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Treatment for relapsed pediatric acute myeloid leukemia: variability and comparative effectiveness of current approaches to re-induction

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Declaration of interests

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Data sharing

Deidentified individual participant data underlying the results reported, the study protocol, and the statistical analysis plan will be made available upon reasonable request to qualified investigators for purposes of reproducing analyses or conducting secondary analyses. Requests will be reviewed and require a brief proposal and execution of a data use agreement to protect participant confidentiality. Data requests should be directed to the corresponding author (elgartenc@chop.edu). Data will be available beginning at publication.

Author contributions

C.W.E., K.D.G and R.A. conceptualized, designed and planned the analysis. K.D.G. and R.A. oversaw all data collection for the REAL AML cohort. C.W.E., L.W. and Y.L. performed the statistical analysis. All authors reviewed the analyses, contributed to interpretation of results and writing of the manuscript, and approved the final version of the submitted report.

Abstract

Post-relapse survival of pediatric acute myeloid leukemia (AML) remains poor and there is a paucity of data to inform relapse regimen selection. We sought to describe the treatment landscape for first AML relapse and compare effectiveness of prevalent salvage regimens. To do this, we conducted a retrospective cohort study using the REAL-AML dataset including pediatric patients with first relapse of AML treated at 13 US pediatric institutions from 2011–2023. Primary analyses compared overall survival (OS) by regimen backbone and by receipt of gemtuzumab ozogamicin (GO), without an *a priori* hypothesis about a specific regimen efficacy. Secondary outcomes included end-of-re-induction clinical remission (CR) and measurable residual disease-negative CR (MRD-CR). 247 patients met inclusion criteria (median post-relapse follow-up 28 months). Two-year OS was 46% (95% CI 39–52%). Thirty-nine unique re-induction regimens were used; 22% received non-intensive regimens. Among 173 patients eligible for comparative analyses, there were no statistically significant differences in OS or end-re-induction responses by backbone chemotherapy. Point estimates suggested benefit with addition of anthracycline to fludarabine/cytarabine±G-CSF for OS (aHR of death vs FLA(G) = 0.38, 95%CI 0.11–1.38), and for CR and MRD-negative CR (aPR = 1.3, for both). Incorporation of GO increased likelihood of CR (aPR 1.3, 95%CI 1.0–1.5) and MRD-negative CR (aPR 1.5, 95% CI 1.1-2.1) but did not improve OS (aHR 1.1, 95%CI 0.6–2.2). These contemporary, real-world data provide updated benchmarks for pediatric first-relapse AML outcomes. Use of GO in relapse may improve end-induction response but survival benefit remains unproven. Prospective evaluation and further work to personalize therapy are needed.

Introduction

Despite intensive frontline treatment regimens that push the limits of tolerance, relapse rates in pediatric acute myeloid leukemia (AML) continue to as high as 35%[1-6] Limited contemporary data are available regarding treatment response for large cohorts of children with relapsed AML. Historical real-world data from the Therapeutic Advances in Childhood Leukemia (TACL) consortium[7] and among patients treated on upfront clinical trials[8-10] report clinical remission (CR) rates from 56-77% after the first cycle of salvage chemotherapy and overall survival (OS) ranging from 29-42%. Single arm studies provide more contemporary estimates of treatment responses for patients receiving a variety experimental regimens and report a wide range of second CR rates, from 23-81%, and highly variable overall survival (OS) estimates ranging between 21 and 60%.[11-18] Given the expanded cytomolecular and improved testing for measurable residual disease (MRD), enhanced supportive care and additional salvage options, updating landmark outcomes among patients receiving standard of care regimens is imperative.

In addition to an absence of contemporary outcomes data, there is no standard approach for treating relapsed pediatric AML.[19] To the extent that the field has observed improvement in outcomes, these advances are largely attributed to improved supportive care rather than the development of more effective treatment approaches.[20, 21] In general, the goal of salvage regimens in relapsed AML is to induce a remission that will allow the patient to undergo transplant, yet the regimen(s) that are most likely to induce remissions or yield long term survival in relapsed pediatric AML have not been established. Historically, fewer than 20% of children with relapsed AML have been treated on clinical trials leading to an absence of comparative efficacy data to guide approaches to therapy.[22] Indeed, the last published randomized study was completed in 2009.[23] However, retrospective comparative effectiveness analyses may help address this knowledge gap.

The Real-world Epidemiology of Acute Leukemia- AML (REAL-AML) cohort is a large, multi-institutional, population-based cohort that includes children with first AML relapse. The aims of this study were first to describe the re-induction regimens used to treat pediatric AML relapse and their outcomes as a means of updating benchmarks for remission rates and survival in this population. This dataset is unique in that it overcomes critical limitations in previously published clinical trial data,[8, 23] namely the concerns for selection bias in enrollment and generalizability of the findings to other AML subtypes and populations.[24, 25] In addition, this dataset allows for specific assessment of patients with first relapse of AML. Patients in first relapse are likely distinct from those with primary refractory disease or second or greater relapse, yet are frequently combined with those groups, leaving analysis vulnerable to missed sub-group trends.[26] We then endeavored to compare outcomes by agents used in first salvage regimens for relapsed pediatric AML to inform data driven treatment decision making for pediatric patients with relapsed AML.

Methods

Data source

REAL-AML includes all patients with AML treated at 13 pediatric institutions across the United States (supplemental table 1). Medical record abstraction includes demographics, diagnosis, treatment (including two

cycles post-relapse), HCT, and treatment response. Abstractors were trained using a standardized protocol and were required to achieve >95% concordance with a trainer prior to conducting chart reviews. The REAL-AML study was approved by the Institutional Review Board (IRB) at Children's Hospital of Philadelphia and by the IRB/ethics committees at each participating institution. A waiver of informed consent was obtained for retrospective medical record abstraction to allow for complete capture of the source population.

Study population (Figure 1)

Patients are ineligible for inclusion in REAL-AML if diagnosed with acute promyelocytic leukemia or >18 years at initial AML diagnosis. Patients were included in these analyses if they were with AML from 1/1/2011-12/31/2023 and did not constitutional trisomy 21 or treatment-associated AML. Patients with primary refractory disease after the first two cycles of therapy which lead to altered upfront treatment were also excluded as these changes likely lead to differential considerations in selection of relapse regimen. Relapse was defined as documentation of relapse by the clinical team with start of new antineoplastic therapy due to efficacy concerns and one for the following: (1) M2/M3 bone marrow (≥5% myeloblasts by any method), (2) M1 marrow with emergence of multichannel flow cytometry MRD after achieving an MRD negative remission,[19] (3) new radiographic or biopsy-proven extramedullary disease (EMD). Those who received only palliative chemotherapy following first relapse (oral hydroxyurea or etoposide monotherapy) were excluded.

Chemotherapy classifications

First salvage regimens were classified as intensive (traditional cytotoxic chemotherapy at myelosuppressive doses) versus non-intensive regimens (e.g., venetoclax, hypomethylating agents). For comparative analyses, intensive regimens were categorized based on the predominant chemotherapy backbone. Common targeted agents (e.g., GO, FLT3 inhibitors) were treated separately. The complete list of chemotherapy regimens and classifications is available in Supplemental Table 2.

Outcomes

The primary outcome was 2-year overall survival (OS), defined as time from date of first relapse to date of last follow-up or death from any cause; patients were administratively censored at 2 years post-HCT. Secondary outcomes included CR (M1 marrow irrespective of peripheral blood counts) and MRD-negative CR (MFC MRD < 0.1%). Patients who died during re-induction were considered as having not achieved a CR. Any death before documentation of a disease assessment, start of next chemotherapy cycle, or documentation of change in goals of care was considered early mortality.

Statistical methods

Covariate operationalization is available in the supplement. Survival analyses used Kaplan–Meier methods and multivariable Cox proportional hazards models. End re-induction response (CR, MRD-negative CR) was evaluated using modified Poisson regression with a log link and robust variance estimators to

estimate prevalence ratios (PRs).[27] For the comparative effectiveness analyses, low frequency chemotherapy regimens and EMD-only disease were excluded (Figure 1). Two independent variables were included in all models: (1) backbone chemotherapy and (2) receipt of GO (yes/no). Adjustment was made for covariates found to both differ by re-induction regimen (≥10% absolute difference) and be associated with outcome (PR >1.2 or <0.8), regardless of statistical significance, defined as a two-sided p value <0.05. As we anticipated that regimens would be differentially implemented based on timing of relapse, in addition to treating this variable as a covariate in the primary models, we performed analyses stratified by early and late relapse,[8] as well as sensitivity analyses that excluded patients who received FLT3 inhibitors and venetoclax.

Results

Cohort assembly and baseline characteristics

There were 273 patients from 13 centers with a first relapse of AML; 247 met inclusion criteria for this analysis (Figure 1). This represents approximately 15% of all relapsed AML patients in the US in this epoch. Only three patients pursued palliative-only chemotherapy. Median follow-up from date of first relapse among patients alive at last contact was 28 months (range 0.7–152). Patient, treatment, and relapse characteristics overall and by intensive re-induction regimen are shown in Tables 1 and 2. Half of relapses occurred within one year. Subject characteristics stratified by early and late relapse are shown in Supplemental Tables 3A–B. Distributions of patient, disease, and relapse characteristics were similar between early and late relapse groups, except late relapse patients were more likely to have favorable cytogenetic/molecular features (30% vs 10%).

Treatment approaches for first relapse

Treatment regimens for first re-induction varied widely; 39 unique regimens were used during the observation period. The permutations of chemotherapy combinations are illustrated in Figures 2A–C. GO was added to re-induction regimens in 24% of cases; FLT3 inhibitors were used as part of re-induction in 8 patients (3%) (Figure 2D). The most common regimens were FLA(G) (n = 56) and CPX-351 (n = 51). FLA(G) was the most common backbone onto which additional agents were added, including anthracyclines (n = 15), hypomethylating agents (n = 19) and histone deacetylase inhibitors (n = 13). All regimen categories were used for both early and late relapse; however, “other” regimens and non-intensive regimens were more common in early relapses.

Most patients (n = 193, 78%) received an intensive regimen, and 54 (22%) received a non-intensive regimen. Patients receiving non-intensive re-induction regimens were more likely to have undergone transplant in CR1 prior to relapse (74% vs 19%) and to have relapsed within one year of diagnosis (69% vs 45%). Temporal trends were observed: clofarabine-based regimens were used less after 2016, use of CPX-351 increased beginning in 2017 (Supplemental Figure 1), and use of non-intensive regimens increased over the past decade driven primarily by venetoclax-containing regimens.

Multiple unique regimens were used at each institution, and most regimens were used at multiple institutions (Supplemental Figure 2). Only 17 (9%) patients were enrolled on a clinical trial for re-induction.

Disease response

Overall, 2-year OS post-relapse was 46% (95% CI 39–52%). Among those treated with intensive regimens 2-year OS was 52% (95% CI 45–60%); for those who received non-intensive regimens OS was 19% (95% CI 9–33%) (Figure 4A). Among early and late relapse, 2-year OS was 36% (95% CI 26–47%) and 67% (95% CI 56–75%), respectively.

Unadjusted risk factors for death after relapse included relapse on frontline therapy, shorter time to relapse, transplant prior to relapse, and only unfavorable cytomolecular features (Supplemental Table 4A). Most patients who were alive at last follow-up had undergone a transplant after relapse (81%); median follow-up time for those who had not undergone HCT was much shorter (7 months vs 3 years).

Overall, 58% achieved CR2 after the first re-induction cycle and 43% achieved an MRD-negative CR. Compared to those who received non-intensive regimens, patients treated with intensive regimens were more likely to achieve CR2 (65% vs 35%) and MRD-negative CR2 (51% vs 16%); those with late relapse were more likely to achieve CR2 and MRD-negative CR2 compared to early relapse. Of those who did not achieve CR2 or MRD-negative CR2 after re-induction, 29% and 35% were still alive at last follow-up (median follow-up 29 and 37 months), showing that some patients survive despite residual disease after re-induction.

Comparative effectiveness of intensive re-induction regimens

There were 173 patients in the comparative effectiveness cohort (Figure 1) with a 2-year OS of 54% (95% CI 46–62%); 66% achieved a CR and 52% achieved an MRD-negative CR after their first cycle of chemotherapy. GO was added to 26% of intensive regimens.

Clinical and disease characteristics did not vary systematically across categories of intensive regimens (Table 2). Patients who received an anthracycline as part of re-induction had similar distributions of unfavorable cytogenetics (26% versus 28%, p = 0.80), completion of frontline therapy (84% versus 80%, p = 0.48), transplant prior to relapse (26% versus 23%, p = 0.30) and relapse within one year of initial diagnosis (43% versus 47%, p = 0.53) compared to patients who did not receive an anthracycline.

