A PHASE 1, OPEN-LABEL, DOSE ESCALATION STUDY OF PF-04518600 AS A SINGLE AGENT AND IN COMBINATION WITH PF-05082566 IN PATIENTS WITH SELECTED LOCALLY ADVANCED OR METASTATIC CANCERS

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Objectives for Part A1 Monotherapy Dose EscalationPrimary Objective:* To assess safety, and tolerability at increasing dose levels of PF 04518600 in patients with selected advanced or metastatic solid tumors in order to establish the MTD.Secondary…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON47576

Source
ToetsingOnline

Brief title
Phase 1 study of PF-04518600 and in combination with Utomilumab

Condition

- Other condition

Synonym
SELECTED LOCALLY ADVANCED OR METASTATIC CANCERS

Health condition

GESELECTEERDE LOKAAL GEVORDERDE OF GEMETASTASEERDE CARCINOMEN

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pfizer Inc.

Intervention

Keyword: cancer, PF-04518600, phase 1, Utomilumab

Outcome measures

Primary outcome

Endpoints for Part A1 Monotherapy Dose Escalation

Primary Endpoints:

* Dose limiting toxicities (DLTs) observed in each patient during the first 98

days in order to determine the MTD.

* Adverse Events (AEs) as characterized by type, frequency, severity (as graded

by National Cancer Institute Common Terminology Criteria for Adverse Events

(NCI CTCAE) v 4.03, timing, seriousness and relationship to study therapy PF

04518600.

* Laboratory abnormalities as characterized by type, frequency, severity (as

graded by NCI CTCAE v. 4.03) and timing.

Endpoints for Part A2 Monotherapy Dose Expansion

Primary Endpoints:

* AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v

4.03), timing, seriousness and relationship to study therapy PF 04518600.

* Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Endpoints for Part B1 Combination Therapy Dose Escalation

Primary Endpoints:

* DLTs observed in each patient during the first 98 days in order to determine the MTD.

* AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to PF 04518600/ PF-05082566 combination.

* Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Endpoints for Part B2 Combination Therapy Dose Expansion

Primary Endpoints:

* AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03), timing, seriousness and relationship to PF 04518600/ PF-05082566 combination.

* Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.

Secondary outcome

Endpoints for Part A1 Monotherapy Dose Escalation

Secondary Endpoints:

* Objective tumor response, as assessed using the RECIST version 1.1 and

irRECIST.

* Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1

and irRECIST and OS

* Overall survival rates at 6 months, 1 year and 2 years.

* Pharmacokinetic parameters of PF 04518600:

SDo-Cmax, AUCsdo, AUCinf, t1/2, as data permit. MD (assuming steady state is

achieved) - Css,max, AUCss, t1/2, Css,min, Css,av, CL, and Vss, and Rac

(AUCss,/AUCsdo,) as data permit.

* Incidence of anti-drug antibody (ADA) and NAb against PF 04518600.

* Levels of free OX40 receptor expressed on T cells in peripheral blood.

Endpoints for Part A2 Monotherapy Dose Expansion

Secondary Endpoints:

* Objective tumor response, as assessed using the RECIST version 1.1 and

irRECIST.

* Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1

and irRECIST and OS.

* Overall survival rates at 6 months, 1 year and 2 years.

* Pharmacokinetic parameters of PF 04518600:

SDo-Cmax, AUCsdo,, AUCinf, t1/2, as data permit. MD (assuming steady state is

achieved)-Css,max, AUCss,, t1/2, Css,min, Css,av, CL, and Vss, and Rac

(AUCss,/AUCsdo,) as data permit.

* Incidence of ADA and NAb against PF 04518600.

Endpoints for Part B1 Combination Therapy Dose Escalation

Secondary Endpoints:

* Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.

* Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.

* Overall survival rates at 6 months, 1 year and 2 years.

* Pharmacokinetic parameters of PF 04518600 and utomilumab: SDo-Cmax, AUCsdo,, AUCinf, t1/2, as data permit. MD (assuming steady state is achieved)-Css,max, AUCss,, t1/2, Css,min, Css,av, CL, and Vss, and Rac (AUCss, /AUCsdo,) as data permit.

* Incidence of ADA and NAb against PF 04518600 and utomilumab.

Endpoints for Part B2 Combination Therapy Dose Expansion

Secondary Endpoints:

* Objective tumor response, as assessed using the RECIST version 1.1 and irRECIST.

* Anti-tumor activity assessments of: PFS, TTP, SD, DR by RECIST version 1.1 and irRECIST and OS.

* Overall survival rates at 6 months, 1 year and 2 years.

* Pharmacokinetic parameters of PF 04518600 and utomilumab: SDo-Cmax, AUCsdo,, AUCinf, t1/2, as data permit. MD (assuming steady state is achieved)-Css,max, AUCss,, t1/2, Css,min, Css,av, CL, and Vss, and Rac (AUCss, /AUCsdo,) as data permit.

* Incidence of ADA and NAb against PF 04518600 and utomilumab.

