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Health-related quality of life with idecabtagene vicleucel in relapsed and refractory multiple myeloma

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Key Points

- A single infusion of ide-cel improved QoL for triple-class exposed patients with RRMM.
- Post–ide-cel treatment, patients had improved pain, fatigue, physical functioning, and overall QoL that was sustained through 15 to 18 months.

Idecabtagene vicleucel (ide-cel), a B-cell maturation antigen–directed chimeric antigen receptor T cell therapy, showed deep, durable responses in patients with triple-class exposed, relapsed and refractory multiple myeloma (RRMM) in the phase 2 KarMMa (Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma) trial. We assessed health-related quality of life (HRQoL) among KarMMa patients. The European Organization for Research and Treatment of Cancer Quality of Life C30 Questionnaire and its supplementary 20-item multiple myeloma module, as well as the EuroQol 5-dimension 5-level instrument, were administered at screening, baseline (≤72 hours before or same day as lymphodepletion), day of ide-cel treatment, and after ide-cel treatment. Mean changes from baseline that exceeded the predetermined threshold of minimally important difference were deemed clinically meaningful. The proportions of patients experiencing clinically meaningful changes in HRQoL were assessed using within-patient change thresholds. Time to stable improvement (≥2 consecutive visits with clinically meaningful HRQoL improvements) was analyzed by using the Kaplan-Meier method. A total of 126 (98%) of 128 patients treated with ide-cel were included in the HRQoL analysis. Pretreatment baseline RRMM burden was high and meaningfully worse than that in the age- and sex-weighted general population. Statistically significant and clinically meaningful improvements from baseline were observed by month 1 for pain (−8.9) and disease symptoms (−10.2), and by month 2 for fatigue (−7.2), physical functioning (6.1), cognitive functioning (6.7), and global health status/QoL (8.0). Clinically meaningful improvements in fatigue, pain, and physical functioning were most prominent at months 9, 12, and 18, respectively, and were sustained through 15 to 18 months after ide-cel treatment. For triple-class exposed patients with RRMM with a poor prognosis and few treatment options, a single ide-cel infusion provides early, sustained, statistically significant, and clinically meaningful improvements in HRQoL. This study was registered at Clinicaltrials.gov as #NCT03361748.

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The BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

The full-text version of this article contains a data supplement.

Introduction

Therapeutic advances in multiple myeloma over the past 10 to 15 years have resulted in notable improvements in treatment response and survival, which are largely attributable to treatment with combination regimens of immunomodulatory drugs, proteasome inhibitors, and anti-CD38 antibodies.[1-3] Despite this, patients with relapsed and refractory multiple myeloma (RRMM) have limited therapeutic options, with poor prognosis and outcomes even after treatment with these agents, defined as triple-class exposed (TCE).[4-7] The burden of disease for patients with MM is high, with persistent pain, fatigue, and functionality substantially reducing health-related quality of life (HRQoL).[8,9] Patients report further deterioration of physical and social functioning as they advance through to second-, third-, and fourth-line therapy.[10,11]

Idecabtagene vicleucel (ide-cel, bb2121), a B-cell maturation antigen (BCMA)–directed chimeric antigen receptor (CAR) T-cell therapy, showed deep, durable responses in TCE patients with RRMM in the pivotal, phase 2, single-arm KarMMa (Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma) clinical trial, and it is approved in the United States for adults with RRMM after ≥4 lines of therapy, including TCE patients.[12,13] Patients receiving ide-cel reported an overall response rate of 73% and median progression-free survival (PFS) of 8.8 months; 33% of patients had a complete response (CR) or better.[12] Of note, 26% of treated patients and 79% of those with a CR or stringent CR had minimal residual disease negative status after ide-cel treatment. Ide-cel showed a manageable tolerability profile, with a 5% incidence of grade ≥3 cytokine release syndrome and 3% incidence of investigator-identified neurotoxicity.[12]

Because therapeutic advances extend survival and improve clinical outcomes for patients with RRMM, increased attention to the quality of these additional life-years for patients is warranted. The novelty of CAR T-cell therapy in RRMM, given its clinical efficacy, unique toxicity profile, one-time administration, and potential for reduced treatment burden, underscores the importance of exploring its potential impact on HRQoL.[14,15] Compared with the chronic administration schedules of historical treatment options, a single infusion could be meaningful for TCE patients who are heavily treated before receiving CAR T-cell therapy, and longer treatment-free periods have been associated with improved HRQoL.[16] To assess if treatment with ide-cel provides any HRQoL benefits in addition to the observed improvements in clinical outcomes, we evaluated patient-reported HRQoL among TCE patients with RRMM in the KarMMa clinical trial.

Methods

Patient-reported HRQoL in KarMMa

In the KarMMa trial (NCT03361748), HRQoL assessments were conducted at screening, baseline (within 72 hours before, or on the same day as, lymphodepleting [LD] chemotherapy day), at ide-cel infusion (day 1), monthly during months 1 to 6 of follow-up, and every 3 months up to 24 months or until study completion (additional information provided in the supplemental Data). This analysis included patients with ≥12 months of posttreatment follow-up at the time of data cutoff for this report (January 14, 2020).

