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ARTICLE

First-in-human study of JNJ-67571244, a CD33 × CD3 bispecific antibody, in relapsed/refractory acute myeloid leukemia and myelodysplastic syndrome

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Abstract

Relapsed/refractory (r/r) acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) outcomes remain poor. A targeted cluster of differentiation (CD)33 × CD3 bispecific antibody, JNJ-67571244, was assessed to identify the maximum tolerated dose (MTD), recommended phase II dose (RP2D), safety and tolerability, and preliminary clinical activity in patients with r/rAML or r/rMDS. This first-in-human, open-label, phase I, dose-escalation/dose-expansion study included patients with r/rAML or r/rMDS who were ineligible for or had exhausted standard therapeutic options. JNJ-67571244 was administered intravenously or subcutaneously using step-up dosing until ≥1 discontinuation condition was met. Outcomes included safety/tolerability, preliminary clinical activity, and systemic pharmacokinetics and pharmacodynamics. The study was terminated after evaluating 10 dose-escalation cohorts ($n = 68$) and before starting dose-expansion. Overall, 11 (16.2%) patients experienced ≥1 dose-limiting toxicity; all experienced ≥1 treatment-emergent adverse event (TEAE; treatment related: 60 [88.2%]); and 64 (94.1%) experienced ≥1 TEAE of Grade ≥3 toxicity (treatment related: 28 [41.2%]). Although some patients had temporary disease burden reductions, no responses were seen. JNJ-67571244 administration increased multiple cytokines, which coincided with incidence of cytokine release syndrome, infusion-related reactions, and elevated liver function tests. A prolonged step-up strategy was tested to improve tolerability, though this approach did not prevent hepatotoxicity. T-cell activation following treatment suggested

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target engagement but did not correlate with clinical activity. Safely reaching the projected exposure level for JNJ-67571244 efficacy was not achieved, thus MTD and RP2D were not determined.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Immunotherapeutics such as cluster of differentiation (CD)33 × CD3-targeted therapies may potentially impact the treatment landscape of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). The goal of such an approach is to try to simultaneously target CD33, a protein expressed on the surface of leukemic and myeloid cells, and CD3, a protein found on T-cells, to attempt to selectively eliminate cancerous cells while largely sparing nonhematopoietic cells.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated whether CD33 × CD3-targeted therapy in AML and MDS with JNJ-67571244 was safe and associated with preliminary efficacy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

While such an approach has potential promise, toxicities such as cytokine release syndrome and hepatotoxicity were found to limit dose escalation.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Further research is needed to optimize this type of targeted therapeutic approach to safely allow optimal dosing, improve efficacy and limit toxicities, and improve outcomes and quality of life in patients with AML and MDS, particularly in chemotherapy-resistant disease.

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by uncontrolled clonal expansion of immature hematopoietic cells (blasts).[1,2] Despite success with initial treatments, relapse remains common, and most patients succumb to their disease. Myelodysplastic syndromes (MDS) represent clonal hemopathies, with major morbidities caused by cytopenias and risk of transformation to AML.[1] Unfortunately, relapsed disease after prior response or nonresponse to initial treatment (refractory)—referred to as relapsed/refractory (r/r) disease—is common in AML and MDS.[3,4]

Patients with r/rAML or r/rMDS have poor prognoses, and treatment remains challenging. For most r/rAML, salvage therapy then allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative approach.[5] However, salvage therapy response generally is low, precluding HSCT for many patients. While 40%–50% of patients with higher risk MDS respond to hypomethylating agents (HMAs),[6,7] responses are generally transient (<2 years), and prognoses post-HMA failure are grim.[6,8,9] Despite new therapeutic strategies, r/rAML and r/rMDS represent high unmet medical needs;[10,11] no single standard-of-care approach exists.

Cluster of differentiation (CD)33, a transmembrane protein absent on pluripotent hematopoietic stem cells,[12,13] is expressed abundantly on AML blasts,[13-15] MDS blasts,[16] and myeloid-derived suppressor cells (MDSCs).[17-19] CD33-positive MDSC depletion using two different anti-CD33 agents increased colony-formation capacity in primary MDS bone marrow samples, suggesting improved hematopoiesis[20,21] and providing a rationale for MDSC and blast depletion in patients with MDS. Abundant CD33 expression on AML and MDS blasts, and absence on normal hematopoietic stem cells, has driven development of CD33-targeting agents. Gemtuzumab ozogamicin (GO)—an anti-CD33, antibody–drug conjugate—is indicated for treatment of newly-diagnosed, CD33-positive AML (adults and children ≥1 month) and CD33-positive r/rAML (adults and children ≥2 years)[22] but can have a risk of hepatotoxicity.[23,24] Alternatively spliced CD33 isoforms include a common polymorphism that produces a variant lacking the V-set domain, the binding site for several anti-CD33 antibodies, including GO.[25,26] Thus, interest in developing alternative CD33-targeting approaches, such as bispecific antibodies (BsAbs) targeting CD3 and CD33, has increased.

The CD3-T-cell receptor provides the first signal needed for T-cell activation.[27] CD3 supports signal

transduction necessary for T-cell activation, and the T-cell receptor confers binding specificity. An anti-CD3, T-cell-redirecting BsAb bridges T-cells and cancer cells so that CD3-positive T-cell cytolytic activity can be directed towards tumor cells independent of major histocompatibility complex binding.[28] For example, blinatumomab—an anti-CD3×anti-CD19 BsAb—has clinical activity in CD19-positive, B-cell precursor, acute lymphoblastic leukemia (B-ALL) that is r/r or in remission with measurable residual disease.[29,30]

JNJ-67571244 is an investigational, anti-CD33×anti-CD3 BsAb with effector function-silencing mutations in the fragment crystallizable (Fc) portion to reduce off-target, immune-cell recruitment. JNJ-67571244 binds the CD33 C2 domain, which is conserved among known isoforms. In vitro, JNJ-67571244 bound CD33-expressing cells, induced T-cell activation, and redirected T-cells to induce cytotoxicity of CD33-expressing cells.[31] In nonclinical studies, JNJ-67571244 bound specifically to CD33-expressing cells in AML cell lines and primary AML patient samples; mediated specific in vitro T-cell-dependent cytotoxicity; induced potent in vivo antitumor activity in AML murine models; cross-reacted with cynomolgus monkey CD33 and CD3; and mediated decrease of cynomolgus monkey CD33 leukocytes in vivo.[31] This first-in-human study aimed to identify the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of JNJ-67571244, and evaluate the safety and preliminary clinical activity of JNJ-67571244 in patients with r/rAML or r/rMDS.

METHODS

Study design and treatment

This first-in-human, open-label, multicenter, phase I, dose-escalation/dose-expansion study was designed to identify the RP2D, administration route, schedule, and MTD; evaluate safety and tolerability at the RP2D; characterize systemic pharmacokinetics and pharmacodynamics; and evaluate preliminary clinical activity of JNJ-67571244 monotherapy in patients with AML or high-risk or very-high-risk MDS who were ineligible for or had exhausted standard therapeutic options.

JNJ-67571244 was administered intravenously (IV) twice-weekly, via a 2-hour infusion then a 1-hour flush (≥3 days between full-treatment doses), or subcutaneously (SC) once-weekly using a step-up dosing schedule (Table S1). Per protocol, 36-hour hospitalization was required following administration of step-up doses, first full-treatment IV dose, and first four full-treatment SC doses, and for certain safety events, including high-grade infusion-related reaction (IRR), cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). For suspected incorrect dosing or safety concerns, or based on emerging data for SC administration, dosing could be less frequent. Patients received JNJ-67571244 until progressive disease (PD), unacceptable toxicity, or any other treatment discontinuation criteria (Supplementary Material S1) were met.

Dose-escalation was initiated at a starting-IV, full-treatment, minimal anticipated-biological-effect level dose of 0.2 μg/kg and a starting-SC, full-treatment dose of 6.3 μg/kg (Table S1). Subsequent dose levels were administered using an adaptive dose-escalation strategy. Initially, ≥1 patient was enrolled at each dose level, starting with IV1, then sequentially following the order patients were enrolled and considered study eligible. When toxicity occurred, cohorts were expanded to ≥3 patients. After IV5, SC1 and SC2 allocation was opened; however, because of toxicities, SC cohorts were closed and IV6 was opened (Table S1).

Appropriate institutional review board or independent ethics committees approved the trial protocol and amendments. The trial was conducted according to the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice, and patients gave written informed consent before enrollment.

Patients

Eligible patients from sites in Spain, the United States, and Germany were ≥18 years old; had an AML diagnosis[32] or had high-risk or very-high–risk MDS;[33] had r/r disease; were ineligible for or had exhausted standard therapeutic options; and had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 or 1 (full eligibility criteria; Table S2). Up to 180 evaluable patients were planned to be treated across dose-escalation and dose-expansion.

Assessments

RP2D, administration route, schedule, and MTD of JNJ-67571244 (primary objective) were to be determined during dose-escalation by evaluating dose-limiting toxicity (DLT) and adverse event (AE) incidence, type, and severity. JNJ-67571244 safety was assessed by physical examination and AE monitoring. CRS, IRR, and ICANS were AEs of special interest. Neurotoxicity was a reporting term but was considered ICANS. AEs were reported from time of informed consent through Day 100 after last JNJ-67571244 dose or until start of subsequent anticancer

therapy, if earlier. AE relationship to JNJ-67571244 was determined by investigators. AEs were considered related if definitely, probably, or possibly associated with JNJ-67571244 or if JNJ-67571244 contribution could not be excluded. Immunogenicity was assessed by detecting anti-drug antibodies (ADAs). Cytokine levels were measured to monitor CRS; inform on safety, dose, and/or schedule selection; and investigate JNJ-67571244 activity.

