MM-491

Daratumumab (DARA) + Bortezomib/Thalidomide/Dexamethasone (D-VTd) Followed by DARA Maintenance in Transplant-eligible (TE) Newly Diagnosed Multiple Myeloma (NDMM): >6-year Update of the Phase 3 CASSIOPEIA Study

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Key Takeaway

These results confirm D-VTd induction/consolidation as a standard of care and demonstrate the benefit of DARA monotherapy maintenance for TE patients with NDMM

Conclusions

In the induction/consolidation phase (median follow-up of nearly 7 years), PFS and OS were significantly improved with D-VTd versus VTd, with median PFS ~2.5 years longer (~7 vs ~4.5 years) and a 45% reduction in the risk of death with the addition of DARA to VTd

In the maintenance phase (median follow-up of ~6 years), DARA reduced the risk of progression or death by 51% versus OBS, with 72-month PFS rates 20% higher with DARA (57.1% vs 36.5%, respectively)

D-VTd induction/consolidation followed by DARA maintenance led to the most pronounced PFS benefit and achieved the highest and most durable rates of MRD negativity, which translated to superior PFS outcomes

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Poster

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Acknowledgments

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Disclosure

TSL is an employee of Janssen and holds stock in Johnson & Johnson.

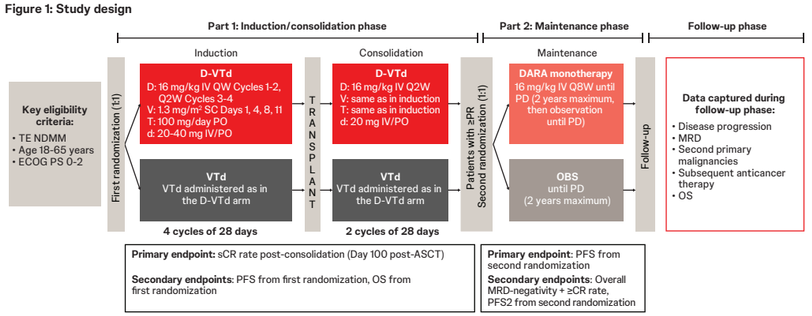
Introduction

- Results from the induction/consolidation phase (Part 1) of the CASSIOPEIA study (ClinicalTrials.gov Identifier: NCT02541383) established daratumumab (DARA) plus bortezomib/thalidomide/dexamethasone (D-VTd) as a standard of care for transplant-eligible (TE) patients with newly diagnosed multiple myeloma (NDMM)[1-3]
  - D-VTd demonstrated superior depth of response (complete response or better [≥CR] and minimal residual disease [MRD] negativity) and significantly prolonged progression-free survival (PFS) and overall survival (OS) versus bortezomib/thalidomide/dexamethasone (VTd), with acceptable safety (median follow-up: 18.8 months from first randomization)[1]
- During the maintenance phase (Part 2) of CASSIOPEIA, DARA monotherapy maintenance every 8 weeks (Q8W) significantly improved PFS and achieved higher rates of MRD negativity versus observation (OBS) and was well tolerated (median follow-up: 35.4 months from second randomization)[4]
- As part of the long-term follow-up of CASSIOPEIA, here we report the long-term outcomes from the induction/consolidation and maintenance phases after a median follow-up of 80.1 months (nearly 7 years) from first randomization and 70.6 months (~6 years) from second randomization

Methods

- In Part 1 of CASSIOPEIA, TE patients with NDMM were randomized (1:1) to 4 pre-transplant induction cycles and 2 post-transplant consolidation cycles with D-VTd or VTd (**Figure 1**)
- In Part 2 of CASSIOPEIA, patients on study who achieved partial response or better were re-randomized (1:1) to DARA maintenance or OBS for up to 2 years
- During the follow-up phase, the following data were captured: disease progression, MRD, second primary malignancies, subsequent anticancer therapy, and OS
  - No additional safety data were collected during the follow-up phase per study protocol, as all patients had completed 2 years' fixed duration of maintenance/observation, discontinued study treatment, and completed the 30-day post-treatment window for adverse event reporting at the time of the previous clinical cutoff
- MRD negativity was assessed via next-generation sequencing and defined as the proportion of patients who achieved ≥CR and MRD negativity in the maintenance-specific intent-to-treat population post-consolidation after the second randomization

