MPDL3280A treatment in patients with locally advanced or metastatic solid tumors after or during investigational imaging

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Primary objective: To evaluate the efficacy of 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…

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

Summary

ID

NL-OMON47630

Source
ToetsingOnline

Brief title
MPDL3280A-treatment-IST-UMCG
ML29755

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: Hoffman-La Roche,Hoffmann-La Roche

Intervention

Keyword: MPDL3280A, solid tumors

Outcome measures

Primary outcome

Response to MPDL3280A therapy as measured by ORR according to standard RECIST v1.1, defined as the proportion of patients whose best overall response is either a partial response (PR) or complete response (CR), as assessed by the investigator.

Secondary outcome

•Evaluation of ORR, PFS and DOR according to modified RECIST, as assessed by the investigator.

- ORR is defined as the proportion of patients whose best overall response is either a PR or CR, as assessed by the investigator.

- PFS is defined as the time from the first full treatment dose of MPDL3280A to time of disease progression per modified RECIST as determined by the investigator or death due to any cause, whichever occurs first.

- DOR will be analyzed for the subset of patients, who achieved an objective response assessed by the investigator per modified RECIST. DOR is defined as the time from the initial occurrence of documented CR or PR until documented disease progression as determined by the investigator or death due to any cause, whichever occurs first.

•Evaluation of PFS and DOR according to standard RECIST v1.1, as assessed by the investigator.

- PFS is defined as the time from the first full treatment dose of MPDL3280A to time of disease progression per standard RECIST v1.1 as determined by the investigator or death due to any cause, whichever occurs first.

- DOR will be analyzed for the subset of patients, who achieved an objective response assessed by the investigator per standard RECIST v1.1. DOR is defined as the time from the initial occurrence of documented CR or PR until documented disease progression as determined by the investigator or death due to any cause, whichever occurs first.

•Safety assessment through:

- Incidence, nature and severity of adverse events, including protocol-defined events of special interest, graded according to NCI CTCAE4.0

- Changes in laboratory test results, vital signs and physical findings.

•89Zr-MPDL3280A, 18F-FB-IL2 or CD8 imaging tumor uptake, as defined and assessed in the investigational imaging protocols MPDL3280A-imaging-IST-UMCG and IL2-imaging-IST-UMCG.

•Number of subjects with and subjects without tumor tracer uptake with 89Zr-MPDL3280A, or 18F-FB-IL2 or 89Zr-CD8 antibody study, who demonstrate response to MPDL3280A therapy.

•Pathological PD-L1 assessment, as defined and evaluated in the investigational imaging protocols MPDL3280A-imaging-IST-UMCG and IL2-imaging-IST-UMCG.

•Status of tumor-infiltrating immune cells in biopsy specimen collected at the first evidence of radiographic disease progression according to standard

RECIST v1.1.

•The fecal microbiome will be analysed in related to antitumor effect. Feces

sampling will be performed before treatment and at cycle three.

Study description

Background summary

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T cell responses against cancer can result in a significant survival benefit in patients with Stage IV cancer. PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7-1. Interruption of the PD L1/PD-1 pathway by the PD-L1 targeting antibody MPDL3280A, represents an attractive strategy to reinvigorate tumor-specific T cell immunity. MPDL3280A is now a registered drug and additional information is given in IBv10. For PD1/PD-L1 pathway inhibition PD-L1 tumor surface expression was proposed as a potential biomarker. In 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 a big patient groups who were PD-L1-negative assessed by a single biopsy. Another obstacle to using PD-L1 expression as predictive biomarker might be its potential heterogeneous expression and fast dynamics
PD-L1 tumor expression and whole body distribution, as well as baseline activation status of the immune system are being assessed in three investigational imaging trials (MPDL3280A-imaging-IST-UMCG, IL2-imaging-IST-UMCG and 89Zr-CD8 imaging).
To be able to evaluate the investigational imaging - 89Zr-MPDL3280A-PET, 18F-FB-IL2-PET and 89Zr-CD8 imaging - as complementary tools for selection of patients to be treated with MPDL3280A, within this treatment trial we will assess safety, tolerability and anti-tumor activity of MPDL3280A in cancer patients, who have undergone investigational imaging. Acquired data could lead to improved, more patient friendly, more easily accessible and possibly less expensive procedures for patient selection. Subsequently, the efficacy of (combinations of) checkpoint inhibition could also be improved, thus preventing unnecessary toxicity and reducing health care costs.

Study objective

Primary objective: To evaluate the efficacy of 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, after investigational imaging, as measured by objective response rate (ORR) according to standard RECIST v1.1. Secondary objectives: i) To evaluate progression free survival (PFS) and duration of response (DOR) according to standard RECIST v1.1 as assessed by the investigator; ii) To evaluate ORR, PFS and DOR according to modified RECIST as assessed by the investigator; iii) To evaluate the safety and tolerability of MPDL3280A; iv) To determine the number of patients with and patients without tumor tracer uptake with 89Zr-MPDL3280A and 18F-FB-IL2 as assessed in the trials MPDL3280A-imaging-IST-UMCG, IL2-imaging-IST-UMCG or 89Zr-CD8 antibody and also demonstrate response to MPDL3280A therapy; v) To correlate PD-L1 biopsy results as assessed in the trials MPDL3280A-imaging-IST-UMCG, IL2-imaging-IST-UMCG or 89Zr-CD8 imaging to response to MPDL3280A therapy; and vi) 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 MPDL3280A (i.e., pseudoprogression/tumor immune infiltration) from true disease progression.

