A Phase 1 Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination with Tremelimumab (Anti-CTLA-4 Antibody) in Subjects with Advanced Solid Tumors

Published: 09-05-2016
Last updated: 16-04-2024

OBJECTIVESPrimary Objectives:To assess the safety and tolerability, describe the dose-limiting toxicities (DLTs), and determine the maximum tolerated dose (MTD) or the highest protocol-defined dose (in the absence of exceeding the MTD) for the…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON47386

Source
ToetsingOnline

Brief title
D4190C00010

Condition

- Other condition

Synonym
Advanced Solid Tumors

Health condition

Gevorderde solide tumoren

Research involving

Human

Sponsors and support

Primary sponsor: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC
Source(s) of monetary or material Support: MedImmune LLC

Intervention

Keyword: Advanced Solid Tumors, MEDI4736, Phase 1, Tremelimumab

Outcome measures

Primary outcome

Primary Endpoints:

The primary safety endpoint as assessed by the presence of adverse events (AEs), serious adverse events (SAEs), DLTs, and changes from baseline in laboratory parameters, physical examinations, electrocardiograms, and vital signs.

The primary efficacy endpoint in subjects with PD-L1 negative UBC is objective response (OR) based on RECIST v1.1 as determined by the investigator.

Secondary outcome

Secondary Endpoints:

Assessment of antitumor activity in subjects with PD-L1 negative UBC includes disease control (DC), duration of response (DoR), and progression-free survival (PFS) based on RECIST v1.1 as determined by the investigator, and overall survival (OS).

Assessment of antitumor activity for subjects with PD-L1 positive UBC, UBC regardless of PD-L1 status, and select advanced solid tumors other than UBC includes OR, DC, DoR, and PFS based on RECIST v1.1 as determined by the

investigator, and OS.

Expression and localization of key molecules including but not limited to PD L1 and programmed cell death 1 (PD-1), within the tumor microenvironment, as well as the frequency, localization, and phenotype of tumor-infiltrating lymphocytes, may be examined in pretreatment and post-treatment biopsy specimens by immunohistochemistry (IHC), immunofluorescence (IF), and/or flow cytometry and correlated with response to treatment and clinical outcome.

The endpoints for assessment of PK of MEDI4736 and tremelimumab include individual MEDI4736 and tremelimumab concentrations and PK parameters.

The endpoints for assessment of immunogenicity of MEDI4736 and tremelimumab include the number and percentage of subjects who develop detectable antidrug antibodies (ADA).

Study description

Background summary

See Protocol Amendment 4, "1.3 MEDI4736 and Tremelimumab Background" on page 21

Study objective

OBJECTIVES
Primary Objectives:
To assess the safety and tolerability, describe the dose-limiting toxicities (DLTs), and determine the maximum tolerated dose (MTD) or the highest protocol-defined dose (in the absence of exceeding the MTD) for the combination of MEDI4736 and tremelimumab in subjects with select advanced solid tumors.
To evaluate the antitumor activity of MEDI4736 in combination with tremelimumab in subjects with programmed cell death ligand 1 (PD L1) negative urothelial bladder cancer (UBC) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary Objectives:

To describe the preliminary antitumor activity of MEDI4736 in combination with tremelimumab based on RECIST v1.1 in subjects with select advanced solid tumors other than UBC.
To evaluate the antitumor activity of MEDI4736 in combination with tremelimumab in subjects with UBC, regardless of PD-L1 status based on RECIST v1.1.
To evaluate the antitumor activity of MEDI4736 in combination with tremelimumab in subjects with PD L1 positive UBC based on RECIST v1.1.
To evaluate the pharmacodynamic activity of MEDI4736 in combination with tremelimumab in the periphery and tumor microenvironment.
To describe the pharmacokinetics (PK) of MEDI4736 in combination with tremelimumab and tremelimumab in combination with MEDI4736 in subjects with select advanced solid tumors.
To determine the immunogenicity of MEDI4736 in combination with tremelimumab and tremelimumab in combination with MEDI4736 in subjects with select advanced solid tumors.

Exploratory Objectives:
To describe the preliminary antitumor activity of MEDI4736 in combination with tremelimumab based on immune-related RECIST (irRECIST) in subjects with select advanced solid tumors.
To evaluate candidate biomarkers of MEDI4736 in combination with tremelimumab in peripheral blood and tumor biopsy specimens that may (1) correlate with biologic activity (pharmacodynamics), or (2) prospectively identify subjects most likely to respond to treatment (predictive).

