ImmunoPET imaging with 89Zr-MPDL3280A in patients with locally advanced or metastatic solid tumors prior to and during MPDL3280A treatment

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Primary objective: To evaluate pharmacokinetics (PK) of 89Zr-MPDL3280A in patients with locally advanced or metastatic solid tumor whom, in the opinion of the investigator, based on available clinical data, may benefit from treatment with anti PD-L1…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47805

Source
ToetsingOnline

Brief title
89Zr-MPDL3280A-PET imaging

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Genentech,Genentech/Hoffman-La Roche,Hoffmann-La Roche

Intervention

Keyword: 89Zr-MPDL3280A-PET, solid tumors

Outcome measures

Primary outcome

Description of 89Zr-MPDL3280A PK by measuring standardized uptake value (SUV) on the 89Zr-MPDL3280A-PET scans 0, 2, 4 and/or 7 days after tracer injection.

Secondary outcome

*Tumor and immune cell PD-L1 expression analysis in a fresh pre-treatment biopsy, and if available archival tumor biopsy, will be correlated to 89Zr-MPDL3280A tumor uptake, evaluated by measuring standardized uptake value (SUV) on the 89Zr-MPDL3280A-PET.

*Safety assessment through summaries of adverse events, changes in laboratory test results (if evaluation is indicated), changes in vital signs, and exposure to 89Zr-MPDL3280A. Adverse event data will be recorded and summarized according to NCI CTCAE v4.0. Serious adverse events, including deaths, will be listed separately and will be summarized. For events of varying severity, the highest grade will be used in summaries.

Relevant laboratory tests and vital signs (heart rate, respiratory rate, blood pressures, and temperature) data will be displayed by time, with Grade 3 and 4 values identified, where appropriate

* To assess the level of MPDL3280A target saturation during treatment with

MPDL3280A.

* To assess the level of inflammation before and during treatment with MPDL3280A.

other:

*89Zr-MPDL3280A normal organ uptake on the 89Zr-MPDL3280A-PET scans will be correlated to (89Zr-)MPDL3280A blood kinetics. Aliquots of whole blood and serum will be measured for 89Zr-activity in an isotope well counter and corrected for decay. Whole blood and serum activity will be expressed as standardized uptake value (SUV). Serum blood samples will also be collected regularly during the study to measure unlabeled MPDL3280A. PK parameters will be derived from the serum concentrations. These will include at least:

- Maximum serum concentration (Cmax)

- Time to reach maximum serum concentration (tmax)

- Area under the concentration-time curve (AUC)

- Serum concentration at the time of the 89Zr-MPDL3280A-PET scans (CPET)

Study description

Background summary

The Programmed cell death protein 1 (PD1)/Programmed death-ligand 1 (PD-L1) axis is an important immune checkpoint for T cell activation that is used by tumors to evade the host immune response. Blocking signaling with the PD-L1 antibody MPDL3280A results in ongoing T cell activity and can induce durable tumor regression across numerous solid tumor types. PD-L1 is not only expressed by tumor cells but also by immune cells, activated vascular endothelial cells

and in immune privileged sites such as the eye. An obstacle to using PD-L1 expression as predictive biomarker might be its potential heterogeneous expression and fast dynamics. For PD1/PD-L1 pathway inhibition PD-L1 tumor surface expression, positive in 40-100% of all melanoma patients and 35-95% of all non-small-cell lung cancer (NSCLC) patients, was proposed as a potential biomarker. In early clinical trials, PD-L1 expression has been associated with response to PD1/PD-L1 inhibition. However, other clinical trials reported response to PD1/PD-L1 checkpoint inhibitors in up to 47% of PD-L1-negative melanomas assessed by a single biopsy. In urothelial carcinoma weak to strong PD-L1 expression has been reported in 30% of the patients, however also response in PD-L1-negative patients has been seen. For triple-negative breast cancer (TNBC) little is known, but early response data are also very promising. Radio-labeling of MPDL3280A with the positron emission tomography (PET) radionuclide Zirconium-89 (89Zr) enables non-invasive imaging and quantification of PD-L1 distribution in cancer patients. By performing a 89Zr-MPDL3280A-PET scan prior to treatment with MPDL3280A, the uptake of the tracer in the primary and metastatic tumor lesions and normal organ distribution can be evaluated, as well as the use of a 89Zr-MPDL3280A-PET as a complementary tool for patient selection in the future.

