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REALiTEC: a multi-country observational retrospective study of teclistamab in patients with relapsed/refractory multiple myeloma outside of clinical trials

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Data availability statement

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

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MCDV served as advisory board member for Takeda, Johnson & Johnson, Sanofi, Pfizer, Amgen, Menarini-Stemline and on a Speakers Bureau for Johnson & Johnson, Sanofi, Pfizer, Menarini-Stemline and GSK. MCDV also received scientific research funding from Johnson & Johnson and Pfizer.

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Author contributions

Specific contributions to the work described in this manuscript are:

- KU, KMK, AP, and RP served as steering committee members.
- KU, KMK, AP, RP, CA, DS, and ERA participated in the conception and design of the study.
- KU, KMK, AP, SLF, MC, BK, CJ, MC, MH, KW, HM, CL, CTH, MEG, TS, MCDV, TDSA, MS, MSR, SM, JA, and RP recruited patients and collected data.
- KU, KMK, AP, CA, PH, PS, DS, ERA and RP, performed the analysis and interpretation of the data.
- All authors revised the manuscript for important intellectual content.

All authors had access to the study data and reviewed and approved the final manuscript.

Abstract

Teclistamab is the first approved anti-BCMA bispecific antibody for patients with triple-class exposed relapsed/refractory multiple myeloma (RRMM), based on the results of MajesTEC-1 clinical trial. Here, we first report the findings from REALiTEC, a retrospective observational study of patients who received teclistamab outside of clinical trials in Europe and Israel. The study included 113 patients from 23 sites in eight countries, with most (88.5%) accessing the medication through pre-approval access programs. The median age was 66 years, and patients had a median of 6 prior lines of therapy. Notably, 78.8% were triple-class refractory, 44.2% penta-class refractory, and 35.4% had previous anti-BCMA treatment. Overall response rate (ORR) was 60.2%, with 52.2% of patients achieving a very good partial response or better (≥VGPR). After a median follow-up of 20.7 months, median duration of response (DoR) was 20.3 months, median progression-free survival (PFS) was 9.7 months, and median overall survival (OS) was 26.3 months. Patients attaining ≥VGPR experienced longer DOR (median 26.1 months), with 12-month PFS and OS rates of 71.2% and 83.1%, respectively. Subgroup analyses demonstrated consistent outcomes across different patient groups, even in those with historically poorer outcomes. Most common adverse events were infections (all grade: 70.8%), cytokine release syndrome (55.8%), neutropenia (35.4%), and anaemia (25.7%), with no new safety signals identified. Infection rates decreased over time, and immunoglobulin replacement therapy was used in up to 60% of patients. REALiTEC corroborates the efficacy observed in MajesTEC-1, supporting teclistamab as an effective treatment option in heavily pre-treated RRMM patients.

Keywords

Observational study; teclistamab; relapsed/refractory multiple myeloma; clinical practice

Introduction

Multiple myeloma is characterized by a pattern of continuous relapses with worsening outcomes at each line of therapy.[1,2] In the relapsed/refractory MM (RRMM) setting, prognosis for patients exposed to the three main classes of drugs for MM (proteasome inhibitors [PI], immunomodulatory drugs [IMiD], and anti-CD38 monoclonal antibodies [CD38 mAb]) (triple-class exposed, TCE) is especially poor, with a median progression-free survival (PFS) of 4.6 months and a median overall survival (OS) of 14.8 months reported when patients were treated with traditional standards of care.[3]

Teclistamab is the first approved B-cell maturation antigen/cluster of differentiation 3 (BCMA/CD3) bispecific monoclonal antibody (EMA approval: July 2022, FDA approval: October 2022), following the results of the recommended Phase II dose (RP2D) of pivotal Phase Ib/II trial MajesTEC-1.[4] The patient population was heavily pre-treated with a median of five prior lines of therapy.[5-8] After a median follow up of 30.4 months, teclistamab demonstrated deep and durable responses, with an overall response rate (ORR) of 63%, with 73% of those being complete response or better (46.1% ≥ complete response [CR] rate). Median duration of response (DOR) was 24 months and median PFS and OS were 11.4 and 22.2 months, respectively.[9] Notably, the recruitment period for MajesTEC-1 coincided with the highest peak of deaths worldwide in the COVID-19 pandemic, which adversely affected patient outcomes. Thus, a post-hoc analysis was conducted to adjust for the deaths related to COVID-19, yielding a median PFS and OS of 15.1 months and 28.3 months, respectively.[10] Additionally, a pooled analysis of three registrational studies of teclistamab monotherapy that included 217 patients showed consistent findings, with median DOR, PFS, and OS of 26.7, 15.1, and 26.3 months, respectively.[11] In the MajesTEC-1 subgroup analysis, teclistamab showed consistent response rates across different subgroups such as penta-refractory patients (resistant to all major drug classes [two PIs, two IMiDs, and CD38 mAb]), patients with high-risk cytogenetics, and patients aged more than 75 years old compared with the overall study population.[12] The most common adverse events (AEs) reported in MajesTEC-1 were infections, haematological toxicities, and cytokine release syndrome (CRS). Moreover, discontinuation rate due to AEs in MajesTEC-1 was low (4.8%, with 3% attributable to infections).[5]

Prior to teclistamab commercialisation, pre-approval access programs (PAAs) were implemented in >20 countries worldwide to allow early access for patients with a justified unmet medical

need, mainly heavily pre-treated patients with no other treatment options available or even eligible for ongoing clinical trials. Generating early data from patients treated outside of clinical trials is critical to complement clinical trial findings in broader patient populations to guide clinical practice and help define therapy management strategies. Here, we first report the results of REALiTEC, a retrospective observational study that describes the management and outcomes of patients with RRMM receiving teclistamab outside of clinical trials.

Methods

Study design

REALiTEC (NCT06285318) is a retrospective, non-interventional, multi-country study, that describes safety and effectiveness of teclistamab in RRMM patients treated outside of the clinical trial setting. Patients were eligible if they had a confirmed diagnosis of RRMM, were ≥18 years, and received ≥1 dose of teclistamab prior to 31st December 2022, outside of an interventional clinical trial. The study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The Institutional Review Board or Ethics Committee at each study site provided protocol approval. All patients provided written informed consent. Patients on PAA programs were included according to country local regulations and treated as per the summary of product characteristics (SMPC) and physician discretion.[13] Teclistamab treatment was administered by subcutaneous injection according to SMPC (step-up doses of 0.06 mg/kg and 0.3 mg/kg then 1.5 mg/kg weekly with possibility of 1.5 mg/kg SC every 2 weeks).[13] Informed consent was obtained for all alive patients prior to data collection; for deceased patients, informed consent waivers were obtained as applicable, based on country/site-specific requirements.

Data collection and outcomes

Data collection was structured using a dedicated, detailed electronic case report form (eCRF), tailored and validated to meet study requirements independently of PAAs. Retrospective data were collected from available medical records from first dose of teclistamab through date of informed consent for patients still under treatment or follow-up, and up to the date of death for deceased patients. Baseline data collected included patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities of clinical interest, haematological and chemistry laboratory parameters, disease characteristics, and prior therapies.

Responses recorded were evaluated according to the International Myeloma Working Group (IMWG) classifications. Treatment outcomes were assessed based on response rates, time to first and best response, DOR, PFS, OS, PFS2, and time to next treatment (TTNT) (see Supplemental information). Exploratory subgroup analyses were conducted in a range of subgroups of patients of clinical interest. Safety outcomes were coded using Medical Dictionary for Regulatory Activities (MedDRA). All AEs except CRS and immune cell-associated neurotoxicity syndrome (ICANS) were graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0, with CRS and ICANS graded per American Society for Transplantation and Cellular Therapy (ASTCT) guidelines.[14]

Statistical analysis

Data on patient demographics and disease characteristics were summarised using medians with a range for continuous variables and as percentages with corresponding 95% confidence intervals (CI) as appropriate for categorical variables. Time-to-event variables (e.g., DOR, PFS, OS, PFS2, and TTNT) were analysed using the Kaplan–Meier approach, with DOR calculated only among responders. Incidence and severity of all grades of CRS, ICANS, infections, and any other AE during treatment were summarized using categorical variables, with 95% Clopper-Pearson confidence intervals. Pre-specified univariate subgroup analyses were conducted for DOR, PFS, and OS. For each subgroup, hazard ratios (HRs) and corresponding 95% CIs were estimated using Cox proportional-hazards regression. Forest plots displaying HR point estimates and 95% CIs were created.

Ethics statement

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The Institutional Review Board or Ethics Committee at each study site provided protocol approval and due consent process as applicable.

Results

Patient disposition

In total, 113 eligible patients who received teclistamab on/before the 31st of December 2022 from 23 sites in eight different countries (Denmark, France, Germany, Israel, Italy, Spain, Sweden, and the United Kingdom) were included in the study. Of the 113 patients, 100 patients

(88.5%) received teclistamab as part of PAA programs. Most patients (89.4%) were treated in academic centres whilst the rest were treated in smaller community centres. All patients were admitted to hospital for step-up dosing, and median inpatient length of stay during the step-up phase, including the first full-dose, was 8 days (2–41).

At time of consent, 36 patients were on treatment and five had their treatment on hold. Seventy-two patients (63.7%) had discontinued treatment primarily due to progressive disease in 42 patients (37.2%), AEs in 18 patients (15.9%), and 6 deaths (5.3%). The 6 deaths were due to disease progression in 4 patients and due to unknown causes in 2 patients. (**Supplementary Figure 1**).

