osseous (unless there is an associated measurable soft-tissue component) lesion documented on intravenous (IV) contrast-enhanced CT or MRI (per RECIST criteria 1.1) prior to first zirconium Zr 89 crefmirlimab berdoxam administration.

3. Has had an adequate amount of time between their prior treatment/procedure and the 1st administration of zirconium Zr 89 crefmirlimab berdoxam

4. Eastern Cooperative Oncology Group (ECOG) performance status <= 2 and anticipated survival of at least 6 months.

5. Male or female, age >= 18 years.

Additional inclusion criterion for iTOX addendum: SOC treatment should be a combination of ipilimumab and nivolumab.

Exclusion criteria

Subjects will NOT be eligible for enrollment in the study if they meet ANY of the following criteria:
1. Bone-only disease without a measurable soft tissue component on conventional imaging (MRI, PET, CT).
2. Subjects with skin-only (cutaneous) lesions will be excluded from the tumor biopsy assessment.
3. Serious nonmalignant disease or conditions that in the opinion of the investigator and/or ImaginAb could compromise the safety of the subject or the protocol objectives.
4. Subjects with splenic dysfunction or who are status post splenectomy. Post-splenectomy subjects who develop an accessory spleen with clinical and radiographic evidence of splenic function will be allowed with prior approval from the Sponsor.
5. Corticosteroid therapy is prohibited if used for the treatment of inflammatory or autoimmune conditions. Patients with adrenal insufficiency from prior surgery or immunotherapy toxicity may be on standard chronic replacement doses of hydrocortisone that also require sporadic use of stress doses of steroid .
6. Pregnant women or nursing mothers.

Additional exclusion criteria apply for patients to be eligible for the iTOX addendum:
1. Clinically active auto-immune disease, active infection or chronic inflammatory disease.
2. Course of antibiotics within 4 weeks prior to ICF signing.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2022
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Zirconium Zr 89 Crefmirlimab Berdoxam
Generic name:	NA

Ethics review

Approved WMO Date:	19-01-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-03-2023
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2021-005610-33-NL
ClinicalTrials.gov	NCT05013099
CCMO	NL79477.091.21