A phase II study investigating preoperative MPDL3280A in operable transitional cell carcinoma of the bladder (ABACUS).

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Primary objectives: - Clinical: To assess the efficacy of MPDL3280A pre-cystectomy with respect to pCRR in patients with T2-T4aN0M0 transitional cell carcinoma of the bladder- Biological: To assess the effect of 2 x 3 weekly cycles of MPDL3280A pre-...

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

Summary

ID

NL-OMON47135

Source
ToetsingOnline

Brief title
ABACUS

Condition

- Other condition

Synonym
Bladder cancer

Health condition

urotheelcelcarcinoom van de blaas

Research involving

Human

Sponsors and support

Primary sponsor: Queen Mary University
Source(s) of monetary or material Support: Farmaceutische industrie,Roche

Intervention

Keyword: Cystectomy, MPDL3280A, Transitional cell carcinoma of the bladder (T2-T4a)

Outcome measures

Primary outcome

Primary endpoints:

- Pathological complete response rate (pCRR) defined as no microscope evidence (pT0/Tis/Cis) of residual disease in the bladder based on histological evaluation of the resected bladder specimen collected during cystectomy (post* treatment).

- Dynamic changes in T cell subpopulations (CD8 and/or CD3) measured in tumour samples collected pre- and post-treatment.

Secondary outcome

Secondary endpoints:

- Incidence, nature and severity of Adverse Events graded according to NCI-CTCAE v4.03 collected during treatment and up to 24 weeks post cystectomy. Surgical complications as assessed by the Clavien-Dindo scoring system.

- RR, defined as a >30% decrease in tumour diameter from the baseline scan based on local investigator assessments

- DFS, defined as time between the date of enrolment to first evidence of relapse based on local investigator assessments or death, whichever occurs

first.

- OS, defined as the time between the date of enrolment and death due to any

cause.

Exploratory endpoints:

- Expression profiling of tumour and/or tumour infiltrating immune cells

- Identification of immunogenic neo-antigens which potentially could promote

anti-tumour T-cell response upon MPDL3280A treatment

- Profiling of immune cell infiltration in tumour and/or blood

- Cytokine assessment

- RNA and DNA analysis exploring dynamic changes to gene signatures and

mutations patterns.

Study description

Background summary

Bladder cancer is the seventh most common cancer in men and nineteenth most common in women globally with 429,793 new diagnoses in 2012 (1). There were 123,051 and 42,033 deaths in men and women worldwide, respectively, in 2012. Similarly, in the UK, it is the seventh most common cancer overall, with 10,399 new diagnoses in 2011 (7,452 in men, 2,947 in women) (2). There were 5,242 deaths in the UK in 2012 due to bladder cancer.

The most common presenting complaint for bladder cancer is painless haematuria, which is present in >80% of patients (3). Other symptoms may include dysuria, urinary frequency or urgency. The key investigations for the diagnosis of bladder cancer are cystoscopy and transurethral resection of bladder cancer (TURBT). Tissue from the TURBT should be sent for histopathological analysis to determine the type and stage of bladder cancer. Ideally, complete resection of all tumour tissue should be achieved at TURBT, but this is not always possible (3).

The major histologic subtype in bladder cancer is transitional cell carcinoma of the bladder (TBC, also termed urothelial bladder cancer or urothelial cell

carcinoma), accounting for 90% of cases (4). Rarer histologies include squamous cell carcinoma, adenocarcinoma and small cell carcinoma. The majority of urothelial tumours arise in the bladder, but also originate from the renal pelvis, ureters or urethra. Smoking is the main risk factor for TBC and accounts for approximately 50% of cases (5). Other risk factors include occupational exposure to certain chemicals and previous treatment with radiotherapy to the pelvic organs (5).

The overall 5-year survival rate for bladder cancer is approximately 70% in the UK (6). Muscle-invasive bladder cancer (T2-T4aN0M0) accounts for around 30% of new cases and has a 5-year survival rate of 25-50% (6, 7). Women are more likely to be diagnosed with muscle-invasive disease (85% vs. 51%) and have a worse cancer-specific survival (8). Survival rates have remained largely unchanged over the past 30 years, reflecting a lack of effective new treatments (9).

Study objective

Primary objectives:
- Clinical: To assess the efficacy of MPDL3280A pre-cystectomy with respect to pCRR in patients with T2-T4aN0M0 transitional cell carcinoma of the bladder
- Biological: To assess the effect of 2 x 3 weekly cycles of MPDL3280A pre-cystectomy on immune parameters in patients with T2-T4aN0M0 transitional cell carcinoma of the bladder
Secondary objectives:
- To evaluate the safety and tolerability of MPDL3280A when given pre-cystectomy in this population
- To assess the efficacy of MPDL3280A given pre-cystectomy with respect to anti-tumour effects as measured by Investigator assessed radiological response (RR)
- To assess the efficacy of MPDL3280A given pre-cystectomy with respect to anti-tumour effects based on Investigator assessed disease free survival (DFS)
- To assess the efficacy of MPDL3280A given pre-cystectomy with respect to overall survival (OS)
Exploratory objectives:
- To further understand the mode of action of MPDL3280A
- To evaluate the relationship between tissue PD-L1 expression and measures of safety and efficacy, including but not limited to ORR, PFS and OS
- To assess predictive and prognostic exploratory biomarkers in collected tumour tissue and plasma and their association with disease status and/or response/failure to study treatment
- To increase knowledge and understanding of disease and immune biology
- To develop diagnostic tests, which may allow for individualized drug therapy for patients in the future

Study design

This is an open-label, international, multicentre window of opportunity phase II trial that aims to evaluate the effects of short-term preoperative therapy with MPDL3280A in patients with histologically confirmed (T2-T4a) transitional cell carcinoma of the bladder. Eligible patients will receive 2 x 3 weekly cycles of MPDL3280A pre-cystectomy. Patients will attend study visits at 4, 12 and 24 weeks following their cystectomy. After the 24 week post cystectomy visit, patients will enter a follow up phase during which they will be contacted annually for 2 years after their cystectomy to collect survival and disease status data. The efficacy of MPDL3280A will be assessed on CT/MRI scan images and tumour tissue samples collected at baseline and after treatment with MPDL3280A.

