Daratumumab (D) in Combination With Vd or D-Rd in Relapsed or Refractory Multiple Myeloma: Subgroup Analysis of CASTOR and POLLUX Studies in Patients With Early or Late Relapse After Initial Therapy

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INTRODUCTION

- High-risk multiple myeloma (MM) is often defined by the presence of cytogenetic abnormalities that have been associated with worse prognosis (ie, t[4;14], t[14;16], and/or del17p)[1]
- However, patients with MM who relapse early (within 12-18 months) after initial therapy are considered a functional high-risk group that is also associated with poor prognosis[1-5]
- Daratumumab (DARA) is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor[6-9] and immunomodulatory[10-12] mechanism of action, demonstrating greater cytotoxicity of MM cells ex vivo compared with analogs of other CD38 antibodies[13]
  - DARA induces higher levels of complement-dependent cytotoxicity, similar levels of antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis, and, in the presence of Fc receptor crosslinking, which occurs naturally in vivo, DARA elicits similar levels of cell death[13]
  - DARA is approved in combination with standard-of-care regimens for the treatment of MM[14-15] and has been used to treat >270,000 patients worldwide[16]
- In the phase 3 CASTOR and POLLUX studies, DARA in combination with bortezomib and dexamethasone (D-Vd) or lenalidomide and dexamethasone (D-Rd) significantly improved progression-free survival (PFS), regardless of cytogenetic risk status, and achieved higher rates of complete response or better (≥CR) and minimal residual disease (MRD) negativity versus bortezomib and dexamethasone (Vd) or lenalidomide and dexamethasone (Rd) alone in patients with relapsed or refractory MM (RRMM)[17,18]
- We conducted post hoc analyses of the CASTOR and POLLUX studies to evaluate the efficacy of D-Vd versus Vd and D-Rd versus Rd in subgroups of patients who had received 1 prior line of therapy based on timing of relapse (early or late) after initiation of the first line of therapy

METHODS

Study design

- Patients with RRMM who had received ≥1 prior line of therapy and had achieved partial response or better to ≥1 previous therapy were randomized 1:1 to D-Vd or Vd in CASTOR[19] and to D-Rd or Rd in POLLUX[20]
- Patients refractory or intolerant to bortezomib or refractory to another proteasome inhibitor were excluded from CASTOR,[19] and patients refractory or intolerant to lenalidomide were excluded from POLLUX[20]

Assessments

- In both studies, the intent-to-treat (ITT) population included all patients who were randomized to planned treatment groups, and the primary endpoint was PFS[19,20]
- Statistical methods have been published previously[17-20]
- In this analysis, the early relapse subgroup included patients with 1 prior line of therapy who relapsed <18 months after initiating their first line of therapy; the late relapse subgroup included patients with 1 prior line of therapy who relapsed ≥18 months after initiating their first line of therapy

MULTIPLE MYELOMA

RESULTS

Patients

- A total of 49 and 186 patients from the ITT population of CASTOR and 99 and 196 patients from the ITT population of POLLUX were included in the early relapse and late relapse subgroups, respectively
  - Patient demographic and baseline characteristics in the ITT population by relapse subgroup are summarized in **Table 1**