Evaluation of JNJ-67571244 preliminary clinical activity was based on investigator-assessed disease response using modified European LeukemiaNet 2017 recommendations for AML[34] and modified International Working Group response criteria (2016) for MDS.[35] Serum JNJ-67571244 concentrations, pharmacokinetic parameters, and pharmacodynamic markers (e.g., systemic cytokine concentrations, T-cell activation markers, CD33-expressing cell depletion) were used to evaluate systemic JNJ-67571244 pharmacokinetics/pharmacodynamics. Planned but not conducted exploratory endpoints are in the Supplementary Material S1.

Sampling and pharmacokinetic/pharmacodynamic assessments

Venous blood samples were collected to measure serum JNJ-67571244 concentrations, ADAs, and cytokines during step-up and full-treatment-dose levels or at times of suspected AEs. A validated electrochemiluminescence-based assay was used to measure JNJ-67571244 levels (lower limit of quantification, 1.20000 ng/mL). Pharmacokinetic parameters included time-to-peak drug concentration (t_{max}), elimination half-life ($t_{1/2}$), area under the concentration (AUC)–time curve, minimal drug concentration (C_{min}), maximum drug concentration (C_{max}), and average drug concentration at steady state ($C_{ss,av}$). ADAs were detected using an electrochemiluminescence immunoassay format on the Meso Scale Discovery platform. Acid dissociation was followed by neutralization with biotin and ruthenium-labeled JNJ-67571244, and the complex was captured on a streptavidin-coated 96-well plate. Cytokines were assessed using a 10-plex, Meso Scale Discovery-based assay. Blood and bone marrow samples were collected to evaluate baseline features and pharmacodynamic changes after treatment, including CD33 expression and T-cell activation using flow cytometry.

Statistical analyses

No formal statistical hypothesis testing was conducted. Dose-escalation was guided by the modified continual reassessment method based on a Bayesian logistic regression model (BLRM) using the full-treatment dose with escalation with overdose control (EWOC) principle along with review of available data, including (but not limited to) safety, pharmacokinetics/pharmacodynamics, and activity, before advancing to the next higher IV or SC dose-escalation cohort. Handling of inadequate, missing, and calculated data, and data deviations, is described in the Supplementary Material S1.

Data were summarized using descriptive statistics by dose level and administration route. Median overall survival (OS) was estimated using the Kaplan–Meier method. Mean and individual serum JNJ-67571244 concentration–time profiles were displayed graphically. Incidence and maximum ADA titers were summarized for patients who received ≥1 JNJ-67571244 dose and had ≥1 post-first-dose sample. Swimmer plots show JNJ-67571244 exposure and best single-observed treatment response (best timepoint response [BTR] regardless of response duration). Waterfall plots show best change in bone marrow blasts from baseline and corresponding BTR for each patient. BTR and overall response (OR) were evaluated to summarize responses for each disease. AEs were summarized by system organ class, preferred term, worst grade experienced, dose level, and administration route.

RESULTS

Patient treatment and baseline characteristics

Among 107 screened patients, 39 (36.4%) were excluded (Table S3), and 68 were enrolled in the dose-escalation phase (Table S1). Overall, 56 (82.4%) patients had AML, and 12 (17.6%) had high-risk or very-high-risk MDS (Table 1). Median (range) patient age was 66.0 (21–83) years; most patients were White (89.7%) and non-Hispanic (86.8%); and more than half (55.9%) were male. Baseline ECOG-PS score was 0 (24 [35.3%]) or 1 (44 [64.7%]). Among 50 patients (73.5% [AML, 43 (86.0%); MDS, 7 (14.0%)]) with baseline mutation results, 39 (78.0% [AML, 32 (74.4%); MDS, 7 (100.0%)]) had a mutation(s) or chromosomal alteration(s). Baseline mean (standard deviation [SD]) bone marrow blast percentage was 34.9% (27.9%). Patients had received a median of 3.00 (range, 1.0–10.0) prior lines of therapy; primary refractory disease at baseline was reported for 34 (50%) patients; and previous HSCT was documented for 22 (32.3%) patients.

All 68 patients received ≥1 JNJ-67571244 dose (twice-weekly IV, 56 [82.4%]; once-weekly SC, 12 [17.6%]) and received ≥1 pre-dose medication per protocol for IRR prophylaxis. Step-up doses were initiated after IV1 (Table S1). Observed toxicity prevented a more rapid ramp-up to first

TABLE 1 Patient demographics and baseline characteristics (all-treated population).

Study population characteristics	JNJ-67571244		
	Twice-weekly IV	Once-weekly SC	Overall
Patients, *n*	56	12	68
Age (years), *n* (%)			
Mean (SD)	62.6 (14.21)	65.8 (19.77)	63.2 (15.21)
Median (range)	64.5 (24–83)	73.0 (21–80)	66.0 (21–83)
18–25	2 (3.6)	1 (8.3)	3 (4.4)
26–50	10 (17.9)	1 (8.3)	11 (16.2)
51–64	16 (28.6)	1 (8.3)	17 (25.0)
≥65	28 (50.0)	9 (75.0)	37 (54.4)
Sex, *n* (%)			
Female	24 (42.9)	6 (50.0)	30 (44.1)
Male	32 (57.1)	6 (50.0)	38 (55.9)
Race, *n* (%)			
White	51 (91.1)	10 (83.3)	61 (89.7)
Asian	2 (3.6)	0 (0.0)	2 (2.9)
American Indian/Alaskan Native	0 (0.0)	1 (8.3)	1 (1.5)
Other	1 (1.8)	0 (0.0)	1 (1.5)
Not reported	2 (3.6)	1 (8.3)	3 (4.4)
Ethnicity, *n* (%)			
Non-Hispanic	48 (85.7)	11 (91.7)	59 (86.8)
Hispanic	7 (12.5)	1 (8.3)	8 (11.8)
Not reported	1 (1.8)	0 (0.0)	1 (1.5)
Country, *n* (%)			
Spain	28 (50.0)	7 (41.7)	35 (51.5)
United States	24 (42.9)	5 (41.7)	29 (42.6)
Germany	4 (7.1)	0 (0.0)	4 (5.9)
Diagnosis, *n* (%)			
AML	48 (85.7)	8 (66.7)	56 (82.4)
Primary	25 (44.6)	4 (33.3)	29 (42.6)
Secondary	23 (41.1)	4 (33.3)	27 (39.7)
With recurrent genetic abnormalities	5 (10.4)	1 (12.5)	6 (10.7)
TP53 assessed	38 (79.2)	8 (100.0)	46 (82.1)
Mutated TP53	4 (10.5)	2 (25.0)	6 (13.0)
With myelodysplasia-related changes[a]	17 (35.4)	5 (62.5)	22 (39.3)
Therapy-related	6 (12.5)	0 (0.0)	6 (10.7)
Prior MDS or MPN	18 (37.5)	3 (37.5)	21 (37.5)
Primary refractory disease	27 (56.3)	5 (62.5)	32 (57.1)
MDS	8 (14.3)	4 (33.3)	12 (17.6)
With a very high IPSS-R score	3 (37.5)	1 (25.0)	4 (33.3)
TP53 assessed	1 (12.5)	1 (25.0)	2 (16.7)
Mutated TP53	1 (100.0)	1 (100.0)	2 (100.0)
Primary refractory disease	2 (25.0)	0 (0.0)	2 (16.7)
Primary refractory disease, *n* (%)	29 (51.8)	5 (41.7)	34 (50.0)

(Continues)

TABLE 1 (Continued)

Study population characteristics	JNJ-67571244		
	Twice-weekly IV	Once-weekly SC	Overall
Number of lines of prior therapy, *n* (%)			
1	12 (21.4)	4 (33.3)	16 (23.5)
2	11 (19.6)	3 (25.0)	14 (20.6)
3	8 (14.3)	3 (25.0)	11 (16.2)
4	12 (21.4)	0 (0.0)	12 (17.6)
5	9 (16.1)	1 (8.3)	10 (14.7)
≥6	4 (7.1)	1 (8.3)	5 (7.4)
Mean (SD)	3.20 (1.813)	2.50 (1.624)	3.07 (1.790)
Median (range)	3.00 (1.0–10.0)	2.00 (1.0–6.0)	3.00 (1.0–10.0)
Prior HSCT, *n* (%)			
Yes	20 (35.7)	2 (16.7)	22 (32.3)
Allogeneic HSCT	18 (32.1)	2 (16.7)	20 (29.4)
≥2 allogeneic HSCTs	4 (7.1)	0 (0.0)	4 (5.9)
Autologous HSCT	1 (1.8)	0 (0.0)	1 (1.5)
Autologous HSCT/allogeneic HSCT	1 (1.8)	0 (0.0)	1 (1.5)
No	36 (64.3)	10 (83.3)	46 (67.6)
Prior systemic therapy, *n* (%)[b,c]			
Azacitidine	24 (42.9)	5 (41.7)	29 (42.6)
Azacitidine, venetoclax	20 (35.7)	1 (8.3)	21 (30.9)
Cytarabine, idarubicin	15 (26.8)	1 (8.3)	16 (23.5)
Decitabine, venetoclax	5 (8.9)	3 (25.0)	8 (11.8)
Cytarabine, daunorubicin	6 (10.7)	1 (8.3)	7 (10.3)
Cytarabine	6 (10.7)	0 (0.0)	6 (8.8)
Decitabine	4 (7.1)	2 (16.7)	6 (8.8)
Cytarabine, fludarabine, granulocyte colony-stimulating factor, idarubicin	5 (8.9)	0 (0.0)	5 (7.4)
Investigational antineoplastic drugs	5 (8.9)	0 (0.0)	5 (7.4)
Busulfan, fludarabine	4 (7.1)	0 (0.0)	4 (5.9)
Cytarabine, fludarabine	4 (7.1)	0 (0.0)	4 (5.9)
Cytarabine, mitoxantrone	4 (7.1)	0 (0.0)	4 (5.9)
Investigational drug	3 (5.4)	1 (8.3)	4 (5.9)
Lenalidomide	2 (3.6)	1 (8.3)	3 (4.4)
Other antineoplastic agents	2 (3.6)	1 (8.3)	3 (4.4)
Cyclophosphamide, fludarabine	1 (1.8)	1 (8.3)	2 (2.9)
Cytarabine, etoposide, mitoxantrone	2 (3.6)	0 (0.0)	2 (2.9)
Cytarabine, fludarabine, idarubicin	2 (3.6)	0 (0.0)	2 (2.9)
Cytarabine, idarubicin, midostaurin	2 (3.6)	0 (0.0)	2 (2.9)
Cytarabine, venetoclax	1 (1.8)	1 (8.3)	2 (2.9)
Decitabine, investigational drug	1 (1.8)	1 (8.3)	2 (2.9)
Gilteritinib	2 (3.6)	0 (0.0)	2 (2.9)
Midostaurin	2 (3.6)	0 (0.0)	2 (2.9)
ECOG performance status, *n* (%)			
0	20 (35.7)	4 (33.3)	24 (35.3)
1	36 (64.3)	8 (66.7)	44 (64.7)