Intervention

2 x MPDL3280A iv and cystectomy

Study burden and risks

Potential benefits
The current standard of care for MIBC is radical cystectomy, which unfortunately is rarely curative. Platinum-based neoadjuvant chemotherapy is associated with an improvement in OS, but is only suitable for a minority of patients. Therefore, new neoadjuvant therapeutic options are required for MIBC. MPDL3280A has significant activity in advanced TBC and therefore may have beneficial outcomes in the neoadjuvant setting (26).

Potential risks
The main potential risks relates to adverse events associated with MPDL3280A. In most European countries, patients currently have to wait an average of 4*8 weeks between establishing the diagnosis of bladder cancer and cystectomy. Participation in this trial of 6 weeks preoperative treatment is not expected to result in relevant delays of surgery for participants. There is no preclinical, clinical or mechanistic evidence to suggest that MPDL3280A has a relevant impact on operability or increases the risks associated with surgery.

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

-Willing and able to provide written informed consent
-Ability to comply with the protocol
-Age * 18 years
-Histopathologically confirmed transitional cell carcinoma (T2-T4a) of the bladder. Patients with mixed histologies are required to have a dominant transitional cell pattern.
-Residual disease after TURBT (surgical opinion, cystoscopy or radiological presence).
-Fit and planned for cystectomy (according to local guidelines).
-N0 or M0 disease CT or MRI (within 4 weeks of registration)
-Representative formalin-fixed paraffin embedded (FFPE) bladder tumour samples with an associated pathology report that are determined to be available and sufficient for central testing.
-Patients who refuse neoadjuvant cisplatin based chemotherapy or in whom neoadjuvant cisplatin based therapy is not appropriate.
-Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
-Negative pregnancy test within 2 weeks of Day 1 Cycle 1 for female patients of childbearing potential.
-For female patients of childbearing potential to use a highly effecting 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 90 days after the last dose of MPDL3280A.
-Adequate hematologic and end-organ function within 4 weeks prior to the first study treatment defined by the following:

a) ANC * 1500 cells/*L (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
b) WBC counts > 2500/*L
c)Lymphocyte count * 500/*L
d) Platelet count * 100,000/*L (without transfusion within 2 weeks prior to Cycle 1, Day 1)
e) Haemoglobin * 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion).
f) AST or ALT, and alkaline phosphatase * 2.5 times the institutional upper limit of normal (ULN) (patients with known Gilbert disease who have serum bilirubin level * 3 × the institutional ULN may be enrolled).
g) INR and aPTT * 1.5 × the institutional ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
h) Calculated creatinine clearance * 20 mL/min (Cockcroft-Gault formula)

Exclusion criteria

-Pregnant and lactating female patients
-Major surgical procedure within 4 weeks prior to enrolment or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
-Previous intravenous chemotherapy for bladder cancer
-Patients with prior allogeneic stem cell or solid organ transplantation
-Prior treatment with CD137 agonists, anti-CTLA-4, anti*programmed death*1 (PD-1), or anti*PD-L1 therapeutic antibody or pathway-targeting agents.
-Patients must not have had oral/IV steroids for 14 days prior to study entry. The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency) and mineralocorticoids (e.g., fludrocortisone) is allowed.
-Received therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to enrolment. (Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible).
-Administration of a live, attenuated vaccine within 4 weeks prior to enrolment or anticipation that such a live, attenuated vaccine will be required during the study
-Treatment with systemic immunostimulatory agents (e.g. interferons or interleukin [IL]*2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to enrolment
-Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to enrolment
-Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
-Malignancies other than UBC within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (Gleason score * 3 + 4 and PSA < 10 ng/mL undergoing

active surveillance and treatment naive)
-Severe infections within 4 weeks prior to enrolment in the study (e.g. hospitalization for complications of infection, bacteraemia, severe pneumonia)
-Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to enrolment, unstable arrhythmias, or unstable angina
-History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan (History of radiation pneumonitis in the radiation field (fibrosis) is permitted)
-Patients with uncontrolled Type 1 diabetes mellitus. Patients with Type 1 diabetes controlled on a stable insulin regimen are eligible.
-Patients with active hepatitis infection (positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA
-Positive test for HIV
-Patients with active tuberculosis
-History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug
-Uncontrolled hypercalcemia (>1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > the institutional ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab. Patients who are receiving bisphosphonate therapy or denosumab to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible. Patients receiving denosumab prior to enrollment must be willing and eligible to receive bisphosphonate instead while on study
-History of autoimmune disease including 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, glomerulonephritis
-Patients with a history of autoimmune-related hypothyroidism, unless on a stable dose of thyroid-replacement hormone
-History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
-Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the MPDL3280A formulation

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-03-2017
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Atezolizumab (MPDL3280A)
Generic name:	Atezolizumab (MPDL3280A)

Ethics review

Approved WMO Date:	18-07-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-11-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-12-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-12-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-03-2020

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2015-001112-35-NL
ClinicalTrials.gov	NCT02662309
CCMO	NL56953.031.16