HRQoL measures included the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life C30 Questionnaire (QLQ-C30 version 3.0), the QLQ-C30 supplementary 20-item multiple myeloma module (QLQ-MY20), and the general health EuroQol 5-dimension 5-level (EQ-5D-5L) instrument. The QLQ-C30 has 30 items addressing 5 multi-item functional domains (physical, social, role, cognitive, and emotional), 3 multi-item symptom scales (fatigue, nausea and vomiting, and pain), 6 single-item symptom domains (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and global health status/QoL.[17] The QLQ-MY20 is a validated supplement to the QLQ-C30 with 20 questions addressing 4 myeloma-specific HRQoL domains (disease symptoms, 6 items; side effects of treatment, 10 items; body image, 1 item; and future perspective, 3 items).[18] For both the QLQ-C30 and QLQ-MY20, raw scores are transformed to a score between 0 and 100. Higher functional domain scores indicate better functioning and QoL, whereas higher symptom or side effect scores indicate worsening symptoms or side effect burden.[19]

The EQ-5D-5L is a validated, self-reported, preference-based measure meant to provide a single value representing overall health status. The EQ-5D-5L health utility index is a self-reported measure of functioning and well-being across 5 dimensions (mobility, self-care, pain, usual activities, and anxiety/depression) with 5 levels of severity. Responses to the 5 items are converted to a weighted health state index utility score by cross-walking to country-specific EQ-5D 3-level (EQ-5D-3L) value sets or based on values derived directly from country-specific general population samples. This analysis used the cross-walk method to the EQ-5D-3L value set from the United Kingdom (UK), where population weights can range from −0.594 to 1.0,[20] with a score of 0 indicating death, 1.0 indicating "full health," and negative scores reflecting states perceived to be worse than death.[21] The EQ-5D visual analog scale (VAS) records self-rated current health status on a vertical scale from 0 ("worst imaginable health state") to 100 ("best imaginable health state").

Clinically meaningful response thresholds

The clinical relevance of HRQoL changes from baseline was determined for individual patients as within-patient changes and for groups of patients as within-group changes from baseline. Changes in instrument scores for individual patients were categorized as "improvement," "no change," or "deterioration," indicating clinically meaningful changes from baseline according to the prespecified within-patient responder definition (RD). The minimally important difference (MID), defined as the smallest difference in mean score within a group, was used to interpret whether a within-group change was clinically meaningful. RDs and MID thresholds for the QLQ-C30 and QLQ-MY20 have been previously published and were based on clinical trial data and prospective patient interviews (supplemental Tables 1 and 2).[22,23] In the absence of established RDs for the EQ-5D-5L, we used the RD and MID values for the EQ-5D-3L health utility index of 0.08 for improvement and −0.08 for deterioration.[24,25] For the EQ-5D VAS, we used the oncology-specific cutoff values of 7.0 for improvement and −7.0 for deterioration, for both the RD and MID.[25,26]

Statistical analysis

The primary objective of this analysis was to examine the effects of ide-cel treatment on fatigue, pain, physical and cognitive functioning, and global health status/QoL from QLQ-C30, and disease

symptoms and treatment side effects from QLQ-MY20. Secondary objectives analyzed all other domains and scales from QLQ-C30 and QLQ-MY20, and patient-reported health status and well-being from the EQ-5D. Primary analyses included changes from baseline and the proportions of patients experiencing clinically meaningful changes from baseline according to the prespecified RD thresholds for each instrument. Secondary analysis included time to stable improvement, defined as having ≥2 consecutive visits with clinically meaningful HRQoL improvements. Primary and secondary analyses included all patients who were treated with ide-cel, regardless of their clinical response. A subgroup analysis was performed for mean change in the EORTC QLQ-C30 primary domain scores from baseline based on target ide-cel dose levels (150×10^6, 300×10^6, and 450×10^6 CAR+ T cells). An exploratory analysis was also conducted to examine the effect of ide-cel treatment on the primary QLQ-C30 scales among patients who achieved a very good partial response (VGPR) or better, defined as a VGPR, CR, or stringent CR.

Analyses were conducted in the HRQoL-evaluable population of patients treated with ide-cel who had an evaluable assessment at baseline and ≥1 postbaseline assessment. Baseline was defined as the last nonmissing assessment on or before LD chemotherapy day. An evaluable assessment for each instrument was defined as completion of ≥15 of the 30 QLQ-C30 items, ≥10 of the 20 QLQ-MY20 items, all 5 of the EQ-5D-5L items, and no missing value for the EQ-5D VAS. Completion rates for each instrument were indicated by the number of patients providing an evaluable assessment at each visit from the number of patients treated with ide-cel who were expected to complete HRQoL questionnaires (ie, alive, on study, and not yet receiving re-treatment with ide-cel). Mean baseline HRQoL scores from KarMMa were assessed alongside published normative data from the general population that were re-weighted by the age and sex distributions of the KarMMa HRQoL-evaluable population. Published scores from the general European population (11 European Union countries, n = 11 343) were used for the QLQ-C30[27] and from the United Kingdom (n = 3395) for the EQ-5D.[28] No normative data were available for the QLQ-MY20.

For each HRQoL instrument, changes in scores from baseline to each posttreatment visit were summarized by using descriptive statistics. Line graphs were used to examine mean changes (95% confidence interval) from baseline at each postbaseline visit for all domains compared with the MID reference lines. For each instrument, the number and proportion of patients with clinically meaningful changes relative to the clinically meaningful response thresholds (improvement, no change, or worsening) in each domain were calculated based on changes from baseline at each postbaseline scheduled visit. Time to stable improvement in each of the QLQ-C30 domains was analyzed by using the Kaplan-Meier product limit method for the QLQ-C30–evaluable population. Time to stable improvement or censoring was calculated and summarized in months as: ([date of stable improvement/censoring] − [date of ide-cel infusion] + 1)/30.4375. No imputation was performed for missing postbaseline values. Because the HRQoL assessments may have been affected by bridging therapy, a sensitivity analysis was conducted by using the screening visit assessment (or the baseline visit assessment if the screening assessment was missing) as the "baseline" value to evaluate the consistency of findings with the primary analysis.