Study objective

Primary objective: To evaluate pharmacokinetics (PK) of 89Zr-MPDL3280A in patients with locally advanced or metastatic solid tumor whom, in the opinion of the investigator, based on available clinical data, may benefit from treatment with anti PD-L1 immunotherapy irrespective of PD-L1 expression. Secondary objectives: i)To assess the heterogeneity of 89Zr-MPDL3280A tumor uptake; ii) To correlate tumor tracer uptake with tumor and immune cell PD-L1 expression as assessed by a fresh, and if available archival tumor biopsy; iii) To assess the level of target saturation; and iv) To describe safety of 89Zr-MPDL3280A. Exploratory objective: To correlate 89Zr-MPDL3280A normal tissue kinetics with 89Zr- and MPDL3280A blood kinetics.

Study design

This is a single-center, single-arm, investigator sponsored trial (IST) designed to evaluate the PK of 89Zr-MPDL3280A in patients with locally advanced or metastatic solid tumor whom, in the opinion of the investigator, based on available clinical data, may benefit from treatment with anti PD-L1 immunotherapy, prior to treatment with MPDL3280A within the MPDL3280A treatment trial (MPDL3280A-treatment-IST-UMCG, ML29755). In cohort A and B0, PET-scans will be made with a subherapeutic dose MPDL3280A before the start of MPDL3280A within the treatemnet study. In cohort B1, the tracer will be given together with the first cycle of MPDL3280A within the treatment study. In cohort B2, the tracer will be given together wth the frist and second dose of MPDL3280A within the treatment study.

Intervention

To investigate whether the experimental drug MPDL3280A ends up in the tumor, and to what extent in healthy tissue, a new scanning method can be used. In this study, prior to treatment with MPDL3280A first a small dose of the drug MPDL3280A coupled with the radioactive substance zirconium-89 (the "tracer" 89Zr-MPDL3280A) will be administered. Several days later the distribution of the tracer over the body can be imaged by positron emission tomography (PET) scans. This information can help to increase knowledge about the drug MPDL3280A. This is the first study in which 89Zr-MPDL3280A is administered to humans in order to investigate whether the drug will enter the tumor.

Study burden and risks

For this imaging side study patients in cohort A, B0 and B1 have to make a maximum of 5 extra visits to the clinic for screening, to receive tracer injection, for 2 PET scans at different time points and the biopsy before (and in case of B1 during) treatment with MPDL3280A. Patients participating in cohort B2 have to make a maximum of 9 study visits to the clinic for screening, twice a tracer injection, four PET scans and twice a biopsy. 89Zr-MPDL3280A-PET implements a radiation burden of about 18 mSv, and 1.5 mSv per low-dose CT scan (radiation burden cohort A, B0 and B1: 21mSv, radiation burden cohort B2: 42 mSv). Besides PET imaging, patients will be asked to give in total 12 blood samples (65 mL for patients A, B0 and B1, 130 mL for patients in B2), which will give minor discomfort. A metastases biopsy will be performed. Based on a literature review, the risk of tumor biopsies is considered low with a small risk on significant/major complications or death. The risk associated with the 89Zr-MPDL3280A seems minor and although patients do not directly benefit from this study, results of this study will be valuable for our understanding of the tumor immune response and will guide further prospective research. After participation within the imaging trial all patients will be allowed to enter the MPDL3280A treatment trial (MPDL3280A-treatment-IST-UMCG, ML29755), provided they continue to meet the eligibility criteria to receive MPDL3280A.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1 DA11
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1 DA11
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Histologically or cytologically documented locally advanced or metastatic solid tumor whom, in the opinion of the investigator, based on available clinical data, may benefit from treatment with anti PD-L1 immunotherapy.
2.Patients are eligible if disease progression during or following first-line systemic therapy or any subsequent treatment lines for locally advanced or metastatic solid tumor whom, in the opinion of the investigator, based on available clinical data, may benefit from treatment with anti PD-L1 immunotherapy
* Additional criteria for cancer of the urinary tract : Patients with disease progression during or following platinum-based adjuvant/neoadjuvant chemotherapy are eligible if * 12 months have elapsed between the last treatment administration and the date of recurrence.
*Additional criteria for NSCLC: Patients with disease progression during or following platinum-based adjuvant/neoadjuvant chemotherapy or concurrent chemoradiation for NSCLC are eligible if * 6 months have relapsed between the last treatment administration and the date of recurrence.
3.Tumor lesion(s) of which a histological biopsy can safely be obtained according to standard clinical care procedures.
4.ECOG performance status of 0 or 1.
5.Life expectancy *12 weeks.
6.Signed Informed Consent Form.
7.Ability to comply with protocol.
8.Age *18 years.
9.Measurable disease, as defined by standard RECIST v1.1. Previously irradiated lesions should not be counted as target lesions.
10.Adequate hematologic and end organ function, defined by the following laboratory results

