# Randomized Phase III SIERRA Trial of $^{131}$I-Apamistamab Before Allogeneic Hematopoietic Cell Transplantation Versus Conventional Care for Relapsed/Refractory AML

Boglarka Gyurkocza, MD[1]; Rajneesh Nath, MD[2]; Stuart Seropian, MD[3]; Hannah Choe, MD[4]; Mark R. Litzow, MD[5]; Camille Abboud, MD[6]; Nebu Koshy, MD[7]; Patrick Stiff, MD[8]; Benjamin Tomlinson, MD[9]; Sunil Abhyankar, MD[10]; James Foran, MD[11]; Parameswaran Hari, MD[12]; George Chen, MD[13,14]; Zaid Al-Kadhimi, MD[15]; Partow Kebriaei, MD[14]; Mitchell Sabloff, MDCM[16]; Johnnie J. Orozco, MD, PhD[17]; Katarzyna Jamieson, MD[18]; Margarida Silverman, MD[19]; Koen Van Besien, MD, PhD[20]; Michael Schuster, MD[21]; Arjun Datt Law, MD[22]; Karilyn Larkin, MD[23]; Neeta Pandit-Taskar, MD[24]; Scott D. Rowley, MD, FACP[25]; Pashna Munshi, MD[26]; Rachel Cook, MD[27]; Moshe Y. Levy, MD[28]; Hillard M. Lazarus, MD[29]; Brenda M. Sandmaier, MD[17]; John M. Pagel, MD, PhD[30]; Vijay Reddy, MD[31]; James MacDougall, PhD[32]; Kathleen McNamara, RN, MA, BS[33]; Jennifer Spross, MA[33]; Elaina Haeuber, MS[33]; Madhuri Vusirikala, MD[33]; Akash Nahar, MD[33]; Avinash Desai, MD[33]; and Sergio Giralt, MD[1]

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## ABSTRACT

**PURPOSE** Older patients with relapsed or refractory AML (RR AML) have dismal prognoses without allogeneic hematopoietic cell transplantation (alloHCT). SIERRA compared a targeted pretransplant regimen involving the anti-CD45 radioconjugate $^{131}$I-apamistamab with conventional care.

**METHODS** SIERRA (ClinicalTrials.gov identifier: NCT02665065) was a phase III open-label trial. Patients age ≥55 years with active RR AML were randomly assigned 1:1 to either an $^{131}$I-apamistamab–led regimen before alloHCT or conventional care followed by alloHCT if initial complete remission (CR)/CR with incomplete platelet recovery (CRp) occurred. Initial response was assessed 28-56 days after alloHCT in the $^{131}$I-apamistamab group and 28-42 days after salvage chemotherapy initiation; patients without CR/CRp or with AML progression could cross over to receive $^{131}$I-apamistamab followed by alloHCT. The primary end point was durable complete remission (dCR) lasting 180 days after initial CR/CRp. Secondary end points were overall survival (OS) and event-free survival (EFS), assessed hierarchically in the intention-to-treat (ITT) population.

**RESULTS** The ITT population included 153 patients ($^{131}$I-apamistamab [n = 76]; conventional care [n = 77]). In total, 44/77 conventional care arm patients crossed over and 40/77 (52%) received $^{131}$I-apamistamab and alloHCT, with six patients (13.6%) experiencing a dCR. In the ITT population, the dCR rate was significantly higher with $^{131}$I-apamistamab (17.1% [95% CI, 9.4 to 27.5]) than conventional care (0% [95% CI, 0 to 4.7]; $P < .0001$). The OS hazard ratio (HR) was 0.99 (95% CI, 0.70 to 1.41; $P = .96$), and the EFS HR was 0.23 (95% CI, 0.15 to 0.34), with HR <1 favoring $^{131}$I-apamistamab. Grade ≥3 treatment-related adverse events occurred in 59.7% and 59.2% of the $^{131}$I-apamistamab and conventional care groups, respectively.

**CONCLUSION** The $^{131}$I-apamistamab–led regimen was associated with a higher dCR rate than conventional care in older patients with RR AML. $^{131}$I-apamistamab was well tolerated and could address an unmet need in this population.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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## INTRODUCTION

The prognosis of older patients with AML is dismal.[1-4] Potentially curative transplant is a treatment option for selected patients with primary refractory AML,[5] but with their poor tolerance for intensive myeloablative regimens, <10% of older patients with active relapsed or refractory (RR) AML are offered allogeneic hematopoietic cell transplantation (alloHCT).[2,4,6,7] Active disease at alloHCT is the most important predictor of post-transplant relapse: The 2-year survival rate post-alloHCT in older patients with active disease and adverse cytogenetics is <10%.[8,9] Novel

## CONTEXT

**Key Objective**

Does a targeted pretransplant regimen with the anti-CD45 radioconjugate $^{131}$I-apamistamab improve outcomes over conventional care in older patients with active relapsed or refractory AML (RR AML), who are not typically offered allogeneic hematopoietic cell transplantation (alloHCT)?

**Knowledge Generated**

The $^{131}$I-apamistamab–led regimen was well tolerated in patients age ≥55 years with active RR AML and demonstrated a significantly higher durable complete remission (dCR) rate than conventional care; the 2-year survival rate among patients with a dCR was 69%. Similar outcomes were seen in patients who failed conventional salvage therapies and crossed over to $^{131}$I-apamistamab.

**Relevance *(C.F. Craddock)***

The incorporation of an anti CD45 immunoconjugate into the transplant regimen in patients with relapsed/refractory AML was well tolerated and improved dCR rate. The use of antibody immunoconjugates as a central component of the conditioning regimen has the potential to improve transplant outcomes in high-risk AML and merits further examination in carefully designed randomized trials.*

*Relevance section written by *JCO* Associate Editor Charles F. Craddock, MD.



approaches are needed to make alloHCT feasible for older patients and improve their chances of long-term remission.[10]

$^{131}$I-apamistamab is a recombinant murine anti-CD45 monoclonal antibody conjugated to radioactive isotope iodine-131. CD45 is expressed only on nucleated hematopoietic cells, including 85%-90% of AML cells.[11-13] Thus, $^{131}$I-apamistamab delivers radiation directly to hematopoietic cells,[13,14] and its myeloablative effects[15,16] facilitate leukemia control before alloHCT.[10] In a phase I study, $^{131}$I-apamistamab followed by reduced-intensity conditioning with fludarabine and total body irradiation (Flu-TBI) resulted in successful engraftment, remission, and a 1-year survival rate of 48% in patients age ≥50 years with RR AML.[12] Based on these results, the Study of Iomab-B in Elderly patients with RR AML (SIERRA) was conducted to compare the efficacy and safety of an $^{131}$I-apamistamab–led regimen followed by alloHCT with those of conventional care.

## METHODS

### Study Design, Treatment, and Patients

SIERRA (ClinicalTrials.gov identifier: NCT02665065) is a prospective, phase III, multicenter, open-label, 1:1 randomized, controlled, optional 1-way crossover study of $^{131}$I-apamistamab followed by Flu-TBI and alloHCT versus the investigator's choice of conventional care. Random assignment, blinded to investigators, was in fixed blocks of 4.

Eligible patients were ≥55 years of age and had active RR AML (Supplementary Methods, online only), expected survival >60 days, circulating blast count <10,000/mm$^3$, CD45+ leukemic cells, Karnofsky score ≥70, no previous alloHCT, adequate organ function, and an 8/8 HLA allele-matched donor. All patients provided written informed consent to participate before enrollment.

Patients in the $^{131}$I-apamistamab group received a dosimetric infusion to determine the therapeutic dose that would deliver ≤24 Gy to the liver or ≤48 Gy to the marrow, whichever resulted in lower administered activity.[12] Patients then received a single therapeutic $^{131}$I-apamistamab infusion—followed by Flu-TBI (fludarabine 30 mg/m$^2$ once daily on days −4, −3 and −2 and 2 Gy TBI on day 0)—12 days before alloHCT (an unmanipulated donor progenitor cell infusion; protocol; Data Supplement [online only], Fig S1B). A calcineurin inhibitor and mycophenolate mofetil were used for graft-versus-host-disease (GVHD) prophylaxis.[12,15]

Conventional care comprised salvage therapy followed by standard-of-care alloHCT (Protocol) if patients achieved a complete remission (CR) or CR with incomplete platelet recovery (CRp; Supplementary Methods) within 28-42 days of treatment initiation. Patients with a CR/CRp per bone marrow (BM) assessment could proceed to conventional alloHCT or continue treatment. Patients without a CR/CRp, or who had AML progression from day 14, could cross over to receive $^{131}$I-apamistamab and Flu-TBI followed by alloHCT (Data Supplement, Fig S1A).

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by the study centers' institutional review boards.