All analyses were conducted by using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

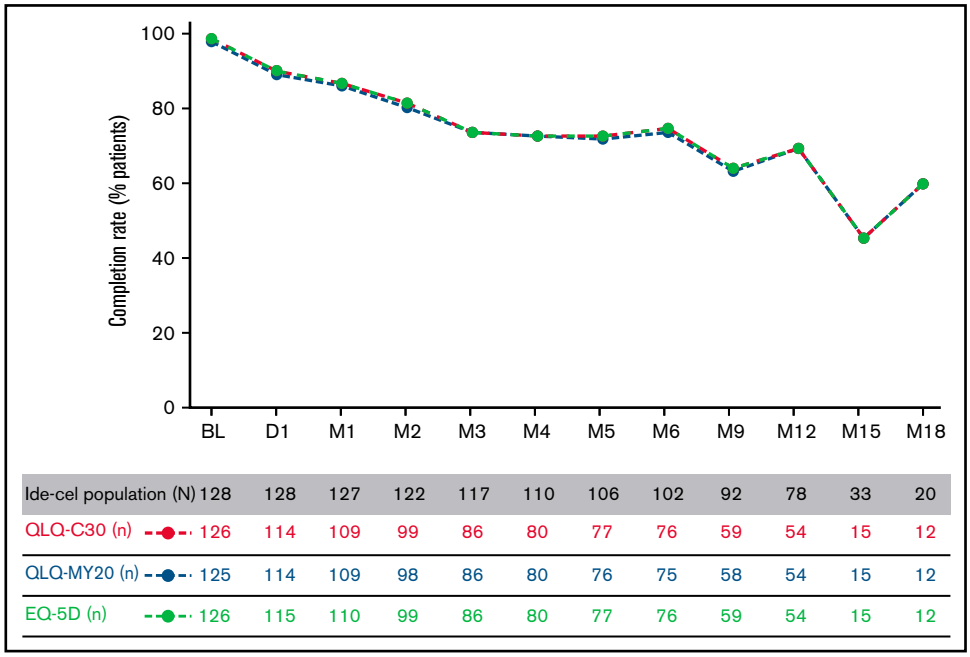
A total of 126 (98%) patients treated with ide-cel were included in the HRQoL-evaluable population (2 of 128 eligible patients had missing baseline or postbaseline assessments). Completion rates were nearly identical across HRQoL instruments, from 98% at baseline to 70% to 90% through month 6 and slightly lower (60%-70%) through month 12 (Figure 1). The baseline burden of RRMM was high among patients enrolled in the KarMMa trial, whose mean baseline QLQ-C30 scores were meaningfully worse alongside those of the re-weighted general population (Figure 2). Baseline EQ-5D scores were also meaningfully worse for KarMMa patients vs the UK normative population, exceeding the MID thresholds for both the EQ-5D-5L health utility index (mean, 0.67 vs 0.81; difference, −0.14) and the EQ-5D VAS (mean, 67.5 vs 80.7; difference, −13.2).

In the exploratory analysis of patients who achieved a VGPR or better (66 [52%] of 126 HRQoL-evaluable patients for QLQ-C30), patients had worse mean baseline scores of ≥10 points for pain, fatigue, and physical functioning compared with the general population, and slightly worse global health status/QoL and cognitive functioning (supplemental Figure 1).

Primary HRQoL analysis

Patients receiving ide-cel treatment reported meaningful improvements in all primary HRQoL analysis measures, most as early as months 1 or 2. Improvements were generally sustained over time, although decreasing sample sizes by months 12 through 18 were observed. Statistically significant and clinically meaningful improvements in QLQ-C30 measures of pain and physical functioning were observed by month 1, and of fatigue, cognitive functioning, and global health status/QoL by month 2 (Figure 3). Clinically meaningful improvements in fatigue, pain, and physical functioning were sustained through 18 months after ide-cel treatment. Cognitive functioning remained generally stable, with statistically significant and clinically meaningful improvements observed from months 2 through 9. The QLQ-MY20 primary analysis measure of disease symptoms revealed statistically significant and clinically meaningful improvements by month 3 that were observed through month 15 after ide-cel treatment ($P < .05$) (Figure 3). Because patients were not receiving active anticancer treatment at the baseline assessment, no substantial improvement in the treatment side effects measure was expected, although statistically significant improvements were observed from month 2 through month 15 after treatment ($P < .05$). This finding may be explained by patients reporting the side effects of bridging therapy or prior therapy at baseline. Similar patterns were observed in patients who achieved a VGPR or better (supplemental Figure 2). When analyzed according to ide-cel dose level, the overall magnitude of improvement was greater for patients who received 300×10^6 or 450×10^6 CAR+ T cells (data not shown). These patients had significant and meaningful improvements from baseline in all primary domains of interest (except for side effects of treatment) across most follow-up visits.

The improvements in QLQ-C30 pain, fatigue, physical functioning, and global health status/QoL observed among patients treated with ide-cel made their posttreatment HRQoL scores comparable to



	BL	D1	M1	M2	M3	M4	M5	M6	M9	M12	M15	M18
Ide-cel population (N)	128	128	127	122	117	110	106	102	92	78	33	20
QLQ-C30 (n)	126	114	109	99	86	80	77	76	59	54	15	12
QLQ-MY20 (n)	125	114	109	98	86	80	76	75	58	54	15	12
EQ-5D (n)	126	115	110	99	86	80	77	76	59	54	15	12

Figure 1. Instrument completion rates in the KarMMa population treated with ide-cel. BL, baseline; EQ-5D, EuroQoL 5-dimension; ide-cel, idecabtagene vicleucel; QLQ-C30, Quality of Life C30 Questionnaire; QLQ-MY20, QLQ-C30 supplementary 20-item multiple myeloma module.

those of the general population within 1 to 3 months, and the scores remained generally comparable through month 18. Because the cognitive functioning score was similar to that of the general population at baseline, scores were comparable from day 1 and showed modest relative improvement over time (supplemental Figure 3). No normative population data for the QLQ-MY20 were available, and thus visual inspection against a normative population was not feasible.