OS by treatment regimen and GO is shown in Figure 3, respectively. Unadjusted and adjusted regression analyses of OS and disease response by treatment regimen and receipt of GO are shown in Table 3 and Supplemental Table 5. There were no statistically significant differences in OS or end-of-re-induction response by chemotherapy regimen. Adjusted point estimates suggested benefit to FLA(G) + anthracycline regimens: compared to FLA(G), the adjusted hazard of death for FLA(G) + anthracycline was 0.4 (95% CI 0.1–1.4). Adjusted prevalence ratios of CR and MRD-negative CR were 1.3 (95% CI 0.9–1.9) and 1.3 (95% CI 0.8–2.3), respectively. After adjustment, estimates of outcomes of CPX-351 were similar to FLA(G): aHR 0.9, aPR for CR 1.1, aPR for MRD negative CR 0.9. Only three patients in the comparative effectiveness cohort received FLT3 inhibitors; results were not meaningfully changed in sensitivity analysis when these patients

were removed (Supplemental Table 6). Similarly, seven patients received venetoclax in combination with intensive regimens and point estimates of association were not changed when these patients were removed (Supplemental Table 7).

The addition of GO was associated with a statistically significant increase in rates of CR and MRD-negative CR (aPR = 1.3 (95% CI 1.0–1.5) and 1.5 (95% CI 1.1–2.1), respectively) after first re-induction but did not translate to a survival benefit (aHR = 1.1 (95% CI 0.6–2.2)). Similar point estimates of the association between GO and end-re-induction response were observed for early and late relapse (Supplemental Table 8, Supplemental Figure 3).

Mortality during first re-induction was rare (3%), with events distributed across several regimens: CPX-351 + dasatinib (1/1), mitoxantrone + cytarabine (1/11), Capizzi cytarabine (1/6), FLA(G) (2/56), and FLA(G) + decitabine and vorinostat (4/13). No patients who received GO experienced mortality during re-induction.

Discussion

In this contemporary, population-based cohort of children and adolescents with first relapse of AML, 2-year OS was 46%, showing limited improvement relative to earlier decades despite changes in supportive care and available therapies.[7, 9, 10, 21, 23, 28, 29] Treatment approaches for first re-induction remain highly heterogeneous, with 39 unique regimens observed and frequent use of non-intensive regimens in selected patients. Less than 10% of patients received re-induction on a clinical trial, underscoring the limited randomized evidence base to inform therapy selection. These data from the REAL-AML cohort provide evidence for existing heterogeneity of salvage regimens used in clinical practice and provide a benchmark for outcomes. These data can also begin to shed light on comparative effectiveness of salvage regimens: we did not identify statistically significant superiority of any single chemotherapy backbone, but point estimates suggested potential benefit from adding an anthracycline to FLA(G) and from incorporating GO to improve end-induction remission and MRD clearance.

In this cohort, almost 60% of patients achieved a second CR after one re-induction cycle. GO was added to nine different chemotherapy backbones with data demonstrating benefit with regards to achieving a second CR and MRD-negative CR after one cycle. This was true for patients with both early and late relapse. These results confirmed the high CR rate seen in a smaller retrospective study when GO was combined with FLA(G) to treat relapsed or refractory disease.[30] Unfortunately, this response rate did not translate to improved survival in this cohort, which may be due to a shorter duration of follow-up in GO-exposed patients and insufficient power. Further research is needed to understand whether this discrepancy is due to toxicity or insufficient depth and non-sustained remission, as well as to confirm that GO efficacy after relapse persists in an era will patients will be nearly universally exposed to GO prior to relapse.

The regimen-specific CR for the intensive regimens including FLA(G), FLA(G)+idarubicin, and CPX-351 were strikingly similar to reported rates on the landmark clinical trials of these agents.[11, 16, 17, 23] While no regimen was clearly superior to the FLA(G) reference regimen, after controlling for GO exposure, the estimates of OS and CR2 were highest among patients who received FLA(G) + anthracycline. This finding is consistent

with results of the randomized trial of FLA(G) versus FLA(G) plus liposomal daunorubicin (DNX) that demonstrated a higher CR rate with the addition of anthracycline (69% versus 59%, p = .07), as well as improved 4-year OS among patients with core binding factor AML (82% versus 48%, p = 0.04).[23] These real world results also lend credence to the high CR rate report on the COG phase II trial of CPX-351 that demonstrated a 76% CR2 after cycle 1, although estimates of survival with CPX-351 were similar to FLA(G).[11]

Although anthracyclines may augment treatment response, exposure is associated with dose-dependent cardiotoxicity, a notable concern given that patients with relapsed AML may have received up to 450-600 mg/m^2 of doxorubicin equivalents during upfront therapy, depending on conversion approach adopted.[31] Our analysis did not assess total cumulative anthracycline exposure as a confounder, however surrogate measures of prior therapy (e.g., completion of upfront therapy, prior transplant) were not systematically different among those who received anthracycline-containing regimens and those who received intensive regimens without anthracycline (Table 1). In an era of near-universal dexrazoxane usage as a cardioprotectant among children receiving upfront AML therapy[32] and an efficacy signal suggesting benefit, one avenue for future research is to understand – and potentially expand – the population who receive anthracycline-containing re-induction regimens.

The observed increased use of venetoclax and other targeted/non-cytotoxic approaches over time—particularly for early relapses and patients with prior transplant—highlights clinician preference for reduced intensity in selected contexts; nevertheless, response and survival outcomes were inferior among non-intensive recipients in unadjusted comparisons, likely reflecting confounding by indication. It is important to note that one-third of patients who received lower intensity regimens achieved a second CR. Further work is needed to define the population that will respond to non-cytotoxic regimens and can be spared toxicity.

Strengths of this study include the multi-institutional, population-based REAL-AML cohort, systematic data abstraction with MRD data, and inclusion of contemporary practice. Limitations include the retrospective design, potential residual confounding in regimen selection, limited sample size for some regimens, limited follow-up time. Despite the relative size of this cohort, there may be some selection bias based on the included sites. While most pediatric AML patients are treated at academic medical centers, as are included in this analysis, the population included in this study only represents about 15% of relapsed AML over this period.[22, 33] Additionally, heterogeneity in post-re-induction management (timing and approach to HCT, subsequent therapies) may influence OS independently of initial re-induction response. Despite limiting eligibility to first AML relapse, we acknowledge the likelihood of cohort heterogeneity by cytomolecular features and baseline cardiac function at time of relapse, warranting further investigation to identify outcomes for specific at-risk subsets. For those who do and do not achieve a CR after re-induction, intensity of subsequent treatment, toxicity and HCT timing all have the potential to impact overall survival.[34] These choices may contribute to discrepancies between end induction response and overall survival benefit with regards to GO. Finally, our analyses did not capture outcomes for the newest available targeted approaches such as menin inhibitors, which have shown promise in the setting of relapse for specific cytogenetic subgroups.[35]

Nevertheless, this analysis is a critical first step to addressing a knowledge gap in understanding the optimal treatment of first AML relapse. These data support incorporation of GO in AML re-induction to augment treatment response and incorporation of anthracyclines, when possible, to both augment response and improve survival. Further understanding of determinants of survival benefit requires evaluation of specific subpopulations and related factors. The substantial heterogeneity in treatment approaches suggests that in addition to the current generation of trials that isolate the impact of adding a single agent to a known backbone (NCT04240002, NCT05183035), research is needed to determine the optimal chemotherapy backbone. These data also complement efforts ongoing through international consortia, including Children's Oncology Group (COG), the International Berlin-Frankfurt-Münster (BFM) Study Group, the BFM-AML study group, and the Pediatric Acute Leukemia Initiative in North America, Australia and New Zealand and the European Pediatric Acute Leukemia Foundation (PedAL/EuPAL), supplementing with population-based response and survival estimates.[21, 36] In the meantime, these data provide the most contemporary benchmark data for efficacy and could be further developed for use in comparative toxicity assessments on future clinical trials.

Conclusions

In this contemporary, multi-institutional cohort of pediatric first relapse AML, re-induction approaches are heterogeneous. Addition of GO and anthracyclines to FLA(G) were associated with improved end-induction responses, but survival benefit was not demonstrated. These data provide contemporary benchmarks for response and survival and support prospective evaluation of optimal chemotherapy backbones for relapsed pediatric AML.

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Table 1. Demographic and treatment characteristics by re-induction intensity

	Intensive regimens including anthracycline (n = 86)	Intensive regimens without anthracycline (n = 107)	Non-intensive regimens (n = 54)
Hospitals used	13	13	12
Number of years used during observation period (2011-2024)	13	14	12
Gemtuzumab (GO) administered with cycle	27 (31%)	18 (17%)	14 (26%)
Sex			
Female	40 (47%)	40 (37%)	24 (44%)
Male	46 (54%)	67 (63%)	30 (56%)
Age at relapse (years)			
Median (Min, Max)	10 (0.6, 20)	9 (0.6, 21)	7 (1, 20)
Race			
Hispanic	23 (27%)	28 (26%)	13 (24%)
NH-Black	16 (19%)	12 (11%)	4 (7%)
NH-White	30 (35%)	48 (45%)	25 (46%)
Other	17 (20%)	19 (18%)	12 (22%)
Cytogenic based risk			
Both Favorable & Unfavorable	5 (6%)	6 (6%)	0 (0%)
Neither Favorable or Unfavorable	32 (37%)	51 (42%)	35 (65%)
Only Favorable	27 (31%)	21 (20%)	2 (4%)
Only Unfavorable	22 (26%)	29 (27%)	17 (32%)
Completed frontline therapy	71 (83%)	86 (80%)	48 (89%)
Transplant prior to relapse	23 (27%)	24 (22%)	40 (74%)
GO exposure prior to relapse	22 (28%)	24 (24%)	18 (43%)
Time from diagnosis to relapse			
<6 months	10 (12%)	19 (18%)	8 (15%)
6 to <12 months	27 (31%)	32 (30%)	29 (54%)
12 or more months	49 (57%)	56 (52%)	17 (32%)
Marrow involvement at relapse*			
M2/M3	82 (95%)	99 (93%)	42 (86%)
MRD-level disease only	4 (5%)	8 (8%)	7 (14%)
Relapse site(s)			
Bone marrow + CNS/EMD	25 (29%)	19 (18%)	5 (9%)
Bone marrow only	60 (70%)	79 (74%)	44 (82%)
CNS/EMD	1 (1%)	9 (8%)	5 (9%)

*proportion of patients with marrow disease; MRD measurable residual disease

Table 2. Demographic and treatment characteristics by first re-induction intensive chemotherapy.