### Assessments

In the $^{131}$I-apamistamab group, patients' BM was evaluated for initial CR or CRp per revised International Working Group Criteria[16] 28 ± 3 days after alloHCT. If CR/CRp could not be confirmed, the patient was reassessed on day 56. In the conventional care group, the initial response (CR, CRp, or treatment failure) was assessed in a BM aspirate/biopsy taken 28-42 days after starting salvage chemotherapy (ie, before standard transplant). In both groups, patients with no evidence of relapse underwent a BM aspirate/biopsy 180 days from the first documented CR/CRp. If the initial CR/CRp lasted ≥180 days from the first assessment, the patient had attained the primary end point of durable complete remission (dCR). Clinical laboratory and safety parameters were assessed per protocol.

Patients are being followed for survival and safety for 5 years.

### End Points

The primary end point was the rate of dCR (defined as CR/CRp lasting ≥180 days from first assessment[16] by an independent endpoint adjudication committee) in the intention-to-treat (ITT) population. dCR required CR/CRp before transplant in the conventional care arm and after transplant in the $^{131}$I-apamistamab arm. Secondary end points included ITT overall survival (OS, defined as time from random assignment to death) and event-free survival (EFS), defined as time from random assignment to (1) failure to receive alloHCT in the $^{131}$I-apamistamab group, (2) salvage treatment failure in the conventional group, (3) morphologic relapse, or (4) death, whichever came first.

Exploratory efficacy end points included dCR, OS, and 1-year OS rates in conventional care patients who crossed over to receive $^{131}$I-apamistamab versus those who did not and subgroup analyses of EFS by baseline characteristics. Post hoc subgroup analyses of OS excluding crossover patients from the conventional care group were also done.

Safety end points included the incidence and severity of treatment-emergent adverse events graded per NCI CTCAE version 4.03. Nonrelapse mortality (NRM) at day 100 and 1 year was assessed in transplanted patients, along with the incidence of GVHD, hemorrhage, infections, and graft rejection or failure. Graft failure was protocol-defined as failure to attain an absolute neutrophil count of ≥500 cells/μL by day 28 after alloHCT over three consecutive measurements but is termed delayed engraftment henceforth for clarity.

### Statistical Analysis

We assumed that 60% of patients in the $^{131}$I-apamistamab group and 30% in the conventional care group would achieve dCR; 122 patients (61 per group) provided approximately 90% power to detect this difference using the Fisher exact test (two-tailed alpha = .05). To detect an 18% improvement in 1-year OS (33% *v* 15% in the $^{131}$I-apamistamab and conventional care groups, respectively) based on a log-rank test (two-tailed $\alpha$ = .05) with 80% power, the sample size was 75 patients per group (n = 150).

A prospective Lan-DeMets alpha-spending function with O'Brien-Fleming stopping boundaries was used to control the overall type I error rate at a two-sided 5% level, with the end points assessed hierarchically as follows: (1) dCR (primary end point); (2) OS (secondary end point); (3) EFS (secondary end point; Supplementary Methods). The nominal two-sided significance level for primary end point dCR after adjustments was 0.04566.

The prespecified primary efficacy and safety cutoff was when all participants had completed the day 180 visit (June 30, 2022). To provide survival data after longer follow-up, additional interim OS and EFS analyses were done on data collected by January 22, 2024.

Efficacy was evaluated in the ITT population, which included all randomly assigned patients. Crossover patients were counted as failing to achieve the primary end point in the conventional care group but were otherwise evaluated for efficacy and safety.

The Fisher exact test was used to compare the dCR rate between treatment groups. The Kaplan-Meier method was used to estimate OS and survival distribution differences were evaluated using a log-rank test. OS in the crossover population was analyzed using crossover as a time-dependent covariate in the Cox model (Supplementary Methods). To address asymmetry in EFS assessment times between treatment groups, EFS was analyzed using a grouped survival analysis approach, in which time to event analyses were grouped into intervals via a complementary log-log mode. Owing to a lack of events, some prespecified time intervals were combined (Supplementary Methods). Additionally, EFS in the ITT population was analyzed per Kaplan-Meier using the actual time of events, with 95% CIs.

Safety was evaluated in all patients who received at least one study treatment dose.

Additional details regarding statistical methods, censoring rules, and handling of missing data are provided in the supplementary methods. Analyses were performed using SAS version 9.4.

## RESULTS

### Study Population and Treatment

Between February 2017 and October 2021, 153 patients at 22 North American sites were randomly assigned to receive the $^{131}$I-apamistamab–led regimen (n = 76) or conventional care (n = 77; Fig 1). In the $^{131}$I-apamistamab group, 72 patients

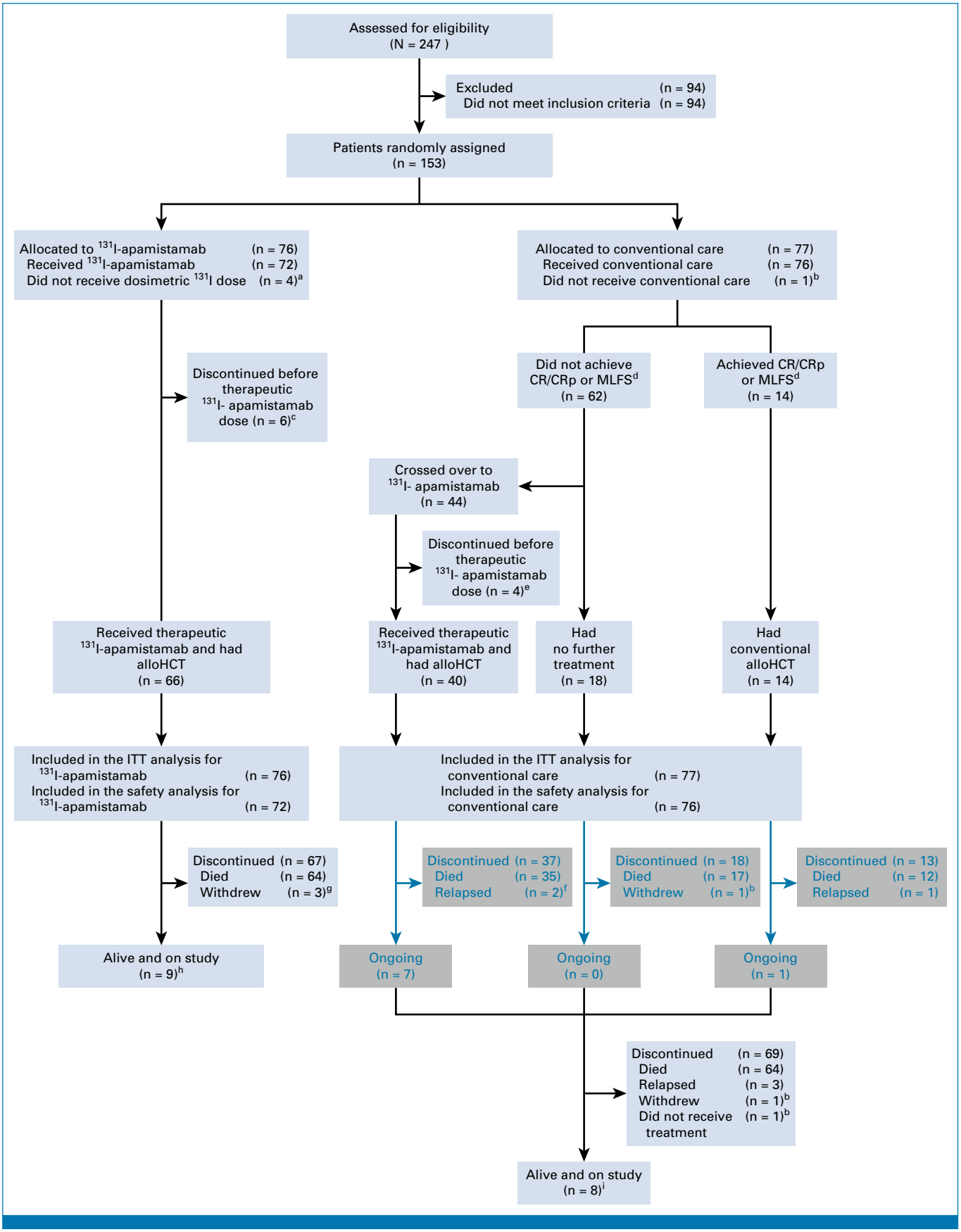


**FIG 1.** Trial profile. [a]Due to death (n = 1), investigator decision (n = 1), insurance (n = 1), did not meet eligibility criteria (n = 1). [b]Patient withdrew consent. [c]Due to investigator decision (n = 3), grade 3 infusion reaction (n = 1), rapid disease progression (n = 1), (continued on following page)