Study description

Background summary

Immunotherapy offers the opportunity to not only stop tumor growth, but also decrease the rate of tumor recurrence. By activating and expanding tumor associated antigen T cells, it may be possible to enhance tumor immunity. However, T cell activation is not mediated by antigen stimulation alone. Instead, co stimulatory receptors are required. OX40 (CD134) and 4-1BB (CD137) are co stimulatory receptors that act on antigen stimulated T cells but not native T cells. OX40 plays a key role in T cell survival, proliferation, and activation. Upon OX40 ligand (also known as OX40L, CD252 or TNFSF4 [tumor necrosis factor (ligand) superfamily, member 4]) binding, OX40 signaling upregulates anti apoptotic molecules including B cell lymphoma 2 (Bcl 2), Bcl xL, and survivin, and increases interleukin 2 (IL 2), IL 4, IL 5, and interferon gamma (IFN *) cytokine secretion. Similarly, activation of 4-1BB signaling leads to an upregulation of pro-survival factors Bfl-1 and Bcl-xL, down-regulation of pro-apoptotic protein Bim, increased T cell proliferation and differentiation into T memory cells.
PF 04518600 is a fully human Immunoglobulin G2 (IgG2) agonistic monoclonal antibody (mAb) specific for human OX40 (CD134). By binding to OX40 on activated tumor infiltrating T cells, PF 04518600 may reverse T cells* anergic state, and enhance tumor immunity.
Utomilumab (PF-05082566) is a fully human IgG2 agonist monoclonal antibody specific for human 4-1BB. The safety and tolerability of utomilumab is currently being evaluated in a First-in-Patient Phase 1 study as a single agent and in combination with rituximab (Study B1641001, IND 109,154). utomilumab has been well tolerated (thus far up to 10 mg/kg) when administered as a single agent every 4 weeks (Q4W). The safety profile of utomilumab either as single agent or in combination with rituximab was manageable without occurrence of treatment related life threatening (>Grade 4) adverse events (AEs).
In this clinical study, PF 04518600 as a monotherapy (Part A), and PF-04518600 in combination with utomilumab (Part B) will be evaluated for the treatment of adult patients with select locally advanced or metastatic cancers who are unresponsive to current available therapies, or for whom no standard therapy is available.

Study objective

Objectives for Part A1 Monotherapy Dose Escalation
Primary Objective:
* To assess safety, and tolerability at increasing dose levels of PF 04518600

in patients with selected advanced or metastatic solid tumors in order to establish the MTD.
Secondary Objectives:
* To assess preliminary anti tumor clinical activity induced by PF 04518600 in patients with selected advanced or metastatic solid tumors solid tumors.
* To characterize the single dose and multiple dose pharmacokinetics (PK) of PF 04518600 following intravenous (IV) administration.
* To evaluate the immunogenicity of PF-04518600 following IV administration.
* To characterize the degree of target engagement (TE) by PF-04518600 at multiple doses by measuring unbound (free) cell surface OX40 in peripheral blood.

Exploratory Objectives
* To assess the pharmacodynamic activity (immune modulatory effects) of PF-04518600 in tumor tissue by measuring the number, distribution and phenotype of tumor infiltrating lymphocytes (TILs).
* To explore the effect of PF-04518600 on the ribonucleic acid (RNA) expression profile in tumor biopsy tissue.
* To explore the effect of PF 04518600 on the abundance of T cell clones and diversity of the T cell repertoire in tumor biopsy tissue and peripheral blood.
* To explore the effect of PF-04518600 on the prevalence and diversity of tumor antigenic epitopes in tumor biopsy tissue.
* To evaluate the effect of PF-04518600 on levels of cytokines, chemokines and soluble OX40.

Objectives for Part A2 Monotherapy Dose Expansion
Primary Objectives:
* To establish the recommended phase 2 dose (RP2D) of PF 04518600 in patients with selected advanced or metastatic HCC.
* To further characterize the safety and tolerability of PF 04518600 in patients with selected advanced or metastatic HCC.
Secondary Objectives:
* To assess preliminary anti tumor clinical activity of PF 04518600 in patients with selected advanced or metastatic HCC.
* To characterize the single dose and multiple dose PK of PF 04518600 following IV administration.
* To evaluate the immunogenicity of PF-04518600 following IV administration

Exploratory Objectives
* To assess the pharmacodynamic activity (immune modulatory effects) of PF-04518600 in tumor tissue by measuring the number, distribution and phenotype of TILs.
* To explore the effect of PF-04518600 on the RNA expression profile in tumor biopsy tissue.
* To explore the effect of PF 04518600 on the abundance of T cell clones and diversity of the T cell repertoire in tumor biopsy tissue and peripheral blood.
* To explore the effect of PF-04518600 on the prevalence and diversity of tumor

antigenic epitopes in tumor biopsy tissue.
* To evaluate the effect of PF-04518600 on levels of cytokines, chemokines and soluble OX40.
* To characterize the degree of TE by PF-04518600 at multiple doses by measuring unbound (free) cell surface OX40 in peripheral blood.

Objectives for Part B1 Combination Therapy Dose Escalation
Primary Objective:
* To assess safety and tolerability at increasing dose levels of PF-04518600 in combination with utomilumab in patients with selected advanced or metastatic solid tumors and to estimate MTD of the combination.

Secondary Objectives
* To assess preliminary anti-tumor clinical activity of PF-04518600 in combination with utomilumab.
* To characterize single and multiple dose pharmacokinetics of PF-04518600 and utomilumab when given in combination.
* To evaluate immunogenicity of PF-04518600 and utomilumab when given in combination.

