3-16-2023

Ide-cel or standard regimens in relapsed and refractory multiple myeloma

Paula Rodriguez-Otero
Universidad de Navarra
Ravi Vij
Washington University School of Medicine in St. Louis
et al.

ORIGINAL ARTICLE

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

P. Rodriguez-Otero, S. Ailawadhi, B. Arnulf, K. Patel, M. Cavo, A.K. Nooka, S. Manier, N. Callander, L.J. Costa, R. Vij, N.J. Bahlis, P. Moreau, S.R. Solomon, M. Delforge, J. Berdeja, A. Truppel-Hartmann, Z. Yang, L. Favre-Kontula, F. Wu, J. Piasecki, M. Cook, and S. Giralt

ABSTRACT

BACKGROUND

Survival is poor among patients with triple-class–exposed relapsed and refractory multiple myeloma. Idecabtagene vicleucel (ide-cel), a B-cell maturation antigen–directed chimeric antigen receptor (CAR) T-cell therapy, previously led to deep, durable responses in patients with heavily pretreated relapsed and refractory multiple myeloma.

METHODS

In this international, open-label, phase 3 trial involving adults with relapsed and refractory multiple myeloma who had received two to four regimens previously (including immunomodulatory agents, proteasome inhibitors, and daratumumab) and who had disease refractory to the last regimen, we randomly assigned patients in a 2:1 ratio to receive either ide-cel (dose range, 150×10^6 to 450×10^6 CAR-positive T cells) or one of five standard regimens. The primary end point was progression-free survival. Key secondary end points were overall response (partial response or better) and overall survival. Safety was assessed.

RESULTS

A total of 386 patients underwent randomization: 254 to ide-cel and 132 to a standard regimen. A total of 66% of the patients had triple-class–refractory disease, and 95% had daratumumab-refractory disease. At a median follow-up of 18.6 months, the median progression-free survival was 13.3 months in the ide-cel group, as compared with 4.4 months in the standard-regimen group (hazard ratio for disease progression or death, 0.49; 95% confidence interval, 0.38 to 0.65; P<0.001). A response occurred in 71% of the patients in the ide-cel group and in 42% of those in the standard-regimen group (P<0.001); a complete response occurred in 39% and 5%, respectively. Data on overall survival were immature. Adverse events of grade 3 or 4 occurred in 93% of the patients in the ide-cel group and in 75% of those in the standard-regimen group. Among the 225 patients who received ide-cel, cytokine release syndrome occurred in 88%, with 5% having an event of grade 3 or higher, and investigator-identified neurotoxic effects occurred in 15%, with 3% having an event of grade 3 or higher.

CONCLUSIONS

Ide-cel therapy significantly prolonged progression-free survival and improved response as compared with standard regimens in patients with triple-class–exposed relapsed and refractory multiple myeloma who had received two to four regimens previously. The toxicity of ide-cel was consistent with previous reports. (Funded by 2seventy bio and Celgene, a Bristol-Myers Squibb company; KarMMa-3 ClinicalTrials.gov number, NCT03651128.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Giralt can be contacted at giralts@mskcc.org or at the Department of Medicine, Adult Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center, 1275 York Ave., Box 235, New York, NY, 10065.

This article was published on February 10, 2023, at NEJM.org.

N Engl J Med 2023;388:1002-14.
DOI: 10.1056/NEJMoa2213614

The treatment landscape for relapsed and refractory multiple myeloma has evolved with the use of immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies in doublet, triplet, or quadruplet combinations in the context of first-line therapy and treatment for relapsed disease.[1-7] Although these combinations have helped control disease, relapse is common.[8] Consequently, patients have triple-class exposure earlier in their treatment course and have limited treatment options.[7] Responses to standard therapies in the triple-class–exposed population are suboptimal, leading to poor survival outcomes (median progression-free survival, 3 to 5 months; median overall survival, <13 months).[9-12] A standard-care approach in this patient population has not been established.[13]

Chimeric antigen receptor (CAR) T-cell therapies that target the B-cell maturation antigen (BCMA) expressed predominantly on myeloma cells[14-16] have recently been approved for the treatment of heavily pretreated relapsed or refractory multiple myeloma.[17,18] In the phase 2 KarMMa trial, the use of the BCMA-directed CAR T-cell therapy idecabtagene vicleucel (ide-cel, also called bb2121) led to deep, durable responses in triple-class–exposed, heavily pretreated patients with relapsed and refractory multiple myeloma.[19] In that trial, a response was observed in 73% of the patients, and the median progression-free survival was 8.8 months. The incidence of grade 3 or 4 cytokine release syndrome was 5%, and the incidence of grade 3 neurotoxic effects was 3%. The toxicity of ide-cel in the KarMMa trial was consistent with that observed in a previous study.[20] These data supported the approval of ide-cel use after the receipt of at least four previous lines of therapy in patients in the United States and after the receipt of at least three previous therapies in patients in the European Union.[17,19,21,22] We conducted KarMMa-3, a randomized clinical trial to evaluate the CAR T-cell therapy ide-cel as compared with standard regimens in patients with triple-class–exposed relapsed and refractory multiple myeloma who had received two to four lines of therapy previously and who had disease refractory to the last regimen.

METHODS

TRIAL DESIGN AND PATIENTS

In this international, randomized, open-label, phase 3 trial, we enrolled patients 18 years of age or older who had received two to four previous therapies including daratumumab, an immunomodulatory agent, and a proteasome inhibitor for at least two consecutive cycles and who had documented disease progression within 60 days after the completion (last dose) of the last therapy (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients had measurable disease and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability). A description of the trial design and the eligibility and exclusion criteria are provided in the protocol, available at NEJM.org.