TABLE 1 (Continued)

Study population characteristics	JNJ-67571244		
	Twice-weekly IV	Once-weekly SC	Overall
Weight (kg)			
Mean (SD)	75.6 (17.52)	76.5 (19.6)	75.74 (17.76)
Median (range)	71.9 (41.3–116.5)	68.10 (59.0–114.7)	71.6 (41.3–116.5)
Bone marrow blasts at baseline, %			
Patients, *n*	53	11	64
Mean (SD)	35.13 (28.0)	33.9 (28.6)	34.9 (27.9)
Median	29.3 (0.0–100.0)	30.0 (2.0–90.0)	29.7 (0.0–100.0)
Bone marrow CD33 expression: receptors per cell at baseline (MESF)			
Patients, *n*	45	9	54
Mean (SD)	4162.9 (3672.3)	5609.0 (5575.7)	4403.9 (4023.0)
Median	3065.0	2521.0	2918.0
Range	(434.0–16,956.0)	(813.0–16,400.0)	(434.0–16,956.0)
Bone marrow CD33 expression: blasts that expressed CD33 at baseline (fraction of total nucleated cells), %			
Patients, *n*	45	9	54
Mean (SD)	16.7 (2.3)	14.0 (22.9)	16.3 (21.4)
Median	6.5 (0.0–8.9)	1.7 (0.5–5.9)	5.9 (0.0–8.9)
Baseline cytopenia Grade ≥3, *n* (%)			
Anemia	20 (35.7)	4 (33.3)	24 (35.3)
Neutropenia	36 (64.3)	8 (66.7)	44 (64.7)
Thrombocytopenia	37 (66.1)	9 (75.0)	46 (67.6)

Note: Percentages were calculated with the number of patients in each group with available data as the denominator. The *n*-values for each parameter reflect non-missing values.

Twice-weekly intravenous (IV) cohorts included dose levels: 0.2 μg/kg, 0.2 then 0.63 μg/kg, 0.2/0.63 then 2 μg/kg, 0.2/0.63/2 then 6.3 μg/kg, 0.2/0.63/2/6.3 then 12.6 μg/kg, 0.63/2/6.3/12.6 then 18.9 μg/kg, 2/9/18.9 then 37.5 μg/kg, 2/18.9 then 37.5 μg/kg, and once-weekly subcutaneous (SC) cohorts included dose levels: 0.63/2 then 6.3 μg/kg, 2/6.3 then 12.6 μg/kg.

Abbreviations: AML, acute myeloid leukemia; CD, cluster of differentiation; ECOG, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet (for patients with AML); HSCT, hematopoietic stem cell transplantation; IPSS-R, International Prognostic Scoring System (for patients with MDS); IV, intravenous; MDS, myelodysplastic syndrome; MESF, molecular equivalent of soluble fluorochrome; SC, subcutaneous; SD, standard deviation.

[a]Includes gene mutations *or* cytogenetic abnormalities.

[b]Patients may have had ≥1 prior systemic therapy.

[c]Only ≥2 prior systemic therapies are presented.

full-treatment dose such that, starting with IV5, all cohorts required a 2-week ramp-up before the first full-treatment dose. Mean (SD) and median (range) treatment duration was 48.6 (50.8) and 34.5 (1–344) days, respectively; median dose intensity was 1.33 (0.06–8.7) μg/kg/day; and median study duration was 101 (14–778) days (IV, 125 days; SC, 59 days).

All 68 patients discontinued treatment, most commonly for PD (35 [51.5%]), physician's decision (13 [19.1%]), and AEs (12 [17.6%]). Overall, 17 (25.0%) patients received a subsequent anticancer therapy within 100 days after last JNJ-67571244 dose; 27 (39.7%) died within 100 days after last JNJ-67571244 dose with no subsequent systemic anticancer therapy; 12 (17.6%) completed the 100-day safety follow-up with no subsequent anticancer therapy during that time; 8 (11.9%) withdrew; and 4 (5.9%) had a trial disposition reason of completed, though duration was <100 days after last JNJ-67571244 dose. Patients able to receive subsequent systemic treatments are shown in Table S4. Major protocol deviations were reported in 13 patients (19.1%): 7 (10.3%) received wrong treatment or incorrect dose, and 6 (8.8%) had other reasons that included missed assessments, omitted premedication, and dosing before sufficient improvement of liver laboratory elevations.

Safety

Eleven (16.2%) patients experienced ≥1 DLT, including gamma-glutamyl transferase (GGT) increased (3 [4.4%]), ICANS (2 [2.9%]), alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased,

acute myocardial infarction, pericardial effusion, CRS, hypersensitivity, posterior reversible encephalopathy syndrome, drug-induced liver injury, and hypoxia (1 [1.5%] each; Table 2). Most DLTs were recovered/resolved or recovering by study end.

All patients experienced ≥1 TEAE (Supplementary Material S2), with 60 (88.2%) experiencing TEAEs considered treatment related by investigators (Table 3). Hepatotoxicity was a recurrent safety signal (Table S5) without clear dose dependency, and no predictive factors in patients' baseline laboratory results, HSCT status, or medical history were identified as associated with its development. Overall, 64 (94.1%) patients experienced ≥1 TEAE of Grade ≥3 toxicity, with 28 (41.2%) having ≥1 Grade ≥3 TEAE considered treatment related (Table 2). Serious TEAEs were reported for 48 (70.6%) patients, 20 (29.4%) of which were deemed treatment related (Table 3).

Forty-three (63.2%) patients experienced ≥1 TEAE of special interest, primarily Grade 1 or 2 severity. Grade≥1 CRS occurred in 29 (42.6%) patients (IV, 18 [32.1%]; SC, 11 [91.7%]). Grade≥1 IRR occurred in 23 (33.8%) patients, all of whom received JNJ-67571244-IV. Grade≥1 ICANS occurred in 5 (7.4%) patients, 2 (3.6%) who received JNJ-67571244-IV and 3 (25.0%) who received JNJ-67571244-SC. Median (range) time to first CRS (Grade ≥2), IRR (Grade ≥2), and ICANS (Grade ≥1) was 10.5 (1–41), 15.0 (4–74), and 24.0 (3–28) days, and median duration of each was 2.0 (1–6), 1.0 (1–3), and 8.0 (2–9) days, respectively (Table S6). When indicated, tocilizumab rapidly improved CRS symptoms.

Thirty-four (50.0%) and 14 (20.6%) patients had TEAEs leading to dose interruption and dose reduction, respectively. Except ALT increased (5 [7.4%] patients), TEAEs leading to dose reduction were reported in <5% of the overall population. TEAEs led to treatment discontinuation in 15 (22.1%) patients, including 9 (13.2%) who discontinued for treatment-related TEAEs (Table 3). Most common TEAEs leading to discontinuation were treatment-related CRS (4 [5.9%]) and disease-related general physical health deterioration (2 [2.9%]).

Among 48 (70.6%) patients with reported death events (Table S7), 1 (1.5%) fatal AE of cardiac arrest was considered treatment related. Thirty (44.1%) patients died because of PD: 11 (16.2%) in the 30 days following the last JNJ-67571244 dose, 9 (13.2%) between Days 31–100 after last dose, and 10 (14.7%) >100 days after last dose. Fifteen (22.1%) patients died from an AE: 11 (16.2%) in the 30 days following the last JNJ-67571244 dose and 4 (5.9%) between Days 31–100 after last dose. Three patients (4.4%) died from other causes >100 days after last dose, including 1 patient (1.5%) each from COVID-19, graft-versus-host disease, and an unknown cause. Notably, 19 patients died after starting the next subsequent anticancer therapy.

No specific persistent changes in vital signs and physical examination findings suggestive of clinically meaningful changes from baseline were observed (Supplementary Material S1).

Immunogenicity

Among 63 treated patients evaluable for immunogenicity testing, 4 (6.3%) were ADA-positive. Incidence of ADA positivity was not dose related, and the proportion of ADA-positive patients was similar between IV (5.9%) and SC (8.3%) administration (Table S8).

