Idecabtagene vicleucel versus standard regimens in patients with triple-class-exposed relapsed and refractory multiple myeloma: KarMMa-3, a phase 3 randomized controlled trial

CT-356

Sergio Giralt,[1] Sikander Ailawadhi,[2] Bertrand Arnulf,[3] Krina Patel,[4] Michele Cavo,[5] Ajay K. Nooka,[6] Salomon Manier,[7] Natalie Callander,[8] Luciano J. Costa,[9] Ravi Vij,[10] Nizar J. Bahlis,[11] Philippe Moreau,[12] Scott R. Solomon,[13] Michel Delforge,[14] Jesús Berdeja,[15] Anna Truppel-Hartmann,[16] Zhihong Yang,*[17] Linda Favre-Kontula,*[17] Fan Wu,[17] Julia Piasecki,[17] Mark Cook,[17,18] Paula Rodríguez-Otero[19]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Mayo Clinic, Jacksonville, FL, USA; [3]Hôpital Saint-Louis, APHP, Université Paris cite, Paris, France; [4]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [6]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [7]CHU Lille, Université de Lille, Lille, France; [8]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; [9]University of Alabama at Birmingham, Birmingham, AL, USA; [10]Washington University School of Medicine in St. Louis, Saint Louis, MO, USA; [11]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; [12]University Hospital of Nantes, Nantes, France; [13]Northside Hospital Cancer Institute, Atlanta, GA, USA; [14]Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [15]Sarah Cannon Cancer Center and Tennessee Oncology, Nashville, TN, USA; [16]2seventy bio, Cambridge, MA, USA; [17]Bristol Myers Squibb, Boudry, Switzerland; [18]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom; [19]Clínica Universidad de Navarra, Pamplona, Spain

*Affiliation at time of study

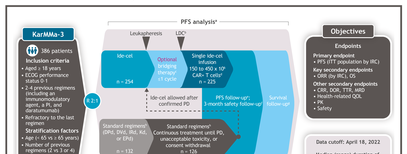
Introduction

- The treatment landscape of relapsed and refractory multiple myeloma (RRMM) has evolved with the use of immunomodulatory agents, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies in doublet, triplet, or quadruplet combinations[1,2]; however, relapse is common[3]
- Consequently, patients become triple-class-exposed (TCE) earlier in treatment and have limited treatment options, resulting in suboptimal survival outcomes (median progression-free survival [PFS], 3-5 months; median overall survival [OS], < 13 months)[3,9-12]
- Chimeric antigen receptor (CAR) T cell therapies that target B-cell maturation antigen (BCMA) expressed predominantly on myeloma cells are approved for the treatment of heavily pretreated RRMM[13,14]
- Therapies with novel mechanisms of action that provide deeper and more durable responses are needed in earlier lines of treatment
- Idecabtagene vicleucel (ide-cel), a BCMA-directed CAR T cell therapy, has demonstrated deep, durable responses in heavily pretreated RRMM[15,16]
  - In the phase 2 KarMMa study (NCT03361748), median PFS was 8.8 months and overall response rate (ORR) was 73% in ide-cel treated patients[15]
- KarMMa-3 (NCT03651128) is the first randomized phase 3 trial to evaluate a CAR T cell therapy, ide-cel, versus standard regimens in patients with TCE RRMM who had received 2 to 4 prior lines of therapy (LoT) and had disease refractory to the last regimen

Methods

- KarMMa-3 is an international, open-label, phase 3 trial; the details of study design have been previously described[17] (**Figure 1**)

Figure 1. KarMMa-3 study design



Ide-cel arm: treated population (patients who underwent either leukapheresis, bridging therapy, LDC, or ide-cel treatment) was used to assess AEs; the safety population (patients who received ide-cel) was used to assess TRAEs, iiNT, and CRS; standard regimens arm: the treated and safety populations included those patients who received any treatment. *Time from randomization to the first occurrence of PD or death from any cause according to IMWG criteria; †3 days fludarabine 30 mg/m² and cyclophosphamide 300 mg/m²; ‡Up to 1 cycle of DPd, DVd, IRd, Rd, or EPd may be given as bridging therapy; §Doses < 540 × 10⁶ cells permitted; ¶PFS assessed monthly for patients randomized to ide-cel for 24 months then every 3 months until PD, and monthly until PD for patients randomized to standard regimens; #Patients randomized to standard regimens and received subsequent ide-cel therapy; ^Every 3 months after PD until end of trial; ‡ years after last patient randomized; &Based on most recent treatment regimen and investigator discretion.
AE, adverse event; CRR, complete response rate; CRS, cytokine release syndrome; DOR, duration of response; DPd, daratumumab, pomalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; EPd, elotuzumab, pomalidomide, and dexamethasone; iiNT, investigator-identified neurotoxicity; IMWG, International Myeloma Working Group; IRC, Independent Response Committee; IRd, ixazomib, lenalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; LDC, lymphodepleting chemotherapy; MRD, minimal residual disease; OS, overall survival; PD, progressive disease; PK, pharmacokinetics; QOL, quality of life; R, randomization; TRAE, treatment-related adverse event; TTR, time to response.