A Quick Take is available at NEJM.org

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 2:1 ratio with the use of an interactive response system to receive either ide-cel or one of five standard regimens that had been chosen before randomization on the basis of the patient's most recent treatment regimen and investigator discretion. Randomization was stratified according to the patient's age (<65 vs. ≥65 years), number of previous regimens (2 vs. 3 or 4), and high-risk cytogenetic profile (defined as t[4;14], t[14;16], or del[17p]; present vs. absent or unknown).

Ide-cel was manufactured after leukapheresis, as previously described.[19,20] After successful manufacturing, patients underwent lymphodepletion with fludarabine (30 mg per square meter of body-surface area per day) and cyclophosphamide (300 mg per square meter per day) for 3 consecutive days, followed by 2 days of no treatment before the administration of a single infusion of ide-cel (target dose range, 150×10^6 to 450×10^6 CAR-positive T cells; doses of $\leq540\times10^6$ CAR-positive T cells were permitted) (see the Methods section in the Supplementary Appendix).

Patients in the standard-regimen group were treated with one of the following regimens according to the investigator's discretion: daratumumab, pomalidomide, and dexamethasone; daratumumab, bortezomib, and dexamethasone; ixazomib, lenalidomide, and dexamethasone; carfilzomib and dexamethasone; or elotuzumab, pomalidomide, and dexamethasone. The regimen was continued until the occurrence of disease progression or unacceptable toxic effects or until withdrawal from the trial. Patients could not receive the same standard regimen as their last previous treatment before trial entry (see

the Methods section in the Supplementary Appendix).

All the patients were followed for disease progression monthly for 24 months, then every 3 months until the occurrence of disease progression. For the analysis of overall survival, patients were followed every 3 months after the occurrence of disease progression until the end of the trial (5 years after the randomization of the last patient).

TRIAL OVERSIGHT

The KarMMa-3 trial was designed by the sponsors, 2seventy bio and Celgene (a Bristol-Myers Squibb company), in collaboration with academic investigators and was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol was approved by the institutional review board or independent ethics committee at each participating center before trial initiation. All the patients provided written informed consent. Medical writing assistance was funded by Bristol Myers Squibb. The authors affirm the accuracy and completeness of the reported data and vouch for the adherence of the trial to the protocol. All the authors contributed to the development of the manuscript (including the first draft) and approved the final version.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival as assessed by the independent response committee according to International Myeloma Working Group (IMWG) criteria.[23] Progression-free survival was defined as the time from randomization to the first occurrence of disease progression or death from any cause. The primary efficacy analysis was conducted in the intention-to-treat population, which included all the patients who had undergone randomization.

Key secondary end points were response (defined as a partial response or better), as assessed by the independent response committee, and overall survival. Additional secondary end points included the time to response, duration of response, detection of minimal residual disease (MRD), cellular kinetic and pharmacokinetic profiles, and safety.

Progression-free survival and overall response were analyzed in prespecified patient subgroups, which were defined according to age group (<65 years vs. ≥65 years; <65 years vs. 65 to 74 years vs. 75 to 84 years), geographic region (North America vs. Europe vs. Japan), sex, race (White vs. non-White; White vs. Asian vs. Black vs. other), ethnic group (Hispanic or Latino vs. not Hispanic or Latino), anti-CD38–class refractory disease (yes vs. no), daratumumab-refractory disease (yes vs. no), double-class–refractory disease (yes vs. no), triple-class–refractory disease (yes vs. no), penta-refractory disease (yes vs. no), Revised International Staging System stage at baseline (I or II vs. III), tumor burden at baseline (<50% vs. ≥50%), extramedullary plasmacytoma (yes vs. no), number of previous antimyeloma regimens (2 vs. 3 or 4; 2 vs. 3 vs. 4), and high-risk cytogenetic abnormalities (presence vs. absence or unknown). Double-class–refractory disease was defined as disease refractory to at least one each of an immunomodulatory agent and a proteasome inhibitor. Triple-class–refractory disease was defined as disease refractory to at least one each of an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody. Penta-refractory disease was defined as disease refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 or higher. Cytokine release syndrome was graded according to Lee's criteria (Table S2).[24] Neurotoxic events were identified by the investigators and graded according to the CTCAE. In the ide-cel group, the treated population of patients who underwent leukapheresis or received bridging therapy, lymphodepleting chemotherapy, or ide-cel was used in the assessment of adverse events. The safety population of patients who received ide-cel was used in the assessment of treatment-related adverse events, investigator-identified neurotoxic events, and cytokine release syndrome. In the standard-regimen group, the treated and safety populations both included all the patients who had received any dose of daratumumab, pomalidomide, lenalidomide, bortezomib, ixazomib, carfilzomib, elotuzumab, or dexamethasone.

STATISTICAL ANALYSIS

The primary efficacy analysis for progression-free survival was conducted with the use of a stratified log-rank test in the intention-to-treat population. Two interim analyses were planned:

one analysis, for futility, was to be based on an information fraction of 33%; and the second analysis, for efficacy, on an information fraction of approximately 80%. The type I error was controlled at 2.5% (one-sided) across interim analyses with an O'Brien–Fleming boundary. We calculated that a planned sample of 381 patients would provide the trial with 94% power to detect an improvement in median progression-free survival from 9 months with standard regimens to 14 months with ide-cel at the final analysis, with 289 events of disease progression or death. The median progression-free survival and two-sided 95% confidence intervals were estimated with the use of the Kaplan–Meier method, and hazard ratios were estimated with Cox proportional-hazards models. The present interim (second) analysis for efficacy was performed after the occurrence of 242 events of disease progression or death, with a boundary for statistical significance of P<0.014 (one-sided according to the statistical analysis plan; two-sided P values are reported). Efficacy end points were assessed in hierarchical fashion in the following order: progression-free survival, response, and overall survival. The 95% confidence intervals were not adjusted for multiplicity and cannot be used as hypothesis tests. Further details are provided in the Methods section in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT

Patients were enrolled from May 2019 through April 2022 at 49 sites in 12 countries (see the Supplementary Appendix). A total of 254 patients were randomly assigned to the ide-cel group and 132 to the standard-regimen group (Fig. 1 and Table 1). The representativeness of the trial population is shown in Table S3. In the standard-regimen group, 43 patients were to receive daratumumab, pomalidomide, and dexamethasone; 30 carfilzomib and dexamethasone; 30 elotuzumab, pomalidomide, and dexamethasone; 22 ixazomib, lenalidomide, and dexamethasone; and 7 daratumumab, bortezomib, and dexamethasone. The efficacy evaluation in the intention-to-treat population included the 29 patients in the ide-cel group and 6 patients in the standard-regimen group who did not receive the assigned therapy.

