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STUDY REVIEW

Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in patients with previously treated multiple myeloma: three-year follow-up of CASTOR

Making Education Easy 2021

About the Expert

Dr Ken Romeril
FRACP, FRCPA

Ken is a haematologist specialising in malignant haematology. He trained in Christchurch, Sydney and Southampton, and is currently at the Bowen Icon Cancer Centre. Ken has a particular interest in translational myeloma research and genetics. He is involved in clinical trials, is the current Chair of Myeloma New Zealand, a former chair of the ALLG Myeloma Sub-Committee, and is the NZ representative on the International Myeloma Working Group, which has around 200 members.

Abbreviations used in this review
ASCT = autologous stem cell transplant
CR = complete remission
ITT = intent-to-treat
MRD = minimal residual disease
ORR = overall response rate
RRMM = relapsed or refractory multiple myeloma
PFS = progression-free survival
PI = proteasome inhibitor

In the primary and follow-up analyses of the phase 3 CASTOR study in patients with relapsed or refractory multiple myeloma (RRMM), a regimen of daratumumab, bortezomib, and dexamethasone significantly prolonged progression-free survival (PFS) and induced higher rates of deeper responses than bortezomib and dexamethasone alone.[1-3] This publication summarises data from an update of the CASTOR study after a median follow-up of 40 months[3] and demonstrated that a regimen of daratumumab, bortezomib, and dexamethasone maintained significant benefits in RRMM patients and with a consistent safety profile.

Introduction

Daratumumab is a human, CD38-targeted, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody with a direct on-tumour and immunomodulatory mechanism of action.[4-6] In phase 3 trials, daratumumab-based regimens reduced either disease progression/death by ≥40%, doubled CR rates, and/or tripled minimal residual disease (MRD) negativity in patients with newly diagnosed multiple myeloma and relapsed or refractory multiple myeloma (RRMM).[1,2, 7-13] In the phase 3 CASTOR study in patients with RRMM, a regimen of daratumumab, bortezomib, and dexamethasone significantly prolonged progression-free survival (PFS) and induced higher rates of deeper responses than bortezomib and dexamethasone alone.[1, 2] In the 2-year, follow-up analysis of the CASTOR study (median follow-up of 19.4 months), median PFS was 16.7 months with daratumumab, bortezomib, and dexamethasone versus 7.1 months with bortezomib and dexamethasone alone (hazard ratio [HR] 0.31; 95% confidence interval [CI] 0.24, 0.39; p<0.0001).[2]

This update of the CASTOR study provides efficacy and safety data from the CASTOR study after a median follow-up of 40.0 months (nearly 3 years after the primary analysis).[3]

Methods

Study design

The study design of the CASTOR study has been previously described (NCT02136134).[1, 2] This phase 3, multicentre, open-label trial enrolled patients with RRMM who had received at least 1 prior line of therapy.

Treatment

Patients were randomised to receive daratumumab, bortezomib, and dexamethasone or bortezomib and dexamethasone alone, with stratification by International Staging System at baseline (I, II, or III), prior lines of therapy (1, 2, or > 3), and prior exposure to bortezomib.[1, 2]

- All patients received eight 21-day cycles of subcutaneous bortezomib 1.3 mg/m^2 (days 1, 4, 8, and 11) and oral dexamethasone 20 mg (days 1, 2, 4, 5, 8, 9, 11, and 12).
- Patients in the daratumumab, bortezomib, and dexamethasone arm received intravenous daratumumab 16 mg/kg:
  - Cycles 1-3: on days 1, 8, and 15 (3-week cycles);
  - Cycles 4 to 8: once every 3 weeks on day 1 (3-week cycles); and
  - Cycle 9 onwards: once every 4 weeks until the patient withdrew consent, the disease progressed, or unacceptable toxic effects developed.

After protocol amendment, patients receiving bortezomib and dexamethasone alone were offered daratumumab monotherapy after disease progression.[3]

Patients

Eligible patients had documented multiple myeloma, had received at least one prior line of therapy (with at least a partial response [PR]), and had disease progression classified per International Myeloma Working Group criteria. Patients were excluded if they had disease refractory to bortezomib or another proteasome inhibitor (prior bortezomib exposure was permitted).

Study endpoints

The primary end point was PFS; secondary end points included, time to disease progression, overall response rate (ORR), MRD negativity, and safety. Efficacy analyses were based on the intent-to-treat (ITT) population unless otherwise specified.[3]

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Results

Patients

A total of 498 patients had received treatment at the time of clinical cut-off for this analysis (October 2, 2018). The demographics and baseline characteristics were well-balanced between the treatment arms (**Table 1**).[1, 2]

In the daratumumab, bortezomib, and dexamethasone arm, the median age of the patients was 64 years (range, 30–88 years), and patients had received a median of two prior lines of therapy (range, 1-9).[3] Patients in the bortezomib plus dexamethasone arm had similar baseline demographics and clinical characteristics.

