haematologica
Journal of the Ferrata Storti Foundation

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Received: June 9, 2024.
Accepted: September 25, 2024.

Citation: Sabine Kayser, Khaled Sanber, Giovanni Marconi, Agnese Mattei, Marlise R. Luskin, Amar Kelkar, Marco Cerrano, Daniel Tuyet Kristensen, Anne Stidsholt Roug, Chiara Sartor, Fabio Giglio, Marta Riva, Lorenzo Rizzo, Francesco Saraceni, Selene Guerzoni, Federica Lessi, Erika Borlenghi, Mark J. Levis, Richard F. Schlenk, Tania Jain, and Cristina Papayannidi. Outcome of adult acute myeloid leukemia patients with extramedullary disease and treatment with venetoclax/hypomethylating agents.
Haematologica. 2024 Oct 3. doi: 10.3324/haematol.2024.285985 [Epub ahead of print]

Outcome of adult acute myeloid leukemia patients with extramedullary disease and treatment with venetoclax / hypomethylating agents

Running title: Outcome of AML with EMD after Venetoclax/HMA

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Word count: Abstract: 250 words; Text: 2176 words; Table/Figure count: 1/4;

References: 37

Version: August 25th, 2024

ACKNOWLEDGMENTS

We acknowledge publication support from the University of Heidelberg.

Authorship contributions: S.K. and C.P. were responsible for the concept of this paper, contributed to the literature search data collection, contributed patients, analyzed and interpreted data, and critically revised the manuscript. R.F.S. was responsible for the concept of this paper, analyzed and interpreted data, and wrote the manuscript. K.S., G.M., M.R.L, A.K., M.C., D.T.K., A.S.R., C.S., F.G., M.R., L.R., F.S., S.G., F.L., E.B., A.E.P., M.J.L., and T.J. contributed patients and critically revised the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest: All authors declare no competing conflict of interest.

Data sharing statement: Questions regarding data sharing should be addressed to the corresponding author.

Key words: acute myeloid leukemia, extramedullary disease, treatment, venetoclax, hypomethylating agents, outcome

Abstract:

We evaluated response to VEN/HMA in 46 patients with acute myeloid leukemia (AML) characterized by extramedullary disease (EMD). Median age was 65 (range, 19-81) years. Patients had a median of two EMD sites (range, 1-5) and 35 (76%) patients had concurrent bone marrow involvement. Twenty (43%) patients had high-risk genetic features according to the European Leukemia Net 2022 classification. Twenty-nine (63%) were relapsed or refractory after intensive chemotherapy (CTX) including 13 (28%) with prior allogeneic hematopoietic cell transplantation (allo-HCT). Patients received a median of 2 cycles of VEN/HMA (range, 1-31). Twenty (43%) patients achieved complete remission (CR) or CR with incomplete hematological recovery (CRi) after VEN/HMA and five (11%) achieved a partial remission (PR). Six patients were subsequently consolidated with allo-HCT (CR/CRi, n=4; PR, n=2). Median follow-up was 49.1 months (95%-CI, 26.1 months - not reached) and median overall survival (OS) 6.4 months (95%-CI, 5.1-11 months). One-year and 2-years OS rates were 29.3% (95%-CI, 18.6-46.2%) and 12.3% (95%-CI, 5.5-27.6%), respectively. Age with a cut-off of 60 years had no impact on OS (P=0.90). Relapse occurred in 12 of 20 (60%) patients who achieved CR/CRi after VEN/HMA treatment. Of those, all except one succumbed to their disease. Six (30%) patients were in CR/CRi at last follow-up and 2 (10%) died in CR. In our cohort of patients with AML with EMD with high-risk features, treatment with VEN/HMA resulted in an encouraging ORR of 54% with a CR/CRi rate of 43.5%. However, VEN/HMA alone may not be effective in maintaining disease control.