We also evaluated individual-level changes for the primary HRQoL measures (Figure 4). For all measures, the proportion of patients who experienced clinically meaningful improvements increased over

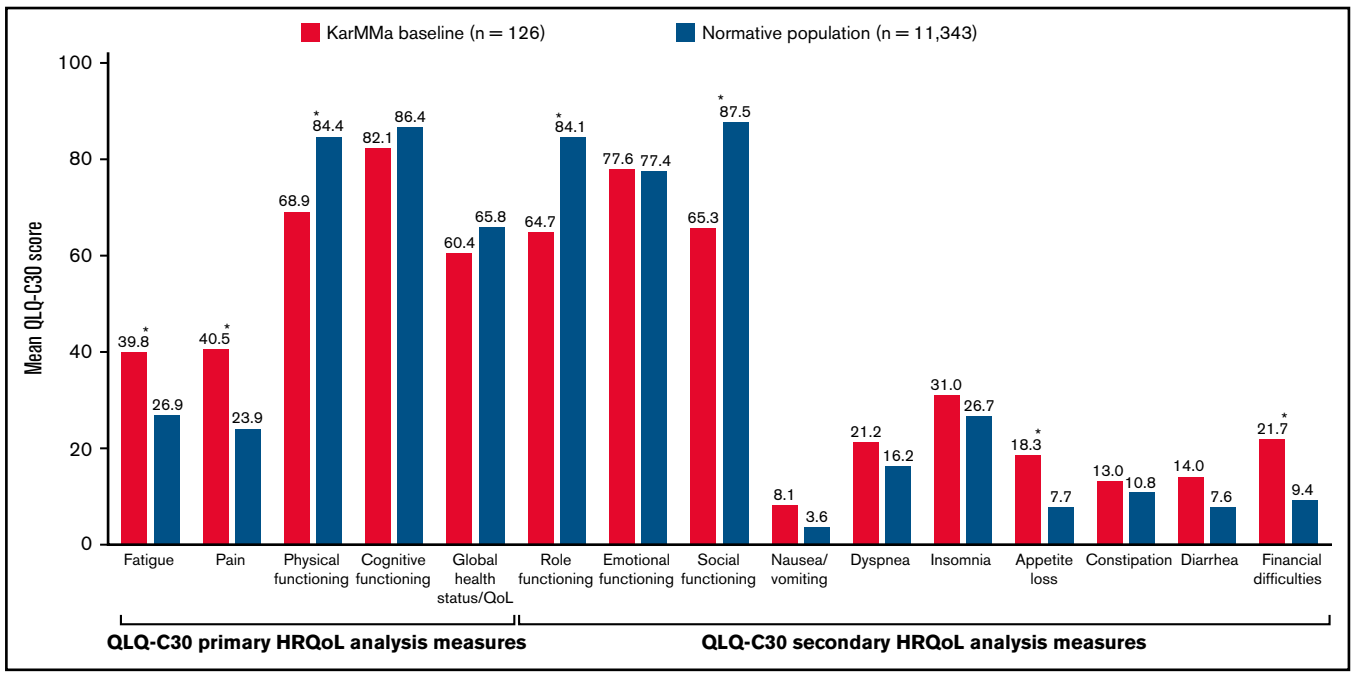


Figure 2. Mean QLQ-C30 scores: baseline KarMMa HRQoL patients and European Union normative population. Re-weighted normative population scores for the QLQ-C30 were from 11 countries in the European Union.[27] *Denotes ≥10-point difference. EU, European Union; HRQoL, health-related quality of life; QLQ-C30, Quality of Life C30 Questionnaire.

