European LeukemiaNet-defined primary refractory acute myeloid leukemia: the value of allogeneic hematopoietic stem cell transplant and overall response

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We sought to appraise the value of overall response and salvage chemotherapy, inclusive of allogeneic hematopoietic stem cell transplant (AH SCT), in primary refractory acute myeloid leukemia (prAML). For establishing consistency in clinical practice, the 2017 European LeukemiaNet (ELN) defines prAML as failure to attain CR after at least 2 courses of intensive induction chemotherapy. Among 60 consecutive patients (median age 63 years) correspondent with ELN-criteria for prAML, salvage was documented in 48 cases, 30/48 (63%) being administered intensive chemotherapy regimens and 2/48 consolidated with AH SCT as first line salvage. 13/48 (27%) attained response: CR, 7/13 (54%), CRI, 2/13 (15%), MLFS, 4/13 (31%). The CR/CRI rate was 9/48 (19%), with CR rate of 7/48 (15%). On univariate analysis, intermediate-risk karyotype was the only predictor of response (44% vs 17% in unfavorable karyotype; $P = 0.04$). Administration of any higher-dose ($>1 \text{g/m}^2$) cytarabine intensive induction ($P = 0.50$), intensive salvage chemotherapy ($P = 0.72$), targeted salvage (FLT3 or IDH inhibitors) ($P = 0.42$), greater than 1 salvage regimen ($P = 0.89$, age < 60 years ($P = 0.30$), and de novo AML ($P = 0.10$) did not enhance response achievement, nor a survival advantage. AH SCT was performed in 12 patients with (n = 8) or without (n = 4) CR/CRI/MLFS. 1/2/5-year overall survival (OS) rates were 63%/38%/33% in patients who received AH SCT (n = 12) vs 27%/0%/0% in those who achieved CR/CRI/MLFS but were not transplanted (n = 5), vs 14%/0%/0% who were neither transplanted nor achieved CR/CRI/MLFS (n = 43; $P = 0.001$); the median OS was 18.6, 12.6 and 5.6 months, respectively. Although CR/CRI/MLFS bridged to AH SCT (n = 8), appeared to manifest a longer median OS (20 months), vs (13.4 months) for those with no response consolidated with AH SCT (n = 4), the difference was not significant $P = 0.47$. We conclude AH SCT as indispensable for securing long-term survival in prAML ($P = 0.03$ on multivariate analysis), irrespective of response achievement.

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INTRODUCTION

The 2017 European LeukemiaNet (ELN) characterizes primary refractory acute myeloid leukemia (prAML) as the absence of complete remission with count recovery (CR), after at least 2 courses of intensive induction chemotherapy [1]. Current literature on prAML is confounded by non-uniform disease definitions and study populations inclusive of relapsed AML [2–7]. AH SCT is proclaimed the best and only curative treatment option [2–6]. In the absence of controlled evidence for guidance, current prAML treatment is focused on achieving CR or CRI without count recovery (CRI) first, through administering a panoply of salvage regimens, possibly affecting transplant candidacy. A 2020 report from MD Anderson Cancer Center (MDACC), cited rates of CR/CRI for AML refractory to one course of intensive higher dose (>1 g/m²) induction, as 11%, 5%, and 2%, after treatment with one, two, and three salvage regimens, respectively [8]. In general, response in prAML has been influenced by younger age (<60 years), favorable karyotypes, de novo context, blast percentage prior to salvage, and intensive salvage regimens [9–11]. In the current retrospective case series of 60 consecutive patients with ELN-defined prAML, we clarify the value and futility of salvage chemotherapy; identifying AH SCT as invaluable for procuring long-term survival regardless of response category prior to transplant.

