Phase 1B/Phase 3 Multicenter Study of Avelumab (MSB0010718c) in Combination Regimens that Include an Immune Agonist, Epigenetic Modulator, CD20 Antagonist and/or Conventional Chemotherapy in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)

Published: 12-04-2017
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Primary objective:- To assess safety, efficacy, and potentially select the most active treatment regimen among 3 treatment arms to advance to the Phase 3 component of the study.Secondary objectives:- Ph1b: evaluate PK & assess immunogenicity of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON47269

Source
ToetsingOnline

Brief title
B9991011

Condition

- Lymphomas non-Hodgkin's B-cell
- Lymphomas non-Hodgkin's B-cell

Synonym
lymphoma cancer, non-Hodgkin lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pharmaceutical industry;Pfizer

Intervention

Keyword: Avelumab, Diffuse Large B-cell Lymphoma, Utomilumab

Outcome measures

Primary outcome

- Dose Limiting Toxicity (DLT).

- Objective Response (OR) as assessed by the Investigator per Lugano Response Classification Criteria.

Secondary outcome

Secondary endpoints:

- Safety: AEs and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Critera for Adverse Events (CTCAE) v.4.03; vital signs (blood pressure, heart rate); electrocardiograms (ECGs).

- Duration of Response (DR), Time to Tumor Response (TTR), Disease Control (DC), Progression-Free Survival (PFS), as assessed by the Investigator per Lugano Response Classification Criteria and Overall Survival (OS).

- Pharmacokinetics: PK parameters of avelumab, rituximab, utomilumab, azacitidine and bendamustine as data permit: maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the plasma

concentration time apparent plasma clearance (CL/F), and apparent volume of distribution (V/F) of each analyte following single and multiple dosing.

- Immunogenicity: Anti-drug antibodies (ADA); neutralizing antibodies (Nab) against avelumab, rituximab, and utomilumab.

- PD-L1 expression levels in tumor cells and cells of the tumor microenvironment at baseline.

- Minimal residual disease burden (MRD) as assessed using serial blood samples.

Exploratory endpoints:

- Molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue and/or feces that may be relevant to the mechanism of action of, or response/resistance to study treatment, including molecular profiling for ABC/GBC cell of origin DLBCL subtypes.

- Patient-Reported Outcomes: Brief Fatigue Inventory (BFI).

Study description

Background summary

Diffuse Large B-Cell Lymphoma (DLBCL) is a heterogeneous disease with subtypes distinguished by various clinical, pathologic, and molecular characteristics.

It is the most common type of lymphoma, accounting for 30-40% of all newly diagnosed cases of non-Hodgkin Lymphoma (NHL), and more than 80% of all aggressive lymphomas The median age at the time of diagnosis is ~70 years.

The World Health Organization (WHO) classification of lymphoid malignancies acknowledges the heterogeneity of DLBCL by recognizing a broad category termed *DLBCL not otherwise specified* (DLBCL-NOS) as well as a variety of DLBCL subtypes.

Within the DLBCL-NOS category, gene expression profiling studies have identified two principal molecular subtypes: (i) germinal center B-cell (GCB) and (ii) activated B-cell (ABC). These subtypes represent lymphomas arising from different stages of lymphoid differentiation. The GCB subtype arises from centroblasts and expresses genes usually
active in germinal center B cells, whereas the ABC subtype arises from B-cells at a plasmatic stage, just prior to germinal center exit, and expresses genes frequently expressed in mature plasma cells. This molecular distinction has prognostic implications in treatment-naïve

DLBCL patients, with the GCB subtype being associated with a more favorable prognosis.
The prognostic significance of the cell of origin beyond first line has not, however, been established.

Approximately 75% of patients with DLBCL present with advanced stage disease. The established frontline standard of care (SOC) is R-CHOP comprised of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (5-year OS 58%). The majority (~60%) of patients with DLBCL may be cured with this regimen, but patients who have treatment failure with R-CHOP have a very poor outcome. Ten to fifteen percent of patients have primary refractory disease (no response, or relapse within 3 months of therapy), and an additional 20-25% relapse following an initial response to therapy. Most relapses occur within the first 2 years following treatment.

Patients who are refractory to induction therapy or who relapse after achieving a complete response may be considered for salvage chemotherapy. If their disease is chemosensitive, they may be considered for high-dose chemotherapy followed by autologous stem cell transplant (ASCT).

