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Efficacy of daratumumab combination regimen in patients with multiple myeloma: a combined analysis of six phase III randomised controlled trials

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INTRODUCTION

- Multiple myeloma (MM) is a hematological malignancy of abnormal clonal plasma cell proliferation which accounts for 1% of all cancers.
- Over the last few years, introduction of novel agents has become a therapeutic landmark in the management of newly diagnosed MM (NDMM) and relapsed or refractory MM (RRMM), in both transplant – eligible and transplant – ineligible patients.
- Studies have shown that daratumumab, a human IgG kappa monoclonal antibody targeting CD38 on myeloma cells, monotherapy or in combination with proteasome inhibitors, immunomodulatory agents and/ or other antimyeloma therapies increased survival in the treatment of MM.

AIM

- We conducted an updated meta-analysis of phase III randomised controlled trials (RCT) to determine the efficacy of daratumumab combination regimen in patients with NDMM and RRMM.

METHOD

- We performed systematically a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts up to 30th April 2020 using the keywords “multiple myeloma AND daratumumab,” OR “plasma cell disorder AND daratumumab.” The references of all potential studies were also reviewed for any additional relevant studies. We limited the search to “humans” and “randomised controlled trials.” All studies written in English or non-English languages were obtained.
- The studies that were eligible to be included in the meta-analysis had to conform with the following characteristics: phase III RCTs utilizing daratumumab in patients with newly diagnosed/untreated multiple myeloma or relapsed/refractory multiple myeloma.

- **The primary outcome of our meta-analysis was progression-free survival (PFS).**
- **The secondary outcome was the overall response rate (ORR), including stringent complete response (sCR), complete response (CR), and MRD negativity (molecular response).**

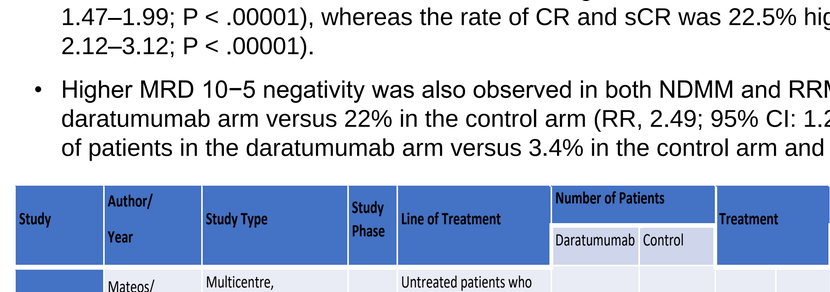
- Six phase III RCTs (POLLUX, CASTOR, CANDOR, ALCYONE, CASSIOPEIA, and MAIA studies) involving 4025 patients (2094 participants in daratumumab group and 1931 cases in control group) were included in the final analysis.
- Studies compared daratumumab based combination regimens with antimyeloma regimens without daratumumab as shown in Table 1
- Daratumumab was utilized in relapsed and refractory multiple myeloma in the POLLUX, CASTOR, and CANDOR studies, and as first-line treatment for patients with multiple myeloma in the ALCYONE, CASSIOPEIA, and MAIA studies.
- The randomization ratio was 1:1 in all studies except 2:1 in the CANDOR trial.
- Mantel-Haenszel (MH) method was used to estimate the pooled hazard ratio (HR) for progression-free survival (PFS), and pooled risk ratio (RR), and risk difference (RD) with 95% confidence interval (CI) for ORR, CR, and sCR and MRD.
- All statistical analyses were performed using the Review Manager, version 5.3 (Nordic Cochrane Centre; Copenhagen, Denmark).
- Heterogeneity was assessed with I2 and Cochran's Q statistic.
- A “P-value” of <.05 was considered significant and I2 > 50% is considered substantially heterogeneous. An HR < 1.0 or RR < 1.0 was in favor of daratumumab.