INTRODUCTION

Extramedullary (EM) manifestations of acute myeloid leukemia (AML) are rare, but have a broad clinical spectrum. The overall incidence of EM reported in the literature is not clearly established, ranging from 2.5%[1] to 30%,[2] and varies among different types of AML; patients with monocytic AML[3] and those with t(8;21)(q22;q22)[4,5] or *KMT2* rearrangements[6] have a relatively higher incidence as compared to other subtypes. Furthermore, the prognostic impact of EM is controversial as it has been associated with worse prognosis in some reports[2,5] but not in others.[7-10] Reports on the prognosis of specific EM sites, such as the central nervous system (CNS), are also contradictory.[11-13] EM has traditionally been approached with conventional chemotherapy (CTX)[14] and/or radiation.[15] Factors influencing treatment approach when EM disease (EMD) is present includes patient age, performance status (PS), and comorbidities, disease context (newly diagnosed, or relapsed, also including post allogeneic hematopoietic cell transplantation [allo-HCT]) and manifestation (isolated EMD versus synchronous marrow involvement, and size and location of the EMD). However, data supporting various therapeutic strategies are limited because of the rarity of the disease and lack of randomized clinical trials.[15] Recently, venetoclax (VEN) in combination with hypomethylating agents (HMA) or low-dose cytarabine was approved for treatment of newly diagnosed AML patients who are ≥ 75 years or ineligible for intensive CTX due to comorbidity.[16,17] Currently, VEN/HMA treatment is standard of care in older/unfit AML patients.[18] VEN/HMA is also frequently used in patients who have previously received intensive CTX. Currently, there is a paucity of data evaluating the outcome of AML patients with EMD and treatment with VEN/HMA due to the lack of prospective clinical or larger retrospective cohort studies. The current analysis evaluated a series of adult AML patients with EMD. Our objectives

were to characterize a series of adult patients with EMD AML and evaluate outcome after VEN/HMA treatment within an international retrospective cohort analysis.

Methods

Patients and treatment

Information on 46 adult AML patients with EMD diagnosed between 2015 and 2022 was collected within a multicenter international cohort, including Denmark, Italy, Germany and the United States of America. Inclusion criteria were adult AML patients with EMD who were treated with VEN/HMA. All patients who fulfilled these criteria were included by clinicians representing the participating groups/institutions. Patients with isolated CNS involvement were excluded since those patients received additional CNS treatment (e.g. high-dose methotrexate, intrathecal cytarabine/ methotrexate/ dexamethasone and/or radiation). Diagnosis of AML was based on revised International Working Group criteria.[19] Detailed case report forms including information on baseline patient and disease characteristics, prior chemotherapy (if applicable), allo-HCT, VEN/HMA treatment and response, and survival were collected from all participating centers. Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.[20] A complex karyotype was defined according to the 2017 European LeukemiaNet classification.[21] *FLT3* mutation screening for ITDs and point mutations within the tyrosine kinase domain (TKD) was carried out at each institution as previously described.[22,23] Additional mutational testing was performed for *NPM1* (n=45), *TP53* (n=42) as well as spliceosomal mutations (n=40).

Data collection and analysis were approved by the Institutional Review Boards of the participating centers.

Treatment

In total, 17 of the 46 (37%) cases of AML with EMD occurred in newly diagnosed patients with no prior treatment. The other 29 (63%) patients were relapsed or refractory to prior chemotherapy (median number of prior lines, n=1, range, 1-4). Of those, 23 (79%) patients received prior intensive chemotherapy including allo-HCT in 13 patients. The remaining six patients were treated less intensively: one patient was treated with surgery and low-dose cytarabine for isolated abdominal myeloid sarcoma and achieved complete remission (CR), however, relapsed with EMD one year later. Five patients received hydroxyurea, of whom 2 were treated with azacitidine ± additional agent (APR-246 + azacitidine within a clinical trial, n=1; azacitidine monotherapy, n=1).

Treatment with VEN/HMA was given as previously published.[16,17] EM morphologic response assessment was performed by computed tomography (CT) scans, magnetic resonance imaging (MRI), or positron emission tomography (PET) with imaging modality and response adjudicated locally.[24] Bone marrow examination and sampling of the cerebral spinal fluid (CSF) was pursued as clinically indicated based on disease presentation and known sites of AML involvement. Response was assessed according to International Working Group recommendations.[25] Disappearance of EMD lesions is termed as complete response (CR) and regression of at least 50% as partial response (PR). All patients provided written informed consent for participation in one of the treatment trials or for therapy according to local standards.