Baseline characteristics

Median age was 66 years; patients received a median of 6 (2–15) prior lines of therapy, with all being TCE, 88.5% penta-class exposed, and 78.8% and 44.2% patients were triple-class and penta-class refractory, respectively (**Table 1**). Of the patients with available data (n=62), 51.6% had high-risk cytogenetics defined as having one or more of the following abnormalities by fluorescent in-situ hybridisation: t(4;14), t(14;16), del17p13, and amp1q21. Of the 113 patients included, 80 (70.8%) would not have been eligible for the MajesTEC-1 trial because of meeting one or more of MajesTEC-1 trial exclusion criteria[9] (**Supplementary Table 1**). Notably, 40 patients (35.4%) were previously exposed to prior BCMA-directed treatments (32 to antibody-drug conjugates [ADCs], 10 to CAR-T-cell therapies, and 3 to bispecific antibody). These patients had similar baseline characteristics but had a longer median time since diagnosis (9.3 years [2.1–18.5] versus 6.1 years [0.7–24.2]) and a median of 6 (3–12) prior lines of therapy versus 5 (2–12), with most of patients having ≥5 lines of therapy (90.0% versus 58.9%). Of note, 20 of these patients received ≥1 lines of therapy in between prior BCMA and teclistamab treatment (median 2; range, 1–4).

Effectiveness

At the time of database lock, the median duration of follow-up was 20.7 months (range, 0.7–35.8) with a median treatment duration of 9.4 months (range, 0.26–35.8). Teclistamab led to an ORR of 60.2% (95% CI, 50.5–69.3%), with 52.2% of patients achieving very good partial response or better (≥VGPR) (95% CI, 42.6–61.7%) and a CR or better response (stringent CR + CR) was achieved in 26.5% of patients (95 % CI, 18.7–35.7%). A near CR (defined as a patient meeting all criteria for CR except for confirmatory bone marrow assessment) was reported in 17.7% of

patients (95% CI, 11.2–26.0%) (**Supplementary Table 2**). Median time to first response was 1.6 months (95% CI, 1.2–1.9), with a median time to best response of 3.8 months (95% CI, 2.8–5.0). Median DOR was 20.3 months (95% CI, 14.8–not estimable; NE) (**Figure 1A**); median PFS was 9.7 months (95% CI, 5.6–18.8) (**Figure 1B**); and median OS was 26.3 months (95% CI, 16.5–NE) (**Figure 1C**). PFS and OS estimates at 12 months were 47.4% (95% CI, 38.0–56.3%) and 61.9% (95% CI, 52.3–70.2%), respectively. Effectiveness was improved in patients achieving ≥VGPR, with a median DOR of 26.1 months (95% CI, 16.7–NE), and median PFS and OS were not reached (95% CI, 17.3–NE and 95% CI 26.3–NE), with 12-month estimates of 71.2% (95% CI, 57.8–81.0%) and 83.1% (95% CI, 70.8–90.5%), respectively (**Figures 1A-C**). Median TTNT (95% CI, 24.4–NE) and median PFS2 (95% CI, NE–NE) were not reached (**Supplementary Figure 2**), with 12-month estimates of 74.3% (95% CI, 65.2–81.4%) and 80.5% (95% CI, 72–86.7%), respectively.

Subgroup analyses

Exploratory subgroup analyses showed response rates to be consistent between the overall patient cohort and across selected subgroups, such as the penta-class refractory (n=50; ORR: 58.0% [95% CI, 43.2–71.8%]; ≥VGPR: 50.0% [95% CI, 35.5–64.5%), high-risk cytogenetics (n=32; ORR: 68.8% [95% CI, 50.0–83.9%]; ≥VGPR: 65.6% [95% CI, 46.8–81.4%]), patients aged ≥75 years (n=17; ORR: 64.7% [95% CI, 38.3–85.8%]; ≥VGPR: 64.7% [95% CI, 38.3–85.8%]), International Staging System III (n=21; ORR: 52.4% [95% CI, 29.8–74.3%]; ≥VGPR: 47.6% [95% CI, 25.7–70.2%]), and participants ineligible for MajesTEC-1 (n=80; ORR: 57.5% [95% CI, 45.9–68.5%], ≥VGPR: 51.3% [95% CI, 39.8–62.6%]) (**Figure 2A**). Patients without prior anti-BCMA exposure (n=73) had 63.0% ORR (95% CI, 50.9–74.0%) and 53.1% ≥VGPR (95% CI, 41.4–65.2%) as compared with 55.0% ORR (95% CI, 38.5–70.7%) and 50.0% ≥VGPR (95% CI, 33.8–66.2%) rates in those previously exposed to BCMA targeted agents (n=40). In the 32 patients previously exposed to ADC, ORR was 53.1% (95% CI, 34.7–70.9%) and ≥VGPR rate was 46.9% (95% CI, 29.1–65.3%), while in those with prior CAR-T (n=10) ORR was 50.0% and ≥VGPR rate was 50.0% (95% CI for both, 18.7–81.3%) (**Figure 2B**). We did not find any notable differences in response rates in patients who had more than 6 months elapsed between prior anti-BCMA and teclistamab treatment compared with those with less than 6 months between them. Patients without prior exposure to BCMA targeted agents had a median DOR of 20.3 months (95% CI, 12.4–NE), a median PFS of 13.8 months (95% CI, 7.5–NE), and a median OS that was not reached (95% CI, 26.3–NE), with a 12-month estimate of 65.8% (95% CI, 53.7–75.4). Conversely, those previously

exposed to anti-BCMA treatments had a median DOR of 17.4 months (95% CI 6.6–NE), a median PFS of 3.4 months (95% CI 2.6–18.8), and a median OS of 15.2 months (95% CI 4.7–NE). Overall, DOR, PFS, and OS were consistent across subgroups, with significant results consistently observed when analysing by prior BCMA exposure, more specifically prior BCMA ADCs, depth of response (≥VGPR) achieved and MajesTEC-1 eligibility. (**Supplementary Figure 3**).

Patients with a dosing schedule change

In our cohort, 45 (39.8%) patients switched to biweekly dosing after a median of 7.0 months of treatment (range, 0–18); the main reason to switch being achievement of deep responses (≥VGPR: 62.2%). Other reasons listed were patient preference in 13.3% of cases, AEs in 8.9%, convenience in 6.7%, and other in 26.7%. Moreover, 26 (23.0%) patients switched to monthly administration after a median of 10.5 months of treatment (range, 1–22), with the main reason for switching being achievement of ≥VGPR in 80.8% of cases. In the 45 patients who switched from weekly to biweekly dosing, an ORR of 82.2% (95% CI, 67.9–92.0%) was observed, with 80.0% (95% CI, 65.4–90.4%) of patients achieving ≥VGPR (**Supplementary Table 3**). Other reasons listed were patient preference in 11.5% of cases, convenience in 7.7%, and other in 19.2%. In this biweekly cohort, median DOR (95% CI, 20.3–NE), PFS (95% CI, 22.2 months–NE), and OS (95% CI, 26.3–NE) were not reached. The 12-month estimates for DOR, PFS, and OS were 85.7% (95% CI, 68.9–93.8%), 86.7% (95% CI, 72.7–93.8%), and 97.8% (95% CI, 85.3–99.7%), respectively. In the 26 patients who switched to monthly dosing, an ORR of 88.5% (95% CI, 69.8–97.6%) was reported, with 84.6% (95% CI, 65.1–95.6%) achieving ≥VGPR (**Supplementary Table 3**). In these patients, median DOR (95% CI, 20.3–NE), PFS (95% CI, 22.2–NE), and OS (95% CI, NE–NE) were also not reached. The 12-month estimates for DOR, PFS, and OS were 95% (95% CI, 69.5–99.3%), 92.3% (95% CI, 72.6–98.0%), and 96.2% (95% CI, 75.7–99.4%), respectively.

Safety findings

The most common all-grade AEs (≥20% of patients) were infections (70.8%), CRS (55.8%), neutropenia (35.4%), and anaemia (25.7%) (**Table 2**). Overall, 18 (15.9%) patients discontinued therapy, 53 (46.9%) delayed a dose, 34 (30.1%) skipped a dose, and one (0.9%) reduced dose due to AEs. A total of 13 patients had fatal AEs, five of which were considered related to teclistamab (**Supplementary Table 4**).

Ninety CRS events occurred in 63 patients (55.8%), with 19 patients (16.8%) experiencing multiple CRS events. Events were grade 1–2 in most patients (98.2%), with grade 3 events occurring in two patients. Most CRS events (94.4%) occurred after a step-up dose or the first maintenance dose and had a median duration of 2 days (range, 1–23) and all of them resolved. CRS was managed with antipyretics in 33 patients (29.2%), tocilizumab in 17 patients (15%), corticosteroids in 11 patients (9.7%), intravenous fluids in 6 patients (5.3%), vasopressors in 1 patient (0.9%), and other treatments in 18 patients (15.9%). No prophylactic tocilizumab was reported in our cohort. Six grade 1–2 ICANS events were observed in 4 (3.5%) patients, with 1 patient experiencing multiple ICANS events that did not worsen with subsequent events. No grade ≥3 ICANS events were observed. Two ICANS events were concurrent with CRS. All ICANS events occurred after a step-up dose or the first maintenance dose and lasted a median of 1.5 days (range, 1–6). No patients discontinued teclistamab due to either CRS or ICANS.

