Supplementary Appendix

Supplement to: Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med 2022;387:495-505. DOI: 10.1056/NEJMoa2203478

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

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Supplementary Methods

Extramedullary Disease

In this study, extramedullary disease was exclusively defined by the presence of extramedullary soft tissue lesions. In contrast, other studies include patients with soft tissue or paraskeletal lesions in this subgroup which historically have better outcomes than patients with soft tissue plasmacytomas.[1]

End Points and Assessments

Cytokine release syndrome (CRS) was graded according to the Lee et al 2014 criteria[2] in phase 1 and American Society for Transplantation and Cellular Therapy (ASTCT) criteria[3] in phase 2 (Table 2). Neurotoxicities were identified as adverse events (AEs) under either the “nervous system disorder” or “psychiatric disorder” system organ classes that were judged by the investigator to be related to study drug, including immune effector cell–associated neurotoxicity syndrome (ICANS) events. Grouped terms were used for aphasia, delirium, encephalopathy, and tremor.

As ICANS events were graded by ASTCT criteria in phase 2, ICE scores were not collected for patients in phase 1. For patients treated at the recommended phase 2 dose (RP2D) in phase 1, all neurotoxicity events and any neurologic AEs that occurred within 28 days after the first dose of teclistamab were evaluated for consistency with ICANS.

Pharmacokinetic analyses

Blood samples were collected for pharmacokinetic analysis on days 1, 2, 3, 4, 6, 8, and 15 of cycles 1 and 3, on days 1 and 15 of cycle 2, and on day 1 of cycle 4 in cohorts treated with the RP2D. Pharmacokinetic analyses were based on a data cutoff of August 9, 2021 and included all 40 patients treated at the RP2D in phase 1 and 123 patients in phase 2.

Serum samples were analyzed for teclistamab concentrations using a validated electrochemiluminescence-based immunoassay format on the Meso Scale Discovery (MSD®) platform.

Immunogenicity

Immunogenicity analyses were based on a data cutoff of August 9, 2021. In phase 1, predose immunogenicity serum samples were collected from patients treated at the RP2D at the following doses: step-up dose 1; Days 1, 8, and 15 Cycle 1; Day 1 of Cycles 2, 3, and 4; approximately at or after 1 year (if the patient remained on treatment); in phase 2, serum samples were collected predose at step-up dose 1, and predose on Day 1 of Cycles 2, 3, 4, 6, 7, 10, and 13, then every 6 months thereafter until end of treatment.

Biomarker Assessment

A data cutoff of August 9, 2021 was used for assessment of soluble B-cell maturation antigen (sBCMA) levels. An aliquot was taken from the pharmacokinetic samples for analysis of sBCMA. Serum samples were analyzed for sBCMA using an electrochemiluminescence ligand-binding assay. The predose sample (collected on cycle 1 day 1 prior to dosing with teclistamab) was used for estimation of baseline sBCMA values.