Efficacy

Median OS was 4.1 months for AML and 5.7 months for MDS (Figure 1a). No patient had an OR greater than stable disease (SD), thus the OR rate was 0.0%. Overall, 52 patients (AML, 44; MDS, 8) had ≥1 disease-response assessment in which a treatment response could be assigned. For AML, 24 of 56 (42.9%) patients had a BTR of SD (Figure 1b), but only 3 (5.4%) met the minimum 3-month duration to count as SD for best overall response. For MDS, 3 of 12 (25.0%) patients had a BTR of SD (Figure 1b); however, only 1 (8.3%) met the minimum 8-week duration to count as SD for best overall response. One patient with MDS (IV7) had a bone marrow complete response at first post-baseline disease evaluation but then had PD at the next evaluation and did not meet the minimum 4-week duration to count as a response. Twenty-seven of 56 (48.2%) patients with AML and 5 of 12 (41.7%) with MDS had PD as their best overall response, and 20 of 56 (35.7%) patients with AML and 4 of 12 (33.3%) with MDS had PD as their BTR. Overall, 14 patients (AML, 10; MDS, 4) discontinued before any disease evaluation, and 2 patients with AML had a non-evaluable disease assessment.

No specific trends in mean bone marrow blast changes were observed in any cohort (Figure 2). Although some transient reductions were observed, decreases for most patients were minor and not sustained.

Pharmacokinetics

After the first full-treatment JNJ-67571244-IV twice-weekly dose (following step-up doses), maximum mean concentrations were observed between end of flush (EOF) and 6 h post-EOF, then concentrations steadily declined in parallel for all dose levels (Figure S1). Median t_{max} (range, 5.0–8.5 h) after EOF and mean $t_{1/2}$ (range, 63.7–100.2 h) were similar for all dose levels, and peak concentrations and AUC–time

TABLE 2 Treatment-emergent adverse events of Grade ≥3 toxicity considered related to study therapy and dose-limiting toxicities by system organ class preferred term (all-treated population).

	JNJ-67571244		
Dose-limiting toxicities	**Twice-weekly IV**	**Once-weekly SC**	**Overall**
Patients, *n*	56	12	68
Patients with ≥1 DLT, *n* (%)	8 (14.3)	3 (25.0)	11 (16.2)
Investigations, *n* (%)	5 (8.9)	0 (0.0)	5 (7.4)
GGT increased	3 (5.4)	0 (0.0)	3 (4.4)
ALT increased	1 (1.8)	0 (0.0)	1 (1.5)
AST increased	1 (1.8)	0 (0.0)	1 (1.5)
Cardiac disorders, *n* (%)	0 (0.0)	2 (16.7)	2 (2.9)
Acute myocardial infarction	0 (0.0)	1 (8.3)	1 (1.5)
Pericardial effusion	0 (0.0)	1 (8.3)	1 (1.5)
Immune system disorders, *n* (%)	2 (3.6)	0 (0.0)	2 (2.9)
Cytokine release syndrome	1 (1.8)	0 (0.0)	1 (1.5)
Hypersensitivity	1 (1.8)	0 (0.0)	1 (1.5)
Nervous system disorders, *n* (%)	1 (1.8)	1 (8.3)	2 (2.9)
Immune effector cell-associated neurotoxicity syndrome	1 (1.8)	1 (8.3)	2 (2.9)
Posterior reversible encephalopathy syndrome	0 (0.0)	1 (8.3)	1 (1.5)
Hepatobiliary disorders, *n* (%)	1 (1.8)	0 (0.0)	1 (1.5)
Drug-induced liver injury	1 (1.8)	0 (0.0)	1 (1.5)
Respiratory, thoracic, and mediastinal disorders, *n* (%)	1 (1.8)	0 (0.0)	1 (1.5)
Hypoxia	1 (1.8)	0 (0.0)	1 (1.5)
TEAEs of Grade ≥ 3 toxicity considered related to study therapy			
Patients, *n*	56	12	68
Patients with ≥1 treatment-related Grade ≥ 3 TEAE, *n* (%)	20 (35.7)	8 (66.7)	28 (41.2)
Investigations, *n* (%)	14 (25.0)	3 (25.0)	17 (25.0)
GGT increased	9 (16.1)	2 (16.7)	11 (16.2)
ALT increased	7 (12.5)	2 (16.7)	9 (13.2)
AST increased	8 (14.3)	1 (8.3)	9 (13.2)
Blood fibrinogen decreased	1 (1.8)	0 (0.0)	1 (1.5)
Blood and lymphatic system disorders, *n* (%)	6 (10.7)	4 (33.3)	10 (14.7)
Neutropenia	4 (7.1)	2 (16.7)	6 (8.8)
Thrombocytopenia	2 (3.6)	3 (25.0)	5 (7.4)
Anemia	3 (5.4)	0 (0.0)	3 (4.4)
Leukopenia	1 (1.8)	0 (0.0)	1 (1.5)
Cardiac disorders, *n* (%)	2 (3.6)	2 (16.7)	4 (5.9)
Acute myocardial infarction	0 (0.0)	1 (8.3)	1 (1.5)
Cardiac arrest	1 (1.8)	0 (0.0)	1 (1.5)
Myocarditis	1 (1.8)	0 (0.0)	1 (1.5)
Pericardial effusion	0 (0.0)	1 (8.3)	1 (1.5)
Immune system disorders, *n* (%)	7 (12.5)	1 (8.3)	8 (11.8)
Cytokine release syndrome	6 (10.7)	1 (8.3)	7 (10.3)
Hypersensitivity	1 (1.8)	0 (0.0)	1 (1.5)
Nervous system disorders, *n* (%)	1 (1.8)	1 (8.3)	2 (2.9)
Immune effector cell-associated neurotoxicity syndrome[a]	1 (1.8)	1 (8.3)	2 (2.9)
Posterior reversible encephalopathy syndrome	0 (0.0)	1 (8.3)	1 (1.5)

(Continues)

TABLE 2 (Continued)

Dose-limiting toxicities	JNJ-67571244		
	Twice-weekly IV	Once-weekly SC	Overall
Hepatobiliary disorders, *n* (%)	1 (1.8)	1 (8.3)	2 (2.9)
Drug-induced liver injury	1 (1.8)	1 (8.3)	2 (2.9)
Metabolism and nutrition disorders	1 (1.8)	0 (0.0)	1 (1.5)
Hypophosphatemia	1 (1.8)	0 (0.0)	1 (1.5)
Respiratory, thoracic, and mediastinal disorders, *n* (%)	1 (1.8)	1 (8.3)	2 (2.9)
Hypoxia	1 (1.8)	1 (8.3)	2 (2.9)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; GGT, gamma-glutamyltransferase; IV, intravenous; MedDRA®, Medical Dictionary for Regulatory Activities; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Twice-weekly intravenous (IV) cohorts included dose levels: 0.2 μg/kg, 0.2 then 0.63 μg/kg, 0.2/0.63 then 2 μg/kg, 0.2/0.63/2 then 6.3 μg/kg, 0.2/0.63/2/6.3 then 12.6 μg/kg, 0.63/2/6.3/12.6 then 18.9 μg/kg, 2/9/18.9 then 37.5 μg/kg, 2/18.9 then 37.5 μg/kg, and once-weekly subcutaneous (SC) cohorts included dose levels: 0.63/2 then 6.3 μg/kg, 2/6.3 then 12.6 μg/kg.

Patients were counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the patient with the worst toxicity was used.

Symptoms of cytokine release syndrome, infusion-related reactions, and immune effector cell-associated neurotoxicity syndrome were excluded from tabulations.

[a]Neurotoxicity was the MedDRA® term used for reporting throughout the trial; however, these events were considered immune effector cell-associated neurotoxicity syndrome.

curve increased with dose level. Mean C_{min} was similar for all dose levels, and mean C_{max} and $C_{ss,av}$ increased with dose. At the three highest dose levels (12.6, 18.9, and 37.5 μg/kg), steady state was reached after the ninth full-treatment dose. Mean concentrations plateaued between EOF and 24 h post-EOF, and increased with dose level.

After the first full-treatment JNJ-67571244-SC weekly dose, mean C_{max} increased until the next dose (Figure S1). After the fifth full-treatment dose, steady state was reached and concentrations subsequently remained stable. C_{max} after Dose 5 and AUC after Dose 1 following SC administration (6.3 μg/kg) were approximately one-third and one-half of values for the same first full-treatment dose after IV administration, respectively. Mean $C_{ss.av}$ was similar for all IV and all SC dose levels, except for a higher mean $C_{ss.av}$ with the IV 37.5-μg/kg dose level (with 2/9/18.9-μg/kg step-up doses). These data suggest dose-related accumulation of JNJ-67571244-IV with repeated administration, with steady state reached within 14–21 days.

Pharmacodynamics

Multiple cytokines, including interferon gamma (IFN-γ) (Figure 3a–c), interleukin (IL)-2 receptor α, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α, were increased with JNJ-67571244-IV and JNJ-67571244-SC. Generally, JNJ-67571244-SC resulted in less cytokine production than JNJ-67571244-IV. Elevated cytokine levels coincided with incidence of CRS (IFN-γ, IL-6, IL-8, IL-10, and TNF-α), IRR (IFN-γ, IL-6, IL-8, IL-10, and TNF-α), and elevated liver function tests (LFTs; IFN-γ, IL-6, IL-10, and TNF-α). Step-up dosing did not mitigate cytokine production; peak levels generally were observed with last step-up or at full-treatment dose.

Consistent with the hypothesized mechanism of action of JNJ-67571244, T-cell activation occurred in bone marrow (Figure 4a) and periphery as indicated by increased CD38-positive/CD8-positive and CD25-positive/CD8-positive T-cells. CD38-positive/CD8-positive T-cell increases were comparable in bone marrow and periphery, while increases were more robust in the periphery than bone marrow for CD25-positive/CD8-positive T-cells. Peripheral T-cell activation occurred transiently over the first DLT period. A range of 434–16,956 CD33 receptors per leukemic blast cell was observed across patients at baseline (Table 1). Similar to T-cell activation, some CD33-positive and total blast reductions were observed in bone marrow (Figure 4b) and periphery, though decreases were minor and not sustained.