	CLA(G) (N=13)	CPX-351 (N=51)	FLA(G) (N=56)	FLA(G) + anthracycline (N=15)	FLA(G) + other (N=21)	Other non-anthracycline (N=12)	Other w. anthracycline (N=15)
Hospitals used	5	9	10	7	8	5	8
Number of years used during observation period (2011-2024)	6	8	11	8	9	7	10
Gemtuzumab administered with cycle	0	25 (49%)	16 (29%)	0	2 (10%)	0	2 (13%)
Median follow-up (months)	85 (40-144)	29 (1-98)	27 (1-133)	19 (1-152)	51 (1-90)	44 (19-102)	101 (5 -122)
Sex							
Female	5 (39%)	22 (43%)	25 (45%)	8 (53%)	4 (19%)	6 (50%)	9 (60%)
Male	8 (62%)	29 (57%)	31 (55%)	7 (47%)	17 (81%)	6 (50%)	6 (40%)
Age at relapse (years)							
Median [Min, Max]	3 [0.9, 16]	12 [2, 20]	10 [0.6, 21]	6.9 [0.6, 19]	8 [1, 18]	3 [1, 18]	7 [0.6, 19]
Race							
Hispanic	3 (23%)	17 (33%)	13 (23%)	3 (20%)	8 (38%)	4 (33%)	1 (7%)
NH-Black	0	10 (20%)	8 (14%)	2 (13%)	0	3 (25%)	4 (27%)
NH-White	9 (70%)	17 (33%)	26 (46%)	5 (33%)	6 (29%)	4 (33%)	7 (47%)
Other	1 (8%)	7 (14%)	9 (16%)	5 (33%)	7 (33%)	1 (8%)	3 (20%)
Cytogenic based risk							
Both Favorable & Unfavorable	1 (8%)	2 (4%)	3 (5%)	0	1 (5%)	1 (8%)	0
Neither Favorable or Unfavorable	8 (62%)	22 (43%)	23 (41%)	6 (40%)	11 (52%)	6 (50%)	4 (27%)
Only Favorable	2 (15%)	16 (31%)	15 (27%)	5 (33%)	2 (10%)	2 (17%)	5 (33%)
Only Unfavorable	2 (15%)	11 (22%)	15 (27%)	4 (27%)	7 (33%)	3 (25%)	6 (40%)
Completed frontline therapy	9 (69%)	46 (90%)	50 (89%)	12 (80%)	17 (81%)	6 (50%)	9 (60%)
Transplant prior to relapse	1 (8%)	18 (35%)	7 (13%)	3 (20%)	11 (52%)	2 (17%)	0
GO exposure prior to relapse	0	14 (30%)	15 (28%)	5 (36%)	6 (32%)	1 (10%)	2 (15%)
Time from diagnosis to relapse							
<6 months	4 (31%)	1 (2%)	6 (11%)	3 (20%)	3 (14%)	5 (42%)	5 (33%)
6 to <12 months	4 (31%)	15 (29%)	13 (23%)	6 (40%)	8 (38%)	5 (42%)	5 (33%)
12 or more months	5 (39%)	35 (69%)	37 (66%)	6 (40%)	10 (48%)	2 (17%)	5 (33%)
Marrow involvement at relapse*							
M2/M3	10 (77%)	51 (100%)	47 (94%)	14 (93%)	21 (100%)	7 (78%)	11 (79%)
MRD-level disease only	3 (23%)	0	3 (6%)	1 (7%)	0	2 (22%)	3 (21%)
Relapse site(s)							
Bone marrow + CNS/EMD	3 (23%)	11 (22%)	11 (20%)	7 (47%)	3 (14%)	2 (17%)	5 (33%)
Bone marrow only	10 (77%)	40 (78%)	39 (70%)	8 (53%)	18 (86%)	7 (58%)	9 (60%)
CNS/EMD**	0	0	6 (11%)	0	0	3 (25%)	1 (7%)
Treated on clinical trial for first reinduction cycle	0	4 (9%)	3 (7%)	0	8 (44%)	0	0

*proportion of patients with marrow disease; **excluded from comparative effectiveness analyses

CLA(G) Clofarabine + cytarabine +/- GCSF; FLA(G) Fludarabine + cytarabine +/- GCSF; GO Gemtuzumab-Ozogamycin; MRD Measurable residual disease

Table 3. Comparative effectiveness of chemotherapy regimens for first re-induction

		Unadjusted estimates			Adjusted estimates*		
	OS/Proportion with response	**HR/PR**	**95% CI**	**p value**	**aHR/PR**	**95% CI**	**p value**
2-year overall survival							
FLA(G)	0.6		*ref*			*ref*	
CLA(G)	0.5	1.4	0.6-3.2	0.50	1.3	0.5-3.2	0.64
CPX-351	0.6	0.9	0.5-1.7	0.69	0.9	0.4-1.9	0.75
FLA(G) + anthracycline	0.8	0.5	0.1-1.7	0.25	0.4	0.1-1.4	0.14
FLA(G) + other	0.5	1.3	0.6-2.7	0.55	1.0	0.4-2.3	0.91
Other non-anthracycline	0.3	2.0	0.8-4.9	0.15	0.8	0.3-2.3	0.66
Other with anthracycline	0.4	1.6	0.7-3.6	0.27	1.6	0.6-3.9	0.34
No GO	0.5		*ref*			*ref*	
GO	0.6	0.8	0.4-1.3	0.35	1.1	0.6-2.2	0.74
End of re-induction clinical remission (CR)							
FLA(G)	0.7		*ref*			*ref*	
CLA(G)	0.5	0.8	0.5-1.3	0.34	0.8	0.4-1.4	0.41
CPX-351	0.7	1.1	0.8-1.4	0.62	1.1	0.9-1.4	0.24
FLA(G) + anthracycline	0.8	1.1	0.8-1.6	0.40	1.3	0.9-1.9	0.13
FLA(G) + other	0.5	0.7	0.4-1.1	0.12	0.9	0.6-1.5	0.73
Other non-anthracycline	0.2	0.3	0.1-1.1	0.07	0.5	0.1-1.5	0.19
Other with anthracycline	0.7	1.0	0.7-1.5	0.92	1.0	0.7-1.5	0.95
No GO	0.6		*ref*			*ref*	
GO	0.8	1.4	1.1-1.7	0.002	**1.3**	**1.0-1.5**	**0.04**
End of re-induction MRD negative remission							
FLA(G)	0.6		*ref*			*ref*	
CLA(G)	0.4	0.6	0.3-1.3	0.21	0.8	0.4-1.6	0.55
CPX-351	0.5	0.8	0.6-1.2	0.23	0.9	0.6-1.3	0.49
FLA(G) + anthracycline	0.7	1.2	0.8-1.8	0.47	1.3	0.8-2.3	0.28
FLA(G) + other	0.5	0.8	0.5-1.3	0.33	1.1	0.6-2.0	0.77

Other non-anthracycline	0.2	0.4	0.1-1.3	0.11	0.8	0.2-2.7	0.68
Other with anthracycline	0.6	0.9	0.6-1.6	0.79	1.1	0.7-1.9	0.70
No GO	0.5		*ref*			*ref*	
GO	0.7	1.4	1.0-1.8	0.03	**1.5**	**1.1-2.1**	**0.02**

CLA(G) Clofarabine + cytarabine +/- GCSF; FLA(G) Fludarabine + cytarabine +/- GCSF; GO Gemtuzumab-Ozogamicin; HR/PR Hazard Ratio/Prevalence Ratio
*Covariates for multivariable models: Overall Survival (age, race/ethnicity, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site, marrow involvement at relapse, recipt of GO); Clinical remission (age, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site, marrow involvement at relapse); MRD negative CR (age, race/ethnicity, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site)

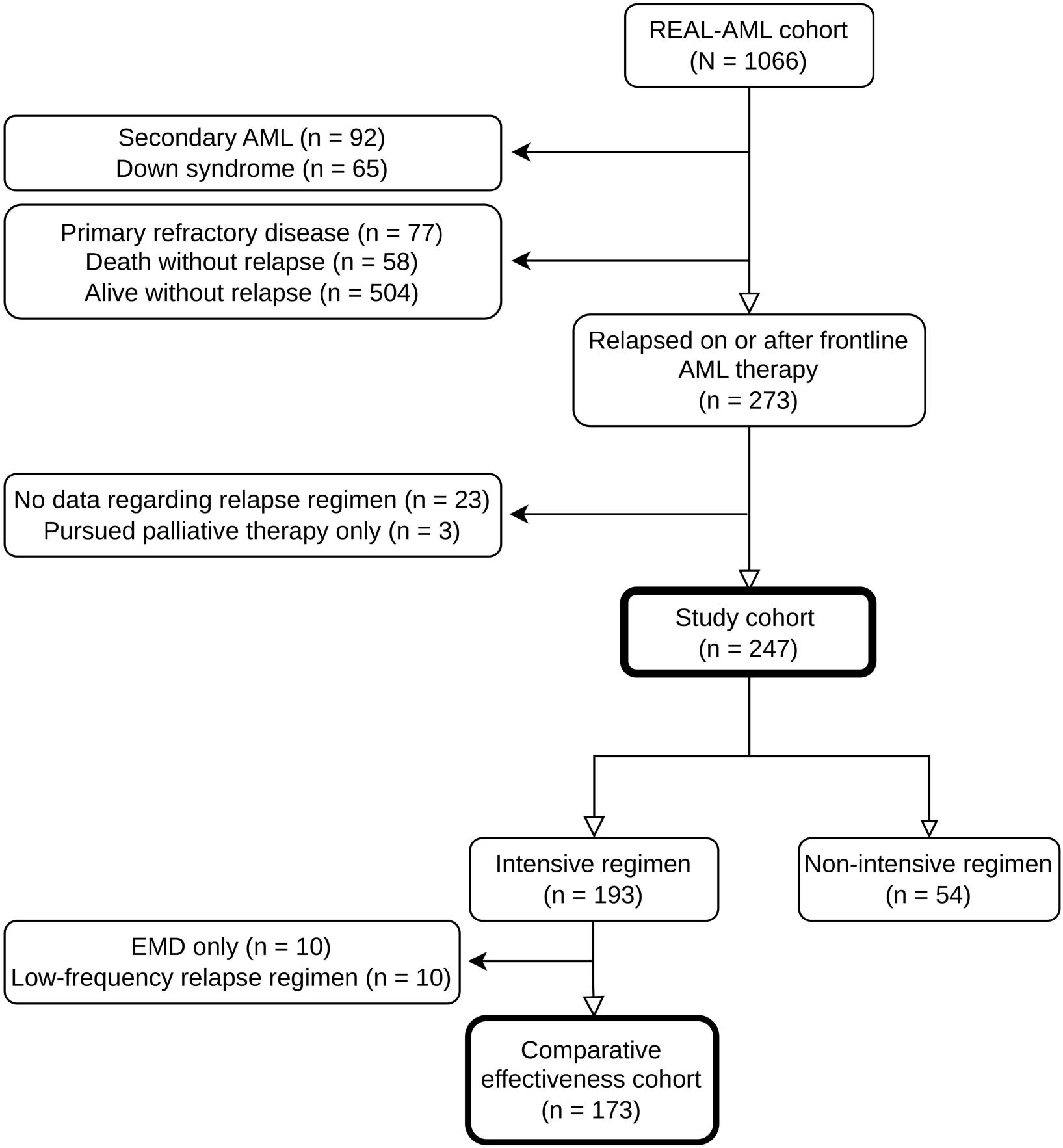
Figure legends

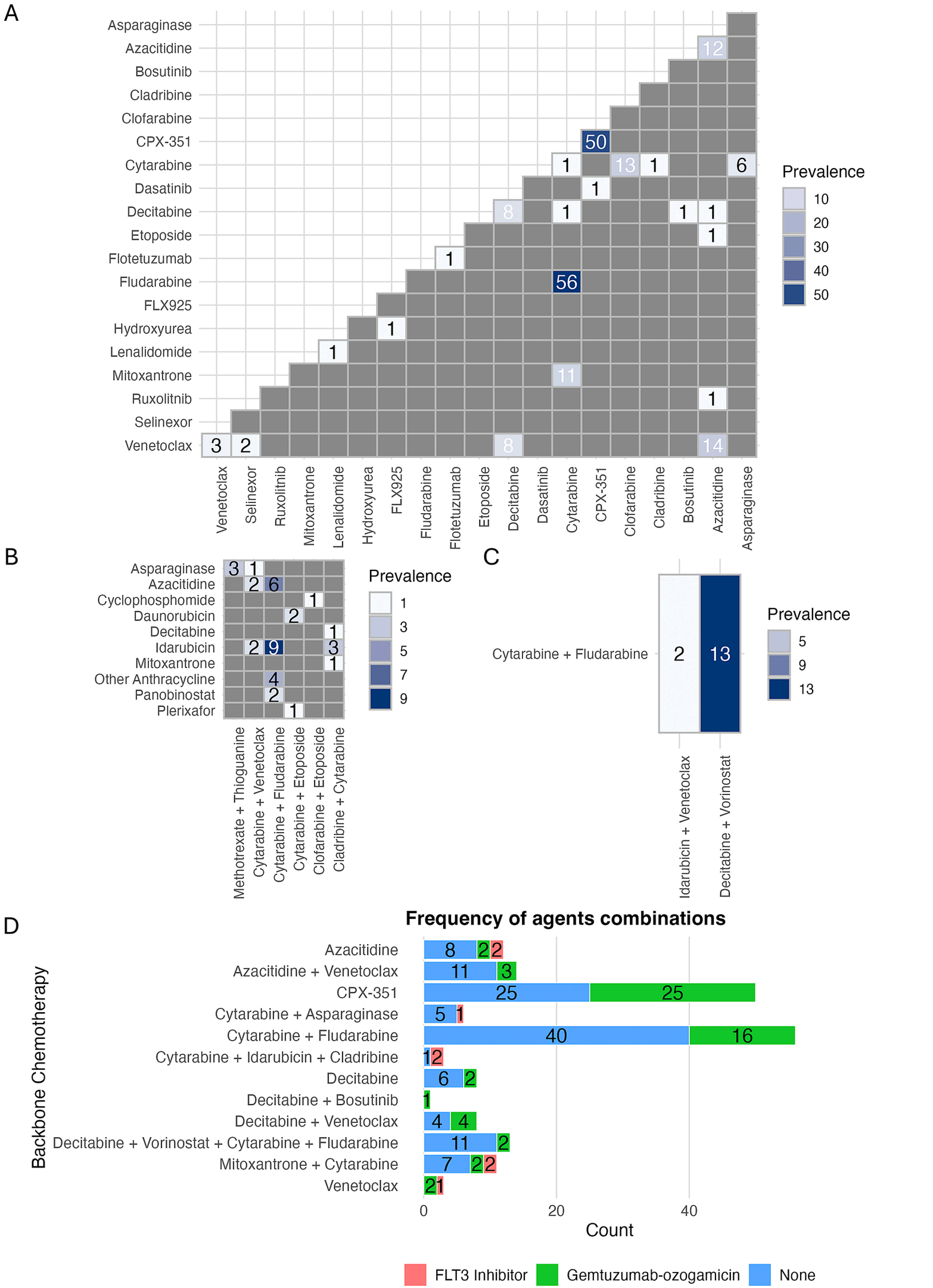
Figure 1. CONSORT-style diagram demonstrating cohort construction and numbers excluded at each step.