Figure S1. CONSORT Diagram

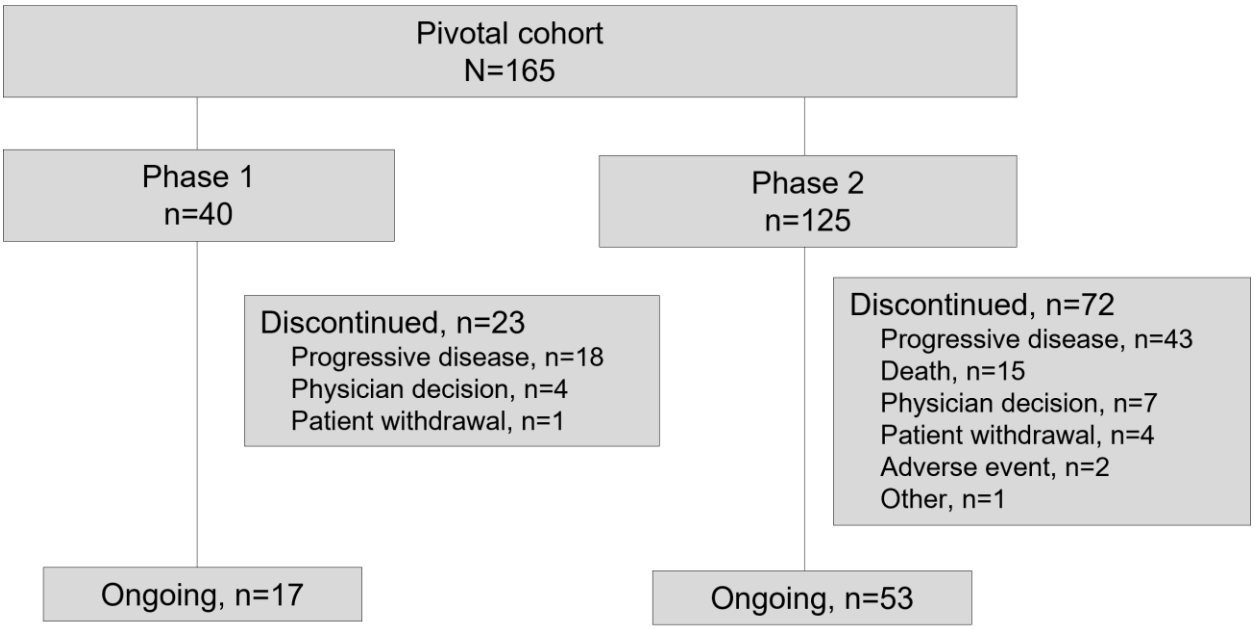
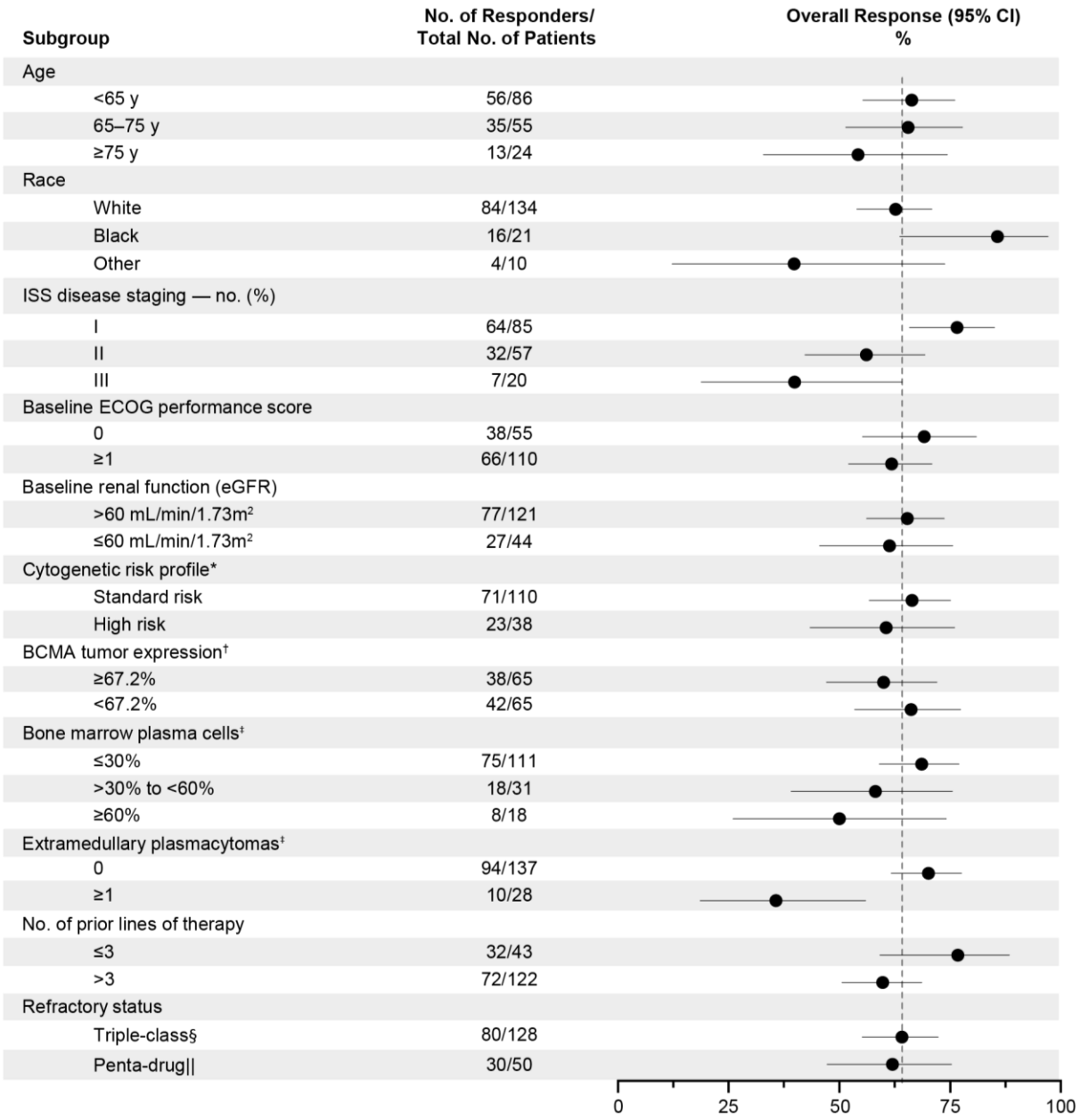