METHODS

After approval from our institutional review board, the Mayo Clinic, Rochester, MN, AML database ($n = 1800$; 2004–2021) was queried to identify 60 patients conforming to the ELN 2017 definition of prAML [1]. All patients displayed persistent leukemia with >5% bone marrow blasts after 2 courses of ELN-classified intensive induction chemotherapy. Supplementary Table 1 delineates these intensive chemotherapy induction regimens. All 60 patients received a lower or higher dose (>1 g/m²) cytarabine-based intensive regimen, either for their first or second induction course (outlined in Supplementary Table 2). A summary of the 2 intensive induction courses, subdivided into lower or higher cytarabine-dose based inductions is as follows:

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Table 1. Clinical characteristics of 60 patients with European LeukemiaNet-defined primary refractory acute myeloid leukemia (AML), stratified by the achievement of response after documented salvage therapy.

| Variables | All patients n = 60 (100%) | Patients receiving documented salvage (n = 48) | P-value A vs B |
|-----------|-----------------------------|-----------------------------------------------|----------------|
| Overall response category | | | |
| CR, n (%) | 7 (54) | 15% | |
| CRi, n (%) | 2 (15) | 4% | |
| MLFS, n (%) | 4 (31) | 8% | |
| Age in years, median (range) | 63 (23–78) | 58 (27–72) | 63 (23–78) | 0.48 |
| Age ≥ 60 years, n (%) | 38 (63) | 6 (46) | 21% | 22 (63) | 0.30 |
| Males, n (%) | 40 (67) | 9 (69) | 29% | 22 (67) | 0.87 |
| AML type | | | |
| De novo (primary), n (%) | 28 (48) | 9 (69) | 38% | 15 (43) | 0.10 |
| Secondary, n (%) | 31 (52) | 4 (31) | 17% | 20 (57) | |
| FLT3/NPM1 distributions: n = evaluable | | | |
| FLT3-ITD and NPM1 negative, n (%) | 23 (66) | 6 (60) | 33% | 12 (63) | |
| FLT3-ITD negative NPM1 positive, n (%) | 1 (3) | 0 (0) | 43% | 0 (0) | |
| FLT3-ITD and NPM1 positive, n (%) | 3 (9) | 0 (0) | 3 (16) | |
| FLT3-ITD positive and NPM1 negative, n (%) | 7 (20) | 3 (30) | 4 (21) | |
| FLT3-TKD positive and NPM1 negative, n (%) | 1 (3) | 1 (10) | 0 (0) | |
| Positive molecular mutations on NGS: n = evaluable | | | |
| ASXL1, n (%) | 1 (3) | 1 (17) | – | |
| BCOR, n (%) | 1 (3) | 1 (3) | |
| CEBPA, n (%)—silent | 1 (3) | 1 (3) | |
| CSF3R, n (%) | 1 (3) | 1 (3) | |
| DNMT3A, n (%) | 2 (6) | 2 (6) | |
| GATA2, n (%) | 1 (3) | 1 (3) | |
| KRAS, n (%) | 1 (3) | 1 (3) | |
| NRAS, n (%) | 1 (3) | 1 (3) | |
| RUNX1, n (%) | 1 (3) | – | |
| SETBP1, n (%) | 1 (3) | 1 (3) | |
| SF3B1, n (%) | 2 (6) | 1 (3) | |
| TET2, n (%) | 1 (3) | 1 (3) | |
| TPS3, n (%) | 4 (11) | 4 (13) | |
| U2AF1, n (%) | 1 (3) | – | |
| WT1, n (%) | 1 (3) | – | |
| IDH2, n (%) | 1 (3) | – | |
| ELN karyotype at diagnosis: n = evaluable | | | |
| Intermediate, n (%) | 24 (51) | 8 (62) | 44% | 10 (29) | 0.04 |
| Unfavorable, n (%) | 35 (59) | 5 (38) | 17% | 24 (71) | |
| % BM blasts before salvage therapy: n = evaluable | | | |
| n = 60 | n = 13 | n = 35 | |
| Median (range) | 23 (0–99) | 25 (5–99) | N/A | 21 (0–90) | 0.66 |
| Documented number of salvage regimens to response or death: n = evaluable | | | |
| n = 48 | n = 13 | n = 35 | |
| One, n (%) | 26 (54) | 7 (54) | 35% | 19 (54) | |
| Two, n (%) | 17 (35) | 6 (46) | 11 (31) | |
| Three or more, n (%) | 5 (10) | 0 (0) | 5 (14) | |
| Salvage intensity: | | | 0.47 |
| Intensive, n (%) | 30 (63) | 9 (69) | 30% | 21 (60) | |
| Less Intensive, n (%) | 13 (27) | 2 (15) | 15% | 11 (31) | |
Table 1. continued

