Midostaurin in addition to intensive chemotherapy in acute myeloid leukemia with t(8;21) and *KIT* and/or *FLT3*-ITD mutations: results of the SAL MIDOKIT trial

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https://doi.org/10.3324/haematol.2022.281636

Suppl. Table 1. Target population and main inclusion/exclusion criteria

Inclusion criteria
- Signed written informed consent and ability to comply with the study protocol according to ICH and local regulations - Previously untreated *KIT* and/or *FLT3*-ITD mutated t(8;21) AML - Chemo-responsiveness after IT1 - Age 18-65 years - Adequate liver test results, defined by meeting all of the following criteria: • total serum bilirubin ≤ 1.5 × the upper limit of normal (ULN) • ALAT and ASAT ≤ 2.5 × ULN - Adequate renal test results: creatinine ≤ 1.5 × ULN - Adequate cardiac test results: LVEF ≥ 50 % as assessed by echocardiography (“M Mode”) or MUGA scan - Eastern Cooperative Oncology Group (ECOG) performance status 0-2 - Life expectancy > 12 weeks - Male patients must agree to use highly effective contraception or be abstinent while on treatment and for 1 month after stopping treatment - Female patients of childbearing potential must use highly effective contraception or be abstinent during screening, while on treatment and until 1 month after stopping treatment
Exclusion criteria
- Primary refractory or previously relapsed AML - Non-eligibility for high-dose cytarabine based consolidation, e.g. intolerance to cytarabine - Inability to swallow oral medications - Subject without legal capacity who is unable to understand the nature, significance and consequences of the study - Investigational drug therapy outside of this trial during or within 4 weeks of study entry - Known or persistent abuse of medication, drugs or alcohol - Current pregnancy, nursing period

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; ECOG PS: Eastern Cooperative Oncology Group performance status; IT1: induction chemotherapy 1; ITD: internal tandem duplication; LVEF: left-ventricular ejection fraction

Suppl. Table 2. Salvage therapies for patients experiencing relapse

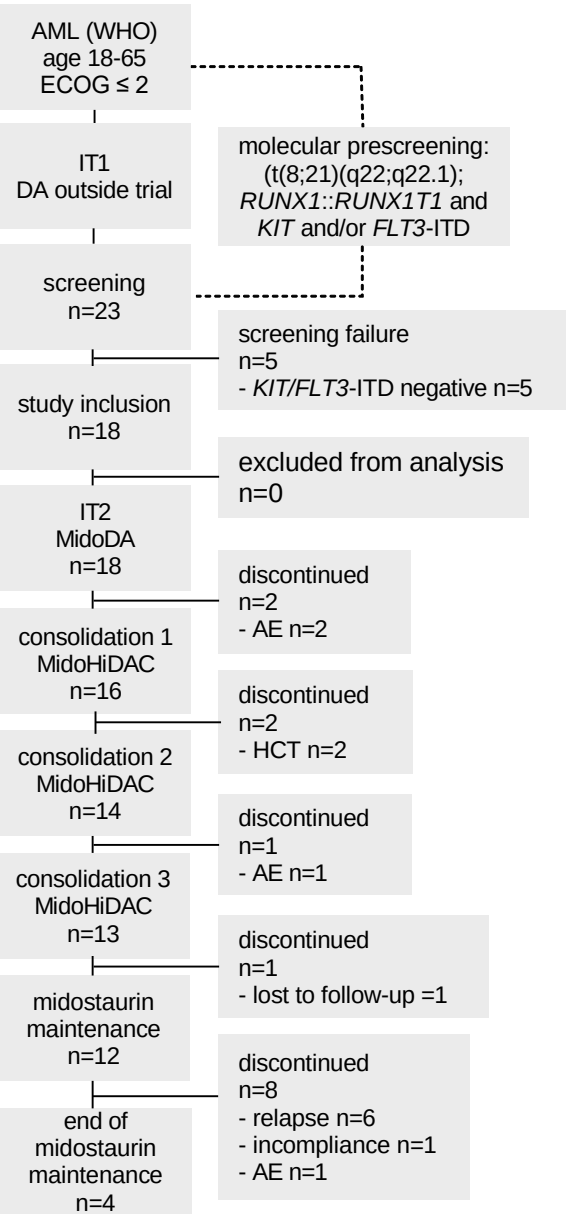
UPN	Clinical course
030-07	030-07 experienced molecular relapse during midostaurin maintenance. He received 2C of azacitidine and underwent alloHCT. On last FU, more than six years after alloHCT he was alive in CR_{MRD-} with only limited cGvHD.
014-12	No data available.
072-08	072-08 received intensive salvage chemotherapy (HDAC, mitoxantrone), achieved CR and underwent alloHCT. She relapsed again and underwent second alloHCT after azacitidine/DLI. However, she experienced another relapse, received LDAC/venetoclax and subsequent decitabine but died due to mucormycosis.
016-10	016-10 received intensive salvage chemotherapy (HDAC, mitoxantrone), and underwent alloHCT in second CR. However, she experienced relapse five months after alloHCT, received azacitidine, but died 16 months after alloHCT due to sepsis.
007-14	007-14 experienced hematologic relapse and underwent alloHCT (sequential conditioning regimen). She achieved CR_{MRD-} and was alive on last FU about 5 years after alloHCT.
030-03	030-03 experienced molecular and subsequent hematologic relapse during midostaurin maintenance and died due to pneumonia after 1C of decitabine.
003-06	003-06 was diagnosed with colorectal cancer (CRC) AJCC stage IVC after IT2, withdrawn from the trial and died five months later due to relapse.