- Patients with RRMM who had received 2-4 prior LoT, were TCE (including an immunomodulatory agent, PI, and daratumumab), and had disease refractory to the last regimen were enrolled
- Patients were randomized 2:1 to receive ide-cel at a target dose range of 150–450 x 10^6 CAR+ T cells (≤ 540 × 10^6 cells) or a standard regimen (DPd, DVd, IRd, Kd, EPd)
- Primary endpoint included IRC-assessed PFS
- Key secondary endpoints were IRC-assessed ORR and OS. Other secondary endpoints included DOR, health-related QOL, PK, and safety
- Efficacy was assessed per ITT population

Table 1. Patient disposition

Characteristic	Ide-cel	Standard regimens
Patients screened	490	
Patients randomized (ITT population), n	254[a]	132 DPd (n = 43) EPd (n = 30) Kd (n = 30) IRd (n = 22) DVd (n = 7)
Patients who received assigned treatment (safety population), n (%) Discontinued from study during PFS follow-up Discontinued from study during survival follow-up	225 21 51	126[b] 12[c] 16
Patients who did not receive assigned treatment, n (%) Continuing in survival follow-up Discontinued study	24 5 19	6 1 5
Patients continuing in study, n (%) Continuing in PFS follow-up Continuing in survival follow-up	158 91 67	29 20[d] 9

[a]Of 254 patients assigned to the ide-cel group (ITT population), 5 patients did not receive leukapheresis, 249 underwent leukapheresis and 1 received bridging therapy but not leukapheresis, leading to a treated population of 250 patients. Of these 250 patients, 249 underwent leukapheresis, 213 received bridging therapy, 227 received LDC, and 225 received a single infusion of ide-cel; [b]Of the patients in the standard regimens arm, 69 received leukapheresis. Disposition of 69 patients in the standard regimens arm who underwent leukapheresis and received ide-cel is not depicted here. Of the patients who received leukapheresis, 60 received ide-cel and 9 did not. One patient discontinued study during pretreatment period without leukapheresis due to death; [c]During treatment and PFS follow-up; [d]Included patients with ongoing treatment.

Results

Patient disposition, baseline characteristics, and prior treatment

- Of 386 randomized patients (ide-cel, n = 254; standard regimen, n = 132), 225 received ide-cel and 126 received standard regimens (**Table 1**)
  - Median dose of ide-cel was 445 (range 175–529) × 10^6 CAR+ T cells
- Baseline characteristics and high-risk clinical features were generally balanced between arms (**Table 2**)
- Overall, 66% of patients had triple-class-refractory RRMM and a short median time from diagnosis (4 years). Disease relapsed at a median of approximately 7 months since last regimen initiation (**Table 2**)

