Trial Results Report[1]

Name of Sponsor/Company: Dekan des Fachbereichs Medizin der Goethe Universität - Frankfurt, Germany To be represented by the coordinating investigator (LKP according to German drug law)	Individual Study Table: [2] Not applicable	*For national authority use only*
Name of Finished Product: Farydak®,		
Name of Active Substance: Panobinostat		

Title of Study[3]

"European Intergroup Trial on panobinostat maintenance after HSCT for high-risk AML and MDS - A randomized, multicenter phase III study to assess the efficacy of panobinostat maintenance therapy vs. standard of care following allogeneic stem cell transplantation in patients with high-risk AML or MDS (ETAL-4 / HOVON-145)"

The trial has been conducted according to
Protocol Version 2.1 (21.12.2017)
Protocol Version 3.0 (03.08.2021)

Investigators

„Leiter der Klinischen Prüfung" according to German drug law:
PD Dr. Gesine Bug

Study centre(s)

18 hospitals

Publication (reference)

Due to premature recruitment stop after, only a descriptive evaluation and publication of data is planned.

[1] § 42b AMG (german drug law), according to ICH E3
[2] Referring to Part of the Dossier (Volume, Page)
Anmerkung: Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich
[3] Anmerkung: Es muss klar hervorgehen, dass die letzte Protokollversion einschließlich aller Amendments gemeint ist, die Amendments sind anzugeben und zu identifizieren

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Studied period (years): date of first enrolment, date of last completed[4]

24.07.2018 - First Patient registration

09.10.2019 - First patient randomization; First Patient In (FPI)

03.08.2020 – Enrolment/randomization of the last patient; Last Patient In (LPI)

04.08.2020 - Recruitment interruption due to change of Marketing Authorization Holder (MAH) and unsecure study medication supply for further patients

21.08.2020 – Premature recruitment stop
As a consequence of the change in MAH, the financial support contract was terminated by the new MAH and the study had to be terminated prematurely.

02.06.2021 - Last randomized patient End of Treatment (LP-EoT)

02.06.2022 – Last patient last visit (LPLV)

13.02.2023 – Data base closed, End of study

Phase of development
Phase III

Objectives

Primary objective:

- determine the efficacy of panobinostat maintenance therapy versus standard of care administered to patients with high-risk MDS or AML in complete hematologic remission after an allogeneic hematologic stem cell transplantation (HSCT)

Secondary objectives:

- To assess the safety and tolerability of panobinostat maintenance therapy after HSCT compared with standard of care
- To evaluate HRQoL of patients under panobinostat maintenance therapy after HSCT
- To study the treatment effect in subgroups of patients defined by treatment approach (i.e. HOVON-approach vs. RIC vs MAC conditioning), donor type (HLA-compatible versus haploidentical) and molecular distinct subgroups of AML/MDS

[4] Anmerkung: Hier sollen auch Studienunterbrechungen und vorzeitige Studienbeendigungen/ Studienabbrüche unter Angabe der Gründe aufgeführt werden

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Methodology

This trial was an open-label, multicenter, phase III study to evaluate the efficacy, safety and tolerability of panobinostat maintenance therapy vs. standard of care after allogeneic stem cell transplantation in adult patients with high-risk AML or MDS.

The primary objective was to determine the efficacy of panobinostat maintenance therapy versus standard of care administered to patients with high-risk MDS or AML in complete hematologic remission after an allogeneic hematologic stem cell transplantation (HSCT)

Number of patients (planned and analysed)

Planned subject number was 350 randomized patients with high-risk AML or MDS (protocol V2.1). Before halt of recruitment in August 2020, 52 patients had been enrolled and could be analyzed.

After halt of recruitment, the planned subject number was reduced to 52 randomized patients (protocol V3.0).

The descriptive analysis will be performed based on the data available from the closed database.

Diagnosis and main criteria for inclusion

Indication:
High-risk AML or MDS

Eligibility criteria for registration prior to HSCT:
Inclusion criteria:

- Adult patients (18-70 years of age)
- AML (except acute promyelocytic leukemia with PML-RARA and AML with BCR-ABL1) according to WHO 2016 classification (Appendix 1) with high-risk features defined as one or more of the following criteria:
  - refractory to or relapsed after at least one cycle of standard chemotherapy
  - > 10% bone marrow blasts at day 14-21 of the first induction cycle
  - adverse risk according to ELN 2017 risk stratification by genetics (Appendix 2) regardless of stage
  - secondary to MDS or radio-/chemotherapy
  - MRD positive before HSCT based on flow cytometry or PCR

or

- MDS with excess blasts (MDS-EB) according to the WHO 2016 classification (Appendix 3), or high-risk or very high-risk according to IPSS-R (Appendix 4)
- and
- First allogeneic HSCT scheduled within the next 4-6 weeks using one of the following donors, conditioning regimens (
- Appendix 5) and strategies for GvHD prophylaxis:
  a) Matched sibling or matched unrelated donor (i.e. 10/10 or 9/10 HLA-matched) or haploidentical family donor
  b) Conditioning regimens:
    (1) Reduced-intensity conditioning:
      - Fludarabine/Melphalan
      - Fludarabine/Busulfan2 (FB2)
    (2) Myeloablative conditioning:
      - Fludarabine/Busulfan4 (FB4)
      - Busulfan/Cyclophosphamide (BU/CY)
      - Fludarabine/TBI 8 Gy
      - Cyclophosphamide/TBI 12 Gy
    (3) Fludarabine/Cyclophosphamide/TBI 2 Gy in combination with post-Tx cyclophosphamide (PT-CY) only
    (4) Thiotepa/Busulfan/Fludarabine (TBF) in the context of an haploidentical HSCT only
    (5) In case of active disease at HSCT, salvage chemotherapy prior to conditioning is permitted
  c) Strategies for GvHD prophylaxis:
    (1) HLA-matched donors:
      - CSA + MMF +/- ATG
      - CSA + MTX +/- ATG
      - PT-CY + CSA
    (2) Haploidentical donors:
      - PT-CY + CSA + MMF
- No history of significant cardiac disease and absence of active symptoms, otherwise documented left ventricular EF ≥ 40%
- Written informed consent for registration