Study design

This is a multicenter, open-label, dose-exploration, and dose expansion study to evaluate the safety, tolerability, antitumor activity, PK, and immunogenicity of MEDI4736 in combination with tremelimumab in subjects with select advanced solid tumors. The dose-exploration phase, conducted across a range of tumor types, has been completed. The dose-expansion phase of the study is ongoing in 7 immunotherapy (IMT)-naive tumor-specific cohorts (UBC, small-cell lung cancer [SCLC], soft tissue sarcoma [STS], triple-negative breast cancer [TNBC], human papilloma virus [HPV]-positive anogenital cancer [including anal, cervical, and vaginal cancers], microsatellite instability-high colorectal cancer [MSI-H CRC], and high-grade epithelial ovarian cancer [including fallopian tubal carcinoma and peritoneal carcinoma]) and 1 IMT-pretreated cohort. The study will be conducted at up to approximately 90 study centers.
The dose-exploration phase will enroll approximately 12 to 24 IMT-naive subjects (defined as no prior exposure to IMT, including, but not limited to, other anti-cytotoxic T-lymphocyte-associated antigen 4 [CTLA 4], anti-PD-1, or anti-PD-L1 monoclonal antibodies [mAbs]) and 3 to 6 IMT-pretreated subjects (defined as prior exposure to IMT, including, but not limited to, other anti-CTLA-4, anti-PD-1, or anti-PD-L1 mAbs).
The IMT-naive dose-exploration phase will include up to 12 IMT-naive subjects

treated in 2 planned cohorts using the every 4 weeks (Q4W) dosing schedule and up to 12 IMT-naive subjects treated in 2 planned cohorts using the every 2 weeks (Q2W) dosing schedule. Additional subjects may be required during the IMT-naive dose-exploration phase if cohorts are expanded or intermediate dose levels are explored.

IMT-naive dose exploration in the current study will begin with parallel enrollment into both Q2W Cohort 1 (10 mg/kg MEDI4736 and 3 mg/kg tremelimumab) and Q4W Cohort 1 (20 mg/kg MEDI4736 and 1 mg/kg tremelimumab); both doses and schedules are being evaluated in subjects with non-small cell lung cancer (NSCLC) in the ongoing Study D4190C00006.

Intermediate dose levels may be explored at the discretion of the sponsor based on emerging data. If unacceptable toxicity is encountered at the starting dose levels, de-escalation will be permitted.

Given the preliminary safety data in the current study (Study D4190C00010) and Study D4190C00006, the selected dose for evaluation in all subjects enrolled in the IMT-pretreated dose-exploration and dose-expansion cohorts of the current study (Study D4190C00010) will be: 20 mg/kg MEDI4736 via intravenous (IV) infusion Q4W for 4 months (up to 4 doses) and 1 mg/kg tremelimumab via IV infusion Q4W for 4 months (up to 4 doses). After completion of the initial 4 doses of combination therapy, single-agent MEDI4736 will continue at 10 mg/kg Q2W to complete a total of 12 months of therapy (up to 18 additional doses). The first MEDI4736 dose at 10 mg/kg Q2W will be 4 weeks after the final dose of the combination regimen. Subjects in the IMT naive dose-exploration cohorts of the current study (Study D4190C00010) will not be switched to this selected dose and schedule, and will continue with the dose and schedule chosen at the time of enrollment.

At the dose and schedule selected for the IMT-naive dose-expansion phase of the current study, 3 to 6 IMT pretreated subjects will be enrolled as part of the IMT-pretreated dose-exploration phase of the current study (Study D4190C00010) following the same dose-exploration guidelines as used for IMT-naive dose exploration. This IMT-pretreated dose-exploration phase will confirm the safety and tolerability of the selected dose/schedule prior to enrolling such subjects in the IMT-pretreated cohort of the dose-expansion phase.

Under Protocol Amendment 3 and beyond, the dose-expansion phase will include a total of 8 cohorts: 7 IMT-naive cohorts and 1 IMT-pretreated cohort (Table 1). The IMT pretreated cohort will include the same tumor types as the IMT-naive cohorts of the dose-expansion phase. The eligibility criteria for the IMT pretreated cohort will be the same as the eligibility criteria used for IMT-naive tumor-specific cohorts, with the exception of allowing previous exposure to IMT.

With the exception of the UBC cohort that may enroll approximately 167 subjects, all other dose expansion cohorts (both IMT-naive and IMT-pretreated) will be limited to approximately 30 subjects each.