Statistical analyses

Patients' characteristics were compared with the Kruskal-Wallis rank sum test for continuous variables and the Fisher exact test for categorical variables. The median follow-up time was computed using the reverse Kaplan-Meier estimate.[26] The Kaplan-Meier method was used to estimate the distribution of relapse-free survival (RFS) and OS.[27] OS was calculated from the start of VEN/HMA treatment until death or censored at last follow-up. RFS was calculated from achievement of CR after the start of VEN/HMA treatment until relapse or death, whatever occurred first, or censored at last follow-up. The confidence interval (CI) estimation for survival curves was based on the cumulative hazard function using the Greenwood formula for variance estimation. Log-rank tests were employed to compare survival curves between groups. The effect of allo-HCT on OS as a time-dependent intervening event was tested by using the Mantel-Byar method for univariable analyses.[28] All statistical analyses were performed with the statistical software environment R, version 4.2.1.[29]

RESULTS

Study cohort

Overall demographic and clinical data were collected from 46 patients at 12 centers diagnosed between 2015 and 2022. Baseline characteristics are summarized in Table 1. Median age was 65 years (range, 19-81 years) and all patients had an ECOG performance status of ≤2. Male patients were more frequently reported (n=30, 65%). Overall, patients had a median of two EMD sites (range, 1-5). Twenty-one (46%) patients had only one EMD manifestation while 25 (54%) had more than one involved site. Of those, 18 (9%) had two sites, 4 (9%) had three, 2 (4%) had four and

one (2%) had five sites involved. Localization of EMD is shown in Figure 1. In addition to EMD disease, most (n=35, 76%) patients had concurrent bone marrow involvement.

Cytogenetic and molecular analyses

Cytogenetic analyses of bone marrow aspirates or peripheral blood were available in 42 (91%) patients. Of those, 17 (40%) had a complex karyotype, 12 a normal karyotype (28.5%), 2 (5%) a translocation t(8;21)(q22;q22) and 11 (26%) other abnormalities, most frequently trisomy 8 (n=5). Of the patients with a normal karyotype, only one had no bone marrow involvement (4% myeloid blasts cells in bone marrow). A total of 45 patients (98%) were tested for *NPM1* and *FLT3* mutations. Of those, 8 (18%) and 3 (7%) harbored *NPM1* and *FLT3*-ITD mutations, respectively. One (2%) patient harbored a *FLT3*-TKD. *TP53* was mutated in 12 (28%) of 43 tested patients. Of those, 8 (67%) had a complex karyotype. Spliceosome mutations were present in 13 (32.5%) of 40 tested patients. According to ELN 2022, 20 patients (43%) had high-risk AML (Table 1).

Response to VEN/HMA, cumulative incidence of relapse (CIR) and death (CID)

A median of 2 cycles (range, 1-31) of VEN/HMA were administered following published regimens.[16,17] Thirty-nine (85%) patients received VEN plus azacitidine (VEN/AZA) and 7 (15%) patients VEN plus decitabine (VEN/DEC).

The CR/CRi rate was 43.5% (n=20/46), of whom 5 were heavily pretreated including allo-HCT. Five (11%) patients achieved a PR, of whom two achieved CR/CRi after allo-HCT (Figure 2). Three patients died in CR/CRi after VEN/HMA due to infections (COVID19 infection, septic shock, infection, n=1, each). Of those patients achieving CR/CRi after VEN/HMA, relapse occurred in 13 of 20 (65%) patients with median

time 2.3 months (range, 0.7 to 44.6 months) on treatment. Of those, all except one succumbed to their disease.

The cumulative incidence of relapse (CIR) and death (CID) for the 20 patients achieving a CR/CRi after 2 years was 56% (95%-CI, 33-80%) and 17% (95%-CI, ND-36%). Six patients were bridged to allo-HCT (CR/CRi, n=4; PR, n=2) including one who received a second allo-HCT. Prior to allo-HCT all patients received ≤3 VEN/HMA cycles. Conditioning was myeloablative in two and non-myeloablative in four patients.

Survival

The median follow-up was 49.1 months (95% CI: 26.1 months - not reached) and the median OS for all patients was 6.4 months (95% CI: 5.1-11 months) (Figure 3). One-year and 2-years OS rates were 29.3% (95%-CI, 18.6-46.2%) and 12.3% (95%-CI, 5.5-27.6%), respectively. Age with a cut-off of 60 years had no impact on OS (P=0.90).

There was no difference in OS (P=0.7) according to whether patients had EMD manifestations only as compared to EMD and bone marrow involvement. Furthermore, no difference in OS (P=0.3) was observed comparing only one EMD site versus more than one site.

Survival from first treatment with VEN/HMA and response to VEN/HMA treatment was superior in patients with newly diagnosed AML and EMD (Figure 4, panel A) compared to those with relapsed or refractory AML and EMD (Figure 4, panel B) with median survival and CR/CRi rate of 8 months (95%-CI, 5.1-20.6 months) and 64% compared to 5.8 months (95%-CI, 3.3-11 months) and 25%, respectively.