Figure 1: Study design



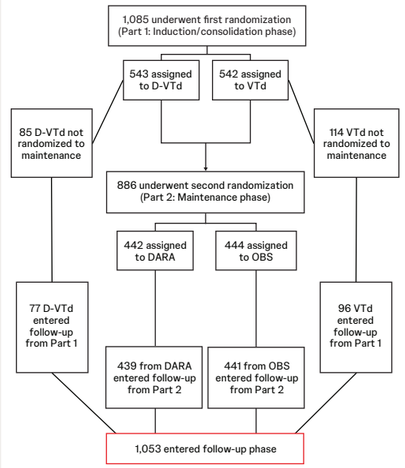
TE, transplant eligible; NDMM, newly diagnosed multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status; D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; D, daratumumab; IV, intravenous; QW, weekly; Q2W, every 2 weeks; V, bortezomib; SC, subcutaneous; T, thalidomide; PO, oral; d, dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; PR, partial response; DARA, daratumumab; Q8W, every 8 weeks; PD, progressive disease; OBS, observation; MRD, minimal residual disease; OS, overall survival; sCR, stringent complete response; ASCT, autologous stem cell transplant; PFS, progression-free survival; CR, complete response; PFS2, progression-free survival on next line of therapy.

Results

Patients

- 1,085 patients were enrolled from 111 sites from September 22, 2015, to August 1, 2017
- More patients in the D-VTd group versus the VTd group completed induction/consolidation per protocol (84.3% vs 79.0%) and underwent second randomization into the maintenance phase (**Figure 2**)
  - 199 patients (85 from D-VTd and 114 from VTd) did not proceed to second randomization
- Nearly all patients entered the follow-up phase (1,053/1,085; 97.1%)

Figure 2: Patient disposition

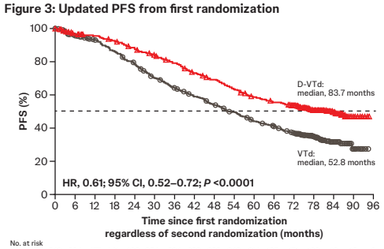


D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; DARA, daratumumab; OBS, observation.

Progression-free and overall survival

- At a median follow-up from first randomization of 80.1 months, PFS from first randomization was significantly improved with D-VTd versus VTd, with a median PFS ~2.5 years longer with the addition of DARA to VTd (~7 vs ~4.5 years; **Figure 3**)

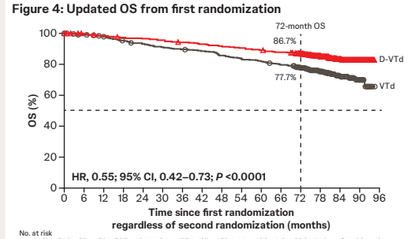
Figure 3: Updated PFS from first randomization



PFS, progression-free survival; D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
P value was calculated using the log-rank test.

- D-VTd significantly reduced the risk of death by 45% versus VTd (**Figure 4**)
  - There were 83 (15.3%) deaths in the D-VTd arm and 139 (25.6%) in the VTd arm

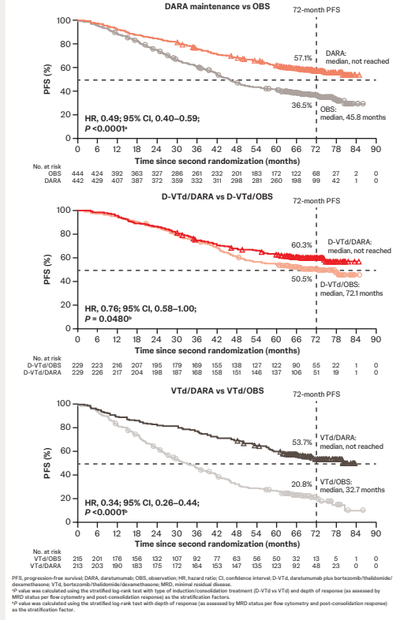
Figure 4: Updated OS from first randomization



OS, overall survival; D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
P value was calculated using the log-rank test.

- At a median follow-up from second randomization of 70.6 months, DARA maintenance reduced the risk of progression or death by 51% versus OBS (HR, 0.49; 95% CI, 0.40–0.59; *P* <0.0001; **Figure 5**)
- The longest PFS was observed in patients who received D-VTd followed by DARA maintenance (**Figure 5**)

Figure 5: PFS from second randomization

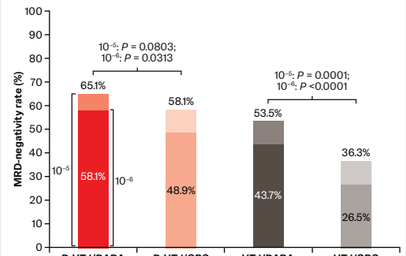


PFS, progression-free survival; DARA, daratumumab; OBS, observation; HR, hazard ratio; CI, confidence interval; D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; MRD, minimal residual disease.
a*P* value was calculated using the stratified log-rank test with type of induction/consolidation treatment (D-VTd vs VTd) and depth of response (as assessed by MRD status per flow cytometry and post-consolidation response) as the stratification factors.
b*P* value was calculated using the stratified log-rank test with depth of response (as assessed by MRD status per flow cytometry and post-consolidation response) as the stratification factor.