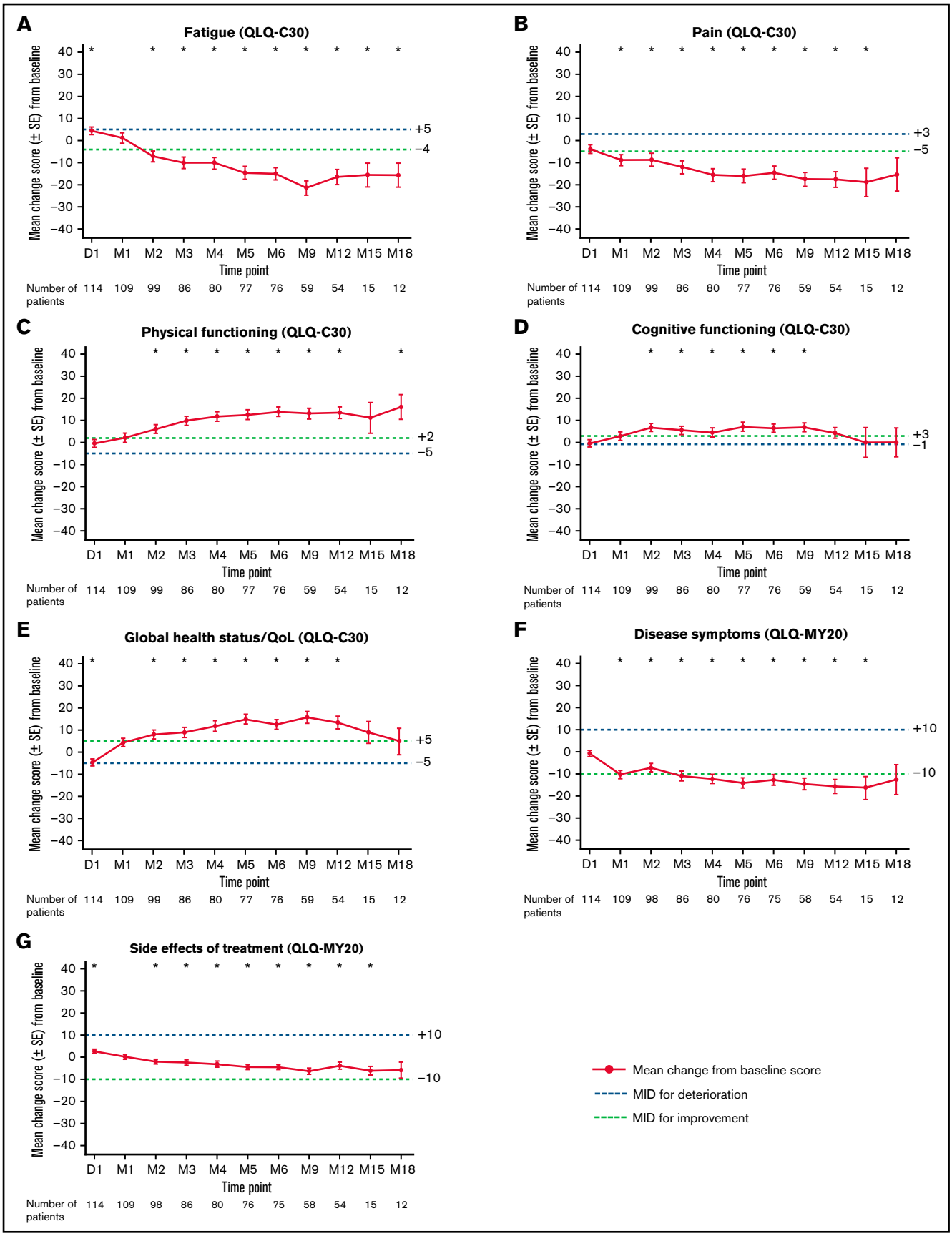


Figure 3. Mean changes from baseline, primary HRQoL analysis measures. Reference lines indicate prespecified group-level MID thresholds for clinically meaningful improvement or deterioration. Patients were included in this analysis regardless of their clinical response. The number of nonresponders is as follows: 31 nonresponders at day 1; 27 nonresponders at month 1; 17 nonresponders at month 2; and 10 nonresponders at month 3. Nonresponders were not considered after this time due to the

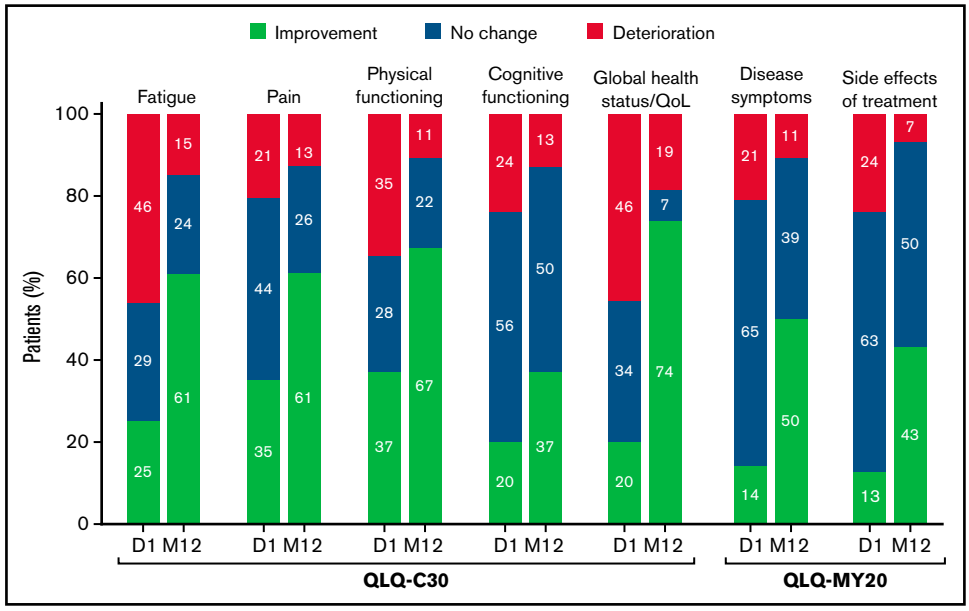


Figure 4. Primary HRQoL assessments at day 1 (D1) and month 12 (M12) after ide-cel treatment. Patients with evaluable assessments at day 1 (n = 114 for all groups), at month 12 (n = 54 for all groups). D, day; HRQoL, health-related quality of life; M, month; QLQ-C30, Quality of Life C30 Questionnaire; QLQ-MY20, QLQ-C30 supplementary 20-item multiple myeloma module; QoL, quality of life.

time from day 1 to month 12. The proportions of patients with clinically meaningful improvements over time increased from day 1 for fatigue, pain, physical functioning, and global health status/QoL on the QLQ-C30 (supplemental Figure 4). The majority of patients (~80%) experienced no change or improvement in cognitive functioning across visits, most of whom had no change (≥50%); this group had comparable scores to the general population at baseline, however, with less room for improvement than in other measures. For the QLQ-MY20, the proportions of patients experiencing clinically meaningful improvements in disease symptoms and side effects increased over time, as those with clinically meaningful worsening decreased from day 1. Approximately one-half of all patients (50%-60%) showed no change in these two QLQ-MY20 measures across most of the follow-up visits.

Improvements in primary HRQoL domains were observed in similar proportions of patients who achieved a VGPR or better (supplemental Figure 5). In this population, the proportion of patients who experienced clinically meaningful improvement in global health status/QoL increased from 16% at day 1 to 76% at month 12, whereas the proportion of patients who experienced clinically meaningful worsening decreased from 50% at day 1 to 15% at month 12.

Median time to stable improvement in QLQ-C30 fatigue, pain, physical functioning, and global health status/QoL was ~4 months after ide-cel treatment, whereas the median time to stable improvement was not reached for cognitive functioning by the end of the data cutoff (supplemental Table 3). In patients who achieved a VGPR or better, similar patterns were observed across all domains (supplemental Table 4).