Eighty (70.8%) patients experienced 261 infections, with 29 patients (25.7%) experiencing maximum grade 1–2 events, 44 (38.9%) had maximum grade 3–4 events, and 6 patients (5.3%) had grade 5 events. A total of 60 patients (53.1%) had multiple infectious events. Fatal infections were 3 septic shock and 3 pneumonia cases (**Table 3; Supplementary Table 4**). Among the classified infections, most infections were viral or bacterial (n=70 and n=66, respectively), with only 5 fungal infection events reported. Bacterial infections (grade 3–4) generally had an earlier onset than viral infections (63.5 days vs 148.0 days), with a median duration of 14.0 (1–181) and 15.5 (1–273) days, respectively (**Table 3**). Median time to infection of any grade was 128.0 days (1–1062), and median time to grade 3–4 was 99.0 days (2–820). Median duration of infectious events was 15.0 days (range, 1–300). Overall, 90.3% of infections resolved, or were resolving, at data cut-off. Generally, infection rates declined over time (**Figure 3**).

Overall, 80.5% of patients received any prophylactic medication before teclistamab initiation (including, n=19 [16.8%] for the management of CRS; n=2 [1.8%] for management of ICANS; n=46 [40.7%] for management of infections). A total of 45.1% of patients received ≥1 growth factors during treatment, 22.1% reported as prophylaxis. Eleven patients (9.7%) received ≥1 cycle of radiotherapy during teclistamab treatment. Immunoglobulin replacement therapy (IgRT) was prescribed in 68 patients (60.2%), with most of these patients receiving it as primary prophylaxis (70.6%). Median start time of IgRT was 78.0 days (range, 0–391). Most patients (n=59) received intravenous IgG whilst some received subcutaneous IgG (n=13). Other infectious

prophylaxis strategies reported before initiation of teclistamab were antibiotics in 23.0% of patients, antivirals in 29.2%, and antifungal agents in 5.3%. Treatments for infections were reported in 74 patients (65.5%), including antibiotics in 72 patients (63.7%), antivirals in 26 (23.0%), antifungals in 11 (9.7%), and IVIg used as treatment in 55 (48.7%), and intravenous fluids in 11 (9.7%). AEs led to teclistamab discontinuation in 20 patients (17.7%), 10 (8.8%) of which were due to infections.

Subsequent treatments

Overall, 39 (34.5%) patients received ≥1 subsequent treatments, of which 5 patients (4.4%) received one subsequent line of therapy, 1 patient (0.9%) each received two and three lines of therapy, and 32 patients (28.3%) received ≥4 lines of therapy. Fifteen patients received talquetamab, 13/15 patients as monotherapy. Other treatments were combinations based on PIs (n=22; 19.5%); alkylating agents (n=17; 15.0%), most commonly cyclophosphamide; IMiDs (n=13; 11.5%), most commonly pomalidomide; and anti-CD38 (n=9; 8.0%). Overall, 19 patients (16.8%) had subsequent treatment regimens containing glucocorticoids (dexamethasone, prednisone, and other corticosteroids). Six patients (5.3%) received BCMA CAR-T.

In patients where responses were reported, the ORR to subsequent treatments (as monotherapy or in combination) were: 45.5% (5/11) with talquetamab (all of them being ≥VGPR); 80.0% (4/5) with BCMA CAR-T (of which 20% were ≥VGPR) and 37.5% (6/16) with PI-based combinations (of which 12.5% patients were ≥VGPR).

Discussion

REALiTEC aimed at comprehensively describing clinical outcomes in RRMM patients treated with teclistamab outside of clinical trials across several European countries. This study's novelty includes a long follow-up (median 20.7 months), the enrolment of a difficult-to-treat patient population, consistent with the expected characteristics of PAA patients, and the use of a detailed electronic case report form (eCRF) modelled on clinical trial case report forms that facilitated the collection of extensive data. Teclistamab showed notable effectiveness results and a safety profile consistent with that previously reported.

We reported an ORR of 60.2% with most responses being ≥VGPR (52.2%), consistent with the ORRs reported in MajesTEC-1 long-term follow-up (30.4 months). In REALiTEC, ≥CR rates were lower compared with MajesTEC-1 (46.1%), because confirmatory bone marrow assessments

were not frequently performed. However, if we account for ≥CR and near CR rates, we observed a rate of 44.2%, in line with the pivotal trial results. Moreover, the ORR of 60.2% and the 52.2% ≥VGPR rate observed fall within the range of ORRs and ≥VGPR rates reported in other real-world studies.[12,15-20]

The 20.7 month follow-up was substantially longer compared with other teclistamab real-world studies, where median follow-ups range between 3.8 and 16 months.[21-23] We observed a median DOR of 20.3 months, a median PFS of 9.7 months, and a median OS of 26.3 months. In the MajesTEC-1 study, median DOR was 24 months, median PFS was 11.4 months, and median OS was 22.2 months. Nevertheless, comparisons with MajesTEC-1 should be made with BCMA naïve patients, as this was an exclusion criterion for the trial. Thus, in our cohort's subgroup of BCMA-naive patients, we observed a median DOR of 20.3 months, a median PFS of 13.8 months, and a median OS that was not reached, which favourably compared with the outcomes of the MajesTEC-1 overall RP2D cohort, especially considering the harder-to-treat patient population of our study. In other real-world cohorts, median PFS ranged from 5.4 to not reached, but due to the short median follow-up of those studies and variable patient characteristics, any comparisons should be made with caution.[12,22] Moreover, consistent with prior findings, we observed that achieving deep responses (≥VGPR) had a significant impact on DOR, PFS, and OS. This was also observed in MajesTEC-1, where achieving deep responses was crucial for prolonged long-term survival outcomes, with 25.6 months median DOR, 26.7 months median PFS, and median OS not reached in patients achieving ≥VGPR. When considering subgroup analyses, we observed similar response rates in subgroups with historically poorer outcomes as compared with the overall cohort. This is concordant with MajesTEC-1, where response rates were close between the overall RP2D population and penta-class refractory patients, patients with high-risk cytogenetics, and patients aged over 75 years.

Considering prior BCMA treatment, we found that teclistamab led to clinically meaningful responses in BCMA exposed patients, with 55.0% ORR and ≥VGPR rate of 50.0%. These results are consistent with those reported in MajesTEC-1 cohort C, in which an ORR of 52.5% and a ≥VGPR of 47.5% were observed. Patients treated with prior ADC and prior CAR-T also had similar response rates in REALiTEC as compared with MajesTEC-1 cohort C; however, comparison of those results need to be made with caution as only 10 patients were treated with prior BCMA CAR-T in our cohort and, of those, five were also treated with BCMA ADC. Interestingly, we

found significantly impaired outcomes in patients treated with prior ADC. Tan *et al*. also found a significant impact of prior BCMA-targeting therapies on PFS, but no significant differences according to type of prior treatment.[17] In contrast with our findings, a recent large US real-world study (n=509) showed that an independent predictor of impaired responses and shorter PFS included BCMA-directed CAR-T therapy in the previous 9 months but not prior ADC exposure, that exhibited a comparable response rate to those without prior BCMA-directed therapy.[18] Taken together, patient characteristics and prior immunotherapies resulting in T-cell exhaustion, as well as BCMA downregulation and shorter washout intervals between BCMA-directed therapies may reduce immune engagement with teclistamab, raising the question about the optimal sequencing of BCMA agents and its management.

As in MajesTEC-1, in REALiTEC, responses were sustained when patients were switched to less frequent dosing after they achieved deep responses.[9] In our cohort, 45 patients switched to biweekly dosing and 26 to monthly dosing after a median of 7.0 and 10.5 months, respectively. These patients were deep responders with high response rates from therapy initiation that were maintained over time, that enabled switching to less frequent dosing even in a heavily pre-treated patient population.

The safety profile in REALiTEC is also consistent with MajesTEC-1, where the most common any-grade AEs were cytopenia (neutropenia 71.5% and anaemia 55.2%), infections (78.8%), and CRS (72.1%). In our cohort, most CRS events were low grade, a common feature of the safety profile of BCMA bispecifics that was also observed in MajesTEC-1[9,10,15] and real-world cohorts.[10-12,16-18,21,22] Similarly, ICANS events were generally mild. No patients discontinued treatment due to CRS and ICANS, consistent with that previously reported.[9,10,15]

Infections are a common complication within the broader setting of RRMM and with BCMA-bispecific antibodies, and still the main cause of death in patients with myeloma.[24] In our study, infections were common with grade 3–4 events occurring in 38.9% of patients and grade 5 events in 5.3%. In the long-term follow-up of MajesTEC-1, all-grade infections were observed in 78.8% of patients, 55.2% of which were grade 3–4. Grade 5 infections occurred in 22 patients (13.3%), but 18 of those were due to COVID-19. Lower rates of grade 3–4 infection and hematologic toxicities in REALiTEC compared with MajesTEC-1 have also been observed in other real-world cohorts[17] and likely reflect improved awareness and more proactive supportive care, as well as differences in reporting and monitoring as real-world clinical management studies

have inherently less intensive AE capture than clinical trials.[25] Also, consistent with MajesTEC-1, the incidence of infections in our study declined over time, coinciding with the switch to less frequent dosing (after months 7 and 10 corresponding to switching to biweekly and monthly dosing) and implementation of IgG supplementation (although no causality was examined).

