A Phase 1 Pharmacokinetic-Pharmacodynamic Study of Avelumab (MSB00100718C) in Patients with Previously Treated Advanced Stage Classical Hodgkin*s Lymphoma

Published: 29-03-2016
Last updated: 17-04-2024

Primary Objective* To characterize the pharmacokinetics (PK) of different dosing regimens of avelumab and its relation to target occupancy (TO) in peripheral blood of patients with classical Hodgkin*s Lymphoma (cHL).Secondary Objectives* To evaluate...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Lymphomas Hodgkin's disease
Study type	Interventional

Summary

ID

NL-OMON43446

Source
ToetsingOnline

Brief title
Javelin Hodgkin's

Condition

- Lymphomas Hodgkin's disease

Synonym
Hodgkin's Lymphoma, lymph node cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Hodgkin's Lymphoma, phase 1

Outcome measures

Primary outcome

Primary Endpoints

* Percent TO by dose/schedule in peripheral blood immune cells, including CD14+ monocytes and CD3+ T cells.

* Pharmacokinetic parameters of avelumab including, but not limited to, Cmax, Tmax, AUClast, Tlast, AUC sd,*, t1/2, AUCsd,inf, CL, and Vz as data permit. Multiple Dose (MD) Css,max, Tss,max, AUCss,*, t1/2, Css,min, Css,av, CL, and Vss, ,Rac (AUCss,* /AUCsd,*) and Rss (AUCss,* /AUCsd,inf) as data permit.

Secondary outcome

Secondary Endpoints

* Adverse Events as characterized by type, 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.

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

* Anti drug antibodies (ADAs; neutralizing antibodies) and serum titers against avelumab.

* Phenotype, quantity, and localization of tumor infiltrating lymphocytes

(TILs) in tumor biopsy tissue by immunohistochemistry (IHC).

* Relative expression of transcripts associated with immune activation and regulation in tumor biopsy tissue by gene expression profiling.

* Phenotype, relative proportions, activation state and PD L1 expression of peripheral blood T cell subsets by flow cytometry.

* Confirmed objective response according to Response Criteria for Malignant Lymphoma.

* Time to event endpoints: time to tumor response (TTR), duration of response (DR), and progression free survival (PFS).

Exploratory Endpoints

* Correlation of TO and tumor immunophenotypic markers (eg, tumor expression of PD L1, CD8 and CD68 by IHC) with tumor responses.

* Abundance and diversity of tumor infiltrating and peripheral blood T cell clones by high throughput sequencing of T-cell receptor (TCR) genes.

* Prevalence and diversity of tumor antigenic epitopes by whole exome sequencing (WES).

* PD L2 protein expression in tumor biopsy tissue by IHC.

Study description

Background summary

Background and Rationale:
Hodgkin*s lymphoma is a B cell malignancy and is a lymphoma involving peripheral lymph nodes, which may also impact organs including liver, lung as well as bone marrow. Hodgkin*s lymphoma affects approximately 9,000 new patients each year and represents approximately 12% of all lymphomas seen in the United States.1 Classical Hodgkin*s lymphoma (cHL) and nodular lymphocyte

predominant Hodgkin*s lymphoma are the two main types of Hodgkin*s lymphoma. cHL accounts for most (~95%) Hodgkin*s Lymphoma diagnosed.2 The standard initial treatment for patients with newly diagnosed cHL include chemotherapy or combined modality therapy, followed by restaging with PET/CT to assess treatment. While patients with cHL commonly respond well to initial therapy, a subset of patients (~25%) continue to experience relapsed disease and have very poor prognosis.3

cHL is defined by the subclassifications of: nodular sclerosis (60 80% of Hodgkin*s lymphoma cases), mixed cellularity (25 30% of cases), lymphocyte rich (5%) and lymphocyte depleted (1%), depending upon histology and phenotype of the tumor cells.2 Hodgkin*s lymphoma tumor cells represent less than 2% of cells in the tissue. Mononucleated Hodgkin*s and bi or multi nucleated Reed Sternberg cells (HRS) are the malignant cells in cHL classical Hodgkin*s lymphoma.13,14

Chromosome 9p24.1 ampliflication, which contains the PD L1 gene, is frequent in cHL.19 It is thought that this leads to an overexpression of PD L1 on the surface of the HRS. PD L1 on the surface of these tumor cells is thought to be responsible in part for the down modulation of potentially cytotoxic anti tumor T cells, which express PD 1. PD L1 on HRS cells may also be capable of down modulating the activity of other cell types expressing PD 1, such as natural killer (NK) cells, which might otherwise be capable of mediating antibody dependent cell mediated cytotoxicity (ADCC) through therapeutic antibodies targeting to the HRS cells. Avelumab may block the binding PD 1 on these key anti tumor effector cells to PD L1 on HRS, thereby restoring anti tumor immunity, while at the same time stimulating NK directed ADCC toward HRS. It is not clear at this time if other mechanisms may also inhibit immune cells in this disease, such as PD L2, another ligand for PD 1. However, this may be mitigated by the direct tumor targeting properties of avelumab through the ADCC mechanism. Therefore, cHL has been chosen as a potentially responsive tumor type for this study.

