MM-349

Teclistamab plus Daratumumab (Tec-Dara) in Patients with Relapsed Refractory Multiple Myeloma (RRMM): Analysis of MajesTEC-3 Based on Cytogenetic and Functional High-Risk

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Key Takeaway

Tec-Dara should be considered a new standard-of-care from second line across all risk groups and practice settings

Conclusions

Tec-Dara, a steroid-sparing combination, improved outcomes versus DPd/DVd regardless of prespecified or expanded cytogenetic risk, presence of ultra high-risk MM, and FHR

- Tec-Dara improved estimated 3-year PFS in standard-risk (87-90%), high-risk (76-82%), and FHR (77%)
- Tec-Dara improved MRD-negative ≥CR 10^{-6} in standard-risk (59-67%), high-risk (48-61%), and FHR (38%)

The trajectory of PFS with Tec-Dara in high-risk disease through 36 months suggests that Tec-Dara mitigates the adverse prognostic impact historically seen with high-risk disease

Acknowledgments

This study was sponsored by Johnson & Johnson. Authors would like to acknowledge the patients who participated in the study and their families and caregivers; the physicians, nurses, and staff members at each site; the members of the Study Safety Committee; Caren Minadeo and Arpan Patel who assisted with data management and programming, respectively, and additional members who were involved in data collection and analysis. Medical writing and editorial support were provided by Holly Clarke, PhD, CMPP™, and Bethany Reinecke, PhD, CMPP™, of Lumanity Communications Inc., and funded by Johnson & Johnson. These data were originally presented at the 31st European Hematology Association (EHA) Annual Meeting; June 11-14, 2026; Stockholm, Sweden. Oral S198.

Disclosure

Omik Patel is a current employee of Johnson & Johnson and holds stock in Johnson & Johnson.

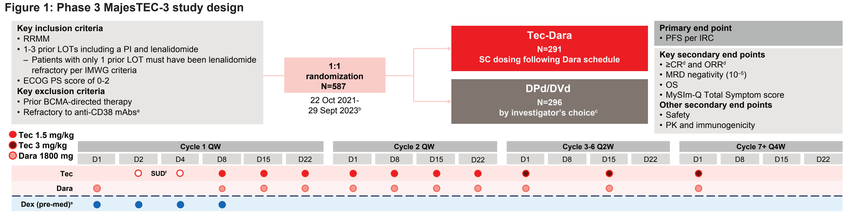
Introduction

- Teclistamab in combination with daratumumab (Tec-Dara) significantly improved progression-free survival (PFS) and overall survival (OS) and increased minimal residual disease (MRD)-negativity rates versus daratumumab with dexamethasone and pomalidomide or bortezomib (DPd/DVd) in patients with relapsed/refractory multiple myeloma (RRMM) and 1 to 3 prior lines of therapy (LOTs) in the phase 3 MajesTEC-3 study[1,2]
  - Benefits with Tec-Dara were consistently observed across prespecified subgroups, including patients with high-risk cytogenetics (defined as 1 or more of del[17p], t[4;14], or t[14;16])
- Based on these results, Tec-Dara received US approval for the treatment of RRMM with ≥1 prior LOT including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD)[3]
- Patients with RRMM and high-risk characteristics have poorer disease outcomes,[4-6] highlighting the need for more effective therapies in such subgroups
- We present an in-depth, post hoc analysis of MajesTEC-3 outcomes in high-risk subgroups, including expanded high-risk cytogenetic abnormalities (HRCAs) and functional high-risk (FHR) status (see **Methods** for definitions)

Methods

- The study design for the phase 3 MajesTEC-3 study is shown in **Figure 1**

Figure 1: Phase 3 MajesTEC-3 study design



BCMA, B-cell maturation antigen; ≥CR, complete response or better; D, Day; Dara, daratumumab; Dex, dexamethasone; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; IRC, independent review committee; mAb, monoclonal antibody; MRD, minimal residual disease; MySIm-Q, Multiple Myeloma Symptom and Impact Questionnaire; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; pre-med, pre-medication; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; SUD, step-up dosing; Tec, teclistamab.
[a]Prior exposure to anti-CD38 mAbs was permitted.
[b]During the COVID-19 pandemic.
[c]DPd/DVd were administered per approved schedules.
[d]Response and disease progression were assessed by a blinded IRC per IMWG criteria.
[e]Dexamethasone, acetaminophen, and diphenhydramine pre-medication was required for the first 2 weeks; subsequent dexamethasone was not required thereafter.
[f]Patients received SUD of 0.06 mg/kg and 0.3 mg/kg on Days 2 and 4, respectively.