| Variables                        | All patients | Patients receiving documented salvage (n = 48) | P-value A vs B |
|----------------------------------|--------------|-----------------------------------------------|----------------|
|                                  | n = 60 (100%)| Patients with response (CR/CRi/MLFS) (Group A) | Response rate (%) | Patients without response (Group B) n = 35 (73%) |
| Targeted, n (%)                  | 5 (10)       | 2 (15)                                        | 40%             | 3 (9)                                       | 0.001 |
| AHST, n (%)                      | 12 (20)      | 8 (62)                                        | N/A             | 4 (12)                                      | 0.09  |
| Relapse after AHST, n (%)        | 8 (25)       | N/A                                           | n = 4           | 3 (75)                                      |       |

ELN European LeukemiaNet, AML acute myelogenous leukemia, BM bone marrow, CR/CRi complete remission with (CR) or without (CRi) blood count recovery, MLFS morphologic leukemia-free state, AHST allogeneic hematopoietic stem cell transplant, Secondary prior chemotherapy or radiation therapy-related AML, AML arising from prior myeloproliferative neoplasm, myelodysplastic syndrome, or chronic myelomonocytic leukemia, FLT3 FMS-like tyrosine kinase 3, ITD internal tandem duplication, TKD tyrosine kinase domain, NPM1 Nucleophosmin 1 = included 1 patient with favorable cytogenetics, N/A not applicable. Bold values indicate statistically significant values.

RESULTS

A total of 60 patients (median age 63 years, range 23–78; 67% males) were diagnosed with current (2017) ELN-defined prAML. 8/60 (13%) received supportive palliative care, while an additional 4 patients were lost to follow-up after 2 courses of intensive induction. Forty-eight patients received documented salvage therapy (inclusive of 2 patients bridged directly to transplant) and were stratified according to response: 13/48 (27%) attained response: CR 7/13 (54%), CRi 2/13 (15%), or MLFS 4/13 (31%) (group A); and 35/48 (73%) no response (group B) (Table 1). The true CR rate was 7/48 (15%). Only 1 patient displayed a favorable karyotype and did not achieve a response (group B). Table 2 highlights the baseline cytogenetics and molecular features of all 13 CR/CRi/MLFS patients. Table 3 in parallel illustrates 27 molecular profiles and outcomes of patients who did not achieve any response. Aside from FLT3/NPM1, TP53 was the most prevalent mutation and only seen in those without a response, 4/31 (13%): all 4 patients had FLT3 WT/ NPM1 WT (wild type) and unfavorable karyotypes (highlighted in blue in Table 3), while only 1/4 (25%) had de novo AML. n = 2/4 (50%) with TP53 mutations proceeded to transplant with active disease (BM blasts > 30%) after being on the investigational Iomab-B salvage trial. OS for TP53 mutations: less than 5 months for n = 3 (75%), each of these patients received only 1 salvage regimen (hypomethylating agent, n = 2; investigational Iomab-B, n = 1), whereas n = 1 (received 3 salvage regimens: 2 intensive, then lomab-B) had OS 22.4 months with AHSTC.