**FIG 1.** (Continued). unfavorable biodistribution (n = 1). [d]Defined as <5% blasts in bone marrow within 28 to 42 days.[16] [e]Due to decline in Karnofsky performance status (n = 2), investigator decision (n = 1), patient withdrew consent (n = 1). [f]Patients listed as relapsed had disease relapse but were alive at the time of last contact/data cutoff. [g]Investigator decision (n = 1), insurance (n = 1), did not meet eligibility criteria (n = 1). [h]At the primary cutoff (June 30, 2022). At the subsequent cutoff on January 22, 2024, eight patients were ongoing, with one having discontinued because of relapse. [i]At the primary cutoff (June 30, 2022). At the subsequent cutoff on January 22, 2024, four patients were ongoing, with two patients in the crossover group having died and one having completed 5-year survival follow-up. alloHCT, allogeneic hematopoietic cell transplantation; CR, complete remission; CRp, complete remission with incomplete platelet recovery; ITT, intention-to-treat; MLFS, morphologic leukemia-free state.

received dosimetric $^{131}$I-apamistamab; six discontinued the study before the therapeutic dose. The remaining 66 received the therapeutic dose followed by Flu-TBI (Data Supplement, Table S1) and alloHCT. At the prespecified data cutoff for the primary analysis (June 30, 2022), nine patients in the $^{131}$I-apamistamab group remained in long-term follow-up. In the conventional care group, 76 patients received salvage therapy (Data Supplement, Table S2), of whom 14 underwent standard-of-care alloHCT: five after achieving CR/CRp and nine at the investigator's discretion following a morphologic leukemia-free state (MLFS; <5% marrow blasts).[16] Of the 62 patients who did not respond, 44 crossed over, of whom 40 received the $^{131}$I-apamistamab–led regimen and underwent alloHCT. The remaining 18 patients in the conventional care group had no further treatment. At the subsequent survival analysis (January 22, 2024), eight patients in the $^{131}$I-apamistamab group were alive and on study versus five in the conventional care group.

The patients' baseline demographic and disease characteristics were similar between the randomized groups and also between patients randomly assigned to $^{131}$I-apamistamab and those originally randomly assigned to conventional care who crossed over to $^{131}$I-apamistamab (Table 1). In the ITT population, the median age was 65 years (range, 55-77), the median BM blast count was 25% (range, 2%-97%), >90% had intermediate to adverse cytogenetics, 57.5% had a Karnofsky performance status <90, 24% had *TP53* mutations, and 40.5% had received prior venetoclax. Prior therapies in 83 patients with primary refractory disease (ie, failed ≥2 cycles of prior therapy) are summarized in the Data Supplement (Table S3).

## Engraftment

Conditioning and transplant characteristics in patients who underwent alloHCT are summarized in Table 2. The median time to alloHCT from random assignment was 29 days in the $^{131}$I-apamistamab group versus 66.5 days in the conventional care group and 61.5 days in crossover patients. The similar rates of engraftment seen after $^{131}$I-apamistamab and crossover were higher than after conventional care (Table 2). The median time to platelet engraftment was longer after $^{131}$I-apamistamab than conventional care; time to neutrophil engraftment was similar between treatment groups. Delayed neutrophil and platelet engraftment rates, respectively, were lower in the $^{131}$I-apamistamab (1.5% and 15.2%) and crossover groups (2.5% and 5.0%) than in the conventional care group (7.1% and 21.4%). No graft rejections occurred in any patients who received $^{131}$I-apamistamab; one patient (7.1%) receiving standard-of-care alloHCT in the conventional care group had a graft rejection.

Post-transplant maintenance therapy with midostaurin, sorafenib, or gilteritinib was received ≥60 days after transplantation by three of 66 patients (4.5%) in the $^{131}$I-apamistamab group, four of 40 crossover patients (10%), and one of 14 patients (7.1%) who received conventional care followed by alloHCT.

## Efficacy

CR/CRp occurred in 46 of 76 (60.5%) patients in the $^{131}$I-apamistamab group after alloHCT, five of 77 (6.5%) patients in the conventional care group after salvage therapy, and in 23 of 44 (52.3%) patients in the crossover group after alloHCT. In the ITT population, the dCR rate was significantly higher in the $^{131}$I-apamistamab group (13 of 76 patients; 17.1% [95% CI, 9.4 to 27.5]) than in the conventional care group (0 of 77 patients; 0% [95% CI, 0 to 4.7]; $P < .0001$). Of the 44 patients who crossed over to $^{131}$I-apamistamab, six achieved a dCR (13.6% [95% CI, 5.2 to 27.4]).

The median duration of follow-up was 36.6 months (95% CI, 24.8 to 49.4) at the primary analysis cutoff and 43.6 months (95% CI, 35.1 to 60.9) at the additional survival analysis on January 22, 2024. In the ITT population, the median OS was similar between the $^{131}$I-apamistamab and conventional care groups at the primary cutoff (6.4 months [95% CI, 5.1 to 7.9]) versus 6.0 months [95% CI, 4.2 to 7.8]; hazard ratio (HR), 0.99; 95% CI, 0.70 to 1.41; $P = .96$; Fig 2A) and at the subsequent analysis (6.3 months [95% CI, 5.1 to 7.9]) versus 5.9 months [95% CI, 4.1 to 7.2]; HR, 0.91; 95% CI, 0.65 to 1.28; $P = .59$; Fig 2A). Prespecified exploratory analysis showed that among conventional care patients who crossed over to receive $^{131}$I-apamistamab, the median OS was 7.1 months (95% CI, 5.2 to 9.2) versus 3.2 months (95% CI, 1.6 to 6.5) among those who did not cross over (HR, 0.53 [95% CI, 0.33 to 0.86]; Data Supplement, Fig S3).

At the January 22, 2024 cutoff, the respective 1- and 2-year OS rates were 25% (95% CI, 15.9 to 35.1) and 15.8% (95% CI, 8.7 to 24.8) in the $^{131}$I-apamistamab group versus 23.4% (95% CI, 14.7 to 33.3) and 15.6% (95% CI, 8.6 to 24.5) in the conventional care group. Among 33 conventional care

**TABLE 1.** Demographic and Disease Characteristics at Baseline (intention-to-treat population and patients in the conventional care group who crossed over to $^{131}$I-apamistamab)

| Characteristic | $^{131}$I-apamistamab (n = 76) | Conventional Care (n = 77) | Crossover[a] (n = 44) |
|---|---|---|---|
| Median age (range), years | 64 (55-77) | 66 (55-76) | 64 (55-76) |
| 55-65 | 46 (60.5) | 38 (49.4) | 26 (59.1) |
| >65 | 30 (39.5) | 39 (50.6) | 18 (40.9) |
| ≥70 | 14 (18.4) | 16 (20.8) | 12 (27.3) |
| Sex, No. (%) | | | |
| Male | 45 (59.2) | 51 (66.2) | 32 (72.7) |
| Female | 31 (40.8) | 26 (33.8) | 12 (27.3) |
| Race or ethnic group, No. (%) | | | |
| White | 72 (94.7) | 72 (93.5) | 40 (90.9) |
| Black or African American | 1 (1.3) | 2 (2.6) | 1 (2.3) |
| Asian | 1 (1.3) | 3 (3.9) | 3 (6.8) |
| Other | 2 (2.6) | 0 | 0 |
| AML status, No. (%) | | | |
| Primary induction failure | 43 (56.6) | 40 (51.9) | 24 (54.5) |
| First early relapse | 16 (21.1) | 22 (28.6) | 11 (25.0) |
| Relapsed or refractory | 10 (13.2) | 10 (13.0) | 7 (15.9) |
| Second or subsequent relapse | 7 (9.2) | 5 (6.5) | 2 (4.5) |
| Cytogenetic and molecular risk status,[b] No. (%) | | | |
| Favorable | 5 (6.6) | 2 (2.6) | 1 (2.3) |
| Intermediate | 27 (35.5) | 31 (40.3) | 21 (47.7) |
| Adverse/poor | 43 (56.6) | 43 (55.8) | 21 (47.7) |
| Missing | 1 (1.3) | 1 (1.3) | 1 (2.3) |
| *TP53* mutation–positive, No. (%) | 17 (22.4) | 20 (26.0) | 10 (22.7) |
| Karnofsky performance status (KPS), No. (%) | | | |
| ≥90 | 31 (40.8) | 34 (44.2) | 22 (50.0) |
| <90 | 45 (59.2) | 43 (55.8) | 22 (50.0) |
| KPS distribution, No. (%) | | | |
| 70 | 15 (19.7) | 12 (15.6) | 4 (9.1) |
| 80 | 26 (34.2) | 28 (36.4) | 16 (36.3) |
| 90 | 29 (38.1) | 32 (41.6) | 20 (45.4) |
| 100 | 3 (3.9) | 2 (2.6) | 1 (2.3) |
| Not reported | 3 (3.9) | 3 (3.9) | 3 (6.8) |
| Duval score, No. (%) | | | |
| 0 | 8 (10.5) | 5 (6.5) | 3 (6.8) |
| 1 | 10 (13.2) | 16 (20.8) | 9 (20.8) |
| 2 | 25 (32.9) | 27 (35.1) | 18 (40.9) |
| ≥3 | 29 (38.2) | 29 (37.7) | 14 (31.8 |
| Patients with circulating blasts, No. (%) | 60 (78.9) | 54 (71.1) | 35 (79.5) |
| Median circulating blasts, range | 7.5% (0-89) | 8.0% (0-95) | 9.0% (0-81) |
| Median bone marrow blasts (range) | 30% (2-97)[c] | 20% (3-97)[c] | 24.5% (3-87)[c,d] |
| | | | 35% (2-89)[c,e] |
| Median No. of previous therapies (range) | 3 (1-8) | 3 (1-8) | 3 (1-8) |
| Received prior targeted therapy, No. (%) | 47 (61.8) | 47 (61.0) | 26 (59.1) |
| BCL-2 | 28 (36.8) | 34 (44.2) | 21 (47.7) |
| IDH | 5 (6.6) | 5 (6.5) | 4 (9.1) |
| FLT3 | 13 (17.1) | 10 (13.0) | 4 (9.1) |