High-dose chemotherapy and ASCT have been shown to provide the best chance of cure for patients with chemotherapy-sensitive relapse. However, due to advanced age and comorbidities, only approximately half of all patients are eligible for this intensive treatment approach, and, of the transplant-eligible patients, only half are chemosensitive to salvage therapy and proceed to transplant, of which less than half will be cured.

The development of more effective salvage strategies consequently remains an area of significant clinical importance, and a very high unmet medical need, especially in patients who are not candidates for high-dose chemotherapy. Patients with primary refractory disease following R-CHOP present the greatest clinical challenge, with less than 10% achieving durable remissions with salvage therapy.

Study objective

Primary objective:

- To assess safety, efficacy, and potentially select the most active treatment regimen among 3 treatment arms to advance to the Phase 3 component of the study.

Secondary objectives:
- Ph1b: evaluate PK & assess immunogenicity of treatments; evaluate PDL1 expression levels in tumor cells and cells of the tumor microenvironment with their relationship to clinical response parameters; evaluate relationship between minimal residual disease burden as assessed using serial blood samples with clinical response parameters

Study design

This is a phase 1b, international, multicenter, randomized, open-label, parallel 3-arm study in which approximately 84 subjects are planned to be randomized in a 1:1:1 ratio to receive either avelumab in combination with rituximab and utomilumab, avelumab in combination with azacitadine and utomilumab or avelumab in combination with rituximab and bendamustine.

Intervention

Patients in arm A will receive:
- Avelumab, intravenously over 1 hour, every 2 weeks.
- Rituximab, intravenously every 4 weeks.
- Utomilumab, intravenously over 1 hour every 4 weeks.

Patients in arm B will receive:
- Avelumab, intravenously over 1 hour, every 2 weeks.
- Azacitadine, by subcutaneous injection for 5 days in a row every 4 weeks.
- Utomilumab, intravenously over 1 hour every 4 weeks.

Patients in arm C will receive:
- Avelumab, intravenously over 1 hour, every 2 weeks.
- Rituximab, intravenously every 4 weeks.
- Bendamustine, intravenously over 1 hour 2 days in a row every 4 weeks.

Study burden and risks

Avelumab, utomilumab, rituximab, azacitidine and bendamustine may all have certain side effects, which can be different in severity. Also the combinations of medicines and the study procedures may yield certain side effects. All side effects are described in the patient information.

Study subjects may undergo the following tests/procedures for the study:
- medical history
- physical exam

- blood sampling
- ECG
- MUGA or echo
- questionnaires
- biopsy (optional)
- fecal sampling
- pregancy tests
- use of contraceptives
- ECOG

Contacts

Public
Pfizer

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New York, NY 10017
US
Scientific
Pfizer

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New York, NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Any of the following as defined by the WHO, 2016 lymphoid neoplasm

classification and histologically confirmed:
- Discussed large B-cell lymphoma (DLBCL), Non Otherwise Specified
(NOS)
- Germinal center B-cell type (GCB)
- Activated B-cell type (ABC)
- High-grade B-cell lymphoma (HGBCL)
- HGBCL with MYC and BCL2 and/or BCL6 rearrangements
- T-cell histocyte-rich large B-cell lymphoma
- EBV+ DLBCL, NOS
- HHV8+ DLBCL, NOS
2.. Documentation that the disease is relapsed or refractory following at least 2 lines (and a maximum of 4 lines) of prior rituximab containing multi-agent chemotherapy which may include an autologous stem cell transplantation unless patients are not considered suitable for intensive second-line chemotherapy or autologous stem cell transplantation. Patients who are ineligible for intensive second line chemotherapy, must have received at least one prior rituximab-containing combination chemotherapy regimen.
3. Patients previously treated with bendamustine must have experienced a response duration 6 months.
4. Documentation of baseline measurable disease with at least 1 bi-dimensional lesion with longest diameter >1.5 cm on CT scan which is fluorodeoxyglucose (FDG) avid on PET scan.
5. A biopsy (archived or Screening/recent) will be collected at Screening.
6. Estimated life expectancy 3 months.
7. At least 18 years of age.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
9. All adverse events must have resolved to NCI CTCAE v.4.03 Grade 1 (with the exception of alopecia and other Grade 2 AEs not considered medically relevant in the judgment of the Investigator).
10. Patients must have an adequate bone marrow function, including:
a. Absolute neutrophil count (ANC) 1.5 x 109/L;
b. Platelet count 100 x 109/L;
c. Hemoglobin 8 g/dL.
11. Patients must have adequate liver function, including:
a. Total bilirubin level 1.5 × upper limit of normal (ULN);
b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 2.5 x ULN.
12. Patients must have an adequate renal function as evidenced by a creatinine clearance 40 mL/min as calculated using the Cockcroft-Gault equation.
13. Serum or urine pregnancy test (for females of childbearing potential) must be negative.
14. Female patients of non-childbearing potential must meet at least 1 of the following criteria:
• Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;
• Have undergone a documented hysterectomy and/or bilateral oophorectomy;
• Have medically confirmed ovarian failure.
All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