Univariate analysis identified intermediate-risk karyotype (44% vs 17% for unfavorable risk; P = 0.04) as predicting the likelihood of response (Table 1). Higher dose cytarabine induction did not predict response (CR/CRi/MLFS) attainment (8/38, 21%) vs lower dose cytarabine intensive induction (5/22, 23%), P = 0.88. Similarly, the receipt of any targeted salvage therapy vs all other non-targeted salvage did not predict response: 2/5 (40%) vs 11/43 (26%), respectively (P = 0.51). FLT3/NPM1 WT status (P = 0.26), BM blast percent prior to salvage (0.66), intensive (P = 0.72) or targeted salvage chemotherapy (FLT3 or IDH inhibitors) (P = 0.42), greater than 1 salvage regimen (P = 0.89) [P values involving salvage chemotherapy reflect those excluding the 2 patients bridged directly to transplant], age ≥ 60 years (P = 0.30), and de novo AML (P = 0.10) also did not predict response, nor a survival advantage.

Patients receiving only less intensive salvage (16/48, 33%) had unfit status or prolonged complications from chemotherapy-induced cytophenias, such as transfusion dependence and neutropenic infections. In excluding the 2 patients bridged directly to transplant, on univariate and multivariate, median survival after any intensive salvage chemotherapy was 8.5 months vs. 7.4 months for only less intensive/targeted therapy (P = 0.08). The majority with only less intensive/targeted therapy received only 1 salvage regimen 14/16 (88%) vs 10/30 (33%) having intensive salvage (P = 0.001) In comparison to patients...
| Response type | Cytogenetics | Molecular profile | Age (years) | Number of salvage regimens to response | SCT | Progression-free survival (months) | OS (months) | Alive |
|---------------|--------------|------------------|-------------|----------------------------------------|-----|----------------------------------|------------|-------|
| MLFS          | 46, XY [20]  | FLT3-ITD positive NPM1 WT | 32          | One: Decitabine + Sorafenib             | No  | 2.6 (relapsed)                   | 11.3       | No    |
| MLFS          | 46, XX t(7;13)(q21.2;q12) [2]/46, XX | FLT3-ITD positive NPM1 WT | 56          | Two: Cycle 1 HIDAC, then Mylotarg       | Yes | 7.1                             |            |       |
| MLFS          | Unfavorable 46, XY, der(1)t(1;3)(p36.1; q21) [20] | FLT3-ITD WT NPM1 WT | 55          | Two: Idarubicin + Clofarabine, then Decitabine | Yes | 13.2                           | 25.4       | No    |
| MLFS          | Unfavorable 45, XY, −7 [10] | KIT positive FLT3-ITD WT NPM1 WT | 60          | Two: Cycle 1 HIDAC, then Clofarabine   | Yes | 114                            | 120        | Yes   |
| CRI           | 46, XY [20]  | FLT3-ITD positive NPM1 WT | 62          | One: Gilteritinib                       | No  | 1.1                             | 5.7        | No    |
| CRI           | Unfavorable 45, XX, der(3;5)(q10;p10) [2]/46, sl, +8 [4]/46, sl, −22 [4] | FLT3-ITD WT NPM1 WT | 66          | One: NK cell infusion with IL-15         | No  | 1 (relapsed)                   | 12.6       | No    |
| CR            | Unfavorable +7, del 13q, +mar [20] | FLT3-ITD WT NPM1 WT | 64          | One: Clofarabine + Cytarabine           | Yes | 48                             | 51.8       | Yes   |
| CR            | 46, XY [20]  | FLT3-ITD WT NPM1 WT | 46          | One: MEC                               | Yes | Relapsed 1.8 months after CR, 2nd relapse 2 months after SCT | 7.8        | No    |
| CR            | Unfavorable 6p+, 7p+, 21q+ [20] | Not done | 72          | One: MEC                               | No  | Unknown whether relapsed    | 24.8       | No    |
| CR            | 46, XY, t(2;11)(p21;q23) [20] | FLT3-ITD WT NPM1 WT | 68          | One: Cycle 1 HIDAC                     | Yes | No                             | 72.8       | Yes   |
| CR            | 46, XY [20]  | FLT3-TKD positive NPM1 WT | 27          | Two: Gilteritinib, then Decitabine + Venetoclax | No  | 1.6 (recent response)       | 9.5        | Yes   |
| CR            | Unfavorable 46, XX, 3, del(5)(q13q33), +8, der(12)add(12)(p11.2) add(12)(q24.1) [20] | Not done | 56          | Two: MEC, then S-HAM                   | Yes | 8                             | 11         | No    |
| CR            | 46, XX, inv(2)(p23q31) [20] | Not done | 58          | Two: Clofarabine + Cytarabine, then MEC | Yes | 6.6 (relapsed)                | 14.8       | No    |