- The following subgroups were explored in this analysis
  - Prespecified standard risk, defined as none of the following HRCAs: del(17p), t(4;14), t(14;16)
  - Prespecified high risk, defined as 1 or more of the following HRCAs: del(17p), t(4;14), t(14;16)
  - Expanded standard risk, defined as none of the following HRCAs: del(17p), t(4;14), t(14;16), gain(1q21), amp(1q21)
  - Expanded high risk, defined as 1 or more of the following HRCAs: del(17p), t(4;14), t(14;16), gain(1q21), amp(1q21)
  - 1 expanded HRCA, defined as the presence of only 1 expanded HRCA
  - ≥2 expanded HRCAs (or "ultra high-risk"), defined as the presence of 2 or more expanded HRCAs
  - Functional high risk, defined as patients with 1 prior LOT with progressive disease within 18 months of autologous stem-cell transplant (ASCT) or start of initial therapy
- Cytogenetic risk was assessed centrally with fluorescence in situ hybridization (FISH) or on local FISH or karyotype testing if central FISH was not available
- End points included PFS and MRD-negative ≥CR rate (10^{-5} and 10^{-6})
  - MRD-negative ≥CR refers to MRD negativity achieved within 3 months prior to achieving CR/stringent CR (CR/sCR) or at any time after CR/sCR and before progression or subsequent therapy
  - Assessed in the MRD next-generation sequencing primary analysis set, defined as all randomized patients except those recruited in China (due to China instead utilizing next-generation flow for MRD assessment)

Results

Patients

- A total of 291 and 296 patients were randomized to the Tec-Dara and DPd/DVd group, respectively
  - Baseline risk profile was inclusive of real-world high-risk disease biology characteristics (**Table 1**)
- A high proportion of patients were classified as having high-risk by the expanded definition
- 24% of Tec-Dara patients had progressed within 18 months of ASCT or initial treatment

Table 1: Disease characteristics

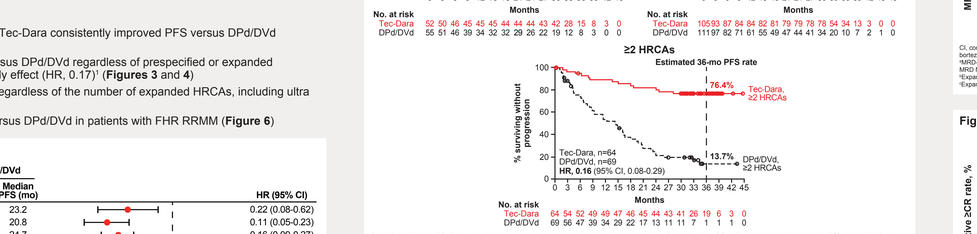
Characteristics, n (%)	Tec-Dara (n=291)	DPd/DVd (n=296)
Baseline cytogenetic risk[a,b] per prespecified definition		
Standard risk	126 (43.3)	145 (49.0)
High risk	104 (35.7)	104 (35.1)
Baseline cytogenetic risk[a,c] per expanded definition		
Expanded standard risk (0 HRCAs)	52 (17.9)	55 (18.6)
Expanded high risk (≥1 HRCA)	169 (58.1)	180 (60.8)
1 HRCA	105 (36.1)	111 (37.5)
≥2 HRCAs	64 (22.0)	69 (23.3)
Functional high-risk status		
No. of patients with 1 prior LOT only	108	114
Yes	26 (24.1)	20 (17.5)
No	82 (75.9)	94 (82.5)

DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; FISH, fluorescence in situ hybridization; HRCA, high-risk cytogenetic abnormality; LOT, line of therapy; Tec-Dara, teclistamab plus daratumumab.
[a]Cytogenetic risk was assessed centrally with FISH or on local FISH or karyotype testing if central FISH was not available.
[b]Prespecified standard risk: none of del(17p), t(4;14), or t(14;16). Prespecified high risk: ≥1 of del(17p), t(4;14), or t(14;16).
[c]Expanded standard risk: none of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21). Expanded high risk: ≥1 of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).