Prior therapies received by patients included bortezomib (66% of patients) and thalidomide (49%), and 48% of patients had received both a proteasome inhibitor (PI) and an immunomodulatory agent; 42% of patients had received prior lenalidomide.[3] Forty seven percent of patients had received one prior line of therapy, most frequently including an alkylating agent (89%), an immunomodulatory agent (65%), or a PI (53%).[3]

Disposition and drug exposure

At the time of this analysis, all patients in both treatment arms had completed the protocol-specified 8 cycles of treatment with bortezomib and dexamethasone or had discontinued study treatment.

For the 243 patients treated with daratumumab, bortezomib, and dexamethasone, the median duration of treatment was 13.4 months (range, 0-46.6 months). For the 237 patients treated with bortezomib and dexamethasone alone, the median duration of therapy was 5.2 months (range, 0.2-8.0 months).[3] A total of 297 (62%) patients discontinued treatment, largely due to progressive disease (213 [44%] patients).[3]

Efficacy

After a median follow-up of 40.0 months, PFS was significantly longer with daratumumab, bortezomib, and dexamethasone than with bortezomib and dexamethasone in the ITT population (median: 16.7 vs 7.1 months; HR 0.31; 95% CI 0.25, 0.40, p <0.0001; **Figure 1**).[3] The PFS benefit was maintained across patient subgroups, including patients aged <65 years and ≥65 years and cytogenetic risk status (high and standard).[3] The PFS benefit for daratumumab, bortezomib, and dexamethasone over bortezomib

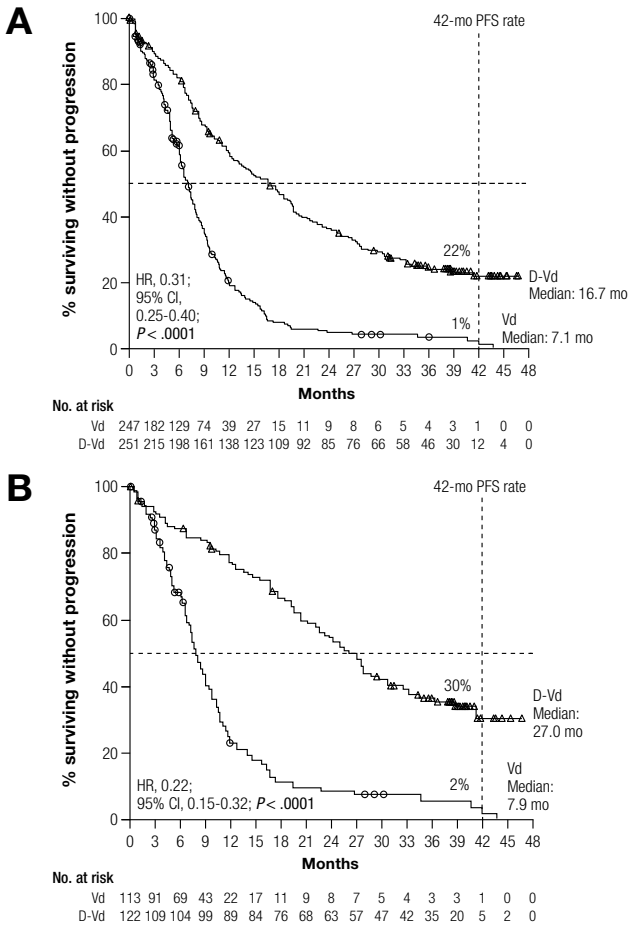

Figure 1. Progression-free survival (PFS) for **A**) the ITT population and **B**) patients who received one prior line of therapy.[3]

D-Vd = daratumumab, bortezomib, and dexamethasone; **HR** = hazard ratio; **mo** = months; **Vd** = bortezomib and dexamethasone.