Exploratory Objectives:
* To assess the pharmacodynamic activity (immune modulatory effects) of PF 04518600 in combination with utomilumab (PF-04518600 / utomilumab) in peripheral blood as measured by expression of activation markers such as Ki67 and human leukocyte antigen-D related (HLA-DR) in T cells.
* To assess the pharmacodynamic activity of PF-04518600 / utomilumab in tumor tissue by measuring the number, distribution and phenotype of TILs.
* To explore the effect of PF-04518600 / utomilumabon the RNA expression profile in tumor biopsy tissue.
* To explore the effect of PF 04518600 / utomilumab on the abundance of T cell clones and diversity of the T cell repertoire in tumor biopsy tissue and peripheral blood.
* To explore the effect of PF-04518600 / utomilumab on the prevalence and diversity of tumor antigenic epitopes in tumor biopsy tissue.
* To evaluate the effect of PF-04518600 / utomilumab on levels of serum cytokines, chemokines, soluble OX40 and soluble 4-1BB.
* To characterize the degree of TE by PF-04518600 when dosed in combination with PF 05082566 by measuring unbound (free) cell surface OX40 in peripheral blood.
* To explore the potential for drug-drug interactions between PF-04518600 and utomilumab.

Objectives for Part B2 Combination Therapy Dose Expansion
Primary Objective:
* To further assess safety and tolerability of PF-04518600 in combination with utomilumab in patients with melanoma or NSCLC in order to establish RP2D for the combination.

Secondary Objectives:
* To assess preliminary anti-tumor clinical activity of PF-04518600 in combination with utomilumab.
* To characterize single and multiple dose pharmacokinetics of PF-04518600 and utomilumab when given in combination.
* To evaluate immunogenicity of PF-04518600 and utomilumab when given in combination.

Exploratory Objectives:
* To assess the pharmacodynamic activity (immune modulatory effects) of PF 04518600 in combination with utomilumab (PF-04518600 / utomilumab) in peripheral blood as measured by expression of activation markers such as Ki67 and HLA-DR in T cells.
* To assess the pharmacodynamic activity of PF-04518600 / utomilumab in tumor tissue by measuring the number, distribution and phenotype of TILs.
* To explore the effect of PF-04518600 / utomilumab on the RNA expression profile in tumor biopsy tissue.
* To explore the effect of PF 04518600 / utomilumab on the abundance of T cell clones and diversity of the T cell repertoire in tumor biopsy tissue and peripheral blood.
* To explore the effect of PF-04518600 / utomilumab on the prevalence and diversity of tumor antigenic epitopes in tumor biopsy tissue.
* To evaluate the effect of PF-04518600 / PF-05082566 on levels of serum cytokines, chemokines, soluble OX40 and soluble 4-1BB.
* To characterize the degree of TE by PF-04518600 when dosed in combination with PF-05082566 by measuring unbound (free) cell surface OX40 and 4-1BB in peripheral blood.
* To explore the potential for drug-drug interactions between PF-04518600 and utomilumab.

Study design

This is a Phase 1, open label, multi center, multiple dose, dose escalation, safety, pharmacokinetic, and pharmacodynamic study of PF 04518600 monotherapy in Part A, and PF-04518600 in combination with utomilumab in Part B. Each part includes a dose escalation phase, and a dose expansion phase. A maximum of approximately 210 patients are expected to be enrolled into the study.
All patients will complete up to 4 weeks of screening. Following the initial dose(s), treatment with investigational product will continue until either disease progression, by immune-related response evaluation criteria in solid tumors (irRECIST), by patient refusal or unacceptable toxicity occurs, or end of study. Patients will be allowed to stay on study, if the treating physician feels that it is in the patient*s best interest in the case of radiological progression, and the absence of clear clinical progression. A follow up visit approximately 4 weeks after the last dose for adverse event (AE) and serious AE (SAE) collection will be conducted. Late immune related responses will be evaluated up to 98 days after the first dose(s) of cycle 1. Because atypical

tumor responses after growth of pre-existing lesions or appearance of new lesions have been observed with immune checkpoint inhibitors, study B0601002 will assess tumor response based on both response evaluation criteria in solid tumor (RECIST) and Immune-related Response Criteria Derived From RECIST v1.1 (irRECIST). Survival data will also be collected. The time on study can vary depending on the observed toxicity and potential benefit an individual subject derives. It*s estimated that patients will remain on treatment for approximately 12-18 weeks, making total study duration approximately 20 26 weeks (exclusive of 2 year survival follow-up). Actual duration can be longer, if a patient derives benefit from study treatment.

Part A Monotherapy

Part A1 Monotherapy Dose Escalation

Part A1 monotherapy dose escalation phase will enroll approximately 58 adult patients with locally advanced or metastatic cancers hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC) or head and neck squamous cell carcinoma (HNSCC). The actual number of patients enrolled will depend on the observed safety and tolerability profile of PF 04518600, the number of dose levels that will be tested and expanded to characterize the pharmacodynamic or immunomodulatory (IM) effects, and the number of dose levels required to identify the maximum tolerated dose (MTD) or optimal biological dose (OBD). Six dose levels are proposed: 0.01, 0.1, 0.3, 1.5, 3.0 and 10.0 mg/kg. Each cohort will include an initial cohort of 2-4 patients that may be expanded to approximately 10 patients. Approximately 3 patients enrolled in Japan will be included for at least 2 dose levels.