DISCUSSION

CD33 is a validated therapeutic target in AML. While various BsAbs, trispecific antibodies, antibody–drug conjugates, and chimeric antigen receptor T-cell approaches targeting CD33 or CD123 have been studied for myeloid neoplasms, clinical efficacy has been limited

TABLE 3 Summary of treatment-emergent adverse events[a] (all-treated population).

	JNJ-67571244		
	Twice-weekly IV	**Once-weekly SC**	**Overall**
Patients, *n*	56	12	68
Patients with ≥1 TEAE, *n* (%)	56 (100.0)	12 (100.0)	68 (100.0)
TEAEs, *n* (%)	56 (100.0)	12 (100.0)	68 (100.0)
Related[b] TEAEs	48 (85.7)	12 (100.0)	60 (88.2)
TEAEs leading to death,[c] *n* (%)	22 (39.3)	6 (50.0)	28 (41.2)
Related TEAEs leading to death[c]	1 (1.8)	0 (0.0)	1 (1.5)
Serious TEAEs, *n* (%)	41 (73.2)	7 (58.3)	48 (70.6)
Related serious TEAEs	16 (28.6)	4 (33.3)	20 (29.4)
Maximum severity of any TEAE, *n* (%)			
Grade 1	1 (1.8)	0 (0.0)	1 (1.5)
Grade 2	3 (5.4)	0 (0.0)	3 (4.4)
Grade 3	11 (19.6)	0 (0.0)	11 (16.2)
Grade 4	19 (33.9)	6 (50.0)	25 (36.8)
Grade 5	22 (39.3)	6 (50.0)	28 (41.2)
TEAEs leading to study drug discontinuation,[d] *n* (%)	10 (17.9)	5 (41.7)	15 (22.1)
Related TEAEs leading to study drug discontinuation[d]	5 (8.9)	4 (33.3)	9 (13.2)
Any dose-limiting toxicity TEAE	8 (14.3)	3 (25.0)	11 (16.2)
Any CRS TEAE	18 (32.1)	11 (91.7)	29 (42.6)
Serious	10 (17.9)	4 (33.3)	14 (20.6)
IRR TEAE, *n* (%)	23 (41.1)	0 (0.0)	23 (33.8)
Serious	4 (7.1)	0 (0.0)	4 (5.9)
Any ICANS[e] TEAE, *n* (%)	2 (3.6)	3 (25.0)	5 (7.4)
Serious	1 (1.8)	2 (16.7)	3 (4.4)
Maximum severity of related TEAE, *n* (%)			
Grade 1 or 2	28 (50.0)	4 (33.3)	32 (47.1)
Grade ≥3	20 (35.7)	8 (66.7)	28 (41.2)
COVID-19 associated TEAEs[f], *n* (%)	4 (7.1)	0 (0.0)	4 (5.9)
Serious TEAEs[f]	3 (5.4)	0 (0.0)	3 (4.4)
Non-serious TEAEs[f]	1 (1.8)	0 (0.0)	1 (1.5)

Note: Symptoms of CRS, IRR, and ICANS were excluded from tabulations.

Twice-weekly intravenous (IV) cohorts included dose levels: 0.2 μg/kg, 0.2 then 0.63 μg/kg, 0.2/0.63 then 2 μg/kg, 0.2/0.63/2 then 6.3 μg/kg, 0.2/0.63/2/6.3 then 12.6 μg/kg, 0.63/2/6.3/12.6 then 18.9 μg/kg, 2/9/18.9 then 37.5 μg/kg, 2/18.9 then 37.5 μg/kg, and once-weekly subcutaneous (SC) cohorts included dose levels: 0.63/2 then 6.3 μg/kg, 2/6.3 then 12.6 μg/kg.

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IRR, infusion-related reaction; IV, intravenous; MedDRA®, Medical Dictionary for Regulatory Activities; SC, subcutaneous; TEAE, treatment-emergent AE.

[a]AE severity was determined using National Cancer Institute Common Terminology Criteria for AEs (Version 5.0) and was reported using Medical Dictionary for Regulatory Activities (Version 24.1).

[b]Assessed by investigators as related to study therapy.

[c]Based on AE outcome of fatal.

[d]Based on action taken of drug withdrawal.

[e]Neurotoxicity was the MedDRA® term used for reporting throughout the trial; however, these events were considered immune effector cell-associated neurotoxicity syndrome.

[f]Based on events that coded to a COVID-19 MedDRA® term.

compared with similar targeted approaches in B-ALL.[37] Low CD33-surface-expression and CD33-internalization rates may impact antibody–drug conjugate efficacy,[38] and the abnormal bone marrow niche is implicated in suboptimal immunotherapy responses in AML[39] and MDS.[40] Recently, development of two CD3×CD33

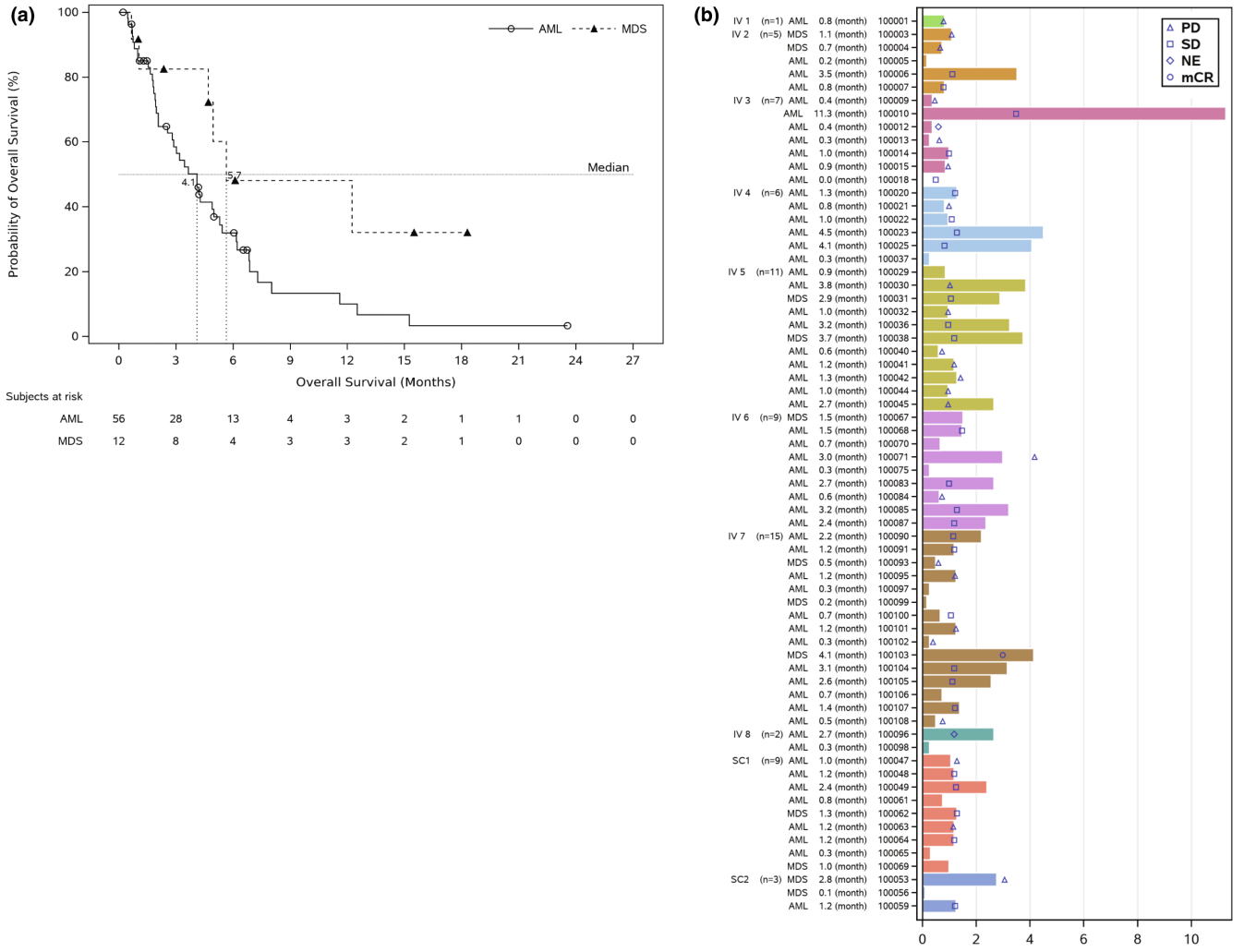

FIGURE 1 Efficacy findings: (a) Kaplan–Meier plot for overall survival (all-treated population) and (b) swimming-lane plot of treatment exposure and best disease timepoint response (JNJ-67571244-IV and JNJ-67571244-SC) (all-treated population); IV1, 0.2 μg/kg twice-weekly IV; IV2, 0.2 then 0.63 μg/kg twice-weekly IV; IV3, 0.2/0.63 then 2 μg/kg twice-weekly IV; IV4, 0.2/0.63/2 then 6.3 μg/kg twice-weekly IV; IV5, 0.2/0.63/2/6.3 then 12.6 μg/kg twice-weekly IV; IV6, 0.63/2/6.3/12.6 then 18.9 μg/kg twice-weekly IV; IV7, 2/9/18.9 then 37.5 μg/kg twice-weekly IV; IV8, 2/18.9 then 37.5 μg/kg twice-weekly IV; SC1, 0.63/2 then 6.3 μg/kg once-weekly SC; SC2, 2/6.3 then 12.6 μg/kg once-weekly SC. Complete response with incomplete recovery and morphologic leukemia-free state were responses for patients with an underlying diagnosis of acute myeloid leukemia (AML) and was based upon modified European LeukemiaNet 2017 recommendations.[34,36] Marrow complete response was a response for patients with an underlying diagnosis of myelodysplastic syndrome and was based upon International Working Group guidelines.[11,35] Overall, 2 (3.6%) patients with AML (IV3 and IV8) were not evaluable for response. Best timepoint response at ≥1 post-baseline disease assessments. Considers only the response values; response confirmation based on the duration of a response was not required. AML, acute myeloid leukemia; IV, intravenous, mCR, marrow complete response; MDS, myelodysplastic syndrome; NE, not evaluable; PD, progressive disease; SD, stable disease; SC, subcutaneous.

