Teclistamab + Nirogacestat in Relapsed/Refractory Multiple Myeloma: The Phase 1b MajesTEC-2 Study

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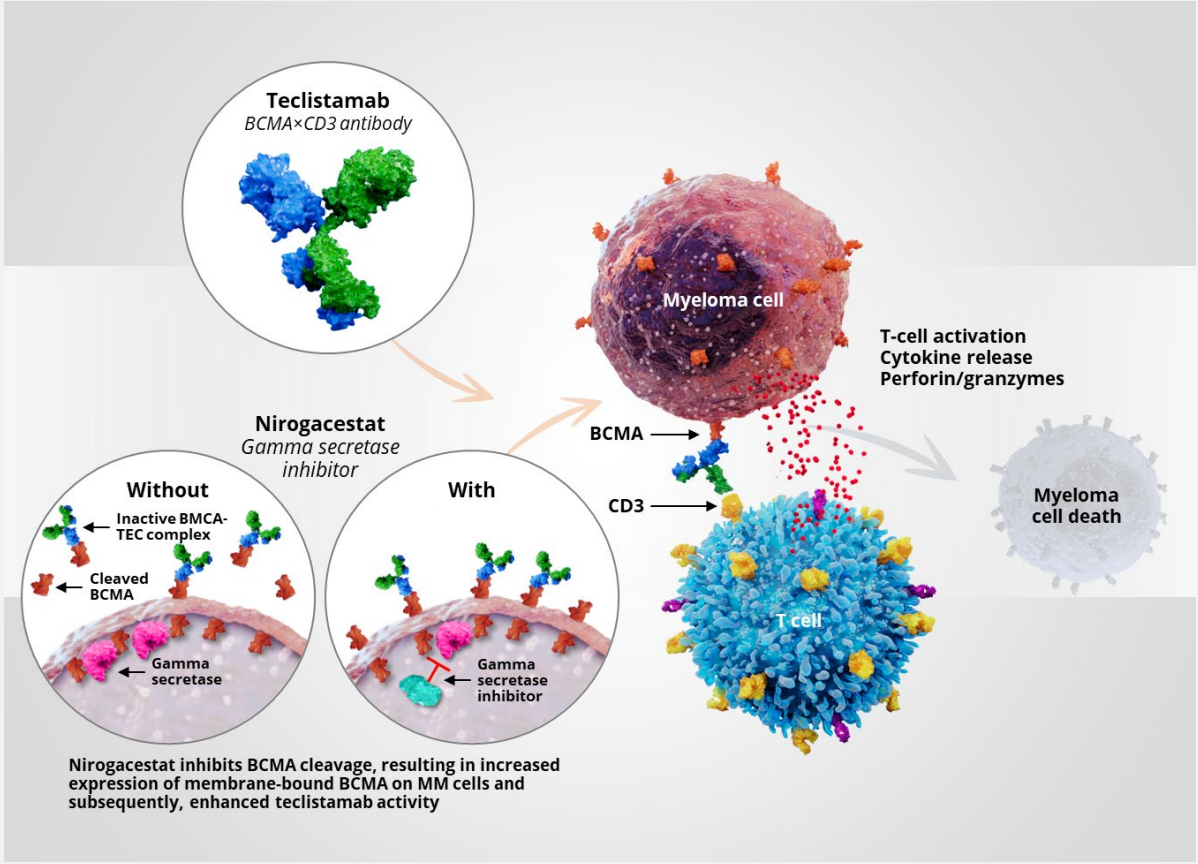
Disclosures

- Advisory committees: BeiGene, Janssen
- Data safety monitoring board: BeiGene

MajesTEC-2: Investigation of Teclistamab in Combination with Nirogacestat

- **Teclistamab** is the only **approved BCMA×CD3 bispecific antibody** with a personalized, weight-based, and flexible dosing schedule for the treatment of triple-class exposed RRMM[1]
  - ORR of 63% in MajesTEC-1[2]
- **Nirogacestat** is an investigational **gamma-secretase inhibitor** that
  - Increases cell surface density of membrane-bound BCMA and reduces soluble BCMA levels[3]
  - Enhances the activity of BCMA-targeted therapies in vitro[4] and in clinical trials[5]
- These properties suggest that adding nirogacestat to teclistamab may enhance its efficacy
- We report initial results from one arm of the phase 1b multicohort **MajesTEC-2** trial (NCT04722146) exploring **teclistamab + nirogacestat in patients with RRMM**



BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CD3, cluster of differentiation 3; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma.