Secondary HRQoL analysis

Mean changes from baseline in most of the secondary HRQoL functional and symptom measures showed trends of improvement over time after ide-cel treatment (supplemental Data; supplemental Figure 6). Mean changes from baseline in both the EQ-5D-5L health utility index scores and the EQ-5D VAS showed statistically significant and consistent, clinically meaningful improvements from baseline by month 3 through month 18.

Sensitivity analysis

The sensitivity analysis using the screening visit assessment as the "baseline" score (before bridging therapy) showed overall trends of improvement consistent with those of the base case analysis (data not shown). Because many of the HRQoL scores were slightly more favorable at the screening visit than at the baseline visit (which occurred just before LD chemotherapy) in both the group-level and individual-level assessments, the magnitude of changes from "baseline" were numerically less than in the base case scenarios. The base case analysis showed clinically meaningful improvements in all primary HRQoL measures at months 1 or 2 with the exception of the QLQ-MY20 side effect of treatment measure. The sensitivity analysis also showed clinically meaningful improvements in all QLQ-C30 primary measures but mostly at month 3 or thereafter (data not

Figure 3 (continued) small sample size (<10 patients). *$P < .05$ based on two-sided Wilcoxon signed-rank test compared with 0. D, day; M, month; SE, standard error. MID for improvement: −4 Fatigue, −5 Pain, +2 Physical functioning, +3 Cognitive functioning, +5 Global health status/QoL, −10 Disease symptoms, −10 Side effects of treatment. MID for deterioration: +5 Fatigue, +3 Pain, −5 Physical functioning, −1 Cognitive functioning, −5 Global health status/QoL, +10 Disease symptoms, +10 Side effects of treatment.

shown). The QLQ-MY20 primary measures (disease symptoms and side effects of treatment) showed trends toward improvement but did not achieve clinically meaningful improvements for most of the follow-up visits in the sensitivity analysis. Findings from the sensitivity analysis of secondary HRQoL measures were also generally consistent with those of the base case analysis, with slightly better "baseline" scores at the screening visit yielding slightly lower magnitude of changes thereafter (data not shown).

Discussion

This analysis of HRQoL outcomes from the KarMMa trial showed that the baseline HRQoL of patients enrolled in KarMMa was substantially worse than that of the general population. Within the first few months of ide-cel treatment, statistically significant and clinically meaningful improvements were observed in most HRQoL measures, including pain and disease symptoms by month 1, and fatigue, physical functioning, cognitive functioning, global health status/QoL, and side effects by month 2. These improvements in HRQoL generally persisted through 15 to 18 months. Results were consistent in the sensitivity analysis using scores from the screening assessment visit as "baseline" values.

In the KarMMa trial, an overall response rate was observed in 73% of patients, and CR or better was observed in 33% of patients treated with ide-cel.[12] A matching-adjusted comparisons analysis also suggested that ide-cel provides efficacy benefits over conventional care regimens in TCE patients with RRMM.[29] The findings presented in this analysis suggest that, in addition to the observed clinical benefits, ide-cel treatment is associated with sustained and clinically meaningful improvements in HRQoL. The relatively rapid posttreatment changes in nearly all functional domains and symptom scales suggest meaningful early and sustained improvements in the quality of the additional life-years gained from ide-cel treatment of TCE patients with RRMM. These HRQoL benefits were also observed among patients who achieved a VGPR or better. These findings are consistent with the ongoing analysis of qualitative data from patient interviews conducted throughout the KarMMa trial.[30,31] Patients reported high levels of pretreatment disease burden, with prominent hopes for remission (34 [85%] of 40 pretreatment interview participants) and improved HRQoL (16 [40%] of 40).[31] Posttreatment interviews described prominent patient-reported fatigue through screening and early posttreatment time points that tended to resolve within 1 month of ide-cel treatment, and 62% of patients reported improvement in physical well-being by 3 months' post-infusion.[30]

Due to many emerging novel therapeutic options for TCE patients with RRMM, HRQoL data in this population are scarce. Although cross-trial comparisons should not be given undue influence, our findings among TCE patients with RRMM are encouraging in the context of those from other RRMM treatments. For example, in the TCE RRMM patient population, HRQoL was shown to be stabilized after treatment with selinexor plus dexamethasone (STORM [Selinexor Treatment of Refractory Myeloma] Part 2)[32] or belantamab mafodotin (DREAMM-2 [A Phase II, Open Label, Randomized, Two-Arm Study to Investigate the Efficacy and Safety of Two Doses of the Antibody Drug Conjugate GSK2857916 in Participants With Multiple Myeloma Who Had 3 or More Prior Lines of Treatment, Are Refractory to a Proteasome Inhibitor and an Immunomodulatory Agent and Have Failed an Anti-CD38 Antibody]).[33] In other heavily pretreated RRMM patient populations, trends of improvement in HRQoL scores were observed at some time points for patients who received isatuximab plus pomalidomide and dexamethasone (ICARIA-MM [A Phase 3 Randomized, Open-label, Multicenter Study Comparing Isatuximab (SAR650984) in Combination With Pomalidomide and Low-Dose Dexamethasone Versus Pomalidomide and Low-Dose Dexamethasone in Patients With Refractory or Relapsed and Refractory Multiple Myeloma])[34] and for those who received pomalidomide and low-dose dexamethasone (MM-003).[35] Similar trends were reported for the A.R.R.O.W. (Once-weekly Versus Twice-weekly Carfilzomib in Combination With Dexamethasone in Adults With Relapsed and Refractory Multiple Myeloma) and PANORAMA-1 (A Multicenter, Randomized, Double Blind, Placebo Controlled Phase III Study of Panobinostat in Combination With Bortezomib and Dexamethasone in Patients With Relapsed Multiple Myeloma) trials.[36,37] Another emerging CAR T-cell therapy for patients with RRMM is ciltacabtagene autoleucel. In the CARTITUDE-1 (A Phase 1b-2, Open-Label Study of JNJ-68284528, A Chimeric Antigen Receptor T-Cell [CAR-T] Therapy Directed Against BCMA in Subjects With Relapsed or Refractory Multiple Myeloma) trial, patients treated with ciltacabtagene autoleucel showed early posttreatment improvements in HRQoL with supportive qualitative interview data.[38,39] Investigation of CAR T-cell therapy candidates for patients with relapsed or refractory B-cell acute lymphoblastic leukemia,[40] large B-cell lymphoma,[41] aggressive B-cell non-Hodgkin lymphoma,[42] or mantle cell lymphoma[43] have also shown substantial baseline burden of disease in heavily pretreated patients with meaningful post-CAR T-cell treatment improvements in HRQoL over time. These improvements in HRQoL are consistent with those reported here after a single infusion of ide-cel in the KarMMa trial.