A staggered start will be employed at all dose levels. A single patient will be dosed and observed for 48 hours. If no safety concerns arise during this 48 hr period, a second patient will be enrolled into the same dose level cohort. A modified toxicity probability interval (mTPI) method, targeting a dose limiting toxicities (DLT) rate of 25% and an acceptable DLT interval (20%-30%) 7, will be utilized for dose escalation. If peripheral blood samples indicate preliminary signs of immune modulation in the first 2-4 patients, the dose level will be expanded for pharmacodynamic evaluation; these additional patients will undergo mandatory pre treatment and on treatment biopsies. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted. Depending on observed safety data and pharmacodynamic data, additional cohorts (lower, intermediate or higher dose levels, up to maximum of 20 mg/kg) may also be tested.

Part A2 Monotherapy Dose Expansion

Part A2 monotherapy dose expansion phase will randomize HCC patients 1:1 to flat dose levels of either 30 mg (Arm 1) or 250 mg (Arm 2) of PF-04518600 given every 2 weeks. Both doses were chosen based on data from Part A1. Each arm in Part A2 will include approximately 20 HCC patients.

Based on emerging data from the 10 mg/kg cohort of Part A1, an additional flat dose level of 800 mg PF-04518600 (approximately equivalent to 10 mg/kg), may be

added after initiation of enrollment into Arms 1 and 2.
Patients will undergo mandatory pre-treatment and on treatment biopsies as specified in the Schedule of Activities. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted (see Section 1.4 Rationale for Pretreatment and On-treatment Biopsies)

Part B Combination Therapy
Part B1 Combination Therapy Dose Escalation
Part B1, the combination therapy dose escalation phase, will enroll approximately 53 patients. At least 6 patients must have been evaluated for the 28 day DLT observation period at the 0.3 mg/kg dose level in Part A1 PF-04518600 (OX40 agonist) monotherapy before Part B1 can be initiated. Part B1 will study sequential dose levels of PF 04518600 (0.1, 0.3, 1.0 and 3 mg/kg with an option of 10 mg/kg pending data from Part A1) combined with either 20 mg or 100 mg of tomilumab (4-1BB agonist) in adult patients with non-small cell lung cancer (NSCLC), HNSCC, melanoma, bladder, gastric or cervical cancer who are unresponsive to currently available therapies or for whom no standard therapy is available. The starting dose level will be 0.1 mg/kg of PF-04518600 and 20 mg of utomilumab, given no sooner than 30 minutes apart. Based on emerging data in the 10 mg/kg Part A1 cohort, an optional cohort of 10 mg/kg PF-04518600 in combination with 100 mg of utomilumab may be evaluated.
A modified toxicity probability interval (mTPI) method, targeting a dose limiting toxicities (DLT) rate of 25% and an acceptable DLT interval (20%-30%) 7, will be utilized for dose escalation. If peripheral blood samples indicate preliminary signs of immune modulation in the first 2-4 patients, the dose level will be expanded for pharmacodynamic evaluation; these additional patients will undergo mandatory pre-treatment and on treatment biopsies. In case of intolerable toxicity at the starting dose level, the dose combination will be reduced to 0.1 mg/kg of PF-04518600 and 10 mg of utomilumab.
Subsequent to the starting dose level, if dose de-escalation is recommended after evaluation, intermediate dose levels between the previous dose combination and current dose combination may be studied. Intrapatient dose reductions are not permitted during the combination therapy with PF-04518600 and PF-05082566 unless, in discussion with the sponsor, a dose combination level is deemed beyond the determined MTD for the combination.. Each dose combination level will include an initial cohort of 2 4 patients that may be expanded up to approximately 10 patients based on peripheral pharmacodynamic assessments. To allow for better characterization of pharmacodynamic effects, these additional patients will undergo mandatory pre treatment and on treatment biopsies. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted. The safety of the first patient at each dose combination level will be observed for 48 hours prior to enrolling subsequent patients.

Part B2 Combination Therapy Dose Expansion
Part B2 combination therapy dose expansion phase will further evaluate safety and anti-tumor activity of PF-04518600/ utomilumab combination with a dosing regimen selected based on results of Part B1 with flat dose equivalents of PF-04518600. Part B2 will be divided into 2 arms: Arm 1 will enroll HNSCC patients who have either: a) never been treated with anti- PD-L1 or PD-1 mAb or b) those who 1) previously received prior anti-PD-L1 or anti-PD-1 mAb as most recent therapy, and 2) did not have progressive disease as best overall response on recent PD-L1/PD-1 therapy (ie stable disease * 3 months, PR, or CR), and 3) who subsequently progressed, or are intolerant to PD-L1/PD-1 therapy

Arm 2 will enroll NSCLC patients who have a) previously received prior anti-PD-L1 or anti-PD-1 mAb as most recent therapy, and 2) did not have progressive disease as best overall response on recent PD-L1/ PD-1 therapy (ie stable disease * 3 months, PR, or CR), and 3) who subsequently progressed, or b) are intolerant to this therapy.

Part B2 will enroll up to 20 patients in each arm, and all patients will undergo mandatory pre- and on-treatment tumor biopsies. If the Investigator judges the risk of certain on-treatment biopsies unacceptable for the patient (eg, based on site of tumor, potential for complications during/after procedure, etc.) the medical monitor must be consulted.

Intervention

Part A Monotherapy:
The dose of PF-04518600 will be administered intravenously (through a vein) over a 60 minute period once every 2 weeks. If the drug is safely tolerated (no unsafe or unacceptable effects on your body), the dose can be increased in group A2.
The patient will have to provide blood samples (during all study visits except day 2 of cyclus 1):
- to check for some viruses (HIV, hepatitis B and C)
- to evaluate the presence of chemicals produced by your immune cells
- for safety tests
- to measure the amount of PF-04518600 in your blood
- to measure antibodies against PF-04518600
- to measure how your body is responding to PF-04518600
- to see how your immune system is responding to PF-04518600
- to evaluate the heart enzymes troponinI and prohormone brain natriuretic peptide (NTproBNP) for patients who have a history of adriamycin (doxorubicin) treatment.
- for banked biospecimens
Also radiology scans and tumor biopsies will be taken to evaluate the tumour (during screening, end of treatment visit and follow-up visit).