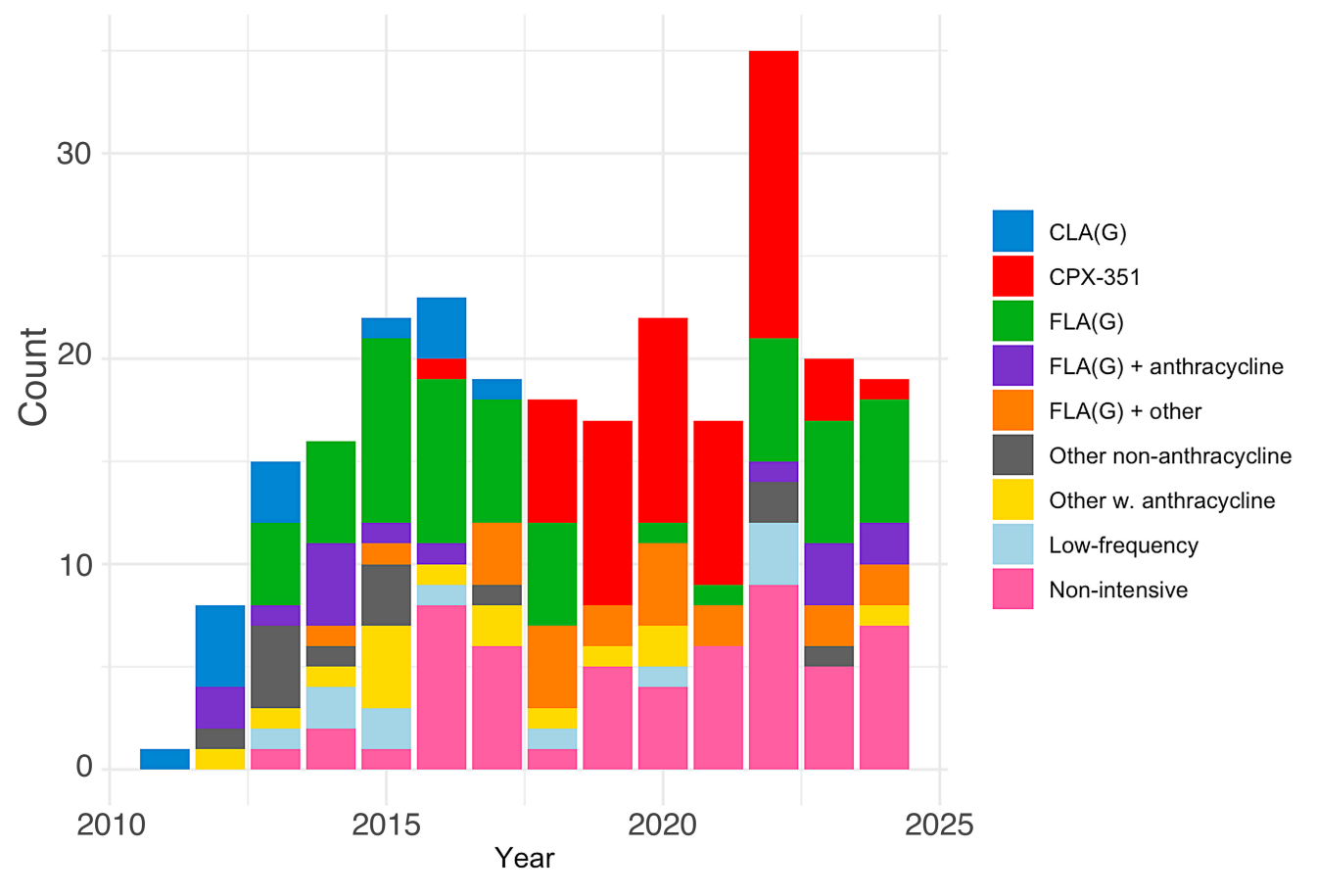
Figure 2. Treatment landscape of first re-induction regimens for pediatric AML. (A–C) Heatmaps demonstrating number of patients who received unique combinations of chemotherapy (two-agent, three-agent, four-agent regimens). Color denotes number of patients per combination. (D) Bar chart illustrating combinations of targeted agents (GO, FLT3 inhibitors).

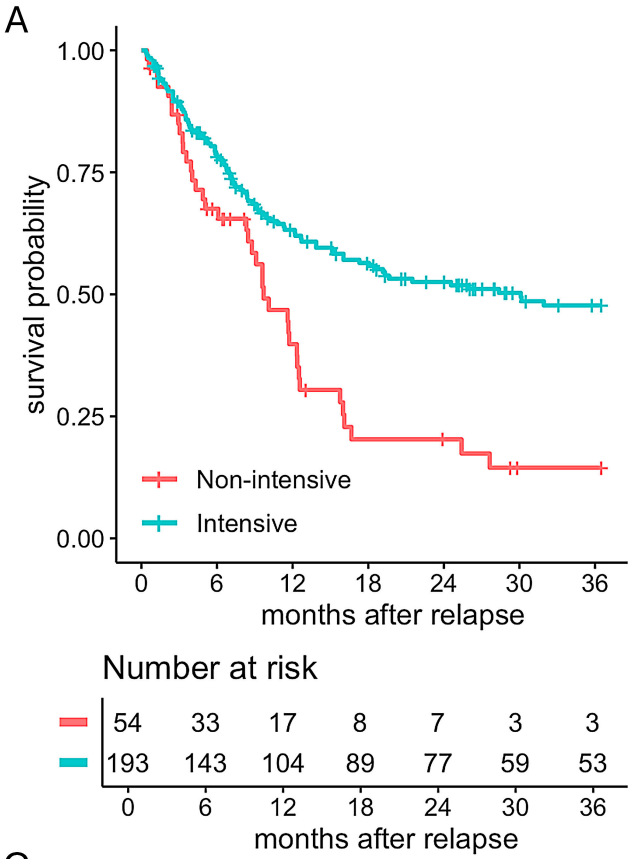
Figure 3. Distribution of re-induction regimens by calendar year (2011–2023).

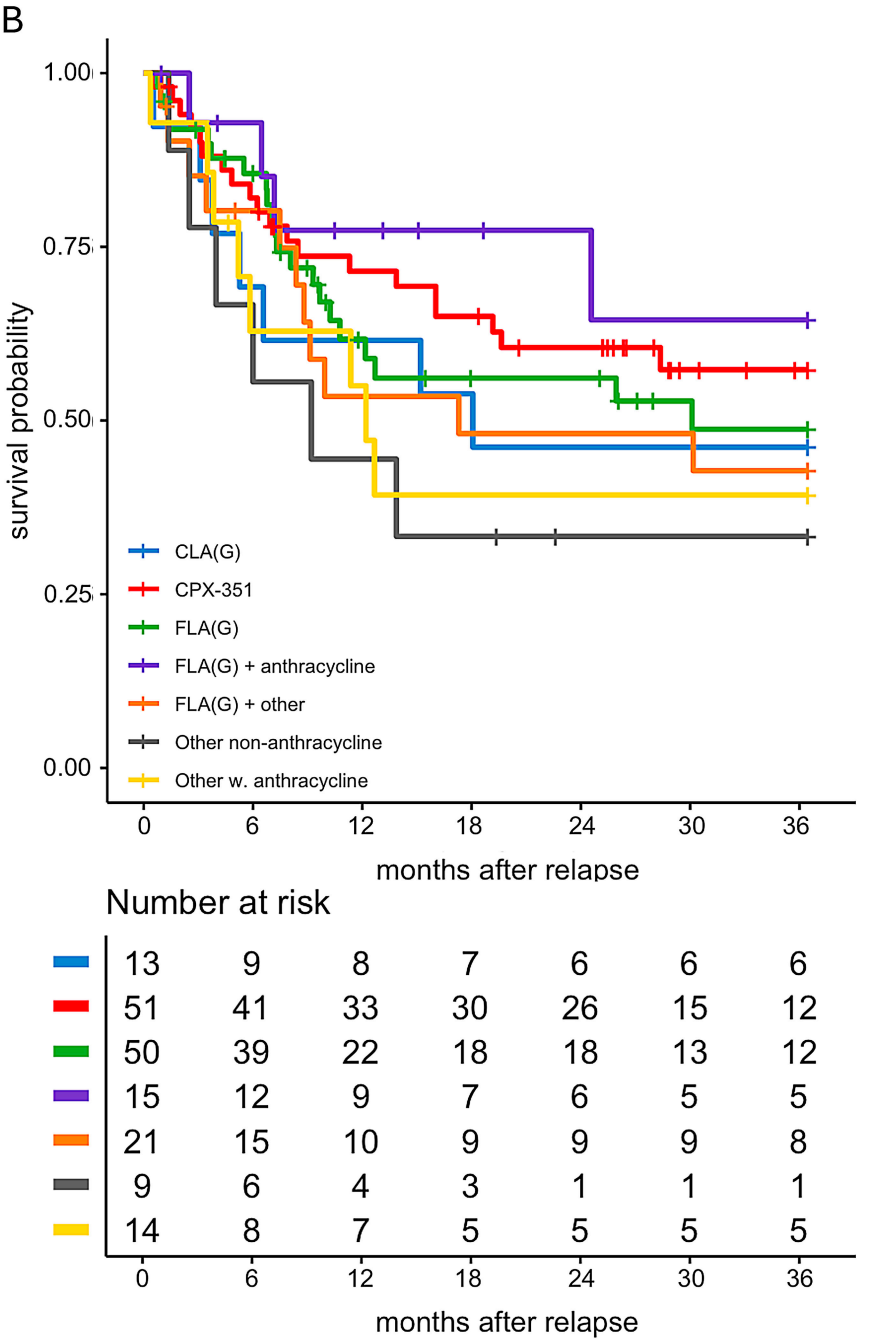
Figure 4. Overall survival by treatment approach. (A) Kaplan–Meier curves for intensive vs non-intensive regimens (full cohort). (B) OS by chemotherapy backbone (comparative effectiveness cohort). (C) OS by receipt of GO (comparative effectiveness cohort). Numbers at risk shown below each plot.