Figure S2. Subgroup Analysis of Response

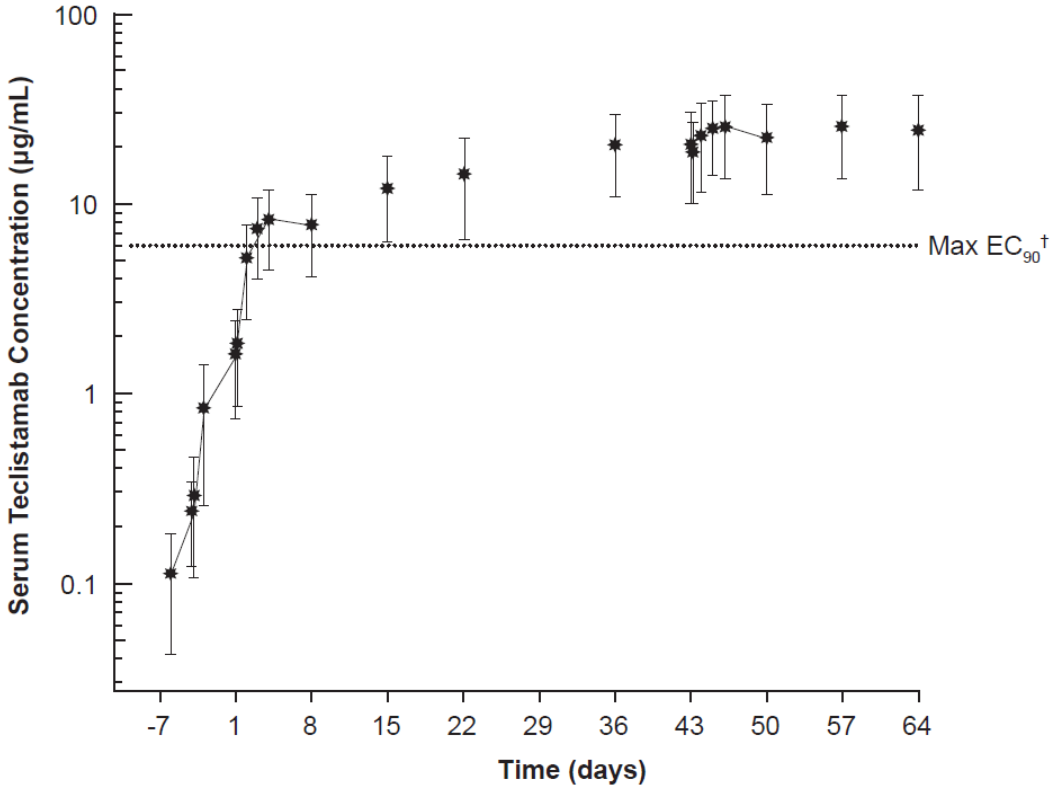
Dashed line indicates the overall response rate in the total population (63.0%).



