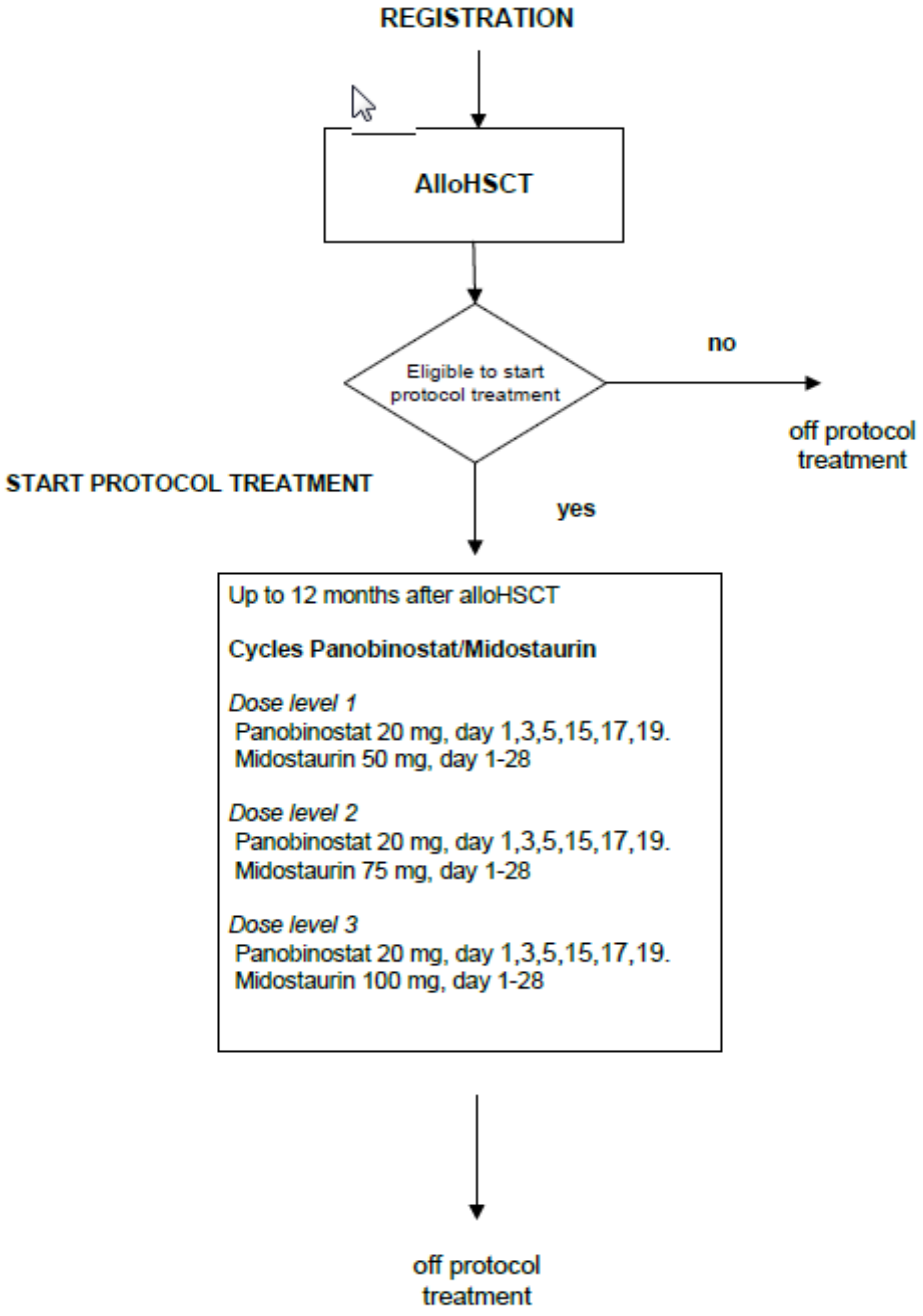
SAMENVATTING HOVON 148

TITEL phase Ib feasibility study of the combination of panobinostat and midostaurin in recipients of allogeneic stem cell transplantation with FLT3-ITD AML

INDICATIE Patients 18-70 years with adverse risk AML or RAEB with IPSS-R >= 4.5 AND with FLT3-ITD with high allelic ratio (>0.5), either newly diagnosed or in first relapse having obtained remission after induction chemotherapy and qualifying for alloHSCToff

SCHEMA



9.1.1 Treatment schedule

Patients will receive combination therapy of panobinostat and midostaurin up to 12 months after alloHSCT. **Patient will be treated at the applicable dose level at that moment.**

Dose level 1

Agent	Dose/day	Route of administration	Days
Panobinostat	20 mg	Oral	1,3,5,15,17,19.
Midostaurin	50 mg divided as 25 mg twice a day	Oral	1-28

Dose level 2

Agent	Dose/day	Route of administration	Days
Panobinostat	20 mg	Oral	1,3,5,15,17,19.
Midostaurin	75 mg divided as 50 mg AM and 25 mg PM	Oral	1-28

Dose level 3

Agent	Dose/day	Route of administration	Days
Panobinostat	20 mg	Oral	1,3,5,15,17,19.
Midostaurin	100 mg given as 50 mg twice daily	Oral	1-28

The first cycle of combination therapy will start between day 30 and day 65 after alloHSCT upon meeting the eligibility criteria as mentioned in section 8.2.
Every next cycle of combination therapy is given at day 29 after start of the previous cycle, or as soon as possible thereafter upon hematological recovery, requiring neutrophils ≥ 1.0 x10^9/L and platelets ≥ 50x 10^9/L. *Do not give the next cycle at a reduced dose but delay if required.*
If a next cycle cannot be started before day 50 after the previous cycle of combination therapy, the patient will go off protocol treatment.