Allo-HCT was associated with an in trend better OS as compared to treatment with VEN/HMA (median survival, 18.8 months vs. 6.4 months P=0.06, Mantel Byar test).

Subgroup analysis according to *TP53* mutational status revealed a shorter OS in *TP53* mutated patients as compared to *TP53* wild-type patients (median survival, 4.0 months vs. 9.6 months; P=0.04). In contrast, *NPM1* mutational status had no impact on OS (P=0.4)

Five patients were alive and in CR/CRi at last follow-up, two after allo-HCT and 3 without. All 26 non-responding patients died due to disease progression (n=22) or other causes (infection, n=2; GvHD, n=1; trauma, n=1).

Discussion

EMD is described in varying incidences, ranging from 2.5%[1] to 30%,[2] and varies among different types of AML[3]. For instance, EMD has been described as occurring more frequently in AML with t(8;21)(q22;q22) abnormalities.[4,5] However, in our cohort, only two patients had AML with t(8;21)(q22;q22) and EMD arguing against a higher incidence in patients with this abnormality. Our data are in line with a recent publication by Ganzel et al., who did not find a higher association of AML with EMD and t(8;21) as compared to other cytogenetic abnormalities.[10] EMD may involve different sites, as observed in our series.[10] Of those, liver/spleen, genito-urinary tract as well as skin lesions were the most common sites reported, with an incidence of 20%, followed by lung/pleural effusions, CNS/cerebral fluid and lymph nodes (15%, each). The relatively high incidence of CNS involvement is consistent with a recent report of 103 adult patients with newly diagnosed AML, who were submitted to a routine explorative lumbar puncture (LP) regardless of neurologic symptoms.[30] In this study, 32% of the patients had CNS involvement at diagnosis, which is higher than previously reported of newly diagnosed AML patients who underwent a routine LP.[31] Thus, the authors concluded, that LP should be performed routinely.[30] Given the relatively large number of cases with CNS involvement and EMD, we suggest to

routinely perform an LP in those patients, particularly since CNS is the only EMD site that mandates a specific therapeutic approach, i.e. intrathecal methotrexate and/or high-dose cytarabine.

In our study, 54% of patients with EMD had more than one involved site; 9% had three sites and some patients even had four or five involved sites. The relatively high rate of multiple-site EMD involvement suggests that the development of EMD is an intrinsic feature of the leukemic cells and depends on factors such as the expression of cell surface adhesion molecules.[2,32] In contrast to published data[10], no impact on outcome was observed if more than one site was affected.

The clinical outcome in our study of patients with EMD compares favorably to recently published data by Bae et al, who reported on 11 patients with r/r AML and EMD.[33] In their study the overall response rate was 36.4% (either marrow or EM responses to VEN combination) and median OS of 5.4 months. In our cohort, particularly patients with newly diagnosed AML with EMD had a superior outcome with a CR rate of 64% and a median OS of 8 months after treatment with VEN/HMA. Thus, there is a misconception that VEN/HMA is less potent against EMD then conventional cytotoxic chemotherapy.

Only a minority of our patients went on to allo-HCT. Nevertheless, 33% were still alive and in an ongoing remission at roughly 61 and 71 months of follow-up. If allo-HCT after disease control with VEN/HMA is a veritable option needs to be evaluated in the future.

Our data are comparable to other reports in patients with blast phase of myeloproliferative disease or myelodysplastic syndrome/AML.[34-37]

Conclusions

VEN/HMA resulted in an encouraging CR/CRi rate of 43.5% in a high-risk EM AML population. Particularly patients with newly diagnosed AML with EMD had a good outcome with a CR rate of 64% and a median OS of 8 months after treatment with VEN/HMA. However, responses were not durable. Whether allo-HCT after disease control with VEN/HMA is a veritable option needs to be evaluated in the future.

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Table 1: Baseline characteristics of the 46 patients with extramedullary manifestations.

