REGULAR ARTICLE

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Aspacytarabine for the treatment of patients with AML unfit for intensive chemotherapy: a phase 2 study

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Key Points

- Aspacytarabine enables delivery of high-dose cytarabine to unfit patients without the prohibitive cerebellar and gastrointestinal toxicities.
- Aspacytarabine treatment resulted in a CR rate of 36.9% with no prolonged neutropenia or thrombocytopenia during postremission therapy.

High-dose cytarabine is associated with gastrointestinal and cerebellar toxicity, precluding its use for older or unfit patients with acute myeloid leukemia (AML). Aspacytarabine, an inactive prodrug of cytarabine, was evaluated as monotherapy in a phase 2b study of patients unfit for intensive chemotherapy (NCT03435848). Sixty-five patients with AML were treated with aspacytarabine 4.5 g/m^2 per day (equimolar to 3 g/m^2 per day cytarabine) for 6 doses per treatment. The median age was 75 years; 60.6% of patients had de novo AML, 28.8% had AML secondary to myelodysplastic syndrome, and 10.6% had therapy-related AML. Overall, 36.9% achieved complete remission (CR) with full count recovery. CR rates in patients with secondary AML, patients with prior treatment with hypomethylating agents, and patients with *TP53* mutation were 26.7%, 25%, and 36%, respectively. Median overall survival was 9 months (range, 6-15.9) and was not reached among responders. Hematologic recovery was observed in all responding patients by day 26 without prolonged cytopenias. Adverse events typically precluding the use of high-dose cytarabine in older or unfit patients were not observed. These data suggest that aspacytarabine may be an effective regimen with a reduction in the attendant toxicities associated with high-dose cytarabine, an important consideration when treating AML and other hematologic disorders that use high-dose cytarabine. This trial was registered at www.clinicaltrials.gov as #NCT03435848.

Introduction

Intensive chemotherapy (IC) remains the standard of care for younger and fit patients with newly diagnosed acute myeloid leukemia (AML). However, IC is unsuitable for many older patients with AML

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The protocol is available on request from the corresponding author, Jessica K. Altman (j-altman@northwestern.edu).

Table 1. Baseline characteristics (safety set)

Demographics		
Overall age (y), N = 66		
Median, 75		
Max-min, 47-88		
Parameter	**Number of patients (N = 66)**	**Proportion (%)**
Age categories (y)		
≥75	34	51.5
65-75	26	39.4
50-65	5	7.6
<50	1	1.5
Sex		
Female	28	42.4
Male	38	57.6
Race		
White	54	81.8
Black or African American	5	7.6
Unknown	4	6.1
Asian	2	3
Multiple	1	1.5
ECOG performance status		
0-1	40	60.6
2-3	26	39.4
AML type		
De novo	40	60.6
Secondary	26	39.4
Previous HMA therapy		
Yes	12	18.2
No	54	81.8
Number of HMA courses		
0	54	81.8
1-2	1	1.5
6-10	4	6.1
>10	7	10.6
WBC counts		
10.0-49.9 × 10^9/L	15	22.7
<10.0 × 10^9/L	51	77.3
ELN 2017 risk group		
Favorable	9	13.9
Intermediate	15	22.7
Adverse	33	50
Unknown	9	13.6
NPM1 mutation		
Missing	14	21.2
No	44	66.7
Yes	8	12.1
FLT3 mutation		
Missing	10	15.2
No	50	75.8
Yes	6 (3 with low ITD, 1 high, and 2 IDT unknown)	9.1
TP53 mutation		
Missing	18	27.3
No	36	54.5
Yes	11	18.2

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; FLT3, FMS-like receptor tyrosine kinase-3; HMA, hypomethylating agents; ITD, intertandem duplication; max, maximum; min, minimum; NPM1, nucleophosmin 1; TP53, tumor protein 53.