BsAbs, AMG330 and AMG673, was halted.[41] The novel CD3 × CD33 BsAb, JNJ-67571244, demonstrated promising preclinical activity,[31] and its safety and preliminary efficacy in patients with r/rAML or r/rMDS were evaluated in the present study.

JNJ-67571244 was administered IV or SC with step-up doses before reaching full-treatment dose. Toxicities such as CRS and LFT elevations, and persistent injection-site reactions with SC dosing, necessitated dose interruptions, repeated step-up doses, and longer-than-planned step-up periods for many patients. Ultimately, 19 of 68 (27.9%; AML, 17/56 [30.3%]; MDS, 2/12 [16.7%]) treated patients did not receive full-treatment doses. AEs limited dose-escalation, and JNJ-67571244 exposure remained well below estimated efficacious dose exposures based on the ex vivo half-maximal, effective-concentration value. Escalation to doses providing optimal pharmacokinetic exposure based on preclinical efficacy models was not feasible with IV or SC administration. Ultimately, minimal clinical activity was observed, and no responses were reported.

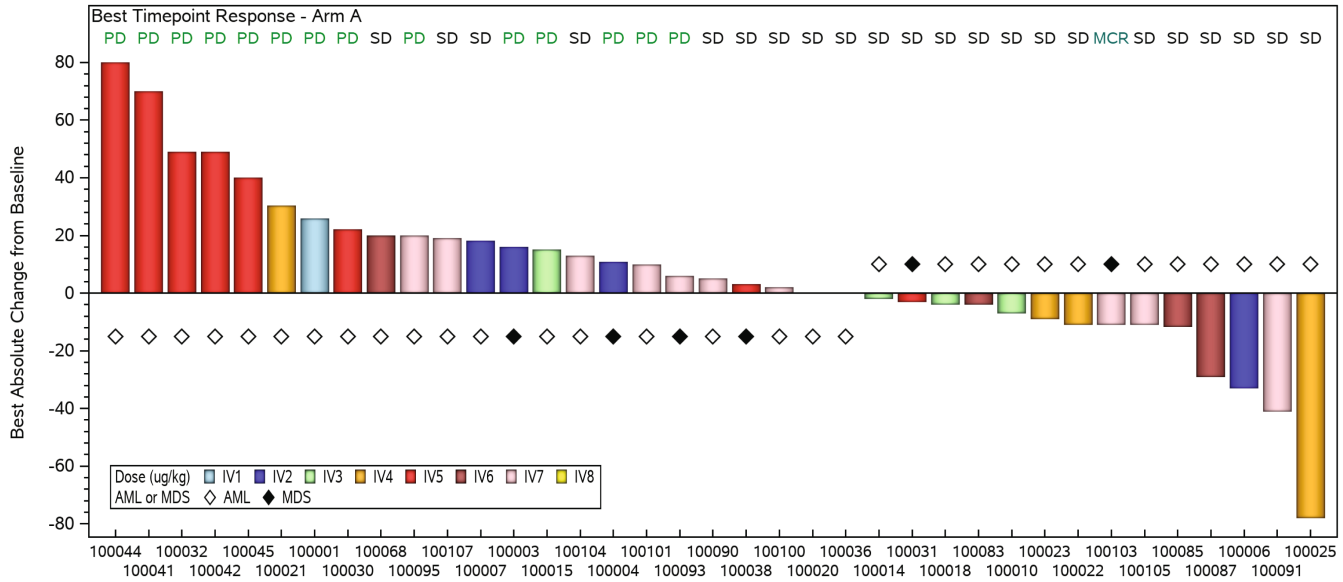

FIGURE 2 Best change in bone marrow blast values from baseline (JNJ-67571244-IV). IV1, 0.2 μg/kg twice-weekly IV; IV2, 0.2 then 0.63 μg/kg twice-weekly IV; IV3, 0.2/0.63 then 2 μg/kg twice-weekly IV; IV4, 0.2/0.63/2 then 6.3 μg/kg twice-weekly IV; IV5, 0.2/0.63/2/6.3 then 12.6 μg/kg twice-weekly IV; IV6, 0.63/2/6.3/12.6 then 18.9 μg/kg twice-weekly IV; IV7, 2/9/18.9 then 37.5 μg/kg twice-weekly IV; IV8, 2/18.9 then 37.5 μg/kg twice-weekly IV. Best timepoint response at ≥1 post-baseline disease assessments. Considers only the response values; response confirmation based on the duration of a response was not required. AML, acute myeloid leukemia; IV, intravenous; mCR, marrow complete response; MDS, myelodysplastic syndrome; PD, progressive disease; SD, stable disease.

No disease or patient factors (e.g., age, sex, diagnosis, tumor burden, history of HSCT, baseline LFT values) correlated with hepatotoxicity. The etiology of LFT elevations is unknown, and elevations were not associated with clinical symptoms, except for one patient in IV7 who experienced a DLT of Grade 3 drug-induced liver injury. Within 24 h, the patient's laboratory values improved and no longer met Hy's law (Supplementary Material S1). Excluding this case, high-grade hepatotoxicity events were limited to transient hepatic enzyme elevations without bilirubin elevations. Mitigation efforts such as post-dose steroids (for cytokine-mediated transaminitis) and step-up dose adjustments were not successful, and liver biopsies were not available to evaluate possible mechanism(s). Preclinical studies with cynomolgus monkeys demonstrated minimal-to-mild elevations in ALT and AST, predominantly after the first dose, and liver tissue obtained following the highest tested dose (30 mg/kg) demonstrated increased cellularity within the sinusoids of the liver and minimal perivascular mononuclear cell infiltrates within the liver. These findings were considered related to systemic inflammation induced by JNJ-67571244 rather than direct hepatotoxicity. Findings from a CD123×CD3 BsAb (JNJ-63709178) study,[42] with a lower hepatotoxicity event rate and no resultant DLTs, suggest this toxicity was target-mediated.

To potentially improve JNJ-67571244 safety, SC administration was studied; however, CRS and LFT elevations continued, all patients had injection-site reactions that persisted across SC administrations, and three patients experienced DLTs. Thus, SC administration was abandoned after two dose-escalation cohorts, and administration reverted to IV administration. Although additional IV dose-escalation cohorts were evaluated—reaching a maximum dose of 37.5 μg/kg—exposure remained well below the estimated efficacious range, with no observed responses and few patients achieving SD. T-cell activation following treatment suggested target engagement, but no correlation with clinical activity was observed.

Attempts of step-up dosing over several weeks allowed some patients to reach full-treatment doses but did not eliminate toxicity. The length of time necessary to reach full-treatment dose was prohibitive in r/rAML and r/rMDS, where disease can progress rapidly. Larger increases between step-up doses to shorten time-to-full–treatment dose led to higher grade CRS and LFT elevations (e.g., IV8), and indicators for severe toxicity development were not ascertained. Safely reaching the projected exposure level for efficacy in a reasonable timeframe was considered not feasible. Concurrently, while trying to create a safe step-up strategy for patients with repeat doses and drug interruptions following toxicity, patients experienced rapid disease progression. Recruitment was halted and the study was terminated, despite attempts at modifying step-up dosing, after evaluating ten dose-escalation cohorts and before initiating dose-expansion (without determining MTD or RP2D) based on review of the risk–benefit profile of JNJ-67571244, minimal clinical activity, and inability to reach optimal pharmacokinetic exposures.

