HOVON 133 MCL/TRIANGLE: autologous Transplantation after a Rituximab/Ibrutinib/Ara-c containing iNduction in Generalized mantle cell Lymphoma - a randomized European MCL Network trial

Published: 18-04-2017
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-511235-10-00 check the CTIS register for the current data. To establish one of three study arms, R-CHOP/R-DHAP followed by ASCT (control arm A), R-CHOP + ibrutinib / R-DHAP followed by ASCT and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON55612

Source
ToetsingOnline

Brief title
HOVON 133 MCL / TRIANGLE

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Mantle cell lymphoma, MCL

Research involving

Human

Sponsors and support

Primary sponsor: Klinikum der Universitat Munchen
Source(s) of monetary or material Support: Janssen-Cilag,KWF subsidie aangevraagd

Intervention

Keyword: Autologous transplantation, Ibrutinib, mantle cell lymphoma

Outcome measures

Primary outcome

FFS defined as time from randomization to stable disease at end of

immuno-chemotherapy, progressive disease, or death from any cause.

Secondary outcome

Secondary Efficacy Endpoints:

-Overall survival (OS)

-Progression-free survival (PFS) from randomization, from end of induction

immuno-chemotherapy in patients with CR or PR at end of induction

immuno-chemotherapy, and from the staging 6 weeks after end of induction

assessment (at month 6)

-Overall response and complete remission rates at midterm, at end of induction,

3 months after end of induction immuno-chemotherapy (at month 6)

-PR to CR conversion rate during follow-up after end of induction

immuno-chemotherapy

Secondary Toxicity Endpoints:

-Rates of AEs, SAEs, and SUSARs by CTC grade (Version 4.03) during induction

immuno-chemotherapy and during periods of follow-up after response to

immune-chemotherapy

-Cumulative incidence rates of SPMs

Study description

Background summary

According to current European guidelines, the standard of care in younger patients with mantle cell lymphoma (MCL) is a dose-intensified approach with a cytarabine containing immunochemotherapy induction followed by autologous transplantation. Ibrutinib has recently shown impressive efficacy data in relapsed MCL while tolerability was rather favorable.
Based on these prerequisites, our study proposal challenges the current standard of care and questions, whether the addition of ibrutinib (arm A+I) to the standard (control arm A) results in a superior clinical outcome. In addition, we investigate whether ASCT which sometimes is hampered by short and long term toxicity is still superior to a (hopefully much better tolerated) conventional treatment without ASCT and with the addition of ibrutinib in induction and maintenance (duration 2 years, arm I and A+I). As so far combination data are only available with the R-CHOP regimen but not for the alternating R-DHAP regimen.16 Ibrutinib will be only given during the R-CHOP regimen, and during an initial safety run-in phase 50 patients randomized will be closely monitored for the observed toxicities during induction therapy.
Analysis of minimal residual disease (MRD) will play a critical role in identifying specific patient subpopulations which may be especially prone to one of the three therapeutical strategies.
Finally, the recently completely recruited LyMa trial has proven a benefit of rituximab maintenance after an ASCT. Therefore, rituximab maintenance will be added to all 3 study arms in the Netherlands.

Study objective

This study has been transitioned to CTIS with ID 2024-511235-10-00 check the CTIS register for the current data.

To establish one of three study arms, R-CHOP/R-DHAP followed by ASCT (control arm A), R-CHOP + ibrutinib / R-DHAP followed by ASCT and ibrutinib maintenance (experimental arm A+I), and R-CHOP + ibrutinib / R-DHAP followed by ibrutinib maintenance (experimental arm I) as future standard based on the comparison of the investigator-assessed failure-free survival (FFS).

Study design

Randomized, three-arm, parallel-group, open label, international phase III trial comparing six alternating courses of R-CHOP/R-DHAP (one cycle every 21 days) followed by ASCT versus the combination with ibrutinib in induction and maintenance (2 years) or the experimental arm without ASCT

Intervention

Arm A: standard of care. Alternating 3 cycles R-CHOP / 3 cycles R-DHAP induction followed by ASCT.
Experimental arm A+I. Alternating 3 cycles R-CHOP+Ibrutinib / 3 cycles R-DHAP induction, followed by ASCT and 2 years Ibrutinib-Maintenance.
Experimental Arm I. Alternating 3 cycles R-CHOP + Ibrutinib / 3 cycles R-DHAP induction, followed by 2 years ibrutinib-maintenance.

