A PHASE 1B/2 OPEN-LABEL STUDY TO EVALUATE SAFETY, CLINICAL ACTIVITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF AVELUMAB* (MSB0010718C) IN COMBINATION WITH OTHER CANCER IMMUNOTHERAPIES IN PATIENTS WITH ADVANCED MALIGNANCIES

Published: 13-01-2016
Last updated: 20-04-2024

Primary Objectives* Phase 1b lead-in: To assess safety and tolerability of a single dose level of avelumab in combination withincreasing dose levels of other immune modulators in combination with a single doselevel of avelumab in patients with...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON44145

Source
ToetsingOnline

Brief title
B9991004

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
advanced solid cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: advanced malignancies, Avelumab, immunotherapies

Outcome measures

Primary outcome

* Phase 1b Lead-in: First 2 Cycles Dose Limiting Toxicity (DLT);

* Phase 2: Confirmed objective response, as assessed by the investigator using

RECIST

v1.1.

Secondary outcome

* Adverse Events as characterized by type, severity (as graded by NCI CTCAE

v.4.03),

timing, seriousness, and relationship to study treatments;

* Laboratory abnormalities as characterized by type, severity (as graded by NCI

CTCAE

v.4.03) and timing;

* Pharmacokinetic parameters (Cmax and Ctrough after single dose and at steady

state). Other

parameters will be calculated including, but not limited to Tmax, AUClast,

Tlast, AUC sd,*, *

t1/2, CL, and Vz, as data permit. Multiple Dose (MD) - Tss,max, AUCss,*, t1/2,

Css,av, CL,

and Vss, ,Rac (AUCss,* /AUCsd,*) and Rss (AUCss,* /AUCsd,inf) as data permit;

* Anti-Drug Antibody levels;

* Time-to-event endpoints including Time to Tumor Response (TTR), Duration of

Response (DR), Progression-free survival (PFS) as assessed

by the investigator using RECIST v1.1, and Overall Survival (OS)

6. Confirmed OR during Phase 1b, as assessed by the investigator using

RECIST v1.1

7. Biomarkers such as PD-L1 expression and tumor infiltrating CD8+

lymphocytes in baseline tumor tissue

Study description

Background summary

It is likely that by combining an agonist mAb (PF-05082566/PF-04518600) with an anti-PD-L1 mAb (avelumab) that a greater spectrum of tumors within specific indications will be responsive to immunotherapy. In addition, safety data in mice indicated that there will not be any additional toxicities. This study will evaluate the safety and preliminary clinical activity of avelumab in combination with PF-05082566.
In addition, after new immunotherapeutic agents are tested in the clinic and found to be tolerable, they may be added as new study arms with avelumab. Please refer to protocol section 1.2.3.

Study objective

Primary Objectives
* Phase 1b lead-in: To assess safety and tolerability of a single dose level of avelumab in combination with
increasing dose levels of other immune modulators in combination with a single dose
level of avelumab in patients with advanced solid tumors in order to select the Recommended Phase 2 Dose(s) (RP2D)/schedule for the combination.
* Phase 2: To assess objective response (OR) of avelumab in combination with other
immune modulators in patients with locally advanced or metastatic cancer [ie, non-small
cell lung cancer (NSCLC), melanoma, or squamous cell carcinoma of the head and neck
(SCCHN)], triple-negative breast cancer (TNBC), or colorectal cancer (CRC).

Secondary Objectives
* To assess the overall safety and tolerability of avelumab and other immune modulators
when given in combination;
* To characterize the pharmacokinetics of avelumab and other immune modulators when
given in combination;
* To evaluate the immunogenicity of avelumab and other immune modulators when given
in combination;
* To assess the antitumor activity of avelumab and other immune modulators when given
in combination in patients with locally advanced or metastatic NSCLC, melanoma,SCCHN, TNBC or CRC;
* To assess the correlation of antitumor activity of avelumab and other immune modulators with immune biomarkers in baseline tumor tissue.

Study design

Initially, avelumab will be combined with PF-05082566 (anti-4-1BB agonist mAb) (combination A) or PF-04518600 (combination B). Up to 18 NSCLC patients will be randomized (6 patients each) to receive PF-05082566 at
500 mg (Cohort A1), 100 mg (Cohort A2), or 20 mg (Cohort A3) in combination with 10 mg/kg of avelumab for 2 cycles (1 cycle = 28 days).