BCMA, B-cell maturation antigen; ECOG Eastern Cooperative Oncology Group; ISS, International Staging System.

* Patients with del(17p), t(4:14), and/or t(14;16) markers were considered to have a high-risk profile.
† Bone marrow plasma cell count include bone marrow biopsy and aspirate.
‡ Extramedullary soft tissue plasmacytomas not associated with the bone were included
§ Patients who were triple-class refractory were refractory to at least one proteasome inhibitor, at least one immunomodulatory drug, and at least one anti-CD38 antibody.
‖ Patients who were penta-drug refractory were refractory to at least two proteasome inhibitors, at least two immunomodulatory drugs, and at least one anti-CD38 antibody.

Figure S3. Teclistamab pharmacokinetic profile following weekly dosing with teclistamab SC 1.5mg/kg*.



* This analysis is based on 40 patients treated in phase 1 at the 1.5 mg/kg weekly subcutaneous level.
† Target exposure level was experimentally-determined based on the 90% maximal effective concentration threshold based on an *ex vivo* cytotoxicity assay using bone marrow mononuclear cells from patients with multiple myeloma.[4]

Figure S4. Induction of (A) IFN-γ, (B) IL-6, (C) IL-10 (D) IL-2Rα in Responders and Nonresponders.

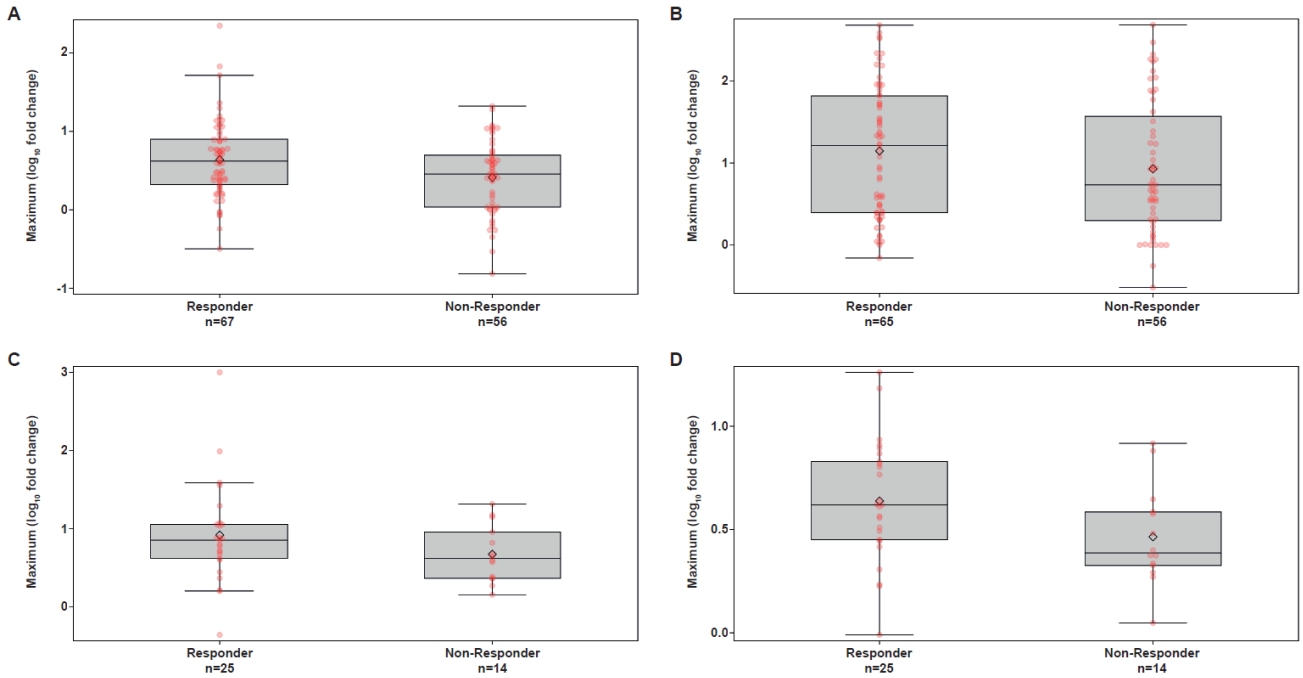


Figure S5. Induction of (A) CD38 and (B) T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) on CD8+ T-cells in Responders and Nonresponders.

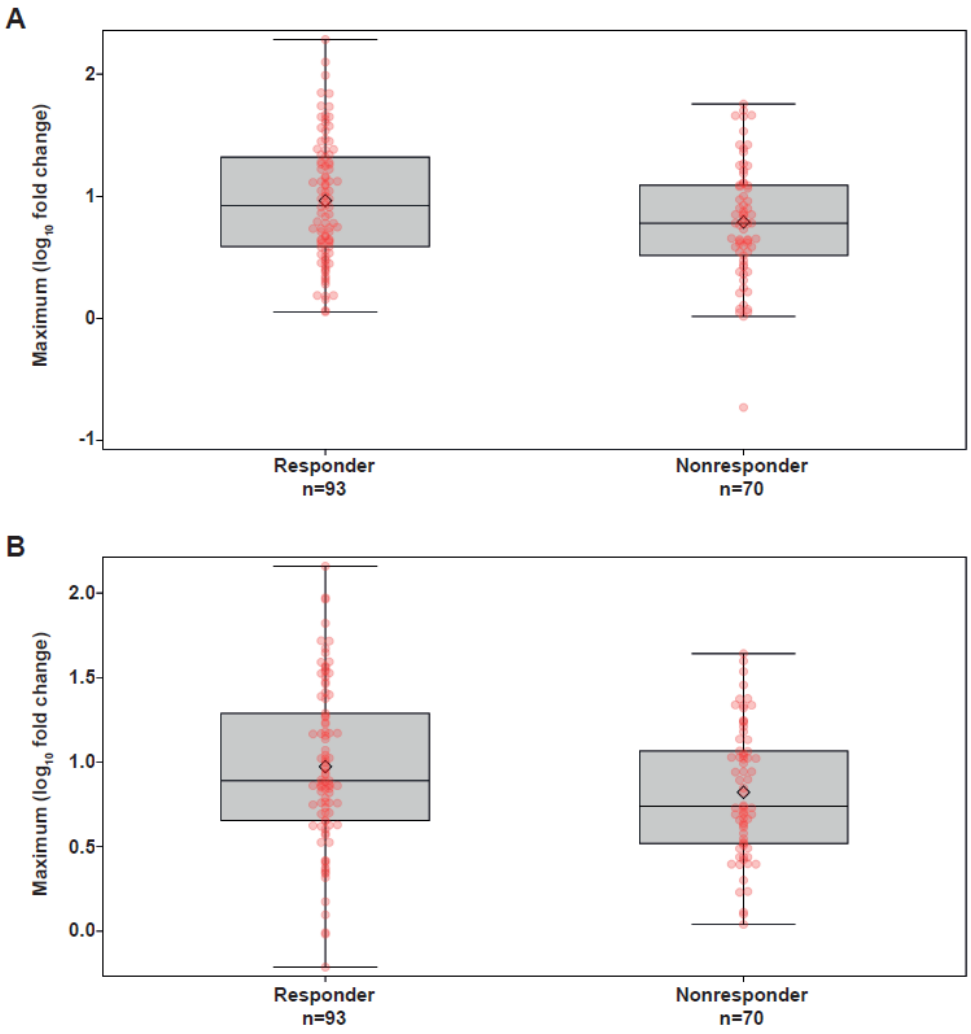


Table S1. International Myeloma Working Group Uniform Response Criteria[5-7]