Exclusion criteria:

- Prior treatment with a DAC inhibitor
- HIV or HCV antibody positivity
- Psychiatric disorder that interferes with ability to understand the study and give informed consent, and/or impacts study participation or follow-up.
- Female patients who are pregnant or breast feeding
- History of another primary malignancy that is currently clinically significant or currently requires active intervention

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Enrolment after HSCT:
Inclusion criteria:

- Adult patients with high-risk AML or MDS as defined above

and

- First allogeneic HSCT performed within 30 - 65 days prior to enrollment
- Eastern Cooperative Group (ECOG) performance status ≤ 2 (Appendix 6)
- Complete hematologic remission or complete hematologic remission with incomplete recovery (see section 14.1) documented by bone marrow aspiration within 14 days prior to randomization
- Laboratory test results maximum 14 days prior to randomization within the following ranges:
  - Absolute neutrophil count ≥ 1.0 x 109/L
  - Platelet count ≥ 75 x 109/L
  - Potassium, magnesium and phosphate within normal limits
  - Serum creatinine clearance ≥ 30 mL/min
  - Total bilirubin ≤ 1.5 x ULN
  - AST (SGOT) and ALT (SGOT) ≤ 2.5 x ULN
- Negative serum pregnancy test (within 14 days prior to enrollment) in women of child-bearing potential (WOCBP)
- Written informed consent, willingness and ability to comply with all study procedures

Exclusion criteria:

- Active acute GvHD grade III-IV according to modified Glucksberg criteria (Appendix 7)
- Active acute GvHD grade II or chronic GvHD moderate/severe according to NIH criteria (Appendix 8) 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), unstable angina pectoris, or clinically significant bradycardia
- Long QT syndrome
- QTcF □480 msec on screening ECG to be performed within 14 days prior to enrollment
- 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 Table 9).
- 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 .
- Serious active infection
- CMV reactivation, which is not responsive to first-line valganciclovir or ganciclovir
- Impaired 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).

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Test product, dose and mode of administration, batch number

Panobinostat 20 mg three times weekly (TIW) every second week

Standard trading packages of Farydak 10 mg and 20 mg tablets have been provided for the trial. Used batch numbers are: BX274, BW618, BDH56, BDL72, BKF41, BKY23, BKY19, BJC60

Duration of treatment

Patients randomized into the treatment arm have received Panobinostat therapy until one year after HSCT as long as hematologic relapse of the disease has not been documented and study drug is tolerable.

Patients experiencing new CTCAE grade 3 non-hematologic AEs considered clinically relevant to the investigator and related to the study drug or any grade 4 AEs had their treatment temporarily discontinued until the adverse event resolved to CTCAE ≤ grade 1 or baseline unless otherwise specified below. If the AE was considered not related to panobinostat, then therapy was restarted when the AE resolves to ≤ grade 2.

In patients experiencing new CTCAE grade 2 non-hematologic events considered by the investigator to be clinically relevant and related to the study drug, it was at the discretion of the investigator to temporarily discontinue treatment until the adverse event resolved to CTCAE ≤ grade 1 or baseline unless otherwise specified below.

After treatment interruption, the patient should wait to take panobinostat until the next schedule treatment day and continue treatment according to the original dosing schedule.

If a patient required a dose delay of > 42 days from the intended day of the next scheduled dose, then the patient had to discontinue panobinostat treatment permanently.

Reference therapy, dose and mode of administration, batch number

Patients randomized to the standard of care arm have been treated according to local standards.

Criteria for evaluation:

Efficacy: The primary endpoint was overall survival, secondary endpoints event-free survival, disease-free survival, cumulative incidence of relapse and cumulative incidence of non-relapse mortality. Due to premature termination of the trial, the analysis of all endpoints is considered to be exploratory.

Safety: Incidence and intensity of adverse events graded according to CTCAE, version 4.0

Statistical methods

Not applicable.

Summary – Conclusions:

Demographic and baseline characteristics of 52 patients randomized were well balanced, except for sex and primary diagnosis:

		Panobinostat N=27	Standard of Care N=25	p*	All patients
Age (N=52)	Median (Min – Max)	52 (21-65)	56 (22-71)		55 (21-71)
	18-25	3 (11%)	1 (4%)	>.05	4 (8%)
	26-35	3 (11%)	1 (4%)		4 (8%)
	36-45	3 (11%)	3 (12%)		6 (12%)
	46-55	6 (22%)	6 (24%)		12 (23%)
	56-65	12 (44%)	11 (44%)		23 (44%)
	66-75	0	3 (12%)		3 (6%)
Sex (N=52)	Male	9 (33%)	20 (80%)	0.0007	29 (56%)
	Female	18 (67%)	5 (20%)		23 (44%)
Initial diagnosis (N=52)	AML	26 (96%)	19 (76%)	0.046	45 (87%)
	MDS	1 (4%)	6 (24%)		7 (13%)
Relapse (N=52)	yes	4 (15%)	4 (16%)	>.05	8 (15%)
	no	23 (85%)	21 (84%)		44 (85%)
Extramedullary manifestations (N=52)	yes	1 (4%)	1 (4%)	>.05	2 (4%)
	no signs	26 (96%)	24 (96%)		50 (96%)
Karyotype (N=52)	normal	11 (41%)	8 (32%)	>.05	19 (37%)
	abnormal	16 (59%)	17 (68%)		33 (63%)
Availability of MRD marker by Flow Cytometry (N=52)	available	20 (74%)	18 (72%)	>.05	38 (73%)
	not available	7 (26%)	7 (28%)		14 (27%)
Availablility of MRD marker by PCR (N=52)	NPM1	7 (26%)	2 (8%)	>.05	9 (17%)
	Other marker	9 (33%)	10 (40%)		19 (37%)
	Not available	11 (41%)	13 (52%)		24 (46%)
AML Group (N=45)	AML and related neoplasms	25 (96%)	18 (95%)	>.05	43 (96%)
	Acute leukemias of ambiguous lineage	1 (4%)	1 (5%)		2 (4%)
AML Subgroup (N=45)	AML with recurrent genetic abnormalities	8 (31%)	5 (26%)	>.05	13 (29%)