RESULTS

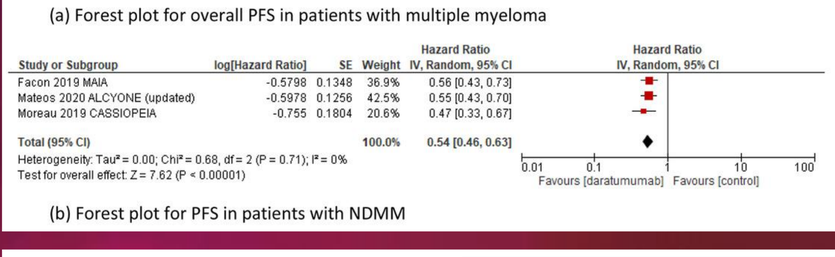
- The I2 statistic showed some heterogeneity among RCTs and the random-effects model was applied to provide a more conservative result.
- The pooled HR for overall PFS was statistically significant at 0.46 (95% CI: 0.38–0.55; P < .00001) Figure 1A.
- The pooled HR for PFS was calculated for each subset; NDMM in Figure 1B (HR, 0.54; 95% CI: 0.46–0.63; P < .00001) and RRMM in Figure 1C (HR, 0.44; 95% CI: 0.30–0.64; P < .0001).
- Although the pooled HR for PFS was significant in standard-risk cytogenetic NDMM cohort in Figure 1D (HR, 0.43; 95% CI: 0.35–0.53; P < .00001), PFS was not statistically significant in high risk cytogenetic NDMM cohort in Figure 1E (HR, 0.76; 95% CI: 0.53–1.10; P = .15).
- A PFS benefit was observed in both standard-risk cytogenetic and high-risk cytogenetic cohorts in RRMM with the pooled HR of 0.38 (95% CI: 0.25–0.58; P < .00001) and the HR of 0.46 (95% CI: 0.31–0.67; P < .0001), respectively in Figure 1F,G.
- According to an analysis of two trials, which enrolled transplant-ineligible NDMM patients (ALCYONE and MAIA trials), the pooled HR for PFS was not significant at 0.81 (95% CI: 0.52–1.26; P = .35) in patients with NDMM who harbored high-risk cytogenetics.
- The benefit in ORR was observed in both NDMM and RRMM who have received a daratumumab-containing regimen.
- In NDMM, ORR was reported in 92.2% in daratumumab arm versus 82.8% in the control arm (RR, 1.13; 95% CI: 1.01–1.26; P = .03).
- In RRMM, ORR was 87% versus 71.3% in the control arm (RR, 1.22; 95% CI: 1.12–1.32; P < .00001).
- In NDMM, the rate of CR and sCR was 17.9% higher in daratumumab combination regimens compared to the control group (RR, 1.71; 95% CI: 1.47–1.99; P < .00001), whereas the rate of CR and sCR was 22.5% higher in daratumumab arm in the RRMM subgroup (RR, 2.57; 95% CI: 2.12–3.12; P < .00001).
- Higher MRD 10−5 negativity was also observed in both NDMM and RRMM. In NDMM, molecular remission was reported in 38.8% in the daratumumab arm versus 22% in the control arm (RR, 2.49; 95% CI: 1.23-5.04; P = .01). In RRMM, molecular remission was reported in 18.4% of patients in the daratumumab arm versus 3.4% in the control arm and the pooled RR was significant at 5.73 (95% CI: 3.75–8.78; P < .00001).

Study	Author/ Year	Study Type	Study Phase	Line of Treatment	Number of Patients		Treatment	
					Daratumumab	Control		
ALCYONE	Mateos/ 2020	Multicentre, Randomised, open-label, active-control	III	Untreated patients who are ineligible for stem cell transplantation	350	356	DVMP	VMP
MAIA	Facon/ 2019	Randomised, open label, multicentre	III	Newly diagnosed multiple myeloma who were ineligible for autologous stem cell transplantation	368	369	DRDex	RDex
CASSIOPEIA	Moreau/ 2019	Multicentre, Randomised, open-label, active-control	III	Newly diagnosed multiple myeloma who were eligible for autologous stem cell transplantation	543	542	DVTDex	VTDex
POLLUX	Bahlis/ 2020	Randomised, open-label, multicentre	III	Relapsed or refractory multiple myeloma	281	276	DRDex	RDex
CASTOR	Spencer/ 2018	Multicentre, randomised, open-label, active-controlled	III	Relapsed or relapsed and refractory multiple myeloma	240	234	DVDex	VDex
CANDOR	Usmani/ 2019	Randomised, open label,	III	Relapsed or relapsed and refractory multiple myeloma	312	154	KDDex	KDex