MRD-negativity rates

- MRD-negativity rates at any time during maintenance (at both 10^{-5} and 10^{-6}) were highest for D-VTd/DARA (**Figure 6**)

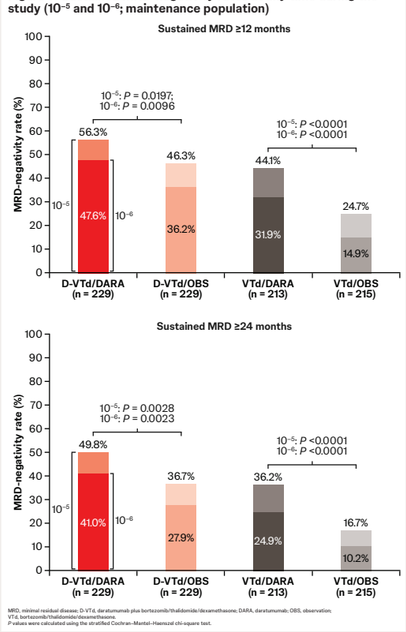
Figure 6: Overall MRD-negativity rates at any time during maintenance (10^{-5} and 10^{-6}; maintenance population)



MRD, minimal residual disease; D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; DARA, daratumumab; OBS, observation; VTd, bortezomib/thalidomide/dexamethasone.
P value was calculated using the stratified Cochran–Mantel–Haenszel chi-square test.

- Rates of sustained MRD negativity for ≥12 and ≥24 months at both 10^{-5} and 10^{-6} were highest for D-VTd/DARA (**Figure 7**)

Figure 7: Sustained MRD-negativity rates at any time during the study (10^{-5} and 10^{-6}; maintenance population)

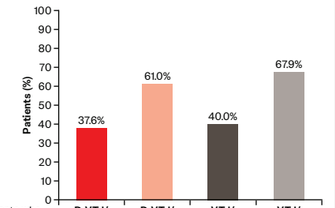


MRD, minimal residual disease; D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; DARA, daratumumab; OBS, observation; VTd, bortezomib/thalidomide/dexamethasone.
P values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test.

Subsequent antimyeloma therapy

- Higher proportions of patients in the OBS versus DARA arms received subsequent antimyeloma therapy; in the OBS arms, these were primarily anti-CD38–based therapies, with the most common subsequent anti-CD38–based regimen received being DARA plus lenalidomide/dexamethasone (D-Rd; **Figure 8**)

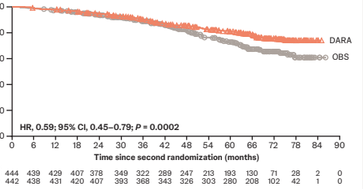
Figure 8: First-line subsequent anti-CD38–based therapies (maintenance population)



D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; DARA, daratumumab; OBS, observation; VTd, bortezomib/thalidomide/dexamethasone.

- At a median follow-up from second randomization of 70.6 months, PFS on next line of therapy (PFS2) was significantly improved with DARA maintenance versus OBS (**Figure 9**)

Figure 9: PFS2 from second randomization

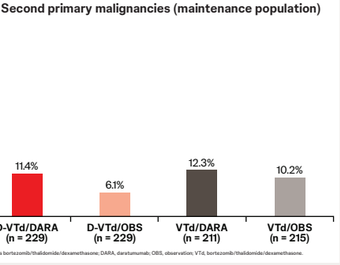


PFS2, progression-free survival on next line of therapy; PFS, progression-free survival; DARA, daratumumab; OBS, observation; HR, hazard ratio; CI, confidence interval; D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; MRD, minimal residual disease.
P value was calculated using the stratified log-rank test with type of induction/consolidation treatment (D-VTd vs VTd) and depth of response (as assessed by MRD status per flow cytometry and post-consolidation response) as the stratification factors.

Second primary malignancies

- Occurrence of second primary malignancies remained low and relatively consistent with ~6 years of follow-up (**Figure 10**)
- Second primary malignancies were non-cutaneous in 47 (5.3%) patients, cutaneous in 27 (3.1%) patients, and hematologic in 16 (1.8%) patients

Figure 10: Second primary malignancies (maintenance population)



D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; DARA, daratumumab; OBS, observation; VTd, bortezomib/thalidomide/dexamethasone.

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Multiple Myeloma

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