15. Must be willing to receive prophylactic granulocyte colony stimulating factor (G-CSF) in all cycles, for patients >=60 years old randomized to arm C.
16. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
17. Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion criteria

1. Active/symptomatic central nervous system (CNS) lymphoma based on clinical evaluation.
2. Prior organ transplantation including prior allogeneic SCT.
3. Prior therapy with an anti PD-1, anti PD-L1, anti PD-L2, anti CD137, or anti-cytotoxic T lymphocyte associated antigen 4 (CTLA-4) antibody (including ipilimumab, tremelimumab or any other antibody, or drug specifically targeting T-cell co-stimulatory or immune checkpoint pathways).
4. Use of any standard or experimental anti-cancer therapy within 2 weeks to first dose of study treatment, including cytoreductive therapy and radiotherapy, immunotherapy, or cytokine therapy (except for erythropoietin).
5. Use of any non-drug anti-cancer therapy including chimeric antigen receptor (CAR) T-Cell (CAR-T-Cell) therapy.
6. Major surgery within 28 days prior to first dose of study treatment.
7. Diagnosis of any other malignancy 3 years prior to first dose of study treatment, with the exception of: (i) adequately treated basal cell or squamous cell skin cancer, (ii) carcinoma in situ of the breast or cervix, or (iii) low-grade (Gleason 6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration).
8. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.
9. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen, positive HBV core antibody or HCV ribonucleic acid (RNA) if anti-HCV antibody screening test positive).
10. Active infection requiring systemic therapy.
11. Vaccination within 4 weeks prior to randomization and while on trial is prohibited except for administration of inactivated vaccines.
12. Current use of immunosuppressive medication, EXCEPT for the following:
a. intranasal, inhaled, eye drops, topical steroids, or local steroid injection (eg, intra-articular injection);
b. Systemic corticosteroids at physiologic doses 10 mg/day of prednisone or equivalent;
c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
13. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.
14. Known anaphylaxis or severe hypersensitivity to rituximab or other monoclonal antibodies, mannitol, or any of the compounds used in this study or to compounds with a similar chemical or biological composition.

15. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke/transient ischemic attack [TIA]/symptomatic pulmonary embolism (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication, other severe acute or chronic medical (including colitis, inflammatory bowel disease, pneumonitis, uncontrolled asthma, or psychiatric conditions 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, would make the patient inappropriate for entry into this study.
16. Known alcohol or drug abuse.
17. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception for a defined timeframe dependent on study treatment assigned per protocol and , where applicable, in agreement with local prescribing information for individual drugs.
18. 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, including their family members, directly involved in the conduct of the study.
19. Participation in other studies involving investigational drugs within 4 weeks prior to Cycle 1 Day 1 and/or during study participation.
20. Current use or anticipated need for treatment with drugs that are known strong CYP1A2 inhibitors, including their administration within 10 days prior to patient randomization (ie, ciprofloxacin, fluvoxamine, clinafloxacin, exoxacin, oltipraz, propranolol, rofecoxib, thiabendole and zafirlukast).
21. Current use or anticipated need for treatment with drugs that are known CYP1A2 inducers, including their administration within 10 days prior to patient randomization (ie, omeprazole, phenytoin).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Avelumab
Generic name:	Avelumab
Product type:	Medicine
Brand name:	Azacitidine
Generic name:	Azacitidine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Bendamustine
Generic name:	Bendamustine hydrochloride
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rituximab
Generic name:	Rituximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Utomilumab
Generic name:	Utomilumab

Ethics review

Approved WMO

Date:	12-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	15-11-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2016-002904-15-NL
ClinicalTrials.gov	NCT02951156
CCMO	NL60036.078.17

Study results

Date completed: 31-10-2018

Results posted: 08-09-2020

Summary results
Trial never started

First publication
26-06-2020