Under Protocol Amendment 3 and beyond, additional PD-L1 positive and PD-L1 negative UBC subjects will be enrolled to evaluate the correlation between PD-L1 expression and response to treatment with the combination of MEDI4736 and tremelimumab. In addition, approximately 7 subjects with non-evaluable PD-L1

status will be enrolled before the interim analysis, assuming a PD-L1 positive prevalence of 60% and approximately 10% of subjects with a non-evaluable tumor sample. Based on the data available to date in NSCLC, it is hypothesized that the MEDI4736 and tremelimumab combination will prove active in both PD-L1 positive and PD-L1 negative subjects.
Under previous amendments of this protocol, approximately 30 UBC subjects were planned to be enrolled, resulting in approximately 20 PD L1 positive and 10 PD-L1 negative subjects, assuming a PD L1 positive prevalence of 60% (and PD L1 negative prevalence of 40%), based on preliminary data from Study CD-ON-MEDI4736-1108. Under Protocol Amendment 4, approximately 137 additional UBC subjects may be enrolled. Initially, approximately 77 UBC subjects will be enrolled to target enrollment of 40 new PD-L1 positive subjects, a minimum of 30 new PD L1 negative subjects, and approximately 7 subjects with non-evaluable PD-L1 status, again assuming a PD L1 positive prevalence of 60% (and non-evaluable PD-L1 prevalence of 10%). These newly enrolled subjects will provide a total of approximately 60 PD-L1 positive, 40 PD L1 negative subjects (including those enrolled prior to Protocol Amendment 3), and approximately 7 PD-L1 non-evaluable subjects to allow for assessment of the activity of the MEDI4736 and tremelimumab combination in the overall population, regardless of PD-L1 status. In addition, it will enable initial analyses to estimate the response rates in the UBC biomarker subgroups. If adequate clinical activity is observed in the PD L1 negative subgroup, further enrollment may continue in the PD L1 negative group only such that 60 additional subjects may be enrolled for a total of 100 PD-L1 negative subjects in order to provide sufficient precision to estimate the objective response rate (ORR) in this group.
Not only will inclusion of PD-L1 positive, PD-L1 negative, and PD-L1 non-evaluable UBC subjects allow for the analysis of clinical activity in each respective subgroup, it will also (1) enable exploratory analyses to potentially refine the PD-L1 positive and PD-L1 negative definition, (2) identify other potential biomarkers to aid in the selection of UBC patients most likely to benefit from treatment with the combination of MEDI4736 and tremelimumab, and (3) provide the tumor tissue necessary to complete cross-comparisons of PD-L1 status as defined by the Ventana (SP263) IHC assay versus other assays, which may become commercially available for use in this population (eg, the Ventana SP142 IHC assay or the Dako 22C3 IHC assay).
To ensure that all of the additional UBC subjects contribute to the biomarker validation, subjects enrolled under Protocol Amendment 3 and beyond must have measurable disease at baseline by BICR. PD-L1 status will be determined by a central testing laboratory and will be derived from a fresh tumor biopsy taken during screening or an available tumor sample taken from <= 6 months prior to study entry. The tumor sample used for PD-L1 analysis must be shipped to, and confirmed as received by, the sponsor or designated central vendor prior to the first dose of MEDI4736 and tremelimumab. However, subjects may be dosed before PD L1 results are known. It is highly recommended that efforts are taken to confirm the presence of tumor cells within the tumor sample prior to shipping for PD-L1 analysis. The tumor PD-L1 status will be determined by IHC with PD L1 positive samples defined as >= 25% tumor cell or IC staining and PD-L1 negative

samples defined as < 25% tumor cell and IC staining. PD-L1 status determined by IHC testing from tumor samples evaluated for screening into Study CD ON MEDI4736 1108 may be used if derived from a sample taken <= 6 months prior to study entry. Additional archival tumor tissue, regardless of age, is also required, if available.
If adequate clinical activity is observed in the PD-L1 negative subgroup (see Section 4.8.2.2), and further enrollment continues in the PD-L1 negative group to target enrollment of 60 additional PD L1 negative subjects, PD-L1 status must be determined prospectively by a central testing laboratory prior to treatment with MEDI4736 and tremelimumab.
In any cohort of the dose-expansion phase, if greater than one-third of subjects experience safety events meeting DLT criteria, enrollment may be paused, and the study data will be reviewed to determine whether additional monitoring or alternate dose levels or treatment schedules should be evaluated prior to further enrollment.
All subjects will be evaluated regularly and their clinical status classified according to RECIST v1.1. All subjects will be followed for survival until the end of study. Evaluation of a possible correlation between clinical activity of MEDI4736 and tremelimumab and potential biomarkers (eg, tumoral PD-L1 expression) will be ongoing throughout the study. Tumoral PD-L1 expression may be monitored throughout the study so as to plan for further enrollment, and if necessary, a decision to enroll may be based on PD-L1 expression status.
Enrollment into dose-expansion cohorts may be discontinued at the discretion of the sponsor should emerging clinical or preclinical data suggest that continued treatment may not be beneficial to a given cohort.

Intervention

Dose: Subjects will be treated in either the dose-exploration or the dose-expansion phase of the study. In the dose-exploration phase, both a MEDI4736 Q2W and Q4W dosing schedule (dosing frequency of tremelimumab is only Q4W) will be explored (Table 2). Once dose exploration is complete, either the Q2W or Q4W dosing schedule will be selected for further evaluation in the dose-expansion phase. Subjects meeting specific criteria may be eligible for up to 12 months of re-induction.