1. TECVAYLI (teclistamab-cqyv). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2022. 2. Moreau P, et al. *New Engl J Med* 2022;387:495-505. 3. Shearer T, et al. *Blood* 2022;140(suppl 1):3080-1. 4. Eastman S, et al. *Blood* 2019;134(suppl 1):4401. 5. Lonial S, et al. *J Clin Oncol* 2022;40(suppl 16;abstr 8019). doi: 10.1200/JCO.2022.40.16_suppl.8019.

MajesTEC-2: Phase 1b, Multicohort Study Design

Key eligibility criteria

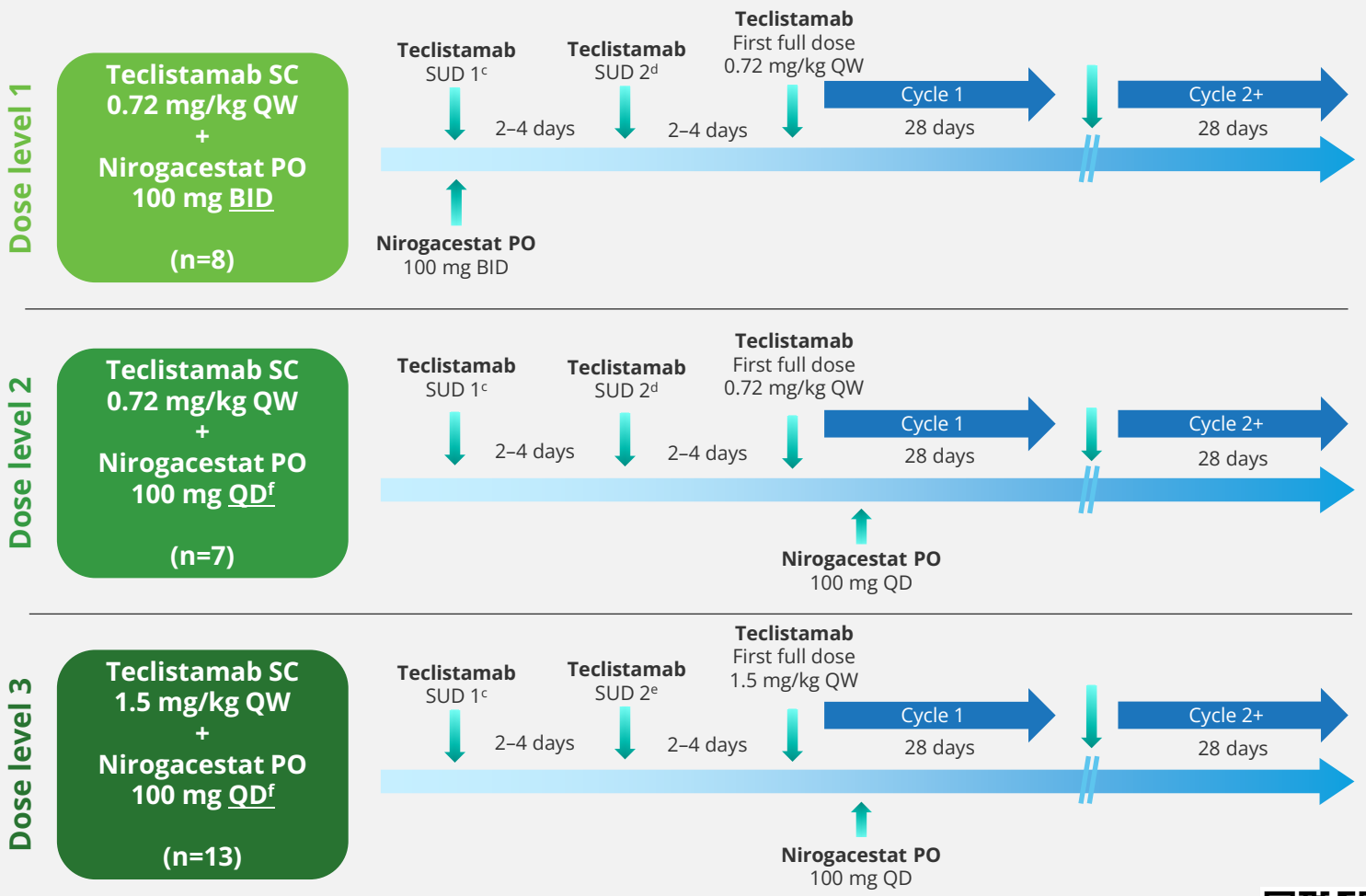
- Measurable MM
- ≥3 prior LOT, *or* double refractory to a PI and an IMiD and triple-class exposed
- Progressive disease within 12 months of last LOT