(continued on following page)

**TABLE 1.** Demographic and Disease Characteristics at Baseline (intention-to-treat population and patients in the conventional care group who crossed over to $^{131}$I-apamistamab) (continued)

| Characteristic | $^{131}$I-apamistamab (n = 76) | Conventional Care (n = 77) | Crossover[a] (n = 44) |
|---|---|---|---|
| CD33 | 2 (2.6) | 6 (7.8) | 3 (6.8) |
| Other | 8 (10.5) | 8 (10.4) | 5 (11.4) |

Abbreviations: BCL-2, B-cell lymphoma 2; dCR, durable complete remission; FLT3, FMS-like tyrosine kinase 3; IDH, isocitrate dehydrogenase.
[a]Includes patients randomly assigned to the conventional care group who did not have a dCR and crossed over to receive $^{131}$I-apamistamab.
[b]Per NCCN Guidelines, Version 3, 2020.
[c]Patients with <5% marrow blasts had circulating leukemic blasts.
[d]At random assignment.
[e]At crossover.

patients who did not cross over, 1- and 2-year OS rates were 12.1% and 9.1% versus 31.8% and 20.5% of 44 who crossed over to $^{131}$I-apamistamab. Of 13 patients who achieved a dCR with $^{131}$I-apamistamab, 92.3% were alive at 1 year, 69.2% were alive at 2 years, and the median OS was not estimable (NE; 95% CI, 13.5 to NE; Fig 2B, Data Supplement, Fig S2B). Among the 14 patients who received standard alloHCT, the median OS was 8.2 months (95% CI, 5.9 to 11.2) and 1- and 2-year OS rates were 21.4% and 14.3%.

Grouped survival analysis showed that EFS was longer in the $^{131}$I-apamistamab than the conventional care group in the

**TABLE 2.** Transplant Characteristics in Patients Who Underwent Allogeneic Hematopoietic Cell Transplantation

| Characteristic | $^{131}$I-apamistamab (n = 66)[a] | Conventional Care (n = 14) | Crossover (n = 40)[b] |
|---|---|---|---|
| alloHCT comorbidity index, No. (%) | | | |
| 0-2 | 30 (45.5) | 9 (64.3) | 20 (50.0) |
| ≥3 | 36 (54.5) | 5 (35.7) | 20 (50.0) |
| Median administered $^{131}$I activity (range), mCi | 664.4 (354-1,027) | NA | 613.3 (313-1,008) |
| Median dose to marrow (range), Gy | 16 (4.6-44.6) | NA | 16 (6.3-39.8) |
| Median time to alloHCT from random assignment (range), days | 29 (23-60) | 66.5 (35-104) | 61.5 (36-161) |
| Donor graft source type, No. (%) | | | |
| Bone marrow | 4 (6.1) | 2 (14.3) | 2 (5.0) |
| Peripheral blood stem cells | 62 (93.9) | 13 (92.9) | 38 (95.0) |
| Donor relationship, No. (%) | | | |
| Sibling | 25 (37.9) | 5 (35.7) | 13 (32.5) |
| Unrelated | 41 (62.1) | 9 (64.3) | 27 (67.5) |
| Median T cells (range), $\times 10^6$ CD3+ cells/kg | 150.4 (0-1,032) | 263.0 (4-273,924) | 174.2 (0-4,289) |
| Median CD34+ cells (range), $\times 10^6$ cells/kg | 5.2 (0.68-207.9) | 5 (1-25) | 5.8 (2-5.98) |
| Patients with engraftment, No. (%) | | | |
| Neutrophil | 61 (92.4) | 12 (85.7) | 38 (95.0) |
| Platelet | 54 (81.8) | 10 (71.4) | 31 (77.5) |
| Median time to engraftment after alloHCT (range), days | | | |
| Neutrophil | 14 (9-31) | 16 (1-83) | 13 (10-35) |
| Platelet | 19 (10-40) | 14.5 (1-35) | 18 (1-38) |
| Patients with delayed engraftment,[c] No. (%) (95% CI) | | | |
| Neutrophil | 1 (1.5) | 1 (7.1) | 1 (2.5) |
| Platelet | 10 (15.2) | 3 (21.4) | 2 (5.0) |
| Patients with graft rejection, No. (%) | 0 | 1 (7.1%)[d] | 0 |

Abbreviation: alloHCT, allogeneic hematopoietic cell transplant.
[a]Ten patients randomly assigned to $^{131}$I-apamistamab did not receive therapeutic dose or undergo alloHCT.
[b]Four patients crossed over but did not receive therapeutic dose or undergo alloHCT.
[c]Defined as the failure to attain an absolute neutrophil count of ≥500 cells/μL by day 28 post-HCT that was maintained for three consecutive measurements.
[d]Salvaged with a second transplant.

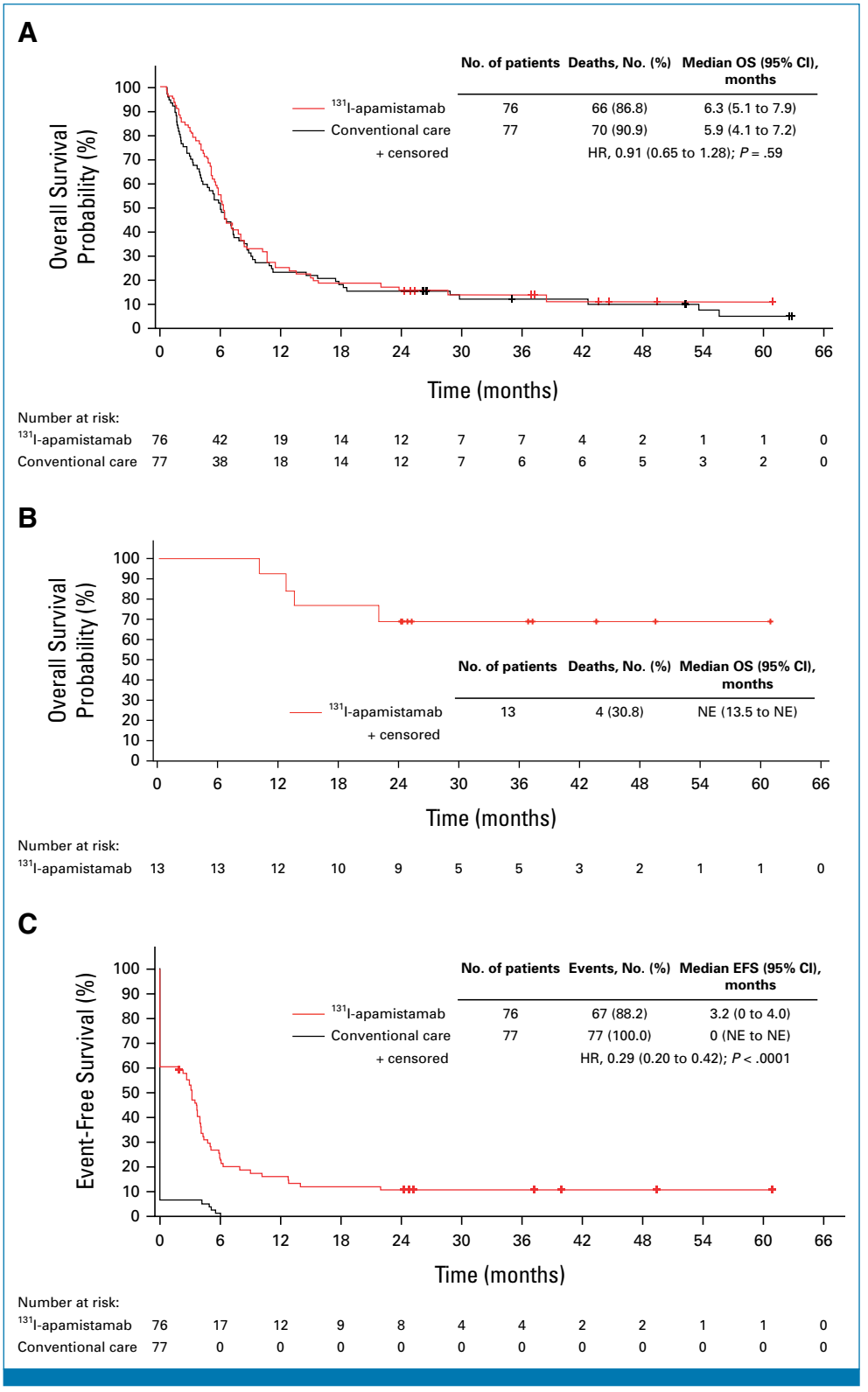


**FIG 2.** OS and EFS. (A) OS in the ITT population. (B) OS in patients who achieved dCR. (C) EFS in the ITT population assessed by actual time. The initial decreases in the Kaplan-Meier curves are due to the patients who failed to achieve initial CR/CRp within the protocol-specified timeframe or those who had induction treatment failure on the day of random assignment. (D) Prespecified exploratory subgroup analyses of EFS assessed by grouped survival analysis in the ITT population. Data are from the January 22, 2024 cutoff. CR, complete remission; CRp, CR with incomplete platelet recovery; dCR, durable complete remission; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; OS, overall survival. (continued on following page)