	AML with myelodysplasia-related changes	9 (35%)	4 (21%)		13 (29%)
	Therapy-related myeloid neoplasms	1 (4%)	0 (0%)		1 (2%)
	AML, NOS	7 (27%)	9 (47%)		16 (36%)
	MPAL with t(v;11q23.3); KMT2A rearranged	1 (4%)	1 (5%)		2 (4%)
ELN Risk-category (N=45)	Favorable	5 (19%)	2 (11%)	>.05	7 (16%)
	Intermediate	7 (27%)	6 (32%)		13 (29%)
	Adverse	14 (54%)	11 (58%)		25 (56%)
WHO classification of MDS (N=7)	MDS with multilineage dysplasia (MDSMLD)	1 (100%)	1 (17%)	>.05	2 (29%)
	MDS-EB-1	0 (0%)	2 (33%)		2 (29%)
	MDS-EB-2	0 (0%)	3 (50%)		3 (43%)
IPSS risk category (N=7)	Intermediate	1 (100%)	0 (0%)	>.05	1 (14%)
	High	0 (0%)	1 (17%)		1 (14%)
	Very high	0 (0%)	5 (83%)		5 (71%)
Refractory to or relapsed after at least one cycle of standard chemotherapy (N=52)	yes	11 (41%)	13 (52%)	>.05	24 (46%)
	no	16 (59%)	12 (48%)		28 (54%)
10% bone marrow blasts at day 14-21 of the first induction cycle (N=52)	yes	10 (37%)	10 (40%)	>.05	20 (38%)
	no	17 (63%)	15 (60%)		32 (62%)
Adverse risk according to ELN 2017 risk stratification by genetics regardless of stage (N=52)	yes	15 (56%)	12 (48%)	>.05	27 (52%)
	no	12 (44%)	13 (52%)		25 (48%)
Secondary MDS (N=52)	yes	4 (15%)	4 (15%)	>.05	8 (15%)
	no	23 (85%)	21 (84%)		44 (85%)
Secondary to radio-/chemotherapy (N=52)	yes	3 (11%)	0 (0%)	>.05	3 (6%)
	no	24 (89%)	25 (100%)		49 (94%)
MRD positive before HSCT based on flow cytometry or PCR (N=52)	yes	10 (37%)	10 (40%)	>.05	20 (38%)
	no	17 (63%)	15 (60%)		32 (62%)
MDS with excess blasts (MDS-EB) according to the WHO 2016	yes	3 (11%)	5 (20%)	>.05	8 (15%)
	no	24 (89%)	20 (80%)		44 (85%)

classification, or high-risk or very high-risk according to IPSS-R (N=52)					
HSC Source (N=52)	PBSC	26 (96%)	24 (96%)	>.05	50 (96%)
	BM	1 (4%)	1 (4%)		2 (4%)
Donor type (N=52)	Matched related donor	5 (19%)	5 (20%)	>.05	10 (19%)
	Matched unrelated donor	16 (59%)	16 (64%)		32 (62%)
	Mismatched unrelated donor	4 (15%)	2 (8%)		6 (12%)
	Haploidentical family donor	2 (7%)	2 (8%)		4 (8%)
HLA-Match (N=52)	5	1 (4%)	2 (8%)	>.05	3 (6%)
	6	1 (4%)	0 (0%)		1 (2%)
	8	0 (0%)	1 (4%)		1 (2%)
	9	3 (11%)	1 (4%)		4 (8%)
	10	22 (81%)	21 (84%)		43 (83%)
CMV status of patient (N=52)	seropositive	16 (59%)	17 (68%)	>.05	33 (63%)
	seronegative	11 (41%)	8 (32%)		19 (37%)
CMV status of donor (N=52)	seropositive	18 (67%)	13 (52%)	>.05	31 (60%)
	seronegative	9 (33%)	12 (48%)		21 (40%)
CMV status patient/donor (N=52)	Patient seropositive – donor seropositive	16 (59%)	12 (48%)	>.05	28 (54%)
	Patient seropositive – donor seronegative	0 (0%)	5 (20%)		5 (10%)
	Patient seronegative – donor seropositive	2 (7%)	1 (4%)		3 (6%)
	Patient seronegative – donor seronegative	9 (33%)	7 (28%)		16 (31%)
HSCT in complete remission? (N=52)	yes	23 (85%)	19 (76%)	>.05	42 (81%)
	no	4 (15%)	6 (24%)		10 (19%)
Salvage therapy (N=10)	yes	0 (0%)	2 (33%)	>.05	2 (20%)
	no	4 (100%)	4 (67%)		8 (80%)
Type of salvage therapy (N=2)	Melphalan	0	2 (100%)		2 (100%)
Conditioning regimens (N=52)	Reduced intensity conditioning regimens	5 (19%)	5 (20%)	>.05	10 (19%)
	Myeloablative conditioning regimens	20 (74%)	17 (68%)		37 (71%)
	Fludarabine/ Cyclophosphamide/ TBI 2 Gy	1 (4%)	0 (0%)		1 (2%)
	TBF	1 (4%)	3 (12%)		4 (8%)
Medication (N=46)	Fludarabine/Melphalan	3 (13%)	4 (18%)	>.05	7 (15%)
	Fludarabine/Busulfan (FB2)	2 (8%)	1 (5%)		3 (7%)
	Fludarabine/Busulfan (FB4)	11 (46%)	11 (50%)		22 (48%)
	Busulfan/Cyclophosphamide (BU/CY)	2 (8%)	2 (9%)		4 (9%)
	Fludarabine/TBI 8 Gy	6 (25%)	4 (18%)		10 (22%)