	Number, n=46	%
Female gender	16	35
Median age (years)	65	19-81 (range)
ECOG status 0 1 2	 12 24 10	 26 52 22
Type of AML **De novo** **s-AML** **t-AML**	 26 19 1	 57 41 2
Disease context **Newly diagnosed** **Relapsed / refractory** - **post allo-HCT**	 17 29 13	 37 63
ELN risk group **favorable** **intermediate** **adverse** **missing**	 5 17 20 4	 11 37 43 9
	Value	**Range**
Median WBC (x10^9/l) **Missing**	6.9 1	0.6-131.2
Platelets (x10^9/l) **Missing**	71 1	6-676
Hemoglobin (g/dl) **Missing**	9 1	3.6-14.2
Median BM blast cells (%) **Missing**	40 5	0-91

Abbreviations: BM, bone marrow; ECOG, eastern cooperative oncology group; WBC, white blood cell count.

Figure 1: Localization of extramedullary involvement. Numbers are indicated in parenthesis (at diagnosis, red; at relapsed / refractory disease, black). Overall, patients had in median 2 extramedullary disease manifestations (range, 1-5). Each localization of extramedullary disease was counted separately; thus, the total number does not add up to the total number of patients. Figure 1 was created with BioRender.com (accessed on August 16th, 2024).

Figure 2: Swim plot showing individual patient, treatment duration and response. CR, complete remission; CRi, complete remission with incomplete hematological recovery; EMD, extramedullary disease; allo-HCT, allogeneic hematopoietic cell transplantation.

Figure 3: Overall survival of patients with acute myeloid leukemia and extramedullary disease after treatment with venetoclax / hypomethylating agents. Green and red dotted lines indicate upper and lower 95% confidence intervals.

Figure 4: Overall survival of patients with acute myeloid leukemia and extramedullary disease after treatment with venetoclax / hypomethylating agents according to disease status. Panel A represents newly diagnosed and panel B relapsed or refractory patients. Green and red dotted lines indicate upper and lower 95% confidence intervals.