Of the 254 patients in the ide-cel group, 249 underwent leukapheresis; 1 patient received bridging therapy without undergoing leukapheresis. Thus, the treated population in the ide-cel group included 250 patients. Three patients in this group could not receive ide-cel because of cell manufacturing failure (see the Results section in the Supplementary Appendix). A total of 225 patients received an ide-cel infusion, at a median dose of 445×10^6 CAR-positive T cells (range, 175×10^6 to 529×10^6); in the standard-regimen group, 126 patients received treatment (Fig. 1 and Table S4).

The characteristics of the patients at baseline were generally balanced in the two groups (Table 1), except for Black race (7% of the patients in the ide-cel group vs. 14% of those in the standard-regimen group). A total of 107 patients (42%) in the ide-cel group and 61 (46%) in the standard-regimen group had high-risk cytogenetic abnormalities. In both groups, the median time since diagnosis was approximately 4 years, and the median time to progression during the last previous antimyeloma therapy was approximately 7 months. The median number of previous regimens was 3 (range, 2 to 4) in each group (Table S5). A total of 348 patients (90%) had disease that was refractory to immunomodulatory agents, 284 (74%) disease that was refractory to proteasome inhibitors, and 365 (95%) disease that was refractory to daratumumab. In the overall trial population, 253 patients (66%; 164 [65%] in the ide-cel group and 89 [67%] in the standard-regimen group) had triple-class–refractory disease.

EFFICACY

At a median follow-up (from randomization to the data-cutoff date of April 18, 2022) of 18.6 months (range, 0.4 to 35.4) for this interim analysis, 242 events of disease progression or death (information fraction, 84%) were noted. In the intention-to-treat population, progression-free survival was significantly longer in the ide-cel group than in the standard-regimen group (median, 13.3 months [95% confidence interval {CI}, 11.8 to 16.1] vs. 4.4 months [95% CI, 3.4 to 5.9]; hazard ratio for disease progression or death, 0.49; 95% CI, 0.38 to 0.65; P<0.001 by a two-sided log-rank test) (Fig. 2). The progression-free survival at 6 months was 73% in the ide-cel group and 40% in the standard-regimen group;