Part B Combinationtherapy:

De dose utomilumab will be administered every 4 week intravenously over a 60 minutes period. PF-04518600 will be administered no sooner than 30 minutes after completion of the utomilumab infusion. If the combinationtherapy is safely tolerated (no unsafe or unacceptable effects on your body), the dose can be increased in group B2. The dose PF-04518600 will range from 0.01 mg/kg to 20 mg/kg and the dose utomilumab will have a range of 10 to 100 mg.
The patient will have to provide blood samples (during all study visits except day 2 of cyclus 1):
- to check for some viruses (HIV, hepatitis B and C)
- to evaluate the presence of chemicals produced by your immune cells
- for safety tests
- to measure the amount of PF-04518600 in your blood
- to measure antibodies against PF-04518600
- to measure how your body is responding to PF-04518600
- to see how your immune system is responding to PF-04518600
- to evaluate the heart enzymes troponinI and prohormone brain natriuretic peptide (NTproBNP) for patients who have a history of adriamycin (doxorubicin) treatment.
- for banked biospecimens
Also radiology scans and tumor biopsies will be taken to evaluate the tumour (during screening, end of treatment visit and follow-up visit).

Study burden and risks

There is no direct benefit for the patient but the study may provide useful data for the future.
Disadvantages which should be taken into account with participation are:
* the extra time it takes you
* an additional hospitalization or prolonged hospitalization
* additional blood tests and other additional studies, which would not otherwise be done
* keeping appointments
* possible side effects as described below:

This is the first study of PF-04518600 in patients, so there is only very limited clinical experience to refer to.
As of the most recent safety update, a total of 58 patients have been treated with PF-04518600, of these, 48 advanced cancer patients have been treated with PF-04518600 alone Among the 48 advanced cancer patients treated with PF-04518600 alone, the following adverse event was reported in at least 10% of patients and considered related to PF-04518600 by the study doctor: * Fatigue (tiredness) (27.1%)

In addition, the following adverse events were related to PF-04518600 by the study doctor and reported in at least 1 patient but no more than 10% of patients:
Abdominal pain, Eosinophil count increased (cells that protect the body against

infection and germs), Nausea, Abdominal pain upper Endocrine disorders, flushes (hot flashes), Neutrophil count decreased (cells that protect the body against infection and germs, Activated partial thromboplastin time (time it takes your blood to clot may be affected), Feeling cold, Edema (abnormal amount of fluid under the skin and in the body), Amylase increased (may be a sign of a problem), Headache, Edema peripheral (abnormal amount of fluid under the skin and in the lower parts of the body), Arthralgia (joint pain), Hyperuricemia (high level of uric acid in the blood), Pain, Basophil count increased (cells that protect the body against infection and germs), Hypophosphatemia (abnormally low levels of phosphate in the blood), Pruritus (itchy skin), Blood alkaline phosphatase increased (may be a sign of a problem with your bones), Increased alanine aminotransferase (indicating adverse effect on liver), Proteinuria (extra protein in the urine that could be a sign of kidney damage), Blood bilirubin increased (indicating adverse effect on liver), Influenza (Flu), Pruritus generalized (itchy all over body), Cardiac failure congestive (heart unable to pump enough to meet the body*s needs), Influenza (Flu) like illness, Rash generalized (rash that covers most of the body), Chills Infusion related reaction, Rash maculo-papular (Skin rash with discolored and raised areas), Constipation, Insomnia (difficulty sleeping or falling asleep), Visual acuity reduced (ability to see clearly), Decreased appetite, International normalized ratio increased (increased risk of bleeding), Vitiligo (skin losing pigment/color), Dry mouth, Lipase increased (may be a sign of a problem), Vomiting, Dyspnea (shortness of breath), Lymphopenia (low levels of cells that protect the body against infection and germs), White blood cell count increased (cells that protect the body against infection and germs), Electrocardiogram QT prolonged (may result in your heart not beating in rhythm), Memory impairment, Electrocardiogram Uwave abnormality (may result in your heart not beating in rhythm), Myalgia (muscle pain)

During animal studies, the following side effects were noted: slight tremor and pupil dilation. Because PF04518600 is an antibody (a type of protein), side effects may occur by administration of an antibody. There may be an allergic reaction with the following symptoms: fever, headache, nausea, vomiting, and decrease in blood pressure. A low count of white blood cells (lymphocytes), fatigue, flu-like symptoms, rash, joint pain, anemia (low red blood cell count), nausea / vomiting, enlargement of spleen, and itching of the skin may also occur. Other drugs similar to PF-04518600 have been linked to a condition called Cytokine Release Syndrome, causing a variety of symptoms, such as sudden onset of fever, chills, headache, nausea, or/and shortness of breath. Whether or not there is a chance this can occur with PF-04518600 is not known.

Possible side effects of PF-05082566:
As of the most recent safety update, a total of 167 patients have been treated with PF-05082566, of these, 86 advanced cancer patients have been treated with PF-05082566 alone.