CR complete remission, CRI CR with incomplete count recovery, MLFS morphologic leukemia-free stat.
Table 3. Molecular profiles and outcomes of 27/47 primary refractory AML patients who received supportive care or documented salvage without response.

| Patient | Molecular mutations | ELN-defined unfavorable karyotype | Age at diagnosis (years) | SCT Number of salvage regimens | Type of salvage to SCT or death | OS (months) |
|---------|---------------------|-----------------------------------|--------------------------|-------------------------------|---------------------------------|-------------|
| 1       | TET2, SF3B1 FLT3/ NPM1 WT | 69                                | None                     |                               |                                 | 4.2         |
| 2       | RUNX1, U2AF1, ASXL1 FLT3/NPM1 WT | 72                                | None                     |                               |                                 | 4.2         |
| 3       | NPM1 positive FLT3 WT | Yes 64                            | None                     |                               |                                 | 4.7         |
| 4       | FLT3/NPM1 WT | 65                                | None                     |                               |                                 | 16.0        |
| 5       | FLT3/NPM1 WT | Yes 52                            | Unknown                  |                               |                                 | 9.2         |
| 6       | FLT3/NPM1 WT | 63                                | Unknown                  |                               |                                 | 21.1        |
| 7       | MPL, NRAS FLT3/ NPM1 WT | Yes 41                            | 1 Decitabine + Venetoclax |                                 |                                 | 2.6         |
| 8       | TP53 FLT3/NPM1 WT | Yes 64                            | 1 Azacitidine            |                               |                                 | 3.6         |
| 9       | GATA2, TP53, DNMT3A FLT3/ NPM1 WT | Yes 62                            | 1 Iomab                  |                               |                                 | 4.4         |
| 10      | TP53 gene deletion FLT3/NPM1 WT | Yes 59                            | 1 Decitabine             |                               |                                 | 4.8         |
| 11      | FLT3/NPM1 WT | Yes 65                            | 1 Azacitidine            |                               |                                 | 7.2         |
| 12      | FLT3/NPM1 WT | Yes 46                            | 1 Azacitidine            |                               |                                 | 7.7         |
| 13      | FLT3-ITD positive NPM1 WT | 65                                | 1 Decitabine + Sorafenib |                                 |                                 | 8.3         |
| 14      | FLT3-ITD positive NPM1 WT | 23                                | 1 CLAG-M                 |                               |                                 | 3.9         |
| 15      | FLT3-ITD positive NPM1 WT | 62                                | 2 CLAG-M, then Quizartinib |                                |                                 | 9.6         |
| 16      | FLT3-ITD positive NPM1 WT | 65                                | 2 Clofarabine + Cytarabine, then Azacitidine + Sorafenib |                                 |                                 | 22.4        |
| 17      | KRAS FLT3/NPM1 WT | 64                                | 2 Decitabine, then Cytarabine (1 g/m²) |                                |                                 | 3.4         |
| 18      | CEBPA silent JAK2 positive FLT3/ NPM1 WT | Yes 58                            | 2 Clofarabine + Cytarabine, then Azacitidine + Sonedegib |                                |                                 | 3.9         |
| 19      | FLT3/NPM1 WT | Yes 61                            | 2 CLAG-M, then Decitabine |                               |                                 | 4.8         |
| 20      | FLT3/NPM1 WT | Yes 63                            | 2 Carboplatin + Topotecan, then Mylotarg |                                |                                 | 5.1         |
| 21      | FLT3-ITD positive NPM1 positive | 58                                | 2 MEC, then Clofarabine |                               |                                 | 5.2         |
| 22      | TP53, SF3B1 FLT3/ NPM1 WT | Yes 64                            | 3 MEC, then Carboplatin + Topotecan, then Iomab |                                |                                 | 22.4        |
| 23      | DNMT3A, IDH2 | 65                                | 3 Azacitidine + Sonedegib, then Enasidenib, then pan-IDH inhibitor |                                |                                 | 12.5        |
| 24      | BCOR/CBF AML FLT3-ITD positive (later in course) | Yes 50                            | 4 5 + 2, then 1 cycle of cytarabine (3 g/m²), then Azacitidine, then Gilteritinib |                                |                                 | 9.1         |
| 25      | FLT3-ITD positive NPM1 WT | 25                                | 5 1 cycle of cytarabine (3 g/ m²), then Carboplatin + Topotecan, then Clofarabine, then Lurbinectedin, then Decitabine |                                |                                 | 12.3        |
| 26      | FLT3-ITD positive NPM1 positive (complicated by myeloid sarcoma of sacrum) | Favorable t(8:21) | 44 | 2 cycles of cytarabine (3 g/m²), then 7 + 3, then 1 cycle cytarabine (3 g/m²), then Clofarabine, then Carboplatin + Topotecan |                                | 18.7        |
| 27      | SETBP1, CSF3R FLT3/ NPM1 WT | 53                                | Yes AHSCT                | Direct transplant (BM blasts 5%) |                                 | 87.5        |
administered intensive salvage, the distribution of intermediate vs.
unfavorable cytogenetics (P = 0.47), FLT3/NPM1 status (P = 0.22),
age ≥60 years (P = 0.31), primary vs. secondary AML at diagnosis
(P = 0.14), % BM blasts prior to salvage (P = 0.24), and attainment of
response CR/CRI/MLFS (P = 0.72) with greater than 1 salvage
(P = 0.30).