Efficacy

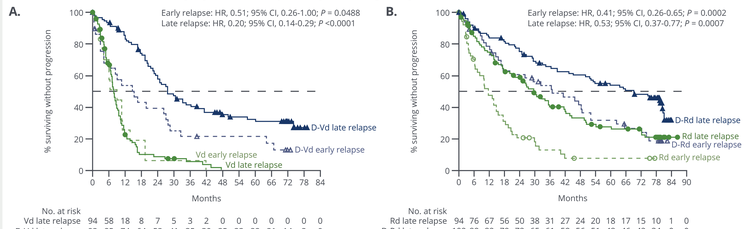
- Median (range) follow-up in the ITT population was 72.6 (0-79.8) months for CASTOR and 79.7 (0-86.5) months for POLLUX
- PFS consistently favored the DARA-containing regimens in the ITT populations across both the early relapse and late relapse subgroups (**Figure 1**)
  - In CASTOR, median PFS with D-Vd versus Vd was 15.4 versus 9.0 months (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.26-1.00; *P* = 0.0488) in the early relapse subgroup and 27.7 versus 7.9 months (HR, 0.20; 95% CI, 0.14-0.29; *P* <0.0001) in the late relapse subgroup (**Figure 1A**)
  - In POLLUX, median PFS with D-Rd versus Rd was 36.9 versus 11.7 months (HR, 0.41; 95% CI, 0.26-0.65; *P* = 0.0002) in the early relapse subgroup and 69.3 versus 29.7 months (HR, 0.53; 95% CI, 0.37-0.77; *P* = 0.0007) in the late relapse subgroup (**Figure 1B**)
- In CASTOR, ≥CR rates were higher with D-Vd versus Vd in the early relapse (20.7% vs 16.7%; *P* = 0.7360) and late relapse (51.1% vs 14.3%; *P* <0.0001) subgroups (**Table 2**)
- In POLLUX, ≥CR rates were higher with D-Rd versus Rd in the early relapse (53.2% vs 11.8%; *P* <0.0001) and late relapse (62.0% vs 38.5%; *P* = 0.0012) subgroups (**Table 2**)
- MRD-negativity rates (10^{-5} sensitivity) were higher with D-Vd or D-Rd versus Vd or Rd, respectively, regardless of relapse timing (**Table 2**)
  - CASTOR: early relapse, 13.3% versus 0%, *P* = 0.1476; late relapse, 22.8% versus 3.2%, *P* <0.0001
  - POLLUX: early relapse, 29.8% versus 3.8%, *P* = 0.0006; late relapse, 34.3% versus 13.8%, *P* = 0.0009

TABLE 1: Patient demographic and baseline characteristics by relapse subgroup[a] in CASTOR and POLLUX

	CASTOR				POLLUX			
	Early relapse		Late relapse		Early relapse		Late relapse	
	D-Vd (n = 30)	Vd (n = 19)	D-Vd (n = 92)	Vd (n = 94)	D-Rd (n = 47)	Rd (n = 52)	D-Rd (n = 102)	Rd (n = 94)
Age, y								
Median (range)	63 (41-83)	65 (40-80)	64 (30-84)	64 (40-85)	66 (36-82)	65 (47-85)	65 (34-89)	65 (42-85)
≥75 y, n (%)	2 (6.7)	3 (15.8)	6 (6.5)	14 (14.9)	6 (12.8)	8 (15.4)	11 (10.8)	8 (8.5)
ISS staging, n (%)[b]								
I	11 (36.7)	7 (36.8)	46 (50.0)	44 (46.8)	24 (51.1)	22 (42.3)	54 (52.9)	59 (62.8)
II	16 (53.3)	11 (57.9)	26 (28.3)	33 (35.1)	17 (36.2)	18 (34.6)	31 (30.4)	23 (24.5)
III	3 (10.0)	1 (5.3)	20 (21.7)	17 (18.1)	6 (12.8)	12 (23.1)	17 (16.7)	12 (12.8)
Cytogenetic risk, n (%)[c]	(n = 19)	(n = 17)	(n = 72)	(n = 62)	(n = 39)	(n = 44)	(n = 79)	(n = 66)
Standard risk	14 (73.7)	14 (82.4)	56 (77.8)	53 (85.5)	30 (76.9)	32 (72.7)	66 (83.5)	58 (87.9)
High risk	5 (26.3)	3 (17.6)	16 (22.2)	9 (14.5)	9 (23.1)	12 (27.3)	13 (16.5)	8 (12.1)

D-Vd, daratumumab plus bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; ISS, International Staging System.
[a]The early relapse subgroup included patients with 1 prior line of therapy who relapsed <18 months after initiating their first line of therapy; the late relapse subgroup included patients with 1 prior line of therapy who relapsed ≥18 months after initiating their first line of therapy.
[b]ISS staging was based on the combination of serum β_2-microglobulin and albumin.
[c]Cytogenetic risk was assessed locally by fluorescence in situ hybridization or karyotype testing; high risk was defined as the presence of t(4;14), t(14;16), or del17p.

FIGURE 1: PFS in the ITT population by relapse subgroup[a] in (A) CASTOR and (B) POLLUX[b]



PFS, progression-free survival; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval; D-Vd, daratumumab plus bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; DARA, daratumumab.
[a]The early relapse subgroup included patients with 1 prior line of therapy who relapsed <18 months after initiating their first line of therapy; the late relapse subgroup included patients with 1 prior line of therapy who relapsed ≥18 months after initiating their first line of therapy.
[b]HRs, 95% CIs, and *P* values are from a Cox proportional hazards model with treatment group as the sole explanatory variable. An HR <1 indicates an advantage for the DARA group.