Primary endpoints

- Safety and tolerability[a]
- Optimal doses

Key secondary endpoints

- ORR[b]
- Rate of ≥VGPR and ≥CR[b]
- Duration of and time to response
- Pharmacokinetics



[a]AEs assessed per CTCAE v5.0, except for CRS and ICANS, which were graded per ASTCT guidelines. [b]Assessed per IMWG 2016 criteria. [c]0.06 mg/kg. [d]0.24 mg/kg. [e]0.30 mg/kg. [f]Nirogacestat dosing initiated after a full dose of teclistamab without CRS.

AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BID, twice daily; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; LOT, line of therapy; MM, multiple myeloma; ORR, overall response rate; PI, proteasome inhibitor; PO, by mouth; QD, once daily; QW, weekly; VGPR, very good partial response; SC, subcutaneous; SUD, step-up dose.

MajesTEC-2: Patient Characteristics

Characteristic	Total (N=28)
Age (years), median (range)	65.5 (46–80)
Male, n (%)	16 (57.1)
Race, n (%)	
White	22 (78.6)
Unknown/not reported	6 (21.4)
Extramedullary plasmacytoma(s), n (%)	7 (25.0)
High-risk cytogenetics,[a] n (%)	5 (20.0)
ISS stage, n (%)	
I	10 (35.7)
II	11 (39.3)
III	7 (25.0)
Time since diagnosis (years), median (range)	5.9 (1.3–15.5)

Characteristic	Total (N=28)
Prior SCT, n (%)	23 (82.1)
Prior LOT, median (range)	4.0 (2–12)
Exposure, n (%)	
Triple-class[b]	28 (100)
Penta-drug[c]	20 (71.4)
Refractory, n (%)	
Triple-class[b]	20 (71.4)
Penta-drug[c]	6 (21.4)
Last line of therapy	26 (92.9)

Data cut-off, March 16, 2023.
[a]Cytogenetic risk is based on FISH or karyotype testing and is defined as ≥1 of the following: del(17p), t(4;14), or t(14;16); n= 25. [b]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [c]≥2 PIs, ≥2 IMiDs, and ≥1 anti–CD38 mAb.
FISH, fluorescence in situ hybridization; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; mAb, monoclonal antibody; PI, proteosome inhibitor; SCT, stem cell transplant.