MRD evaluation after response in this cohort was limited, due to
earlier period of AML diagnoses when MRD statuses were not
routinely performed. MRD was assessed in 7/13 (54%) patients who
achieved either CR (n = 5)/CRI (n = 1)/MLFS (n = 1). Only 1 of these
7 patients was CR-MRD Negative and bridged to transplant, the
remaining 6 were MRD Positive (n = 2 were bridged to transplant).
Irrespective of bridging to AHSCST, the univariate analysis did not
display a significant difference in median survival P = 0.26. Median
survival of MRD Positive patients was 14.8 months, the median
survival of the n = 1 MRD Negative patient has not yet been
reached. Similarly, there was no difference in median overall
survival between MRD Positive >1% (n = 3, median 15 months) or
MRD Positive >0.1% and <1% (n = 3, median 18 months), P = 0.59;
or progression-free survival (6.6 months for MRD Positive >1% vs
12 months for MRD Positive >0.1%), P = 0.87.

Progression-free survival after CR/CRI/MLFS (3–12 months and
greater than 12 months), on univariate analysis: was determinant
on FLT3 WT and NPM1 WT status (range 2.5 – 120 months); at last follow up, only 5 (8%) patients were alive, including 4/13 (31%) from group A and 1/35 (3%) from group B;
4/5 (80%) alive had been bridged to AHSCST. On univariate analysis,
median OS after administration of intensive salvage chemotherapy
(n = 30, 8.5 months vs n = 16, 7.4 months vs. n = 2 bridged directly
to transplant, median not reached) (P = 0.15), achievement of CR, CRI,
or MLFS (n = 7, median 25 months vs n = 2, 9 months, vs n = 4,
19 months vs no response, n = 47, 5.6 months) (P < 0.001), and
bridging to AHSCST (n = 12, median 18.6 months vs n = 48,
5.7 months) (P < 0.001) prognosticated survival benefit (Fig. 1).
Survival was not affected by higher dose cytarabine induction
regimens (median survival 8.1 months vs 5.1 months for less
intensive) (P = 0.69) or receipt of targeted salvage therapy (P = 0.93),
(median survival 9.6 months (n = 5) vs 7.6 months (n = 43) with all
other salvage therapy (intensive and less intensive/investigational)).
Patients with CR/CRI/MLFS bridged to AHSCST (n = 8), appeared to
manifest a longer median OS (20 months), vs (13.4 months) for those
with no response consolidated with AHSCST (n = 4), P = 0.47 (Fig. 2).
Multivariate analysis of the following predictive variables further
confirmed AHSCST (Fig. 1) as the strongest predictor for long-term
survival (P = 0.027), while achieving any response (P = 0.06) resulted
in longer median survival, which was not durable in the absence of
consolidation with AHSCST (Fig. 2); the type of response CR/CRI
or MLFS vs no response (P = 0.88) became insignificant.

DISCUSSION
The current study addresses a frequent and practical question in
the care of patients with prAML: is salvage chemotherapy and
overall response worth pursuing, and what are the conditions for
success or failure in that regard? Our observations suggest that
salvage chemotherapy in prAML is clearly justified in the setting of