Among the 86 advanced cancer patients treated with PF-05082566 alone, the following adverse event was reported in at least 10% of patients and considered related to PF 05082566 by the study doctor:
* Fatigue (tiredness) (11.6%)
The fatigue cases were generally mild to moderate with only 1 severe case reported.

In addition, the following adverse events were related to PF-05082566 and reported in at least 1 patient but no more than 10% of patients:
Abdominal pain, Hypertension (high blood pressure), Paresthesia (tingling or numbness in hands or feet), Anemia (low number of red blood cells), Hyponatremia (abnormally low levels of sodium in the blood), Paresthesia oral (tingling or numbness in and around mouth), Back pain, Increased alanine aminotransferase (indicating adverse effect on liver), Pneumonitis (damage to the lungs that may cause difficulty breathing), Chills, Increased aspartate aminotransferase (indicating adverse effect on liver), Pruritus (itchy skin), Decreased appetite, Influenza (Flu) like illness, Pyrexia (fever), Diarrhea, Insomnia (difficulty sleeping or falling asleep), Rash, Dizziness, Joint pain, Skin rash with discolored and raised areas, Dyspnea (shortness of breath), Muscle pain, Thrombocytopenia (low number of a type of blood cell (that helps the blood to clot), Ear discomfort, Muscle spasm, Vaginal infection, Enterocolitis (damage to the small and large bowel), Nausea, Vomiting, Eye irritation, Oropharyngeal pain (throat pain), Weight Loss, Gout (swelling and pain in the joints), Pain, Headache, Papule (small raised pimple)

During animal studies, the following side effects were noted: decrease in blood platelets (which can increase your risk of bleeding or bruising), decrease in red blood cells (which can make you feel tired), decrease in white blood cells (which can increase your risk of getting an infection including upper respiratory infection and pneumonia), vomiting, respiratory distress (difficulty breathing), abnormalities in the tissue of the liver. Because PF-05082566 is an antibody (a type of protein), side effects may occur by administration of an antibody and cause an allergic reaction. Other drugs similar to PF-05082566 have been linked to liver injury and a condition called Cytokine Release Syndrome, causing a variety of symptoms, such as sudden onset of fever, chills, headache, nausea, or/and shortness of breath. Whether or not there is a chance these side effects can occur with PF-05082566 is not known.

Potential side effects of PF-04518600 plus PF-05082566:
As of the most recent safety update, a total of 10 advanced cancer patients have been treated with PF-04518600 in combination with PF-05082566.

Among the 10 advanced cancer patients treated with PF-04518600 in combination with PF-05082566, the following adverse event was reported in at least 10% of patients and considered related to study drug(s) by the study doctor:
* Nausea (20%)

In addition, the following adverse events were related to study drug(s) by the study doctor and reported in at least 1 patient but no more than 10% of patients:
Diarrhea, Eosinophil count increased (cells that protect the body against infection and germs), Flushing, Dysphonia (hoarseness), Fatigue (tired), Vomiting

Contacts

Public
Pfizer

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part A Monotherapy
1. Part A1 only: Patients with histological or cytological diagnosis of HNSCC, HCC, melanoma, or clear cell RCC who progressed on or are intolerant to standard therapy, for which no standard therapy is available or who decline standard therapy.

2. Part A2 only: Patients with histological or cytological diagnosis of advanced/metastatic HCC who are treatment naïve and have declined standard of care, or have had at least 1 prior line of systemic therapy. Prior anti-PD-L1/PD-1 therapy is allowed.
3. Patients must have at least one measurable lesion as defined by RECIST version 1.1, be willing to undergo the mandatory biopsies and there is no excessive risk from biopsy as judged by the Investigator.
4. Adults (men and women) age *18 years (for Japan only: *20 years of age).
5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
6. Adequate Bone Marrow Function, including:
* ANC * 1,500/mm3 or *1.5 x 109/L.
* Platelets *100,000/mm3 or *100 x 109/L.
* Platelets for HCC only: * 60,000/mm3.
* Hemoglobin *9 g/dL. Limited transfusions to reach this value are allowed, after discussion with sponsor*s medical monitor. There should not be a chronic need for transfusions in the recent (approximately 3 month) past.
7. Adequate Renal Function, including:
* Serum creatinine *1.5 x upper limit of normal (ULN) or estimated creatinine clearance *60 ml/min as calculated using the method standard for the institution. If an estimated creatinine clearance is believed to be inaccurate for a patient, 24 hr urine collection with actual assessment of creatinine clearance is allowed.
8. Adequate Liver Function (all patients, except HCC, see Inclusion Criteria 9), including:
* Total serum bilirubin *1.5 x ULN unless the patient has documented Gilbert syndrome.
* Aspartate and alanine aminotransferase (AST & ALT) *2.5 x ULN; *5.0 x ULN if there is liver involvement secondary to tumor.
9. Inclusion for HCC patients only:
- Child-Pugh Class A or B with a score of 7 (see Appendix 3) and no prior history of hepatic encephalopathy.
- Serum bilirubin * 3 mg/dL.
- Serum Albumin * 2.8 g/dL.
- AST and ALT * 5.0 x ULN.
- International Normalized Ratio (INR) * 2.3 or Prothrombin Time (PT) * 6 seconds above control.
10. Resolved acute effects of
10. Resolved acute effects of any prior therapy to baseline severity or Grade *1 CTCAE except for AEs not constituting a safety risk by investigator judgment.
11. Serum or urine pregnancy test (for women of childbearing potential) negative at screening and at the baseline visit before the patient may receive the investigational product).
12. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective method(s) of contraception throughout the study and for at least 90 days after the last dose of assigned treatment.
Female patients who are not of childbearing potential as defined below, are eligible to be included (ie, meet at least one of the following criteria):
* Have undergone a documented hysterectomy and/or bilateral oophorectomy.
* Have medically confirmed ovarian failure; or
* Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or laboratory*s reference range