obtained within *14 days prior to 89Zr-MPDL3280A injection:
*ANC *1500 cells/*L (without granulocyte colony-stimulating factor support within 2 weeks prior to 89Zr-MPDL3280A injection)
*WBC counts >2500/*L
*Lymphocyte count *500/*L
*Platelet count *100,000/*L (without transfusion within 2 weeks prior to 89Zr-MPDL3280A injection)
*Hemoglobin *9.0 g/dL. Patients may be transfused or receive erythropoietic treatment to meet this criterion.
*AST, ALT, and alkaline phosphatase * 2.5× the upper limit of normal (ULN), with the following exceptions:
Patients with documented liver metastases: AST and/or ALT * 5 × ULN; Patients with documented liver or bone metastases: alkaline phosphatase * 5 × ULN
*Serum bilirubin * 1.5 × ULN. Patients with known Gilbert disease who have serum bilirubin level * 3 × ULN may be enrolled.
*INR and aPTT * 1.5 × ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
*Creatinine clearance * 30 mL/min
11.For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception (i.e., one that results in a low failure rate < 1% per year] when used consistently and correctly).

Exclusion criteria

1.Any approved anti-cancer therapy, including chemotherapy or hormonal therapy within *14 days prior to 89Zr- MPDL3280A injection; the following exceptions are allowed: *Hormone-replacement therapy or oral contraceptives *TKIs approved for treatment of NSCLC discontinued >7 days prior to tracer injection. The baseline scan must be obtained after discontinuation of prior TKIs. 2.Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to the 89Zr-MPDL3280A injection.
3.Unstable brain metastases.
4.Unstable leptomeningeal disease.
5.Uncontrolled tumor-related pain.
*Patients requiring pain medication must be on a stable regimen at study entry.
*Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period. *Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
6.Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g.,

PleurX) are allowed.
7.Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab. *Patients, who are receiving bisphosphonate therapy or denosumab
specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
8.A second malignancy within 5 years prior to 89Zr-MPDL3280A injection, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent).
9.Pregnant and lactating women.
10.History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
11.Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cell products or any component of the MPDL3280A formulation.
12.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 a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
*Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.
* Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
o Rash must cover less than 10% of body surface area (BSA).
o Disease is well controlled at baseline and only requiring low potency topical steroids.
o No acute exacerbation of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
13.History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), druginduced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
*History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
14.Serum albumin < 2.5 g/dL.
15.Positive test for HIV.
16.Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. *Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to 89Zr-MPDL3280A injection. *Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
17.Active tuberculosis.

18.Severe infections within 4 weeks prior to 89Zr-MPDL3280A injection, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
19.Signs or symptoms of infection within 2 weeks prior to 89Zr-MPDL3280A injection.
20.Received therapeutic oral or IV antibiotics within 2 weeks prior to 89Zr-MPDL3280A injection. *Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
21.Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina. *Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
22.Major surgical procedure other than for diagnosis within 28 days prior to 89Zr-MPDL3280A injection or anticipation of need for a major surgical procedure during the course of the study. 23.Prior allogeneic bone marrow transplantation or solid organ transplant.
24.Administration of a live, attenuated vaccine within 4 weeks before 89Zr-MPDL3280A injection or anticipation that such a live attenuated vaccine will be required during the study. *Influenza vaccination should be given during influenza season only (example: approximately October to March in the Northern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g. FluMist®) within 4 weeks prior to 89Zr-MPDL3280A injection or at any time during the study treatment or within 5 months after the last dose of MPDL3280A.
25.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.
26.Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti*PD-1, and anti*PD-L1 therapeutic antibodies. *Patients who have had prior anti*CTLA-4 treatment may be enrolled, provided the following requirements are met: - Minimum of 6 weeks from the last dose of anti*CTLA-4 - No history of severe immune related adverse effects from anti*CTLA-4 (CTCAE Grade 3 and 4)
27.Treatment with systemic immunostimulatory agents (including but not limited to IFNs,IL-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to 89Zr-MPDL3280A injection.
28.Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti*tumor necrosis factor agents) within 2 weeks prior to 89Zr-MPDL3280A injection. *Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g. a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the sponsor. *The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g. fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-02-2016
Enrollment:	54
Type:	Actual

Ethics review

Approved WMO Date:	01-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2015-000996-29-NL
ClinicalTrials.gov	NCT02453984
CCMO	NL52825.042.15