Response	Response criteria
Stringent complete response	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells) or negative 2-4 color flow cytometry
Complete response*	• Negative immunofixation of serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow • No evidence of initial monoclonal protein isotype(s) on immunofixation of the serum and urine†
Very good partial response*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-component plus urine M-component <100 mg/24 hours • In addition to the above criteria, if present at baseline >90% reduction in the sum of the maximal perpendicular diameter (SPD) compared with baseline for soft tissue plasmacytoma
Partial response	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to < 200 mg/24 hours • If serum and urine M-protein are not measurable, a decrease ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • In addition to the above criteria, if present at baseline, ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
Minimal response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	• Not meeting criteria for sCR, CR, VGPR, PR, MR, or progressive disease

Progressive disease‡	Any one or more of the following criteria:
	• Increase of 25% from lowest response value in any of the following:
	  ○ Serum M-component (absolute increase must be ≥0.5 g/dL), *and/or*
	  ○ Urine M-component (absolute increase must be ≥200 mg/24 hours), *and/or*
	  ○ Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
	• Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis

	• Definite development of new bone lesions or definite increase in the size of existing bone lesions • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

CR, complete response; FLC, free light chain; MR, minimal response; PC, plasma cell; PD, progressive disease, PR, partial response; sCR, stringent complete response; SD, stable disease; SPD, sum of the products of the maximal perpendicular diameters of measured lesions; VGPR, very good partial response

*Clarifications to the criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a >90% decrease in the difference between involved and uninvolved FLC levels.
†In some cases it is possible that the original M-protein light-chain isotype is still detected on immunofixation but the accompanying heavy-chain component has disappeared; this would not be considered as a CR even though the heavy-chain component is not detectable, since it is possible that the clone evolved to one that secreted only light chains. Thus, if a patient has IgA lambda myeloma, then to qualify as CR there should be no IgA detectable on serum or urine immunofixation; if free lambda is detected without IgA, then it must be accompanied by a different heavy-chain isotype (IgG, IgM, etc.).
‡ Clarifications to the criteria for coding progressive disease: bone marrow criteria for progressive disease are to be used only in patients without measurable disease by M-protein and by FLC levels; “25% increase” refers to M-protein, FLC, and bone
marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value.

Table S2. ASTCT Cytokine Release Syndrome Revised Grading System.[3]

Grade	Toxicity
Grade 1	Fever* (Temperature ≥38°C)
Grade 2	Fever* (Temperature ≥38°C) with either: • Hypotension not requiring vasopressors. • And/or† hypoxia requiring low-flow nasal cannula‡ or blow-by.
Grade 3	Fever* (Temperature ≥38°C) with either: • Hypotension requiring a vasopressor with or without vasopressin • And/or† hypoxia requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask.
Grade 4	Fever* (Temperature ≥38°C) with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), • And/or† hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).
Grade 5	Death

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
* Fever not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.
‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute or blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Table S3. Representativeness of Study Participants.

Category	Example
Disease under investigation	Relapsed/refractory multiple myeloma (RRMM)
Special considerations related to	
Sex and gender	MM affects men more than women (3:2 ratio).[8,9]
Age	MM prevalence increases with age. The median age of patients at diagnosis is approximately 66-70 years of age, with 37% of patients being younger than 65 years of age.[10,11]
Race or ethnic group	Black patients have a higher incidence of MM compared to other ethnicities, representing approximately 20% of the patients with MM in the US. [12]
Geography	MM incidence and mortality appears highest in Western Europe, the United States, Canada and Australia.[13]
Overall representativeness of the study	The patients enrolled in the present study had the expected ratio of men to women. The median age at study entry was 64 (range: 33–84), which aligns well with the median age at diagnosis reported in the literature. Although the proportion of Black patients enrolled in the study overall (12.7%) was lower than the overall incidence in the US population, 30% of patients in the pivotal analysis in North America were Black.

Table S4. Summary of Responses.