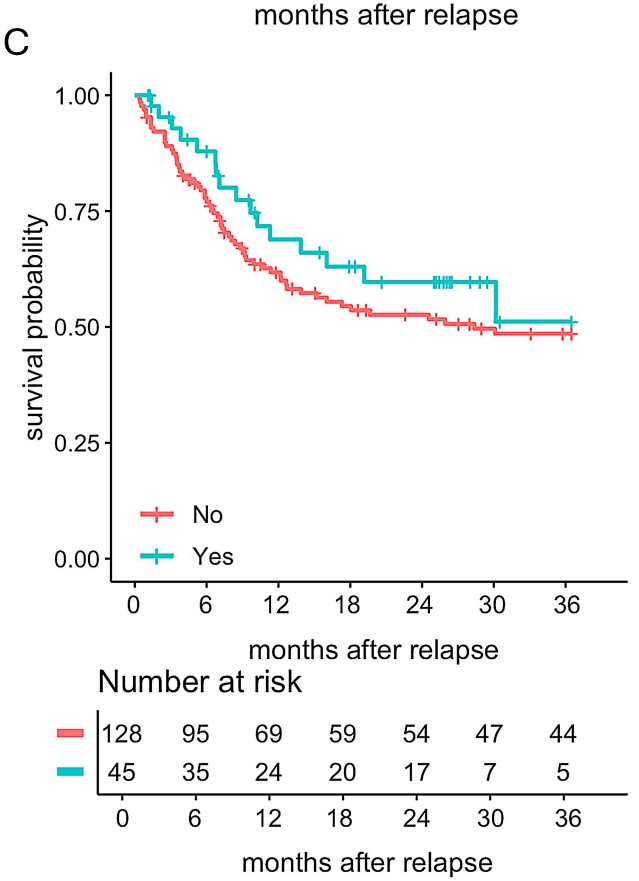

REAL-AML cohort
(N = 1066)
Secondary AML (n = 92)
Down syndrome (n = 65)
Primary refractory disease (n = 77)
Death without relapse (n = 58)
Alive without relapse (n = 504)
Relapsed on or after frontline
AML therapy
(n = 273)
No data regarding relapse regimen (n = 23)
Pursued palliative therapy only (n = 3)
Study cohort
(n = 247)
Intensive regimen
(n = 193)
Non-intensive regimen
(n = 54)
EMD only (n = 10)
Low-frequency relapse regimen (n = 10)
Comparative
effectiveness cohort
(n = 173)


A
Asparaginase
Azacitidine
Bosutinib
Cladribine
Clofarabine
CPX-351
Cytarabine
Dasatinib
Decitabine
Etoposide
Flotetuzumab
Fludarabine
FLX925
Hydroxyurea
Lenalidomide
Mitoxantrone
Ruxolitnib
Selinexor
Venetoclax
Prevalence
10
20
30
40
50
B
Asparaginase
Azacitidine
Cyclophosphomide
Daunorubicin
Decitabine
Idarubicin
Mitoxantrone
Other Anthracycline
Panobinostat
Plerixafor
Methotrexate + Thioguanine
Cytarabine + Venetoclax
Cytarabine + Fludarabine
Cytarabine + Etoposide
Clofarabine + Etoposide
Cladribine + Cytarabine
Prevalence
1
3
5
7
9
C
Cytarabine + Fludarabine
Idarubicin + Venetoclax
Decitabine + Vorinostat
Prevalence
5
9
13
D
Frequency of agents combinations
Backbone Chemotherapy
Azacitidine
Azacitidine + Venetoclax
CPX-351
Cytarabine + Asparaginase
Cytarabine + Fludarabine
Cytarabine + Idarubicin + Cladribine
Decitabine
Decitabine + Bosutinib
Decitabine + Venetoclax
Decitabine + Vorinostat + Cytarabine + Fludarabine
Mitoxantrone + Cytarabine
Venetoclax
0
20
40
Count
FLT3 Inhibitor
Gemtuzumab-ozogamicin
None


30
20
10
0
Count
2010
2015
2020
2025
Year
CLA(G)
CPX-351
FLA(G)
FLA(G) + anthracycline
FLA(G) + other
Other non-anthracycline
Other w. anthracycline
Low-frequency
Non-intensive


A
survival probability
1.00
0.75
0.50
0.25
0.00
Non-intensive
Intensive
0
6
12
18
24
30
36
months after relapse
Number at risk
54 33 17 8 7 3 3
193 143 104 89 77 59 53
0 6 12 18 24 30 36
months after relapse


B
survival probability
1.00
0.75
0.50
0.25
0.00
CLA(G)
CPX-351
FLA(G)
FLA(G) + anthracycline
FLA(G) + other
Other non-anthracycline
Other w. anthracycline
0
6
12
18
24
30
36
months after relapse
Number at risk
13 9 8 7 6 6 6
51 41 33 30 26 15 12
50 39 22 18 18 13 12
15 12 9 7 6 5 5
21 15 10 9 9 9 8
9 6 4 3 1 1 1
14 8 7 5 5 5 5
0 6 12 18 24 30 36
months after relapse


C
survival probability
1.00
0.75
0.50
0.25
0.00
No
Yes
0
6
12
18
24
30
36
months after relapse
Number at risk
128 95 69 59 54 47 44
45 35 24 20 17 7 5
0 6 12 18 24 30 36
months after relapse

Data Supplement

Treatment for relapsed pediatric AML: Variability and comparative effectiveness of current approaches to re-induction
Elgarten et al.

Supplemental methods

Covariate operationalization

Baseline covariates included patient characteristics (age at relapse, sex, race/ethnicity) and disease/relapse characteristics (cytomolecular-based risk, receipt of transplant in CR1, time from diagnosis to relapse, degree of marrow involvement at relapse [M1 with MRD only vs M2/M3], CNS involvement, and EMD at relapse). All available cytogenetic and molecular reports were collected; identified cytomolecular features were categorized as favorable, neutral, or unfavorable according to the risk stratification used on the most recent COG clinical trial (i.e. AAML1831), even if they did not inform risk stratification at the time the patient was treated. For multivariable analysis the presence of both favorable and unfavorable features was considered neutral.

Supplemental table 1. Contributing sites.

Supplemental table 1: Contributing Institutions

Name	City, State
Arkansas Children's Hospital	Little Rock, AR
CS Mott Children's Hospital	Ann Arbor, MI
Children's Healthcare of Atlanta/Aflac Cancer and Blood Disorders Center	Atlanta, GA
Children's Hospital of Los Angeles	Los Angeles, CA
Children's Hospital of Michigan	Detroit, MI
Children's Hospital of Philadelphia	Philadelphia, PA
Dana Farber Cancer Center	Boston, MA
Nemours Children's Health	Wilmington, DE
Primary Children's Hospital	Salt Lake City, UT
Rady Children's Hospital	San Diego, CA
Seattle Children's Hospital	Seattle, WA
Texas Children's Hospital	Houston, TX
University of Texas Southwestern Medical Center	Dallas, TX

Supplemental table 2. Chemotherapy regimens and operationalized categorization.

Regimen cateogry	Intensive Regimen Category	Re-induction regimen	Patients (n)
intensive w. anthracycline	CPX-351	CPX-351	50
		CPX-351 + Dasatinib	1
	FLA(G) + anthracycline	Fludarabine + Cytarabine + Idarubicin	9
		Fludarabine + Cytarabine + Idarubicin + Venetoclax	2
		Fludarabine + Cytarabine + Other Anthracycline	4
	Low-frequency, excluded from comparative effectiveness analyses	Cladribine + Cytarabine + Idarubicin	3
		Cladribine + Cytarabine + Mitoxantrone	1
	Other w. anthracycline	Cytarabine + Daunorubicin + Etoposide	2
		Cytarabine + Idarubicin + Venetoclax	2
		Mitoxantrone + Cytarabine	11
intensive, no anthracycline	CLA(G)	Clofarabine + Cytarabine	13
	FLA(G)	Fludarabine + Cytarabine	56
	FLA(G) + other	Fludarabine + Cytarabine + Azacitadine	6
		Fludarabine + Cytarabine + Panobinostat	2
		Fludarabine + Cytarabine + Decitabine + Vironostat	13
	Low-frequency, excluded from comparative effectiveness analyses	Clofarabine	1
		Clofarabine + Cyclophosphomide + Etoposide	1
		Cytarabine + Cladribine	1
		Cytarabine + Cladribine + Decitabine	1
		Thioguanine + Methotrexate + Aspariginase	3
	Other non-anthracycline	Cytarabine	1
		Cytarabine + Asparaginase	6
		Cytarabine + Asparaginase + Venetoclax	1
		Cytarabine + Azacitidine + Venetoclax	2
		Cytarabine + Decitabine	1
		Cytarabine + Etoposide + Plerixafor	1
non-intensive, excluded from comparative effectiveness analyses		Azacitidine	12
		Azacitidine + Etoposide	1
		Azacitidine + Ruxolitnib	1
		Azacitidine + Venetoclax	14
		Decitabine	8
		Decitabine + Azacitidine	1
		Decitabine + Bosutinib	1
		Decitabine + Venetoclax	8
		Flotetuzumab	1
		FLX925 + hydroxyurea	1
		Lenalidomide	2
		Selinexor + Venetoclax	2
		Venetoclax	3

Supplemental Tables 3. Stratified demographic and disease related characteristics. (A) Early relapse, (B) Late relapse, (C) Therapy Intensity, (D) Gemtuzumab-ozogamycin exposure.

(A) EARLY RELAPSE (< 12M)

	Overall	Intensive Regimens								Non-intensive regimens
		CLA(G)	CPX-351	FLA(G)	FLA(G) + anthracycline	FLA(G) + other	Other non-anthracycline	Other w. anthracycline	Other, low frequency*	
	125	N = 8	N = 16	N = 19	N = 9	N = 11	N = 10	N = 10	N = 5	N = 37
Hospitals used	12	4	7	6	5	6	5	6	2	11
Number of years used during observation period (2011-2024)	14	6	6	8	5	8	6	8	4	12
Gemtuzumab administered with cycle										
No	102 (82%)	8 (100%)	11 (69%)	16 (84%)	9 (100%)	9 (82%)	10 (100%)	8 (80%)	5 (100%)	26 (70%)
Yes	23 (18%)	0	5 (31%)	3 (16%)	0	2 (18%)	0	2 (20%)	0	11 (30%)
Median potential follow-up (months)	26 (1-133)	55 (3-77)	17 (1-55)	93 (8-133)	13 (11-119)	40 (1-90)	23 (19-65)	28 (5-51)	11 (2-32)	8 (5-24)
Sex										
Female	53 (42%)	3 (38%)	5 (31%)	8 (42%)	6 (67%)	4 (36%)	5 (50%)	6 (60%)	0	16 (43%)
Male	72 (58%)	5 (63%)	11 (69%)	11 (58%)	3 (33%)	7 (64%)	5 (50%)	4 (40%)	5 (100%)	21 (57%)
Age at relapse										
Median [Min, Max]	5 [0.6, 19]	3 [0.9, 14]	7 [2, 18]	6 [0.6, 19]	2 [0.6, 15]	7 [1, 17]	3 [1, 18]	7 [0.6, 19]	5 [1, 15]	4 [1, 19]
Race										
Hispanic	31 (25%)	2 (25%)	5 (31%)	4 (21%)	2 (22%)	4 (36%)	3 (30%)	1 (10%)	1 (20%)	9 (24%)
NH-Black	15 (12%)	0	2 (13%)	4 (21%)	1 (11%)	0	3 (30%)	2 (20%)	1 (20%)	2 (5%)
NH-White	53 (42%)	5 (63%)	5 (31%)	9 (47%)	3 (33%)	5 (46%)	3 (30%)	6 (60%)	1 (20%)	16 (43%)
Other	26 (21%)	1 (13%)	4 (25%)	2 (11%)	3 (33%)	2 (18%)	1 (10%)	1 (10%)	2 (40%)	10 (27%)
Cytogenic based risk										
Both Favorable & Unfavorable	6 (5%)	0	1 (6%)	1 (5%)	0	1 (9%)	1 (10%)	0	2 (40%)	0
Neither Favorable or Unfavorable	64 (51%)	6 (75%)	8 (50%)	8 (42%)	4 (44%)	6 (54%)	4 (40%)	3 (30%)	2 (40%)	23 (62%)
Only Favorable	13 (10%)	0	5 (31%)	2 (11%)	2 (22%)	1 (9%)	2 (20%)	1 (10%)	0	0
Only Unfavorable	42 (34%)	2 (25%)	2 (13%)	8 (42%)	3 (33%)	3 (27%)	3 (30%)	6 (60%)	1 (20%)	14 (38%)
Completed frontline therapy										
No	38 (30%)	4 (50%)	4 (25%)	5 (26%)	3 (33%)	3 (27%)	6 (60%)	6 (60%)	1 (20%)	6 (16%)
Yes	87 (70%)	4 (50%)	12 (75%)	14 (74%)	6 (67%)	8 (73%)	4 (40%)	4 (40%)	4 (80%)	31 (84%)
Transplant prior to relapse										
No	78 (62%)	8 (100%)	12 (75%)	17 (90%)	8 (89%)	5 (46%)	9 (90%)	10 (100%)	1 (20%)	8 (22%)
Yes	47 (38%)	0	4 (25%)	2 (11%)	1 (11%)	6 (55%)	1 (10%)	0	4 (80%)	29 (78%)
GO exposure prior to relapse^										
No	80 (76%)	8 (100%)	8 (62%)	17 (94%)	6 (75%)	7 (70%)	7 (88%)	6 (76%)	4 (80%)	17 (61%)
Yes	26 (25%)	0	5 (39%)	1 (6%)	2 (25%)	3 (30%)	1 (13%)	2 (25%)	1 (20%)	11 (39%)
Marrow involvement at relapse										
M2/M3	109 (94%)	7 (88%)	16 (100%)	14 (82%)	8 (89%)	11 (100%)	5 (100%)	6 (75%)	8 (89%)	29 (88%)
MRD	7 (6%)	1 (13%)	0	3 (18%)	1 (11%)	0	0	2 (25%)	1 (11%)	4 (12%)
Relapse site(s)										
Bone marrow + CNS/EMD	21 (17%)	1 (13%)	2 (13%)	3 (16%)	5 (56%)	0	2 (20%)	3 (30%)	0	5 (14%)
Bone marrow only	95 (76%)	7 (88%)	14 (88%)	14 (74%)	4 (44%)	11 (100%)	6 (60%)	6 (60%)	5 (100%)	28 (76%)
CNS/EMD	9 (7%)	0	0	2 (11%)	0	0	2 (20%)	1 (10%)	0	4 (11%)