IMT-naive Dose Exploration:
Q4W Dosing Schedule: In dose-exploration phase for IMT-naive subjects, MEDI4736 will be administered via IV infusion Q4W for 12 months (up to 13 doses). Tremelimumab will be administered Q4W for 7 doses and then every 12 weeks (Q12W) for 2 doses (for a total of up to 9 doses) for 12 months.
Q2W Dosing Schedule: In dose-exploration phase for IMT-naive subjects, MEDI4736 will be administered via IV infusion Q2W for 12 months (up to 26 doses). Tremelimumab will be administered Q4W for 7 doses and then Q12W for 2 doses (for a total of up to 9 doses) for 12 months.

IMT-pretreated Dose Exploration and Dose Expansion:

Q4W Dosing Schedule: IMT-pretreated subjects enrolled in the dose-exploration and dose-expansion phases will receive 20 mg/kg MEDI4736 via IV infusion Q4W for 4 months (up to 4 doses) and 1 mg/kg tremelimumab via IV infusion Q4W for 4 months (up to 4 doses). After completion of the initial 4 doses of combination therapy, single-agent MEDI4736 will continue at 10 mg/kg Q2W to complete a total of 12 months of therapy (up to 18 additional doses). The first MEDI4736 dose at 10 mg/kg Q2W will be administered 4 weeks after the final dose of the combination regimen.

Mode of Administration: Tremelimumab will be administered first and the infusion duration will be approximately 1 hour. The MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion and the infusion will be administered over approximately 1 hour.

Study burden and risks

Side effects that may be experienced as a result of the defence system*s reaction to medications that activate the defence system may include but are not limited to the following:
• Fever (temperature above 38°C)
• Fatigue
• Rash or hives with or without itchiness and swelling
• Change in blood pressure sometimes significant
• Decrease in blood platelets (cells that stop bleeding) with symptoms such as unexpected bruising, bleeding from the nose or gums, blood in vomit or stools or red spots under the skin
• Inflammation of the lungs (pneumonitis) with symptoms including difficulty breathing. Pneumonitis can be fatal.
• Inflammation of the nervous system with symptoms including a tingling or burning feeling, sharp pain, weakness, numbness or reduced ability to feel pain and temperature changes especially in the fingers and toes and pain while walking
• Inflammation of the pancreas with symptoms such as abnormal laboratory blood tests (increases in specific proteins measure how your pancreas is working, stomach pain, nausea, vomiting and tenderness when touching the stomach
• Inflammation of the liver (hepatitis) with symptoms such as stomach swelling, bloating, diarrhoea, discolored urine or stools, loss of appetite, tiredness, nausea with or without vomiting, yellowing of the skin and whites of the eyes. Hepatitis can be fatal. Increases in the blood levels of substances called enzymes found within your liver cells may occur.
• Inflammation of the intestines with symptoms such as stomach pain, loose or more frequent stools, blood in stools which may require you to receive additional fluids. If left untreated this may lead to a tear in the wall of the intestine
• Symptoms related to changes (increases or decreases) in the release of thyroid hormones from your thyroid gland including, but not limited to, increased heart rate, headaches, nausea, vomiting, fatigue, dizziness,

weakness, tiredness, mood changes, loss of appetite, weight changes and sexual dysfunction
• Problems with your adrenal glands (Adrenal Insufficiency): May cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality.
• Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to a decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland in the brain (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women.
• Inflammation of the kidneys with changes in urinary volume pain in the abdomen and abnormal blood tests
• Type 1 Diabetes mellitus which may cause increased blood glucose levels (called *hyperglycaemia*): Symptoms may include weight loss, increased urination, increased thirst, and increased hunger. Type 1 diabetes will require replacement of insulin through injection. Tell your study doctor right away if you have any of these symptoms.

Possible risks associated with MEDI4736 and tremelimumab
Very common side effects (>=10%) (affects more than 1 in 10 patients treated):
• Diarrhea
• Rash/dry itchy skin
• Liver problems: Increases in the blood level of substances called enzymes found within your liver cells may occur. The enzyme changes are unlikely to make you feel unwell. However if these blood enzyme levels become very high, your study doctor may need to stop the study medication. A patient may develop inflammation of the liver called hepatitis, however this is uncommon. Signs and symptoms of this include yellowing of the skin or whites of the eyes, dark urine, severe nausea and vomiting, pain in the upper right side of your abdomen, skin itchiness, not feeling hungry and bleeding or bruising more easily than normal.
• As well as the important possible risks described above patients with different types of cancer who have been treated with MEDI4736 alone and in combination with tremelimumab in clinical trials have very commonly (i. e. in more than 10% of patients) reported: feeling tired, abdominal pain, accumulation of fluid causing swelling, pneumonia, upper respiratory tract infections, nausea, vomiting, decreased appetite, shortness of breath, cough, fever and pain in muscles and joints.
Common side effects (>=1% to <10%) (affects between 1 in 100 and 1 in 10 patients treated):
• Inflammation in the lungs (pneumonitis): Symptoms may include but are not limited to a new or worsening cough, shortness of breath possibly with fever. Tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently.
• Low thyroid (Hypothyroidism): This is when the thyroid gland produces less thyroid hormone than it should which causes the metabolism to run too slow. Symptoms may include but are not limited to fatigue, increased sensitivity to