Study design

This is a Phase II, single-center, single-arm, investigator sponsored trial (IST) designed to evaluate the efficacy and safety of MPDL3280A in patients with solid tumors irrespective of PD-L1 status, who participate investigational imaging within the 18F-FB-IL2 imaging trial (IL2-imaging-IST-UMCG), the 89Zr-MPDL3280A antibody imaging trial (MPDL3280A-imaging-IST-UMCG) prior to or during treatment or the 89Zr-CD8 antibody imaging trial .

Intervention

All patients, who have participated in one of the two investigational imaging trials, will be allowed to enter this MPDL3280A treatment trial within 7 days after the last visit of the imaging trial (being the last PET scan or the biopsy visit), provided they continue to meet the eligibility criteria to receive MPDL3280A. Before MPDL3280A administration on Day 1 Cycle 1 eligibility will be reevaluated. MPDL3280A IV (fixed dose of 1200 mg) will be administered on Day 1 of 21-day cycles. MPDL3280A treatment may be continued as long as patients are demonstrating clinical benefit as assessed by the investigator, i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed by investigators, at the first evidence of radiographic disease progression according to standard RECIST v1.1. These data will be used to confirm that radiographic findings are consistent with the presence of tumor.

Study burden and risks

Treatment with MPDL3280A offers the potential for clinical benefit in patients. Because most MPDL3280A-related toxicities observed to date have been mild and transient in nature and do not overlap with the adverse effects of chemotherapy, patients who do not respond to study treatment are considered likely to be able to subsequently receive standard therapies for which they would otherwise have been eligible. Patients will be fully informed of the risk of continuing study treatment in spite of apparent radiographic progression, and investigators should make a careful assessment of the potential benefit of doing so, considering radiographic data, biopsy results, and the clinical status of the patient. A tumorbiopsy 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.

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.Participation within the 18F-IL2 imaging trial (IL2-imaging-IST-UMCG) or 89Zr-MPDL3280A antibody imaging trial (MPDL3280A-imaging-IST-UMCG) or CD8 imaging trail (ZED88082-img-UMCG-2018) before participation in the MPDL3280A treatment trial.
3.Assessment of the PD-L1-tumor status of a fresh tumor biopsy as determined by an IHC assay based on PD-L1 expression on immunocells and/or tumor cells performed by a central laboratory, performed as part of one of the investigational imaging trials.
4.Patients are eligible if disease progression during or following first-line chemotherapy 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 elapsed between the last treatment administration and the date of recurrence.
- Patients with a known sensitizing mutation in the epidermal growth factor receptor (EGFR) gene must also have experienced disease progression (during or after treatment) or intolerance to treatment with erlotinib, gefitinib, or another EGFR tyrosine kinase inhibitor (TKI).
Patients with a known Anaplastic Lymphoma Kinase (ALK) fusion oncogene must also have experienced disease progression (during or after treatment) or intolerance to treatment with crizotinib or another ALK inhibitor.
5.Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6.Life expectancy >=12 weeks.
7.Signed Informed Consent Form.
8.Ability to comply with protocol.
9.Age >=18 years.
10.Measurable disease, as defined by standard RECIST v1.1. Previously irradiated lesions should not be counted as target lesions.
11.Adequate hematologic and end organ function, defined by the following laboratory results obtained within <=28days prior to the first full dose of MPDL3280A:
•ANC >=1500 cells/µL (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
•WBC counts >2500/µL
•Lymphocyte count >=500/µL
•Platelet count >=100,000/µL (without transfusion within 2 weeks prior to Cycle 1, Day 1)
•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
12.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) and to continue its use for 6 months after the last dose of MPDL3280A.

Exclusion criteria

1.Any approved anti-cancer therapy, including chemotherapy or hormonal therapy within <=21 days prior to the first full dose of MPDL3280A.
•Hormone-replacement therapy or oral contraceptives.
•TKIs approved for treatment of NSCLC discontinued >7 days prior to the first full dose of MPDL3280A. The baseline scan must be obtained after discontinuation of prior TKIs.
2.Treatment with any other investigational agent, other than the investigational tracer 89Zr-MPDL3280A, 18F-FB-IL2 or 89Zr-CD8-imaging, or participation in another clinical trial with therapeutic intent within 28 days prior to the first full dose of MPDL3280A.
3.Unstable brain metastases.
4.Unstable leptomeningeal disease.
5.Uncontrolled tumor-related pain.
•Subjects 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. Subjects 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. •Subjects, 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.
•Subjects who are receiving denosumab prior to enrollment must be willing and eligible to

receive a bisphosphonate instead while on study.
8. A second malignancy within 5 years prior to Cycle 1 Day 1, 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.
•Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
•Subjects 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), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
14.Serum albumin lower than 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.
•Subjects 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 subjects prior to Cycle 1, Day 1.
•Subjects 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 the first full dose of MPDL3280A, 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 Cycle 1, Day 1.
20.Received therapeutic oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1.
•Subjects 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.
22.Major surgical procedure other than for diagnosis within 28 days prior to Cycle 1, Day 1 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 Cycle 1, Day 1or 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). PatientSubjects must not receive live, attenuated influenza vaccine (e.g. FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study treatment of 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.
•Subjects who have had prior anti*CTLA-4 treatment may be enrolled, provided the following requirements are met:
oMinimum of 6 weeks from the last dose of anti*CTLA-4
oNo 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 the first full dose of MPDL3280A.
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 Cycle 1, Day 1.

Study design

Design

Study phase:	2
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:	98
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MPDL3280A
Generic name:	MPDL3280A

Ethics review

Approved WMO Date:	12-06-2015
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:	27-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-10-2016
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:	19-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-07-2017
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:	20-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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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)
Approved WMO Date:	30-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2022
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	EUCTR2015-000907-19-NL
ClinicalTrials.gov	NCT02478099
CCMO	NL52740.042.15