Eligibility for registration

All patients must be registered before alloHSCT and must meet all of the following eligibility criteria

INCLUSIE CRITERIA

♦ Adult patients (18-70 years of age);
♦ AML (except acute promyelocytic leukemia, AML M3 and bcr/abl positive AML) according to WHO 2016 classification (Appendix A) or RAEB with IPSS-R > 4.5 with high mutant to wild-type allelic ratio of FLT3-ITD;
♦ Newly diagnosed or in first relapse having obtained remission after induction chemotherapy;
♦ First allogeneic HSCT scheduled within the next 2 months upon having achieved hematological remission (< 5% blasts at the bone marrow level);
♦ Matched sibling or matched unrelated donor (i.e. 10/10 or 9/10 HLA-matched) or haploidentical donor;
♦ Using one of the following conditioning regimens:
- Fludarabine/Cyclophosphamide/TBI 2 Gy in combination with post-Tx cyclophosphamide (PT-CY) only;
- Fludarabine/Busulfan or Melphalan/Fludarabine/TBI or fludarabin/TBI 8 Gy with post-transplant cyclophosphamide
or one of the alternative regimen in appendix B; NB: Preferably using for GvHD prophylaxis:
- HLA-matched donors: PT-CY + CSA (or tacrolimus)
- Haploidentical donors: PT-CY + CSA (or tacrolimus) + MMF
♦ No history of significant cardiac disease and absence of active symptoms, otherwise documented left ventricular EF > 40%;
♦ Negative serum pregnancy test for female patients of childbearing potential, at registration;

♦Female patients of childbearing potential and all men must be willing and able to use an effective contraceptive method during the study and for a minimum of 6 months after study treatment;
♦ Written informed consent.

EXCLUSIE CRITERIA

♦ Known HIV or HCV positivity;
♦ History of active malignancy during the past 2 years with the exception of basal carcinoma of the skin or carcinoma “in situ” of the cervix or breast;
♦ Pregnant or breast-feeding female patients.
♦ Psychiatric disorder that interferes with ability to understand the study and give informed consent, and/or impacts study participation or follow-up;

Eligibility criteria for start of protocol treatment after alloHSCT

INCLUSIE CRITERIA

♦ Eastern Cooperative Group (ECOG)/WHO performance status ≤ 2 (Appendix D);
♦ Complete hematologic remission or complete hematologic remission with incomplete recovery (appendix C) documented by bone marrow aspiration;
♦ Laboratory test results maximum 14 days prior to start protocol treatment within the following ranges:
- Absolute neutrophil count ≥ 1.0 x 109/L
- Platelet count ≥ 50 x 109/L
- Serum creatinine clearance > 35 mL/min
- Total bilirubin ≤ 2.5 x ULN
- AST (SGOT) and ALT (SGOT) ≤ 3 x ULN
♦ Negative serum pregnancy test (within 14 days prior to start protocol treatment) in women of child-bearing potential (WOCBP);
♦ Willingness of WOCBP to use double-barrier contraception or oral contraceptive plus barrier contraceptive during the study and for 6 months following the last dose of study drug, or must have undergone clinically documented total hysterectomy and/or bilateral oophorectomy, bilateral tubal ligation or be postmenopausal defined by amenorrhea for at least 12 months;
♦ Willingness of male subjects whose sexual partners are WOCBP to use a double barrier method of contraception or oral contraceptive (WOCBP) plus barrier contraceptive during the study and for 6 months following the last dose of study drug or the partner must have undergone clinically documented total hysterectomy and/or bilateral oophorectomy, bilateral tubal ligation or be postmenopausal defined by amenorrhea for at least 12 months.

EXCLUSIE CRITERIA

♦ Active acute GvHD grade III-IV according to modified Glucksberg criteria (Appendix G);
♦ Active acute GvHD grade II requiring systemic corticosteroids > 0.5 mg/kg body weight of methylprednisolone equivalent or combination immunosuppressive treatment;
♦ Uncontrolled or significant heart disease, including recent myocardiac infarction, cardiac failure (NYHA II-IV, appendix F), unstable angina pectoris, or clinically significant bradycardia;
♦ QTcF>480 msec on screening ECG (Bazett's formula) to be performed within 14 days prior to start protocol treatment;
♦ Concurrent use of medications that have a relative risk of prolonging QT interval or of inducing Torsade de Pointes, if such treatment cannot be discontinued or switched to a different medication prior to the first dose of study drug (see appendix H);
♦ Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes mellitus, chronic obstructive or chronic restrictive pulmonary disease including dyspnoea at rest from any cause) or history of serious organ dysfunction or disease involving the heart, kidney, or liver and/or seropositive HIV or HCV (screening HIV or HCV testing is not required);
♦ Serious active infection;
♦ CMV reactivation, which is not responsive to first-line valganciclovir or ganciclovir;

♦ Impaired of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral panobinostat (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, obstruction, or stomach and/or small bowel resection);
♦ Female patients who are pregnant or breast feeding;
♦ History of another primary malignancy that is currently clinically significant or currently requires active intervention;
♦ Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.