cold, constipation, dry skin, unexplained weight gain, puffy face, muscle weakness, slow heart rate, thinning hair, impaired memory. The condition can be treated with replacement thyroid hormone.
• High thyroid (Hyperthyroidism): This is when the thyroid gland produces too much thyroid hormone. Symptoms include anxiety or nervousness, weight loss, frequent and loose bowel movements, breathlessness, feeling hot and possibly having heart palpitations. Depending on the severity of the symptoms treatment may include just monitoring the symptoms, treating the symptoms themselves and/or giving medicine to block the thyroid hormone.
• Kidney problems: You may have an increase of creatinine levels in a blood test (creatinine is a protein marker that measures kidney function) but not have any symptoms or feel unwell. Less commonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly.
• Nervous system problems: Symptoms can include unusual weakness of legs, arms, or face, numbness or tingling in hands or feet. In rare situations there is the potential for the inflammation of the nervous system to be severe and cause damage to the nerve cells or breakdown in the communication between nerves and muscles: Tell your study doctor right away if you have problems swallowing, if you start to feel weak very quickly and you are having trouble breathing.
• Infusion Related Reactions: Reactions may occur during or after the infusion of study medication. The reaction may cause fever or chills and a change in blood pressure or difficulty in breathing which might be serious. Tell your study doctor right away if you experience any of these symptoms even if it has been several days after the infusion has been completed.
• Inflammation of the intestine (colitis). It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, in rare occasions, this may lead to a tear in the wall of the intestine which can be serious and life threatening. Tell your study doctor right away if you have any of these symptoms.
• As well as the important possible risks described above patients with different types of cancer who have been treated with MEDI4736 alone and in combination with tremelimumab in clinical trials have commonly (ie 1% to less than 10% of patients) reported: a hoarse voice, painful urination, night sweats, oral thrush and, pain in muscles and joints.

Common (>=1% to <10%) (affects between 1 in 100 and 1 in 10 patients treated)/ Uncommon (<1%) (affects between 1 in 1,000 and 1 in 100 patients treated)
• Problems with your adrenal glands (Adrenal Insufficiency): May cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality. This event can occur commonly in patients who receive a combination of MEDI4736 and tremelimumab but has been reported uncommonly in patients who received MEDI4736 on its own. These complications may be permanent and may require hormone replacement.
• Dental and oral soft tissue infections and influenza have been reported

commonly in patients who have received MEDI4736 alone and uncommonly in patients who have received a combination of MEDI4736 and tremelimumab.
Uncommon side effects (<1%) (affects between 1 in 1,000 and 1 in 100 patients treated)
• Inflammation of the pancreas (pancreatitis). Pancreatitis usually causes symptoms of persistent upper abdominal pain (sometimes made worse by eating and drinking), nausea, vomiting and general weakness. Pancreatitis usually settles with simple measures but it can be a serious condition and can be fatal. You should immediately tell your study doctor if you develop any unusual symptoms. You may get an increase of lipase and amylase levels in a blood test (related to the pancreas) but not have any symptoms or feel unwell. Lipase and amylase are enzymes or protein markers that measure the function of your pancreas. Uncommonly these increases may be associated with pancreatitis.
• Allergic reactions: These can cause swelling of the face, lips and throat, breathing difficulties along with hives or nettle like rash. You should immediately tell your study doctor if you develop any of these symptoms.

Uncommon (<1%) (affects between 1 in 1,000 and 1 in 100 patients treated) / Rare (0.1%) (affects between 1 in 10,000 and 1 in 1,000 patients treated)
• Inflammation of the muscles or associated tissues, such as blood vessels that supply the muscles (Myositis/polymyositis). Symptoms can include muscle weakness and aches, tired feeling when standing or walking, muscle pain and soreness that does not resolve after a few weeks. This side effect has been reported uncommonly in patients who have received MEDI4736 alone and rarely in patients who have received a combination of MEDI4736 and tremelimumab
• Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement. This side effect has been reported uncommonly in patients who have received a combination of MEDI4736 and tremelimumab and rarely in patients who have received MEDI4736 alone.

