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Disease course of *FLT3* mutated extramedullary acute myeloid leukemia and efficacy of gilteritinib

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Running head: Extramedullary AML with FLT3 mutations

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Data sharing statement
The data generated and presented in this manuscript are available upon reasonable request from the corresponding author

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Authors' contributions

F.A. wrote the manuscript, performed statistical analyses, created figures and tables and collected data; E.B., C.S., M.B.G., G.M., E.T., M.T., F.L., E.A., V.F., C.V. and F.G. collected data, reviewed the manuscript and provided intellectual output, A.V., F.F., L.T. and C.G revised the manuscript and provided intellectual output; F.L. conceptualized the study, reviewed the manuscript and provided intellectual output.

Conflicts of interest disclosure

C.V. received honoraria and attended advisory boards from AbbVie Inc, Astellas Pharma, Jazz Pharmaceuticals, BMS; G.M. received research funds from AbbVie, Astellas, AstraZeneca, Daiichi Sankyo, Pfizer, and Syros and was a consultant or was included in the speakers bureau for AbbVie, Astellas, AstraZeneca, Enable lifescience, FlowView Diagnostics, Immunogen, Janssen, Jazz, Menarini/Stemline, Pfizer, Ryvu, Servier, Syros, Takeda and Uknequas. F.A., E.B, C.S., M.B.G., E.T., M.T., F.L., E.A., V.F., F.G., A.V., F.F., C.G., F.L. have no conflicts of interest to declare within this study.

Dear editor,

Extramedullary involvement by acute myeloid leukemia (AML) refers to the proliferation of neoplastic blasts outside the bone marrow and can occur in any organ or tissue. It can present either concurrently with AML or in an isolated form, which is however almost invariably followed by development of disease in the bone marrow. At the time of AML diagnosis, extramedullary AML (eAML) has a reported incidence ranging from 0.2 to 2.8%, which increases up to 25% in cases relapsed post-allogenic hematopoietic stem cell transplantation (alloHSCT)[1]. A higher risk of developing eAML has been reported in association with the expression of specific surface antigens (CD11b and CD56), cytogenetic abnormalities such as t(8;21), inv(16) and trisomy 8, and different mutations (NPM1, FLT3-ITD, PTPTN11)[1,2]. The prognostic impact of eAML remains controversial, and even more limited evidence exists regarding the disease course of eAML in the context of specific mutations.[1] This is particularly relevant for those with targetable mutations such as *FLT3*-ITD/TKD, since clinical trials investigating the FLT3 inhibitor gilteritinib did not report the outcomes of patients with eAML and excluded those with CNS disease[3,4]. While evidence regarding the activity of targeted agents in eAML is starting to appear, most previous studies were conducted before the emergence of these therapies[1,5]. In this study, we set out to investigate the disease course and treatment patterns of patients with eAML and FLT3 mutations, with a particular focus on outcomes after treatment with gilteritinib.

We conducted a multicentric retrospective study across 10 referral hematology centers in Italy. Institutions were chosen based on their willingness to participate and availability of data. Each institutional record was screened by the local investigators for patients with eAML diagnosed from January 2010 until May 2024 and cross referenced with mutational data. Eligible patients had a diagnosis of AML with FLT3 mutations detected in bone marrow or peripheral blood and histologically confirmed synchronous eAML presenting either at diagnosis or at disease relapse. In case of isolated eAML the presence of FLT3 mutations had to be confirmed on eAML tissue. Response assessment was performed by PET/CT or PET/MRI according to each institutional protocol, and by full clinical examination in case of skin eAML. CNS involvement required presence of AML blasts in

the cerebrospinal fluid by cytological examination or flow-cytometry. CNS sterilization required both flow-cytometry negativity and disappearance of any contrast-enhancing lesions by MRI. Data regarding clinical and biological variables were obtained from each institution after review of the medical records. Overall survival (OS) was calculated from the time of eAML presentation until death or last follow-up date (censored). All patients provided written informed consent. The study was conducted in accordance with the declaration of Helsinki and approved by the local ethics committee (1430/A3).

