Daratumumab, Bortezomib and dexamethasone (DVd) at first relapse for patients with Relapsed/ Refractory Multiple Myeloma (RRMM): a UK Myeloma Research Alliance (UK-MRA) real-world multicentre analysis

Authors:
Annabel McMillan[1], Supratik Basu[2], Kamaraj Karunanithi[3], Elizabeth Parkins[4], Edward Lau[4], Gordon Cook[5], Christopher Parrish[5], Firas Al-Kaisi[6], Guy Pratt[7], Salim Shafeek[8], Stephen Jenkins[9], Shivir Moosai[9], Danish Memon[9], Ceri Bygrave[10], Xenofon Papanikolaou[11], Tara Maisel[12], Sandra Hassan[12], Gurvin Chander[13], Bhuvan Kishore[13], Farheen Karim[2], Georgina Talbot[2], Farooq Wandroo[14], Dunsi Bolarinwa[1], Kwee Yong[1], Rakesh Popat[1]

Institutions:
1. University College London Hospitals NHS Trust/University College London
2. Royal Wolverhampton Hospitals NHS Trust and University of Wolverhampton
3. Royal Stoke University Hospital
4. Royal Cornwall Hospitals NHS Trust
5. Leeds Teaching Hospital NHS Trust
6. Royal Derby Hospital
7. Queen Elizabeth Hospital Birmingham
8. Worcestershire Royal Hospital
9. Russell Hall Hospital
10. University Hospital of Wales
11. The Lister Hospital
12. Queen's Hospital
13. University Hospitals Birmingham NHS Foundation Trust
14. Sandwell and West Birmingham Hospitals NHS Trust

Introduction: Daratumumab in combination with bortezomib and dexamethasone (DVd) demonstrated a superior overall response rates (ORR) and progression free survival (PFS) compared to Vd in the CASTOR phase 3 trial for patients with RRMM. On this basis, DVd was recommended in March 2019 for UK patients with RRMM that had 1 prior line (PL). Discrepancies in outcomes between patients treated in clinical trials compared to routine practice is well recognised due to a combination of patient, disease and treatment-related factors. In addition, bortezomib is often administered once-weekly in routine practice to minimise neuropathy, while CASTOR used bi-weekly bortezomib dosing. As a result, the real-world outcomes of patients treated with DVd are yet to be determined.
The primary aims of this analysis was to assess the ORR and PFS for patients with RRMM with 1PL treated with DVd in routine practice. Secondary aims were to assess OS, time to next treatment (TTNT), and efficacy in different sub-groups (high risk cytogenetics, previous proteasome inhibitor (PI) exposure, refractoriness of prior therapies, bi-weekly vs weekly bortezomib schedule, and previous treatment free interval (TFI)).

Methods: This was a retrospective analysis from 14 centres (academic and community hospitals; 7 within the West Midlands Research Consortium (WMRC)) treated with DVd between March 2019 and June 2021. Patients received daratumumab (IV and then SC from June 2020) weekly in cycles 1-3, on day 1 of a 3-week cycle during cycles 4-8, and then monthly from cycle 9 to progression. SC Bortezomib was predominantly given weekly for

cycles 1-8 although 5 centres used bi-weekly dosing for selected patients with aggressive disease. Adverse events were graded as per CTCAE criteria.

Results: 288 patients were included, with a median age of 69 years (range 20-88) (Table 1). Patients received a median of 1 PL (range 1-2) with 93% (269) 1PL, 7% (18) 2 PL (due to COVID-19 measures). The majority had an ECOG performance status of 0-2 (98%) and most received weekly bortezomib (n=201). This population differed from those with 1PL treated on CASTOR in being older, more were ISS 3 (31% vs 19%, p=0.0145), and more had prior bortezomib exposure (71% vs 51%, p=0.0003), 4% were PI refractory, 9% had a GFR of <30ml/min (<20ml/min was an exclusion from CASTOR), and 2% had an ECOG performance status of ≥3. The ORR was 76%, with >VGPR in 54% (Table 2), with no significant difference in response between patients receiving biweekly vs weekly bortezomib (85% vs 83%; p=0.71). The median time to response was 1.6m.