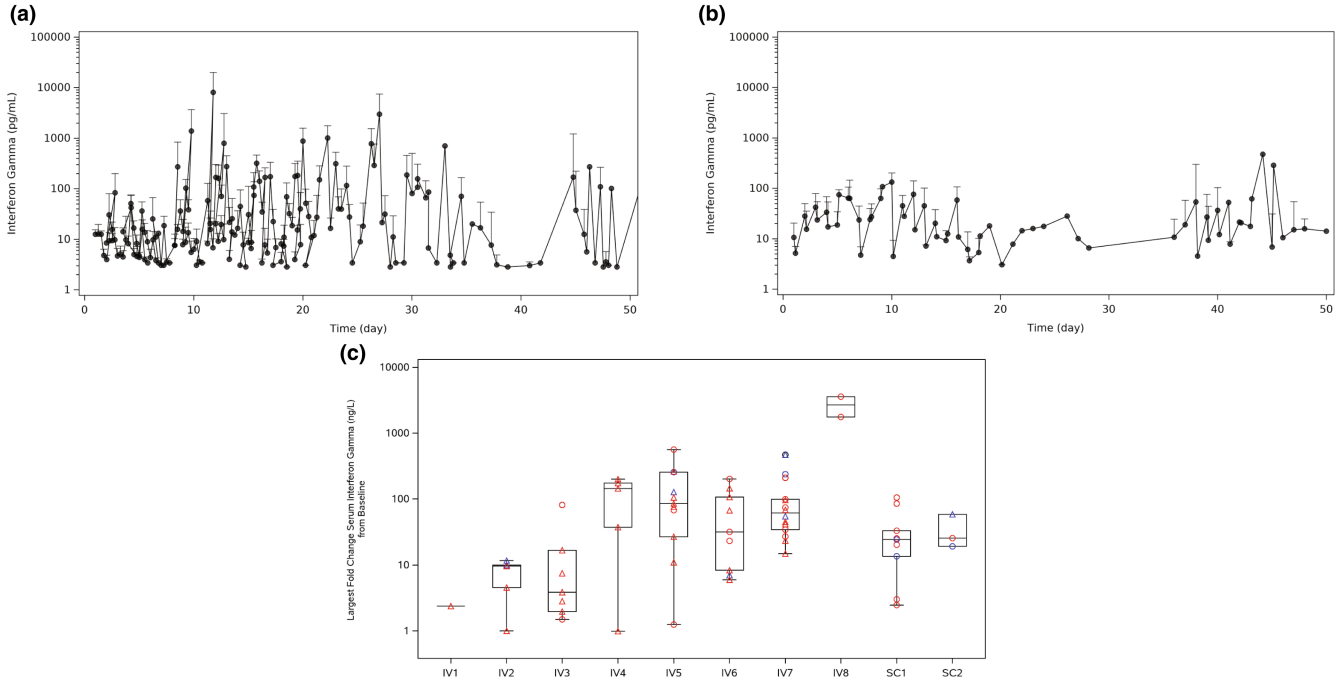

FIGURE 3 Pharmacodynamic effects of JNJ-67571244:[a] concentration of interferon gamma (IFN-γ) (pg/mL) over treatment course in patients receiving (a) JNJ-67571244 IV[b] or (b) JNJ-67571244-IV SC[b], and (c) comparison of largest fold change in IFN-γ (pg/mL) concentration from baseline across all dosing cohorts in patients with acute myeloid leukemia (red) or myelodysplastic syndrome (blue)[c,d] (all-treated population). IV1, 0.2 μg/kg twice-weekly IV; IV2, 0.2 then 0.63 μg/kg twice-weekly IV; IV3, 0.2/0.63 then 2 μg/kg twice-weekly IV; IV4, 0.2/0.63/2 then 6.3 μg/kg twice-weekly IV; IV5, 0.2/0.63/2/6.3 then 12.6 μg/kg twice-weekly IV; IV6, 0.63/2/6.3/12.6 then 18.9 μg/kg twice-weekly IV; IV7, 2/9/18.9 then 37.5 μg/kg twice-weekly IV; IV8, 2/18.9 then 37.5 μg/kg twice-weekly IV; SC1, 0.63/2 then 6.3 μg/kg once-weekly SC; SC2, 2/6.3 then 12.6 μg/kg once-weekly SC. [a]Cytokine levels were measured during step-up dosing, cycle 1, and with suspected adverse event including cytokine release syndrome (CRS), infusion-related reaction, or elevated liver enzymes using a Meso Scale Discovery platform. [b]Data are reported as mean ± standard error. [c]Patients without occurrence of CRS (triangle) and patients with CRS occurrence (circle) are also indicated. T-cell activation in bone marrow was assessed in a subset of patients using flow cytometry. [d]Data shown as outlier boxplots and reported on a logarithmic scale. Outliers in these boxplots were considered either less than 25th percentile – 1.5*interquartile range or greater than 75th percentile +1.5*interquartile range. CD, cluster of differentiation; CRS, cytokine release syndrome; IV, intravenous; SC, subcutaneous.

Effective, durable AML and MDS therapies remain elusive, particularly for r/r disease. Immunotherapies remain a promising strategy theoretically, though disease aggressiveness and disease-associated abnormalities in immune fitness present implementation challenges. BsAbs require a nuanced treatment regimen, often comprising step-up dosing intended to prime patients' T-cells and prevent an uncontrolled CRS followed by regular, full-treatment doses. Treatment is continued until PD for some BsAbs, while others use a fixed duration to minimize T-cell exhaustion risk. During phase I BsAb studies, step-up and full-treatment-dose levels and schedules are evaluated. Model-informed drug development, and in particular quantitative systems pharmacology, can provide greater insight into predicted efficacious dose levels, particularly in the setting of variable disease burdens. Treatments potentially associated with high CRS, IRR, and/or ICANS risks may require multiple hospitalizations during schedule-finding. For viability, treatments must be effective and cannot be overly burdensome. Requiring multiple hospitalizations might unintentionally select patients with more aggressive and advanced, heavily pretreated disease. While GO remains the only approved CD33-targeting agent in AML, ongoing efforts with other CD33-targeting investigational agents provide insight into potential therapeutic benefit and challenges with this target.

Successful BsAb applications in AML and MDS, particularly in r/r populations, likely will require a tolerable, rapid, step-up period (preferably <2 weeks) to reduce chances of interval disease progression; efficacious full-treatment doses; and manageable toxicities given necessary repeat doses at regular intervals. Additional research is needed to understand the potential mechanism(s) of hepatotoxicity observed with CD33 targeting (e.g., target- or immune-mediated) and whether it can be mitigated with supportive therapies. Additionally, further study with T-cell engagers in this heavily pretreated, immunocompromised population is needed to determine whether patients'

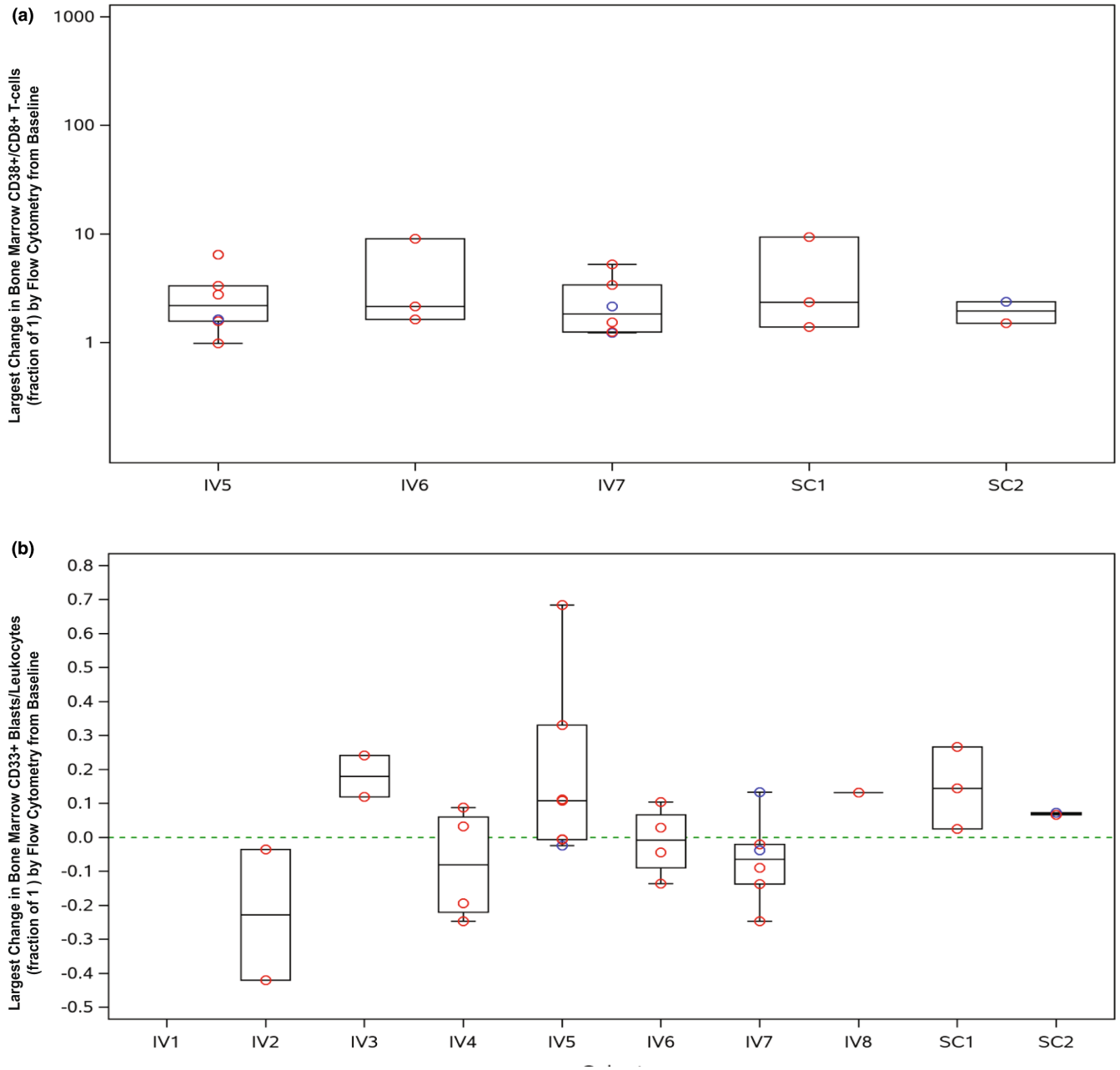

FIGURE 4 Pharmacodynamic effects of JNJ-67571244 (cont):[a] Comparison of largest fold change in percent of (a) CD38-positive CD8-positive T-cells[b] and (b) CD33-positive blasts[b,c] in bone marrow from baseline across all dosing cohorts in patients with acute myeloid leukemia (red) or myelodysplastic syndrome (blue); no change in percent from baseline indicated (green dashed line) (all-treated population). [a]Cytokine levels were measured during step-up dosing, Cycle 1, and with suspected adverse event including cytokine release syndrome, infusion-related reaction, or elevated liver enzymes using a Meso Scale Discovery-based platform. [b]Data shown as outlier boxplots and reported on a logarithmic scale. Outliers in these boxplots were considered either <25th percentile – 1.5*interquartile range or greater than 75th percentile +1.5*interquartile range. [c]Change in percent of CD33-positive blasts in bone marrow were monitored during treatment course using flow cytometry. CD, cluster of differentiation; IV, intravenous; SC, subcutaneous.

