A randomized phase II multicenter study to assess the tolerability and efficacy of the addition of ibrutinib to 10-day decitabine in UNFIT (i.e. HCT-CI >= 3) AML and high risk myelodysplasia (MDS) (IPSS-R > 4.5) patients aged >= 66 years.
A study in the frame of the masterprotocol of parallel randomized phase II studies in UNFIT-older AML/high-risk MDS patients

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Primary objectives1. To assess in a randomized comparison the effect of Ibrutinib added to 10-day decitabine treatment on the cumulative CR/CRi rate after 3 cycles.Secondary objectives1. To assess the safety and tolerability of Ibrutinib added to 10...

Ethical review	Approved WMO
Status	Pending
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON53140

Source
ToetsingOnline

Brief title
HOVON 135 AML

Condition

- Leukaemias

Synonym
Acute myeloid leukemia, myelodysplastic syndromes

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Janssen-Cilag International NV,Stichting HOVON;Janssen-Cilag International NV;subsidie aangevraagd bij KWF

Intervention

Keyword: AML/MDS, Decitabine, Ibrutinib, UNFIT

Outcome measures

Primary outcome

• Cumulative CR/CRi rate after 3 cycles

Secondary outcome

• Safety and tolerability (frequency and severity of toxicities and the

durations of neutropenia and thrombocytopenia).

• Efficacy profile (response rate (CR, CRi, PR), event free survival (EFS) and

overall survival (OS)).

• Days of staying in hospital and transfusion needs.

• Prognostic value of MRD (by flowcytometry or PCR).

• Gene mutations predictive of response, EFS and OS by exploratory analysis.

• Prognostic value of baseline physical and functional conditions using

comprehensive geriatric assessment tools (short physical performance battery

(SPPB) and activities of daily living (ADL) on treatment outcome.

Translational endpoints

• To determine the impact of 3 days ibrutinib monotherapy (pre-treatment) on WBC count, circulating blast count, and kinome (using mass cytometry kinome).

• To identify potential biomarkers (using mass cytometry kinome; methylome) in bone marrow and peripheral blood which are of prognostic importance in both arms, and whether they are of predictive importance for response.

• To identify methylome profiles in CD34+ bone marrow blasts and stroma cells which are of prognostic importance in both arms, and whether they are of predictive importance for response.

Study description

Background summary

This trial aims to develop effective treatments for UNFIT (i.e. hematopoietic cell transplantation co-morbidity index (HCT-CI) >= 3) in older (>= 66 yrs) AML patients, for whom current treatment strategies are highly unsatisfactory. Therefore new treatment modalities are introduced and evaluated in multiple parallel randomized phase II studies that will be conducted within the frame of a master protocol. The scheme of this new design consists of one arm with one of the currently considered best available treatments for UNFIT older AML patients (i.e. 10-day decitabine). After a maximum of 3 10-day courses, or less in case of good response, treatment will be continued with 5-day decitabine courses. This treatment will be compared to investigational treatments in combination with decitabine.

The first competitor of the 10-day decitabine schedule will be 10-day decitabine combined (sequential) with the BTK inhibitor ibrutinib. The rationale for ibrutinib is:1) its high expression and phosphorylation in AML cell lines and CD34+ AML blasts; 2) the central role of BTK within many important signaling pathways in AML (e.g. CXCR4, TLR, Flt3-ITD); 3) the in-vitro activity of ibrutinib against AML blasts; 4) extensive experience with

ibrutinib combined with chemotherapy in mantle cell lymphoma and CLL.

Study objective

Primary objectives
1. To assess in a randomized comparison the effect of Ibrutinib added to 10-day decitabine treatment on the cumulative CR/CRi rate after 3 cycles.