As part of infection prevention, patients receiving teclistamab should undergo comprehensive viral screening, maintain up-to-date vaccinations, and receive tailored prophylaxis as well as routine IgG replacement therapy (IgRT). The importance of IgRT has been established, with primary prophylaxis with IVIg being associated with a significantly lower risk of serious infections (5.3% incidence at 6 months with IVIg vs 54.8% with observation in MajesTEC-1). Likewise, in a retrospective, real-world study, it was observed that primary IVIg prophylaxis significantly improved all-grade and grade ≥3 infection-free survival[21]. In our cohort, we observed 60.2% of patients receiving IgG replacement with most patients receiving it as primary prophylaxis. All this emphasizes how critical it is to use IgG replacement to avoid infections and maintain patients on treatment to achieve the best outcomes.[26]

Limitations of our study are its retrospective design, evaluation without a comparator and without longer-term clinical outcomes. Other limitations of REALiTEC, typical of real-world studies, include differences in patient selection, prior therapies, supportive care, treatment algorithms, and management as well as variations in toxicity and response assessments. The absence of data for some assessments (e.g. MRD negativity rates) and key prognostic variables, such as cytogenetics and detailed IgG levels over time has also impeded further detailed analysis. Accordingly, in some subgroup analyses, only a small number of patients could be considered for the analysis. Contrarily, the study's strengths include its design, the abovementioned detailed eCRF, capturing diverse patient populations not routinely included in clinical trials, and including many early teclistamab-treated patients.

Overall, our findings provide robust data to support treatment decisions around the use of teclistamab in patients with hard-to-treat RRMM. More than >20,800 patients have been treated worldwide to date with commercial teclistamab [Data on file. Johnson & Johnson. 2025]. Data generation in the subsequent cohort of REALiTEC, REALiTEC-2, will help inform optimal patient management, sequencing, and outcomes in the real world.

Conclusions

REALiTEC demonstrates comparable effectiveness and safety to those reported in MajesTEC-1 in patients treated outside of clinical trials. Overall, these findings further validate teclistamab as an effective standard of care in this difficult-to-treat patient population.

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Tables and Figures

Table 1 – Summary of baseline characteristics in REALiTEC (N=113 patients)[a]

Characteristic	**n=113[b]**
Age, years, median (range)	66.0 (43–83)
<65 years, n (%)	47 (41.6)
≥65 to <75 years, n (%)	49 (43.4)
≥75 years, n (%)	17 (15.0)
Male, n (%)	57 (50.4)
Weight, kg, median (range)	71.9 (42.0–118.1)
Race, n (%)	
White	83 (73.5)
Black	3 (2.7)
Multiple	1 (0.9)
Unknown/not reported	26 (23.0)
ECOG PS ≥1, n/N (%)	27/49 (55.1)
LDH >245 U/L, n/N (%)[c]	28/86 (32.6)
Years since diagnosis, median (range)	7.4 (0.7–24.2)
Extramedullary plasmacytoma, n/N (%)	9/59 (15.3)
ISS stage, n/N (%)	
I	32/94 (34.0)
II	41/94 (43.6)
III	21/94 (22.3)
High-risk cytogenetics,[d] n/N (%)	32/62 (51.6)
t(4;14)	12/62 (19.4)
t(14;16)	1/62 (1.6)
del17p13	18/62 (29.0)
amp1q21	13/62 (21.0)
Previous lines of therapy, median (range)	6 (2–12)
Triple-refractory, n (%)	89 (78.8)

Penta-refractory, n (%)	50 (44.2)
Refractory to the last line of therapy, n (%)	86 (76.1)
Prior autoSCT, n (%)	86 (76.1)
Prior alloSCT, n (%)	8 (7.1)
Prior BCMA, n (%)	40 (35.4)
Number of prior BCMA therapies	45
CAR-T	10
ADC	32
BsAbs	3
Patients ineligible for MajesTEC-1, n (%)	80 (70.8)
Creatinine clearance/GFR, mL/min or mL/min/1.73 m^2	
<30	3/104 (2.9)
≥30 to <40	11/104 (10.6)
≥40	90/104 (86.5)
Hb ≥80 g/L, n/N (%)	103/112 (92.0)
Platelet count ≥75 × 10^9 cells/L, n/N (%)	86/112 (76.8)
ANC ≥1 × 10^9 cells/L, n/N (%)	91/102 (89.2)

[a]17 patients from 3 sites in the REALiTEC cohort overlap with the French EAP cohort (RetrosTECtive study, which enrolled patients from 14th October 2022 to 14th September 2023). Since REALiTEC only included patients treated prior to 31st December 2022, these patients had an overlap of approximately 3 months. Given the limited temporal window and the small number of patients from the overlapping sites, any duplication is expected to be minimal. [b]Data available added as denominators if some were missing and not available in the clinical chart for the whole cohort. [c]Baseline LDH stratification value of 245 U/L represents the institutional ULN. [d]High-risk cytogenetics defined as having presence of t(4;14), t(14;16), del17p13, and amp1q21 by fluorescent in situ hybridization.

ADC, antibody-drug conjugate; ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T-cell therapy; ECOG, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; Hb, hemoglobin; Ig, immunoglobulin; ISS, International Staging System; LDH, lactate dehydrogenase; SCT, stem cell transplant; ULN, upper limit of normal.

Table 2 – Summary of safety outcomes in REALiTEC (N=113 patients)

TEAE, n (%)	n=113	
	Any grade, n (%)	Grade 3/4, n (%)
Patients with any TEAE	108 (95.6)	83 (73.5)
Infections	80 (70.8)	49 (43.4)
Pneumonia	24 (21.2)	16 (14.2)
SARS-CoV2 virus (COVID-19)	17 (15.0)	8 (7.1)
Infection (unknown)	12 (10.6)	2 (1.8)
Upper respiratory tract infection	11 (9.7)	0
CMV reactivation	3 (2.7)	1 (0.9)
Hematologic TEAEs		
Neutropenia	40 (35.4)	37 (32.7)
Anemia	29 (25.7)	19 (16.8)
Thrombocytopenia	21 (18.6)	17 (15.0)
Nonhematologic TEAEs		
CRS	63 (55.8)	2 (1.8)
Diarrhea	17 (15.0)	0
Neurologic TEAEs of interest		
Peripheral sensory neuropathy	5 (4.4)	0
ICANS	4 (3.5)	0
Motor dysfunction	1 (0.9)	0
Encephalopathy[a]	3 (2.7)	1 (0.9)

[a]Includes toxic encephalopathy and encephalopathy.

CMV, cytomegalovirus; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; TEAE, treatment-emergent adverse event.

Table 3 – Summary of infections in REALiTEC (N=113 patients)

Infections	Total	Bacterial[a]	Viral[a]
Patients with any event, n (%)	**80 (70.8)**	**36 (31.9)**	**36 (31.9)**
Patients with multiple events, n (%)	60 (53.1)	18 (15.9)	17 (15.0)
Patients with grade 3/4, n (%)	44 (38.9)	25 (22.1)	14 (12.4)
Patients with grade 5, n (%)	6 (5.3)	2 (1.8)	1 (0.9)
Number of infection events	**261**	**66[a]**	**70[a]**
Time to onset, median days to event (range)	128.0 (1–1062)	101.0 (2–1062)	126.0 (1–859)
Grade 3/4 infection onset, median days to event (range)	99.0 (2–820)	63.5 (2–734)	148.0 (4–820)
Duration, median event days (range)	15.0 (1–300)	14.0 (1–181)	15.5 (1–273)
Patients with AE leading to dose interruption, n (%)	**52 (46.0)**	**19 (16.8)**	**25 (22.1)**
Patients with AE leading to discontinuation, n (%)	**10 (8.8)**	**2 (1.8)**	**4 (3.5)**
Events recovering, recovered or resolved,[b] n (%)	**236/261 (90.4)**	**62/66 (93.9)**	**64/70 (91.4)**

[a]Classifications of some infections (n=120) were not recorded due to unavailability of medical records; 5 fungal infections were also reported. [b]Includes recovered/resolved, recovered/resolved with sequelae, recovering/resolving.