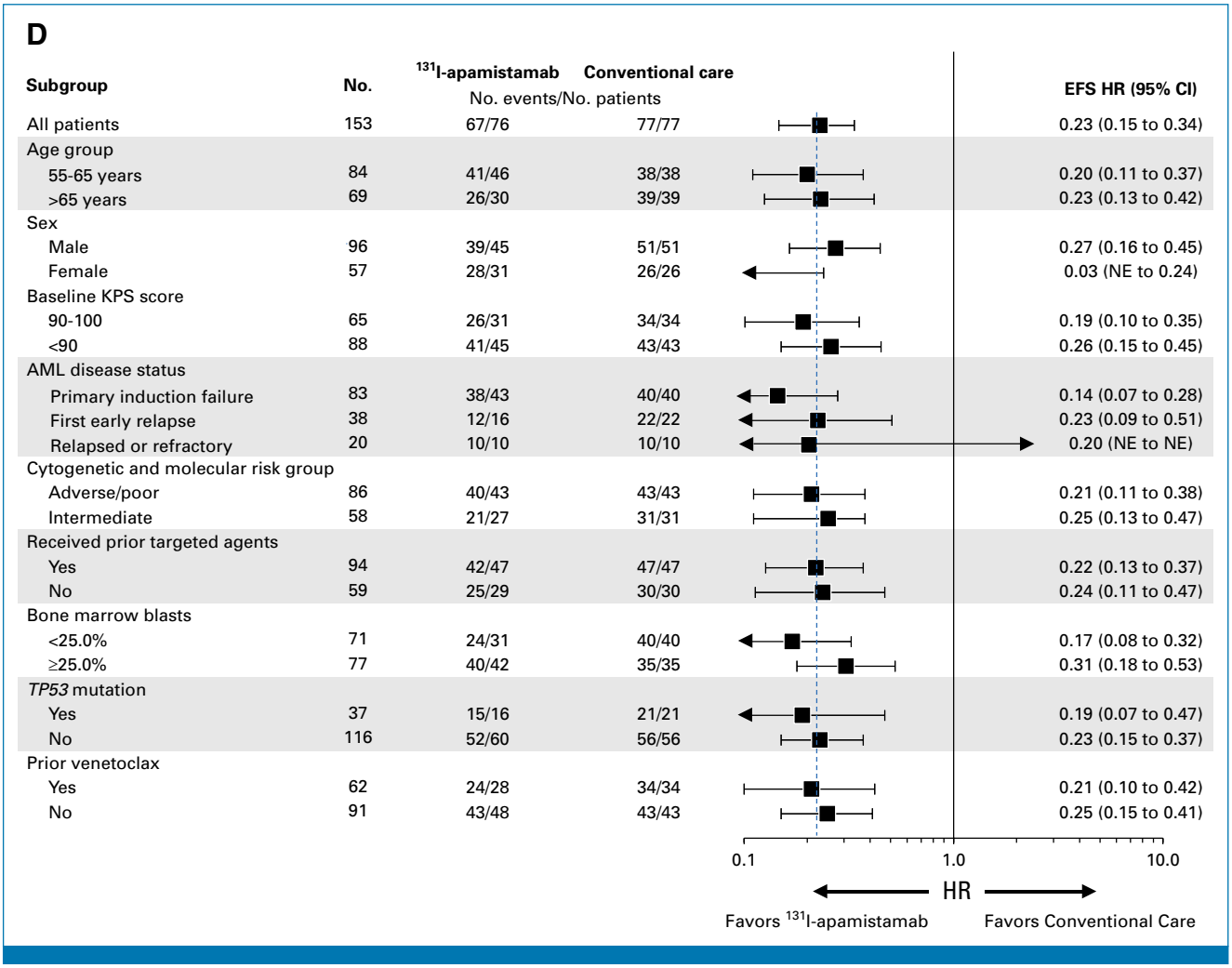


**FIG 2.** (Continued).

ITT population (HR, 0.23; 95% CI, 0.15 to 0.34; descriptive $P < .0001$; Data Supplement, Table S4). The median EFS assessed by actual time did not differ between cutoff dates (Fig 2C, Data Supplement, Fig S2C). Exploratory ITT subgroup analyses of EFS showed consistent benefit favoring [131]I-apamistamab in all groups analyzed (Fig 2D). EFS was similar between patients with primary induction failure (PIF; EFS HR, 0.14 [95% CI, 0.07 to 0.28]), first early relapse (HR, 0.23 [95% CI, 0.09 to 0.51]), and RR AML (HR 0.20 [95% CI, NE to NE]).

When crossover patients were excluded from the conventional care group post hoc, the OS HR among all patients was 0.63 (95% CI, 0.41 to 0.97), and an OS trend favoring [131]I-apamistamab was seen in most subgroups (Data Supplement, Fig S4).

The cumulative incidence of relapse after CR/CRp was 48.8% (21 of 43 patients) in the [131]I-apamistamab group and 83.3% (five of six patients by investigator assessment) in the conventional care group (HR, 0.7 [95% CI, 0.3 to 1.3]; $P = .25$).

## Safety

The safety population included 72 and 76 patients in the [131]I-apamistamab and conventional care groups, respectively. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 59.7% versus 59.2% of these respective groups (Table 3). The most common grade ≥3 TRAE was febrile neutropenia (18.1% *v* 22.4%; Data Supplement, Table S5). Grade 3 infusion-related reactions occurred in five (4.3%) of 116 patients exposed to [131]I-apamistamab. Treatment-related SAEs occurred in 30.6% and 31.6% of the respective treatment groups, with one patient randomly assigned to [131]I-apamistamab (1.4%) discontinuing treatment because of TRAEs (angina pectoris, nausea, and hypoxia). Three patients (4.2%) in the [131]I-apamistamab group had treatment-related deaths (respiratory failure, sepsis leading to acute respiratory failure, and sepsis leading to hepatic sinusoidal obstruction syndrome [SOS]). Two patients (4.5%) in the crossover group died from treatment-related acute GVHD and SOS, respectively. In the conventional care group, four treatment-related deaths (5.3%) occurred (sepsis, septic shock, systemic mycosis, and intracranial hemorrhage).

**TABLE 3.** Safety Summary in the Safety Population, Patients Who Crossed Over to Receive $^{131}$I-Apamistamab, and Patients Who Underwent Transplantation