T-cells can be activated in a controlled manner to effectively drive disease-directed cytotoxicity without excessive damage to normal cells and with limited CRS and ICANS risk. A major unmet treatment need persists for this patient population and, while this study did not corroborate preclinical findings in the clinic, it provided valuable insights into challenges associated with targeting CD33, barriers to immunotherapy approaches in r/rAML and r/rMDS, and various approaches that may inform more tolerable and efficacious therapies for these patients in future.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. R.N., A.A.P., W.B.D., A.M.Y., M.A.-H., U.P., M.S., T.M.K., J.M.A.-D., J.M., K.B.,

M.C., N.D., C.G., X.L., and D.E. designed the research. R.N., A.A.P., W.B.D., A.M.Y., M.A.-H., U.P., M.S., T.M.K., J.M.A.-D., J.M., K.B., M.C., N.D., and C.G. performed the research. R.N., K.B., M.C., C.G., B.H., J.M., X.L., and K.D. analyzed data.

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DATA AVAILABILITY STATEMENT

The data-sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this website, requests for access to study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Myeloid Leukemia. Version 3.2023 — April 5, 2023. National Comprehensive Cancer Network, Inc. Accessed October 20, 2023. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
2. Visser O, Trama A, Maynadie M, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. *Eur J Cancer.* 2012;48(17):3257-3266. doi:10.1016/j.ejca.2012.05.024
3. *Leukemia – Acute Myeloid – AML: Subtypes*. American Society of Clinical Oncology; 2022. Accessed October 20, 2023. https://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/subtypes
4. *Myelodysplastic Syndromes –MDS: Subtypes and Classification*. American Society of Clinical Oncology; 2023. Accessed October 20, 2023. https://www.cancer.net/cancer-types/myelodysplastic-syndromes-mds/subtypes-and-classification
5. Thol F, Heuser M. Treatment for relapsed/refractory acute myeloid leukemia. *Hemasphere.* 2021;5(6):e572. doi:10.1097/HS9.0000000000000572
6. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol.* 2009;10(3):223-232. doi:10.1016/S1470-2045(09)70003-8
7. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer.* 2006;106(8):1794-1803. doi:10.1002/cncr.21792
8. Jabbour E, Garcia-Manero G, Batty N, et al. Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. *Cancer.* 2010;116(16):3830-3834. doi:10.1002/cncr.25247
9. Prebet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol.* 2011;29(24):3322-3327. doi:10.1200/JCO.2011.35.8135
10. Russell-Smith TA, Gurskyte L, Muresan B, et al. Efficacy of non-intensive therapies approved for relapsed/refractory acute myeloid leukemia: a systematic literature review. *Future Oncol.* 2022;18(16):2029-2039. doi:10.2217/fon-2021-1355
11. Platzbecker U, Kubasch AS, Homer-Bouthiette C, Prebet T. Current challenges and unmet medical needs in myelodysplastic syndromes. *Leukemia.* 2021;35(8):2182-2198. doi:10.1038/s41375-021-01265-7
12. Cowan AJ, Laszlo GS, Estey EH, Walter RB. Antibody-based therapy of acute myeloid leukemia with gemtuzumab ozogamicin. *Front Biosci (Landmark ed).* 2013;18(4):1311-1334. doi:10.2741/4181
13. Clark MC, Stein A. CD33 directed bispecific antibodies in acute myeloid leukemia. *Best Pract Res Clin Haematol.* 2020;33(4):101224. doi:10.1016/j.beha.2020.101224
14. Jilani I, Estey E, Huh Y, et al. Differences in CD33 intensity between various myeloid neoplasms. *Am J Clin Pathol.* 2002;118(4):560-566. doi:10.1309/1WMW-CMXX-4WN4-T55U
15. Kapoor S, Champion G, Basu A, Mariampillai A, Olnes MJ. Immune therapies for myelodysplastic syndromes and acute myeloid leukemia. *Cancers (Basel).* 2021;13(19):5026. doi:10.3390/cancers13195026
16. Ogata K, Nakamura K, Yokose N, et al. Clinical significance of phenotypic features of blasts in patients with myelodysplastic syndrome. *Blood.* 2002;100(12):3887-3896. doi:10.1182/blood-2002-01-0222
17. Chen X, Eksioglu EA, Zhou J, et al. Induction of myelodysplasia by myeloid-derived suppressor cells. *J Clin Invest.* 2013;123(11):4595-4611. doi:10.1172/JCI67580
18. Velegraki M, Stiff A, Papadaki HA, Li Z. Myeloid-derived suppressor cells: new insights into the pathogenesis and therapy of MDS. *J Clin Med.* 2022;11(16):4908. doi:10.3390/jcm11164908
19. Kittang AO, Kordasti S, Sand KE, et al. Expansion of myeloid derived suppressor cells correlates with number of T regulatory cells and disease progression in myelodysplastic syndrome. *Oncoimmunology.* 2016;5(2):e1062208. doi:10.1080/2162402X.2015.1062208

20. Eksioglu EA, Chen X, Heider KH, et al. Novel therapeutic approach to improve hematopoiesis in low risk MDS by targeting MDSCs with the fc-engineered CD33 antibody BI 836858. *Leukemia*. 2017;31(10):2172-2180. doi:10.1038/leu.2017.21
21. Cheng P, Chen X, Dalton R, et al. Immunodepletion of MDSC by AMV564, a novel bivalent, bispecific CD33/CD3 T cell engager, ex vivo in MDS and melanoma. *Mol Ther*. 2022;30(6):2315-2326. doi:10.1016/j.ymthe.2022.02.005
22. *Mylotarg™ (Gemtuzumab Ozogamicin) for Injection Prescribing Information*. Pfizer Inc.; 2021.
23. Rajvanshi P, Shulman HM, Sievers EL, McDonald GB. Hepatic sinusoidal obstruction after gemtuzumab ozogamicin (Mylotarg) therapy. *Blood*. 2002;99(7):2310-2314. doi:10.1182/blood.v99.7.2310
24. Giles FJ, Kantarjian HM, Kornblau SM, et al. Mylotarg (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. *Cancer*. 2001;92(2):406-413. doi:10.1002/1097-0142(20010715)92:2<406::aid-cncr1336>3.0.co;2-u
25. Laszlo GS, Harrington KH, Gudgeon CJ, et al. Expression and functional characterization of CD33 transcript variants in human acute myeloid leukemia. *Oncotarget*. 2016;7(28):43281-43294. doi:10.18632/oncotarget.9674
26. Hernandez-Caselles T, Martinez-Esparza M, Perez-Oliva AB, et al. A study of CD33 (SIGLEC-3) antigen expression and function on activated human T and NK cells: two isoforms of CD33 are generated by alternative splicing. *J Leukoc Biol*. 2006;79(1):46-58. doi:10.1189/jlb.0205096
27. Menon AP, Moreno B, Meraviglia-Crivelli D, et al. Modulating T cell responses by targeting CD3. *Cancers (Basel)*. 2023;15(4):1189. doi:10.3390/cancers15041189
28. Singh A, Dees S, Grewal IS. Overcoming the challenges associated with CD3+ T-cell redirection in cancer. *Br J Cancer*. 2021;124(6):1037-1048. doi:10.1038/s41416-020-01225-5
29. *Blincyto® (Blinatumomab) for Injection Prescribing Information*. Amgen Inc.; 2022.
30. Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol*. 2011;29(18):2493-2498. doi:10.1200/JCO.2010.32.7270
31. Nair-Gupta P, Diem M, Reeves D, et al. A novel C2 domain binding CD33xCD3 bispecific antibody with potent T-cell redirection activity against acute myeloid leukemia. *Blood Adv*. 2020;4(5):906-919. doi:10.1182/bloodadvances.2019001188
32. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114(5):937-951. doi:10.1182/blood-2009-03-209262
33. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465. doi:10.1182/blood-2012-03-420489
34. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196
35. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108(2):419-425. doi:10.1182/blood-2005-10-4149
36. Bloomfield CD, Estey E, Pleyer L, et al. Time to repeal and replace response criteria for acute myeloid leukemia? *Blood Rev*. 2018;32(5):416-425. doi:10.1016/j.blre.2018.03.006
37. Kubicka E, Lum LG, Huang M, Thakur A. Bispecific antibody-targeted T-cell therapy for acute myeloid leukemia. *Front Immunol*. 2022;13:899468. doi:10.3389/fimmu.2022.899468
38. Damiani D, Tiribelli M. Present and future role of immune targets in acute myeloid leukemia. *Cancers (Basel)*. 2022;15(1):253. doi:10.3390/cancers15010253
39. Tettamanti S, Pievani A, Biondi A, Dotti G, Serafini M. Catch me if you can: how AML and its niche escape immunotherapy. *Leukemia*. 2022;36(1):13-22. doi:10.1038/s41375-021-01350-x
40. Zheng L, Zhang L, Guo Y, et al. The immunological role of mesenchymal stromal cells in patients with myelodysplastic syndrome. *Front Immunol*. 2022;13:1078421. doi:10.3389/fimmu.2022.1078421
41. *Amgen reports first quarter 2022 financial results*. PRN Newswire; 2022. Accessed October 20, 2023. https://www.prnewswire.com/news-releases/amgen-reports-first-quarter-2022-financial-results-301534573.html
42. Boyiadzis M, Desai P, Daskalakis N, et al. First-in-human study of JNJ-63709178, a CD123/CD3 targeting antibody, in relapsed/refractory acute myeloid leukemia. *Clin Transl Sci*. 2023;16(3):429-435. doi:10.1111/cts.13467

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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