Variable	All treated N=165*
Best overall response — no. (%)	
Stringent complete response	54 (32.7)
Complete response	11 (6.7)
Very good partial response	32 (19.4)
Partial response	7 (4.2)
Minimal response	2 (1.2)
Stable disease	27 (16.4)
Progressive disease	24 (14.5)
Not evaluable	8 (4.8)
Overall response — no. (%)†	104 (63.0)
Very good partial response or better — no. (%)	97 (58.8)
Complete response or better — no. (%)	65 (39.4)
Median time to first response (range) — mo	1.2 (0.2–5.5)
Median time to best response (range) — mo	3.8 (1.1–16.8)
Negative status for minimal residual disease — no. (%)‡	44 (26.7)

IMWG, International Myeloma Working Group; NR, not reached.
* Includes all enrolled patients who received at least one dose of teclistamab on or before September 7, 2021.
† Includes stringent complete response, complete response, very good partial response, and partial response. Response was assessed by an independent review committee, based on 2016 IMWG consensus criteria.
‡ Assessed using next-generation sequencing with a threshold of 1 tumor cell per 10^5 bone marrow cells. 44 out of 54 patients (81.5%) who were MRD-evaluable were MRD-negative. Reported here with the all-treated population, N=165, as the denominator.

Table S5. Adverse Events Reported in ≥10% of Patients in the Safety Population (N=165).*

Event	Any Grade	Grade 3/4
	Patient no (percent)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Pyrexia	45 (27.3)	1 (0.6)
Injection site erythema	43 (26.1)	0 (0)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0 (0)
Cough	33 (20.0)	0 (0)
Pneumonia	30 (18.2)	21 (12.7)
COVID-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Hypogammaglobulinemia	24 (14.5)	3 (1.8)
Hypokalemia	23 (13.9)	8 (4.8)
Bronchitis	22 (13.3)	0 (0)

Hypomagnesaemia	22 (13.3)	0(0)
Vomiting	21 (12.7)	1 (0.6)
Pain in extremity	21 (12.7)	1 (0.6)
Hypophosphatemia	20 (12.1)	10 (6.1)
Decreased appetite	20 (12.1)	1 (0.6)
Hypertension	20 (12.1)	9 (5.5)
Hypercalcemia	19 (11.5)	5 (3.0)
Blood alkaline phosphatase increased	18 (10.9)	3 (1.8)
Asthenia	18 (10.9)	1 (0.6)
Upper respiratory tract infection	18 (10.9)	0 (0)
Peripheral edema	18 (10.9)	0 (0)
Musculoskeletal chest pain	17 (10.3)	3 (1.8)
Dyspnea	17 (10.3)	1 (0.6)

*The safety population included all the patients who received at least one dose of treatment. Adverse events of any grade that were reported in ≥10% of patients are listed here.
† In this analysis, cytokine release syndrome events were graded per ASTCT criteria.

Table S6. Characteristics and Management of Cytokine Release Syndrome.

Variable	Total (N=165)
Patients with a CRS event — no. (%)	119 (72.1)
Maximum toxicity grade * — no. (%)	
Grade 1	83 (50.3)
Grade 2	35 (21.2)
Grade 3	1 (0.6)
Occurrence of CRS†	
Step-up Dose 1	72 (43.6)
Step-up Dose 2	58 (35.2)
Repeat Step-up‡	1 (0.6)
Cycle 1 Day 1	40 (24.2)
Cycle 1 Day 8	8 (4.8)
Cycle 1 Day 15	4 (2.4)
Cycle 1 Day 22	2 (1.2)
Cycle 2+§	6 (3.6)
Median time to onset relative to most recent dose (range), days	2 (1–6)
Median duration (range), days	2 (1–9)
Patients with supportive measures — no. (%)‖	110 (66.7)
Tocilizumab	60 (36.4)
>1 dose at any time during the study	5 (3.0)
>1 dose for a single CRS event	4 (2.4)
Steroids	14 (8.5)
Low-flow oxygen by nasal cannula**	21 (12.7)
Single vasopressor	1 (0.6)

CRS, cytokine release syndrome; IV, intravenous.
* Assessed per ASTCT criteria.[3]
† Breakdown of CRS occurrence by independent event. Patients may appear in more than 1 category.
‡ Dose prior to cycle 1.
§ Two patients had CRS following a repeat step-up dose in cycle 2+
‖ Patients may have received more than one supportive measure for CRS. Other supportive measures not listed include IV fluids and acetaminophen.
**Flow rate of 6L/min or lower.