Localization of extramedullary disease

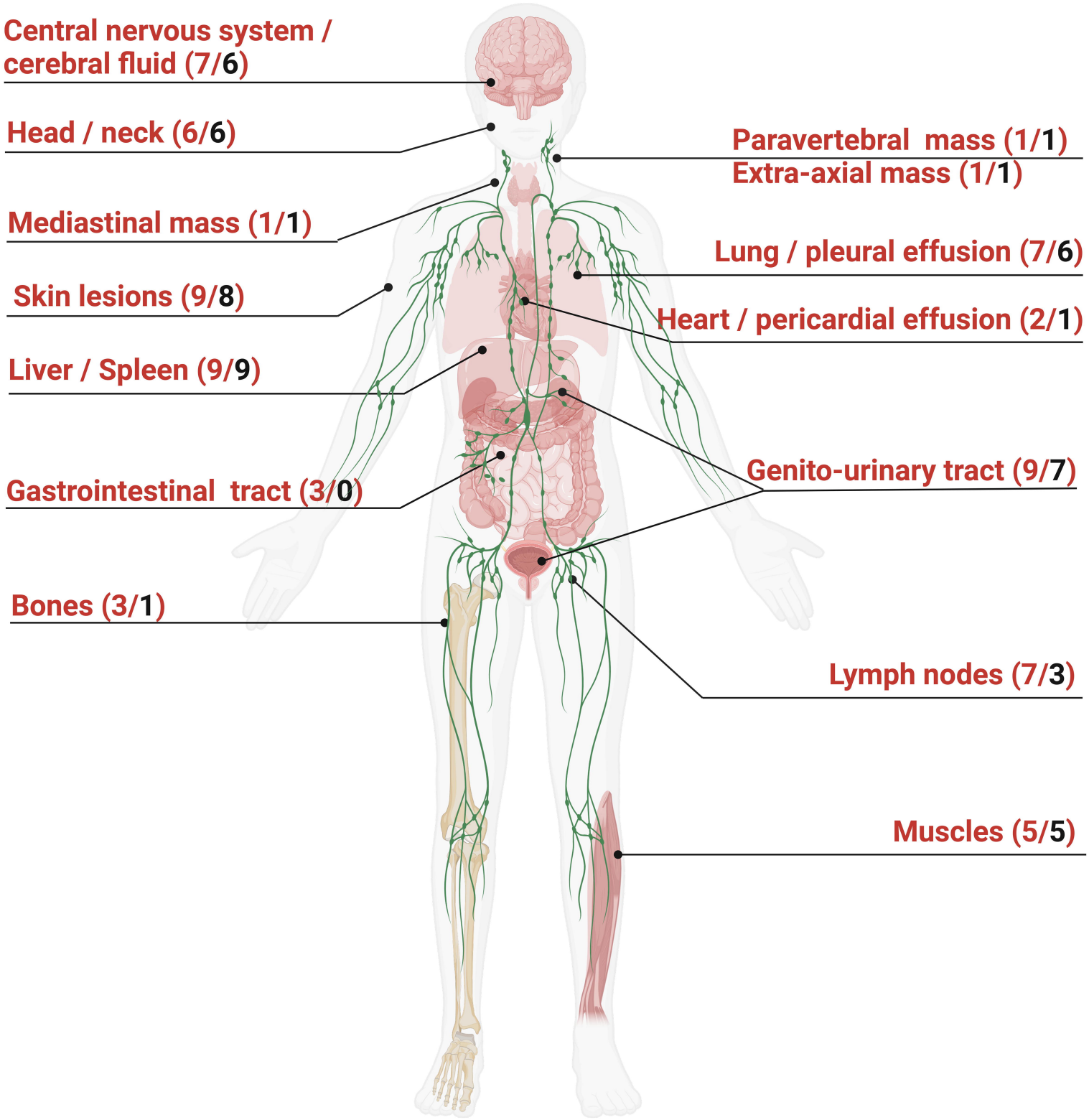


Figure 2

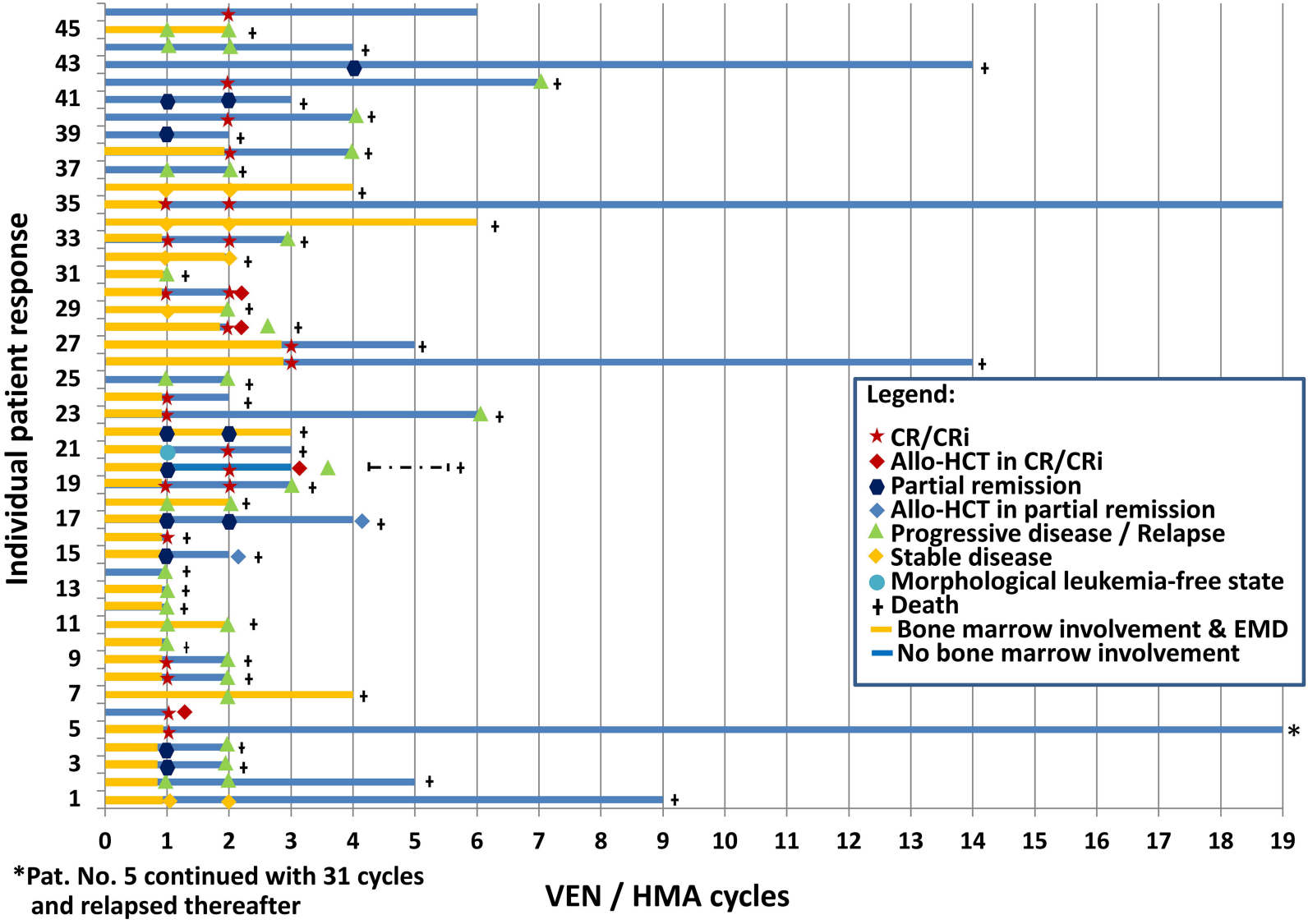

Individual patient response
45
43
41
39
37
35
33
31
29
27
25
23
21
19
17
15
13
11
9
7
5
3
1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
VEN / HMA cycles
Legend:
CR/CRi
Allo-HCT in CR/CRi
Partial remission
Allo-HCT in partial remission
Progressive disease / Relapse
Stable disease
Morphological leukemia-free state
Death
Bone marrow involvement & EMD
No bone marrow involvement
*Pat. No. 5 continued with 31 cycles and relapsed thereafter

