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.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON19923

Source
Nationaal Trial Register

Brief title
HOVON 135 AML

Health condition

Acute Myeloid Leukemia (AML), Myelodysplasia

Sponsors and support

Primary sponsor: HOVON Data Center
Source(s) of monetary or material Support: KWF Kankerbestrijding, HOVON, Janssen Pharmaceutica NV

Intervention

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 outcomes:

- 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

Randomized phase II study

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).

Patient population:

Patients with AML (except FAB M3) or high risk MDS (IPSS-R > 4.5), previously untreated, age >= 66 yrs AND Hematopoietic Cell Transplantation Co-morbidity Index (HCT-CI) >= 3.

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.
The scheme of this design consists of one arm with the standard treatment for AML (the 10-day decitabine schedule) as compared to various arms with experimental treatments.

Duration of treatment:

Expected duration of 3 cycles of 10-day decitabine with or without Ibrutinib, including evaluation, is about 4-5 months. Continuation treatment (5-day decitabine with or without Ibrutinib) will last until progression

All patients will be followed until 5 years after registration. Patients who are still on continuation treatment at 5 years after registration will be followed until progression or death.

Target number of patients:

Per treatment arm a maximum of 70 patients at the final dose level.

Study objective

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.

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).

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.

To determine the impact of 3 days ibrutinib monotherapy (pre-treatment) on WBC count, circulating blast count, and translational endpoints.

To measure MRD by immunophenotyping and PCR in relation to clinical response parameters.

To identify potential biomarkers predictive of response, EFS and OS by exploratory analysis.

To evaluate the prognostic value of baseline physical and functional conditions using comprehensive geriatric assessment tools

Study design

Clinical, laboratory and questionnaire evaluations:
1; at entry
2; after cycle 1, 2 and 3
3; during continuation treatment
4; at off protocol treatment or relapse
5; during follow up (evry 3-6 months)

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.

Contacts

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Eligibility criteria

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 as indicated by the following laboratory values:

- Serum creatinine =< 2.5 mg/dL (=< 221.7 ìmol/L), unless considered AML-related

- Serum bilirubin =< 2.5 x upper limit of normal (ULN), unless considered AML-related or due to Gilbert’s syndrome

- Alanine transaminase (ALT) =< 2.5 x ULN, unless considered AML-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.

♦ Patient is capable of giving 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 any anti-coagulants (including ascal)
♦ Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease etc.)

♦ Cardiac dysfunction as defined by:
- Myocardial infarction within the last 3 months of study entry, or
- Reduced left ventricular function with an ejection fraction < 40% as measured by MUGA scan or echocardiogram or
- Unstable angina or
- New York Heart Association (NYHA) grade IV congestive heart failure (see Appendix I) or
- Unstable cardiac arrhythmias
♦ 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 type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-09-2016

Enrollment:	185
Type:	Anticipated

Ethics review

Positive opinion Date:	06-09-2016
Application type:	First submission

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
NTR-new	NL5751
NTR-old	NTR6017
Other	2015-002855-85 : HO135

Study results

Summary results
N/A