for postmenopausal women.
13. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
14. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.;Part B Combination Therapy
1. Part B1 only: Patients with histological or cytological diagnosis of NSCLC, HNSCC, melanoma, urothelial bladder carcinoma (including renal pelvis, ureters, urinary bladder, and urethra), gastric or squamous cell carcinoma of the uterine cervix who progressed on or are intolerant to standard therapy, for which no standard therapy is available, or who decline standard therapy.
2. Part B2 Arm 1 only: a. Ocular melanoma patients with advanced/metastatic disease; or, b. Cutaneous/acral melanoma patients with advanced/metastatic
disease who have received checkpoint inhibitor (anti-PD-L1, anti-PD-1, or anti-CTLA4) based treatment on which disease progressed. [Note: Checkpoint inhibitor may have been part of a combination therapy, as long as the combination did not contain OX40 or 4-1BB agonist.] Any questions on prior treatment may be discussed with the Sponsor.
3. Part B2 Arm 2 only: Histological or cytological diagnosis of NSCLC with advanced/metastatic disease. Patients must have previously received prior anti-PD-L1 or anti-PD-1 mAb on which disease progressed. [Note: Previous anti-PD-L1 or anti-PD-1 mAb may have been part of a combination therapy, eg, in combination with chemotherapy, as long as the combination did not contain OX40 or 4-1BB agonist.]
4. Patients must have at least one measurable lesion as defined by RECIST version 1.1, be willing to undergo the mandatory biopsies and there is no excessive risk from biopsy as judged by the Investigator.
5. Adults (men and women) age *18 years (for Japan only: *20 years of age).
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
7. Adequate Bone Marrow Function, including:
* ANC *1,500/mm3 or *1.5 x 109/L.
* Platelets *100,000/mm3 or *100 x 109/L.
Hemoglobin *9 g/dL. Limited transfusions to reach this value are allowed, after discussion with sponsor*s medical monitor. There should not be a chronic need for transfusions in the recent (approximately 3 month) past.
8. Adequate Renal Function, including:
* Serum creatinine *1.5 x upper limit of normal (ULN) or estimated creatinine clearance * 60 ml/min as calculated using the method standard for the institution.
If an estimated creatinine clearance is believed to be inaccurate for a patient, 24 hr urine collection with actual assessment of creatinine clearance is allowed.
9. Adequate Liver Function including:
* Total serum bilirubin *1.5 x ULN unless the patient has documented Gilbert syndrome.
* Aspartate and alanine aminotransferase (AST & ALT) *2.5 x ULN.
10. Resolved acute effects of any prior therapy to baseline severity or Grade *1 CTC AE except for AEs not constituting a safety risk by investigator judgment.
11. Serum or urine pregnancy test (for women of childbearing potential) negative at screening and at the baseline visit before the patient may receive the investigational product).
12. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective method(s) of contraception throughout the study and for at least

90 days after the last dose of assigned treatment.
Female patients, who are not of childbearing potential as defined below, are eligible to be included (ie, meet at least one of the following criteria):
* Have undergone a documented hysterectomy and/or bilateral oophorectomy.
* Have medically confirmed ovarian failure; or
* Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; a serum follicle stimulating hormone (FSH) level within the laboratory*s reference range for postmenopausal women.
13. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
14. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

Exclusion criteria

Part A Monotherapy
1. Patients with known symptomatic brain metastases requiring systemic corticosteroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to the start of study medication, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable. Mild neurological deficits are allowed, if they do not interfere
with the ability to judge the safety profile of PF-04518600.
2. History of or active autoimmune disorders (including but not limited to: Crohn*s Disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave*s disease) and other conditions that compromise or impair the immune system.
3. Active bacterial, fungal or viral infection including hepatitis B (HBV, see exception below for patients with HCC), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) -related illness.
For patients with HCC only: after the safety profile of a cohort has been established in 2-4 patients, and escalation to the next higher dose level has taken place, HCC patients enrolled into the expansion lower dose cohort meeting the following criteria can be enrolled: patients infected with the HBV or HCV but with minimal viral load (<20 IU/ml) at the moment of screening and who are being treated with either entecavir or tenofovir during the full study period.
4. Bleeding esophageal or gastric varices <2 months prior to informed consent document (ICD) date.
5. Unmanageable ascites (limited medical treatment to control ascites is permitted, but all patients with ascites will require review by sponsor*s medical monitor).
6. Major surgery within 4 weeks of starting study treatment.
7. Patients who have undergone solid organ or hematopoietic transplant.
8. Systemic anti-cancer therapy within 4 weeks of starting study treatment (6 weeks for mitomycin C or nitrosoureas). If systemic anti-cancer therapy was given within 4 weeks, patient may be included if 4-5 times elimination half-life of drug has passed.

