A Randomized Multicenter, Open-label, Phase 2 Study Evaluating the Efficacy and Safety of Azacitidine Subcutaneous in Combination With Durvalumab (MEDI4736) in Previously Untreated Subjects with Higher-Risk Myelodysplastic Syndromes (MDS) or in Elderly (>= 65 years) Acute Myeloid Leukemia (AML) Subjects Not Eligible for Hematopoietic Stem Cell Transplantation (HSCT).

Published: 03-02-2016
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Primary Objective:Efficacy:· Evaluate the efficacy of subcutaneous (sc) azacitidine in combination with durvalumab as compared with subcutaneous azacitidine alone in the defined study population.Secondary Objectives:Safety:· Assess the safety and...

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

Summary

ID

NL-OMON46021

Source
ToetsingOnline

Brief title
FUSION HR MDS/ELDERLY AML 001 STUDY

Condition

- Other condition
- Plasma cell neoplasms
- Leukaemias

Synonym
MYELODYSPLASTIC SYNDROMES (MDS)

Health condition

MYELODYSPLASTIC SYNDROMES (MDS)

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Celgene International

Intervention

Keyword: AML 001 STUDY, FUSION HR MDS

Outcome measures

Primary outcome

The primary objective of the study is to evaluate the efficacy of subcutaneous

azacitidine in combination

with durvalumab as compared with subcutaneous azacitidine alone in the defined

study population.

Secondary outcome

. Assess the safety and tolerability of subcutaneous azacitidine in

combination with

durvalumab as compared with subcutaneous azacitidine alone in the defined study

population

. Assess the pharmacokinetics (PK) of durvalumab when given in combination with

subcutaneous azacitidine in the defined study population.

Study description

Background summary

1.1.1. Rationale for the Study Design and Choice of Control Arm
· Although historical data with azacitidine in higher-risk MDS and AML is available, these data have been generated in a population that varies from that proposed in this study due to the differences in the prognostic classification (shift in the MDS/AML definition from 30% to 20% blasts) risk classification (move from IPSS to IPSS-R in MDS) and response criteria have evolved over time.
· This study will be conducted as a randomized Phase 2 study with two separate disease cohorts. The randomization will allow having a controlled study design with internal consistency being independent from historic control.
· Both MDS and AML indications will be assessed in one study. Standard treatment with azacitidine will be the same for both cohorts. Potential study subjects will be assigned during screening to the MDS or AML cohort according to their percentage of blasts.
· The selection of higher-risk MDS is based on the IPSS-R. Subjects with IPSS-R intermediate risk in combination with > 10% bone marrow blasts, poor or very poor cytogenetics are also eligible as these risk factors have poor survival rates of less than 1.5 years (Greenberg, 2012).
· Both MDS and AML will be analyzed in separate cohorts as assessment of MDS and AML has evolved differently with specific response assessment guidelines and specific inclusion criteria. In addition there is a major difference in the outcome for MDS and AML which makes separate analysis for MDS and AML required.
· Azacitidine is approved globally and is the standard of care for higher-risk MDS. A positive opinion by the EMA CHMP for the treatment of elderly AML was obtained in September 2015 and in October 2015 the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has approved an expanded indication for the treatment of adult patients aged 65 years or older with AML who are not eligible for HSCT. The expanded indication now covers patients who have > 30% myeloblasts according to the WHO classification; previously, the indication covered AML patients with <= 30% blasts.
· The primary endpoint ORR was chosen to allow early assessment of activity of the combination treatment in comparison to standard treatment. Time-to-event data (OS, PFS and other) will be analyzed as secondary endpoints for this Phase 2 trial.
· The interim analysis on futility will support early assessment of efficacy and may minimize the number patients exposed to the investigational regimen in the absence of signs of efficacy.

· The combination of azacitidine and durvalumab is currently being evaluated in other studies. Currently there is no evidence for drug interactions in terms of dosing or overlapping toxicity. The combination of azacitidine with other PD-1 inhibitors (nivolumab, pembrolizumab) and PD-L1 inhibitors (atezolizumab) are under clinical investigation.
· The azacitidine dosing schedule for MDS and AML is identical (as per the EU approved dosing regimen). Due to the similar nature of MDS and AML in terms of toxicity, dose regimens will be identical in both disease cohorts.

Study objective

Primary Objective:
Efficacy:
· Evaluate the efficacy of subcutaneous (sc) azacitidine in combination with durvalumab as compared with subcutaneous azacitidine alone in the defined study population.
Secondary Objectives:
Safety:
· Assess the safety and tolerability of subcutaneous (sc) azacitidine in combination with durvalumab compared with subcutaneous azacitidine alone in the defined study population.
Pharmacokinetics:
· To assess the pharmacokinetics (PK) of durvalumab when given in combination with subcutaneous azacitidine in the defined study population.