consolidation with AHSCST. Although the number of informative
cases was too small to allow definitive conclusions, we were
encouraged that AHSCST retained its value in the absence of CR/
CRI/MLFS, at the time of transplant. The latter point is noteworthy
considering the limited merit of administering multiple salvage
regimens for achieving CRI/MLFS before transplant. For prAML
patients who did not undergo AHSCST, the benefit from salvage
chemotherapy was limited to prolongation of survival by a few
months, and only in patients with intermediate-risk karyotype.

Consistent with existing literature on prAML, we confirm its dire
prognosis with cited median survival ranging from 3 to 3.8 months
in patients treated with supportive care alone [9] and 3–19 months
for those receiving salvage therapy [9–14]. The ELN denotes
regimens containing higher doses of cytarabine (≥1000 mg/m²)

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A 2020 study by Short et al. [18] at the MD Anderson Cancer Center focused on those undergoing AHSCT after response (CR/CRi/MLFS) with MRD negative or positive status. The cohort involved 141 patients with relapsed or refractory AML (88/141, 62% were refractory to induction or had remission lasting <1 year) in whom CR/CRi/MLFS was achieved after 1 cycle of salvage therapy and MRD status evaluated. Refractoriness was defined as refractory to 1 cycle of intensive chemotherapy or 2 cycles of less intense chemotherapy. 90 patients (64%) received intensive cytarabine chemotherapy, and 51 patients (36%) had lower-intensity therapy (mainly HMA). Thirteen patients (9%) had undergone AHSCT. CR-MRD negativity was noted in 43% and manifested lower rates of early relapse, however, the 13 patients undergoing AHSCT (all in second remission) had the best outcomes despite MRD status or type of response. MRD status evaluation was limited in our cohort, with assessment in 7/13 (54%), and only n = 1 manifesting CR-MRD negativity, with a median survival not yet reached. The CR-MRD negative patient was bridged to SCT, and MRD positivity, >1% (n = 2) pre-AHSCT did not impact relapse risk (P = 0.31) or OS (P = 0.48) post-AHSCT. Though a limited sample, our findings corroborate with Short et al, in MRD status not affecting outcome post-SCT.

Limited clinical data exists on the significance of ELN-defined MLFs. Particularly, in our prAML cohort, outcomes were similar in MLFS vs. CR/CRi with or without transplant. This is consistent with a 2015 retrospective study on 270 AML patients, without primary induction failure, undergoing AHSCT [19], where 206 patients were in CR, 45 in CRi, and 19 in MLFS at time of transplant, with respective 3-year survival rates, post-transplant, of 40%, 46%, and 47% (P = 0.88). Survival after AHSCT, in prAML, requires further validation that should consider confounding effects from age, number of chemotherapy cycles before transplant, BM and peripheral blood blast %, and karyotype [20, 21].