who have consistently demonstrated a lower response rate and higher treatment-related mortality and morbidity, leaving this population with few effective treatments.[1]

Aspacytarabine (BST-236) is a novel cytarabine prodrug composed of cytarabine covalently bound to asparagine via its cytosine residue. This formulation is designed to deliver high doses of cytarabine with lower systemic exposure to peak levels of free cytarabine, thereby reducing systemic toxicity. In a phase 1/2 study conducted in patients with AML and acute lymphoblastic leukemia, aspacytarabine was found to be well-tolerated, with 6 g/m^2 per day determined to be the maximal tolerated dose.[2]

Given these data, an open-label, multicenter, phase 2b study was conducted to assess the efficacy and safety of aspacytarabine in patients with previously untreated de novo or secondary AML unfit for IC.

Methods

This study was conducted at 20 sites in the United States and Israel and was approved by the local institutional review boards. Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. Newly diagnosed patients with AML (de novo, secondary to myelodysplastic syndrome, or therapy-related, with or without prior treatment with hypomethylating agents [HMAs] for myelodysplastic syndrome) not eligible for IC because of advanced age (≥75 years) or significant comorbidities were enrolled.

Treatment consisted of 1 or 2 induction courses followed by up to 3 consolidation courses. Patients who did not reach at least a complete remission (CR) with incomplete count recovery (CRi) after 2 induction courses received no additional treatment in the study.

Induction and consolidation courses consisted of aspacytarabine monotherapy at 4.5 g/m^2 per day, administered IV over 1 hour for 6 consecutive days. The third course of consolidation was permitted for those with evidence of measurable residual disease (MRD) after the second course. The induction course was administered at the hospital, and subsequent treatment was permitted in an outpatient setting. The dose of aspacytarabine was reduced to 2.3 g/m^2 per day in any course beyond the first induction for any grade ≥3 nonhematologic, treatment-related adverse event (AE) and during