Table 2. Baseline demographics, disease characteristics, and prior therapy

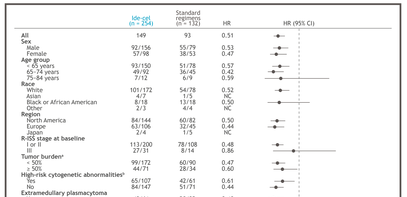
Characteristic	Ide-cel (n = 254)	Standard regimens (n = 132)
Female, n (%)	98 (39)	53 (40)
Male, n (%)	156 (61)	79 (60)
Median age (range), years	63 (30-81)	63 (42-83)
ECOG performance status score, n (%)[a] 0 1	120 (47) 133 (52)	66 (50) 62 (47)
Median time (range) from diagnosis to screening, years	4.1 (0.6-21.8)	4.0 (0.7-17.7)
Previous autologous HSCT, n (%)	214 (84)	114 (86)
R-ISS disease stage, n (%)[a] I II III	50 (20) 150 (59) 31 (12)	26 (20) 82 (62) 14 (11)
Extramedullary disease, n (%)[a]	61 (24)	32 (24)
High tumor burden, n (%)[a]	71 (28)	34 (26)
High-risk cytogenetics, n (%)[a] del(17p) t(4;14) t(14;16)	107 (42) 66 (26) 43 (17) 8 (3)	61 (46) 42 (32) 18 (14) 4 (3)
1q gain/amplification, n (%)	125 (49)	51 (39)
Ultra-high-risk cytogenetics, n (%)[a]	67 (26)	29 (22)
Median number (range) of prior regimens	3 (2-4)	3 (2-4)
Median time (range) to progression on last prior antimyeloma therapy, months	7.1 (0.7-67.7)	6.9 (0.4-66.0)
Refractory status, n (%) Immunomodulatory agent refractory PI refractory Daratumumab refractory[b] Double-class refractory[c] Triple-class refractory[c]	224 (88) 189 (74) 242 (95) 169 (67) 164 (65)	124 (94) 95 (72) 123 (93) 91 (69) 89 (67)

Adapted from Rodríguez-Otero P, et al. 2023.[17]
There was an imbalance in the proportion of Black/African American patients; however, no difference in treatment effect by race was apparent.
[a]All patients had score 0 or 1 at screening but may be > 1 at baseline; [b]The minimum value shown represents the second lowest value in the database; the lowest value was determined to be a data entry error that was corrected in the database after database lock. The patient whose data was incorrectly entered had a time from initial diagnosis to screening of 3.2 years, which was incorrectly reported as 0.2 years; [c]ISS was calculated using baseline values of albumin and B2-microglobulin. R-ISS was derived using baseline ISS stage, cytogenetic abnormality, and serum lactate dehydrogenase; [d]including extramedullary soft tissue-only disease as well as soft tissue bone-related plasmacytomas; [e] ≥ 50% CD138+ plasma cells in bone marrow; [f]included del(17p), t(4;14), or t(14;16); [g] ≥ 2 del(17p), t(4;14), t(14;16), t(14;20), or 1q amp; [h]patient in each arm was refractory to ixazomib; [i]refractory to ≥ 1 each of an immunomodulatory agent and a PI; [j]refractory to ≥ 1 each of an immunomodulatory agent, a PI, and an anti-CD38 antibody.
HSCT, hematopoietic stem cell transplantation; R-ISS, revised International Staging System.

Efficacy

- The PFS benefit of ide-cel was consistently observed across multiple patient subgroups (**Figure 4**)
- Median DOR was numerically longer with ide-cel versus standard regimens (14.8 vs 9.7 months)
- OS was immature at data cutoff

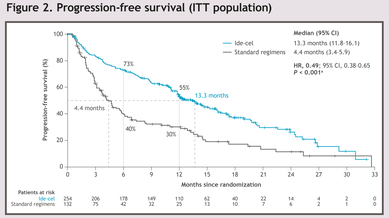
Figure 4. Subgroup analysis of PFS



Adapted from Rodríguez-Otero P, et al. 2023.[17]
Per IRC based on IMWG criteria. Assumption of proportional hazards was assessed using a treatment*(log)time) interaction term in each model. *Determined by the higher value between bone marrow aspirate and bone marrow biopsy CD138+ plasma cell. Low: < 50%. High: ≥ 50%; †Defined as t(4;14), t(14;16), or del(17p); ‡Refractory to ≥ 1 each of an immunomodulatory agent, a PI, and an anti-CD38 antibody; §Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.
NC, not computed.

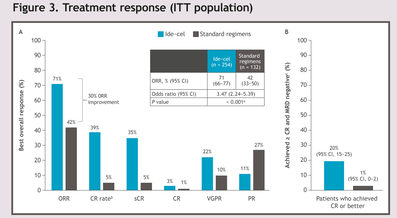
With a median follow-up from randomization to data cutoff of 18.6 months, treatment with ide-cel resulted in a significantly longer PFS (13.3 vs 4.4 months; HR, 0.49; *P* < 0.001; Figure 2), with a 51% lower risk of disease progression or death, and significantly higher ORR (71% vs 42%; Figure 3A) with more patients achieving ≥ CR and MRD-negative status (20% vs 1%; Figure 3B), than standard regimens

Figure 2. Progression-free survival (ITT population)



Adapted from Rodríguez-Otero P, et al. 2023.[17]
PFS based on IMWG criteria per IRC. *Based on stratified log-rank test.
IMWG, International Myeloma Working Group.