Table 1. Baseline characteristics

Characteristic (% pts)	ITT population		Patients receiving one prior line of therapy	
	Daratumumab, bortezomib, and dexamethasone (n=251)	Bortezomib and dexamethasone (n=247)	Daratumumab, bortezomib, and dexamethasone (n=122)	Bortezomib and dexamethasone (n=113)
Median age, years (range)	64 (30-88)	64 (33-85)	63 (30-84)	64 (40-85)
Median time from diagnosis, years (range)	3.87 (0.7-20.7)	3.72 (0.6-18.6)	2.81 (0.7-14.9)	2.98 (0.6-18.1)
Prior lines of therapy				
Median, n (range)	2 (1-9)	2 (1-10)	1 (1-1)	1 (1-1)
1, % pts	49	46	100	100
2, % pts	28	30		
3, % pts	15	13		
>3, % pts	9	11		
Prior PI, % pts	67	70	53	52
Prior bortezomib, % pts	65	66	51	50
Prior IMiD, % pts	71	80	59	72
Prior thalidomide, % pts	50	49	48	43
Prior lenalidomide, % pts	36	49	12	29
Prior PI + IMiD, % pts	45	52	24	29
Refractory to lenalidomide, % pts	24	33	5	16

IMiD = immunomodulatory drug; **ITT** = intent-to-treat; **PI** = proteasome inhibitor.

Table 2. Response and MRD-negativity rates in the ITT population[3]

Characteristic (% pts)	ITT population		Patients receiving one prior line of therapy	
	Daratumumab, bortezomib, and dexamethasone (n=240)	Bortezomib and dexamethasone (n=234)	Daratumumab, bortezomib, and dexamethasone (n=119)	Bortezomib and dexamethasone (n=109)
ORR	85**	63	92*	74
≥CR	30**	10	43**	15
PR	22	34	15	32
MRD-negative (10^{-5})	14**	2	20**	3

*p<0.001, **p<0.0001 vs bortezomib and dexamethasone. **CR** = complete response; **ORR** = overall response rate; **PR** = partial response.

and dexamethasone alone was evident in patients treated with one prior line of therapy (median PFS 27.0 vs 7.9 months; HR 0.22; 95% CI 0.15, 0.32; p<0.0001; **Figure 1**), including those whose first-line regimen included bortezomib (median 20.4 vs 8.0 months; HR 0.22; 95% CI 0.13, 0.37; p<0.0001) or lenalidomide (median 21.2 vs 7.0 months; HR 0.30; 95% CI 0.11, 0.82; p=0.0140). In patients who were refractory to lenalidomide in any prior line of therapy, median PFS with daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone alone was relatively short but still superior in patients that received daratumumab, bortezomib and dexamethasone at 7.8 vs 4.9 months (HR 0.44; 95% CI 0.28, 0.68; p<0.0002).[3]

ORR were significantly higher with daratumumab-based triple therapy than with bortezomib and dexamethasone alone in the ITT population (85% vs 63%; p<0.0001; **Table 2**), as were CR or better (30% vs 10%; p< 0.0001).[3] These deep responses correlated with longer PFS, with patients with ≥CR achieving 42-month PFS rates of 53% and 10%, respectively. Similarly in patients who had received one prior line of therapy, ORR were higher with daratumumab-based triple therapy than with bortezomib and dexamethasone alone (92% vs 74%; p<0.0001), as were CR or better (43% vs 15%, p<0.001; **Table 2**).[3]

MRD negativity rates (10^{-5}, assessed via next-generation sequencing on bone marrow aspirate samples) were greater with daratumumab, bortezomib, and dexamethasone than with bortezomib and dexamethasone alone in the ITT population (14% vs 2%; p<0.0001), as well as in patients who had one prior line of therapy (20% vs 3%; p<0.0001; **Table 2**).[3] Median overall survival had not been reached.[3]

Safety

The safety profile remained consistent after a median 40 months of follow-up, with no new safety concerns identified.[3] The most commonly reported (>5%) grade 3 or 4 treatment-emergent adverse events (TEAEs) in the daratumumab, bortezomib, and dexamethasone arm compared with the bortezomib and dexamethasone arm were thrombocytopenia (46% vs 33%), anaemia (16% vs 16%), and pneumonia (10% vs 10%).[3] Grade 3-4 infections were more common with the triple therapy regimen than with bortezomib and dexamethasone alone (29% vs 19%); however, after adjusting for exposure, grade 3-4 infection events per patient-year were lower with daratumumab, bortezomib, and dexamethasone than with bortezomib and dexamethasone alone (0.26 vs 0.68). Rates of discontinuation due to TEAE were similar for both treatment arms (10% vs 9%).[3]

Second primary malignancies (cutaneous, invasive, and haematologic) were reported in 6% of patients in the daratumumab, bortezomib, and dexamethasone arm (4 new cases since the previous analysis) and 2% of the patients in the bortezomib, and dexamethasone arm (4 new cases since the previous analysis).