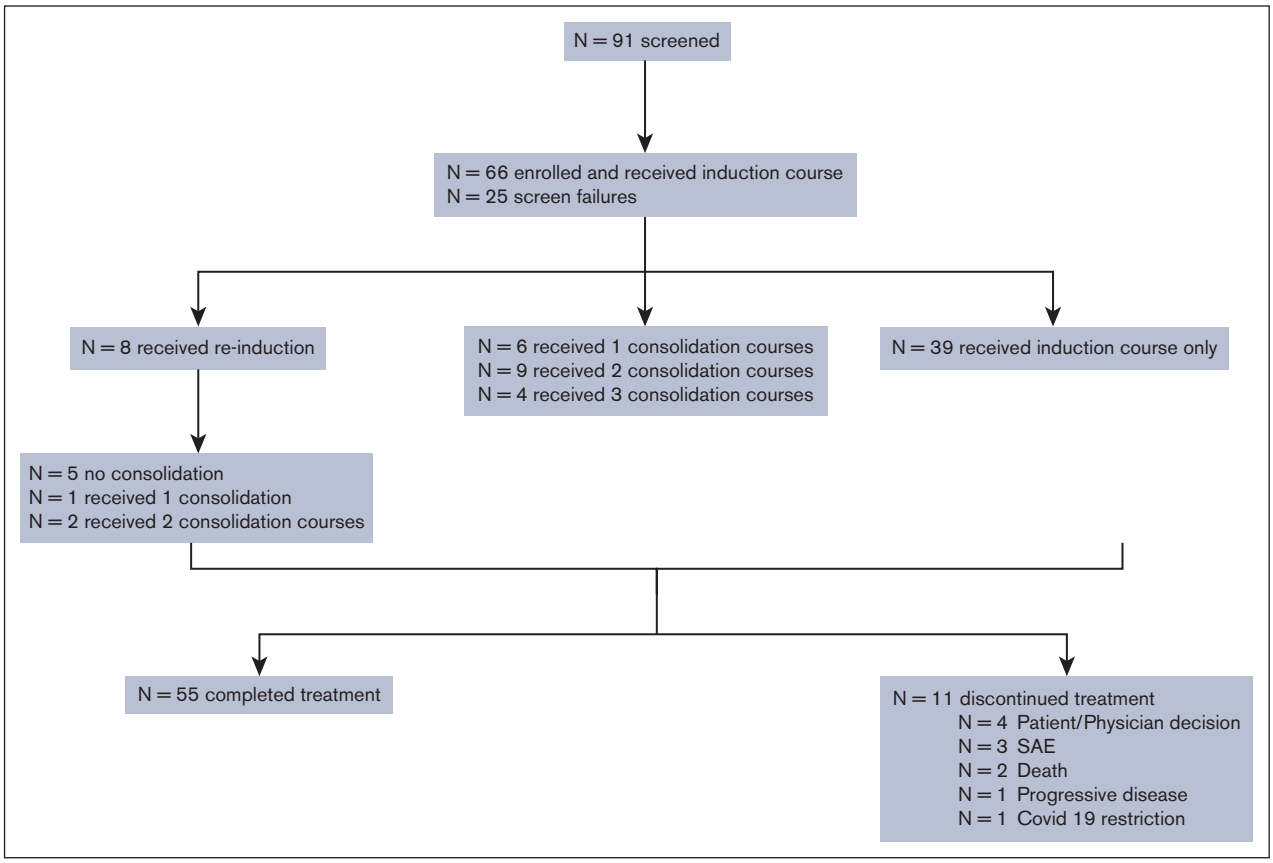

Figure 1. CONSORT diagram. SAE, serious adverse event.

the second and third consolidation courses regardless of toxicity at the discretion of the treating physician. During treatment courses, patients received supportive care as per institutional standards. Only 1 dose reduction was allowed in the study. Response was assessed at the time of count recovery (absolute neutrophil count $\geq$ 1000/μL and/or platelet count $\geq$ 100 × 10^3/μL) or by day 42 (±3) in the absence of recovery, whichever came first. Consolidation was offered when CR, CRi, or CR with partial count recovery (CRh) was achieved.

Responses were assessed based on the revised International Working Group Response Criteria.[3] The overall response rate included patients who achieved CR, CRh, CRi, or morphologic leukemia–free state. MRD was assessed in each bone marrow aspirate using multicolor flow cytometry performed centrally at the University of Washington (sensitivity, 10^{-3}).

AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

This study was designed to evaluate the efficacy and safety of aspacytarabine compared with an age-matched control, which was the best standard of care used at protocol initiation. Specifically, the primary end point of CR was compared with an age-matched, random effects meta-analysis of the historical CR rate of 1530 patients from 10 multicenter studies of low-dose cytarabine (LDAC) and HMA in an older and unfit AML population.

The assumptions were that administration of aspacytarabine may 1) enable delivery of safer high-dose cytarabine to a population otherwise unfit for IC and 2) result in a better response compared with standard LDAC/HMA. The trial was designed to have 80% power to demonstrate a 1-sided *P* value $<$ .025, in comparison with a meta-analysis of historical studies if the true CR rate was between 26% and 29%.

Results

Sixty-six patients were enrolled, and 65 were evaluable for response. One patient was excluded when re-evaluation of the bone marrow did not reveal AML. Baseline demographics and disease characteristics are summarized in Table 1. Most of the patients were ineligible to receive standard IC because of their age (51.5%). Clinically significant cardiac or pulmonary comorbidities accounted for an additional 24% of the study population, and the remaining patients had either a comorbidity that the investigator judged incompatible with intensive induction chemotherapy or a contraindication to anthracycline therapy.

