A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in combination with Pembrolizumab in Adult Subjects with Relapsed or Refractory Diffuse Large B Cell Lymphoma (DLBCL)

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• Primary- To determine the maximum tolerated dose (MTD) of blinatumomab in combination with pembrolizumab in adult subjects with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL).• Secondary-To evaluate the safety, efficacy, and...

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

Summary

ID

NL-OMON49694

Source
ToetsingOnline

Brief title
20150290

Condition

- Other condition

Synonym
Cancer, Lymphoma, Non-Hodgkin□s Lymphoma

Health condition

Kanker in de bloedcellen

Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: Diffuse large B Cell lymphoma, Open label, Phase 1

Outcome measures

Primary outcome

Incidence of dose limiting toxicities (DLTs)

Secondary outcome

• Objective response (OR) (including CR and PR) by the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007)during the first 12 weeks since starting blinatumomab and during the treatment period

• Complete response (CR) by the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first 12 weeks since starting blinatumomab and during the treatment period

• Duration of response (DOR) for subjects with OR (ie, CR and partial remission (PR) by the Lugano Classification (Cheson et al, 2014) during the first 12 weeks since starting blinatumomab)

• Progression free survival (PFS)

• Overall survival (OS)

• Blinatumomab PK parameters

• Pembrolizumab PK parameters

Study description

Background summary

The annual incidence of Non-Hodgkin Lymphoma (NHL) in Europe and the USA is estimated to be 15 to 20 cases/100,000 (Fisher and Fisher, 2004). Diffuse Large B-Cell Lymphoma is the most common lymphoid malignancy in adults, accounting for 31% of all NHL in Western countries and 37% of all B-cell tumors worldwide (NHL classification project, Blood 1997; Swerdlow et al, WHO classification 2016). The peak incidence of DLBCL is in the seventh decade (Martelli et al, 2013), with incidences increasing from 0.3/100.000/y (35-39 years) to 26.6/100,000/y (80-84 years; Morgan et al, 1997).
Blinatumomab (BLINCYTO®, AMG 103, formerly also known as MT103 or bscCD19xCD3) is a member of a novel class of bispecific antibody constructs called BiTE®, or bispecific T-cell engagers (Dreier et al, 2002; Schlereth et al, 2006).
Blinatumomab is a BiTE® antibody construct with dual binding specificities. T cells are bound by its anti-CD3 moiety, whereas B lymphoblasts and other B cells are bound by the anti-CD19 moiety. This unique feature of blinatumomab allows it to transiently connect malignant cells with T cells, thereby inducing T cell mediated killing of the bound malignant cell.
Blinatumomab specifically targets cells that express CD19, a marker solely expressed by B cells, including B-precursor acute lymphoblastic leukemia (ALL) cells, with an affinity of 1.6 x 10-9 M. Blinatumomab recruits and activates T cells via a lower affinity interaction with CD3 (8.7 x 10-8 M). These activated T cells then induce a half-maximal target cell lysis ranging in vitro between 10 to 100 pg/mL showing blinatumomab to be an extremely potent molecule (Dreier et al, 2002).
As of July 2017, blinatumomab (BLINCYTO) is indicated for the treatment of relapsed or refractory B-cell precursor ALL in the United States. It is indicated in multiple countries outside of the United States for Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (eg, European Union [EU], Mexico, Canada, Norway, Iceland, Australia, and South Korea). Additionally, confirmation of clinical benefit is a condition of approval in multiple countries (eg, European Medicines Agency [EMA]).
Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.
Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advance malignancies.

KeytrudaTM (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Study objective

• Primary
- To determine the maximum tolerated dose (MTD) of blinatumomab in combination with pembrolizumab in adult subjects with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL).
• Secondary
-To evaluate the safety, efficacy, and pharmacokinetics (PK) of blinatumomab in combination with pembrolizumab in adult subjects with r/r DLBCL.
• Exploratory
- To evaluate blood and tissue biomarkers.
- To evaluate minimal residual disease (MRD) response by next generation sequencing (NGS).

Study design

This is an open label, multicenter, phase 1b study testing the combination of blinatumomab with
pembrolizumab in r/r DLBCL.
The study will consist of 2 portions:
• Part 1 (n = 6 - 30) will test the safety of up to 3 different blinatumomab target dose levels in combination with pembrolizumab in a rolling
6 design. A Dose Level Review Team (DLRT) will review the safety data to evaluate possible drug effects and DLTs. Subjects who are not on the dose ultimately selected for part 2 will remain on their initial dose throughout the study.
• Part 2 (n = 40) will consist of an expansion cohort to assess PK, safety, and preliminary efficacy data at the chosen target dose. The part 2 dose will be determined by the totality of the clinical data from part 1 as determined by the DLRT.
The study design includes:
• A 21-day screening period
• A standard (core) treatment period of blinatumomab (first cycle) of 8 weeks
• A second (consolidation) cycle of blinatumomab of 28 days after a 28-day (± 3 days)
• blinatumomab treatment free period, that can be administered to subjects with stable
• disease (SD), PR, or CR.
• Pembrolizumab treatment until disease progression or up to 35 cycles in the absence of
• disease progression:
• *to begin on study day 15 for subjects in cohort Ia
OR

• *to begin on study day 19 for subjects in cohort IIa and IIIa
• A safety follow-up visit after 30 days (+ 7 days) of last dose of each protocol specified
therapy.
Follow-up for survival and collection of subsequent anticancer therapies will occur every 12 weeks (± 28 days) following blinatumomab safety follow-up visit until approximately 24 months from the last dose of pembrolizumab. For complete details regarding design and escalation rules, please refer to Section 3.

Intervention

Please refer to section study design

Study burden and risks

See E9 and E9a

Contacts

Public
Amgen

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NL
Scientific
Amgen

Minervum 7061
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

This study seeks to enroll adult subjects with histologically confirmed Diffuse Large B Cell Lymphoma that is either:
-refractory after at least one regimen of systemic chemotherapy and/or targeted therapy, and refractory is defined as progressive or stable disease as the best response to the most recent systemic chemotherapy regimen or disease progression or relapse within 12 months after autologous stem cell transplantation; when using PET for assessment, for subjects with refractory disease and who have received radiotherapy, PET positivity should be demonstrated no less than 6 weeks after the last dose of radiotherapy (Crump et al, 2017; Neelapu et al, 2017; Cheson et al, 2007), or
-in first or later relapse if have received at least 2 systemic regimens since time of diagnosis, or
-relapsed post autologous or allogeneic HSCT with adequate organ function after proximity to transplantation time exclusions as specified in Exclusion Criteria 208 and 209.
For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2

Exclusion criteria

Subjects will be excluded if they have Richter's transformation (DLBCL arising in the setting of
prior chronic lymphocytic leukemia) or Primary Mediastinal B cell Lymphoma (PMBCL) or have
history or presence of clinically relevant central nervous system (CNS) pathology such as
epilepsy, paresis, aphasia, stroke, severe brain injury, dementia, Parkinson*s disease, cerebellar disease, organic brain syndrome, or psychosis or has evidence of active, non-infectious
pneumonitis, or has a history of interstitial lung disease.
For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	03-03-2020
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Blincyto
Generic name:	Blinatumomab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Keytruda
Generic name:	pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-12-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	01-07-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2021
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2021
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	EUCTR2016-002191-27-NL
ClinicalTrials.gov	NCT03340766
CCMO	NL67477.078.18

Study results

Date completed:	08-01-2021
Results posted:	22-02-2024

First publication
01-01-1900