MajesTEC-2: Improved Safety Profile With Delayed vs Concurrent Nirogacestat Plus Teclistamab

- At dose level 1 (tec 0.72 mg/kg QW + concurrent niro 100 mg BID): 3 DLT events in 2 patients
  - 1 patient with grade 3 GI bleed + grade 3 diarrhea
  - 1 patient with grade 3 ICANS
- No DLTs or grade 3 CRS noted at dose levels 2 and 3 (tec 0.72 mg/kg QW *or* 1.5 mg/kg + delayed-start, reduced-dose niro [100 mg QD])
- Grade 5 TEAEs (n=5)
  - Sepsis, septic shock, COVID-19, cardiac arrest, *Pneumocystis jirovecii* pneumonia

	Total (N=28)	
Median (range) follow-up, months	14.7 (0.5[a]–22.9)	
	Any Grade	**Grade 3/4**
Any AE	28 (100)	26 (92.9)[b]
	Teclistamab	**Nirogacestat**
Median (range) treatment duration, months	9.4 (0.03–22.9)	4.7 (0.16–15.6)
AEs leading to		
Discontinuation, n (%)	2 (7.1)[c]	17 (60.7)[d]
Dose reduction, n (%)[e]	3 (10.7)	11 (39.3)
On treatment	12 (42.8)	4 (14.3)

Data cut-off date, March 16, 2023.
[a]Patient who died. [b]2 patients with DLTs. [c]Due to confusional state (n=1) and neutropenia and pneumonia (n=1). [d]Each patient could have >1 AE leading to discontinuation; reasons included diarrhea (n=3); ALT increased (n=2), AST increased (n=2), fatigue (n=2), and cholecystitis, confusional state, COVID-19, general physical health deterioration, hyperamylasemia, malaise, meningitis, mental disorder, muscular weakness, nausea, *Pneumocystis jirovecii* pneumonia, pneumonia, septic shock, upper gastrointestinal hemorrhage, and vomiting (n=1 each). [e]Patient specific and not related to the stated dose levels/study design dose levels.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; GI, gastrointestinal; ICANS, immune effector cell–associated neurotoxicity syndrome; PD, progressive disease; QD, once daily; QW, weekly; TEAE, treatment-emergent adverse event.

MajesTEC-2: No New Hematologic Events With Combination Therapy Compared to Teclistamab Monotherapy

AE[a] (≥20% overall), n (%)	Total (N=28)	
	Any Grade	Grade 3/4
Hematologic AEs		
Neutropenia	23 (82.1)	21 (75.0)
Anemia	10 (35.7)	9 (32.1)
Thrombocytopenia	7 (25.0)	4 (14.3)

- Rates of grade 3/4 hematologic AEs generally low, except neutropenia
- 1 discontinuation due to neutropenia
- Febrile neutropenia in 1 patient (3.6%) across all dose levels

Data cut-off date, March 16, 2023.
[a]AEs were graded by CTCAE v5.0. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

MajesTEC-2: Nonhematologic AEs Were Generally Low Grade

AE[a] (≥25% overall), n (%)	Total (N=28)	
	Any Grade	Grade 3/4
Nonhematologic AEs		
CRS	21 (75.0)	1 (3.6)
Diarrhea	18 (64.3)	7 (25.0)
Injection-site erythema	15 (53.6)	0
Decreased appetite	14 (50.0)	0
Fatigue	12 (42.9)	2 (7.1)
Pyrexia	10 (35.7)	1 (3.6)
Arthralgia	9 (32.1)	0
Cough	9 (32.1)	0
Hypophosphatemia	9 (32.1)	0
Nausea	9 (32.1)	0
Hypogammaglobulinemia	8 (28.6)	2 (7.1)
COVID-19	8 (28.6)	2 (7.1)
Pneumonia	8 (28.6)	6 (21.4)
Back pain	8 (28.6)	0
Dyspnea	7 (25.0)	2 (7.1)
Headache	7 (25.0)	0
Hypokalemia	7 (25.0)	1 (3.6)

- Most frequent nonhematologic AEs: CRS, diarrhea, injection-site erythema, decreased appetite, fatigue
- Rates of grade 3/4 nonhematologic AEs generally low, except diarrhea (25%) and pneumonia (21%)
- 2 ICANS events
  - 1 at dose level 1 (grade 3)
  - 1 at dose level 2 (grade 2)