^19 missing

(B) LATE RELAPSE (> 12M)

	Overall	Intensive Regimens								Non-intensive regimens
		CLA(G)	CPX-351	FLA(G)	FLA(G) + anthracycline	FLA(G) + other	Other non-anthracycline	Other w. anthracycline	Other, low frequency*	
	122	N = 5	N = 35	N = 37	N = 6	N = 10	N = 2	N = 5	N = 5	N = 17
Hospitals used	13	3	8	9	4	6	2	4	3	9
Number of years used during observation period (2011-2024)	14	3	8	11	5	6	2	3	4	9
Gemtuzumab administered with cycle										
No	86 (71%)	5 (100%)	15 (43%)	24 (65%)	6 (100%)	10 (100%)	2 (100%)	5 (100%)	5 (100%)	14 (82%)
Yes	36 (30%)	0	20 (57%)	13 (35%)	0	0	0	0	0	3 (18%)
Median follow-up (months)	29 (0.7-152)	77 (40-144)	29 (7-98)	14 (1-107)	53 (1-152)	53 (5-87)	102	103 (101-122)	23 (21-24)	10 (1-46)
Sex										
Female	51 (42%)	2 (40%)	17 (49%)	17 (46%)	2 (33%)	0	1 (50%)	3 (60%)	1 (20%)	8 (47%)
Male	71 (58%)	3 (60%)	18 (51%)	20 (54%)	4 (67%)	10 (100%)	1 (50%)	2 (40%)	4 (80%)	9 (53%)
Age at relapse										
Median [Min, Max]	12 [2-21]	6 [2, 16]	13 [2, 20]	13 [3, 21]	14 [4, 19]	9 [3, 18]	3 [3, 3]	9 [2, 15]	11 [2, 15]	15 [2, 20]
Race										
Hispanic	33 (27%)	1 (20%)	12 (34%)	9 (24%)	1 (17%)	4 (40%)	1 (50%)	0	1 (20%)	4 (24%)
NH-Black	17 (14%)	0	8 (23%)	4 (11%)	1 (17%)	0	0	2 (40%)	0	2 (12%)
NH-White	40 (41%)	4 (80%)	12 (34%)	17 (46%)	2 (33%)	1 (10%)	1 (50%)	1 (20%)	3 (60%)	9 (53%)
Other	22 (18%)	0	3 (9%)	7 (19%)	2 (33%)	5 (50%)	0	2 (40%)	1 (20%)	2 (12%)
Cytogenic based risk										
Both Favorable & Unfavorable	5 (4%)	1 (20%)	1 (3%)	2 (5%)	0	0	0	0	1 (20%)	0
Neutral/Other/Unknown	54 (44%)	2 (40%)	14 (40%)	15 (41%)	2 (33%)	5 (50%)	2 (100%)	1 (20%)	1 (20%)	12 (71%)
Only Favorable	37 (30%)	2 (40%)	11 (31%)	13 (35%)	3 (50%)	1 (10%)	0	4 (80%)	1 (20%)	2 (12%)
Only Unfavorable	26 (21%)	0	9 (26%)	7 (19%)	1 (17%)	4 (40%)	0	0	2 (40%)	3 (18%)
Completed frontline therapy										
No	4 (3%)	0	1 (3%)	1 (3%)	0	1 (10%)	0	0	1 (20%)	0
Yes	118 (97%)	5 (100%)	34 (97%)	36 (97%)	6 (100%)	9 (90%)	2 (100%)	5 (100%)	4 (80%)	17 (100%)
Transplant prior to relapse										
No	86 (71%)	4 (80%)	21 (60%)	32 (87%)	4 (67%)	5 (50%)	1 (50%)	5 (100%)	4 (80%)	6 (35%)
Yes	40 (33%)	1 (20%)	14 (40%)	5 (14%)	2 (33%)	5 (50%)	1 (50%)	0	1 (20%)	11 (65%)
GO exposure prior to relapse^										
No	77 (67%)	5 (100%)	24 (73%)	22 (61%)	3 (50%)	6 (67%)	2 (100%)	5 (100%)	3 (60%)	7 (50%)
Yes	38 (33%)	0	9 (27%)	14 (39%)	3 (50%)	3 (33%)	0	0	2 (40%)	7 (50%)
Marrow involvement at relapse										
M2/M3	104 (90%)	3 (60%)	35 (100%)	33 (100%)	6 (100%)	20 (100%)	1 (100%)	4 (100%)	5 (100%)	13 (81%)
MRD	12 (10%)	2 (40%)	0	0	0	0	0	0	0	3 (19%)
Relapse site(s)										
Bone marrow + CNS/EMD	28 (23%)	2 (40%)	9 (26%)	8 (22%)	2 (33%)	3 (30%)	0	2 (40%)	2 (40%)	0
Bone marrow only	88 (72%)	3 (60%)	26 (74%)	25 (68%)	4 (67%)	7 (70%)	1 (50%)	3 (60%)	3 (60%)	16 (94%)
CNS/EMD	6 (5%)	0	0	4 (11%)	0	0	1 (50%)	0	0	1 (6%)

^missing in 7

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(C) Demographic and treatment characteristics by receipt of gemtuzumab-ozogamycin (GO) among those who received intensive chemotherapy

	Overall (N = 193)	GO (N = 45)	No GO (N = 148)
Hospitals used	13	11	13
Number of years used during observation	14	9	14
Chemotehrapy administered with this cycle			
FLA(G)	56 (29%)	16 (36%)	40 (27%)
CLA(G)	13 (7%)	0	13 (9%)
CPX-351	51 (26%)	25 (56%)	26 (18%)
FLA(G) + anthracycline	15 (8%)	0	15 (10%)
FLA(G) + other	21 (11%)	2 (4%)	19 (13%)
Other non-anthracycline	15 (8%)	0	12 (8%)
Other with anthracycline	12 (6%)	2 (4%)	13 (9%)
Other, low frequnecy	10 (5%)	0	10 (7%)
Median potential follow-up (months)	30 (1-150)	51 (1-150)	23 (1-62)
Sex			
Female	80 (42%)	22 (49%)	58 (39%)
Male	113 (59%)	23 (51%)	90 (61%)
Age at relapse (years)			
Median [Min, Max]	10 (0.6-21)	13 (1-20)	9 (0.6-21)
Race			
Hispanic	51 (26%)	10 (22%)	41 (28%)
NH-Black	28 (15%)	8 (18%)	20 (14%)
NH-White	78 (40%)	20 (44%)	58 (39%)
Other	36 (19%)	7 (16%)	29 (20%)
Cytogenic based risk			
Both Favorable & Unfavorable	11 (6%)	3 (7%)	8 (5%)
Neither Favorable or Unfavorable	83 (43%)	16 (36%)	67 (45%)
Only Favorable	48 (25%)	13 (29%)	35 (24%)
Only Unfavorable	51 (26%)	13 (29%)	38 (26%)
Completed frontline therapy			
No	36 (19%)	7 (16%)	29 (20%)
Yes	157 (81%)	38 (84%)	119 (80%)
Transplant prior to relapse			
No	146 (76%)	34 (76%)	112 (76%)
Yes	47 (24%)	11 (24%)	36 (24%)
GO exposure prior to relapse^			
No	133 (74%)	21 (50%)	112 (82%)
Yes	46 (26%)	21 (50%)	25 (28%)
Time from diagnosis to relapse			
<6 months	29 (15%)	3 (7%)	26 (18%)
6 to <12 months	59 (31%)	9 (20%)	50 (34%)
12 or more months	105 (54%)	33 (73%)	72 (49%)
Marrow involvement at relapse*			
M2/M3	171 (93%)	43 (96%)	138 (93%)
MRD-level disease only	12 (7%)	2 (4%)	10 (7%)
Relapse site(s)			
Bone marrow + CNS/EMD	44 (23%)	8 (18%)	36 (24%)
Bone marrow only	139 (72%)	37 (82%)	102 (69%)
CNS/EMD**	10 (5%)	0	10 (7%)

^missing in 14, not included in comparative effectiveness (CE) analysis; *proportion of patients with marrow disease; ** not included in CE analysis

7 CLA(G) Clofarabine + cytarabine +/- GCSF; FLA(G) Fludarabine + cytarabine +/- GCSF; MRD Measurable residual disease

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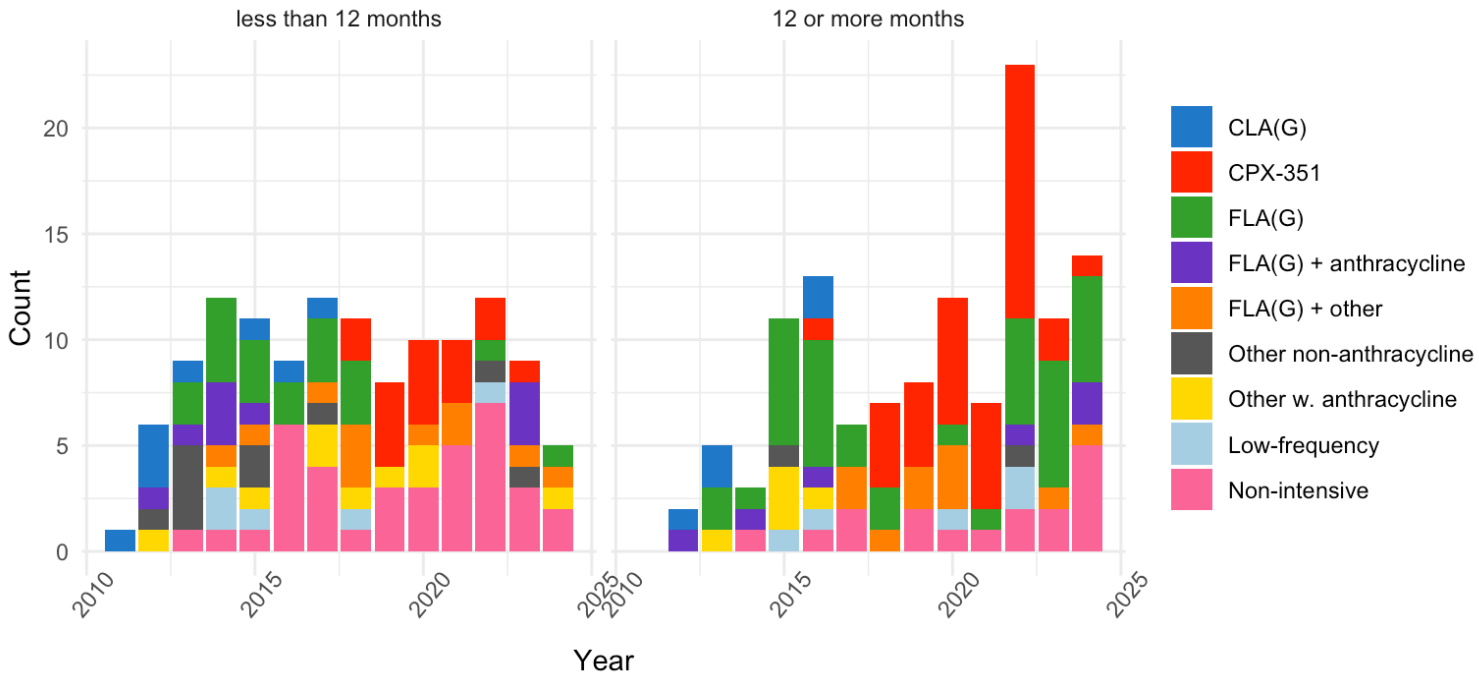
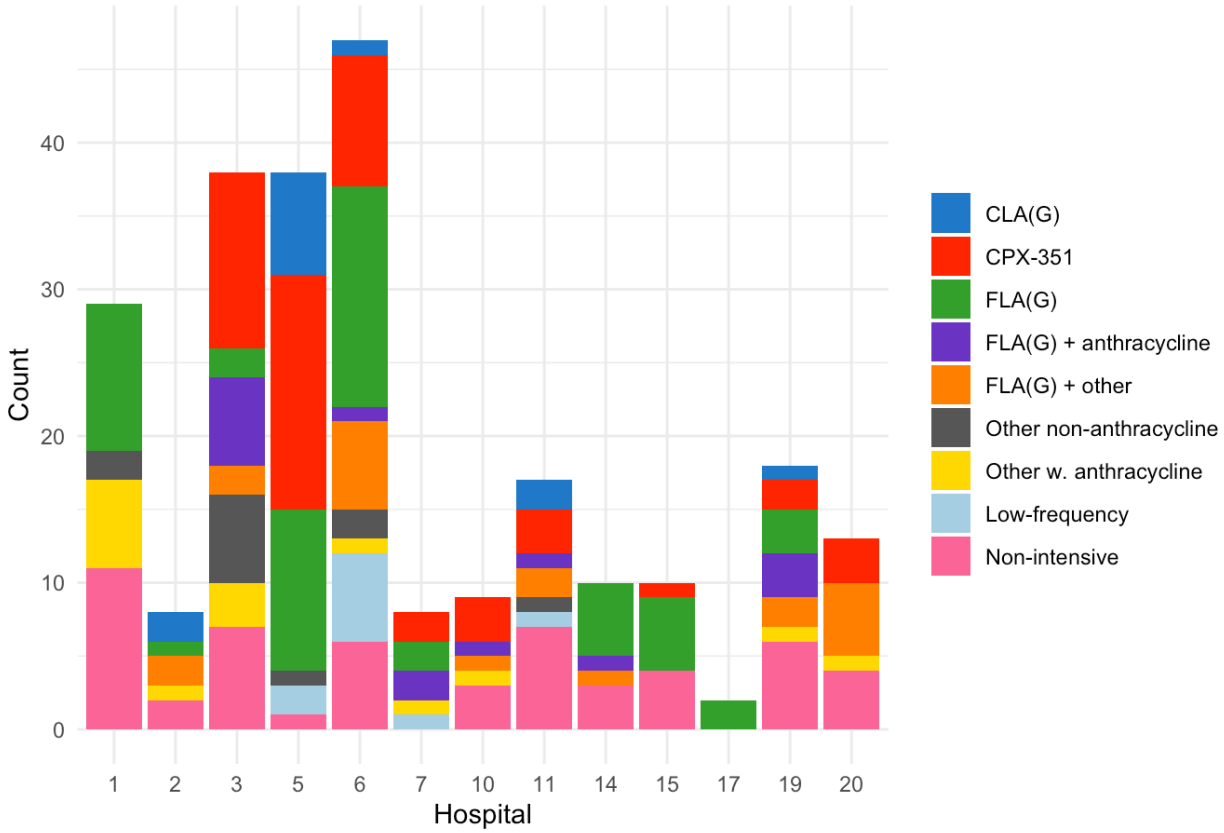
Supplemental Figure 1. Trends in treatment approaches over time. (A) Overall (B) Early relapse (<12m) and (C) Late relapse ≥12m). Abbreviations: CLA(G) Clofarabine + cytarabine +/- GCSF; FLA(G) Fludarabine + cytarabine +/- GCSF.