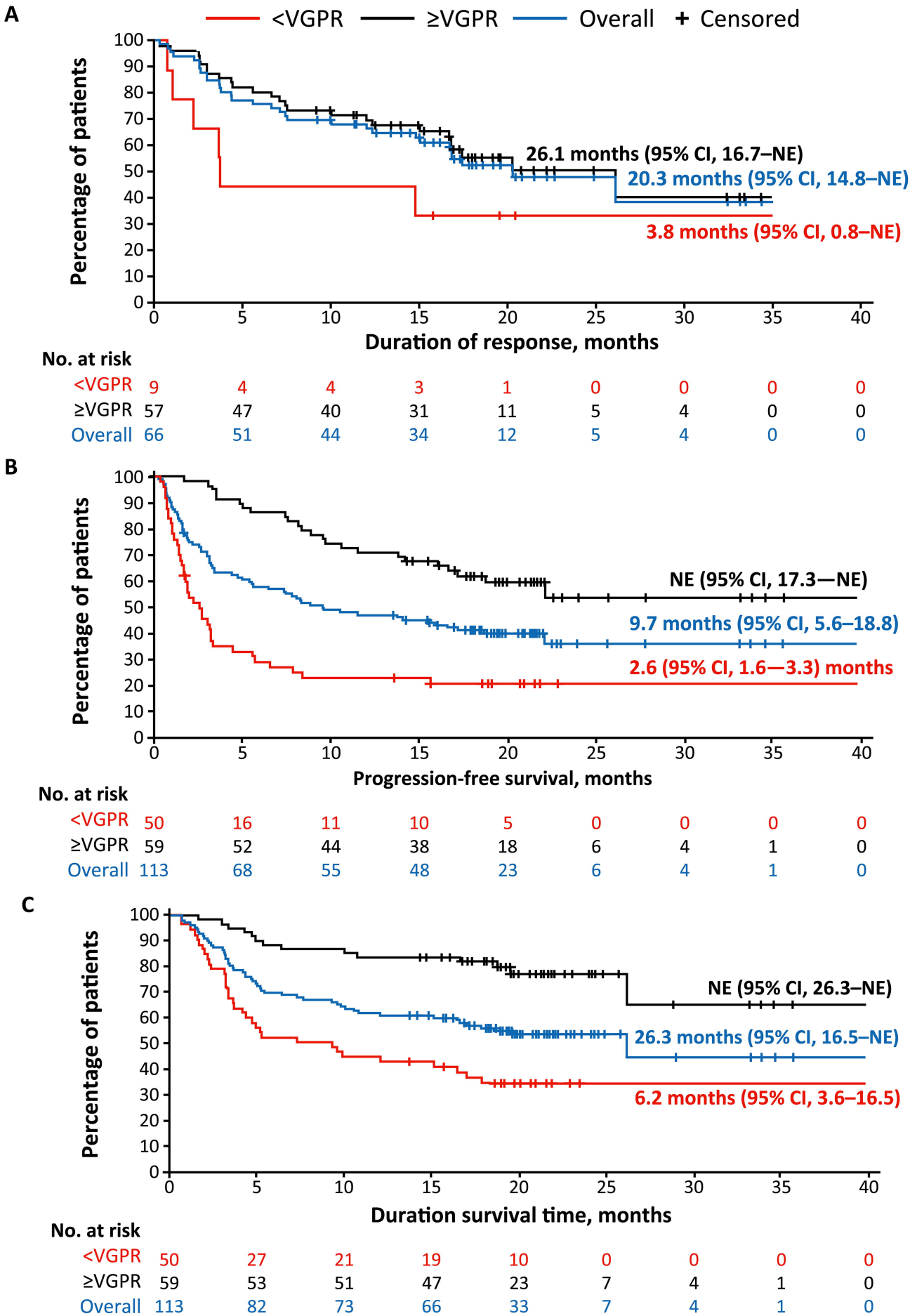
Figure 1. Kaplan–Meier plots in the overall REALiTEC patient population and in patients achieving ≥VGPR and <VGPR. A) DOR; B) PFS and C) OS.

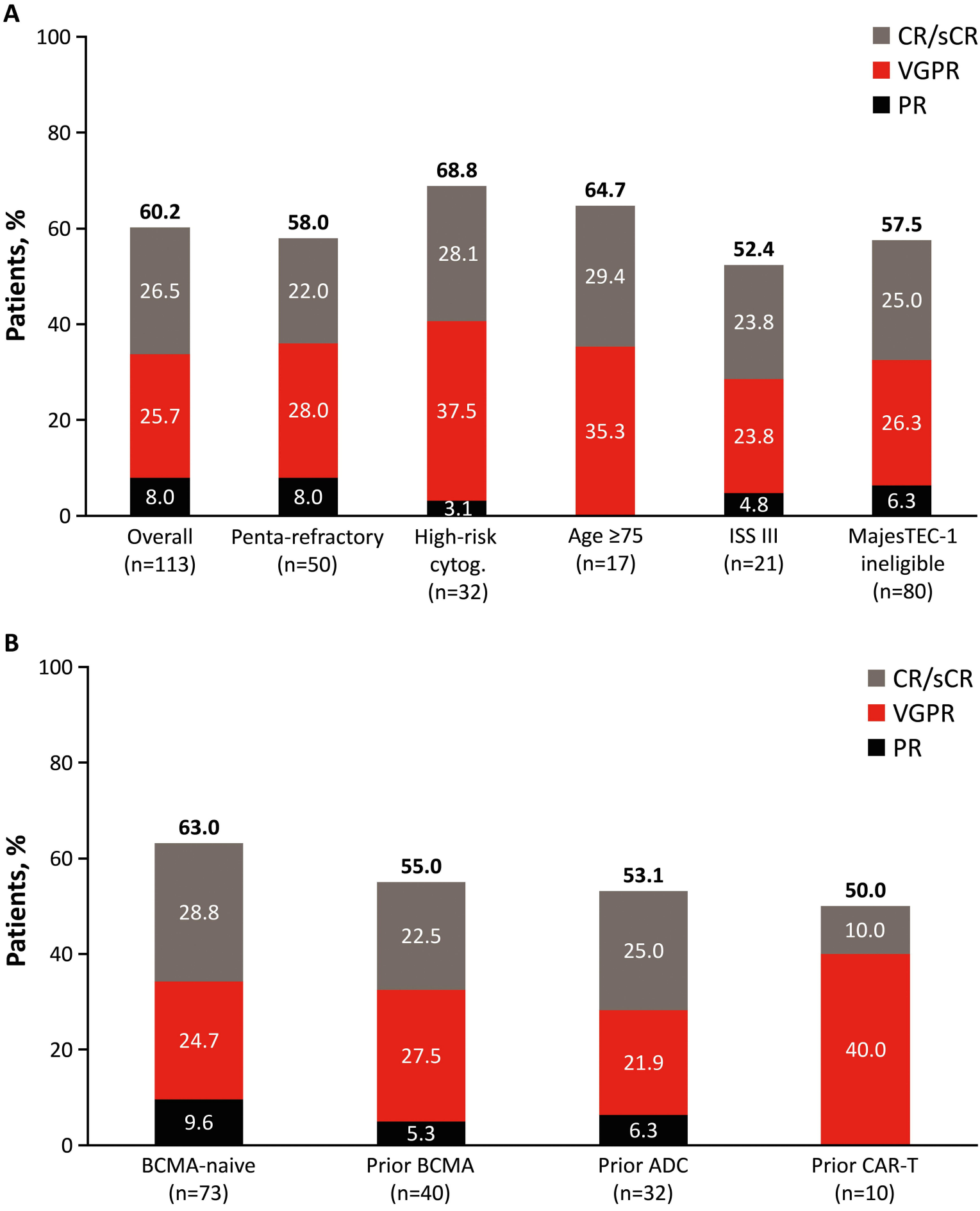
Summary data shown are median (95% CI). CI, confidence interval; DOR, duration of response; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response.

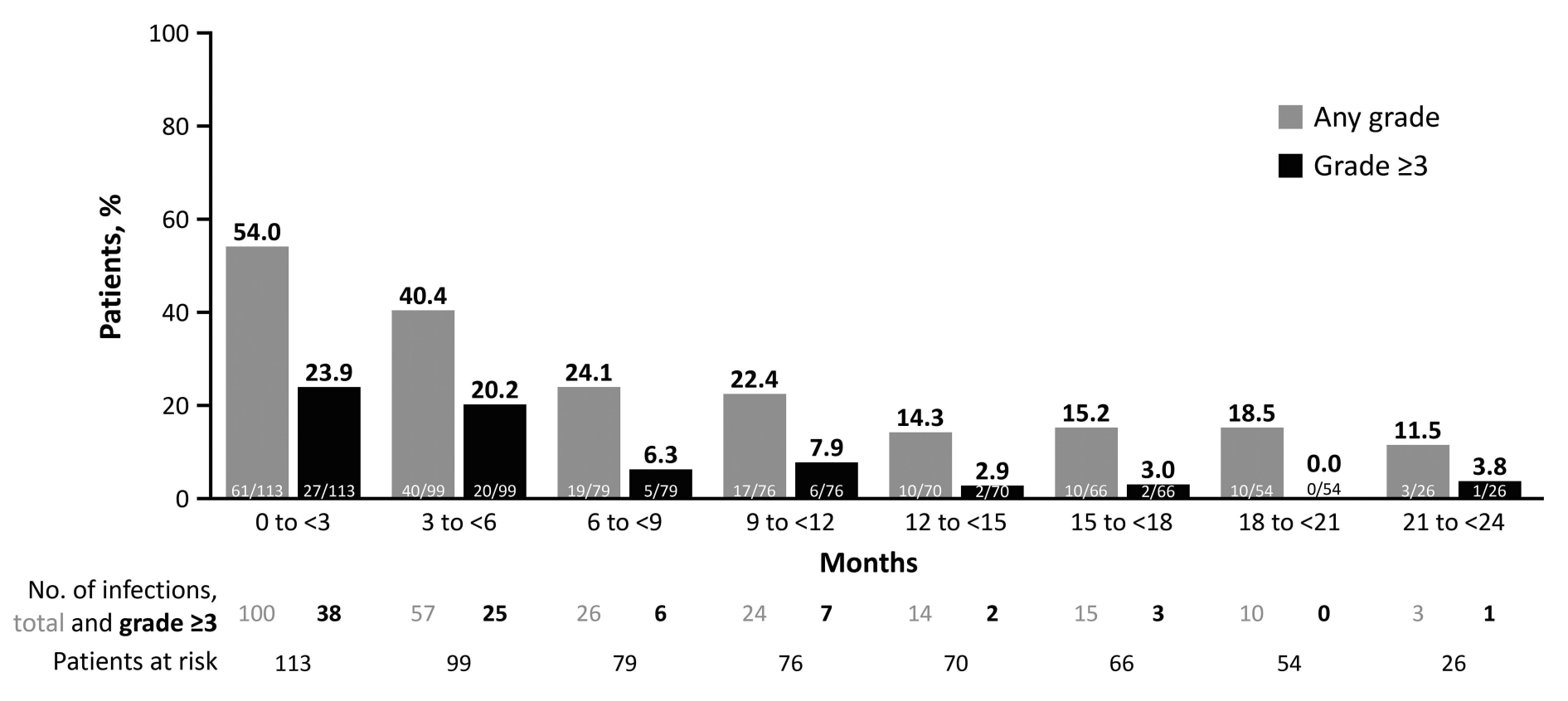
Figure 2. Bar graph showing response rates (ORRs [≥VGPR and PR]) across selected subgroups of patients in REALiTEC. A) Patients with high-risk subgroups and B) with prior BCMA (ADC and CAR-T).