Figure 3

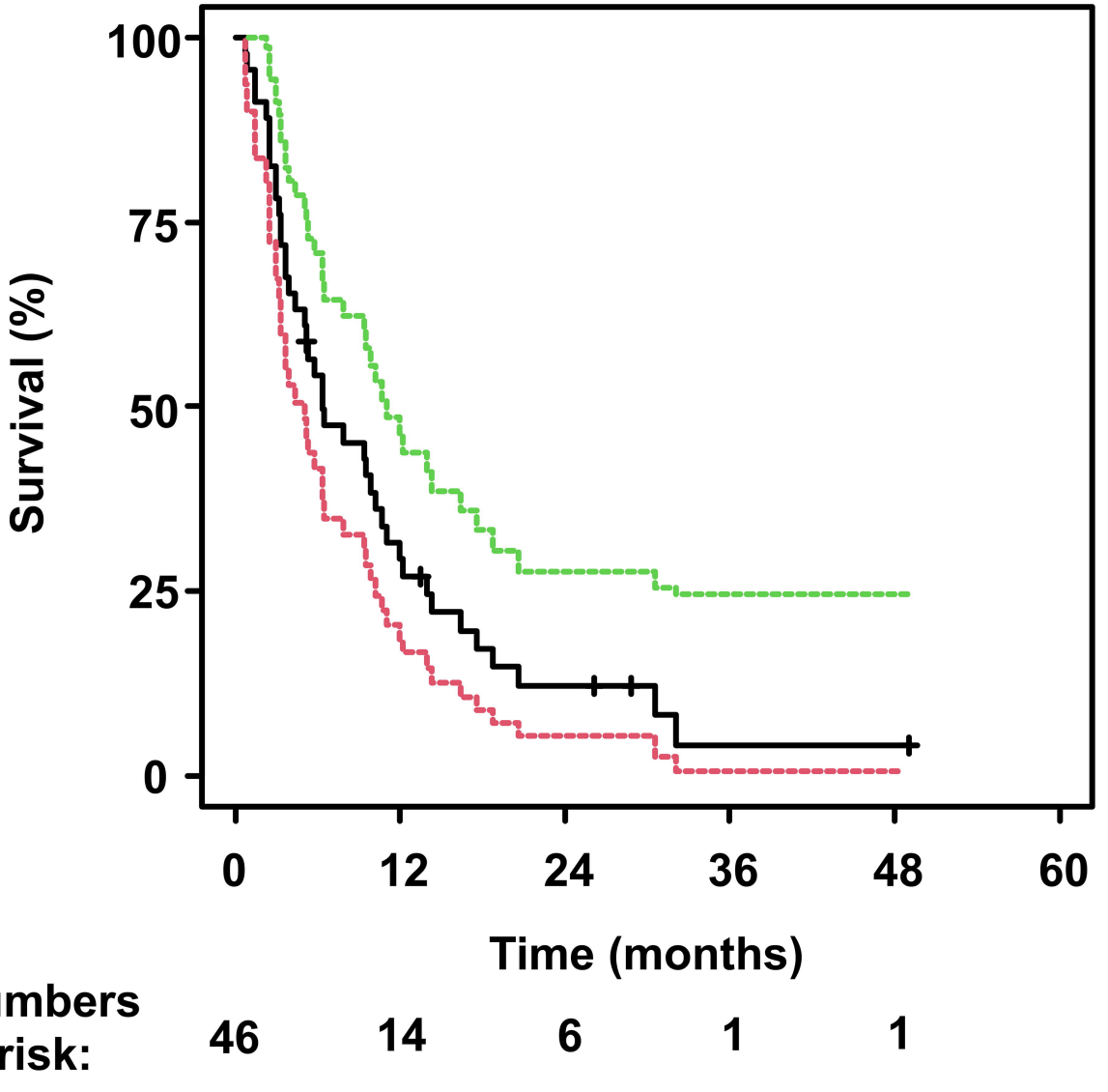
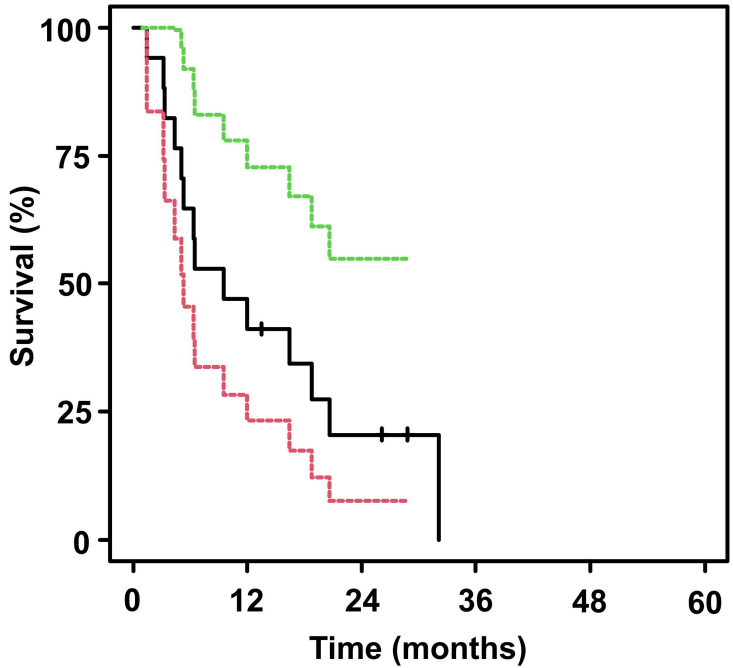
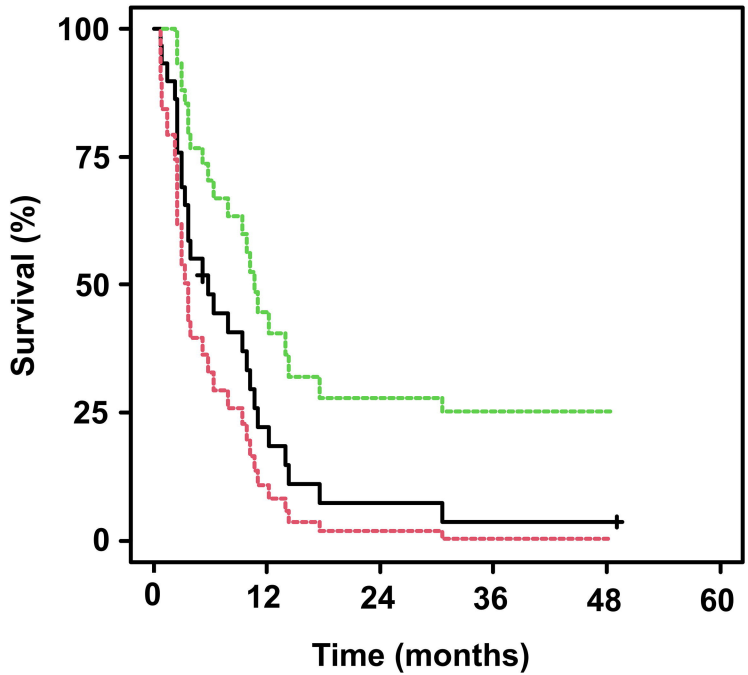

100
75
50
25
0
Survival (%)
0
12
24
36
48
60
Time (months)
Numbers at risk:
46
14
6
1
1

Figure 4, Panel A



Numbers at risk: 17 7 3

Figure 4, Panel B



Numbers at risk: 29 6 2 1 1