MultipleMyelomaHub

General MM, Patients non-eligible for transplant, Patients eligible for transplant

US Food and Drug Administration and European Medicines Agency approvals sought for new combined drug regimens in multiple myeloma

Emily Smith | Apr 03, 2019

During March 2019, several applications were filed with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for potential new combined drug regimens in newly diagnosed multiple myeloma (NDMM). These are summarized below and the founding trial information is included in **Tables 1 and 2**.

Daratumumab, bortezomib, thalidomide and dexamethasone (dara-VTd) for transplant eligible NDMM

A type II variation application (having a significant effect on quality, safety or efficacy of a medicinal product) was submitted to the EMA for this 4-drug regimen in transplant eligible NDMM, alongside a supplemental biologics license (sBLA) to the FDA.[1,2] These applications are based on the findings from part 1 of the CASSIOPEIA trial.

Table 1: Summary of CASSIOPEIA clinical trial part 1[1–3]

Trial name	CASSIOPEIA (MMY3006)
NCT reference	NCT02541383
Drug combination	Dara-VTd (daratumumab, bortezomib, thalidomide, dexamethasone) VTd (bortezomib, thalidomide, dexamethasone)
Patient setting	Transplant eligible NDMM
Trial phase	Phase III
Trial design	Dara-VTd *versus* VTd
N	1085

Dosing schedule	Four cycles of VTd induction +/- daratumumab (16 mg/kg), high-dose therapy and autologous stem cell transplant (ASCT) followed by two cycles of VTd consolidation +/- daratumumab (16 mg/kg)
Primary endpoint	Stringent complete response (sCR)
Efficacy	sCR (dara-VTd *vs* VTd): 28.9% *vs* 20.3% (odds ratio: 1.60, 95% CI, 1.21–2.12, $P \leq 0.001$)
Safety	Safety profile of dara-VTd consistent with that of VTd and daratumumab alone.

Daratumumab, lenalidomide and dexamethasone (DRd) for transplant ineligible NDMM

A type II variation application was submitted to the EMA for DRd in transplant ineligible NDMM, alongside a sBLA to the FDA.[4] These applications are based on the findings from the MAIA trial.

Table 2: Summary of MAIA clinical trial[4,5]

Trial name	MAIA (MMY3008)
NCT reference	NCT02252172
Drug combination	DRd (daratumumab, lenalidomide, dexamethasone) Rd (lenalidomide, dexamethasone)
Patient setting	Transplant ineligible NDMM
Trial phase	Phase III
Trial design	DRd *versus* Rd

N	737
Dosing schedule	Rd: oral lenalidomide (25 mg) on days 1–21 of a 28-day cycle with 40 mg dexamethasone once per week. DRd: As per Rd arm with the addition of intravenous daratumumab (16 mg/kg) once weekly for cycles 1–2, every 2 weeks for cycles 3–6 and every 4 weeks for cycle 7 onwards until disease progression, unacceptable toxicity or study end
Primary endpoint	Progression-free survival (PFS)
Efficacy *(Given as DRd vs Rd)*	Median follow-up: 28 months Median PFS: not reached *vs* 31.9 months ≥Complete response (CR): 47.6% *vs* 24.7% Overall response rate (ORR): 93% *vs* 81% Risk of reduction of disease progression or death with DRd *vs* Rd alone: 44% (HR 0.56, 95% CI, 0.43–0.73, $P < 0.0001$)
Safety	In the DRd arm, there were higher rates (≥5% difference) of grade 3/4 pneumonia, neutropenia and leukopenia Safety profile is in line with previously reported daratumumab studies

References

1. EU Application Filed for Daratumumab in Newly Diagnosed, Transplant-Eligible Myeloma. https://www.onclive.com/web-exclusives/eu-application-filed-for-daratumumab-in-newly-diagnosed-transplanteligible-myeloma [accessed 2019 March 28]
2. FDA Approval Sought for Frontline Daratumumab Regimen in Transplant-Eligible Myeloma. https://www.onclive.com/web-exclusives/fda-approval-sought-for-frontline-daratumumab-regimen-in-transplant-eligible-myeloma [accessed 2019 March 28]
3. Genmab. Genmab Announces Positive Topline Results in Phase III CASSIOPEIA Study of Daratumumab in Front Line Multiple Myeloma.https://ir.genmab.com/news-releases/news-release-details/genmab-announces-positive-topline-results-phase-iii-cassiopeia [accessed 2019 April 02]
4. EU Approval Sought for Frontline Daratumumab/Rd in Transplant-Ineligible Myeloma. https://www.onclive.com/web-exclusives/eu-approval-sought-for-frontline-daratumumabrd-in-transplantineligible-myeloma [accessed 2019 March

28]

5. Facon T. *et al*. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Abstract #LBA-2. 2018 Dec 1–4. ASH 60th Annual Meeting and Exposition, San Diego, CA.