| Event | $^{131}$I-Apamistamab (n = 72) | Conventional Care[a] (n = 76) | Crossover[b] (n = 44) |
|---|---|---|---|
| All-cause any-grade AEs,[c] No. (%) | 72 (100.0) | 75 (98.7) | 44 (100.0) |
| Grade ≥3 | 68 (94.4) | 61 (80.3) | 43 (97.7) |
| Grade 5 | 13 (18.1) | 8 (10.5) | 5 (11.4%) |
| SAEs | 47 (65.3) | 40 (52.6) | 31 (70.5) |
| Study treatment-related AEs, No. (%) | | | |
| Any-grade | 66 (91.7) | 61 (80.3) | 37 (84.1) |
| Grade ≥3 | 43 (59.7) | 45 (59.2) | 29 (65.9) |
| Grade 5 | 3 (4.2) | 4 (5.3) | 2 (4.5) |
| SAEs | 22 (30.6) | 24 (31.6) | 13 (29.5) |
| Discontinuation of study drug, No. (%) | | | |
| Due to any AEs | 2 (2.8) | 0 (0.0) | 0 (0.0) |
| Due to treatment-related AEs | 1 (1.4) | 0 (0.0) | 0 (0.0) |
| Grade ≥3 AEs of interest in patients who had alloHCT, No. (%) | | | |
| No. of patients | n = 66 | n = 14[d] | n = 40 |
| Febrile neutropenia | 27 (40.9) | 7 (50.0) | 19 (47.5) |
| Sepsis[e] | 4 (6.1) | 4 (28.6) | 8 (20.0) |
| Mucositis[f] | 10 (15.2) | 3 (21.4) | 7 (17.5) |
| Acute GVHD (grade 2 to 4) | 18 (27.3) | 5 (35.7) | 15 (37.5) |
| Cumulative incidence of acute GVHD (grade 2 to 4) at day 100,[g,h] % (95% CI) | 26.1 (16.1 to 37.3) | 35.7 (12.2 to 60.5) | 37.5 (22.6 to 52.4) |
| Acute GVHD (grade 3 to 4) | 6 (9.1) | 2 (14.3) | 3 (7.5) |
| Cumulative incidence of acute GVHD (grade 3 to 4) at day 100,[g,h] % (95% CI) | 9.4 (3.8 to 18.2) | 14.3 (2.1 to 37.6) | 7.5 (1.9 to 18.5) |
| Cumulative non-relapse mortality at day 100, % (95% CI)[i] | 12.2 (5.6 to 21.4) | 14.3 (2.09 to 4.6) | — |
| Cumulative non-relapse mortality at 1 year, % (95% CI)[i] | 26.1 (16.02 to 4.4) | 28.6 (7.9 to 54.0) | — |
| Hazard ratio (95% CI)[j] | 0.89 (0.30 to 2.62) | | — |
| *P*[j] | 0.84 | | |

NOTE. Data are from the primary analysis cutoff date (June 30, 2022).

Abbreviations: AE, adverse event; aGVHD, acute graft-versus-host-disease; alloHCT, allogeneic hematopoietic cell transplantation; CTCAE, Common Terminology Criteria for Adverse Events; CR, complete remission; CRp, CR with incomplete platelet recovery; GVHD, graft-versus-host-disease; SAE, serious adverse event.

[a]Percentages for the conventional care group include all patients randomly assigned to conventional care who received treatment, regardless of whether they crossed over to receive $^{131}$I-apamistamab; AEs for the conventional care group do not include the AEs for crossover patients that were considered treatment-emergent to $^{131}$I-apamistamab.

[b]Does not include AEs that were considered treatment-emergent to conventional care.

[c]Treatment-emergent AEs, defined as occurring on or after the initial dose of assigned therapy or, if they were present before administration of the first dose of study treatment, they increased in severity during the study, excluding those that started/increased after the end of the protocol-defined collection period.

[d]Includes only the patients who received conventional alloHCT after achieving CR/CRp following investigator's choice of salvage chemotherapy induction and did not cross over to receive $^{131}$I-apamistamab.

[e]Includes preferred terms of sepsis, septic shock, neutropenic sepsis, and septic embolus.

[f]Includes preferred terms of stomatitis and mucosal inflammation.

[g]All $^{131}$I-apamistamab patients received cyclosporine and mycophenolate mofetil for GVHD prophylaxis.

[h]Cumulative incidence and 95% CI at day 100 post-alloHCT were estimated using the cumulative incidence function with relapse and death without acute GVHD as competing risks.

[i]Estimated using the cumulative incidence function with relapse, disease progression, and initiation of new antileukemic therapies as competing risks.

[j]Based on Fine and Gray model with treatment as a covariate and relapse, disease progression, and initiation of new antileukemic therapies as competing risks. *P* value from the Gray test.

Among transplanted patients, 100-day and 1-year cumulative incidences of NRM were not significantly different between treatment groups ($P$ = .84; Table 3). No secondary malignancies or late radiation effects occurred. Grade ≥3 post-transplant AEs are summarized in Table 3. Hospitalization, hemorrhage, and infection data are summarized in the Data Supplement (Tables S6-S8).

## DISCUSSION

The optimal therapy for patients with RR AML has not been established. A subset of patients achieve long-term remission with alloHCT. However, few older patients with RR AML are offered alloHCT, and SIERRA was designed to address this unmet need. A crossover design was deemed essential to provide best patient care and facilitate accrual. In a previous study of alloHCT that included 1,256 patients in first relapse and 1,440 with PIF, 42% and 40%, respectively, were alive and in remission 100 days post-alloHCT; their 2-year OS rates were 27% and 29%.[17] Our initial assumption based on these data—that 30% of control arm patients would achieve CR and 1.2% would cross over—proved to be inaccurate: 57% crossed over to the $^{131}$I-apamistamab arm. This high crossover rate might account for the similar OS between randomized treatment arms and confounds assessment of the impact of $^{131}$I-apamistimab on both OS and TRAEs in the ITT population. In SIERRA, 90% of patients had Duval scores ≥2 and 21% were refractory or beyond second relapse, which may explain the lower-than-expected dCR rates and suboptimal responses to salvage chemotherapy.[18,19] Nevertheless, the significant difference in dCR rates between arms (and the longer survival in patients with dCR) demonstrate the therapeutic potential of $^{131}$I-apamistamab in this patient population. Patients who crossed over to receive $^{131}$I-apamistamab after failing salvage therapy had similar outcomes to those originally randomly assigned to $^{131}$I-apamistamab.

Baseline disease characteristics in crossover patients were balanced with those in the randomized treatment groups. Their median BM blasts were 35% at cross over, compared with 24.5% at random assignment (and 30% in the $^{131}$I-apamistamab group), suggesting a higher disease burden at cross over. Prespecified exploratory analyses within the conventional care group showed that median OS was longer among patients who failed salvage therapy and crossed over to $^{131}$I-apamistamab than those who did not; 2-year OS rates were 31.8% and 9.1% in crossover and non-crossover patients, respectively.

The protocol specified that conventional care patients who achieved CR/CRp could undergo alloHCT, but nine of 14 transplanted patients in the conventional care group underwent alloHCT following MLFS to improve their outcomes. Two of these patients had ≥6-month remission, of whom one remained alive and in remission at the final data cutoff. These patients were not adjudicated as having a dCR because they had not achieved CR/CRp after salvage treatment. Had they been adjudicated as having dCR, the difference between treatment groups would still be statistically significant (17.1% *v* 2.6%; $P$ = .0026).

In crossover studies, EFS is a more reliable indicator of response than OS because it is not confounded by crossover or subsequent AML therapies. SIERRA had the additional limitation of a difference in time to occurrence of an early EFS event between arms. In the conventional care arm, an EFS event (salvage treatment failure, inability to receive alloHCT, relapse, or death) could happen as early as 14 days post-random assignment if AML progressed soon after initiating chemotherapy. However, in the $^{131}$I-apamistamab arm, an EFS event was unlikely to occur until 2-4 weeks after alloHCT, which could be 6 weeks after random assignment. Despite this bias against the control arm, the EFS HR was 0.23 (95% CI, 0.15 to 0.34) in the ITT population, indicating that patients in the $^{131}$I-apamistamab group had a 77% greater chance of avoiding an EFS event than those assigned to conventional care. The EFS benefit with $^{131}$I-apamistamab was maintained across patient subgroups.

Comparing $^{131}$I-apamistamab with the standard of care in a randomized, multicenter trial to minimize selection bias and population heterogeneity was a study strength. The crossover design precluding assessment of the true impact of $^{131}$I-apamistamab on survival was a study limitation that led to prespecified exploratory analyses within the conventional care group and post hoc OS analyses with crossover patients excluded from the conventional care group. These findings suggested that survival may be improved with the $^{131}$I-apamistamab–led regimen compared with conventional care. Assessing CR/CRp before and after alloHCT in the control and $^{131}$I-apamistamab arms, respectively, was a limitation imposed by current practice: BM is not typically assessed between conditioning and alloHCT. Restricting post-transplant maintenance therapy to tyrosine kinase and FLT3 inhibitors was another limitation; antileukemic agents such as IDH inhibitors and hypomethylating agents for post-transplant maintenance are now the standard of care in patients at high risk of relapse.[20] The dCR outcomes with $^{131}$I-apamistamab might be improved with other reduced-intensity conditioning regimens and post-transplant[21] therapies. The lack of diversity in the SIERRA population is a limitation common to many alloHCT-related clinical trials. Factors contributing to the <10% of minority patients enrolled in these studies[22] include socioeconomic factors and the challenge of finding HLA-matched donors because of their underrepresentation in registries. Investigator-led studies of $^{131}$I-apamistamab are planned in donor-mismatched, donor-related, and haploidentical settings in patients with other hematological malignancies and with alternative GVHD prophylaxis regimens.

In conclusion, the $^{131}$I-apamistamab–led regimen led to a higher dCR rate than conventional care and was well tolerated in older, heavily pretreated patients with active RR AML. Although the OS comparison was confounded by a majority of crossover patients, the results were encouraging for this patient population.