A total of 27 patients were included in the study. The median age was 61 years (range: 30 – 81 years). Sixteen (59%) patients were female. At diagnosis, 5 (19%) were classified as favorable, 20 (74%) as intermediate and 2 (7%) as adverse risk according to ELN 2022 risk classification. Fourteen (52%) patients presented with eAML at diagnosis while 13 (48%) at the time of disease relapse. Among the latter, all patients received a single line of therapy before eAML occurrence and only 1 (8%) had a previous alloHSCT. Twenty-six patients (96.3%) had synchronous eAML and one (3.7%) isolated eAML. Cytogenetic and molecular analyses were performed on bone marrow/peripheral blood blasts in all 26 cases with synchronous eAML. *FTL3* testing was performed also on eAML tissue from 4 patients (n=3 in blasts form cerebrospinal fluid; n=1 skin biopsy) detecting the same mutation identified in the bone marrow, and in the 1 patient with isolated eAML in the mammary gland. The most common *FLT3* mutation was *FLT3*-ITD (n=21, 78%) versus *FLT3*-TKD (n=6, 22%). Nineteen (70%) patients harbored concomitant *NPM1* mutations (Table 1).

Most patients had a single eAML localization (n=23, 89%) while 4 (11%) had multiple localizations. The most common sites of initial eAML presentation were the skin in 15 (56%) patients and the CNS in 8 (30%), followed by soft tissues in 3 (11%), and the mammary gland, ovary, rectum, stomach, lymph nodes and spleen (n=1, 4% for each) (Figure 1). Out of the 4 patients with multiple sites affected by eAML, 2 had disease in the skin and CNS ,1 in the skin and soft tissues, and another 1 in skin, lymph nodes and spleen.

eAML at the first occurrence was treated with intensive chemotherapy (ICT) in 14 (56%) patients of whom 5 (19%) also received midostaurin, with gilteritinib in 10 (37%) patients,

and with triple intrathecal therapy (TIT) alone, upfront alloHSCT and venetoclax-decitabine each in 1 (4%) patient. The overall response rate (ORR) was 81.5%, with 18 (66.7%) complete remissions (CR) and 4 (14.8%) partial responses (PR). Out of the 5 patients not responding to initial treatment, 2 received no further treatment, 2 were treated with salvage ICT and 1 with gilteritinib. Twelve (59%) out of the 22 responding patients eventually relapsed, 5 only with disease recurrence in bone marrow and 7 with recurrence in both bone marrow and eAML. Among the latter, 5/7 (71.4%) relapsed in the same site originally affected by eAML, one relapsed with CNS disease after previous skin eAML, and the last one with previous skin and CNS disease relapsed only with skin eAML. These received further therapy with ICT (n=4, 33%), gilteritinib (n=5, 42%) or venetoclax-azacitidine (n=2, 17%), while 1 (8%) died without receiving further treatment. Upon further relapse or disease refractoriness, 2 more patients received gilteritinib and 1 ICT. The ORR for the 14 patients receiving salvage therapy was 64.3% (9 CR, 4 SD, 1 not evaluable). eAML treatments are summarized in supplementary table 1 and treatment trajectories for all patients are represented in Figure 2. At the time of eAML diagnosis 23/27 (85.2%) patients were considered eligible for allo-HSCT, with 9/23 (39%) undergoing allo-HSCT.

The median OS was 11.1 months (95%CI: 10.3 - NR) in the whole cohort (Supplementary Figure 1), 11.1 months (95%CI: 10.4 – NR) in patients with the first presentation of eAML at diagnosis and 10.7 months (95%CI: 4.14 - NR) in those with first eAML presentation at relapse. There was no significant difference in survival between newly diagnosed and R/R patients (p = 0.5). Skin localization of eAML was associated with longer OS (HR: 0.27; 95% CI: 0.08 – 0.95; p = 0.03), and the same was true for undergoing alloHSCT (HR: 0.10; 95%CI: 0.01 – 0.78; p = 0.004). CNS involvement at diagnosis was associated with a trend towards shorter OS (HR: 3.3; 95% CI: 0.98 – 10.9; p = 0.05). The presence of *NPM1* mutations (HR: 1.10; p=0.9), type of FLT3 mutations (ITD vs. TKD; HR: 0.66; p=0.5), or age (HR: 1.04; p=0.1) had no impact on OS.

In total, 19 (70.4%) patients received gilteritinib for the treatment of eAML in the context of R/R disease, achieving an ORR of 63% (11 CR, 1 PR and 4 no responses). Moreover, out of 11 patients with CNS involvement, 7 (64%) were treated with gilteritinib + TIT achieving a CR in 6 (85.7%). The median OS from the start of therapy with gilteritinib was

9.6 months (95% CI: 9.0 - NR). Before the start of gilteritinib treatment, 12/19 patients (63%) were considered eligible for allo-HSCT, with 4/12 (33%) being successfully bridged to allo-HSCT and 2 also receiving post-allo-HSCT maintenance.