Twenty-four patients (36.9% of the intention-to-treat [ITT] population) achieved CR (with full count recovery); 16 reached CR after the first induction and 8 after the second induction. This CR rate is significantly higher than that achieved in an age-matched meta-analysis of historical studies of LDAC and HMA, in which the CR

rate for a similarly aged population was 14.9% ($P < .0001$). The CR rates among patients with de novo and secondary AML were 43.6% and 26.9%, respectively. Of 12 patients with prior HMA therapy, 3 (25%) achieved CR, whereas 21 of 53 patients (39.6%) with HMA-naïve AML achieved CR. Patients with *FLT3*, *NPM1*, *FLT3* + *NPM1*, or *TP53* mutations had CR rates of 66.7%, 50.0%, 66%, and 36.4%, respectively. MRD negativity was achieved in 12 patients (18.5% of the ITT) and in 50% of the responders (12 of 24). One patient with a complex karyotype achieved morphologic leukemia–free state. Patient disposition is described in Figure 1. The majority (59.1%) received only 1 induction course because of disease progression or study termination, and 33.3% received at least 1 consolidation course. Treatment was completed as planned for 55 of the 65 patients with AML, but 11 discontinued treatment before the completion of all intended courses, including the 1 patient who did not have AML. Reasons for treatment discontinuation included death (n = 2), withdrawal of consent (n = 2), physician preference (n = 2), disease progression (n = 1), and inability to travel because of COVID restrictions (n = 1). Three patients discontinued because of AEs; 1 patient discontinued the second treatment 6 days course because of symptomatic acute or chronic left subdural hemorrhage.

Of 66 patients, 56 (84.8%) received dose intensity as planned (4.5g/m^2 per day), and the others had reduced dose intensity either because of AEs or the physician's decision, as allowed per protocol in the second consolidation.

The median number of courses to CR was 1, with a median CR duration of 6.5 months (95% CI, 3.9-7.5). The median time for absolute neutrophil count to reach ≥500 cells per μL after

Table 2. ANC and platelet count recovery per course in patients who reached CR/CRi/CRh

		ANC		Platelets	
Course	**Course day**	**Mean cells per μL**	**±SE cells per μL**	**Mean cells per μL**	**±SE cells per μL**
Induction	4	1174	616-1731	44 412	35 570-53 255
	10	302	106-499	21 846	18 874-24 818
	17	227	64-390	21 349	17 256-25 442
	24	1224	805-1642	136 166	109 964-162 368
	31	3342	2392-4291	219 239	185 154-253 324
	38	5038	3271-6805	250 873	210 604-291 143
	45	4565	3380-5749	151 500	128 026-174 973
Reinduction	4	2399	1493-3305	124 833	76 248-182 418
	10	954	604-1304	46 357	29 896-62 828
	17	87	35-139	21 000	9 255-32 744
	24	1087	293-1882	171 805	105 242-238 368
	31	2746	1459-4033	490 666	436 622-544 710
	38	5565	5330-5800	475 000	464 000-486 000
	45	10 020	NA	404 000	NA
First consolidation	4	4791	4173-5408	202 401	174 579-230 224
	10	3056	2453-3659	46 062	35 856-56 268
	17	1605	963-2247	31 666	18 211-45 121
	24	3405	2426-4383	183 218	145 852-220 585
	31	8395	5505-11 284	354 145	300 442-407 849
	38	3380	2909-3850	227 500	198 591-256 408
Second consolidation	4	4146	2916-5375	245 479	212 279-278 678
	10	5385	2019-8751	66 937	53 911-79 953
	17	735	452-1018	21 791	15 155-28 427
	24	2460	1686-3235	186 645	111 170-262 120
	31	2850	2429-3270	279 125	199 853-358 396
	38	2810	NA	145 000	NA
Third consolidation	4	4700	NA	19 516 667	92 333-298 000
	10	2856	NA	57 000	34 000-80 000
	17	190	NA	1250	500-2000
	24	2390	NA	118 000	30 000-206 000
	31	3776	NA	236 500	142 000-331 000
	38	3503	NA	131 666	NA

NA, not applicable.

induction and consolidation was 24 and 21 days, respectively, and to reach >1000 cells per μL was 26 and 21 days, respectively (Table 2). The median time for platelets to reach ≥50 000 cells per μL after induction and consolidation was 24 and 23.5 days, respectively, and to reach >100 000 cells per μL was 24 and 25.5 days, respectively (Table 2). The time to count recovery in the consolidation courses compared with that of the induction courses was not prolonged.