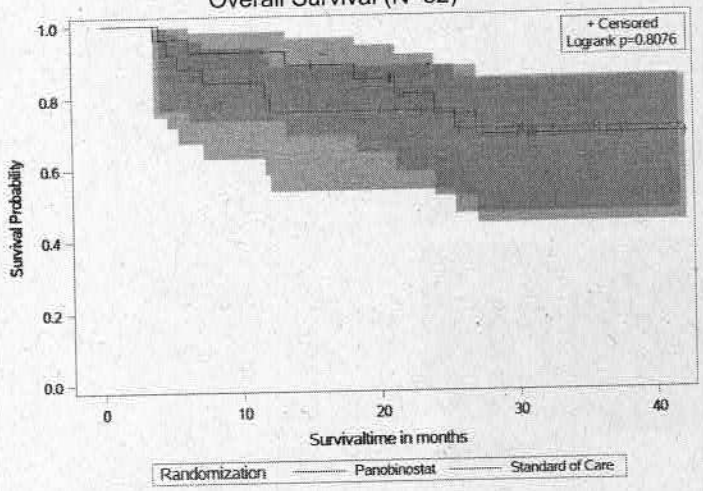
Dose modification? (N=52)	yes	7 (26%)	5 (20%)	>.05	12 (23%)
	no	20 (74%)	20 (80%)		40 (77%)
PT-CY + CSA + MMF prophylaxis (N=4)	yes	2 (100%)	1 (50%)	>.05	3 (75%)
	no	0 (0%)	1 (50%)		1 (25%)
Strategy of GvHD prophylaxis (N=48)	CSA + MMF	14 (56%)	11 (48%)	>.05	25 (52%)
	CSA + MTX	5 (20%)	6 (26%)		11 (23%)
	PT-CY + CSA	6 (24%)	6 (26%)		12 (25%)
ATG added (N=36)	yes	15 (79%)	16 (94%)	>.05	31 (86%)
	no	4 (21%)	1 (6%)		5 (14%)
ATG-Fresenius (N=31)	yes	15 (100%)	14 (88%)	>.05	29 (94%)
	no	0 (0%)	2 (13%)		2 (6%)
Thymoglobulin (N=31)	yes	0 (0%)	1 (6%)	>.05	1 (3%)
	no	15 (100%)	15 (94%)		30 (97%)
Outcome of transplant - Status (N=52)	Alive	27 (100%)	25 (100%)		52 (100%)
Outcome of transplant - CR (N=52)	yes	27 (100%)	25 (100%)		52 (100%)
Outcome of transplant - MRD (N=44)	positive	6 (26%)	2 (10%)	>.05	8 (18%)
	negative	17 (74%)	19 (90%)		36 (82%)
Known previous or ongoing diseases (N=52)	yes	20 (74%)	18 (72%)	>.05	38 (73%)
	no	7 (26%)	7 (28%)		14 (27%)
HCT-CI (N=52)	0	12 (44%)	10 (40%)	>.05	22 (42%)
	1	1 (4%)	0 (0%)		1 (2%)
	2	7 (26%)	6 (24%)		13 (25%)
	3	5 (19%)	4 (16%)		9 (17%)
	4	1 (4%)	5 (20%)		6 (12%)
	5	1 (4%)	0 (0%)		1 (2%)
HCT-CI (N=52)	low	12 (44%)	10 (40%)	>.05	22 (42%)
	intermediate	8 (30%)	6 (24%)		14 (27%)
	high	7 (26%)	9 (36%)		16 (31%)
EBMT Risk Score (N=52)	1	1 (4%)	0 (0%)	>.05	1 (2%)
	2	5 (19%)	0 (0%)		5 (10%)
	3	9 (33%)	13 (52%)		22 (42%)
	4	4 (15%)	7 (28%)		11 (21%)
	5	5 (19%)	4 (16%)		9 (17%)
	6	3 (11%)	1 (4%)		4 (8%)
Integrated EBMT and Seattle Score (N=51)	0	5 (19%)	4 (17%)	>.05	9 (18%)
	1	4 (15%)	1 (4%)		5 (10%)
	2	1 (4%)	3 (13%)		4 (8%)
	3	3 (11%)	5 (21%)		8 (16%)
	4	4 (15%)	5 (21%)		9 (18%)

	5	3 (11%)	3 (13%)		6 (12%)
	6	5 (19%)	3 (13%)		8 (16%)
	7	2 (7%)	0 (0%)		2 (4%)
ECOG prior to HSCT (N=52)	0	14 (52%)	9 (36%)	>.05	23 (44%)
	1	12 (44%)	15 (60%)		27 (52%)
	2	1 (4%)	1 (4%)		2 (4%)
ECOG prior to HSCT (N=52)	≤ 1	26 (96%)	24 (96%)	>.05	50 (96%)
	> 1	1 (4%)	1 (4%)		2 (4%)
ECG result at screening after HSCT (N=49)	normal	21 (81%)	15 (65%)	>.05	36 (73%)
	Clinically non-significant abnormalities	5 (19%)	8 (35%)		13 (27%)

*p: Chi²-test, if the expected values are less than 5

Efficacy: No significant difference in survival, cumulative incidence of relapse or non-relapse mortality, resp., was observed between the panobinostat and standard of care arm, as shown below:

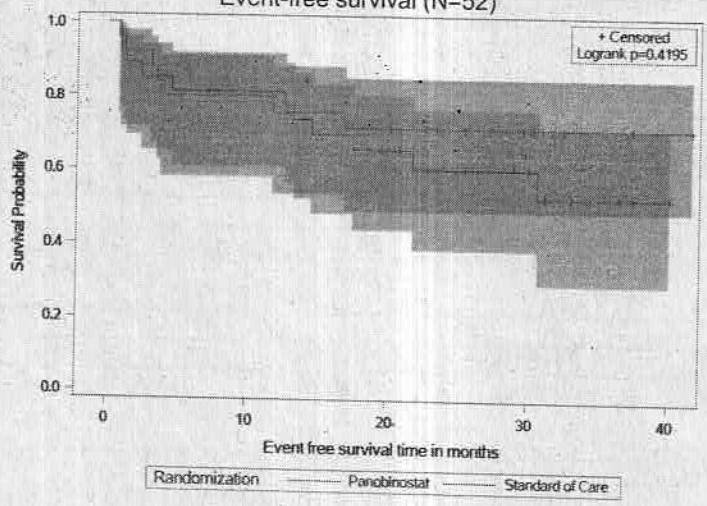
Overall Survival (N=52)[1]



OS[2]		Median survival	Survival at 1 yr (CI)	Survival at 2 yrs (CI)
Panobinostat	N=27, 7 Events	Not reached	93% (74; 98)	75% (52; 88)
Standard of Care	N=25, 7 Events	Not reached	80% (58; 91)	76% (54; 88)

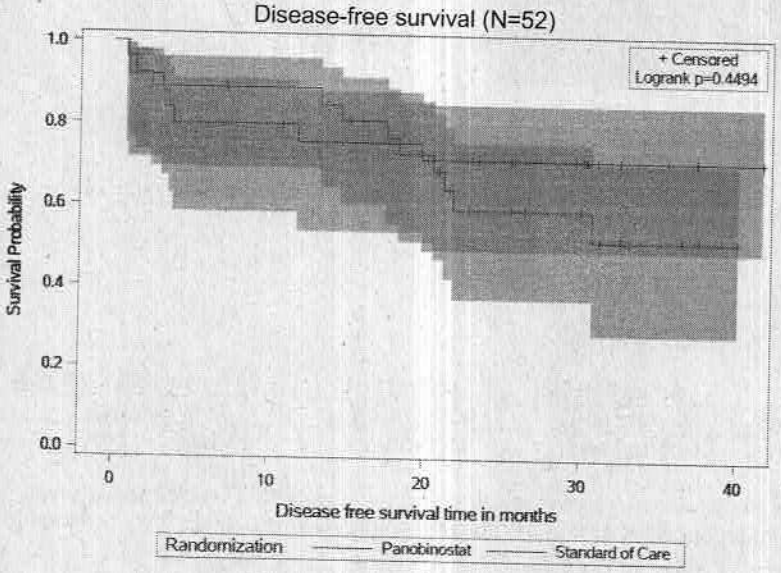
[1]Number and percentage of censored observations, median survival with two-sided 95% confidence interval, Kaplan-Meier survival curves. [2]Survival probabilities at meaningful time points (with two-sided 95% confidence intervals)

Event-free survival (N=52)

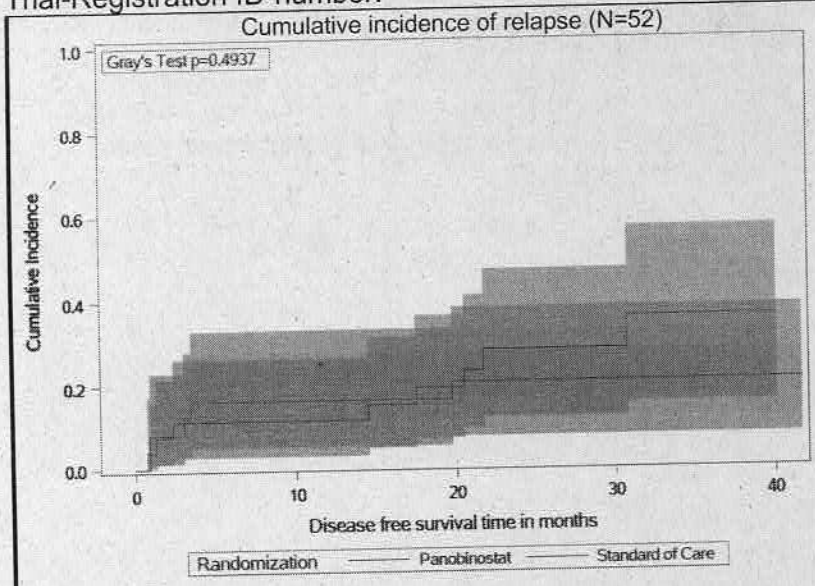


EFS		Median survival	Survival at 1 yr (CI)	Survival at 2 yrs (CI)
Panobinostat	N=27, 11 Events: 7 Relapse, 1 Death in CR, 3 Any treatment of molecular relapse (except DLI)	Not reached	81% (61; 92)	61% (39; 77)
Standard of Care	N=25, 7 Events: 4 Relapse, 2 Death in CR, 1 Any treatment of molecular relapse (except DLI)	Not reached	76% (54; 88)	72% (49; 85)