Figure 3. Treatment response (ITT population)

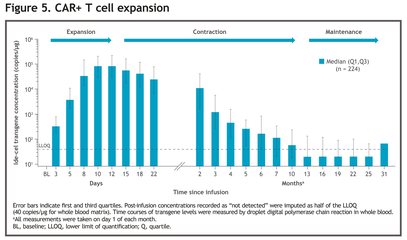


Per IMWG criteria.[18]
Percentages may not add up due to rounding.
*One-sided *P* value from Cochran-Mantel-Haenszel test stratified by stratification factors; †CR or sCR; ‡Defined as ≥ 1 negative MRD value within 3 months prior to achieving ≥ CR until PD or death. MRD was assessed by NGS at a sensitivity of 10^{-5} per IMWG Uniform Response Criteria and as specified by the protocol. 95% CI was calculated using 2-sided Wald interval.
NGS, next-generation sequencing; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Cellular kinetics

- CAR+ T cells underwent a rapid multi-log expansion and maximum expansion occurred at a median of 11 days (**Figure 5**)

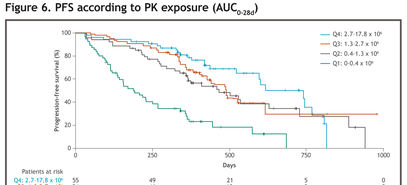
Figure 5. CAR+ T cell expansion



Error bars indicate first and third quartiles. Post-infusion concentrations recorded as "not detected" were imputed as half of the LLOQ (40 copies/µg for whole blood matrix). Time courses of transgene levels were measured by droplet digital polymerase chain reaction in whole blood.
*All measurements were taken on day 1 of each month.
BL, baseline; LLOQ, lower limit of quantification; Q, quartile.

- Higher quartiles of ide-cel expansion measured by PK exposure (area under the curve [AUC_{0-28d}]) were associated with longer PFS (**Figure 6**)
  - Considerable inter-patient variability in cell expansion was noted; the lowest quartile of expansion was present across all actual dose levels

Figure 6. PFS according to PK exposure (AUC_{0-28d})

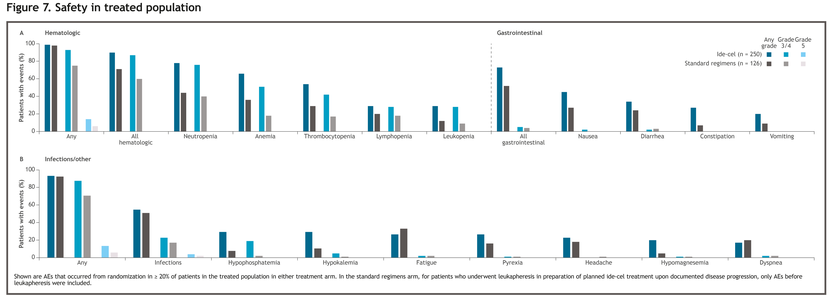


Adapted from Rodríguez-Otero P, et al. 2023.[17]
In ide-cel arm, AUC_{0d} denotes area under the curve from day 0 to day 28 and is measured in days*copies/µg.