The median follow-up for all patients was 13.7 months (range, 12.5-15.3). Thirty-six patients (55%) died, including 28 nonresponders and 8 who achieved CR. Causes of death among patients who achieved CR were AML recurrence (n = 6), sepsis (n = 1), and acute respiratory failure (n = 1). The median relapse-free survival was 8.7 months, with a 1-year rate of 40.6%. The median overall survival (OS) was 9.0 (95% CI, 6.0-15.9) months in the ITT population and not reached among patients who achieved CR (n = 24) compared with 4 months (95% CI, 2.0-7.9 months) (n = 41) in nonresponding patients. The median OS calculated according to landmark analysis from day 30 (N = 50) was 10.7 months (Figure 2A). The 1-year OS for responders was 79.2%. CR rates by subgroups are presented in Figure 2B.

All patients were evaluable for safety. All experienced at least 1 treatment-emergent AE (TEAE), with 62 patients (94%) experiencing a grade ≥3 TEAE. The most common grade ≥3 nonhematologic TEAEs (>10%) were hypokalemia (18.2%), pneumonia (13.6%), hypoxia (10.6%), and sepsis (10.6%; Figure 3). Grade ≥3 gastrointestinal AEs were reported by 13.6% of patients; diarrhea grade >2 by 3% of patients, and stomatitis grade >1 by 4.5% of patients. There were no TEAEs of cerebellar toxicity grade ≥3.

Ten patients died after TEAEs. The most common causes were sepsis (n = 4) and pulmonary edema (n = 2). One patient each died of multiorgan failure, COVID-19 pneumonia, cerebrovascular