ADC, antibody-drug conjugate; BCMA, B cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; ISS, International Scoring System; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

Figure 3. Incidence of infections over time in the overall REALiTEC population.


A
<VGPR
≥VGPR
Overall
Censored
Percentage of patients
26.1 months (95% CI, 16.7–NE)
20.3 months (95% CI, 14.8–NE)
3.8 months (95% CI, 0.8–NE)
Duration of response, months
No. at risk
<VGPR 9 4 4 3 1 0 0 0 0
≥VGPR 57 47 40 31 11 5 4 0 0
Overall 66 51 44 34 12 5 4 0 0
B
Percentage of patients
NE (95% CI, 17.3—NE)
9.7 months (95% CI, 5.6–18.8)
2.6 (95% CI, 1.6—3.3) months
Progression-free survival, months
No. at risk
<VGPR 50 16 11 10 5 0 0 0 0
≥VGPR 59 52 44 38 18 6 4 1 0
Overall 113 68 55 48 23 6 4 1 0
C
Percentage of patients
NE (95% CI, 26.3–NE)
26.3 months (95% CI, 16.5–NE)
6.2 months (95% CI, 3.6–16.5)
Duration survival time, months
No. at risk
<VGPR 50 27 21 19 10 0 0 0 0
≥VGPR 59 53 51 47 23 7 4 1 0
Overall 113 82 73 66 33 7 4 1 0


A
CR/sCR
VGPR
PR
Patients, %
100
80
60
40
20
0
60.2
26.5
25.7
8.0
58.0
22.0
28.0
8.0
68.8
28.1
37.5
3.1
64.7
29.4
35.3
52.4
23.8
23.8
4.8
57.5
25.0
26.3
6.3
Overall (n=113)
Penta-refractory (n=50)
High-risk cytog. (n=32)
Age ≥75 (n=17)
ISS III (n=21)
MajesTEC-1 ineligible (n=80)
B
CR/sCR
VGPR
PR
Patients, %
100
80
60
40
20
0
63.0
28.8
24.7
9.6
55.0
22.5
27.5
5.3
53.1
25.0
21.9
6.3
50.0
10.0
40.0
BCMA-naive (n=73)
Prior BCMA (n=40)
Prior ADC (n=32)
Prior CAR-T (n=10)


Patients, %
100
80
60
40
20
0
Any grade
Grade ≥3
54.0
23.9
40.4
20.2
24.1
6.3
22.4
7.9
14.3
2.9
15.2
3.0
18.5
0.0
11.5
3.8
61/113
27/113
40/99
20/99
19/79
5/79
17/76
6/76
10/70
2/70
10/66
2/66
10/54
0/54
3/26
1/26
0 to <3
3 to <6
6 to <9
9 to <12
12 to <15
15 to <18
18 to <21
21 to <24
Months
No. of infections, total and grade ≥3
100 38
57 25
26 6
24 7
14 2
15 3
10 0
3 1
Patients at risk
113
99
79
76
70
66
54
26

Supplementary material

Methods

Definitions of response

Duration of response (DOR) was defined as the time interval from the date of first response to the date of first evidence of progressive disease based on available data, or death due to any cause, whichever occurs first. For patients who did not progress, their outcome was censored at the last date collected from the medical records before the start of any subsequent antimyeloma therapy.

Progression-free survival (PFS) was defined as the time interval from the date of first response to the date of first evidence of progressive disease, as assessed by the investigator based on available data, or death due to any cause, whichever occurred first. For patients who did not progress, the patient's outcome was censored at the last date collected from the medical records before the start of any subsequent antimyeloma therapy.

PFS2 was defined as the time interval from the date of first dose of teclistamab to the date of progressive disease occurring after the start of subsequent antimyeloma therapy, as assessed by the investigator based on available data, or death from any cause, whichever occurred first. For patients who received subsequent antimyeloma therapy and were alive without documented disease progression, or who did not receive subsequent therapy, or who died before receiving subsequent therapy, the patient's outcome was censored at the last date collected from the medical records.

Overall survival (OS) was defined as the time interval from the date of first dose of teclistamab to the date of patient death due to any cause. If the patient was alive or vital status was unknown, then the patient's outcome was censored at the last date collected from the medical records (not restricted by the start of any subsequent antimyeloma therapy).

Time to next treatment (TTNT) was defined as the time from the date of first dose of teclistamab to the start of the next line of antimyeloma treatment.

Supplementary Table 1. Summary of baseline characteristics that would have made patients ineligible for MajesTEC-1 clinical trial at baseline (All Treated Analysis Set; N=113) [8]

Baseline characteristics in REALiTEC that are ineligibility criteria for MajesTEC-1	**Number of participants**
Total meeting ineligibility criteria	80 (70.8%)
Prior BCMA therapy received	40 (35.4%)
Baseline ECOG score ≥2	8 (7.1%)
Baseline cytopenia (including either of the following)	31 (27.4%)
Haemoglobin <8.0 g/dL	9 (8.0%)
Platelet count <50 x 10^9/L	22 (19.5%)
Absolute neutrophil count <1.0 x 10^9/L	11 (9.7%)
ALT >3 x ULN	0
AST >3 x ULN	0
Compromised renal status (including either of the following)	23 (20.4%)
Serum creatinine >1.5 mg/dL	19 (16.8%)
Creatinine clearance/GFR <40 mL/min or mL/min/1.73m^2	14 (12.4%)
Cardiac comorbidities (including any of the following)	3 (2.7%)
NYHA stage III or IV congestive heart failure ≤28 days before starting teclistamab	0
Myocardial infarction or CABG ≤6 months prior to the first dose of teclistamab	1 (0.9%)

History of clinically significant ventricular arrhythmia or unexplained syncope ≤28 days before starting teclistamab	1 (0.9%)
History of severe non-ischaemic cardiomyopathy ≤28 days before starting teclistamab	2 (1.8%)
Active autoimmune disease or a documented history of autoimmune disease ≤28 days before starting teclistamab	1 (0.9%)
Active malignancies other than MM ≤28 days before starting teclistamab (including any of the following)	4 (3.5%)
Plasma cell leukaemia (>2.0 x 10^9/L plasma cells by standard differential)	1 (0.9%)
Myelodysplastic syndrome	1 (0.9%)
Other active malignancies	2 (1.8%)
Active CNS involvement or clinical signs of meningeal involvement of MM ≤28 days before starting teclistamab	1 (0.9%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCMA, B cell maturation antigen; CABG, coronary artery bypass graft; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; MM, multiple myeloma; NYHA, New York Heart Association; ULN, upper limit of normal.

Supplementary Table 2: Summary of overall best confirmed response in overall (all-treated) study population (N=113)

	N (%)	95% CI for %
Response category		
Stringent complete response (sCR)	6 (5.3)	2.0–11.2
Complete response (CR)	24 (21.2)	14.1–29.9
Very good partial response (VGPR)	29 (25.7)	17.9–34.7
Partial response (PR)	9 (8.0)	3.7–14.6
Minimal response	1 (0.9)	0.0–4.8
Stable disease	11 (9.7)	5.0–16.8
Progressive disease	18 (15.9)	9.7–24.0
Not available / not reported	15 (13.3)	7.6–20.9
Overall response (sCR + CR + VGPR + PR)	68 (60.2)	50.5–69.3
VGPR or better (sCR + CR + VGPR)	59 (52.2)	42.6–61.7
CR or better (sCR + CR)	30 (26.5)	18.7–35.7
Near CR	20 (17.7)	11.2–26.0

Responses were as assessed by the investigator per IMWG response criteria. Near CR is defined as the proportion of patients who have a near CR as assessed by the investigator per IMWG response criteria. Per such criteria, a patient is considered to have a Near CR if both of the following are recorded: 'Very Good Partial Response' and 'Yes, CR can't be confirmed due to missing bone marrow assessment, whereas all other criteria for CR are met.'

Supplementary Table 3: Efficacy data in patients who switched from weekly dosing to either biweekly (N=45) or monthly dosing (N=26)

	Switch to biweekly (n=45)	Switch to monthly (n=26)
Time to switch, median (range)	7.0 months (0–18)	10.5 months (1–22)
Overall response (sCR + CR + VGPR + PR), % (95% CI)	82.2 (67.9–92.0)	88.5 (69.8–97.6)
≥ VGPR (sCR + CR + VGPR), % (95% CI)	80.0 (65.4–90.4)	84.6 (65.1–95.6)
CR or better, % (95% CI)	44.4 (29.6–60.0)	42.3 (23.4–63.1)
Near CR, % (95% CI)	31.1 (18.2–46.6)	34.6 (17.2–55.7)
DoT, months, median (range)	18.9 (2.6–35.8)	18.1 (1.4–35.8)
DoR, median (range)	NE (20.3–NE)	NE (20.3–NE)
PFS, median (range)	NE (22.2–NE)	NE (22.2–NE)
12 month estimate, %	86.7	92.3
OS, median (range)	NE (26.3–NE)	NE (NE–NE)
12 month estimate, %	97.8	96.2

95% CI, 95% confidence interval; CR, complete response; DoR, duration of response; DoT, duration of treatment; NE, not evaluable; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response. Responses were as assessed by the investigator per IMWG response criteria. Near CR is defined as the proportion of patients who have a near CR as assessed by the investigator per IMWG response criteria. Per such criteria, a patient is considered to have a Near CR if both of the following are recorded: 'Very Good Partial Response' and 'Yes, CR can't be confirmed due to missing bone marrow assessment, whereas all other criteria for CR are met.'