Patients will initially be treated at PF-04518600 dose level 0 (DL0), 0.3 mg/kg, in combination with 10 mg/kg avelumab.
Once the MTD or MAD is identified in Phase 1b, Phase 2 will begin with enrollment into
tumor type specific cohorts.

Intervention

PF-05082566 /PF-04518600 and avelumab will be administered at the investigational site on an outpatient
basis. After Cycle 1, investigational products may be administered up to 2 days before or
after the scheduled treatment day of each cycle for administrative reasons. However, if the
administration is given 2 days before or after the scheduled treatment day, and both
investigational products are to be administered, they should both be given on the same day.
Avelumab will be administered at 10 mg/kg as a 1-hour IV infusion once every 2 weeks on
Days 1 and 15 of each cycle.
PF-05082566 will be administered as a 1-hour IV infusion, once every 4 weeks on Day 1 of
each cycle. PF-05082566 will be administered at 500 mg in Cohort A1, 100 mg in Cohort A2, and 20 mg in Cohort A3 in patients with NSCLC.
Patients will initially be treated at PF-04518600 dose level 0
(DL0), 0.3 mg/kg, in combination with 10 mg/kg avelumab.

Study burden and risks

See 'schedule of activities' in the protocol. Patients will have the following procedures during the study:
Medical history, use medication and side effects
Physical examination and vital signs
ECG
Functional status
Blood- and urine samples
Tumor biopsy
CT or MRI scan
Intake study medication

Main side effects:
Side effects of Avelumab Observed in 10% or more of patients:
Reactions (including allergic reactions) that occur during or following infusion (may include chills, fever, muscle pain, shortness of breath, low of high blood pressure)
Tiredness
Nausea Diarrhea

Side effects of Avelumab Observed in 2-9% of patients:
Chills
Reduced appetite

Joint pain
Fever
Reduced function of the thyroid gland
Itchy skin
Vomiting
Flu-like symptoms (including body aches, fever and chills)
Skin rash
Low number of red blood cells
Increased blood levels of liver enzymes
Muscle pain
Weakness
Headache
Shortness of breath
Constipation

Side effects of PF-05082566 Observed in 10% or more of patients:
Pyrexia (fever)

Research is still in experimental phase. It is therefore not sure if patient will benefit directly; the research may lead to useful scientific data for future patients.

Contacts

Public
Pfizer

Science Center Drive 10555
San Diego CA 92121
US
Scientific
Pfizer

Science Center Drive 10555
San Diego CA 92121
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histological or cytological diagnosis of advanced/metastatic solid tumor with the following tumor types. Combinatie A: For Phase 1b,
patients with NSCLC that have progressed on standard therapy or for which no standard therapy is available, and for Phase 2, patients with NSCLC, melanoma, SCCHN, and TNBC in any line of therapy.
NSCLC patients in Phase 2 with tumor anaplastic lymphoma kinase (ALK) translocations or epidermal growth factor receptor (EGFR) mutations must have received or been refractory/intolerant to standard therapy.
Patients with a history of PD-1 or PD-L1 refractory disease (best response of PD) will not be eligible.
Combination B:
For phase 1b, patients with advanced solid tumors that have progressed on standard therapy or for which no standard therapy is available. For Phase 2, patients with NSCLC, melanoma, or SCCHN in any line of therapy, or locally advanced/metastatic CRC that has progressed after at least 1 line of standard therapy. NSCLC patients in Phase 2 with tumor ALK translocations or EGFR mutations must have received or been refractory / intolerant to standard therapy. Measurable disease by RECIST v1.1 with at least 1 measureable lesion that has not previously been irradiated.Availability of tumor specimens: For Phase 1b: Archival formalin-fixed
paraffin-embedded (FFPE) tissue is required if available. For Phase 2: FFPE tissue must be available from the most recent primary or metastatic tumor biopsy or resection prior to start of study therapy, taken within 1 year prior to study entry, with no intervening systemic anti-cancer therapy. This tissue may be prepared from a de novo biopsy obtained prior to study entry. Core needle or excision biopsies are preferred.
Human papilloma virus (HPV) status based on locally approved testing for patients with SCCHN, and microsatellite instability (MSI) status based on locally approved testing for patients with CRC.
2. Age >=18 years.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
4. Estimated life expectancy of at least 3 months.
5. Adequate Bone Marrow Function, defined as:
a. Absolute Neutrophil Count (ANC) >=1.5 x 109/L (>=1,500/µl);
b. Platelets >=100 x 109/L (>=100,000/ µl);