Study design

This is a randomized, multicenter, open-label, Phase 2 study evaluating the efficacy and safety of subcutaneous azacitidine in combination with durvalumab in two separate cohorts. Cohort 1 comprises subjects with previously untreated MDS IPSS-R intermediate risk (in combination with more than 10% bone marrow blasts or poor or very poor IPSS-R cytogenetic risk), IPSS-R high and IPSS-R very high risk, who are not eligible for HSCT. Cohort 2 comprises subjects with previously untreated AML who are elderly (>= 65 years) and not eligible for HSCT, with intermediate or poor cytogenetic risk.
Subjects will be randomized (1:1 ratio) to receive one of the two treatment arms:
· Arm A (subcutaneous azacitidine plus durvalumab)
· Arm B (subcutaneous azacitidine alone)
The randomization process will aim to balance prognostic factors between study arms. For both cohorts (MDS and AML), subjects will be randomized and stratified according to their cytogenetic risk:
· Intermediate versus poor for AML (Appendix J),
· Very good, good and intermediate versus poor and very poor for MDS (Appendix H).
The randomized study will be conducted in 2 stages, with an interim analysis

for futility purpose for each of the 2 disease cohorts as outlined in Section 9 of the protocol. The primary analysis will follow completion of Stage 2 (ie after all subjects have completed 6 cycles and had disease assessment) with additional analyses conducted approximately 12 months after the last subject is enrolled, as described in Section 9 of the protocol. In addition an early safety monitoring will be performed using approximately the first 12 subjects randomized.

Intervention

see appendix 2 of the sisicf

Study burden and risks

The risk benefit assessment is included in the submission package as section D2a.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For both cohorts:
1. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
2. Have an ECOG performance status of 0, 1, or 2 (Appendix E).
3. Female subjects of childbearing potential may participate, providing they meet the following conditions:
a. Have 2 negative pregnancy tests as verified by the Investigator prior to starting any IP therapy: serum pregnancy test at screening and negative serum or urine pregnancy test (Investigator's discretion) within 72 hours prior to starting treatment with IP (Cycle 1, Day 1). They must agree to ongoing pregnancy testing during the course of the study (before beginning each subsequent cycle of treatment), and after the last dose of any IP. This applies even if the subject practices complete abstinence from heterosexual contact.
b. Agree to practice true abstinence (which must be reviewed on a monthly basis and source documented) or agree to the use of a highly effective method of contraception from 28 days prior to starting durvalumab or azacitidine, and must agree to continue using such precautions while taking durvalumab or azacitidine (including dose interruptions) and for up to 90 days after the last dose of durvalumab or azacitidine. Cessation of contraception after this point should be discussed with a responsible physician.
c. Agree to abstain from breastfeeding during study participation and for at least 90 days after the last dose of IP.
d. Refrain from egg cell donation while taking durvalumab and for at least 90 days after the last dose of durvalumab.
4. Male subject must:
a. Either practice true abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to avoid fathering a child, to use highly effective methods of contraception, to use male condom plus spermicide during sexual contact with a pregnant female or a female of childbearing potential (even if he has undergone a successful vasectomy) from starting dose of IP (Cycle 1 Day 1), including dose interruptions through 90 days after receipt of the last dose of durvalumab or azacitidine.
b. Refrain from semen or sperm donation while taking IP and for at least 90 days after the last dose of IP.;More inclusion criteria can found in the protocol version 17Nov2015 on page 47.

Exclusion criteria

For both cohorts:
1. Prior hematopoietic stem cell transplant.
2. Considered eligible for hematopoietic stem cell transplant (allogeneic or autologous) at the

time of signing the ICF.
3. Prior exposure to azacitidine, decitabine or prior exposure to the investigational oral formulation of decitabine, or other oral azacitidine derivative.
4. Inaspirable bone marrow.
5. Use of any of the following within 28 days prior to the first dose of IP:
· Thrombopoiesis-stimulating agents (eg, romiplostim, eltrombopag, Interleukin-11)
· Any hematopoietic growth factors (ESAs and other RBC hematopoietic growth factors (eg, Interleukin-3)
· Any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment ;More exclusion criteria can found in the current protocol version, and clinical trial application form.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Durvalumab
Generic name:	Durvalumab
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Vidaza®
Generic name:	Azacitidine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-02-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2017
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	EUCTR2015-003596-30-NL
ClinicalTrials.gov	NCT02775903;U1111-1182-9884
CCMO	NL56382.029.16

Study results

Results posted: 11-01-2023

Summary results
Trial never started

First publication
01-01-1900