Expert comment

This study summarises data from an extended follow up of the phase 3 CASTOR study in patients with RRMM. On an ITT basis it clearly demonstrates the superiority of the triplet combination of daratumab, bortezomib and dexamethasone over bortezomib and dexamethasone alone. The CR rate of 30% vs 10% and a MRD negativity rate of 14% vs 2% (p<0.001) is much superior with the triplet regimen. The patients in the triple therapy arm who achieved a >CR had an excellent PFS rate of 53%. This compares with only 10% in the doublet treated patients who achieved >CR being progression free at 42 months. It is now well established that patients who go on to achieve MRD negativity tend to have better PFS figures and this was 14% vs 2% in the ITT population.

In the triplet treated patient group the patients had received a median of two prior lines of therapy (range of 1-9). The doublet treated population had similar baseline demographics. It was clear from the study that patients who had only received one line of therapy and got triplet therapy did better both in terms of the ORR and also achieving a CR or better (43% vs 15%). This then translates into a marked improvement in PFS benefit for patients with the triplet and one prior line of therapy. This came out at a median of 27.0 months vs 7.9 months for bortezomib and dexamethasone alone. This benefit was observed independently of whether the patient was exposed to bortezomib in their first-line regimen (median PFS 20.4 vs 8.0 months) or lenalidomide (median PFS 21.2 vs 7.0 months).

The safety profile was consistent after a median follow-up of 40 months and no new safety concerns were identified. It was apparent that grade 3-4 infections were more common in the triplet therapy arm but this was not significant when adjusted for exposure. Also second primary malignancies were quite low and may have been related to prior lenalidomide exposure.

It was of interest that only 8 cycles of bortezomib were used in this study for reasons that were not clear. If we extrapolate to the New Zealand scene, the recent switch to generic lenalidomide and increased access would mean that if this triplet approach were adopted then a longer exposure to a PI in conjuction with daratumumab could confer even better results. Other studies such as POLLUX and CANDOR did not discontinue the daratumab partner which was lenalidomide and carfilzomib, respectively.

The increasing use of lenalidomide as maintenance post ASCT in the New Zealand setting may impact on the response to daratumumab when these particular patients relapse. It does appear that the group of lenalidomide refractory patients do not fare as well on the triplet therapy but still do better than the doublet group (7.8 months vs 4.9 months).

In summary, the triplet therapy approach incorporating daratumumab was shown in this study to confer significant benefit to patients with myeloma relapsing after one line of therapy.

Interpretation

In the ongoing CASTOR study, a triple regimen that included daratumumab, bortezomib, and dexamethasone maintained significant PFS, ORR, and MRD-negativity rates compared with bortezomib, and dexamethasone alone in patients with RRMM.[3] The safety profile remained consistent after a median 40 months of follow-up, emphasising the tolerability and predictability of maintenance therapy with daratumumab alone following 8 cycles of bortezomib, and dexamethasone.

The benefit of triple therapy with daratumumab, bortezomib, and dexamethasone was more pronounced in patients who had received one prior line of treatment, and this benefit occurred regardless of whether the first-line regimen included bortezomib or lenalidomide.[3] Daratumumab, bortezomib, and dexamethasone also improved outcomes compared with bortezomib, and dexamethasone alone for the clinically important group of patients who were refractory to lenalidomide in any prior line of treatment.

EXPERT'S CONCLUDING COMMENTS

The original CASTOR study was published in 2016 and presented solid evidence for the value of adding daratumamab to bortezomib and dexamethasone. This follow-up study 40 months later confirms the initial concept and clearly shows that the triplet regimen:

- confers better defined outcomes in terms of ORR, CR or better and PFS
- tells us that the optimal benefit is obtained if the regimen is utilised following the failure of first line therapy
- the deep responses as measured by MRD analysis translate into prolonged PFS

In New Zealand we currently do not have an effective regime to offer our relapsed patients. This unmet clinical need would be met if we were able to introduce this effective triplet regime into clinical practice.

TAKE-HOME MESSAGES

- In the ongoing CASTOR study, after an extended median follow-up of 40 months, triple therapy with daratumumab, bortezomib, and dexamethasone showed improved efficacy outcomes (including PFS, ORR, and MRD-negativity rate) compared with bortezomib and dexamethasone alone.
- The most pronounced improvement in response was observed in patients who had one prior line of therapy.
- Triple therapy with daratumumab, bortezomib, and dexamethasone showed improved efficacy outcomes compared with bortezomib and dexamethasone alone in patients who were refractory to lenalidomide in any prior line of treatment.
- The safety profile remained consistent after a median 40 months of follow-up, emphasising the tolerability and predictability of maintenance therapy with daratumumab alone.

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