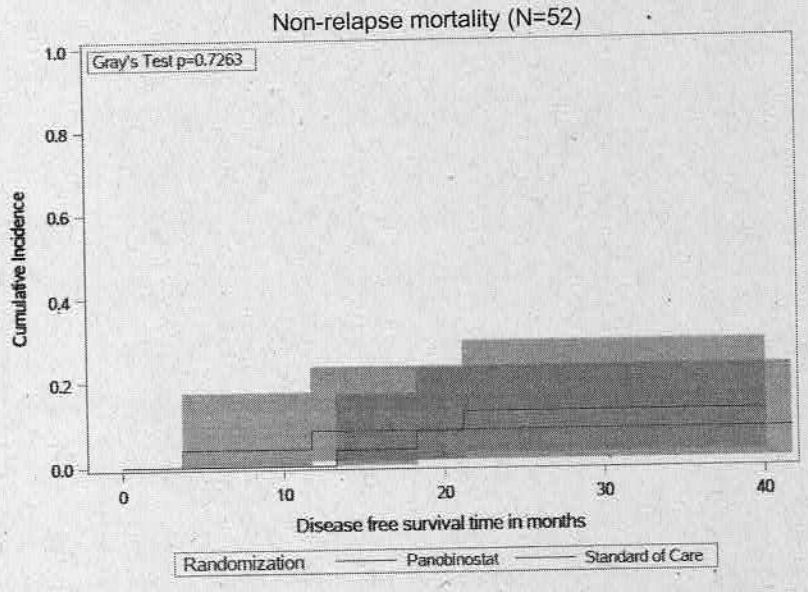
Disease-free survival (N=52)



DFS		Median survival	Survival at 1 yr (CI)	Survival at 2 yrs (CI)
Panobinostat	N=27, 11 Events 8 Relapse, 3 Death in CR	Not reached	89% (69; 96)	59% (37; 76)
Standard of Care	N=25, 7 Events 5 Relapse, 2 Death in CR	Not reached	76% (54; 88)	72% (49; 85)



RR		Median survival	Relapse Risk at 1 yr (CI)	Relapse Risk at 2 yrs (CI)
Panobinostat	N=27, 8 Events	Not reached	11% (3; 26)	28% (15; 57)
Standard of Care	N=25, 5 Events	Not reached	16% (5; 33)	20% (7; 38)



NRM		Median survival	Non-relapse Mortality at 1 yr (CI)	Non-relapse Mortality at 2 yrs (CI)
Panobinostat	N=27, 3 Events	Not reached	0% (0; 0)	13% (3; 29)
Standard of Care	N=25, 2 Events	Not reached	4% (0; 17)	8% (1; 23)

Safety: In the standard of care arm, 88% of patients developed at least one adverse event versus 100% of patients in the panobinostat arm as detailed below.

AEs affecting at least 10% of patients in the SOC arm included dry eye (12%), diarrhea (24%), nausea (24%), other gastrointestinal disorder (36%), other general disorders and administration site conditions (36%), mucosal infection (12%), other infections and infestations (28%), pneumonitis (12%), other skin and subcutaneous tissue disorders (20%) and macula-papular rash (12%).

In the panobinostat arm, AEs reported for at least 10% of patiens included hypothyroidism (11%), other eye disorders (19%), abdominal pain (19%), diarrhea (44%), nausea (59%), other gastrointestinal disorder (15%), vomiting (37%), fatigue (37%), other infections and infestations (15%), upper respiratory infection (11%), urinary tract infection (11%), neutrophil count decreased (11%), platelet count decreased (15%), headache (15%), other skin and subcutaneous tissue disorders (26%).

Randomisation: SOC **N=25**

Any AE **N=22 (88%)**

SOC	Term	Grade 1	Grade 2	Grade 3	Grade 4	Affected patients (N/%)	Total (N)
Blood and lymphatic system disorders	Anemia	0	0	2	0	2 (8%)	2
Blood and lymphatic system disorders	Febrile neutropenia	0	0	1	0	1 (4%)	1
Blood and lymphatic system disorders	Other, specify	0	0	2	1	2 (8%)	3
Cardiac disorders	Pericarditis	0	1	0	0	1 (4%)	1
Ear and labyrinth disorders	Vestibular disorder	0	1	0	0	1 (4%)	1
Endocrine disorders	Hypothyroidism	0	1	0	0	1 (4%)	1
Eye disorders	Blurred vision	0	1	0	0	1 (4%)	1
Eye disorders	Dry eye	2	1	0	0	3 (12%)	3
Eye disorders	Other, specify	2	0	0	0	1 (4%)	2
Gastrointestinal disorders	Diarrhea	4	1	1	0	6 (24%)	6
Gastrointestinal disorders	Gastritis	0	1	0	0	1 (4%)	1
Gastrointestinal disorders	Gastroparesis	1	0	0	0	1 (4%)	1
Gastrointestinal disorders	Mucositis oral	3	0	0	0	2 (8%)	3
Gastrointestinal disorders	Nausea	5	3	0	0	6 (24%)	8
Gastrointestinal disorders	Other, specify	6	6	2	0	9 (36%)	14
Gastrointestinal disorders	Vomiting	1	0	1	0	2 (8%)	2
General disorders and administration site conditions	Edema limbs	1	0	0	0	1 (4%)	1
General disorders and administration site conditions	Fatigue	2	0	0	0	2 (8%)	2

General disorders and administration site conditions	Non-cardiac chest pain	1	0	0	0	1 (4%)	1
General disorders and administration site conditions	Other, specify	3	0	0	0	3 (12%)	3
Infections and infestations	Enterocolitis infectious	0	0	1	0	1 (4%)	1
Infections and infestations	Mucosal infection	1	3	1	0	4 (16%)	5
Infections and infestations	Nail infection	1	0	0	0	1 (4%)	1
Infections and infestations	Other, specify	2	5	1	0	7 (28%)	8
Infections and infestations	Sinusitis	0	1	0	0	1 (4%)	1
Infections and infestations	Upper respiratory infection	0	1	0	0	1 (4%)	1
Infections and infestations	Urinary tract infection	0	1	1	0	2 (8%)	2
Investigations	Alanine aminotransferase increased	1	0	0	0	1 (4%)	1
Investigations	Alkaline phosphatase increased	1	0	0	0	1 (4%)	1
Investigations	Aspartate aminotransferase increased	1	0	0	0	1 (4%)	1
Investigations	Cholesterol high	1	0	0	0	1 (4%)	1
Investigations	Creatinine increased	0	1	0	0	1 (4%)	1
Investigations	GGT increased	0	2	0	0	2 (8%)	2
Investigations	Other, specify	1	1	0	3	3 (12%)	5
Investigations	Platelet count decreased	0	0	2	0	2 (8%)	2
Investigations	Weight loss	2	0	0	0	2 (8%)	2
Metabolism and nutrition disorders	Anorexia	1	2	0	0	2 (8%)	3
Metabolism and nutrition disorders	Hypertriglyceridemia	0	1	0	0	1 (4%)	1
Metabolism and nutrition disorders	Hypomagnesemia	1	0	0	0	1 (4%)	1
Metabolism and nutrition disorders	Hyponatremia	0	0	1	0	1 (4%)	1
Metabolism and nutrition disorders	Iron overload	0	0	1	0	1 (4%)	1