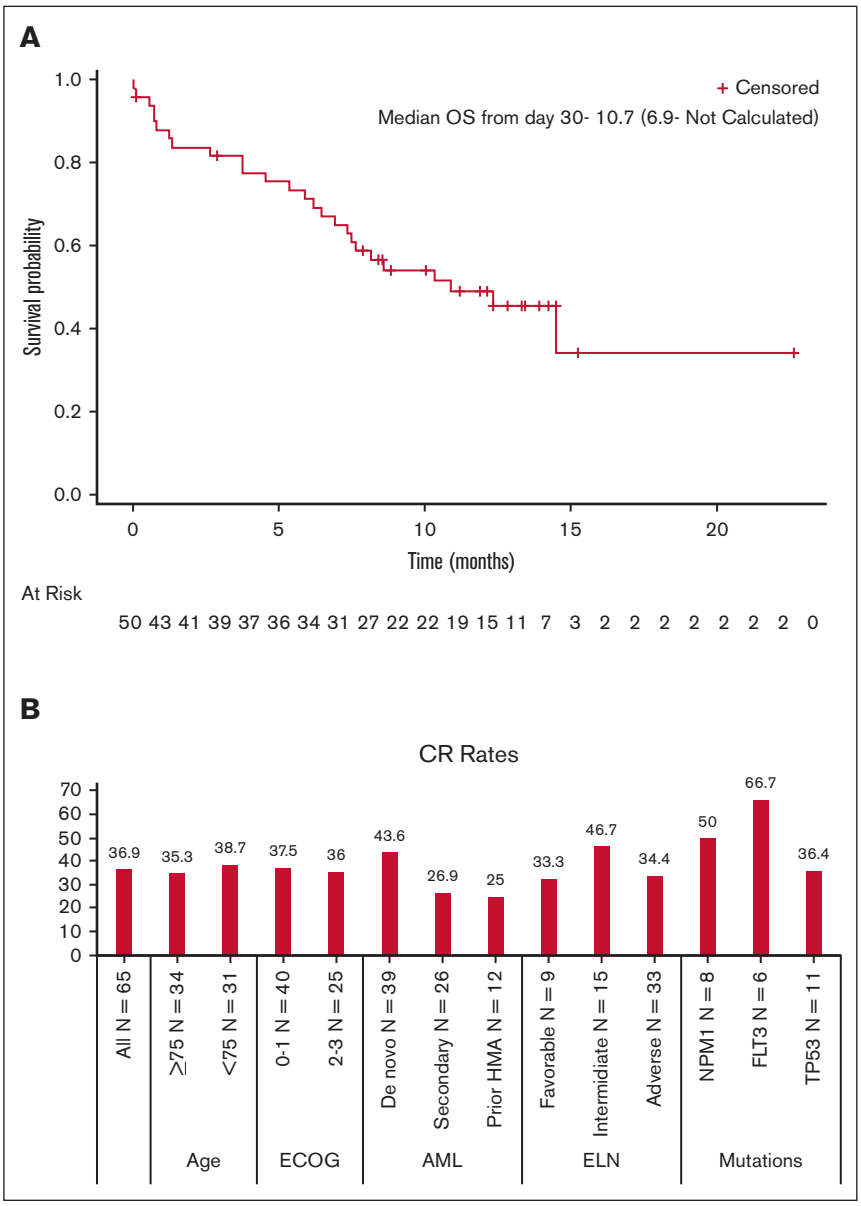

Figure 2. Efficacy results. (A) OS for all patients using landmark analysis. Efficacy results: OS for all patients using a landmark analysis. (B) Efficacy results: CR rates according to subgroups. CR rates based on subgroups.ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet.

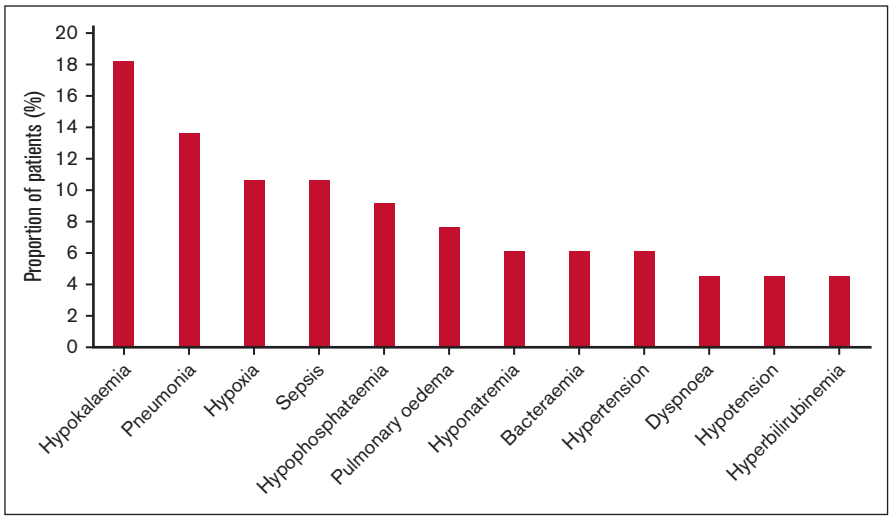

Figure 3. Nonhematologic grade >2 AEs in >2 patients.

accident, and unknown cause. The 30-day all-cause mortality rate was 12.6%.

AEs leading to dose modification occurred in 1 patient (1.5%). Discontinuation of aspacytarabine because of an AE occurred in 1 patient because of cognitive disorder, dysarthria, and confusional state in the context of acute on chronic subdural hemorrhage. Two patients in CR discontinued the study after induction and did not receive any consolidation course; 1 because of fluctuations in creatinine levels and the other because of fluid overload due to transfusions. No gastrointestinal toxicities above grade 3 and no cases of grade ≥3 cerebellar toxicity were reported. Thus, AEs precluding the use of high-dose cytarabine in unfit patients, including severe gastrointestinal and cerebellar toxicity, were minimal in the study population, even though the median age was 75 and patients with moderate renal failure (lower limit of creatinine clearance = 45 mL/min) were eligible to enroll.