The impact of intensive salvage chemotherapy for attaining CR/CRi prior to AHSCT has been studied in 845 AML cases failing one course of intensive induction chemotherapy [10], in which multivariate analysis revealed CR/CRi prior to transplant, predicted the best survival while older age and unfavorable karyotype adversely affected CR/CRi. Other reports have similarly addressed the importance of attaining CR before transplant [11]. On the other hand, AHSCT as first-line salvage, irrespective of achieving remission, has also been investigated in prAML [21–23]. In one retrospective cohort from MDACC involving patients refractory to 1 course of intensive induction, median survival was 16 months (3-year survival 39%) in those bridged directly to AHSCT (n = 28) vs 3 months (3-year survival 2%) with salvage alone (n = 149) (P = 0.001) [12].

Venetoclax (an oral highly selective Bcl-2 inhibitor) in combination with HMA, as opposed to venetoclax single-agent therapy, has shown promise in refractory/relapsed AML (defined as refractory or relapsed after one induction regimen of either intense or less intense (inclusive of HMA alone), or relapse post-AHSCT) [24–26]. Most patients received at least ≥2 salvage regimens prior to initiation. Toxicities (particularly grade 3 and 4 cytopenias: neutopenia and thrombocytopenia) complicate its use in refractory or relapsed AML. Nonetheless, activity has been shown in FLT3, TP53 mutations, and unfavorable karyotypes. After a median of 1 to 2 cycles of HMA + Venetoclax, overall response rates (CR/CRi) have ranged from 46% (41/90), median OS (7.8 months for all patients and 16.6 months for CR/CRi) [24]; to 33% (14/42), median OS 3 months vs 15 months for CR/CRi [25]; to 42% (23/55), 62% (34/55), median OS 7.8 months with response, and duration of response 16.8 months [26]. In this study, 2 patients received HMA + Venetoclax as a first or second line of salvage. One patient with NRAS, MPL positivity, FLT3/NPM1 WT had received 2 courses of high-dose cytarabine inductions with residual BM blast burden 80% and dural myeloid sarcoma. 1 cycle of decitabine + venetoclax was started, though discontinued due to severe pancytopenias (OS 2.6 months). The second patient was FLT3-TKD positive, NPM1 WT, biallelic WT1, who started...
on gilteritinib as first-line salvage, cycle 2 halted due to elevated liver enzymes. BM blast burden had reduced >50% (from 40% to 11%). 2 months after, with BM blasts rising to 60%, FISH positive for RUNX1 in 53% of nuclei and a cryptic 3:1 translocation, cycle 1 of decitabine + venetoclax was started. CR was achieved after 1 cycle of decitabine + venetoclax with the disappearance of FLI3-TKD positivity and FISH abnormalities. MRD positivity on flow cytometry was observed to be 0.13%. The patient has continued with at least 3 cycles of decitabine + venetoclax, cycle 3 delayed due to a neutropenic PICC line infection.

In summary, our findings highlight the importance of AHSCCT for securing long-term survival in a homogeneously exclusive cohort of ELN-defined prAML (primary induction failure), regardless of the degree of hematologic recovery. Currently, available salvage chemotherapy regimens (either intensive or less intensive (inclusive of targeted therapy)) for this prAML population were similar in regard to response or survival benefits. The promising clinical data acquired for HMA + venetoclax in combined refractory and relapsed AML requires further investigation in patients with primary induction failure and molecular mutations.

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AUTHOR CONTRIBUTIONS
All authors contributed to patients or were involved in data analysis, review of pathology, or cytogenetic information. KHB and AT designed the study, collected data, performed data analysis, and wrote the manuscript. JK collected data, performed analysis, and wrote the manuscript. CAH reviewed pathology slides, RPK reviewed cytogenetic studies.

COMPETING INTERESTS
The authors declare no competing interests.

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