Major limitations of this study include the small sample size, retrospective nature, and the heterogeneity of administered treatments. Furthermore, the efficacy of gilteritinib on CNS disease should be interpreted with caution given the inability to separate its effect from TIT. Given the small cohort, particular caution should be also exercised in interpreting the prevalence of eAML localization in different organs and the better outcomes observed with skin localization.

Despite these limitations, the observed high rate of CNS localization is in keeping with evidence suggesting that AML with *FLT3* mutations has a predisposition for disease dissemination in the CNS, accounting for 29% of AML with CNS involvement[6]. The purported mechanisms driving CNS dissemination by AML are still unknown, but may be related to *FLT3* fostering cell survival and proliferation in both hematopoietic and neural tissue[6,7]. Also, previous case reports demonstrated high gilteritinib penetration in the cerebrospinal fluid, possibly pointing towards a role in eradication of CNS disease[8–11].

Patients developing eAML at diagnosis in our cohort had a similar OS to those developing eAML at relapse which may indicate reduced survival in the former. However, this finding is likely affected from the small sample size and previous studies have not demonstrated consistent inferior survival in patients with eAML at diagnosis[12].

Nonetheless, and still considering the aforementioned limitations, a relevant finding of this study is the favourable activity of gilteritinib in FLT3-mutated eAML, including in patients with CNS involvement when coupled with TIT. The response rates and survival outcomes observed in our cohort after treatment with gilteritinib were comparable with those reported from both real-life studies and the prospective trials ADMIRAL and COMMODORE[3,13], and are in keeping with evidence demonstrating extensive tissue distribution of gilteritinib[14,15].

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Table 1. Complete population's clinical and biological characteristics at the time of first occurrence of eAML.

	Total patients n= 27
Disease status	
ND	14 (52%)
R/R	13 (48%)
Sex	
F	11 (41%)
M	16 (59%)
Age, median (range)	61 (30 – 81)
2022 ELN risk category*	
Favourable	5 (19%)
Intermediate	20 (74%)
Adverse	2 (7%)
Karyotype	
Normal	20 (74%)
Complex	2 (7%)
Other	5 (19%)
FLT3 mutations	
ITD	21 (78%)
TKD	6 (22%)
NPM1	
Mutated	19 (70%)
Wild type	8 (30%)
IDH	
IDH1	3 (11%)
IDH2	2 (7%)
Wild type	12 (45%)
Not done	10 (37%)
WBC $x10^9$/uL, median (range)	15.1 (0.8 - 285)
Neutrophils $x10^9$/uL, median (range)	5.3 (0.4 - 48)
Hb g/L, median (range)	87 (64 - 119)
PLT $x10^9$/uL, median (range)	47 (11 - 196)
Bone marrow blast %, median (range)	56.5 (0 – 93)
Peripheral blood blast %, median (range)	30 (0 - 98)

ND: Newly diagnosed AML; R/R: relapsed/refractory AML; ELN: European Leukemia Net; WBC: White blood cell count; Hb: Hemoglobin; PLT: Platelets