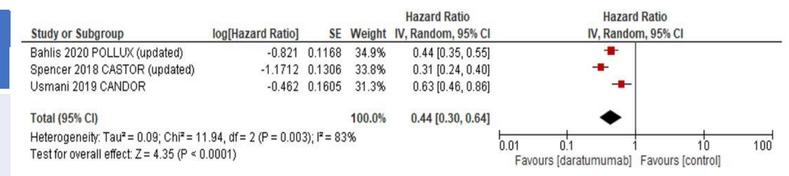
Abbreviations: D, Daratumumab; V, Bortezomib; M, Melphalan; P, Prednisolone; R, Lenalidomide; Dex, Dexamethasone; T, Thalidomide; K, Carfilzomib
Table 1. Characteristics of the studies included in the meta-analysis



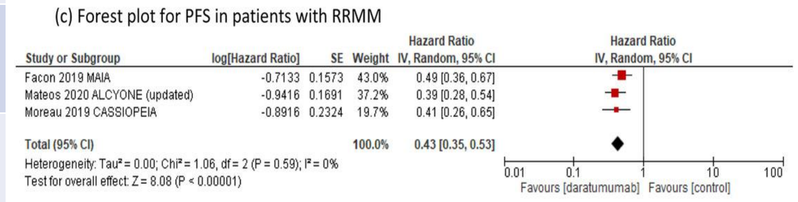
(a) Forest plot for overall PFS in patients with multiple myeloma



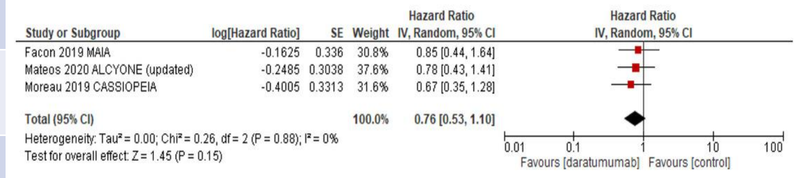
(b) Forest plot for PFS in patients with NDMM



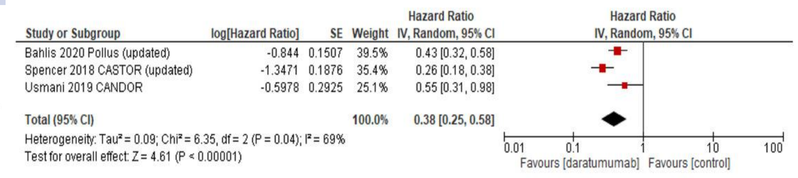
(c) Forest plot for PFS in patients with RRMM



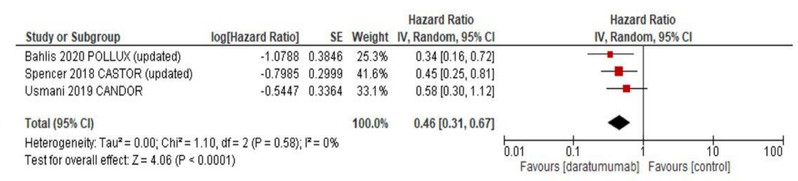
(d) Forest plot for PFS in patients with NDMM with standard risk cytogenetics



(e) Forest plot for PFS in patients with NDMM with high risk cytogenetics



(f) Forest plot for PFS in patients with RRMM with standard risk cytogenetics



(g) Forest plot for PFS in patients with RRMM with high risk cytogenetics

Figure 1 Pooled HR for PFS in patients with multiple myeloma: A, overall; B, NDMM; C, RRMM; D, SRC NDMM; E, HRC NDMM; F, SRC RRMM; G, HRC RRMM receiving daratumumab containing regimen versus control

CONCLUSIONS

- Our meta-analysis showed that daratumumab combination regimens significantly improved PFS, ORR, CR, and sCR, and MRD negativity compared to control arms in patients with NDMM and RRMM.
- The improvement in PFS was noted across all subgroups except in NDMM with high-risk cytogenetics.
- More randomized studies are necessary in the future to explore further novel therapies and the optimal combination of anti-myeloma therapies to improve survival in patients with NDMM within the high-risk cytogenetic subset.

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Full article at

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