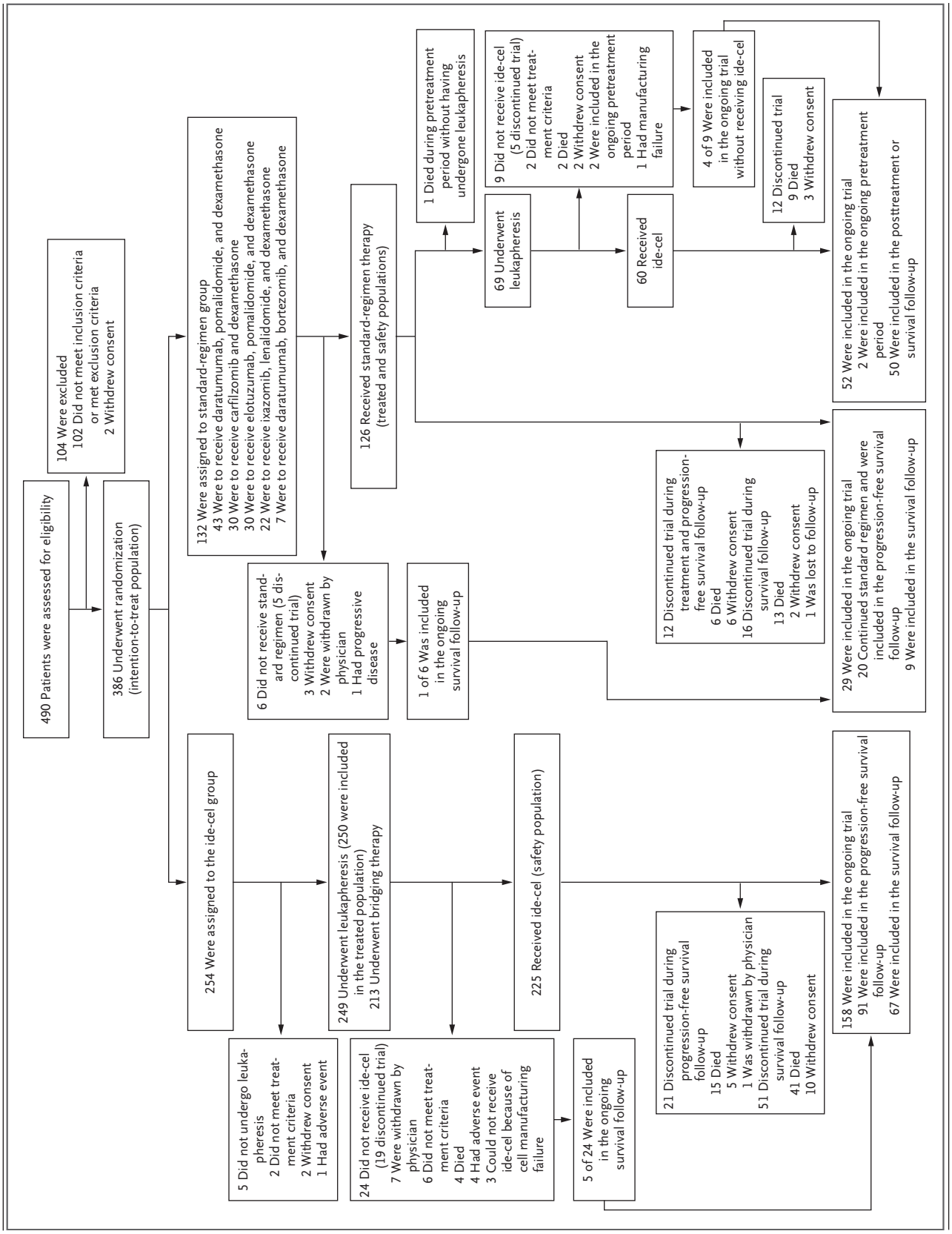

Figure 1 (facing page). Randomization, Treatment, and Follow-up of the Patients.

In the standard-regimen group, one of five standard regimens was chosen before randomization for each patient by the investigator. The treated population included all the patients in the intention-to-treat (randomized) population who underwent leukapheresis or received bridging therapy, lymphocyte-depleting chemotherapy, or idecabtagene vicleucel (ide-cel; ide-cel group) or who received any dose of daratumumab, pomalidomide, lenalidomide, bortezomib, ixazomib, carfilzomib, elotuzumab, or dexamethasone (standard-regimen group). The safety population included all the patients who received any trial treatment. At the data-cutoff date (April 18, 2022), efficacy and safety data for patients who had been treated with standard regimens and had disease progression and received ide-cel subsequently were not yet available. Of 254 patients in the ide-cel group in the intention-to-treat population, 249 underwent leukapheresis and 1 received bridging therapy but not leukapheresis, leading to a total of 250 patients in the treated population. Of these 250 patients, 249 underwent leukapheresis, 213 received bridging therapy, 227 received lymphocyte-depleting chemotherapy, and 225 received a single infusion of ide-cel.

12-month progression-free survival was 55% and 30%, respectively. The progression-free survival benefit with ide-cel therapy was consistently observed across prespecified subgroups, including those defined according to age, race, number of previous regimens, or presence or absence of high-risk cytogenetic abnormalities, extramedullary disease, high tumor burden, or triple-class–refractory status (Fig. S1).

Ide-cel therapy resulted in a significantly higher percentage of patients with a response than standard regimens: 181 of 254 patients (71%; 95% CI, 66 to 77) in the ide-cel group and 55 of 132 patients (42%; 95% CI, 33 to 50) in the standard-regimen group had a partial response or better (odds ratio, 3.47; 95% CI, 2.24 to 5.39; P<0.001 by a two-sided Cochran–Mantel–Haenszel test) (Table 2 and Figs. S2 and S3). The percentage of patients with a complete response or stringent complete response were higher with ide-cel than with standard regimens (39% vs. 5%). The median time to response was 2.9 months (range, 0.5 to 13.0) among patients in the ide-cel group and 2.1 months (range, 0.9 to 9.4) among those in the standard-regimen group. The median duration of response was 14.8 months (95% CI, 12.0 to 18.6) in the ide-cel group and 9.7 months (95% CI, 5.4 to 16.3) in the standard-regimen group. MRD-negative status within 3 months before the occurrence of at least a complete response was confirmed in 51 patients (20%) in the ide-cel group and 1 patient (1%) in the standard-regimen group (Table S6). Overall survival data were immature and remained blinded at data cutoff.

CELLULAR KINETICS

At the data-cutoff date (March 1, 2022), a total of 224 patients could be evaluated for ide-cel pharmacokinetics. After infusion, CAR-positive T cells underwent rapid multi-log expansion; maximum expansion occurred at a median of 11 days (Fig. S4). Exploratory analyses indicated that higher quartiles of ide-cel expansion were associated with longer progression-free survival (Fig. S5). Considerable interpatient variability in cell expansion (a situation inherent to CAR T-cell biology) was noted, and the lowest quartile of expansion was present across all actual dose levels.

BCMA EXPRESSION

Although evaluable samples from ide-cel–treated patients at disease progression were limited, BCMA-expressing bone marrow tumor cells were observed in all 6 evaluable biopsy samples. Soluble BCMA was detectable at disease progression in 82 of 84 evaluable patients (see the Results section in the Supplementary Appendix).

SAFETY

Adverse events were reported in 248 of 250 patients (99%) in the ide-cel group and in 123 of 126 (98%) in the standard-regimen group, with grade 3 or 4 events occurring in 233 (93%) and 94 (75%), respectively, and grade 5 events in 36 (14%) and 8 (6%), respectively (Table 3 and Table S7). The most common hematologic adverse events were neutropenia (in 78% of the patients in the ide-cel group and in 44% of those in the standard-regimen group), anemia (in 66% and 36%, respectively), and thrombocytopenia (in 54% and 29%). Among patients in the ide-cel group in whom grade 3 or 4 thrombocytopenia or neutropenia that persisted beyond 1 month developed, the median time to recovery was 1.9 months (95% CI, 1.5 to 2.1) after thrombocytopenia and 1.7 months (95% CI, 1.5 to 1.9) after neutropenia (Figs. S6 and S7 and Table S8).