*As evaluated at the time of AML diagnosis

Figure legends

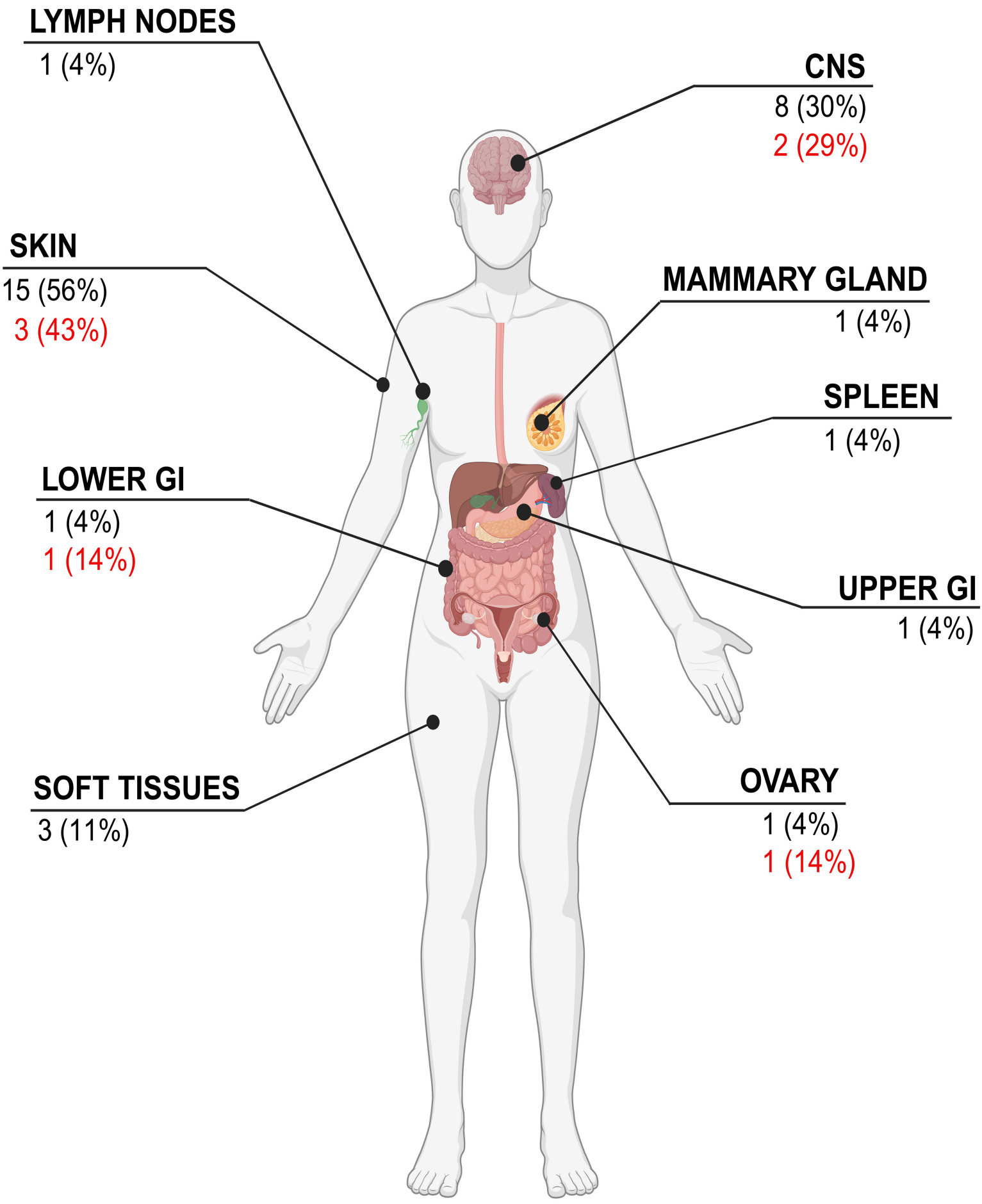
Figure 1. Prevalence of sites affected by eAML at first occurrence (black) and at relapse (red). Percentages are calculated out of the total number of patients at first diagnosis (n=27; including 4 patients with multiple localization) and at eAML relapse (n=7). Created in BioRender. Angotzi, F. (2026) https://BioRender.com/kmgknbx