alloHCT: allogeneic hematopoietic cell transplantation; CR_{MRD-}: complete remission and minimal residual disease negativity; FU: follow-up; HDAC: high dose cytarabine; cGVHD: chronic graft versus host disease; IT2: induction therapy 2

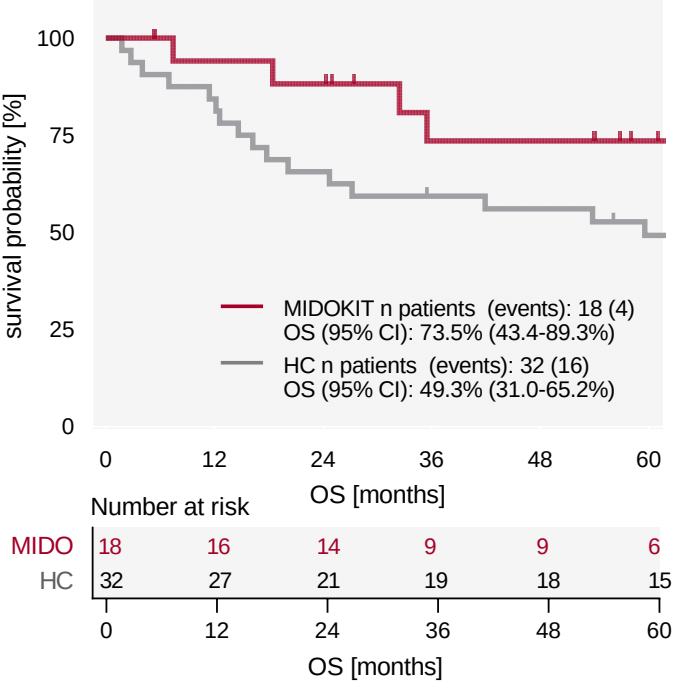
Supplementary figure legends

Suppl. Figure 1 Patient disposition and long-term follow-up overall survival. A) Patient disposition B) Long-term follow-up overall survival in MIDOKIT patients as compared to historical controls (patients with AML with t(8;21) with *KIT* and/or *FLT3*-ITD mutations treated with IC without midostaurin within the AML96 trial (#NCT00180115), the AML2003 trial (#NCT00180102) and the AML60+ trial (#NCT00180167).AE adverse event; DA: daunorubicin/cytarabin; ECOG: Eastern Cooperative Oncology Group performance status; HCT: hematopoietic cell transplantation; IT: induction therapy; MidoDA: midostaurin + daunorubicin/cytarabine; MidoHiDAC midostaurin + high-dose cytarabine;

A


AML (WHO)
age 18-65
ECOG ≤ 2
IT1
DA outside trial
screening
n=23
molecular prescreening:
(t(8;21)(q22;q22.1);
RUNX1::*RUNX1T1* and
KIT and/or *FLT3*-ITD
screening failure
n=5
- *KIT/FLT3*-ITD negative n=5
study inclusion
n=18
excluded from analysis
n=0
IT2
MidoDA
n=18
discontinued
n=2
- AE n=2
consolidation 1
MidoHiDAC
n=16
discontinued
n=2
- HCT n=2
consolidation 2
MidoHiDAC
n=14
discontinued
n=1
- AE n=1
consolidation 3
MidoHiDAC
n=13
discontinued
n=1
- lost to follow-up =1
midostaurin
maintenance
n=12
discontinued
n=8
- relapse n=6
- incompliance n=1
- AE n=1
end of
midostaurin
maintenance
n=4

B


survival probability [%]
100
75
50
25
0
MIDOKIT n patients (events): 18 (4)
OS (95% CI): 73.5% (43.4-89.3%)
HC n patients (events): 32 (16)
OS (95% CI): 49.3% (31.0-65.2%)
0
12
24
36
48
60
OS [months]
Number at risk
MIDO 18 16 14 9 9 6
HC 32 27 21 19 18 15
0
12
24
36
48
60
OS [months]