Infection occurred in 146 patients (58%) in the ide-cel group and in 68 patients (54%) in the

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Ide-cel (N=254)	Standard Regimen (N=132)
Age		
Median (range) — yr	63 (30–81)	63 (42–83)
Distribution — no. (%)		
<65 yr	150 (59)	78 (59)
≥65 yr	104 (41)	54 (41)
≥75 yr	12 (5)	9 (7)
Male sex — no. (%)	156 (61)	79 (60)
Race — no. (%)†		
Asian	7 (3)	5 (4)
Black	18 (7)	18 (14)
White	172 (68)	78 (59)
Other	3 (1)	4 (3)
Not available or not reported	54 (21)	27 (20)
Median time from initial diagnosis to screening (range) — yr	4.1 (0.6–21.8)‡	4.0 (0.7–17.7)
Median time to progression during last previous antimyeloma therapy (range) — mo	7.1 (0.7–67.7)	6.9 (0.4–66.0)
Extramedullary disease — no. (%)§	61 (24)	32 (24)
High tumor burden — no. (%)¶	71 (28)	34 (26)
ECOG performance-status score — no. (%)‖		
0	120 (47)	66 (50)
1	133 (52)	62 (47)
≥2	1 (<1)	4 (3)
R-ISS disease stage — no. (%)**		
I	50 (20)	26 (20)
II	150 (59)	82 (62)
III	31 (12)	14 (11)
Unknown	23 (9)	10 (8)
Cytogenetic abnormalities — no. (%)		
High-risk abnormality††	107 (42)	61 (46)
del(17p)	66 (26)	42 (32)
t(4;14)	43 (17)	18 (14)
t(14;16)	8 (3)	4 (3)
Other cytogenetic abnormalities		
1q gain or amplification	125 (49)	51 (39)
13q14 deletion	85 (33)	40 (30)
1p deletion	17 (7)	8 (6)
13q34 monosomy	51 (20)	27 (20)
t(14;20)	2 (1)	3 (2)
Median no. of previous regimens (range)	3 (2–4)	3 (2–4)
Previous autologous HSCT — no. (%)	214 (84)	114 (86)
1 Transplantation	167 (66)	87 (66)
>1 Transplantation	47 (19)	27 (20)

Table 1. (Continued.)

Characteristic	Ide-cel (N=254)	Standard Regimen (N=132)
Previous radiation therapy — no. (%)	90 (35)	46 (35)
Refractory status — no. (%)		
Immunomodulatory agent	224 (88)	124 (94)
Lenalidomide	186 (73)	104 (79)
Pomalidomide	127 (50)	70 (53)
Thalidomide	10 (4)	2 (2)
Proteasome inhibitor	189 (74)	95 (72)
Bortezomib	112 (44)	60 (45)
Carfilzomib	104 (41)	43 (33)
Ixazomib or ixazomib citrate	35 (14)	23 (17)
Anti-CD38 monoclonal antibody	242 (95)	124 (94)
Daratumumab	242 (95)	123 (93)
Isatuximab	1 (<1)	1 (1)
Double-class–refractory disease‡‡	169 (67)	91 (69)
Triple-class–refractory disease§§	164 (65)	89 (67)
Penta-refractory disease¶¶	15 (6)	5 (4)

* The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. HSCT denotes hematopoietic stem-cell transplantation, and ide-cel idecabtagene vicleucel.
† Race was reported according to the data in the electronic medical record, with no prospective guidance from the sponsor.
‡ The minimum value of the range represents the second-lowest value in the database, because the lowest value was determined to be a data-entry error that was corrected in the database after the database lock. The patient whose data were incorrectly entered had a time from initial diagnosis to screening of 3.2 years, which was incorrectly reported as 0.2 years.
§ Extramedullary disease included extramedullary soft-tissue–only disease as well as soft-tissue bone-related plasmacytomas.
¶ A high tumor burden was defined as at least 50% CD138-positive plasma cells in bone marrow.
‖ Eastern Cooperative Oncology Group (ECOG) performance status is assessed on a 5-point scale, with higher scores indicating greater disability. All the patients had an ECOG score of 0 or 1 at screening, but the score may have been greater than 1 at baseline (randomization).
** The disease stage as determined on the derived International Staging System (ISS) was calculated with the use of baseline values of albumin and β_2-microglobulin. The disease stage as assessed on the Revised ISS (R-ISS) was derived on the basis of baseline ISS stage, cytogenetic abnormality, and serum lactate dehydrogenase level.
†† High-risk cytogenetic abnormalities included del(17p), t(4;14), and t(14;16).
‡‡ Double-class–refractory disease was defined as disease refractory to at least one each of an immunomodulatory agent and a proteasome inhibitor.
§§ Triple-class–refractory disease was defined as disease refractory to at least one each of a immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.
¶¶ Penta-refractory disease was defined as disease refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.

standard-regimen group; grade 3 or 4 events occurred in 61 (24%) and 23 (18%), respectively, and grade 5 events in 11 (4%) and 3 (2%), respectively (Table 3). The most common infections were upper respiratory tract infection (in 29 patients [12%] in the ide-cel group and in 9 [7%] in the standard-regimen group) and pneumonia (in 26 [10%] and 9 [7%], respectively). In the ide-cel group, infection occurred during or after the infusion in 120 of 146 patients (82%).

Serious adverse events occurred in 130 patients (52%) in the ide-cel group and in 48 patients (38%) in the standard-regimen group (Table S9). Grade 5 treatment-related adverse events occurred in 6 of 225 patients (3%) in the ide-cel group and in 1 of 126 patients (1%) in the standard-regimen group; the most common of these events was sepsis, which occurred in 5 patients (2%) and 1 patient (1%), respectively (Table S10). The incidence of second primary