Secondary objectives
1. To assess the safety and tolerability of Ibrutinib added to 10-day decitabine treatment for AML (frequency and severity of toxicities and the durations of neutropenia and thrombocytopenia).
2. To determine the efficacy profile: response rate (CR, CRi, PR), event free survival (EFS) and overall survival (OS) associated with the two therapy regimens (i.e. decitabine vs decitabine + ibrutinib.
3. To determine the impact of 3 days ibrutinib monotherapy (pre-treatment) on WBC count, circulating blast count, and translational endpoints (mass cytometry).
4. To measure MRD by immunophenotyping and PCR in relation to clinical response parameters.
5. To identify potential biomarkers predictive of response, EFS and OS by exploratory analysis (gene mutations, kinome, methylome).
6. To evaluate the prognostic value of baseline physical and functional conditions using comprehensive geriatric assessment tools (short physical performance battery (SPPB) and activities of daily living (ADL) on treatment outcome).

Study design

This is a prospective, open label, multicenter study that is conducted in the frame of a masterprotocol with multiple parallel randomized phase II arms.

Intervention

Patients in this study are treated with 10-day decitabine treatment with or without ibrutinib. The starting dose of ibrutinib will be 560 mg once daily. During the part A run-in phase the dose level of ibrutinib will be established.

Study burden and risks

The benefit of this study is that older AML patients with co-morbidities: 1) do not receive toxic intensive chemotherapy (which has been shown to be associated with an almost 30% day-28 mortality); 2) do receive treatment (instead of not being considered for treatment at all).
The burden and risks associated with participation mainly involve an additional bone marrow aspirate and blood draw at day+1 in arm B and taking off additional

material during routine examinations (blood draws/bone marrow aspirates). Furthermore, a geriatric assessment will be performed.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)

Inclusion criteria

• Patients with:
- a diagnosis of AML and related precursor neoplasms according to WHO 2008 classification (excluding acute promyelocytic leukemia) including secondary AML (after an antecedent hematological disease (e.g. MDS) and therapy-related AML, or
- acute leukemia's of ambiguous lineage according to WHO 2008 or
- a diagnosis of refractory anemia with excess of blasts (MDS) and IPSS-R > 4.5
• Patients 66 years and older.

• Patients NOT eligible for standard chemotherapy, defined as HCT-CI >= 3. OR patient NOT eligible for standard chemotherapy for other reasons (wish of patient).
• WBC <= 30 x10^9/L (prior hydroxyurea allowed for a maximum of 5 days, stop 2 days before start decitabine treatment)
• Adequate renal and hepatic functions unless clearly disease related
• WHO performance status 0, 1 or 2
• Male patients must use an effective contraceptive method during the study and for a minimum of 6 months after study treatment.
• Written informed consent.

Exclusion criteria

• Acute promyelocytic leukemia.
• Patients previously treated for AML (any antileukemic therapy including investigational agents), a short treatment period (<= 5 days) with Hydroxyurea is allowed
• Diagnosis of any previous or concomitant malignancy is an exclusion criterion: except when the patient completed successfully treatment (chemotherapy and/or surgery and/or radiotherapy) with curative intent for this malignancy at least 6 months prior to randomization.
• Blast crisis of chronic myeloid leukemia.
• Inability to discontinue anti-coagulants
• Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease etc.)
• Cardiac dysfunction
• Patient has had major surgery within the past 4 weeks or a major wound that has not fully healed.
• Vaccinated with live, attenuated vaccines within 4 weeks prior to randomization.
• History of stroke or intracranial hemorrhage within 6 months prior to randomization.
• Patient has a history of human immunodeficiency virus (HIV) or active infection with Hepatitis C or B.
• Patient has symptomatic central nervous system (CNS) leukemia (NO routinely lumbar puncture required to investigate CNS involvement)
• Patients with a history of non-compliance to medical regimens or who are considered unreliable with respect to compliance.
• Patients with any serious concomitant medical condition which could, in the opinion of the investigator, compromise participation in the study.
• Patients who have senile dementia, mental impairment or any other psychiatric disorder that prohibits the patient from understanding and giving informed consent.
• Current concomitant chemotherapy, radiation therapy, or immunotherapy; other than hydroxyurea

• Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

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:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-02-2016
Enrollment:	70
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Dacogen
Generic name:	Decitabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	IMBRUVICA
Generic name:	ibrutinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-11-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-03-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2015-002855-85-NL
CCMO	NL55164.042.15