Supplemental Figure 2. Use of reinduction approaches by REAL-AML institution. Most hospitals use multiple different re-induction regimens. Abbreviations: CLA(G) Clofarabine + cytarabine +/- GCSF; FLA(G) Fludarabine + cytarabine +/- GCSF.



Supplemental tables 4A-C. Unadjusted predictors of oncomes after relapse. (A) 2-year overall survival, (B) Clinical remission (<5% myeloblasts), (C) Measurable residual disease negative remission.

Supplemental Table 4A: Predictors of 2-year overall survival

	Overall			Intensive Regimens			Non-intensive regimen		
	2y OS	Unadjusted HR	95% CI	2y OS	Unadjusted HR	95% CI	2y OS	Unadjusted HR	95% CI
Sex									
Female	0.4	*ref*		0.5	*ref*		0.2	*ref*	
Male	0.4	1.0	0.7-1.4	0.5	1.0	0.6-1.4	0.1	1.0	0.5-1.8
Age at relapse									
0-1	0.3	2.0	1.2-3.2	0.3	2.4	1.3-1.4	NR		
2-12	0.4	*ref*		0.5	*ref*		0.2	NR	
13-22	0.4	1.0	0.7-1.5	0.5	1.0	0.6-1.6	NR		
Race/Ethnicity									
Hispanic	0.4	0.8	0.5-1.2	0.5	0.8	0.5-1.3	NR		
NH-Black	0.4	0.9	0.4-1.6	0.5	0.9	0.5-1.7	NR	NR	
NH-White	0.4	*ref*		0.4	*ref*		0.2		
Other	0.5	0.7	0.4-1.1	0.6	0.5	0.3-1.0	NR		
Cytogenic based risk									
Neutral/Other/Unknown	0.4	*ref*		0.5	*ref*		0.2		
Only Favorable	0.7	0.4	0.2-0.7	0.7	0.5	0.3-0.8	NR	NR	
Only Unfavorable	0.3	1.2	0.8-1.8	0.4	1.1	0.7-1.8	NR		
Completed frontline therapy									
No	0.2	2.1	1.4-3.1	0.2	2.6	1.7-4.1	NR	NR	
Yes	0.5	*ref*		0.6	*ref*		0.2		
Transplant prior to relapse									
No	0.5	*ref*		0.5	*ref*		NR	NR	
Yes	0.3	1.9	1.4-2.7	0.4	1.6	1.0-2.5	0.1		
Time from diagnosis to relapse									
<6 months	0.2	3.4	2.1-5.5	0.2	2.5	2.0-6.0	NR	NR	
6 to <12 months	0.3	2.7	1.1-4.0	0.4	2.3	1.4-3.7	0	3.0	1.3-7.0
12 or more months	0.6	*ref*		0.6	*ref*		0.4	*ref*	
Bone marrow involvement									
M2/M3	0.4	*ref*		0.5			0.2		
MRD only	0.4	0.9	0.4-1.7	0.6	0.8	0.3-1.9	NR	0.9	0.3-2.7
Relapse site(s)									
Bone marrow + CNS/EMD	0.4	1.2	0.8-1.8	0.4	1.2	0.8-2.0	NR		
Bone marrow only	0.4	*ref*		0.5	*ref*		0.2	NR	
CNS/EMD	0.4	1.2	0.6-2.4	0.5	1.1	0.4-2.6	NR		

Supplemental Table 4b: Predictors of EOI CR

	Overall			Intensive Regimens			Non-intensive regimen		
	n (%)	Unadjusted PR	95% CI	n (%)	Unadjusted PR	95% CI	n (%)	Unadjusted PR	95% CI
Sex									
Female	66 (64%)	*ref*		57 (71%)	*ref*		9 (38%)	*ref*	
Male	78 (55%)	0.9	0.7-1.1	68 (60%)	0.8	0.7-1.0	10 (33%)	0.9	0.4-1.8
Age at relapse									
0-2	13 (45%)	0.7	0.5-1.1	11 (52%)	0.8	0.5-1.2	2 (25%)	0.7	0.2-2.6
3-12	81 (62%)	*ref*		71 (69%)	*ref*		10 (36%)	*ref*	
13-22	50 (58%)	0.9	0.7-1.2	43 (62%)	0.9	0.7-1.1	7 (39%)	1.1	0.5-2.4
Race/Ethnicity									
Hispanic	40 (63%)	1.1	0.8-1.4	34 (67%)	1.0	0.8-1.3	6 (46%)	1.4	0.6-3.3
NH-Black	21 (66%)	1.1	0.8-1.5	19 (68%)	1.0	0.8-1.4	2 (50%)	1.6	0.5-4.9
NH-White	60 (58%)	*ref*		52 (67%)	*ref*		8 (32%)	*ref*	
Other	23 (48%)	0.8	0.6-1.2	20 (56%)	0.8	0.6-1.2	3 (25%)	0.8	0.3-2.5
Cytogenic based risk									
Neutral/Other/Unknown	71 (55%)	*ref*		57 (61%)	*ref*		14 (40%)	*ref*	
Only Favorable	40 (80%)	1.5	1.2-1.8	39 (81%)	1.3	1.1-1.7	1 (50%)	1.3	0.3-5.4
Only Unfavorable	33 (49%)	0.9	0.7-1.2	29 (57%)	0.9	0.7-1.3	4 (24%)	0.6	0.2-1.5
Completed frontline therapy									
No	20 (48%)	0.8	0.6-1.1	18 (50%)	0.7	0.5-1.0	2 (33%)	0.9	0.3-3.1
Yes	124 (61%)	*ref*		107 (68%)	*ref*		17 (35%)	*ref*	
Transplant prior to relapse									
No	108 (68%)	*ref*		101 (69%)	*ref*		7 (50%)	*ref*	
Yes	36 (41%)	0.6	0.5-0.8	24 (51%)	0.7	0.6-1.0	12 (30%)	0.6	0.3-1.2
Time from diagnosis to relapse									
less than 12 months	91 (75%)	0.6	0.5-0.7	43 (49%)	0.6	0.5-0.8	10 (27%)	0.5	0.3-1.0
12 or more months	53 (42%)	*ref*		82 (78%)	*ref*		9 (53%)	*ref*	
Bone marrow involvement									
M2/M3	132 (58%)	*ref*		115 (64%)	*ref*		17 (36%)	*ref*	
MRD only	12 (63%)	1.1	0.8-1.6	10 (83%)	1.3	1.0-1.7	2 (29%)	0.8	0.2-2.7
Relapse site(s)									
Bone marrow + CNS/EMD	38 (78%)	1.4	1.2-1.8	35 (80%)	1.3	1.1-1.6	3 (60%)	1.8	0.8-4.1
Bone marrow only	99 (54%)	*ref*		84 (60%)	*ref*		15 (34%)	*ref*	
CNS/EMD	7 (47%)	0.9	0.5-1.5	6 (60%)	1.0	0.6-1.7	1 (20%)	0.6	0.1-3.6

Supplemental Table 4c: Predictors of EOI MRD negative CR

	Overall			Intensive Regimens			Non-intensive regimen		
	n (%)	Unadjusted PR	95% CI	n (%)	Unadjusted PR	95% CI	n (%)	Unadjusted PR	95% CI
Sex									
Female	39 (42%)	*ref*		35 (49%)	*ref*		4 (18%)	*ref*	
Male	62 (44%)	1.1	0.8-1.5	58 (52%)	1.1	0.8-1.4	4 (14%)	0.8	0.2-2.8
Age at relapse									
0-2	8 (29%)	0.6	0.3-1.2	8 (38%)	0.7	0.4-1.3	0	NR	
3-12	58 (46%)	*ref*		53 (54%)	*ref*		5 (19%)	*ref*	
13-22	35 (44%)	1.0	0.7-1.3	32 (50%)	0.9	0.7-1.3	3 (19%)	1.0	0.3-3.7
Race/Ethnicity									
Hispanic	25 (40%)	0.9	0.6-1.4	23 (50%)	1.0	0.7-1.4	2 (15%)	0.6	0.1-2.6
NH-Black	12 (39%)	0.9	0.5-1.5	12 (43%)	0.9	0.5-1.4	0	NR	
NH-White	41 (43%)	*ref*		35 (49%)	*ref*		6 (26%)	*ref*	
Other	23 (50%)	1.2	0.8-1.7	23 (66%)	1.4	1.0-1.9	0	NR	
Cytogenic based risk									
Neutral/Other/Unknown	50 (41%)	*ref*		44 (49%)	*ref*		6 (19%)	*ref*	
Only Favorable	30 (64%)	1.5	1.1-2.0	29 (64%)	1.3	1.0-1.8	1 (50%)	2.6	0.5-12.5
Only Unfavorable	21 (32%)	0.8	0.5-1.2	20 (41%)	0.8	0.6-1.2	1 (6%)	0.3	0.0-2.4
Completed frontline therapy									
No	9 (22%)	0.5	0.3-0.8	9 (26%)	0.5	0.3-0.8	0	NR	
Yes	92 (48%)	*ref*		84 (56%)	*ref*		8 (18%)	*ref*	
Transplant prior to relapse									
No	80 (53%)	*ref*		78 (56%)	*ref*		2 (17%)	*ref*	
Yes	21 (25%)	0.5	0.3-0.7	15 (33%)	0.6	0.4-0.9	6 (16%)	1.0	0.2-4.2
Time from diagnosis to relapse									
less than 12 months	34 (28%)	0.5	0.3-0.6	31 (36%)	0.6	0.4-0.8	3 (8%)	0.2	0.1-0.9
12 or more months	67 (60%)	*ref*		62 (63%)	*ref*		5 (36%)	*ref*	
Bone marrow involvement									
M2/M3	93 (43%)	*ref*		86 (50%)	*ref*		7 (16%)	*ref*	
MRD only	8 (42%)	1.0	0.6-1.7	7 (58%)	1.2	0.7-1.9	1 (14%)	0.9	0.1-6.2
Relapse site(s)									
Bone marrow + CNS/EMD	32 (68%)	1.8	1.4-2.4	30 (70%)	1.6	1.2-2.0	2 (50%)	4.1	1.1-14.9
Bone marrow only	64 (37%)	*ref*		59 (45%)	*ref*		5 (12%)	*ref*	
CNS/EMD	5 (33%)	0.9	0.4-1.9	4 (40%)	0.9	0.4-2.0	1 (20%)	1.6	0.2-11.6

Supplemental Table 5A-C. Full multivariable models associated with the primary and secondary comparative effectiveness analyses.