Our findings should be considered in the context of certain strengths and limitations. This study is one of the first to report a positive impact on HRQoL among TCE patients with RRMM treated with CAR T-cell therapy. In this analysis, the use of electronic data collection may have contributed to the high completion rates observed for HRQoL instruments (>70% in months 1-6, and ~60%-70% thereafter), increasing the reliability and validity of the data. Functional and overall HRQoL in patients treated with ide-cel reached levels comparable to those of the age- and sex-matched general population, supporting a beneficial improvement in holistic treatment outcomes for a patient population with historically high disease and treatment burden, and poor prognosis and treatment options. Although HRQoL data were collected monthly during months 1 to 6 and every 3 months thereafter in the KarMMa trial, the most recent recommendations for CAR T-cell trials suggest collecting HRQoL data as frequently as once a week during the first month postinfusion.[44] Although not assessed in the current study, HRQoL may have been negatively affected by adverse events such as cytokine release syndrome immediately after ide-cel infusion. However, meaningful improvements were observed in most HRQoL measures as early as months 1 or 2 postinfusion, suggesting that patients quickly recovered from any early potential decreases in HRQoL. It should also be noted that the QLQ-MY20 instrument was developed in the context of traditional antimyeloma treatments and may not have captured the impact of side effects. Finally, the size of the HRQoL-evaluable population gradually decreased over time, and the extent of missing data was high among those remaining in the study at later follow-up visits. Because no imputation of missing HRQoL data was performed, patients with no data at later time points may have had different experiences than those who remained in the study. Therefore, data from later time points should be interpreted with caution due to the possibility that

HRQoL scores could be overestimated if patients with better HRQoL were more likely to complete the questionnaires.[45,46]

These findings have revealed HRQoL improvements complementary to the positive survival and clinical response outcomes observed with a single infusion of ide-cel in the KarMMa trial. Early and sustained improvements in pain, fatigue, and functionality were commensurate with improved overall HRQoL over time. For heavily pretreated TCE patients with RRMM who have had a poor prognosis and few treatment options, a single ide-cel infusion offered meaningful improvements in clinical and humanistic outcomes, providing patient-reported HRQoL ultimately comparable to the general population.

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The authors are fully responsible for all content and editorial decisions for the manuscript.

Authorship

Contribution: J.B., D.S.D., L.S., S.G., P.Y., W.L., and T.B.C. analyzed the data; all authors contributed to the design of the study, data acquisition, and data interpretation; and all authors participated in drafting the manuscript, provided feedback, and approved the final version ahead of submission.

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References

1. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. *J Clin Oncol.* 2010;28(5):830-834.
2. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia.* 2014;28(5):1122-1128.
3. Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc.* 2016;91(1):101-119.
4. Mikhael J. Treatment options for triple-class refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 2020;20(1):1-7.
5. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia.* 2019;33(9):2266-2275.
6. Nijhof IS, van de Donk NWCJ, Zweegman S, Lokhorst HM. Current and new therapeutic strategies for relapsed and refractory multiple myeloma: an update. *Drugs.* 2018;78(1):19-37.
7. Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia.* 2017;31(11):2443-2448.
8. Johnsen AT, Tholstrup D, Petersen MA, Pedersen L, Groenvold M. Health related quality of life in a nationally representative sample of haematological patients. *Eur J Haematol.* 2009;83(2):139-148.
9. Jordan K, Proskorovsky I, Lewis P, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. *Support Care Cancer.* 2014;22(2):417-426.
10. Engelhardt M, Ihorst G, Singh M, et al. Real-world evaluation of health-related quality of life in patients with multiple myeloma from Germany. *Clin Lymphoma Myeloma Leuk.* 2021;21(2):e160-e175.
11. Despiégel N, Touboul C, Flinois A, et al. Health-related quality of life of patients with multiple myeloma treated in routine clinical practice in France. *Clin Lymphoma Myeloma Leuk.* 2019;19(1):e13-e28.

12. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med.* 2021;384(8):705-716.

13. ABECMA® (idecabtagene vicleucel) [package insert]. Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; 2021.

14. Ruark J, Mullane E, Cleary N, et al. Patient-reported neuropsychiatric outcomes of long-term survivors after chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant.* 2020;26(1):34-43.

15. Chakraborty R, Sidana S, Shah GL, Scordo M, Hamilton BK, Majhail NS. Patient-reported outcomes with chimeric antigen receptor T cell therapy: challenges and opportunities. *Biol Blood Marrow Transplant.* 2019;25(5):e155-e162.

16. Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer.* 2013;21(2):599-607.

17. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.

18. Cocks K, Cohen D, Wisløff F, et al; EORTC Quality of Life Group. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. *Eur J Cancer.* 2007;43(11):1670-1678.

19. Fayers PM, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 2001.

20. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health.* 2012;15(5):708-715.

21. EuroQol Research Foundation. EQ-5D-5L User Guide: basic information on how to use the EQ-5D-5L instrument. https://euroqol.org/publications/user-guides/. Accessed 5 July 2021.

22. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer.* 2012;48(11):1713-1721.