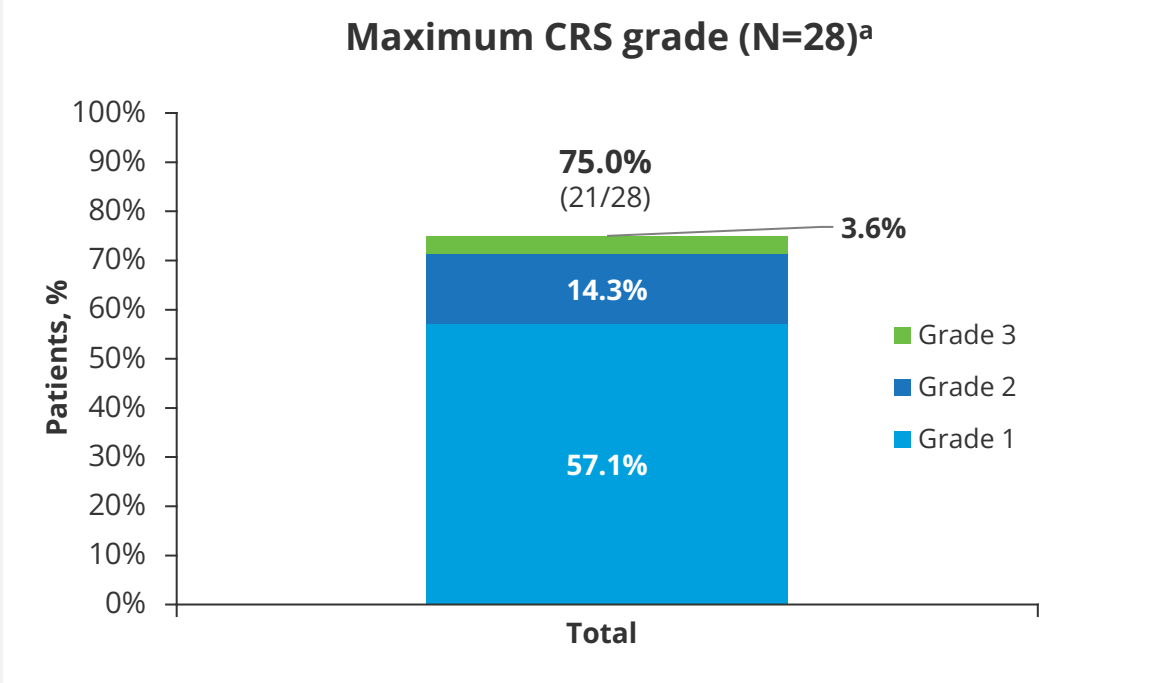
Data cut-off date, March 16, 2023.

[a]AEs were graded by CTCAE v5.0 with CRS events graded per ASTCT criteria.

AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

MajesTEC-2: Incidence and Severity of Cytokine Release Syndrome Consistent With Teclistamab Monotherapy

Parameter	Total (N=28)
Patients with CRS[a], n (%)	21 (75.0)
Time to onset (days)[b], median (range)	2 (1–3)
Duration (days), median (range)	2 (1–33)
Patients who received supportive measures[c], n (%)	
Tocilizumab[d]	10 (35.7)
Steroids	0
Oxygen	4 (14.3)
Vasopressor	1 (3.6)



- Most CRS events occurred during step-up dosing or cycle 1
- 1 event was grade 3 (dose level 1 [concurrent administration]); no severe CRS events observed at dose levels 2 and 3 (delayed nirogacestat administration)
- All CRS events resolved by data cut-off

Data cut-off date, March 16, 2023.
[a]CRS was graded by ASTCT criteria. [b]Relative to the most recent dose. [c]Patients could receive >1 supportive therapy. [d]Tocilizumab was allowed for all CRS events and was allowed at grade 1 CRS; the protocol did not recommend prophylactic tocilizumab use. ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome.