TABLE 2: Response and MRD-negativity rates by relapse subgroup[a] in CASTOR and POLLUX

	CASTOR					
	Early relapse			Late relapse		
	D-Vd	Vd	*P* value	D-Vd	Vd	*P* value
Response, n (%)[b]	(n = 29)	(n = 18)		(n = 90)	(n = 91)	
ORR	23 (79.3)	16 (88.9)	0.4007[c]	86 (95.6)	65 (71.4)	<0.0001[c]
≥CR	6 (20.7)	3 (16.7)	0.7360[c]	46 (51.1)	13 (14.3)	<0.0001[c]
sCR	1 (3.4)	0		17 (18.9)	5 (5.5)	
CR	5 (17.2)	3 (16.7)		29 (32.2)	8 (8.8)	
≥VGPR	16 (55.2)	7 (38.9)	0.2828[c]	75 (83.3)	39 (42.9)	<0.0001[c]
VGPR	10 (34.5)	4 (22.2)		29 (32.2)	26 (28.6)	
PR	7 (24.1)	9 (50.0)		11 (12.2)	26 (28.6)	
MRD (10^{-5})[d]	(n = 30)	(n = 19)		(n = 92)	(n = 94)	
MRD negative, n (%)	4 (13.3)	0	0.1476[e]	21 (22.8)	3 (3.2)	<0.0001[e]
	POLLUX					
	Early relapse			Late relapse		
	D-Rd	Rd	*P* value	D-Rd	Rd	*P* value
Response, n (%)[b]	(n = 47)	(n = 51)		(n = 100)	(n = 91)	
ORR	44 (93.6)	39 (76.5)	0.0191[c]	93 (93.0)	75 (82.4)	0.0252[c]
≥CR	25 (53.2)	6 (11.8)	<0.0001[c]	62 (62.0)	35 (38.5)	0.0012[c]
sCR	9 (19.1)	0		37 (37.0)	18 (19.8)	
CR	16 (34.0)	6 (11.8)		25 (25.0)	17 (18.7)	
≥VGPR	39 (83.0)	18 (35.3)	<0.0001[c]	78 (78.0)	62 (68.1)	0.1246[c]
VGPR	14 (29.8)	12 (23.5)		16 (16.0)	27 (29.7)	
PR	5 (10.6)	21 (41.2)		15 (15.0)	13 (14.3)	
MRD (10^{-5})[d]	(n = 47)	(n = 52)		(n = 102)	(n = 94)	
MRD negative, n (%)	14 (29.8)	2 (3.8)	0.0006[e]	35 (34.3)	13 (13.8)	0.0009[e]

MRD, minimal residual disease; D-Vd, daratumumab plus bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; ORR, overall response rate; CR, complete response; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.
[a]The early relapse subgroup included patients with 1 prior line of therapy who relapsed <18 months after initiating their first line of therapy; the late relapse subgroup included patients with 1 prior line of therapy who relapsed ≥18 months after initiating their first line of therapy.
[b]Response-evaluable population, which included patients who had a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening, received ≥1 administration of study treatment, and had ≥1 post-baseline disease assessment.
[c]*P* value was calculated using the Cochran-Mantel-Haenszel chi-square test.
[d]Intent-to-treat population.
[e]*P* value was calculated using Fisher's exact test.

KEY TAKEAWAY

Our results support the use of D-Vd and D-Rd in patients with RRMM and 1 prior line of therapy, including in patients who relapse early after initial therapy and are considered to have functional high-risk disease

CONCLUSIONS

- Patients with functional high-risk MM who relapse early after initial therapy are becoming an increasingly recognized subgroup that is associated with poor outcomes and represents an unmet therapeutic need
- These post hoc analyses of CASTOR and POLLUX showed PFS and depth of response benefits of DARA-containing regimens in patients with 1 prior line of therapy, regardless of relapse timing (early or late)
  - At a median follow-up of >6 years, PFS consistently favored the DARA-containing regimen in both the early relapse and late relapse subgroups in both studies
  - In both CASTOR and POLLUX, ≥CR and MRD-negativity rates were higher with D-Vd or D-Rd versus Vd or Rd, respectively, regardless of relapse timing
- The results from these post hoc analyses combined with previous subgroup analyses of CASTOR and POLLUX[17,18] show that DARA-containing regimens maintain consistent clinical benefits in high-risk RRMM patients, as defined either by cytogenetics or by early relapse

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DISCLOSURES

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