23. Sully K, Trigg A, Bonner N, et al. Estimation of minimally important differences and responder definitions for EORTC QLQ-MY20 scores in multiple myeloma patients. *Eur J Haematol.* 2019;103(5):500-509.

24. Kvam AK, Fayers PM, Wisloff F. Responsiveness and minimal important score differences in quality-of-life questionnaires: a comparison of the EORTC QLQ-C30 cancer-specific questionnaire to the generic utility questionnaires EQ-5D and 15D in patients with multiple myeloma. *Eur J Haematol.* 2011;87(4):330-337.

25. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes.* 2007;5(1):70.

26. Long GV, Atkinson V, Ascierto PA, et al. Effect of nivolumab on health-related quality of life in patients with treatment-naïve advanced melanoma: results from the phase III CheckMate 066 study. *Ann Oncol.* 2016;27(10):1940-1946.

27. Nolte S, Liegl G, Petersen MA, et al; EORTC Quality of Life Group. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the United States. *Eur J Cancer.* 2019;107:153-163.

28. Szende A, Janssen B. Population norms for the EQ-5D. In: Szende A, Janssen B, Cabases J, eds. Self-Reported Population Health: An International Perspective Based on EQ-5D. Dordrecht, The Netherlands: Springer; 2014:19-30.

29. Shah N, Ayers D, Davies FE, et al. A matching-adjusted indirect comparison of efficacy outcomes for idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy versus conventional care in triple-class-exposed relapsed and refractory multiple myeloma. *Blood.* 2020;136(suppl 1):6-7.

30. Braverman J, Dhanda DS, Moshkovich O, et al. Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy: qualitative analyses of early post-treatment interviews with relapsed and refractory multiple myeloma (RRMM) patients in the KarMMa clinical trial. *Value Health.* 2021;24(suppl 1):S61.

31. Braverman J, Mashkovich O, Miera M, et al. Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy: qualitative analyses of pretreatment patient interviews in the KarMMa trial. *J Clin Oncol.* 2020;38(suppl 29):155.

32. Jagannath S, Mehta J, Breeze H, et al. Quality-of-life (QOL) analyses in patients with multiple myeloma: results from the selinexor (KPT-330) treatment of refractory myeloma (STORM) phase IIb study. *J Clin Oncol.* 2020;38(suppl 15):e20522.

33. Popat R, Lonial S, Lee HC, et al. DREAMM-2: belantamab mafodotin effect on disease symptoms and health-related quality of life in patients with relapsed/refractory multiple myeloma. *HemaSphere.* 2020;4(suppl 1):EP1746.

34. Dimopoulos M, Campana F, Bury DP, et al. Health-related quality of life in heavily pre-treated and renally impaired patients with relapsed/refractory multiple myeloma receiving isatuximab plus pomalidomide and dexamethasone: the ICARIA-MM study. *HemaSphere.* 2020;4(suppl 1):EP1028.

35. Song KW, Dimopoulos MA, Weisel KC, et al. Health-related quality of life from the MM-003 trial of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed and/or refractory multiple myeloma. *Haematologica.* 2015;100(2):e63-e67.

36. Moreau P, Kumar S, Boccia R, et al. Convenience, satisfaction, health-related quality of life of once-weekly 70 mg/m^2 vs. twice-weekly 27 mg/m^2 carfilzomib (randomized A.R.R.O.W. study). *Leukemia.* 2019;33(12):2934-2946.

37. Richardson PG, Schlossman RL, Roy AN, et al. Patient-reported outcomes of multiple myeloma patients treated with panobinostat after ≥2 lines of therapy based on the international phase 3, randomized, double-blind, placebo-controlled PANORAMA-1 trial. *Br J Haematol.* 2018;181(5):628-636.

38. Martin T III, Lin Y, Agha M, et al. Health-related quality of life in the CARTITUDE-1 study of ciltacabtagene autoleucel for relapsed/refractory multiple myeloma. *Blood.* 2020;136(suppl 1):41-42.

39. Cohen AD, Hari P, Htut M, et al. Patient expectations and perceptions of treatment in CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel in relapsed/refractory multiple myeloma. *Blood.* 2020;136(suppl 1):13-15.

40. Laetsch TW, Myers GD, Baruchel A, et al. Patient-reported quality of life after tisagenlecleucel infusion in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: a global, single-arm, phase 2 trial. *Lancet Oncol.* 2019;20(12):1710-1718.

41. Lin VW, Jiang Y, Chuang LH, et al. Health utilities for patients with relapsed or refractory large B-cell lymphoma (R/R-LBCL): ad hoc analysis from an axicabtagene ciloleucel (Axi-cel) safety management study. *Bone Marrow Transplant.* 2019;53:878-887.

42. Patrick DL, Powers A, Parisi M, et al. Impact of lisocabtagene maraleucel (liso-cel) treatment on health-related quality of life and health utility in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma: TRANSCEND NHL 001 (NCT02631044). *Br J Haematol.* 2020; 189(suppl 1):220-221.

43. Kersten MJ, Munoz J, Milpied N, et al. PCN324 patient reported outcomes among KTE-X19 CAR T treated patients with relapsed/refractory mantle cell lymphoma (R/R MCL). *Value Health.* 2020;23(suppl 2):S479.

44. Lasiter L, Campbell A, Basch E, et al. Use of patient-reported outcomes to understand & measure the patient experience of novel cell and gene therapies. *Ther Innov Regul Sci.* 2020;54(6):1566-1575.

45. Fairclough DL, Peterson HF, Chang V. Why are missing quality of life data a problem in clinical trials of cancer therapy? *Stat Med.* 1998;17(5-7): 667-677.

46. Mercieca-Bebber R, Palmer MJ, Brundage M, Calvert M, Stockler MR, King MT. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: a systematic review. *BMJ Open.* 2016;6(6):e010938.