Progression-free survival

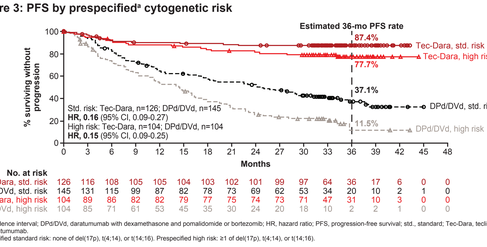
- After a median follow-up of 34.5 months, Tec-Dara consistently improved PFS versus DPd/DVd regardless of disease biology (**Figure 2**)
- Tec-Dara demonstrated superior PFS versus DPd/DVd regardless of prespecified or expanded cytogenetic risk, mirroring the overall study effect (HR, 0.17)[1] (**Figures 3** and **4**)
  - Tec-Dara consistently improved PFS regardless of the number of expanded HRCAs, including ultra high-risk RRMM (**Figure 5**)
- Tec-Dara substantially prolonged PFS versus DPd/DVd in patients with FHR RRMM (**Figure 6**)

Figure 2: PFS by risk status (ITT)



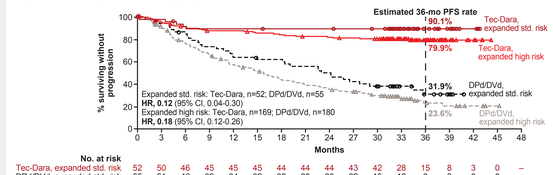
CI, confidence interval; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; HR, hazard ratio; HRCA, high-risk cytogenetic abnormality; ITT, intent-to-treat; NE, not estimable; PFS, progression-free survival; std., standard; Tec-Dara, teclistamab plus daratumumab.
[a]Prespecified standard risk: none of del(17p), t(4;14), or t(14;16). Prespecified high risk: ≥1 of del(17p), t(4;14), or t(14;16).
[b]Expanded standard risk: none of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21). Expanded high risk: ≥1 of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).

Figure 3: PFS by prespecified[a] cytogenetic risk



CI, confidence interval; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; HR, hazard ratio; PFS, progression-free survival; std., standard; Tec-Dara, teclistamab plus daratumumab.
[a]Prespecified standard risk: none of del(17p), t(4;14), or t(14;16). Prespecified high risk: ≥1 of del(17p), t(4;14), or t(14;16).

Figure 4: PFS by expanded[a] cytogenetic risk

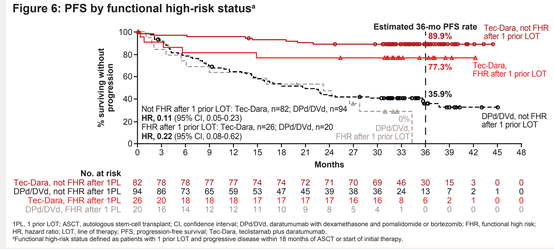


CI, confidence interval; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; HR, hazard ratio; PFS, progression-free survival; std., standard; Tec-Dara, teclistamab plus daratumumab.
[a]Expanded standard risk: none of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21). Expanded high risk: ≥1 of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).

Figure 5: PFS by number of expanded[a] HRCAs

CI, confidence interval; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; HR, hazard ratio; HRCA, high-risk cytogenetic abnormality; PFS, progression-free survival; Tec-Dara, teclistamab plus daratumumab.
[a]HRCA number is defined as the number of abnormalities present from the following: del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).

Figure 6: PFS by functional high-risk status[a]

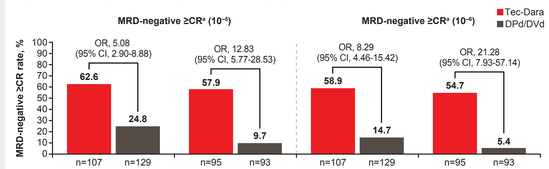


1PL, 1 prior LOT; ASCT, autologous stem-cell transplant; CI, confidence interval; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; FHR, functional high risk; HR, hazard ratio; LOT, line of therapy; PFS, progression-free survival; Tec-Dara, teclistamab plus daratumumab.
[a]Functional high-risk status defined as patients with 1 prior LOT and progressive disease within 18 months of ASCT or start of initial therapy.

MRD negative ≥CR

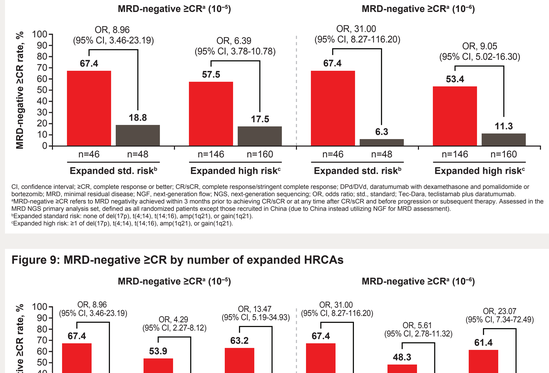
- Tec-Dara substantially increased MRD-negative ≥CR rates regardless of prespecified or expanded cytogenetic risk
- MRD-negative ≥CR (10^{-6}) rate was 10-fold, ~5-fold, and >9-fold that of DPd/DVd in patients with prespecified high-risk, expanded high-risk, and ultra high-risk RRMM, respectively (**Figures 7** through **9**)
- Tec-Dara consistently increased MRD-negative ≥CR rates versus DPd/DVd at both 10^{-5} and the more stringent 10^{-6} threshold in patients with FHR RRMM (**Figure 10**)