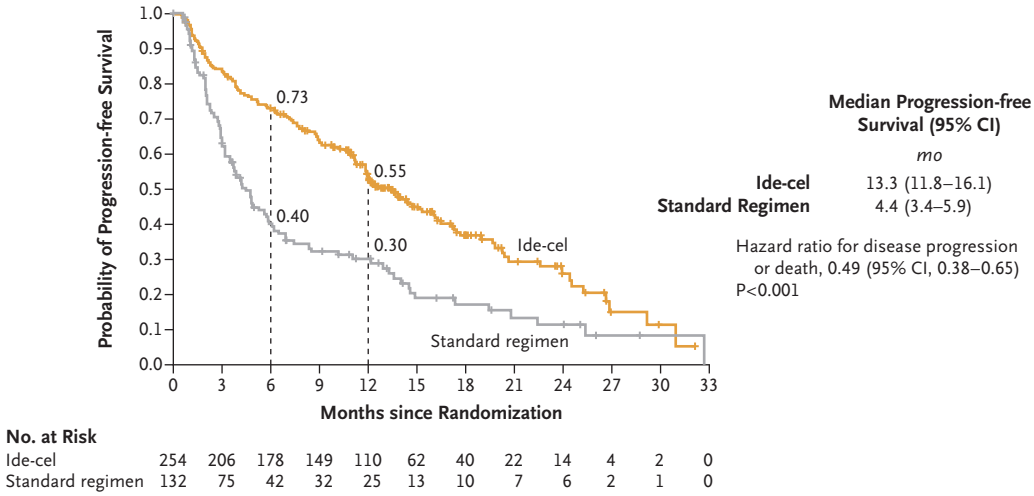

Figure 2. Progression-free Survival (Intention-to-Treat Population).

Progression-free survival was assessed by the independent response committee on the basis of International Myeloma Working Group criteria.[23] The P value was based on a stratified two-sided log-rank test. Data at the dashed lines show the probability of progression-free survival at 6 months and 12 months. Tick marks indicate censored data.

cancer was similar in the ide-cel group and the standard-regimen group (6% and 4%, respectively) (Table S11).

Cytokine release syndrome occurred in 197 of 225 patients (88%) who received ide-cel and was mostly of grade 1 or 2 (in 186 [83%]). A total of 11 patients (5%) had an event of grade 3 or higher; 9 patients (4%) had grade 3 or 4 cytokine release syndrome, and 2 (1%) had grade 5 cytokine release syndrome (Table 3 and Table S12). The causes of death in these 2 patients were a decline of organ function (in 1 patient) and concomitant grade 5 candida-related sepsis (in 1). The median time to the first onset of cytokine release syndrome was 1 day (range, 1 to 14), and the median duration was 3.5 days (range, 1 to 51). Cytokine release syndrome was primarily managed with the use of tocilizumab (in 161 of 225 patients [72%]) and glucocorticoids (in 64 [28%]).

Investigator-identified neurotoxic events occurred in 34 of 225 patients (15%) in the ide-cel group and were mostly of grade 1 or 2 (in 12%); a total of 7 patients (3%) had a neurotoxic event of grade 3 or higher (Table 3 and Table S13). The median time to the first onset of a neurotoxic event (from the infusion day+1) was 3 days (range, 1 to 317), and the median duration was 2 days (range, 1 to 37). Neurotoxic events were managed with glucocorticoids in 15 of 225 patients (7%). Encephalopathy was reported in 1 patient 317 days after the ide-cel infusion; the event was considered by the investigator to be related to worsening pneumonia and to *Clostridium difficile* colitis, not to treatment with ide-cel.

In the intention-to-treat population, 109 patients (28%) died during the trial: 75 (30%) in the ide-cel group and 34 (26%) in the standard-regimen group. Death was most commonly due to disease progression (in 44 patients [17%] in the ide-cel group and in 23 [17%] in the standard-regimen group) (Table S14). The incidence of death from infectious disease was similar in the two groups (12 patients [5%] in the ide-cel group and 6 [5%] in the standard-regimen group). Further details are provided in the Results section in the Supplementary Appendix.

DISCUSSION

The KarMMa-3 trial was a phase 3, randomized, clinical trial for the direct comparison of a CAR T-cell therapy with standard regimens in triple-class–exposed relapsed and refractory multiple myeloma. Although multiple therapeutic regimens including immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies are available, the increasing use of daratumumab-based triplet and quadruplet combinations in the

Table 2. Treatment Response as Assessed by Independent Response Committee (Intention-to-Treat Population) and Duration of Response.*

Variable	Ide-cel (N=254)	Standard Regimen (N=132)	P Value
Overall response			
No. of patients with response	181	55	
Percentage of patients with response (95% CI)†	71 (66–77)	42 (33–50)	<0.001‡
Complete response — no. (%)			
No. of patients with complete response	98	7	
Percentage of patients with complete response (95% CI)†	39 (33–45)	5 (2–9)	
Best overall response — no. (%)			
Stringent complete response	90 (35)	6 (5)	
Complete response	8 (3)	1 (1)	
Very good partial response	55 (22)	13 (10)	
Partial response	28 (11)	35 (27)	
Minimal response	4 (2)	9 (7)	
Stable disease	31 (12)	48 (36)	
Progressive disease	24 (9)	10 (8)	
Response could not be evaluated or was not reported§	14 (6)	10 (8)	
Median duration of response (95% CI) — mo¶	14.8 (12.0–18.6)	9.7 (5.4–16.3)	

* Definitions of response and disease progression were modified from International Myeloma Working Group (IMWG) criteria[23] (see the Supplementary Appendix). An overall response was defined as a partial response or better. Complete response was defined as a complete response or a stringent complete response. A stringent complete response was defined as a complete response with a normal serum free light-chain ratio and an absence of clonal plasma cells according to the IMWG response criteria. Percentages may not total 100 because of rounding.
† The confidence interval is a two-sided Wald confidence interval.
‡ The two-sided P value is from the Cochran–Mantel–Haenszel test, with stratification according to stratification factors.
§ The analysis included patients who did not have any response-assessment data or whose only assessment was that the response was not evaluable.
¶ Duration of response was assessed among patients who had a response as assessed by the independent response committee on the basis of IMWG criteria.

context of first-line therapy and in patients with a first relapse limits treatment options in second relapse and beyond. In this patient population with hard-to-treat disease, ide-cel therapy resulted in significantly longer progression-free survival than standard regimens, with a 51% lower risk of disease progression or death. In addition, treatment with ide-cel resulted in a significantly higher percentage of patients with a response and with deeper responses than were observed in the standard-regimen group. The efficacy of ide-cel therapy was striking considering that 65% of patients had triple-class–refractory disease in a short time from diagnosis (4 years), with disease relapse at a median of approximately 7 months during the last previous regimen.