Study burden and risks

Participation in this study will be associated with extra investigations compared to standard patient care.
Although most investigations are standard care, patients will have to visit the hospital more frequently.
During maintenance/observation a CT-scan will be performed regularly.
When given consent, extra investigations consist of MRD measurement in blood and bone marrow.
It is possible that the patient will experience different adverse events in comparison to standard care.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

-Histologically confirmed diagnosis of MCL according to WHO classification
-Suitable for high-dose treatment including high-dose Ara-C
-Stage II-IV (Ann Arbor)
-Age >= 18 years and <= 65 years
-Previously untreated MCL
-At least 1 measurable lesion; in case of bone marrow infiltration only, bone marrow aspiration and biopsy is mandatory for all staging evaluations.
-ECOG/WHO performance status <= 2
-The following laboratory values at screening (unless related to MCL):
-Absolute neutrophil count (ANC) >=1000 cells/µL
-Platelets >=100,000 cells/µL
-Transaminases (AST and ALT) <=3 x upper limit of normal (ULN)
-Total bilirubin <=2 x ULN unless due to known Morbus Meulengracht [Gilbert-Meulengracht- Syndrome])
-Creatinine <=2 mg/dL or calculated creatinine clearance >= 50 mL/min
-Written informed consent form according to ICH/EU GCP and national regulations
-Sexually active men and women of child-bearing potential must agree to use one of
the highly effective contraceptive methods (combined oral contraceptives using two
hormones, contraceptive implants, injectables, , intrauterine devices, sterilized
partner) together with one of the barrier methods (latex condoms, diaphragms, contraceptive caps) while on study; this should be maintained for 90 days after the last dose of study drug and 12 months after the last dose of rituximab.

Exclusion criteria

-Major surgery within 4 weeks prior to randomization.
-Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon).
-History of stroke or intracranial hemorrhage within 6 months prior to randomization.
-Requires treatment with strong CYP3A4/5 inhibitors.
-Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator*s opinion, could compromise the subject*s safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.
-Vaccinated with live, attenuated vaccines within 4 weeks prior to randomization.
-Known CNS involvement of MCL
-Clinically significant hypersensitivity (e.g., anaphylactic or anaphylactoid reactions to the compound of ibrutinib itself or to the excipients in its formulation)
-Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies
-Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon except prephase therapy outlined in this trial protocol
-Serious concomitant disease interfering with a regular therapy according to the study protocol:
-Cardiac (Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification or LVEF below LLN)
-Pulmonary (chronic lung disease with hypoxemia)
-Endocrinological (severe, not sufficiently controlled diabetes mellitus)
-Renal insufficiency (unless caused by the lymphoma): creatinine > 2x normal value and/or creatinine clearance < 50 ml/min)
-Impairment of liver function (unless caused by the lymphoma): transaminases > 3x normal or bilirubin > 2,0 mg/dl unless due to Morbus Meulengracht (Gilbert-Meulengracht-Syndrome)
-Positive test results for chronic HBV infection (defined as positive HBsAg serology) (mandatory testing)
Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody (HBSAb) after vaccination are eligible.
-Positive test results for hepatitis C (mandatory hepatitis C virus [HCV] antibody serology testing). Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

-Patients with known HIV positive infection (mandatory test).
-Prior organ, bone marrow or peripheral blood stem cell transplantation
-Concomitant or previous malignancies within the last 3 years other than basal cell skin cancer or in situ uterine cervix cancer
-Pregnancy or lactation
-Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule
-Subjects not able to give consent
-Subjects without legal capacity who are unable to understand the nature, scope, significance and consequences of this clinical trial
-Participation in another clinical trial within 30 days before randomization in this study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-11-2017
Enrollment:	140
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Imbruvica
Generic name:	Ibrutinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2024
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
EU-CTR	CTIS2024-511235-10-00
EudraCT	EUCTR2014-001363-12-NL
CCMO	NL56406.078.16