Figure 7: MRD-negative ≥CR by prespecified cytogenetic risk



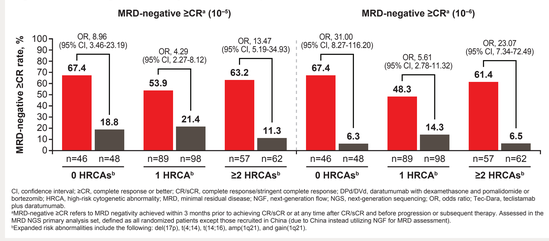
CI, confidence interval; ≥CR, complete response or better; CR/sCR, complete response/stringent complete response; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; OR, odds ratio; std., standard; Tec-Dara, teclistamab plus daratumumab.
[a]MRD-negative ≥CR refers to MRD negativity achieved within 3 months prior to achieving CR/sCR or at any time after CR/sCR and before progression or subsequent therapy. Assessed in the MRD NGS primary analysis set, defined as all randomized patients except those recruited in China (due to China instead utilizing NGF for MRD assessment).
[b]Prespecified standard risk: none of del(17p), t(4;14), or t(14;16).
[c]Prespecified high risk: ≥1 of del(17p), t(4;14), or t(14;16).

Figure 8: MRD-negative ≥CR by expanded cytogenetic risk



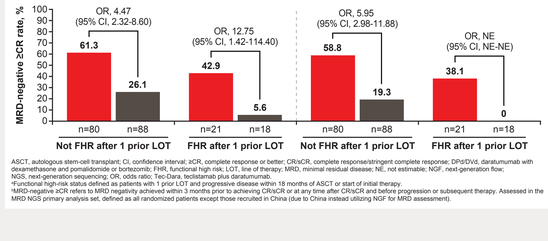
CI, confidence interval; ≥CR, complete response or better; CR/sCR, complete response/stringent complete response; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; OR, odds ratio; std., standard; Tec-Dara, teclistamab plus daratumumab.
[a]MRD-negative ≥CR refers to MRD negativity achieved within 3 months prior to achieving CR/sCR or at any time after CR/sCR and before progression or subsequent therapy. Assessed in the MRD NGS primary analysis set, defined as all randomized patients except those recruited in China (due to China instead utilizing NGF for MRD assessment).
[b]Expanded standard risk: none of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).
[c]Expanded high risk: ≥1 of del(17p), t(4;14), t(14;16), amp(1q21), or gain(1q21).

Figure 9: MRD-negative ≥CR by number of expanded HRCAs



CI, confidence interval; ≥CR, complete response or better; CR/sCR, complete response/stringent complete response; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; HRCA, high-risk cytogenetic abnormality; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; OR, odds ratio; Tec-Dara, teclistamab plus daratumumab.
[a]MRD-negative ≥CR refers to MRD negativity achieved within 3 months prior to achieving CR/sCR or at any time after CR/sCR and before progression or subsequent therapy. Assessed in the MRD NGS primary analysis set, defined as all randomized patients except those recruited in China (due to China instead utilizing NGF for MRD assessment).
[b]Expanded risk abnormalities include the following: del(17p), t(4;14), t(14;16), amp(1q21), and gain(1q21).

Figure 10: MRD-negative ≥CR by functional high-risk status[a]



ASCT, autologous stem-cell transplant; CI, confidence interval; ≥CR, complete response or better; CR/sCR, complete response/stringent complete response; DPd/DVd, daratumumab with dexamethasone and pomalidomide or bortezomib; FHR, functional high risk; LOT, line of therapy; MRD, minimal residual disease; NE, not estimable; NGF, next-generation flow; NGS, next-generation sequencing; OR, odds ratio; Tec-Dara, teclistamab plus daratumumab.
[a]Functional high-risk status defined as patients with 1 prior LOT and progressive disease within 18 months of ASCT or start of initial therapy.
[b]MRD-negative ≥CR refers to MRD negativity achieved within 3 months prior to achieving CR/sCR or at any time after CR/sCR and before progression or subsequent therapy. Assessed in the MRD NGS primary analysis set, defined as all randomized patients except those recruited in China (due to China instead utilizing NGF for MRD assessment).

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Multiple Myeloma

Presented by O Patel at the Society of Hematologic Oncology (SOHO) Annual Meeting; September 9-12, 2026; Houston, TX, USA