Supplementary Table 4. Listing of fatal (Grade 5) treatment-emergent adverse events – All treated analysis set

Age (years)	Sex	Preferred term	Reported term	Day of AE onset[a]	Duration of AE (days)	Relationship to teclistamab[b]	Action taken	Concomitant or additional therapy
66	Male	Acute kidney injury	Acute renal failure	109	1	Not related	Not applicable	Yes
68	Male	General physical health deterioration	Poor general condition	54	22	Not related	Drug withdrawn	Yes
82	Female	Febrile neutropenia	Febrile neutropenia	165	1	Related	Drug withdrawn	Yes
72	Male	Pneumonia escherichia	Bacteremic pneumonia due to *Escherichia coli*	96	1	Not related	Drug withdrawn	No
70	Male	Respiratory distress	Febrile respiratory distress	94	1	Not related	Not applicable	No
73	Male	Septic shock	Septic shock	131	1	Related	Not applicable	No
66	Male	Hyponatraemia Hypovolaemia	Hyponatraemia Mild hypovolumia	20 20	1 1	Related Not related	Not applicable Drug withdrawn	Unknown Unknown
74	Male	Septic shock	Septic shock	101	1	Not related	Dose not changed	No
62	Female	Septic shock	Septic shock	152	1	Not related	Drug withdrawn	Yes

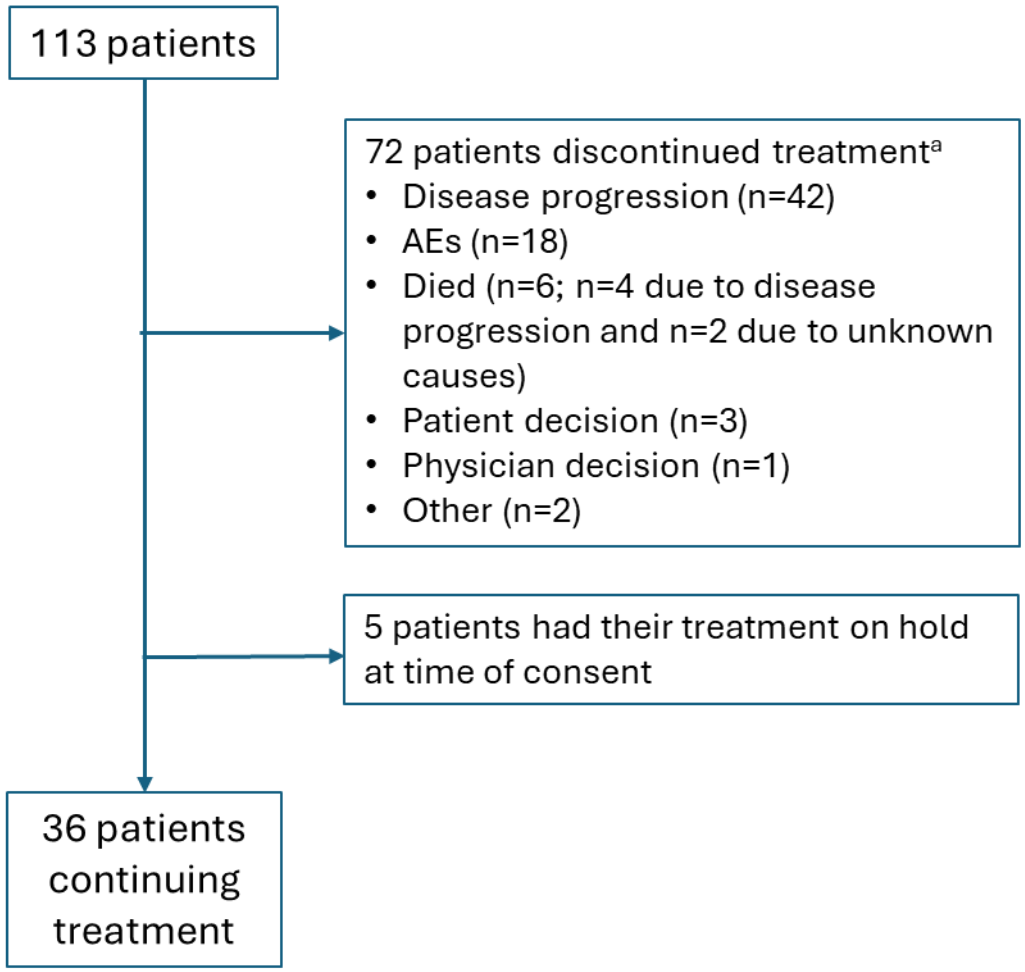
68	Female	Pneumonia	Lung infection	49	1	Not related	Not applicable	Yes
75	Female	Pneumonia Toxic encephalopathy/	Pneumonia Neurotoxicity encephalopathy	104 104	1 1	Related Related	Dose not changed Not applicable	Yes Yes
61	Female	Multiple fractures	Multiple fracture	131	1	Not related	Not applicable	No
72	Female	General physical health deterioration	Progressive multiple myeloma with impaired general condition	110	1	Not related	Not applicable	No

Adverse events are coded using MedDRA Version 26.1. AE, Adverse Event

[a]Day of AE onset is calculated relative to the date of first dose of teclistamab treatment as: AE start date - date of first dose of treatment + 1.

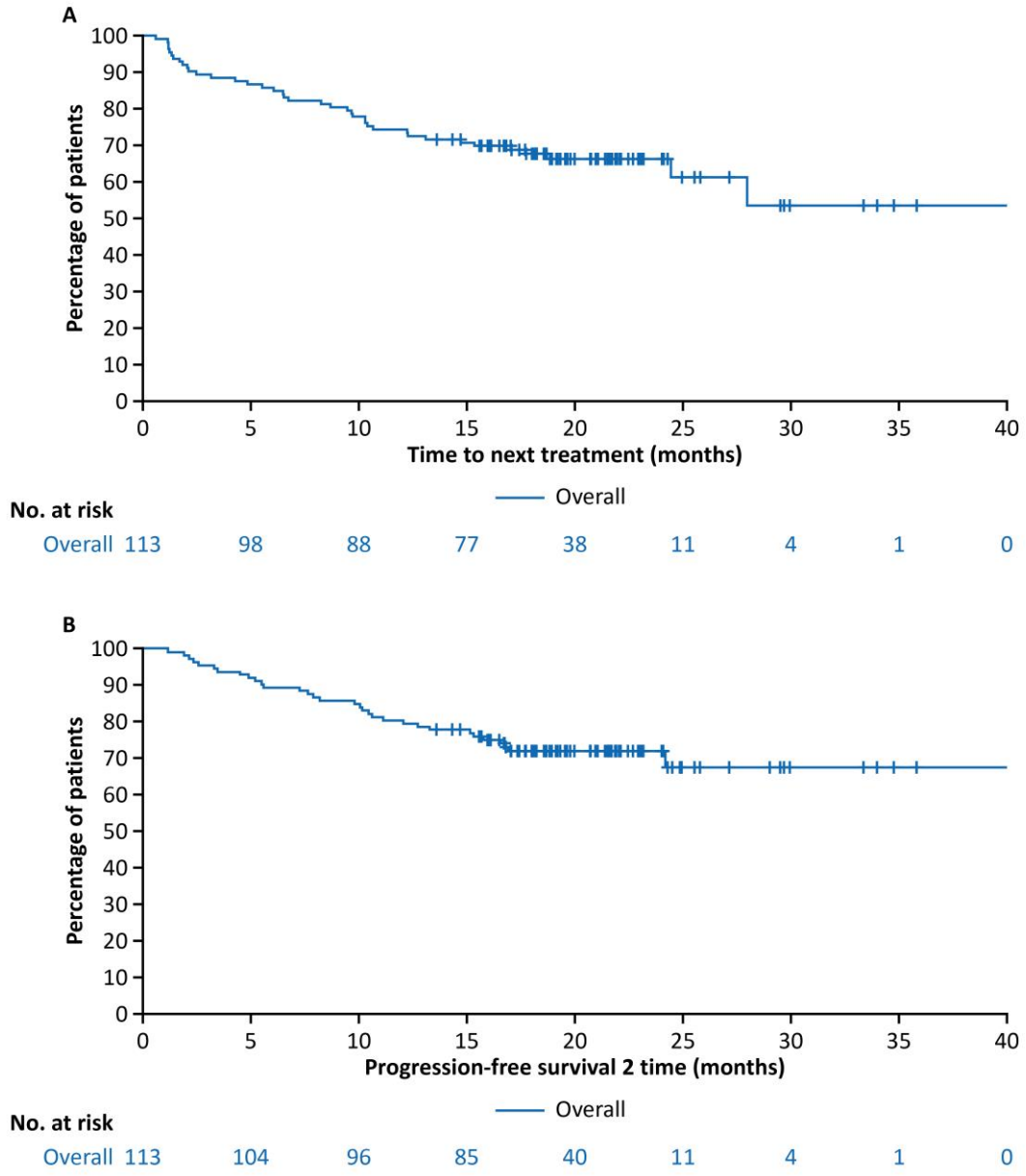
[b]Relationship to teclistamab is assessed by the Investigator.

Supplementary Figure 1. Treatment disposition



AE, adverse event

Supplementary Figure 2. Kaplan-Meier plot showing A) time to next treatment and B) progression-free survival 2 in overall study population



Progression-free survival 2 is defined as the time interval from the date of first dose of teclistamab to the date of event occurring after the start of subsequent antimyeloma therapy, defined as progressive disease, as assessed by the investigator per IMWG response criteria based on available data, or death from any cause, whichever occurs first. For patients who receive subsequent antimyeloma therapy and are alive without documented disease progression, or who do not receive subsequent therapy, or who die before receiving subsequent therapy, the patient's outcome is censored at the last date collected from the medical records.