A. Overall survival				B. End of reinduction clinical remission			C. End of reinduction MRD negative remission		
Regimen									
FLA(G)		*ref*			*ref*			*ref*	
CLA(G)	1.3	0.5-3.2	0.64	0.8	0.4-1.4	0.41	0.8	0.4-1.6	0.55
CPX-351	0.9	0.4-1.9	0.75	1.1	0.9-1.4	0.24	0.9	0.6-1.3	0.49
FLA(G) + anthracycline	0.4	0.1-1.4	0.14	1.3	0.9-1.9	0.13	1.3	0.8-2.3	0.28
FLA(G) + other	1.0	0.4-2.3	0.91	0.9	0.6-1.5	0.73	1.1	0.6-2.0	0.77
Other non-anthracycline	0.8	0.3-2.3	0.66	0.5	0.1-1.5	0.19	0.8	0.2-2.7	0.68
Other with anthracycline	1.6	0.6-3.9	0.34	1.0	0.7-1.5	0.95	1.1	0.7-1.9	0.70
Gemtuzumab-ozogamycin (GO)									
No GO		*ref*			*ref*			*ref*	
GO	1.1	0.6-2.2	0.74	**1.3**	**1.0-1.5**	**0.04**	**1.5**	**1.1-2.1**	**0.02**
Additional covariates									
Age at relapse (years)									
<2	1.7	0.7-4.1	0.24	1.0	0.6-1.6	0.85	0.9	0.5-1.6	0.67
2-13		*ref*							
>13	1.2	0.7-2.1	0.57	0.9	0.7-1.0	0.12	0.9	0.7-1.2	0.39
Race									
Hispanic		*ref*						*ref*	
NH-Black	1	0.4-2.3	1.00				0.8	0.5-1.2	0.22
NH-White	1.0	0.5-1.8	0.90				1	0.7-1.4	0.98
Other	0.3	0.1-0.8	0.01				1.3	0.9-2.0	0.16
Cytogenic based risk									
Neutral		*ref*			*ref*			*ref*	
Only Favorable	0.5	0.2-1.2	0.13	1.0	0.8-1.2	0.87	1.0	0.8-1.4	0.93
Only Unfavorable	0.8	0.5-1.5	0.49	1.1	0.8-1.5	0.72	1.0	0.7-1.6	0.98
Completed frontline therapy									
No		*ref*			*ref*			*ref*	
Yes	0.4	0.2-0.9	0.21	1.4	0.9-2.2	0.15	1.9	1.0-3.4	0.05
Transplant prior to relapse									
No		*ref*			*ref*			*ref*	
Yes	2.0	.0-4.1	0.50	0.7	0.5-0.9	0.02	0.5	0.3-0.8	0.01
Time from diagnosis to relapse									
<12 months		*ref*			*ref*			*ref*	
12 or more months	2.2	1.2-3.9	0.01	0.7	0.6-0.9	0.02	0.8	0.5-1.1	0.13
Marrow involvement at relapse									
M2/M3		*ref*			*ref*				
MRD-level disease only	0.5	0.2-1.4	0.20	1.7	1.2-2.6	0.01			
Relapse site(s)									
Bone marrow + CNS/EMD	1.7	1.0-3.1	0.08	0.8	0.7-1.0	0.06	0.7	0.5-1.0	0.02
Bone marrow only		*ref*			*ref*			*ref*	

Supplemental Table 6. Comparative effectiveness of chemotherapy regimens for first re-induction excluding patients with FLT3 mutations who received FLT3 inhibitors.

		Adjusted estimates*		
	OS/Proportion with response	**aHR/PR**	**95% CI**	**p value**
2-year overall survival				
FLA(G)	0.6		*ref*	
CLA(G)	0.5	1.1	0.4-2.9	0.80
CPX-351	0.6	0.8	0.4-1.8	0.61
FLA(G) + anthracycline	0.8	0.4	0.2-1.5	0.18
FLA(G) + other	0.5	0.8	0.3-2.0	0.63
Other non-anthracycline	0.3	1.2	0.4-3.5	0.78
Other with anthracycline	0.5	1.4	0.4-3.7	0.54
No GO	0.5		*ref*	
GO	0.6	1.1	0.2-1.3	0.13
End of re-induction clinical remission (CR)				
FLA(G)	0.7		*ref*	
CLA(G)	0.5	0.8	0.5-1.4	0.42
CPX-351	0.8	1.1	0.9-1.4	0.24
FLA(G) + anthracycline	0.8	1.3	0.9-1.9	0.15
FLA(G) + other	0.5	0.9	0.6-1.4	0.70
Other non-anthracycline	0.3	0.5	0.2-1.6	0.24
Other with anthracycline	0.8	1.1	0.8-1.6	0.57
No GO	0.6		*ref*	
GO	0.8	**1.2**	**1.0-1.5**	**0.04**
End of re-induction MRD negative remission				
FLA(G)	0.6		*ref*	
CLA(G)	0.4	0.8	0.4-1.6	0.50
CPX-351	0.5	0.9	0.6-1.3	0.55
FLA(G) + anthracycline	0.7	1.3	0.8-2.2	0.30
FLA(G) + other	0.5	1.1	0.6-2.0	0.80
Other non-anthracycline	0.3	0.8	0.2-2.9	0.80
Other with anthracycline	0.7	1.3	0.8-2.0	0.36
No GO	0.5		*ref*	
GO	0.7	**1.5**	**1.1-2.0**	**0.02**

*Covariates for multivariable models: Overall Survival (age, race/ethnicity, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site, marrow involvement at relapse, recipt of GO); Clinical remission (age, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site, marrow involvement at relapse); MRD negative CR (age, race/ethnicity, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site)

Supplemental Table 7. Comparative effectiveness of chemotherapy regimens for first re-induction excluding patients who received venetoclax.

		Adjusted estimates*		
	OS/Proportion with response	**aHR/PR**	**95% CI**	**p value**
2-year overall survival				
FLA(G)	0.6		*ref*	
CLA(G)	0.5	1.1	0.4-2.8	0.89
CPX-351	0.6	0.9	0.4-1.9	0.70
FLA(G) + anthracycline	0.8	0.3	0.1-1.6	0.18
FLA(G) + other	0.5	0.9	0.4-2.0	0.72
Other non-anthracycline	0.3	0.8	0.2-2.6	0.68
Other with anthracycline	0.3	1.5	0.6-3.8	0.38
No GO	0.5		*ref*	
GO	0.6	1.1	0.6-3.8	0.82
End of re-induction clinical remission (CR)				
FLA(G)	0.7		*ref*	
CLA(G)	0.5	0.8	0.4-1.5	0.48
CPX-351	0.7	1.1	0.9-1.4	0.27
FLA(G) + anthracycline	0.8	1.2	0.8-1.8	0.31
FLA(G) + other	0.5	0.9	0.6-1.5	0.78
Other non-anthracycline	0.2	0.4	0.1-2.4	0.29
Other with anthracycline	0.7	1.1	0.7-1.6	0.80
No GO	0.6		*ref*	
GO	0.8	**1.2**	**1.0-1.5**	**0.05**
End of re-induction MRD negative remission				
FLA(G)	0.6		*ref*	
CLA(G)	0.4	0.8	0.4-1.5	0.48
CPX-351	0.5	1.1	0.9-1.4	0.27
FLA(G) + anthracycline	0.7	1.2	0.8-1.8	0.31
FLA(G) + other	0.5	0.9	0.6-1.5	0.78
Other non-anthracycline	0.2	0.4	0.1-2.4	0.29
Other with anthracycline	0.5	1.1	0.7-1.6	0.82
No GO	0.5		*ref*	
GO	0.7	**1.4**	**1.0-2.0**	**0.03**

*Covariates for multivariable models: Overall Survival (age, race/ethnicity, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site, marrow involvement at relapse, recipt of GO); Clinical remission (age, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site, marrow involvement at relapse); MRD negative CR (age, race/ethnicity, cytogenic risk, completion of upfront therapy, transplant prior to relapse, time to relapse, relapse site)

Supplemental Table 8. Comparative effectiveness of chemotherapy regimens and GO, stratified by timing of relapse.

Assessment of comparative effectiveness of backbone chemotherapy regimens stratified by timing of relapse.	EARLY RELAPSE (<12M)				LATE RELAPSE (> 12M)			
	OS/ Proportion with response	aHR/PR	95% CI	p value	OS/ Proportion with response	aHR/PR	95% CI	p value
2-year overall survival								
FLA(G)	0.5		*ref*		0.6		*ref*	
CLA(G)	0.3	1.6	0.4-5.1	0.43	0.8	1.1	0.1-10.2	0.94
CPX-351	0.4	2.1	0.5-6.4	0.23	0.7	0.5	0.2-1.4	0.19
FLA(G) + anthracycline	0.7	0.7	0.2-3.7	0.65	1.0		NR	
FLA(G) + other	0.4	1.3	0.5-5.5	0.70	0.7	1.4	0.4-5.6	0.64
Other non-anthracycline	0.4	1.2	0.4-4.1	0.80				
Other with anthracycline	0.1	1.8	0.4-4.3	0.31				
No GO	0.4		*ref*		0.7		*ref*	
GO	0.3	1.3	0.5-3.6	0.64	0.7	1.0	0.4-2.6	0.93
End of re-induction clinical remission								
FLA(G)	0.9		*ref*		0.8		*ref*	
CLA(G)	0.6	1.6	0.8-3.6	0.21	0.4	0.4	0.2-0.8	0.02
CPX-351	0.4	0.9	0.4-2.1	0.74	0.9	1.2	1.0-1.5	0.07
FLA(G) + anthracycline	0.5	2.0	1.1-3.7	0.04	0.7	0.9	0.5-1.6	0.80
FLA(G) + other	0.3	0.6	0.2-2.0	0.42	0.7	1.1	0.7-1.6	0.75
Other non-anthracycline	0.3	0.5	0.1-1.8	0.30				
Other with anthracycline	0.6	1.1	0.6-2.3	0.74				
No GO	0.5		*ref*		0.7		*ref*	
GO	0.6	1.5	0.76-2.89	0.25	0.9	1.2	1.0-1.4	0.14
End of re-induction MRD negative remission								
FLA(G)	0.4		*ref*		0.7		*ref*	
CLA(G)	0.4	1.0	0.5-2.3	0.93	0.4	0.6	0.2-1.9	0.41
CPX-351	0.3	0.4	0.2-0.9	0.03	0.6	1.0	0.8-1.4	0.89
FLA(G) + anthracycline	0.9	1.5	0.6-3.8	0.38	0.5	0.9	0.4-2.3	0.81
FLA(G) + other	0.3	0.5	0.2-1.4	0.17	0.7	1.5	0.9-2.5	0.14
Other non-anthracycline	0.3	0.7	0.2-2.9	0.66				
Other with anthracycline	0.4	1.0	0.4-2.3	0.98				
No GO	0.4		*ref*		0.6		*ref*	
GO	0.4	1.9	0.8-4.3	0.15	0.8	1.4	1.0-1.9	0.04

CLA(G) Clofarabine + cytarabine +/- GCSF; FLA(G) Fludarabine + cytarabine +/- GCSF; HR/PR Hazard Ratio/Prevalence Ratio

Supplemental Figure 3. Overall survival by treatment approach, stratified by timing of relapse. (A) By chemotherapy regimen and (B) Receipt of GO.