## AFFILIATIONS

[1]David H. Koch Center for Cancer Care at Memorial Sloan Kettering Cancer Center, New York, NY
[2]Banner MD Anderson Cancer Center, Gilbert, AZ
[3]Yale University School of Medicine—Yale Cancer Center, New Haven, CT
[4]The Ohio State University, Columbus, OH
[5]Mayo Clinic, Rochester, MN
[6]Washington University School of Medicine, St Louis, MO
[7]Texas Oncology—Baylor Charles A. Sammons Cancer Center, Dallas, TX
[8]Loyola University Medical Center, Maywood, IL
[9]University Hospitals Cleveland Medical Center, Cleveland, OH
[10]University of Kansas Cancer Center, Kansas City, KS
[11]Mayo Clinic, Jacksonville, FL
[12]Froedtert Hospital and the Medical College of Wisconsin, Milwaukee, WI
[13]Roswell Park Comprehensive Cancer Center, Buffalo, NY
[14]MD Anderson Cancer Center, Houston, TX
[15]University of Nebraska Medical Center, Omaha, NE
[16]University of Ottawa and The Ottawa Hospital Research Institute, Ottawa, ON, Canada
[17]Fred Hutchinson Cancer Center and University of Washington School of Medicine, Seattle, WA
[18]University of North Carolina (UNC), Chapel Hill, NC
[19]University of Iowa, Iowa City, IA
[20]Weill Cornell Medical College, New York, NY
[21]Stony Brook University Cancer Center, Stony Brook, NY
[22]Hans Messner Allogeneic Blood and Marrow Transplant Program, Princess Margaret Cancer Centre, Toronto, ON, Canada
[23]The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH
[24]Department of Radiology, Memorial Sloan Kettering, New York, NY
[25]Hackensack University Medical Center, Hackensack, NJ
[26]MedStar Georgetown University Hospital, Washington, DC
[27]Oregon Health & Science University, Portland, OR
[28]Baylor Scott & White Health, Dallas, TX
[29]Case Western Reserve University, Cleveland, OH
[30]Loxo Oncology at Lilly, Stamford, CT
[31]D2V Clinical, Raleigh, Durham, NC
[32]Statistical Consultant to Actinium Pharmaceuticals, New York, NY
[33]Actinium Pharmaceuticals, New York, NY

## CORRESPONDING AUTHOR

Sergio Giralt, MD; e-mail: GiraltS@mskcc.org.


## PRIOR PRESENTATION

Presented in part at: Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR Annual Tandem Meeting, Orlando, FL, February 15-19, 2023; The European Society of Blood and Marrow Transplantation 49th Annual Meeting, Paris, France, April 23-26, 2023; The European Hematology Association Annual Meeting, Frankfurt, Germany, June 8-11, 2023; and the Society of Nuclear Medicine & Molecular Imaging Annual Meeting, Chicago, IL, June 24-27, 2023.


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## AUTHOR CONTRIBUTIONS

**Conception and design:** Boglarka Gyurkocza, Rajneesh Nath, Zaid Al-Kadhimi, Michael Schuster, Moshe Y. Levy, Hillard M. Lazarus, Brenda M. Sandmaier, John M. Pagel, Vijay Reddy, Madhuri Vusirikala
**Administrative support:** Parameswaran Hari, Neeta Pandit-Taskar, Kathleen McNamara, Jennifer Spross, Elaina Haeuber
**Provision of study materials or patients:** Rajneesh Nath, Mark R. Litzow, Camille Abboud, Nebu Koshy, Patrick Stiff, Parameswaran Hari, George Chen, Zaid Al-Kadhimi, Partow Kebriaei, Mitchell Sabloff, Johnnie J. Orozco, Katarzyna Jamieson, Michael Schuster, Arjun Datt Law, Neeta Pandit-Taskar, Brenda M. Sandmaier, Vijay Reddy, Jennifer Spross, Elaina Haeuber
**Collection and assembly of data:** Boglarka Gyurkocza, Rajneesh Nath, Stuart Seropian, Hannah Choe, Mark R. Litzow, Camille Abboud, Nebu Koshy, Patrick Stiff, Benjamin Tomlinson, James Foran, Parameswaran Hari, George Chen, Zaid Al-Kadhimi, Partow Kebriaei, Mitchell Sabloff, Johnnie J. Orozco, Katarzyna Jamieson, Margarida Silverman, Arjun Datt Law, Neeta Pandit-Taskar, Moshe Y. Levy, Hillard M. Lazarus, Vijay Reddy, Kathleen McNamara, Jennifer Spross, Elaina Haeuber, Madhuri Vusirikala, Avinash Desai
**Data analysis and interpretation:** Boglarka Gyurkocza, Rajneesh Nath, Stuart Seropian, Hannah Choe, Mark R. Litzow, Camille Abboud, Patrick Stiff, Sunil Abhyankar, James Foran, Parameswaran Hari, George Chen, Zaid Al-Kadhimi, Partow Kebriaei, Mitchell Sabloff, Johnnie J. Orozco, Koen Van Besien, Michael Schuster, Arjun Datt Law, Karilyn Larkin, Neeta Pandit-Taskar, Scott D. Rowley, Pashna Munshi, Rachel Cook, Moshe Y. Levy, Hillard M. Lazarus, John M. Pagel, Vijay Reddy, James MacDougall, Jennifer Spross, Elaina Haeuber, Madhuri Vusirikala, Akash Nahar, Avinash Desai, Sergio Giralt
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Randomized Phase III SIERRA Trial of $^{131}$I-Apamistamab Before Allogeneic Hematopoietic Cell Transplantation Versus Conventional Care for Relapsed/Refractory AML**

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**Boglarka Gyurkocza**
**Research Funding:** Actinium Pharmaceuticals (Inst)

**Rajneesh Nath**
**Stock and Other Ownership Interests:** Pfizer
**Honoraria:** AlloVir, Incyte, ADC Therapeutics, Autolus, Alimera Sciences, Bristol Myers Squibb/Celgene/Juno
**Consulting or Advisory Role:** Actinium Pharmaceuticals

**Stuart Seropian**
**Consulting or Advisory Role:** Carrum Health

**Hannah Choe**
**Consulting or Advisory Role:** Actinium Pharmaceuticals, AbbVie, Incyte, REGiMMUNE, Sanofi, Ironwood Pharmaceuticals
**Research Funding:** GlaxoSmithKline, Opna Bio
**Travel, Accommodations, Expenses:** Actinium Pharmaceuticals

**Mark R. Litzow**
**Honoraria:** BeiGene Shanghai, Amgen
**Speakers' Bureau:** BeiGene Shanghai, Amgen
**Research Funding:** Amgen, Astellas Pharma, Actinium Pharmaceuticals, Syndax
**Travel, Accommodations, Expenses:** BeiGene Shanghai, Amgen
**Other Relationship:** Biosight

**Camille Abboud**
**Stock and Other Ownership Interests:** AbbVie, Abbott Laboratories, Gilead Sciences, Bristol Myers Squibb, Johnson & Johnson
**Research Funding:** Selvita (Inst), Forty Seven (Inst), Novartis (Inst)

**Patrick Stiff**
**Honoraria:** MorphoSys
**Consulting or Advisory Role:** CRISPR therapeutics
**Research Funding:** Kite, a Gilead company, Seagen, Gamida Cell, Incyte, Amgen (Inst), MacroGenics (Inst), Actinium Pharmaceuticals (Inst), Pfizer (Inst)

**Benjamin Tomlinson**
**Honoraria:** OncLive Clinical Congress Consultants
**Consulting or Advisory Role:** Bristol Myers Squibb/Celgene, Chimerix
**Research Funding:** Celgene

**Sunil Abhyankar**
**Stock and Other Ownership Interests:** Merck, Pfizer, Lilly, Johnson and Johnson
**Consulting or Advisory Role:** Kite, a Gilead company
**Speakers' Bureau:** Incyte, Therakos
**Research Funding:** CSL Behring
**Travel, Accommodations, Expenses:** Incyte, Therakos

**James Foran**
**Stock and Other Ownership Interests:** Aurinia Pharmaceuticals
**Consulting or Advisory Role:** PeerView, CTI BioPharma Corp, Remix Therapeutics, Cardinal Health, Medscape, Syndax, Autolus Therapeutics
**Research Funding:** AbbVie (Inst), Actinium Pharmaceuticals (Inst), Kura Oncology (Inst), Sellas Life Sciences (Inst), Novartis (Inst), Roivant (Inst), Celgene/Bristol Myers Squibb (Inst), Astellas Pharma (Inst), SERVIER (Inst), Chordia Therapeutics
**Travel, Accommodations, Expenses:** PeerView

**Parameswaran Hari**
**Employment:** Obsidian Therapeutics
**Research Funding:** Millennium (Inst), Celgene (Inst), Onyx (Inst), Spectrum Pharmaceuticals (Inst)

**Zaid Al-Kadhimi**
**Stock and Other Ownership Interests:** Moderna Therapeutics, PACB, INTELLIA THERAPEUTICS, REGENERON, CRISPR therapeutics
**Honoraria:** Sanofi
**Patents, Royalties, Other Intellectual Property:** Own small portion of galaxy medical device company