Rare side effects (<0.1%) (affects between 1 in 10,000 and 1 in 1,000 patients treated)
• Inflammation of the heart muscle (myocarditis). Symptoms can include chest pain, rapid or abnormal heart beat, shortness of breath and swelling of your legs. Tell your study doctor right away if you experience any of these symptoms.
• Type 1 Diabetes mellitus which may cause increased blood glucose levels (called *hyperglycaemia*): Symptoms may include weight loss, increased urination, increased thirst, and increased hunger. Type 1 diabetes will require replacement of insulin through injection. Tell your study doctor right away if you have any of these symptoms.

Please see ICF paragraph 4. Possible side effects/discomforts/risks and

appendix 2 for further information.

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

Subjects must meet all of the following criteria:
1. Male and female subjects; age >= 18 years at the time of study entry.
2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.
3. Subjects must have histologic documentation of UBC, SCLC, STS, TNBC, HPV-positive anogenital cancer (anal, cervical, and vaginal), MSI-H CRC, or high-grade epithelial ovarian cancer (including fallopian tubal carcinoma and peritoneal carcinoma).

4. Under Protocol Amendment 3 and beyond, subjects with UBC must meet the following criteria in addition to those for the overall study population:
a. Subjects must have histologically or cytologically confirmed inoperable or metastatic transitional cell (including transitional cell and mixed transitional cell/non-transitional cell histologies) carcinoma of the urothelium (including the urinary bladder, ureter, urethra, and renal pelvis).
b. Subjects must have received and have progressed or are refractory to at least 1 but not more than 2 prior lines of systemic therapy for inoperable or metastatic disease, including a standard platinum-based regimen. Interval progression between 2 lines of therapy defines separate lines of therapy. Prior definitive chemoradiation for locally advanced disease, adjuvant treatment, or neoadjuvant treatment will be considered a prior line of therapy, provided that progression has occurred < 12 months from therapy [for chemoradiation and adjuvant treatment] or < 12 months from surgery [for neoadjuvant treatment].
c. Subjects must have documented radiographic disease progression as assessed by the investigator at the time of study entry.
d. Subjects with UBC must consent to provide an archived tumor specimen from within 6 months prior to study entry (ie, from subject signing consent to participate in the study) for PD-L1 IHC analysis. If not available, subjects must have at least 1 lesion amenable to biopsy and consent to provide a pre-treatment fresh biopsy. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions. Tumor tissue for PD-L1 analysis must be shipped to, and confirmed as received by the Sponsor or designated central vendor prior to the first dose of investigational product. However, subjects may be dosed before PD-L1 results are known. It is highly recommended that efforts are taken to confirm the presence of tumor cells within the tumor sample prior to shipping for PD-L1 analysis. Additional archival tumor tissue, regardless of age, is also required, if available, to support exploratory analyses. On treatment and end of treatment biopsies are optional for UBC subjects. PD-L1 status determined by IHC testing from tumor samples evaluated for screening into Study CD ON MEDI4736 1108 may be used if derived from a sample taken <= 6 months prior to study entry.
e. After enrollment of approximately 77 UBC subjects (and a minimum of 30 PD-L1 negative UBC subjects) under Protocol Amendment 3 and beyond, further enrollment may be restricted to PD-L1 negative subjects only as described in Section 3.1.1. If enrollment is restricted to PD-L1 negative subjects only, subjects must have known PD-L1 status prior to treatment with MEDI4736 and tremelimumab.
f. Subjects in the UBC cohort must have measurable disease per RECIST v1.1 that is confirmed by BICR prior to enrollment.
5. Subjects in all other cohorts must have received and have progressed, are refractory or are intolerant to at least 1 line of standard systemic therapy in the recurrent or metastatic disease setting, appropriate for the specific tumor type. Subjects who are therapy-naive in the recurrent or metastatic disease setting may be permitted to enroll on a case-by-case basis with prior discussion and agreement between the investigator and the sponsor; these subjects must have been offered and declined standard therapy or be ineligible to receive standard therapy.
6. Subjects must meet the following criteria regarding prior lines of systemic therapy for recurrent or metastatic disease (including both standard of care and investigational therapies). Interval progression between 2 lines of therapy defines separate lines of therapy:
a. Subjects with high-grade epithelial ovarian cancer (including fallopian tubal carcinoma and