In this trial, the median progression-free survival in the standard-regimen group was 4.4 months, a finding that is consistent with real-world data in later lines of therapy. A recent real-world analysis showed that patients who had been exposed to five previous regimens within a median of no more than 4 years since diagnosis had a median progression-free survival of just 3.7 months.[11] In addition, the observational LocoMMotion study, which involved patients with triple-class–exposed relapsed or refractory (or both) multiple myeloma and in which 74% of the patients had triple-class–refractory disease, showed poor survival (median progression-free survival, 4.6 months; median overall survival, 12.4 months) with 92 unique standard regimens and a median of four previous lines of therapy.[10] These obser-

Table 3. Adverse Events in the Treated Population and Cytokine Release Syndrome and Neurotoxic Events in the Safety Population.

Event	Ide-cel (N=250)			Standard Regimen (N=126)		
	Any Grade	Grade 3 or 4	Grade 5	Any Grade	Grade 3 or 4	Grade 5
Any adverse event — no. (%)*	248 (99)	233 (93)	36 (14)†	123 (98)	94 (75)	8 (6)†
Hematologic event	224 (90)	218 (87)	0	90 (71)	75 (60)	0
Neutropenia	195 (78)	189 (76)	0	55 (44)	50 (40)	0
Anemia	165 (66)	127 (51)	0	45 (36)	23 (18)	0
Thrombocytopenia	136 (54)	106 (42)	0	36 (29)	22 (17)	0
Lymphopenia	73 (29)	70 (28)	0	25 (20)	23 (18)	0
Leukopenia	72 (29)	71 (28)	0	15 (12)	11 (9)	0
Gastrointestinal event	182 (73)	13 (5)	0	65 (52)	5 (4)	0
Nausea	112 (45)	4 (2)	0	34 (27)	0	0
Diarrhea	85 (34)	4 (2)	0	30 (24)	4 (3)	0
Constipation	67 (27)	0	0	9 (7)	0	0
Vomiting	51 (20)	0	0	11 (9)	0	0
Other adverse event						
Infection	146 (58)	61 (24)	11 (4)	68 (54)	23 (18)	3 (2)
Hypophosphatemia	78 (31)	50 (20)	0	10 (8)	3 (2)	0
Hypokalemia	78 (31)	12 (5)	0	14 (11)	1 (1)	0
Fatigue	69 (28)	4 (2)	0	44 (35)	3 (2)	0
Pyrexia	69 (28)	2 (1)	0	22 (17)	1 (1)	0
Headache	59 (24)	0	0	24 (19)	1 (1)	0
Hypomagnesemia	52 (21)	2 (1)	0	6 (5)	1 (1)	0
Dyspnea	44 (18)	4 (2)	0	27 (21)	2 (2)	0
Cytokine release syndrome — no./total no. (%)‡	197/225 (88)	9/225 (4)	2/225 (1)§	0/126	0/126	0/126
Neurotoxic event — no./total no. (%)¶	34/225 (15)	7/225 (3)	0/225	0/126	0/126	0/126

* Shown are adverse events that occurred after randomization in at least 20% of the patients in the treated population in either group. The treated population included all the patients in the intention-to-treat population (randomized population) who underwent leukapheresis or received bridging therapy, lymphocyte-depleting chemotherapy, or ide-cel (ide-cel group) or who received any dose of daratumumab, pomalidomide, lenalidomide, bortezomib, ixazomib, carfilzomib, elotuzumab, or dexamethasone (standard-regimen group). For patients in the standard-regimen group who underwent leukapheresis in preparation for planned ide-cel treatment during documented disease progression while they were receiving a standard regimen, only adverse events that occurred before leukapheresis were included. Cytokine release syndrome and investigator-identified neurotoxic events were reported in the safety population, which included all the patients who received any trial treatment.

† Grade 5 all-cause adverse events according to system organ class in the ide-cel group and the standard-regimen group were as follows: general disorders and administration-site conditions (in 15 [6%] and 4 [3%] patients, respectively; infections and infestations (in 11 [4%] and 3 [2%]); benign, malignant, and unspecified neoplasms including cysts and polyps (in 4 [2] and 0); immune system disorders (in 2 [1%] and 0); nervous system disorders (in 2 [1%] and 0); respiratory, thoracic, and mediastinal disorders (in 2 [1%] and 1 [1%]); and renal and urinary disorders (in 1 [<1%] and 0). Further details are provided in Table S7.

‡ The clustered term includes the preferred term. Cytokine release syndrome was graded according to modified Lee's criteria.[24] Maximum-grade events are reported; patients could have had more than one event.

§ Grade 1 cytokine release syndrome developed in one patient on the same day of the ide-cel infusion, with the grade of the event increasing to grade 2 on day 3. After a decline in organ function, acute myocardial infarction potentially related to anemia, and rapid atrial flutter, the patient died on day 6. The second patient died 21 days after ide-cel infusion from grade 5 cytokine release syndrome and concomitant grade 5 candida-related sepsis. In both patients, the cytokine release syndrome was treated with tocilizumab, anakinra, and dexamethasone.