Metabolism and nutrition disorders	Other, specify	1	2	0	0	2 (8%)	3
Musculoskeletal and connective tissue disorders	Bone pain	0	2	0	0	2 (8%)	2
Musculoskeletal and connective tissue disorders	Flank pain	1	0	0	0	1 (4%)	1
Musculoskeletal and connective tissue disorders	Other, specify	1	0	0	0	1 (4%)	1
Musculoskeletal and connective tissue disorders	Pain in extremity	1	0	0	0	1 (4%)	1
Nervous system disorders	Dizziness	1	0	0	0	1 (4%)	1
Nervous system disorders	Other, specify	1	0	0	0	1 (4%)	1
Psychiatric disorders	Depression	1	0	0	0	1 (4%)	1
Renal and urinary disorders	Proteinuria	0	0	1	0	1 (4%)	1
Renal and urinary disorders	Urinary frequency	1	0	0	0	1 (4%)	1
Reproductive system and breast disorders	Erectile dysfunction	1	0	0	0	1 (4%)	1
Respiratory, thoracic and mediastinal disorders	Cough	2	1	0	0	2 (8%)	3
Respiratory, thoracic and mediastinal disorders	Dyspnea	0	1	0	0	1 (4%)	1
Respiratory, thoracic and mediastinal disorders	Other, specify	1	1	0	0	2 (8%)	2
Respiratory, thoracic and mediastinal disorders	Pneumonitis	0	1	2	1	3 (12%)	4
Skin and subcutaneous tissue disorders	Dry skin	1	0	0	0	1 (4%)	1
Skin and subcutaneous tissue disorders	Erythema multiforme	1	0	0	0	1 (4%)	1
Skin and subcutaneous tissue disorders	Other, specify	8	5	0	0	5 (20%)	13
Skin and subcutaneous tissue disorders	Pruritus	1	0	0	0	1 (4%)	1
Skin and subcutaneous tissue disorders	Rash maculo-papular	1	1	1	0	3 (12%)	3

Vascular disorders	Hypertension	0	0	2	0	2 (8%)	2
Vascular disorders	Lymphedema	1	0	0	0	1 (4%)	1

Randomisation:
Panobinostat **N=27**

Any AE **N=27 (100%)**

SOC	Term	Grade 1	Grade 2	Grade 3	Grade 4	Affected patients (N/%)	Total (N)
Blood and lymphatic system disorders	Anemia	0	0	1	0	1 (4%)	1
Blood and lymphatic system disorders	Lymph node pain	0	1	0	0	1 (4%)	1
Blood and lymphatic system disorders	Other, specify	2	0	0	0	2 (7%)	2
Blood and lymphatic system disorders	Thrombotic thrombocytopenic purpura	0	0	0	1	1 (4%)	1
Cardiac disorders	Atrioventricular block first degree	1	0	0	0	1 (4%)	1
Ear and labyrinth disorders	Hearing impaired	0	0	1	0	1 (4%)	1
Ear and labyrinth disorders	Tinnitus	0	0	1	0	1 (4%)	1
Ear and labyrinth disorders	Vertigo	1	0	0	0	1 (4%)	1
Endocrine disorders	Hyperthyroidism	0	1	0	0	1 (4%)	1
Endocrine disorders	Hypothyroidism	2	1	0	0	3 (11%)	3
Eye disorders	Dry eye	2	0	0	0	2 (7%)	2
Eye disorders	Other, specify	2	3	0	0	5 (19%)	5
Gastrointestinal disorders	Abdominal pain	4	2	0	0	5 (19%)	6
Gastrointestinal disorders	Constipation	1	0	0	0	1 (4%)	1
Gastrointestinal disorders	Diarrhea	9	8	3	0	12 (44%)	20
Gastrointestinal disorders	Dry mouth	2	0	0	0	2 (7%)	2
Gastrointestinal disorders	Dyspepsia	0	1	0	0	1 (4%)	1

Gastrointestinal disorders	Gastroesophageal reflux disease	0	1	0	0	1 (4%)	1
Gastrointestinal disorders	Mucositis oral	2	0	0	0	2 (7%)	2
Gastrointestinal disorders	Nausea	9	12	3	0	16 (59%)	24
Gastrointestinal disorders	Other, specify	1	5	1	0	4 (15%)	7
Gastrointestinal disorders	Stomach pain	1	0	0	0	1 (4%)	1
Gastrointestinal disorders	Toothache	1	0	0	0	1 (4%)	1
Gastrointestinal disorders	Vomiting	5	7	2	0	10 (37%)	14
General disorders and administration site conditions	Edema limbs	2	0	0	0	2 (7%)	2
General disorders and administration site conditions	Fatigue	5	4	13	0	10 (37%)	22
General disorders and administration site conditions	Fever	0	1	0	0	1 (4%)	1
General disorders and administration site conditions	Localized edema	1	0	0	0	1 (4%)	1
General disorders and administration site conditions	Other, specify	2	0	1	0	2 (7%)	3
Hepatobiliary disorders	Cholecystitis	0	0	0	2	2 (7%)	2
Hepatobiliary disorders	Other, specify	0	1	0	0	1 (4%)	1
Infections and infestations	Bronchial infection	0	1	0	0	1 (4%)	1
Infections and infestations	Enterocolitis infectious	0	0	1	0	1 (4%)	1
Infections and infestations	Eye infection	0	0	1	0	1 (4%)	1
Infections and infestations	Mucosal infection	0	2	0	0	2 (7%)	2
Infections and infestations	Other, specify	1	5	0	0	4 (15%)	6
Infections and infestations	Papulopustular rash	1	0	0	0	1 (4%)	1
Infections and infestations	Skin infection	0	0	1	0	1 (4%)	1
Infections and infestations	Upper respiratory infection	0	3	0	0	3 (11%)	3
Infections and infestations	Urinary tract infection	0	1	2	0	3 (11%)	3
Infections and infestations	Vulval infection	1	0	0	0	1 (4%)	1