9. Radiation therapy within 4 weeks of starting study treatment, except: palliative radiotherapy to a limited field is allowed after consultation with sponsor*s medical monitor at any time during study participation, including during screening.
10. Previous high dose chemotherapy requiring stem cell rescue.
11. Prior treatment with an OX40 agonist.
12. Currently require doses of systemic immune suppressive medication [eg, (* 10 mg of prednisone or equivalent ((*1.5 mg of dexamethasone)].
13. History of Grade 3 or higher immune-mediated adverse event (including AST/ALT elevations that where considered drug related and cytokine release syndrome) that was considered related to prior immune-modulatory therapy (eg, checkpoint inhibitors, co-stimulatory agents etc.) or any grade immune-related AEs that required immune suppressive therapy.
14. Patients with intolerance to or who have had a severe (* Grade 3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins, or patients who have had a severe allergic or anaphylactic reaction to any of the substances included in the investigational product (including excipients).
15. Patients with a previous history of anthracycline treatment and are at risk of cardiac failure (New York Heart Association [NYHA] Class II or above).
16. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, torsade*s de points, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block) , unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism or other clinical significant episode of thrombo-embolic disease*. Ongoing cardiac dysrhythmias of NCI CTCAE grade (*2, atrial fibrillation of any grade, or QTcF interval >470 msec at screening (except in case of right bundle branch block, these cases must be discussed with sponsor*s medical monitor). *Cases must be discussed in detail with sponsor*s medical monitor to judge eligibility. Anticoagulation (heparin only, no vitamin-K antagonists or factor Xa inhibitors) will be allowed if indicated.
17. Participation in other interventional studies within 28 days before the current study begins and/or during study participation. Before joining Study B0601002, at least 28 days must have passed from last systemic study therapy administration. Participation in long term follow up is allowed if no procedures which may interfere with the interpretation of study results will be performed.
18. Patients in the 0.01 mg/kg cohort must not be *50 kg in weight.
19. Pregnant female patients; breastfeeding female patients (including patients who are weaning their infants).
20. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or sponsor*s medical monitor,
would make the patient inappropriate for entry into this study.
21. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.4;Part B

Combination Therapy
1. Patients with known symptomatic brain metastases requiring systemic corticosteroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to the start of study medication, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable. Mild neurological deficits are allowed, if they do not interfere
with the ability to judge the safety profile of PF-04518600/utomilumab.
2. History of or active autoimmune disorders (including but not limited to: Crohn*s Disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave*s disease) and other conditions that compromise or impair the immune system.
3. Active bacterial, fungal or viral infection including HBV, HCV, known human HIV or AIDS - related illness.
4. Bleeding esophageal or gastric varices <2 months prior to ICD date.
5. Unmanageable ascites (limited medical treatment to control ascites is permitted, but all patients with ascites will require review by sponsor*s medical monitor).
6. Major surgery within 4 weeks of starting study treatment.
7. Patients who have undergone solid organ or hematopoietic transplant.
8. Systemic anti-cancer therapy within 4 weeks of starting study treatment (6 weeks for mitomycin C or nitrosoureas). If systemic anti-cancer therapy was given within 4 weeks, patient may be included if 4-5 times elimination half-life of drug has passed.
9. Radiation therapy within 4 weeks of starting study treatment, except: palliative radiotherapy to a limited field is allowed after consultation with sponsor*s medical monitor at any time during study participation, including during screening, unless it is clearly indicative of disease progression.
10. Previous high dose chemotherapy requiring stem cell rescue.
11. Prior treatment with an OX40 agonist or a 4-1BB agonist.
12. Currently require doses of systemic immune suppressive medication [eg, *10 mg of prednisone or equivalent (*1.5 mg of dexamethasone)].
13. History of Grade 3 or higher immune-mediated adverse event (including AST/ALT elevations that where considered drug related and cytokine release syndrome) that was considered related to prior immune-modulatory therapy (eg, checkpoint inhibitors, co-stimulatory agents etc.) or any grade immune-related AEs that required immune suppressive therapy.
14. Patients with intolerance to or who have had a severe (*Grade 3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins, or patients who have had a severe allergic or anaphylactic reaction to any of the substances included in the investigational products (including excipients).
15. Patients with a previous history of anthracycline treatment and are at risk of cardiac failure (NYHA Class II or above).
16. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, torsade*s de points, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism or other clinical significant episode of thrombo-embolic

disease*. Ongoing cardiac dysrhythmias of NCI CTCAE grade *2, atrial fibrillation of any grade, or QTcF interval >470 msec at screening (except in case of right bundle branch block, these cases must be discussed with sponsor*s medical monitor). *Cases must be discussed in detail with sponsor*s medical monitor to judge eligibility. Anticoagulation (heparin only, no vitamin-K antagonists or factor Xa inhibitors) will be allowed if indicated.
17. Participation in other interventional studies within 28 days before the current study begins and/or during study participation. Before joining Study B0601002, at least 28 days must have passed from last systemic study therapy administration. Participation in long term follow up is allowed if no procedures which may interfere with the interpretation of study results will be performed.
18. Pregnant female patients; breastfeeding female patients (including patients who are weaning their infants).
19. Patients that will receive 0.01 mg/kg PF-04518600 must not be *50 kg in weight.
20. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of would make the patient inappropriate for entry into this study.
21. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	utomilumab
Generic name:	NA

Ethics review

Approved WMO Date:	12-03-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-07-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-05-2016
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:	12-04-2017

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-04-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-02-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	17-10-2018
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:	27-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-10-2019
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)
Approved WMO Date:	01-04-2020
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	EUCTR2014-004107-75-NL
CCMO	NL51911.031.15
Other	www.clinicaltrials.gov: NCT02315066