Blocking the PD 1/PD L1 interaction is a novel immunotherapeutic approach for cHL. Preliminary data suggests that PD 1 blockade in specific hematologic cancers provide an additional therapeutic strategy.6,7,8 Nivolumab, a high affinity, fully human anti PD 1 monoclonal antibody (mAb) has shown therapeutic activity in patients with previously treated relapsed or refractory Hodgkin*s lymphoma.9 In a cohort of n=23 patients, an objective response was reported in 20 patients (87%), including 17% with a complete response (CR) and 70% with a partial response; the remaining 3 patients (13%) had stable disease. The rate of progression free survival at 24 weeks was 86%. Therefore, there is room for improvement with immune therapies that could increase the CR rate.

For those patients who are refractory to standard initial therapy, immunomodulation via PD L1 inhibition may provide clinical benefit to the management of cHL. PD L1 blockade along with ADCC using avelumab may remove the inhibition of tumor infiltrating cytotoxic CD8+ T cells mediated by HRS, restore anti tumor immunity and directly target HRS by the innate immune system.

Study objective

Primary Objective
* To characterize the pharmacokinetics (PK) of different dosing regimens of avelumab and its relation to target occupancy (TO) in peripheral blood of patients with classical Hodgkin*s Lymphoma (cHL).
Secondary Objectives
* To evaluate the overall safety and tolerability of different dosing regimens of avelumab.
* To assess the immunogenicity of different dosing regimens of avelumab.
* To evaluate the effect of different dosing regimens of avelumab on pharmacodynamic biomarkers of tumor immunophenotype and anti tumor immune response.
* To evaluate the anti tumor activity of avelumab in patients with cHL.
Exploratory Objectives
* To characterize the association of TO and tumor immunophenotype with tumor responses.
* To explore the effects of different dosing regimens of avelumab on the abundance of T cell clones and the diversity of the T cell repertoire in tumor biopsy tissue and peripheral blood.
* To explore the effects of different dosing regimens of avelumab on the prevalence and diversity of tumor antigenic epitopes in tumor biopsy tissue.
* To measure the expression of PD L1/PD L2 in tumor biopsy tissue and in tumor infiltrating macrophages.
* Measure time course of potential plasma biomarkers.
* To collect exploratory biomarker/genomics samples for biobanking.

Study design

This is a Phase 1b, open label, multi center, multiple dose, randomized, parallel arm, pharmacokinetic and pharmacodynamic study of avelumab as a single agent in adult patients with cHL. Patients enrolled in this study are required to have failed a prior course of high dose chemotherapy as a part of a first line salvage chemotherapy regimen for cHL. The study will include a lead in phase and a dose expansion phase.
In the lead in phase of the study, a total of approximately 30 patients will be randomized across 5 treatment cohorts in a ratio of 1:1:1:1:1, with 6 patients per treatment cohort. The 5 treatment cohorts will be 70 mg Q2W (Cohort A), 350 mg Q2W (Cohort B), 500 mg Q3W (Cohort C), 500 mg Q2W (Cohort D), and 10 mg/kg Q2W (Cohort E). The goal of the lead in phase is to determine the doses and schedules of avelumab that provide greater than a mean of 90% TO.
Up to 3 treatment cohorts will be expanded in the dose expansion phase, including 10 mg/kg Q2W plus up to 2 other treatment cohorts to be determined from the lead in phase. Up to 12 additional patients will be randomized in an equal ratio to each of the dose expansion treatment cohorts. Selection criteria for dose expansion cohorts will include achieving greater than a mean

90% TO after 1 treatment cycle and observing at least 3 confirmed objective responses per Response Criteria for Malignant Lymphoma (Appendix 2) at that cohort. In the case that greater than 2 additional treatment cohorts meet these criteria, the lowest doses meeting these criteria will be used for the dose expansion phase. For patients not achieving a 90% TO after C1D1, the dose may be escalated to 10 mg/kg (Treatment Cohort E) starting at C2D1, after C1 assessment of TO.
Up to approximately 70 patients are expected to be randomized in the study overall to obtain at least 66 patients with TO and PK data. The 5 different treatment cohorts in the lead in phase and the 3 different treatment cohorts in the dose expansion phase will be randomized in parallel within each phase. Patients who complete the maximum number of cycles/months on investigational product and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the investigational product will be given the opportunity to continue treatment upon agreement between investigator and Sponsor.

Intervention

Lead-in phase:
All patient receive Avelumab:
Corhort A 70 mg once per 2 weeks
Corhort B 350 mg once per 2 weeks
Corhort C 500 mgonce per 3 weeks
Corhort D 500 mg once per 2 weeks
Corhort E 10mg/kg once per 2 weeks

The Dose Expansion Phase of the Study
There will be 3 dose groups of avelumab determined from the doses used in the lead-in phase; 1 of them would be 10 mg/kg given once every 2 weeks

Study burden and risks

During this study the patient has to (assuming approximately 2 cycles) come 11 times to the clinic. During these visits a physical examination is done and blood will be taken, between 3,5 and 36,5 ml each time). If the patient is included in the dose expansion phase a tumor biopsy is required. In addition the patient needs to indicate their performance status (ECOG questionnaire)

Potential side effects are listed in the investigator's brochure and are summarized in the patient information sheet.