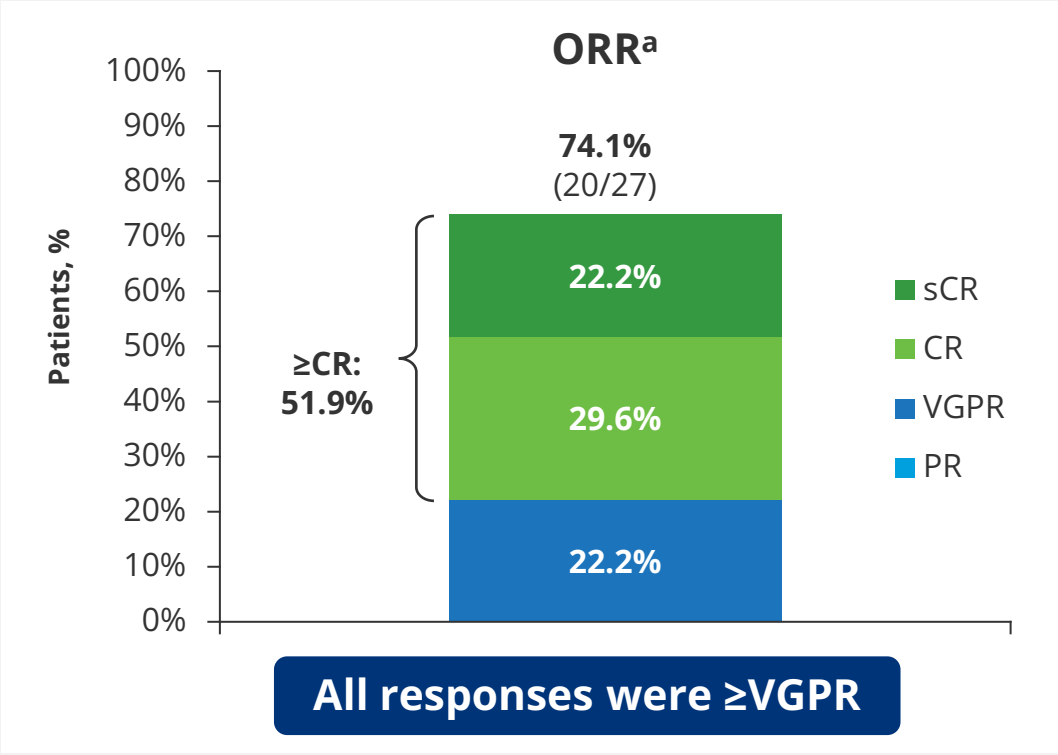
MajesTEC-2: Infection Profile

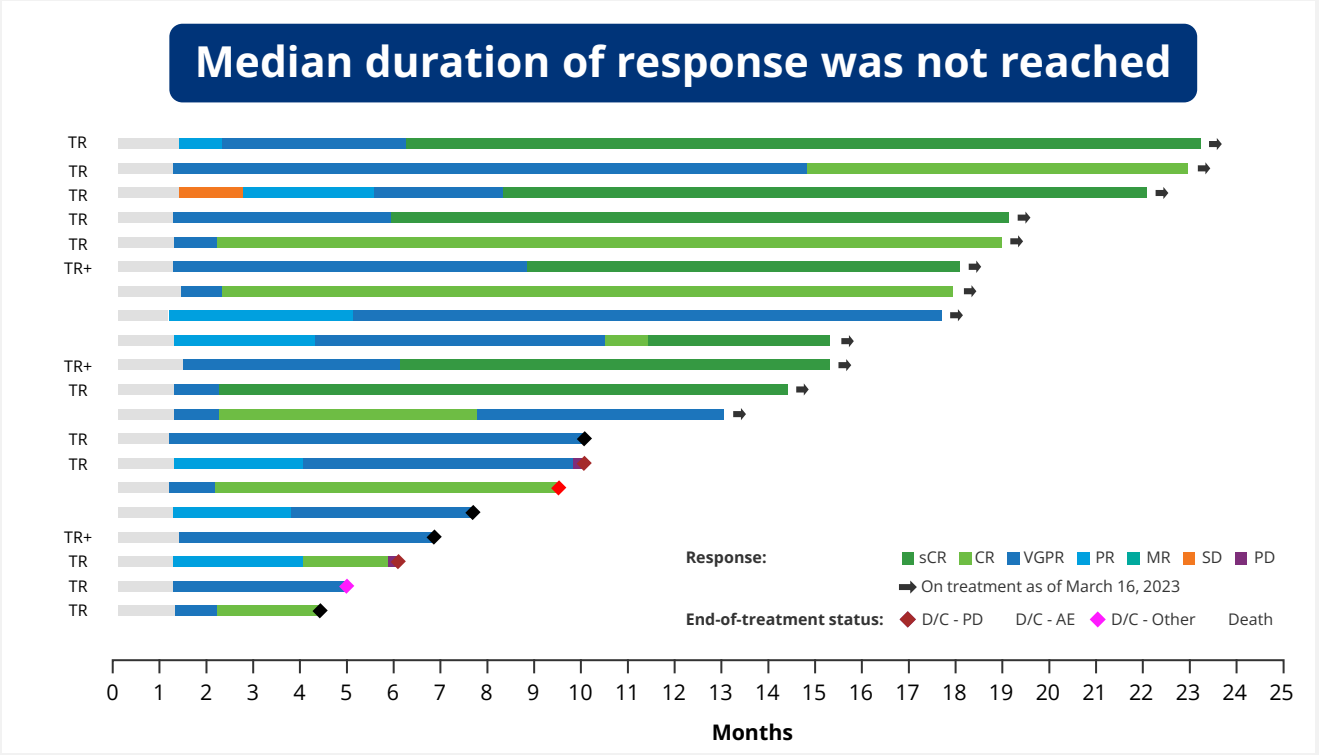
AE[a] (≥20% overall), n (%)	Total (N=28)	
	Any Grade	Grade 3/4
Infections		
COVID-19	8 (28.6)	2 (7.1)
Pneumonia	8 (28.6)	6 (21.4)
Bronchitis	6 (21.4)	0
Upper respiratory tract infection	6 (21.4)	1 (3.6)

- No DLTs due to infections
- 1 teclistamab discontinuation due to infection (pneumonia)
- 4 infection-related deaths[b]
- 78.6% with ≥1 postbaseline IgG value <500 mg/dL or hypogammaglobulinemia TEAE
  - 42.9% of patients received IVIg

Data cut-off date, March 16, 2023.
[a]AEs were graded by CTCAE v5.0. [b]COVID-19, sepsis, septic shock, *Pneumocystis jirovecii* pneumonia. AE, adverse event; DLT, dose-limiting toxicity; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; TEAE, treatment-emergent adverse event.

MajesTEC-2: ORR Was High and Deepened Over Time





- Median (range) follow-up: 14.7 (0.5[b]–22.9) months
- Time to first response[c]: 1.18 (1.1–2.7) months
- 87.2% of patients maintained response ≥12 months

Data cut-off date, March 16, 2023.
[a]Response assessed by investigators, based on International Myeloma Working Group criteria; response-evaluable patients received ≥1 study treatment and had ≥1 postbaseline response evaluation.
[b]Patient who died. [c]For patients with confirmed response ≥PR. AE, adverse event; CR, complete response; D/C, discontinued; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; TR, triple refractory; TR+, penta refractory; VGPR, very good partial response.

MajesTEC-2: Conclusions

- High and deep response rates observed with teclistamab + nirogacestat in patients with RRMM
  - 74% ORR, 52% ≥CR across all dose levels assessed
  - 87.2% responders remained in response at 12 months
- Safety profile optimized with delayed administration of lower-dose nirogacestat
  - 3 DLTs observed in 2 patients when teclistamab + higher-dose nirogacestat administered concurrently during teclistamab step-up dosing
  - No DLTs observed when lower-dose nirogacestat was initiated after the first full dose of teclistamab (at the approved dosing schedule)
  - Grade 3 diarrhea was observed in 25% of patients overall
- The clinical profile of teclistamab + nirogacestat in this phase 1b study suggests careful evaluation is warranted when combining BCMA-targeted bispecific therapies with a gamma-secretase inhibitor

BCMA, B-cell maturation antigen; CR, complete response; DLT, dose-limiting toxicity; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma sCR, stringent complete response.

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