Discussion

Recently, venetoclax in combination with HMA or LDAC and targeted therapies, such as FLT3 and isocitrate dehydrogenase inhibitors, have transformed the treatment landscape in AML, including for patients unfit for IC. However, 34% to 39% of reported newly diagnosed older patients may not respond to venetoclax-based lower-intensity regimens,[4,5] and patients without specific mutations do not benefit from targeted therapies. In addition, responses to venetoclax-based regimens are often short-lived, accompanied by prolonged cytopenias,[6] and associated with an extremely poor prognosis upon relapse with a median OS of 2.9 months.[7] Thus, there is still an unmet need for effective treatment for unfit patients with AML.

Collectively, given the response achieved in this study with limited treatment courses, without prolonged cytopenias after repeated administration, and a relatively favorable toxicity profile, these data suggest that aspacytarabine may provide an alternative firstline treatment option for patients with AML who are either old or otherwise unfit for IC. Studies of aspacytarabine in other hematologic diseases that commonly incorporate high-dose cytarabine, such as acute lymphoblastic leukemia or lymphoma, have been proposed, and a phase 1 study combining aspacytarabine with venetoclax as induction treatment for newly diagnosed unfit patients with AML is currently ongoing (NCT05503355).

Authorship

Contribution: J.K.A. and J.M.R. performed and designed research, and wrote the manuscript; T.Z. and A.G. designed and performed research; J.K., J.M., V.K., M.K., O.F., D.L.B., A.E., M.B., B.B., S.M.L., M.-E.P., O.W., M.C., C.G., G.R., I.L. performed research; Y.A. wrote the manuscript; L.F. and R.B.Y. designed research, analyzed and interpreted data, and wrote the manuscript; S.T. designed research and analyzed and interpreted data; C.B. collected data and analyzed and interpreted data; and S.G. designed research.

Conflict-of-interest disclosure: J.K.A. is on the data monitoring committee at GlycoMimetics; received consulting or advisory fees from AbbVie, Astellas Pharma, BioSight, bluebird bio, Curio, Daiichi Sankyo, Gilead, Kura Oncology, Kymera, Rigel Pharmaceuticals, Stemline Therapeutics, and Syros; received personal fees from the American Society of Hematology, Aptitude Health, HMP Education, MD Education, PeerView, and VJ HemOnc; received travel support from BioSight, Insights in Hematology, and National Comprehensive Cancer Network; received research funding (all to institution) from AbbVie, Agios, ALX Oncology, Amgen, Amphivena, Aprea AB, Aptose Biosciences, Astellas Pharma, BioSight, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Celgene, Cyclacel, Fujifilm, ImmunoGen, Kartos Therapeutics, Kura Oncology, Loxo, Pfizer, and Telios; and received travel, accommodations, expenses from Astellas Pharma, BioSight, and Dava Oncology. T.Z. is a paid consultant for BioSight and received honorarium from AbbVie, Gilead Sciences, Janssen, Novartis, BMS, Sanofi, and Takeda. J.K. is on the advisory board/consultant for Apellis, Novartis, GlaxoSmithKline, and Alexion, and on the speaker's bureau for Alexion, Apellis, Amgen, Jazz, CTI, BMS, and AbbVie. V.K. is on the advisory board for Pfizer and Novartis. Y.A. received research funding (to institution) from ALX Oncology, BioSight, Curis, Biomea, and Novartis, and is on the advisory board/received honoraria from BMS, Kite, Pfizer, Servier, Astellas, and Rigel. B.B. received

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