Safety

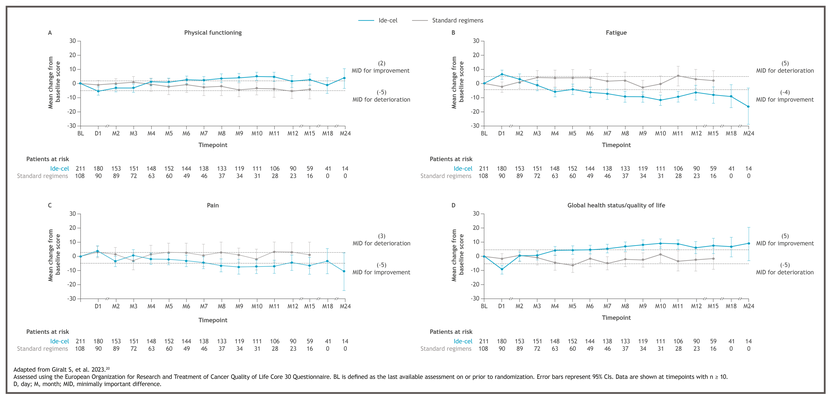
- AEs occurred in 99% (248/250) and 98% (123/126) of patients in the ide-cel and standard regimens arms, respectively; grade 3/4 AEs occurred in 93% and 75%, and grade 5 AEs occurred in 14% and 6% (**Figure 7**)
- For patients in the ide-cel group who developed grade 3/4 thrombocytopenia or neutropenia that persisted beyond 1 month, the median time to recovery was 1.9 months (95% CI, 1.5–2.1) after thrombocytopenia and 1.7 months (95% CI, 1.5–1.9) after neutropenia
- Second primary malignancies occurred in 6% of patients in the ide-cel arm and 4% in the standard regimens arm
- Of patients who experienced grade 5 AEs, 18/36 in the ide-cel arm and 3/8 in the standard regimens arm had grade 5 AEs consistent with myeloma progression. In the ide-cel arm, 6 of these 18 patients never received ide-cel
- In the safety population, grade 5 TRAEs occurred in 6/225 (3%) and 1/126 (1%) patients in the ide-cel and standard regimens arms, respectively; the most common grade 5 TRAE was sepsis, which occurred in 5/225 (2%) and 1/126 (1%) patients
- The incidence of high-grade (grade ≥ 3) CRS and iiNT was low and resolved within a median of 3.5 and 2 days, respectively. No parkinsonism was reported (**Figure 8A**)
  - One of the grade 5 CRS events occurred after a decline in organ function (acute myocardial infarction potentially related to anemia and rapid atrial flutter) and 1 from concomitant grade 5 *Candida* sepsis
  - Grade 2 encephalopathy, unrelated to ide-cel, was reported in 1 patient 317 days after ide-cel infusion and was considered by the investigator to be related to worsening pneumonia and *C. difficile* colitis, not ide-cel. The next longest duration of onset to a neurotoxicity event was 46 days
- CRS was primarily managed using tocilizumab and iiNT was managed using steroids (**Figure 8B**)

Figure 7. Safety in treated population



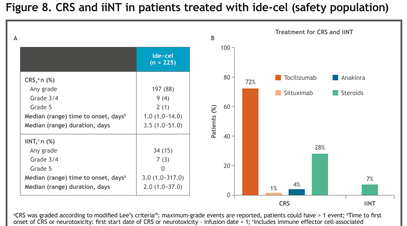
Shown are AEs that occurred from randomization in ≥ 20% of patients in the treated population in either treatment arm. In the standard regimens arm, for patients who underwent leukapheresis in preparation of planned ide-cel treatment upon documented disease progression, only AEs before leukapheresis were included.

Figure 9. Patient-reported outcomes



Adapted from Giralt S, et al. 2023.[19]
Assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire. BL is defined as the last available assessment on or prior to randomization. Error bars represent 95% CIs. Data are shown at timepoints with n ≥ 10.
D, day; M, month; MID, minimally important difference.

Figure 8. CRS and iiNT in patients treated with ide-cel (safety population)



*CRS was graded according to modified Lee's criteria[20]; maximum-grade events are reported, patients could have > 1 event; †Time to first onset of CRS or neurotoxicity: first start date of CRS or neurotoxicity – infusion date + 1; ‡Includes immune effector cell-associated neurotoxicity syndrome reported by investigator as a neurologic toxicity AE.

Patient-reported outcomes

- Ide-cel demonstrated clinically meaningful improvements in patient-reported outcomes versus standard regimens (**Figure 9**)

Conclusions

- KarMMa-3 is the first randomized phase 3 clinical study to compare directly a CAR T cell therapy with standard regimens in triple-class-exposed RRMM
- In this high-risk TCE and highly refractory population, a single infusion of ide-cel treatment demonstrated significant and clinically meaningful improvement in PFS and ORR versus standard regimens
  - Risk of disease progression or death with ide-cel was 51% lower than with standard regimens (*P* < 0.001)
  - Ide-cel significantly increased the ORR versus standard regimens (odds ratio, 3.47; *P* < 0.001)
    - A higher proportion of patients in the ide-cel arm achieved CR or better and MRD-negative status than with standard regimens
  - Ide-cel treatment benefit was consistent across highly refractory and difficult-to-treat populations
  - Higher quartiles of ide-cel expansion were associated with longer PFS
  - Ide-cel treatment provided clinically meaningful improvements in health-related QOL compared with standard regimens
  - OS data were immature at the time of analysis and remain blinded
- The toxicity profile of ide-cel was manageable and consistent with previous studies,[15,16] and no parkinsonism was reported
- These results support the use of ide-cel in patients with early-line relapse and TCE RRMM, a patient population with poor survival outcomes

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