c. Hemoglobin >=9 g/dL (>5.6 mmol/L).
Patients must be transfusion independent (ie, no blood product transfusions for a period of at least 14 days prior to study entry).
6. Adequate Renal Function, including estimated creatinine clearance >=50 mL/min as calculated using the Cockcroft-Gault (CG) equation.
7. Adequate Liver Function, including:
a. Total serum bilirubin <=1.5 x upper limit of normal (ULN);
b. Aspartate and Alanine aminotransferase (AST & ALT) <=2.5 x ULN.
6. Resolved acute effects of any prior therapy to baseline severity or NCI CTCAE v4.03 Grade <=1 (except alopecia and Grade <=2 sensory neuropathy are acceptable).
9. Negative serum pregnancy test (for females of childbearing potential) at screening.
10. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 60 days after the last dose of assigned treatment, as required by local regulations.
Female patients who are not of childbearing potential (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.
11. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
12. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other procedures.

Exclusion criteria

1. Monoclonal antibody based anti-cancer therapy within 28 days prior to study entry or small-molecule based anti-cancer therapy (targeted therapy or chemotherapy) within 14 days prior to study entry.
2. Current or prior use of immunosuppressive medication within 7 days prior to study entry The following are exceptions to this exclusion criterion: Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent; Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
3. Active autoimmune disease that requires systemic steroids (equivalent of >10 mg prednisone) or immunosuppressive agents within 7 days prior to study entry. Exceptions include: patients with controlled diabetes type 1, controlled hypo- or hyperthyroidism, resolved childhood asthma/atopy, vitiligo, or psoriasis not requiring immunosuppressive treatment.

4. Known prior or suspected hypersensitivity to investigational products or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade >=3), and any history of anaphylaxis, or uncontrolled asthma (ie, 3 or more features of partly controlled asthma).33
5. Major surgery within 4 weeks or radiation therapy within 14 days prior to study entry. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed 48 hours prior to study entry and there is at least one measurable lesion that has not been irradiated.
6. Patients with known symptomatic brain metastases requiring steroids. 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 study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks prior to study entry, and are neurologically stable.
7. Previous high-dose chemotherapy requiring stem cell rescue.
8. Prior allogeneic stem cell transplant or organ graft.
9. Any of the following within the 6 months prior to study entry: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.
10. Symptomatic pulmonary embolism within 6 months prior to study entry
11. Known HIV or AIDS-related illness
12. Active infection requiring systemic therapy
13. Positive HBV or HCV test indicating acute or chronic infection
14. Administration of a live vaccine within 4 weeks prior to study entry
15. Diagnosis of other malignancy within 5 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or cervix, or low-grade (Gleason <=6) prostate cancer
16. Patients who are 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
17. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry and/or during study participation
18. Persisting toxicity related to prior therapy NCI CTCAE v4.03 Grade >1 (alopecia and Grade <=2 sensory neuropathy is acceptable).
19. Other severe acute or chronic medical condition, including colitis, inflammatory bowel disease, and pneumonitis or psychiatric condition, recent or active suicidal ideation or behavior, or end stage renal disease on hemodialysis, or laboratory abnormality that may increase the risk associated with study participation or investigational products administration or may interfere with the interpretation of results and, in the judgment of the Investigator, would make the patient inappropriate study entry
20. Male and female patients able to have children who are unwilling or unable to use 2 highly effective method(s) of contraception for the duration of the study and for at least 60 days after the last dose of

investigational product or longer as required by local regulations.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	13
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Avelumab
Generic name:	Avelumab
Product type:	Medicine
Brand name:	PF-04518600
Generic name:	PF-04518600
Product type:	Medicine
Brand name:	PF-05082566
Generic name:	PF-05082566

Ethics review

Approved WMO

Date:	13-01-2016

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-07-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2015-002552-27-NL
ClinicalTrials.gov	NCT02554812
CCMO	NL55255.031.16