The conduct of this trial can be justified because the patients did not benefit (enough) with their first line therapy for their classical Hodgkin lymphoma. this form of cancer is a serious disease that can lead to death. A good understanding of the effects of avelumab in this patient population is

important to achieve the most optimal treatment.

Contacts

Public
Pfizer

East 42nd Street 235
New York NY10017
US
Scientific
Pfizer

East 42nd Street 235
New York NY10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histological confirmation of classical Hodgkin's Lymphoma (cHL) with relapsed or refractory disease, who either have had prior autologous or allogenic stem cell transplantation (SCT) or are not eligible for SCT.
2. Patients must be off previous cHL therapy for at least 28 days prior to randomization.
3. At least 1 FDG-PET-avid (Deauville 4/5) measurable lesion >1.5 cm as defined by Response Criteria for Malignant Lymphoma that has not previously been irradiated.
4. Age *18 years.
5. Estimated life expectancy of at least 3 months.

6. ECOG Performance Status (PS) 0 or 1.
7. Adequate bone marrow function including:
a. Absolute neutrophil count (ANC) *1,000/mm3 or *1.0 x 109/L (may have received G-CSF support);
b. Platelets *50,000/mm3 or *50 x 109/L;
c. Hemoglobin *8.0 g/dL (>4.9 mmol/L) (may have been transfused).
8. A pre-treatment tumor biopsy (lymph node or bone marrow) is mandatory at baseline for the expansion phase. A pre-treatment tumor biopsy in the lead in phase and an on-treatment biopsy in both phases are optional. Baseline biopsy must be collected within 28 days prior to randomization.
9. Adequate Renal Function: Estimated creatinine clearance *30 mL/min as calculated using the Cockcroft-Gault (CG) equation.
10. Adequate Liver Function, including:
a. Total serum bilirubin *1.5 x upper limit of normal (ULN);
b. Aspartate and Alanine transaminase (AST and ALT) *2.5 x ULN.
11. International Normalized Ratio (INR) or prothrombin time (PT) <1.5 x ULN.
12. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.
13. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective method(s) of contraception throughout the study and for at least 60 days after the last dose of assigned treatment. 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.
14. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study. As inclusion of adult patients for whom consent must be provided by a legally authorized representative is not appropriate for this research, this protocol excludes adult individuals who lack capacity to consent for themselves.
15. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.

Exclusion criteria

1. Patients with prior allogeneic stem cell transplantation (SCT) who have had:
a. allo-SCT performed <12 months prior to randomization; or
b. immunosuppressive treatment for acute or chronic graft-versus-host disease (GVHD) within 3 months prior to randomization (with the exception of those patients who required *

15 mg/day oral prednisone or equivalent); or
c. acute Grade 3 or Grade 4 GVHD at any time in the past (as defined by the modified Seattle Glucksberg Criteria29); or
d. prior chronic GVHD (as defined by the NIH Consensus Development Project30), persisting for >6 months, which required systemic immunosuppression (with the exception of those patients who required * 15 mg/day oral prednisone or equivalent); or
e. a donor lymphocyte infusion (DLI) within 6 months prior to randomization.
2. Prior therapy with an anti-PD-1 or anti-PD-L1. May be enrolled if patient had stopped prior anti-PD1 therapy more than one year ago and had responded.
3. Persisting toxicity related to prior therapy NCI CTCAE v4.0 Grade >1, except alopecia; also, sensory neuropathy Grade * 2 is acceptable.
4. Major surgery within 4 weeks or radiation therapy within 14 days prior to study entry.
5. Prior palliative radiotherapy to lesion(s) is permitted as long as there is at least one target lesion evaluable for anti-tumor activity.
6. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy, or known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
7. Current or prior use of immunosuppressive medication within 7 days prior to randomization, except the following: Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); Systemic corticosteroids at physiologic doses * 10 mg/day of
prednisone or equivalent; Steroids as premedication for hypersensitivity
reactions (eg, CT scan premedication).
8. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
9. Known severe hypersensitivity reactions to monoclonal antibodies
(Grade * 3 NCI-CTCAE v 4.03).
10. Active infection requiring systemic therapy.
11. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).
12. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism.
13. Diagnosis of any other malignancy within 5 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or lowgrade (Gleason 6 or below) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration).
14. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry and/or during study participation.
15. 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.
16. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 60 days after the last

dose of investigational product or longer based upon the compound's half-life characteristics.
17. Other severe acute or chronic medical conditions including but not limited to colitis, inflammatory bowel disease and pneumonitis or psychiatric condition, recent (within the past year) 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 product administration or may interfere with the interpretation of study results and, in the judgment of the
investigator, would make the patient inappropriate for entry into this study.
18. Vaccination with live vaccine within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines.

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:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Avelumab
Generic name:	Avelumab

Ethics review

Approved WMO

Date:	29-03-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2015-002636-41-NL
ClinicalTrials.gov	NCT02603419

Register	ID
CCMO	NL56578.029.16