**Partow Kebriaei**
**Honoraria:** Kite, a Gilead company, Pfizer
**Consulting or Advisory Role:** Jazz Pharmaceuticals
**Travel, Accommodations, Expenses:** Kite, a Gilead company, Pfizer

**Mitchell Sabloff**
**Honoraria:** AbbVie, Astellas Pharma, Bristol Myers Squibb/Celgene, Pfizer, Jazz Pharmaceuticals, Taiho Pharmaceutical
**Research Funding:** Astellas Pharma (Inst), Jazz Pharmaceuticals (Inst), Taiho Pharmaceutical (Inst), Astex Pharmaceuticals (Inst)
**Patents, Royalties, Other Intellectual Property:** Treatment of Acute Myeloid Leukemia
**Travel, Accommodations, Expenses:** Astellas Pharma

**Johnnie J. Orozco**
**Research Funding:** Actinium Pharmaceuticals (Inst)

**Margarida Silverman**
**Research Funding:** Marker Therapeutics (Inst)

**Koen van Besien**
**Leadership:** HemOgenyx
**Stock and Other Ownership Interests:** Hemogeny, Avertix
**Consulting or Advisory Role:** Hemogenyx, SNIPR BIOME, MorphoSys, Incyte, Autolus, ADC Therapeutics, Incyte, Adbio, AstraZeneca, Realta
**Research Funding:** Precision Biosciences, Orca Bio, Bristol Myers Squibb/Celgene, Calibr, Actinium Pharmaceuticals
**Open Payments Link:** https://openpaymentsdata.cms.gov/physician/707406

**Michael Schuster**
**Stock and Other Ownership Interests:** Amgen, Bristol Myers Squibb/Medarex, Merck
**Consulting or Advisory Role:** Novartis, Regeneron
**Speakers' Bureau:** Amgen, Astellas Pharma, AbbVie, Bristol Myers Squibb/Medarex, Beigene, Genentech, Janssen Oncology, Pharmacyclics (Inst), Takeda, epizyme, MorphoSys, Karyopharm Therapeutics, Sobi, Incyte, Sanofi Pasteur, Pfizer, ADC Therapeutics
**Research Funding:** Actinium Pharmaceuticals, Kura Oncology, Equillium, Takeda, Syndax, Regeneron
**Travel, Accommodations, Expenses:** Janssen Oncology, Genentech, Astellas Pharma, AbbVie, BeiGene, Karyopharm Therapeutics, Pfizer, Amgen

**Arjun Datt Law**
**Honoraria:** Kite/Gilead

**Karilyn Larkin**
**Consulting or Advisory Role:** Gilead/Forty Seven
**Research Funding:** Debiopharm Group
**Uncompensated Relationships:** Debiopharm Group

**Neeta Pandit-Taskar**
**Honoraria:** Actinium Pharmaceuticals
**Consulting or Advisory Role:** Actinium Pharmaceuticals
**Speakers' Bureau:** Telix Pharmaceuticals
**Research Funding:** Imaginab (Inst), Regeneron (Inst), Bristol Myers Squibb (Inst), Janssen (Inst), Clarity Pharmaceuticals (Inst), Bayer Health (Inst), Fusion Pharmaceuticals (Inst), Ymabs Therapeutics Inc (Inst)
**Travel, Accommodations, Expenses:** Bayer, Actinium Pharmaceuticals

**Scott D. Rowley**
**Consulting or Advisory Role:** SIRPant Immunotherapeutics, Realta Life Sciences

**Pashna Munshi**
**Consulting or Advisory Role:** Sanofi, Sanofi, Incyte
**Speakers' Bureau:** Incyte, Kite, a Gilead company

**Moshe Y. Levy**
**Stock and Other Ownership Interests:** Actinium Pharmaceuticals, Karyopharm Therapeutics
**Honoraria:** AbbVie, Amgen, AZ, BeiGene, BMS, Genmab, GSK, Incyte, Ipsen, Janssen, Jazz, Karyopharm, Kite, Lilly, PharmaEssentia, Sanofi, Sobi, Seagen, Takeda
**Consulting or Advisory Role:** AbbVie, Amgen, AZ, BeiGene, BMS, Genmab, GSK, Incyte, Ipsen, Janssen, Jazz, Karyopharm, Kite, Lilly, PharmaEssentia, Sanofi, Sobi, Seagen, Takeda
**Speakers' Bureau:** AbbVie, Amgen, AZ, BeiGene, BMS, Genmab, GSK, Incyte, Ipsen, Janssen, Jazz, Karyopharm, Kite, Lilly, PharmaEssentia, Sanofi, Sobi, Seagen, Takeda
**Travel, Accommodations, Expenses:** AbbVie, Amgen, AZ, BeiGene, BMS, Genmab, GSK, Incyte, Ipsen, Janssen, Jazz, Karyopharm, Kite, Lilly, PharmaEssentia, Sanofi, Sobi, Seagen, Takeda

**Hillard M. Lazarus**
**Employment:** Partner Therapeutics, Case Western Reserve University
**Stock and Other Ownership Interests:** Partner Therapeutics
**Honoraria:** Jazz Pharmaceuticals, Actinium Pharmaceuticals, Seagen, Celgene, Pluristem Therapeutics, Bristol Myers Squibb, AstraZeneca, biosight, CSL Behring, GlycoMimetics, Amgen
**Consulting or Advisory Role:** Jazz Pharmaceuticals, Pluristem Therapeutics, Actinium Pharmaceuticals, Seagen, BioSight, Bristol Myers Squibb/Medarex, Celgene, CSL Behring, GlycoMimetics
**Speakers' Bureau:** Seagen, Jazz Pharmaceuticals, AstraZeneca, Amgen
**Travel, Accommodations, Expenses:** Actinium Pharmaceuticals, Seagen, Jazz Pharmaceuticals, BioSight, AstraZeneca, Amgen

**Brenda M. Sandmaier**
**Leadership:** AnaptysBio, Oncoresonse, Inipharm, Frazier Healthcare Ventures, Ranar, Lassen Therapeutics, Sudo Bioscience, Trestle Biotherapeutics
**Stock and Other Ownership Interests:** Blaze Bioscience, AnaptysBio, Oncoresponse, Inipharm, Ranar Therapeutics, Sudo Biosciences, Trestle Biotherapeutics
**Consulting or Advisory Role:** Actinium Pharmaceuticals
**Patents, Royalties, Other Intellectual Property:** Agreement with Actinium for Development of humanized BC8. Cash royalties provided to employer (Fred Hutch)

**John M. Pagel**
**Employment:** Loxo
**Leadership:** Loxo
**Stock and Other Ownership Interests:** Loxo
**Consulting or Advisory Role:** Gilead Sciences, AstraZeneca, Actinium Pharmaceuticals, BeiGene, Loxo, MEI Pharma, TG Therapeutics, MorphoSys, Epizyme

**Vijay Reddy**
**Employment:** D2V Clinical, Actinium Pharmaceuticals
**Leadership:** D2V Clinical
**Stock and Other Ownership Interests:** Actinium Pharmaceuticals, D2V Clinical

**James MacDougall**
**Employment:** Edgewise Therapeutics
**Consulting or Advisory Role:** Vigil Neuro, Actinium Pharmaceuticals, Neurogastrx, MOMA Therapeutics, Enterin Therapeutics, KSQ Therapeutics, Luminopia, Lyra Therapeutics, Storm Therapeutics, Synlogic

**Kathleen McNamara**
**Employment:** Actinium Pharmaceuticals

**Jennifer Spross**
**Employment:** Actinium Pharmaceuticals
**Stock and Other Ownership Interests:** Actinium Pharmaceuticals
**Travel, Accommodations, Expenses:** Actinium Pharmaceuticals

**Madhuri Vusirikala**
**Employment:** Actinium Pharmaceuticals
**Leadership:** Actinium Pharmaceuticals

**Akash Nahar**
**Employment:** Actinium Pharmaceuticals
**Stock and Other Ownership Interests:** Actinium Pharmaceuticals

**Avinash Desai**
**Employment:** Actinium Pharmaceuticals
**Stock and Other Ownership Interests:** Actinium Pharmaceuticals, Johnson & Johnson/Janssen

**Sergio Giralt**
**Honoraria:** Amgen, Jazz Pharmaceuticals, Sanofi
**Consulting or Advisory Role:** Sanofi, Jazz Pharmaceuticals, Amgen, Janssen, Actinuum, Bristol Myers Squibb, Johnson & Johnson, Pfizer, Incyte
**Research Funding:** Celgene (Inst), Miltenyi Biotec (Inst), Johnson & Johnson, Amgen, Actinuum, Sanofi
**Travel, Accommodations, Expenses:** Celgene, Sanofi, Amgen, Jazz Pharmaceuticals, Jazz Pharmaceuticals

No other potential conflicts of interest were reported.