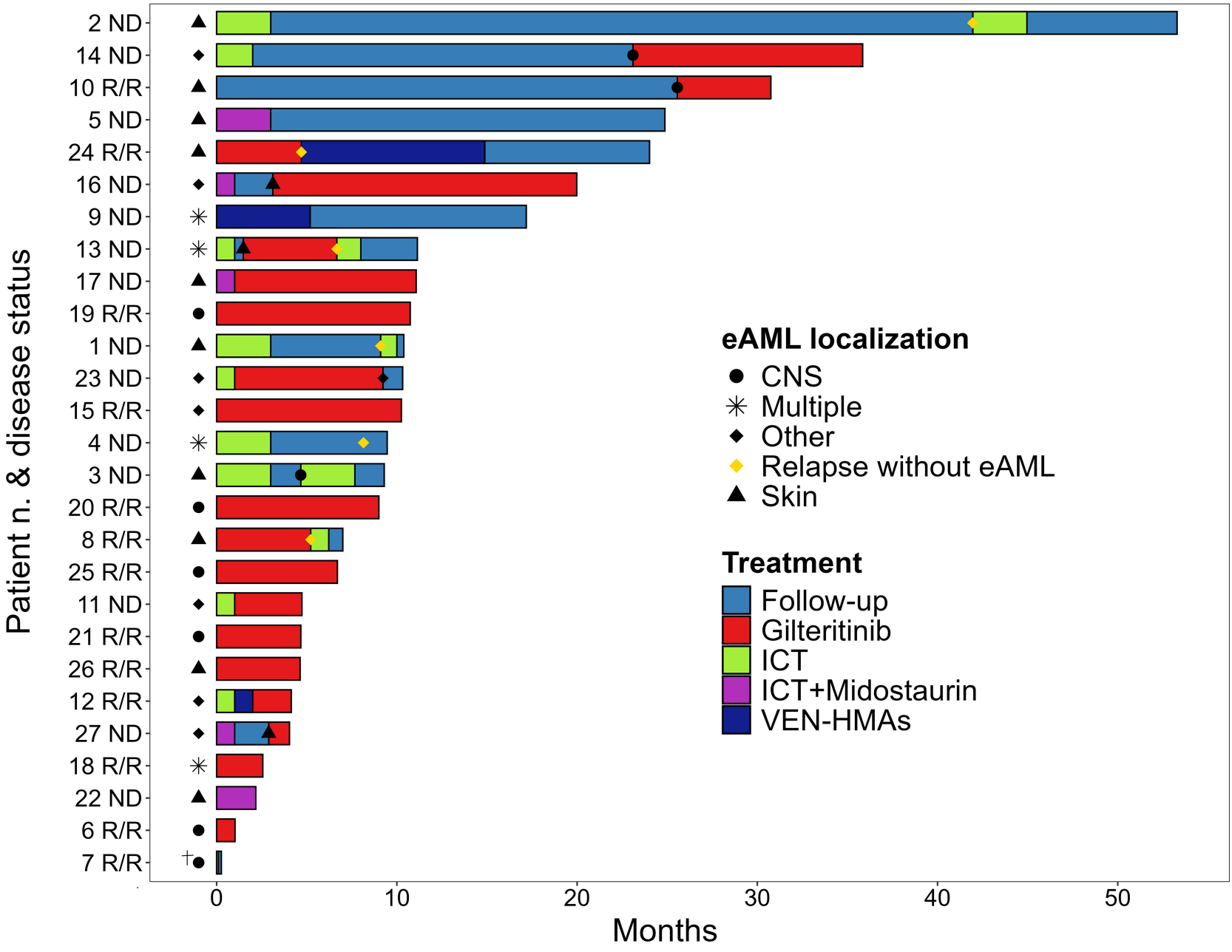
CNS: Central nervous system; GI: Gastrointestinal System.

Figure 2. Swimmer plot outlining treatment trajectories and eAML localization for the enrolled patients

ND: Newly diagnosed AML; R/R: relapsed/refractory AML; CNS: Central nervous system; ICT: intensive chemotherapy; VEN-HMAs: Venetoclax-Hypomethylating agents

[†]Received TIT only as treatment


LYMPH NODES
1 (4%)
CNS
8 (30%)
2 (29%)
SKIN
15 (56%)
3 (43%)
MAMMARY GLAND
1 (4%)
SPLEEN
1 (4%)
LOWER GI
1 (4%)
1 (14%)
UPPER GI
1 (4%)
SOFT TISSUES
3 (11%)
OVARY
1 (4%)
1 (14%)


Patient n. & disease status
2 ND
14 ND
10 R/R
5 ND
24 R/R
16 ND
9 ND
13 ND
17 ND
19 R/R
1 ND
23 ND
15 R/R
4 ND
3 ND
20 R/R
8 R/R
25 R/R
11 ND
21 R/R
26 R/R
12 R/R
27 ND
18 R/R
22 ND
6 R/R
7 R/R
0
10
20
30
40
50
Months
eAML localization
CNS
Multiple
Other
Relapse without eAML
Skin
Treatment
Follow-up
Gilteritinib
ICT
ICT+Midostaurin
VEN-HMAs

Supplementary Table 1. Summary of administered therapies for eAML after first presentation and upon refractoriness/relapse. Patients relapsing only with bone marrow disease but not eAML not shown.

	First eAML presentation Total patients n = 27	**Salvage treatment for eAML Total patients n = 12**
ICT		
7+3+Midostaurin	5 (18.5%)	0
7+3	3 (11.1%)	0
FLAG-IDA	2 (7.4%)	2 (16.7%)
ICE	4 (14.8%)	0
Gilteritinib	5 (18.5%)	6 (50%)
Gilteritinib + TIT	5 (18.5%)	1 (8.3%)
TIT only	1 (3.7%)	0
Upfront Allo-HSCT	1 (3.7%)	0
VEN-HMAs	1 (3.7%)	1 (8.3%)
No treatment	0	2 (16.7%)

ICT: Intensive chemotherapy; FLAG-IDA: Fludarabine, cytarabine, idarubicin, G-CSF; ICE: Idarubicin, cytarabine, etoposide; TIT: Triple intrathecal therapy; Allo-HSCT: allogenic hematopoietic stem cell transplant; VEN-HMAs: Venetoclax + hypomethylating agents (decitabine or azacitidine).

Supplementary Figure 1. Survival curve for the whole population with eAML