Investigations	Alanine aminotransferase increased	0	0	1	0	1 (4%)	1
Investigations	Aspartate aminotransferase increased	1	0	1	0	1 (4%)	2
Investigations	Blood bilirubin increased	0	1	0	0	1 (4%)	1
Investigations	Cholesterol high	1	0	0	0	1 (4%)	1
Investigations	Creatinine increased	0	1	0	0	1 (4%)	1
Investigations	GGT increased	0	2	1	0	2 (7%)	3
Investigations	Neutrophil count decreased	0	0	1	2	3 (11%)	3
Investigations	Other, specify	1	0	0	0	1 (4%)	1
Investigations	Platelet count decreased	1	1	1	2	4 (15%)	5
Investigations	Weight loss	0	1	0	0	1 (4%)	1
Metabolism and nutrition disorders	Anorexia	0	1	0	0	1 (4%)	1
Metabolism and nutrition disorders	Hypertriglyceridemia	0	0	1	0	1 (4%)	1
Metabolism and nutrition disorders	Other, specify	1	0	0	0	1 (4%)	1
Musculoskeletal and connective tissue disorders	Back pain	0	1	0	0	1 (4%)	1
Musculoskeletal and connective tissue disorders	Bone pain	1	0	0	0	1 (4%)	1
Musculoskeletal and connective tissue disorders	Generalized muscle weakness	1	0	0	0	1 (4%)	1
Musculoskeletal and connective tissue disorders	Myositis	1	0	0	0	1 (4%)	1
Musculoskeletal and connective tissue disorders	Osteoporosis	1	0	0	0	1 (4%)	1
Musculoskeletal and connective tissue disorders	Other, specify	1	0	0	0	1 (4%)	1

Musculoskeletal and connective tissue disorders	Pain in extremity	2	0	0	0	1 (4%)	2
Nervous system disorders	Concentration impairment	1	0	0	0	1 (4%)	1
Nervous system disorders	Dizziness	1	2	0	0	2 (7%)	3
Nervous system disorders	Dysgeusia	2	0	0	0	2 (7%)	2
Nervous system disorders	Headache	5	0	0	0	4 (15%)	5
Nervous system disorders	Other, specify	1	0	0	0	1 (4%)	1
Nervous system disorders	Peripheral sensory neuropathy	1	0	0	0	1 (4%)	1
Nervous system disorders	Syncope	0	0	1	0	1 (4%)	1
Psychiatric disorders	Anxiety	0	1	0	0	1 (4%)	1
Psychiatric disorders	Depression	0	1	0	0	1 (4%)	1
Psychiatric disorders	Insomnia	0	1	0	0	1 (4%)	1
Renal and urinary disorders	Urinary tract pain	1	0	0	0	1 (4%)	1
Reproductive system and breast disorders	Vaginal hemorrhage	2	0	0	0	2 (7%)	2
Respiratory, thoracic and mediastinal disorders	Allergic rhinitis	1	0	0	0	1 (4%)	1
Respiratory, thoracic and mediastinal disorders	Dyspnea	0	1	0	0	1 (4%)	1
Respiratory, thoracic and mediastinal disorders	Sore throat	1	1	0	0	2 (7%)	2
Skin and subcutaneous tissue disorders	Dry skin	1	0	0	0	1 (4%)	1
Skin and subcutaneous tissue disorders	Other, specify	11	7	0	0	7 (26%)	18
Skin and subcutaneous tissue disorders	Rash maculo-papular	2	0	0	0	2 (7%)	2
Skin and subcutaneous tissue disorders	Skin atrophy	1	0	0	0	1 (4%)	1
Skin and subcutaneous tissue disorders	Skin hyperpigmentation	1	0	0	0	1 (4%)	1
Vascular disorders	Hot flashes	1	0	0	0	1 (4%)	1
Vascular disorders	Hypertension	0	2	2	0	2 (7%)	4
Vascular disorders	Other, specify	2	0	1	0	2 (7%)	3

Conclusions:

In this prospective, randomized multicenter study, the prophylactic administration of the deacetylase inhibitor panobinostat did not result in a statistically different survival, cumulative incidence of relapse or non-relapse mortality compared with standard of care. This was largely attributable to grade 1 and grade 2 toxicities that prevented prolonged administration of the investigational drug in AML or MDS patients who had undergone allogeneic HSCT. Despite its use at the dose clinically approved for myeloma, the vast majority of patients discontinued panobinostat prematurely, suggesting poorer tolerability in this patient cohort, without a significant excess of serious (grades 3-5) AEs. Overall and event-free survival in both randomized treatment arms was very good given the patients risk profile. These results do not invalidate the therapeutic potential of post-transplant maintenance for AML but highlight the need for drugs with substantially better tolerability for long-term administration.

I hereby confirm that the data in the results report are collected properly and are correct.

Date of report: 16 Feb 2024

Print name: Gesine Bug, MD

Signature: G Bug