¶ Investigator-identified neurotoxic events included immune effector cell–associated neurotoxicity syndrome reported by the investigator as a neurologic toxic effect. Maximum-grade events are reported; patients could have had more than one event.

vations reflect the lack of an established standard of care in triple-class–exposed relapsed or refractory (or both) multiple myeloma, a situation that further emphasizes the need for new treatments. The standard regimens that were used in the KarMMa-3 trial represent available treatments in various countries and allowed investigators to choose the most appropriate regimen on the basis of the patient's previous treatment exposure. The use of daratumumab-based combinations is supported by reports of a median progression-free survival of approximately 9 months among patients with disease refractory to an immunomodulatory agent and daratumumab and by the finding that combination therapy can potentially overcome refractoriness to individual agents.[25,26] The benefit of ide-cel was observed regardless of the number of previous regimens (two, three, or four). As newer treatments become available, including recent and upcoming approvals for BCMA-targeting bispecific antibodies, treatment sequencing will be an important consideration.

In this trial, most patients who received ide-cel had grade 1 cytokine release syndrome that resolved within 5 days; events of grade 3 or higher were reported in 5% of the patients. The incidence of high-grade neurotoxic events (grade ≥3) that was reported in the KarMMa-3 trial (3%) was consistent with the observations in the KarMMa and CRB-401 trials; neurotoxic events of any grade mostly resolved within 5 days.[19,20] Two patients had grade 5 cytokine release syndrome: one after a decline in organ function, and one from concomitant grade 5 candida-related sepsis. The incidence of hematologic toxic effects was higher with ide-cel than with standard regimens. Although neutropenia was more common in the ide-cel group than in the standard-regimen group, the incidence of infection was not proportionally higher than with standard regimens. Overall, the incidence, type, and severity distribution of the adverse events that were observed with ide-cel therapy in the KarMMa-3 trial were consistent with those of previous studies, with no new safety signals identified.[19,20]

Potential limitations of this trial include imbalance in the proportion of Black patients; however, subgroup analyses showed no apparent difference in treatment effect according to race. The investigator's choice of standard regimens in this trial reflected available treatment options and was consistent with trial design recommendations,[27] but this situation may have introduced treatment heterogeneity in the standard-regimen group. Finally, the mechanisms of ide-cel resistance remain to be elucidated. In contrast to CD19-directed CAR T-cell therapy for acute lymphocytic leukemia,[28,29] in which antigen loss is relatively common, BCMA antigen loss was reported in only 3% of the patients in the KarMMa trial.[19] Consistent with previous data,[19] preliminary findings from the KarMMa-3 trial showed the presence of BCMA expression in tumor cells (in 6 of 6 samples [100%]) and soluble BCMA (in 82 of 84 samples [98%]) that were obtained from ide-cel–treated patients at myeloma progression — a finding suggesting that antigen loss is not the primary mechanism of ide-cel resistance in this context. Investigations are under way to assess potential mechanisms of resistance. In addition, exploration of new combination-therapy approaches to extend the durability of disease control that was observed with monotherapy may be warranted.

In the KarMMa-3 trial, ide-cel treatment resulted in significantly longer progression-free survival than was seen with standard regimens, and responses were deeper. The benefits of ide-cel therapy were derived from a single infusion, whereas standard regimens required continuous treatment. The safety profile of ide-cel was consistent with that observed in previous studies.[19,20] Given the prolonged progression-free survival and improved response that were observed with ide-cel therapy across multiple patient subgroups, ide-cel may provide benefit to patients with difficult-to-treat relapsed and refractory multiple myeloma. These findings provide potential support for the use of ide-cel in patients with triple-class–exposed relapsed and refractory multiple myeloma, a population with poor survival outcomes.

Supported by 2seventy bio (formerly bluebird bio) and Celgene, a Bristol-Myers Squibb company.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families for making this trial possible; the clinical trial teams; and Simon Wigfield, Ph.D., of Caudex, for assistance in preparing an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: Paula Rodriguez-Otero, M.D., Ph.D., Sikander Ailawadhi, M.D., Bertrand Arnulf, M.D., Ph.D., Krina Patel, M.D., Michele Cavo, M.D., Ajay K. Nooka, M.D., M.P.H., Salomon Manier, M.D., Ph.D., Natalie Callander, M.D., Luciano J. Costa, M.D., Ph.D., Ravi Vij, M.D., Nizar J. Bahlis, M.D., Philippe Moreau, M.D., Scott R. Solomon, M.D., Michel Delforge, M.D., Jesus Berdeja, M.D., Anna Truppel-Hartmann, M.D., Zhihong Yang, Ph.D., Linda Favre-Kontula, Ph.D., Fan Wu, Ph.D., Julia Piasecki, B.A., Mark Cook, M.B., Ch.B., Ph.D., and Sergio Giralt, M.D.

The authors' affiliations are as follows: Clínica Universidad de Navarra, Pamplona, Spain (P.R.-O.); Mayo Clinic, Jacksonville, FL (S.A.); Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris, Université Paris Cité, Paris (B.A.), Centre Hospitalier Universitaire de Lille, Université de Lille, Lille (S.M.), and University Hospital of Nantes, Nantes (P.M.) — all in France; M.D. Anderson Cancer Center, University of Texas, Houston (K.P.); IRCCS Azienda Ospedaliero–Universitaria di Bologna, Seràgnoli Institute of Hematology, and the Department of Experimental, Diagnostic, and Specialty Medicine, Bologna University School of Medicine, Bologna, Italy (M. Cavo); Winship Cancer Institute of Emory University (A.K.N.) and Northside Hospital Cancer Institute (S.R.S.) — both in Atlanta; the University of Wisconsin Carbone Cancer Center, Madison (N.C.); the University of Alabama at Birmingham, Birmingham (L.J.C.); Washington University School of Medicine in St. Louis, St. Louis (R.V.); Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada (N.J.B.); Universitaire Ziekenhuizen Leuven, Leuven, Belgium (M.D.); Sarah Cannon Research Institute and Tennessee Oncology, Nashville (J.B.); 2seventy bio, Cambridge, MA (A.T.-H.); Bristol Myers Squibb, Princeton, NJ (Z.Y., L.F.-K., F.W., J.P., M. Cook); Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom (M. Cook); and Memorial Sloan Kettering Cancer Center, New York (S.G.).

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