With a median follow up of 15m, the median PFS was 14m (95% CI 11.6-16). High cytogenetic risk patients had inferior outcomes: median PFS 10m (95% CI 6-14) for high risk vs not reached for standard risk (p=0.043); as did those with advanced ISS: median PFS was not reached, 15 and 12m for stage I, II and III respectively (p=0.05). For 15 patients with extramedullary disease (EMD), the median PFS was 3m (95% CI 1-5). Median PFS for patients who were PI refractory was shorter (10m vs 15m for PI sensitive patients (p=0.006)). There was no difference in median PFS for patients with prior PI exposure vs no prior PI (15 vs 13m; p=0.75), or according to weekly or bi-weekly bortezomib schedule (11 vs 15m; p=0.14). The median TTNT was 21m (95% CI 17-25). Overall, the median duration of treatment was 8m and 25 patients (9%) stopped treatment to receive a second autologous stem cell transplant. Those that had a prior TFI of >12m had a longer median PFS of 21m vs 10m (p=0.0004). The median OS has not been reached, with an estimated 2-year OS of 74% (Figure 1). For patients with high risk cytogenetics the median OS was 16m (95% CI 9-23; vs not reached for standard risk; p=0.0006), with estimated 2-year OS in the high risk group of 36%. There was no difference in OS for patients treated with biweekly vs weekly bortezomib (not reached for either; p=0.38).

DVd was generally well tolerated with 6% stopping due to adverse events (CASTOR 9.5%). Grade 3 or 4 toxicity occurred in 62 (22%) most commonly neutropenia and thrombocytopenia, with any grade infusion reactions reported in 27 (9%).

Conclusions: These real-world data of DVd at 1st relapse demonstrated good tolerability and high response rates with a weekly bortezomib schedule despite a more heterogenous population. However, high risk patients by cytogenetics, ISS or EMD had inferior outcomes as did those treated within 12 months from first line treatment.

Table 1. Baseline characteristics of patients in CASTOR trial vs UK real-world patients

	CASTOR DVd arm ITT (n=251)	CASTOR DVd arm 1PL (n=122)	UK real world (n=288)	Fisher's exact T test *
Median age (range)	64 (30-88)	63 (30-84)	69 (20-88)	
Median prior lines	2 (range 1-9)	1 (1-1)	1 (range 1-2)	
1	122 (49)	122 (100)	269 (93)	
>1	129 (51)		18 (7)	
ISS				
n	251	122	208	
I	98 (39)	57 (47)	81 (39)	
II	94 (37.5)	42 (34)	62 (30)	
III	59 (23.5)	23 (19)	65 (31)	*P*=0.0145
Cytogenetics#				
n	167		97	
Standard risk	123 (73.7)		76 (78)	
High risk	44 (26.3)		21 (22)	
GFR				
n			278	
<30 ml/min/1.73/m2			25 (9)	
Previous treatment				
n			278	
ASCT	157 (62.5)		135 (49)	
Bortezomib	162 (64.5)	62 (51)	196 (71)	*P*=0.0003
Lenalidomide	89 (35.5)	15 (12)	44 (16)	
Thalidomide	125 (49.8)	58 (48)	126 (45)	
Prior thalidomide (no PI)			44 (16)	
Refractory to last line	45 (17.9)		25 (9)	
Refractory to PI	-	-	12 (4)	
Treatment free interval				
n	251		284	
>12 months	118 (47)		194 (68)	
<12 months	133 (53)		90 (32)	

DVd= daratumumab, bortezomib, dexamethasone; ITT= intention to treat; 1PL= one prior line of therapy; ISS=International staging system; ASCT= autologous stem cell transplantation; PI= proteasome inhibitor

* Comparing CASTOR 1PL to UK data

High risk cytogenetics defined as one or more of: 17p deletion, t(4;14), t(14;16)

Table 2. DVd responses in CASTOR and UK real world data

Response	CASTOR DVd arm ITT (n=240)	CASTOR DVd arm 1PL (n=119)	UK real world (n=288)
ORR (%)	203 (85)	109 (92)	220 (76)
VGPR or better (%)	151 (63)	91 (77)	155 (54)
PR (%)	52 (22)	18 (15)	65 (23)
MR (%)	9 (4)	-	12 (4)
SD (%)	5 (2)	-	14 (5)
PD (%)	5 (2)	-	18 (6)

ITT= intentional to treat; 1PL= one prior line; ORR= overall response rate; VGPR= very good partial response; PR= partial response; MR= minimal response; SD= stable disease; PD=progressive disease;