peritoneal carcinoma) should not have received more than 3 prior lines of therapy for recurrent or metastatic disease.
b. Subjects with TNBC should not have received more than 5 prior lines of therapy for recurrent or metastatic disease.
c. Subjects with MSI-H CRC should not have received more than 4 prior lines of therapy for recurrent or metastatic disease.
d. For all other tumor types, subjects should not have received more than 3 prior lines of therapy for recurrent or metastatic disease.
7. For subjects with the following malignancies, the following criteria also apply:
a. Small-cell lung cancer
i. Extensive stage disease
ii. Histological diagnosis of SCLC by World Health Organization classification (Travis, 2004). Combined SCLC is excluded.
b. Soft-tissue sarcoma
i. Histologic diagnosis of STS by World Health Organization classification (Fletcher et al, 2013). The following tumor types are excluded: embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, GIST, dermatofibrosarcoma protuberans, Ewing sarcoma/primitive neuroectodermal tumors, inflammatory myofibroblastic tumor, and malignant mesothelioma
c. Triple-negative breast cancer, according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (Hammond et al, June 2010; Hammond et al, July 2010; Wolff et al, 2013)
i. No additional criteria
d. HPV-positive anogenital cancers
i. Histologic diagnosis of cervical cancer (squamous cell carcinoma or adenocarcinoma), vaginal cancer (squamous cell carcinoma or adenocarcinoma), or squamous cell carcinoma of the anus
ii. Documentation of HPV-positive tumor by local laboratory
e. MSI-H CRC
i. MSI-H CRC cancers must have defective DNA mismatch repair defined by one of the following criteria:
ii. High-frequency microsatellite instability with changes detected in 2 or more panels of microsatellite markers (BAT-25, BAT-26, NR-21, NR-24 and MONO 27)
iii. Immunohistochemical analysis demonstrating absence of protein expression of any 1 or more of the following proteins: MLH1, MSH2, MSH6, PMS2.
iv. Subjects must have progressed after receipt of a systemic regimen containing a fluoropyrimidine or irinotecan.
f. High-grade epithelial ovarian cancer (including fallopian tubal carcinoma and peritoneal carcinoma)
i. Up to approximately 10 subjects with a documented germline BRCA1 or BRCA2 mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) will be enrolled.
ii. No evidence of partial small bowel obstruction or small bowel obstruction within 4 weeks prior to the first scheduled dose.
iii. Should be able to maintain weight and hydration with oral intake only, without requirement for IV or supplemental enteral nutrition or hydration (ie, no G-tubes, J-tubes, total parenteral nutrition, or hydration requirements).

iv. Subjects with ascites that require active ongoing paracentesis (within 4 weeks prior to the first scheduled dose) to control their disease are excluded.
8. Prior IMT requirements are as follows:
a. Immunotherapy-naive subjects (including UBC subjects under Protocol Amendment 3) must have no prior exposure to IMT, including, but not limited to, other anti-CTLA-4, anti-PD-1, or anti PD L1 mAbs, tumor necrosis factor receptor superfamily agonists, checkpoint inhibitors or NK cell inhibitors including agents targeting KIR, PD-1, PD-L1, CTLA 4, OX40, CD27, CD137 (4 1BB), CD357 (GITR), and CD40. Prior treatment with Bacillus Calmette-Guerin therapy is permitted for UBC cohort.
b. Immunotherapy pretreated subjects must have had prior exposure to single-agent IMT (including, but not limited to anti-CTLA-4, anti-PD-1, or anti PD L1 mAbs), and meet all of the criteria below.
i. Last dose of IMT must have been administered at least 60 days prior to the planned first dose of investigational products.
ii. Must not have experienced a treatment-related toxicity that led to permanent discontinuation of prior IMT.
iii. All treatment-related AEs while receiving prior IMT must have resolved to <= Grade 1 or baseline prior to screening for this study. Must not have experienced a >= Grade 3 treatment-related AE or neurologic or ocular AE of any grade while receiving prior IMT. NOTE: Subjects with endocrine AE of any grade are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.
iv. Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.
9. Subjects must have at least 1 lesion amenable to biopsy and provide a pretreatment fresh biopsy prior to enrollment. If clinically feasible, the subject will also be required to provide an on-treatment tumor biopsy. If clinically feasible and the subject agrees, an End of Treatment (if subject has disease progression) tumor biopsy will also be requested. Tumor lesions used for biopsy should not be lesions used as target lesions. Sites are encouraged to confirm adequacy of tumor biopsy material at the time of the procedure. See Inclusion Criterion 4 for tumor tissue requirements for UBC subjects.
10. Subjects must have at least 1 lesion that is measurable by RECIST v1.1 (Eisenhauer et al, 2009).
a. A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable per RECIST, and has clearly progressed.
11. Subjects who have the following tumor types must have imaging to evaluate for brain metastases: SCLC, TNBC, UBC, and MSI-H CRC. Subjects who have the following tumor types must have imaging to evaluate for brain metastases only if the subject has neurologic symptoms or is suspected to have brain metastases: STS, HPV-positive anogenital cancers, and high-grade epithelial ovarian cancer (including fallopian tubal carcinoma and peritoneal carcinoma).
12. Subjects must consent to provide archived tumor specimens for correlative biomarker studies, if available, regardless of whether a fresh biopsy was provided during the screening period. See Inclusion Criterion 4 for tumor tissue requirements for UBC subjects.
13. ECOG performance status of 0 or 1.
14. Adequate organ function as determined by:

a. Hematological (without growth factor or transfusion support within 28 days prior to first dose of investigational product):
i. Absolute neutrophil count >= 1.5 × 109/L (1,500/mm3)
ii. Platelet count >= 100 × 109/L (100,000/mm3)
iii. Hemoglobin >= 9.0 g/dL
b. Renal:
i. Calculated CrCl or 24 hour urine CrCl >= 50 mL/min (or >= 30 mL/min for subjects with UBC) determined by the Cockcroft-Gault formula (using actual body weight) will be used to calculate CrCl
c. Hepatic:
i. Total bilirubin <= 1.5 × ULN; for subjects with documented/suspected Gilbert's disease, bilirubin <= 3 × ULN
ii. AST and ALT <= 2.5 × ULN; for subjects hepatic metastases, ALT and AST <= 5 × ULN
15. Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 4) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of investigational product. Male partners of a female subject must use male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female subjects should refrain from breastfeeding throughout this period.
a. Non-sterilized males who are sexually active with a female partner of childbearing potential must use a use male condom plus spermicide from screening through 180 days after the last dose of investigational product. Male subjects should refrain from sperm donation throughout this period. Female partners of a male subject must use a highly effective method of contraception (see Table 4) throughout this period.
b. Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
c. Highly effective methods of contraception are described in Table 4. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Exclusion criteria

Any of the following would exclude the subject from participation in the study:
1. Prior participation in clinical studies that include MEDI4736 alone or in combination with other agents, where the study has registrational intent and the analyses for the primary

endpoint have not yet been completed.
2. History of severe allergic reactions (ie, Grade 4 allergy, anaphylactic reaction from which the subject did not recover within 6 hours of institution of supportive care) to any unknown allergens or any components of the study drug formulations.
3. Active or prior documented autoimmune disease (including inflammatory bowel disease, celiac disease, Wegener syndrome) within the past 2 years. Subjects with childhood atopy or asthma, vitiligo, alopecia, Hashimoto syndrome, Grave*s disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
4. Untreated central nervous system metastatic disease, leptomeningeal disease, or cord compression. Subjects with previously treated central nervous system metastases that are radiographically and neurologically stable for at least 6 weeks and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to first dose of MEDI4736 and tremelimumab are permitted to enroll.
5. Concurrent enrollment in another clinical study, unless it is an observational (non interventional) clinical study or the follow-up period of an interventional study.
6. Receipt of any conventional or investigational anticancer therapy not otherwise specified above within 28 days prior to the first dose of MEDI4736 and tremelimumab.
7. Any concurrent chemotherapy, IMT, or biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. In addition, local treatment (eg, by local surgery or radiotherapy) of isolated lesions for palliative intent is acceptable beyond the DLT evaluation period with prior consultation and in agreement with the medical monitor.
8. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 Grade 0 or 1 with the exception of alopecia and laboratory values listed per the inclusion criteria. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by any of the investigational products may be included (eg, hearing loss) after consultation with the medical monitor.
9. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of MEDI4736 or tremelimumab. The following are exceptions to this criterion:
a. Intranasal, inhaled, topical steroids or local steroid injections (eg, intra-articular injection).
b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.
c. Steroids as premedication for hypersensitivity reactions (eg, computedtomography [CT] scan premedication).
10. History of primary immunodeficiency, solid organ transplantation, or previous clinical diagnosis of tuberculosis.
11. Known positive for human immunodeficiency virus (HIV), chronic or active hepatitis B or C or active hepatitis A.
12. Receipt of live, attenuated vaccine within 28 days prior to the first dose of investigational products (NOTE: Subjects, if enrolled, should not receive live vaccine during the study and 180 days after the last dose of investigational products).
13. Pregnant or breastfeeding women.
14. Major surgery (as defined by the investigator) within 4 weeks prior to first dose of MEDI4736 or tremelimumab or still recovering from prior surgery. Local surgery of isolated lesions for palliative intent is acceptable.
15. Other invasive malignancy within 2 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin or ductal carcinoma in

situ of the breast that has/have been surgically cured. Cancer subjects with incidental histologic findings of prostate cancer (tumor/node/metastasis stage of T1a or T1b or prostate-specific antigen < 10) who have not received hormonal treatment may be included, pending a discussion with the study physician.
16. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from MEDI4736 or tremelimumab, or compromise the ability of the subject to give written informed consent.
17. Any condition that, in the opinion of the investigator or sponsor, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-12-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MEDI4736
Generic name:	MEDI4736
Product type:	Medicine
Brand name:	Tremelimumab
Generic name:	Tremelimumab

Ethics review

Approved WMO Date:	09-05-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-07-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-09-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	19-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	12-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	13-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	11-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	25-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	08-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Not approved

Date:	30-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	04-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-03-2019
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	EUCTR2015-005518-31-NL
ClinicalTrials.gov	NCT02261220
CCMO	NL57363.031.16