Table S7. Characteristics and Management of Investigator-Identified Neurotoxic Events.*

Variable	Total (N=165)
Patients with at least one neurotoxic event— no. (%)	24 (14.5)
Headache	14 (8.5)
ICANS†	5 (3.0)
Lethargy	2 (1.2)
Tremor	2 (1.2)
Apathy	1 (0.6)
Cogwheel rigidity	1 (0.6)
Dizziness	1 (0.6)
Dysgeusia	2 (1.2)
Encephalopathy‡	1 (0.6)
Hypoesthesia	1 (0.6)
Hypokinesia	1 (0.6)
Peripheral sensory neuropathy	1 (0.6)
Seizure	1 (0.6)
Maximum toxicity grade — no. (%)	
Grade 1	14 (8.5)
Grade 2	9 (5.5)
Grade 3	0 (0)
Grade 4	1 (0.6)
Median time to onset relative to most recent dose (range), days	3.0 (1–13)
Duration, median (range), days	7.0 (1–291)
Patients requiring supportive measures for neurotoxic events — no. (%)§	14 (8.5)
Tocilizumab	3 (1.8)
Dexamethasone	3 (1.8)
Levetiracetam	2 (1.2)
Gabapentin	1 (0.6)

ICANS, immune effector cell–associated neurotoxicity syndrome.
* TEAEs under the “nervous system disorder” or “psychiatric disorder” system organ class that were judged by the investigator to be related to study drug, including ICANS events.
† Includes 1 patient from phase 1 who experienced an event (grade 1 confusional state) consistent with ICANS.
‡ Reported as the preferred term of confusional state.
§ Includes supportive measures to treat ICANS.

Table S8. Serious Adverse Events Reported in ≥2% of Patients in the Safety Population.

	Total (N=165)
Any serious adverse event	107 (64.8)
Cytokine release syndrome	14 (8.5)
COVID-19	24 (14.5)
Pneumonia	17 (10.3)
General physical health deterioration	9 (5.5)
Pyrexia	9 (5.5)
Acute kidney injury	8 (4.8)
Pneumocystis jirovecii pneumonia	6 (3.6)
Diarrhea	5 (3.0)
Bone pain	4 (2.4)
Cellulitis	4 (2.4)
Febrile neutropenia	4 (2.4)
Hypoxia	4 (2.4)

Table S9. Summary of Deaths During the Study.

Primary Cause — No. (%)	Total (N=165)
Overall deaths	68 (41.2)
Progressive disease	41 (24.8)
Adverse event-unrelated to study drug	14 (8.5)
COVID-19	10 (6.1)
Pneumonia	1 (0.6)
Hemoperitoneum	1 (0.6)
Pseudomonal pneumonia	1 (0.6)
Hypovolemic shock	1 (0.6)
Adverse event-related to study drug	5 (3.0)
COVID-19	2 (1.2)
Hepatic failure	1 (0.6)
Streptococcal pneumonia	1 (0.6)
Progressive multifocal leukoencephalopathy	1 (0.6)
Other causes*	8 (4.8)
Unknown	2 (1.2)
respiratory failure due to pneumonia	1 (0.6)
trauma after fall	1 (0.6)
sepsis/bronchopneumonia/multiple myeloma	1 (0.6)
COVID-19	1 (0.6)
presumed pneumonia, but not clinically diagnosed as such	1 (0.6)
left pneumonitis complicated by multi-visceral failure	1 (0.6)

*These deaths were not considered treatment emergent, as these patients had died after subsequent myeloma therapy was initiated.

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