IMWG, International Myeloma Working Group.

Supplementary Figure 3. Forest plots showing hazard ratios following the subgroup analysis examining each of two categorial variables for each risk factor (with 95% confidence intervals) A) duration of response (assessed by time to next treatment), B) progression-free survival, C) overall survival across different subgroups analysed (all treated analysis set).

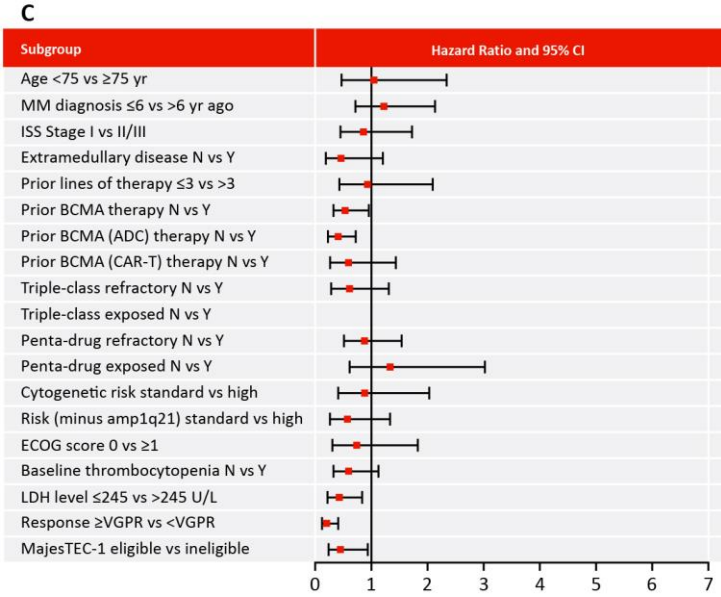
A

Subgroup	Hazard Ratio and 95% CI	n1	n2	Med1	Med2	HR	LCL	UCL	LR pval
Age <75 vs ≥75 yr		56	11	26.12	20.27	1.03	0.40	2.69	0.950
MM diagnosis ≤6 vs >6 yr ago		25	42	16.82	26.12	1.29	0.63	2.64	0.485
ISS Stage I vs II/III		16	40	NE	26.12	0.84	0.33	2.12	0.712
Extramedullary disease N vs Y		30	3	17.41	6.64	0.61	0.14	2.69	0.511
Prior lines of therapy ≤3 vs >3		10	57	NE	20.27	0.80	0.24	2.66	0.720
Prior BCMA therapy N vs Y		46	21	20.27	17.41	0.80	0.38	1.67	0.549
Prior BCMA (ADC) therapy N vs Y		51	16	26.12	16.69	0.51	0.24	1.09	0.083
Prior BCMA (CAR-T) therapy N vs Y		62	5	20.27	NE	0.98	0.23	4.10	0.973
Triple-class refractory N vs Y		15	52	NE	20.27	1.12	0.48	2.61	0.791
Triple-class exposed N vs Y		2	65	NE	NE	NE	NE	NE	NE
Penta-drug refractory N vs Y		38	29	16.82	20.27	1.27	0.62	2.60	0.517
Pentar-drug exposed N vs Y		8	59	NE	20.27	0.48	0.11	2.03	0.320
Cytogenetic risk standard vs high		15	22	20.27	16.82	0.84	0.35	1.99	0.687
Risk (minus amp1q21) standard vs high		19	18	20.27	8.72	0.53	0.22	1.26	0.149
ECOG score 0 vs ≥1		18	14	NE	10.02	0.44	0.15	1.29	0.134
Baseline thrombocytopenia N vs Y		52	14	26.12	12.35	0.56	0.24	1.28	0.168
LDH level ≤245 vs >245 U/L		36	17	NE	16.82	0.46	0.21	1.01	0.054
Response ≥VGPR vs <VGPR		58	9	26.12	3.78	0.42	0.17	1.04	0.061
MajesTEC-1 eligible vs ineligible		22	45	NE	16.69	0.46	0.20	1.07	0.070

B

Subgroup	Hazard Ratio and 95% CI	n1	n2	Med1	Med2	HR	LCL	UCL	LR pval
Age <75 vs ≥75 yr		96	17	9.59	22.21	1.17	0.58	2.36	0.663
MM diagnosis ≤6 vs >6 yr ago		46	67	8.34	10.58	1.07	0.66	1.75	0.771
ISS Stage I vs II/III		32	62	9.26	14.16	1.05	0.60	1.86	0.858
Extramedullary disease N vs Y		50	9	10.58	4.76	0.48	0.21	1.10	0.084
Prior lines of therapy ≤3 vs >3		17	96	15.67	9.59	0.85	0.42	1.72	0.651
Prior BCMA therapy N vs Y		73	40	13.83	3.42	0.75	0.46	1.23	0.250
Prior BCMA (ADC) therapy N vs Y		81	32	15.67	3.14	0.51	0.31	0.85	0.009
Prior BCMA (CAR-T) therapy N vs Y		103	10	9.66	4.99	0.98	0.39	2.44	0.966
Triple-class refractory N vs Y		24	89	10.12	9.59	0.89	0.49	1.60	0.686
Triple-class exposed N vs Y		2	111	NE	NE	NE	NE	NE	NE
Penta-drug refractory N vs Y		63	50	14.16	7.66	0.79	0.49	1.28	0.347
Penta-drug exposed N vs Y		13	100	16.69	9.63	0.93	0.43	2.04	0.861
Cytogenetic risk standard vs high		27	32	10.58	10.61	1.37	0.72	2.61	0.341
Risk (minus amp1q21) standard vs high		32	27	14.00	9.59	1.02	0.53	1.94	0.963
ECOG score 0 vs ≥1		22	27	NE	8.87	0.44	0.19	1.01	0.053
Baseline thrombocytopenia N vs Y		86	26	13.83	4.88	0.60	0.35	1.03	0.062
LDH level ≤245 vs >245 U/L		58	28	22.21	4.88	0.59	0.33	1.04	0.070
Response ≥ VGPR vs < VGPR		59	50	NE	2.56	0.23	0.14	0.39	<0.001
MajesTEC-1 eligible vs ineligible		33	80	NE	7.39	0.47	0.26	0.85	0.013

C



Subgroup	Hazard Ratio and 95% CI	n1	n2	Med1	Med2	HR	LCL	UCL	LR pval
Age <75 vs ≥75 yr		96	17	26.25	NE	1.05	0.47	2.33	0.904
MM diagnosis ≤6 vs >6 yr ago		46	67	19.55	NE	1.23	0.71	2.13	0.454
ISS Stage I vs II/III		32	62	NE	26.25	0.88	0.45	1.71	0.712
Extramedullary disease N vs Y		50	9	NE	4.76	0.48	0.19	1.19	0.112
Prior lines of therapy ≤3 vs >3		17	96	NE	26.25	0.94	0.42	2.10	0.887
Prior BCMA therapy N vs Y		73	40	NE	15.15	0.55	0.32	0.96	0.034
Prior BCMA (ADC) therapy N vs Y		81	32	NE	9.94	0.42	0.24	0.73	0.002
Prior BCMA (CAR-T) therapy N vs Y		103	10	26.25	8.64	0.61	0.26	1.44	0.263
Triple-class refractory N vs Y		24	89	NE	26.25	0.62	0.29	1.31	0.207
Triple-class exposed N vs Y		2	111	NE	NE	NE	NE	NE	NE
Penta-drug refractory N vs Y		63	50	NE	26.25	0.89	0.51	1.53	0.661
Penta-drug exposed N vs Y		13	100	16.69	26.25	1.35	0.61	3.01	0.457
Cytogenetic risk standard vs high		27	32	NE	26.25	0.89	0.40	2.02	0.789
Risk (minus amp1q21) standard vs high		32	27	NE	26.25	0.59	0.26	1.34	0.206
ECOG score 0 vs ≥1		22	27	26.25	NE	0.74	0.30	1.82	0.516
Baseline thrombocytopenia N vs Y		86	26	26.25	8.84	0.61	0.33	1.12	0.109
LDH level ≤245 vs >245 U/L		58	28	NE	11.45	0.43	0.22	0.84	0.013
Response ≥VGPR vs <VGPR		59	50	NE	6.24	0.21	0.11	0.40	<0.001
MajesTEC-1 eligible vs ineligible		33	80	26.25	17.02	0.47	0.24	0.94	0.033

ADC, antibody-drug conjugate; BCMA, B cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ISS, International Staging System; LCL, lower confidence limit; LDH, lactic acid dehydrogenase; LR, log-rank; MM, multiple myeloma; N, no; n1, n2, number of patients with responses in subgroup 1 versus subgroup 2; NE, not estimable; UCL, upper confidence limit; VGPR, very good partial response; Y, yes.

Columns n1 and n2 and columns Med1 and Med2 are the sample sizes and median DOR, PFS, and OS (respectively) for the first and second (reference) subgroups, respectively. Included in extramedullary disease subgroup 'Y' are patients with soft tissue plasmacytomas that were not associated with bone. Time to next treatment was defined as the time interval from the date of first dose of teclistamab to the start date of the next line of antimyeloma treatment (i.e., first line of subsequent therapy). If no subsequent therapy was documented, then the patient's outcome was censored at the last date collected from the medical records.