Cost-effectiveness of Daratumumab Plus Bortezomib and Dexamethasone Versus Bortezomib and Dexamethasone for Treatment of Patients With Multiple Myeloma Who Have Received at Least One Prior Therapy: an Analysis of the CASTOR Trial

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BACKGROUND

- The safety and efficacy of daratumumab, a CD38-directed cytolytic monoclonal antibody, in combination with bortezomib and dexamethasone (DVd) is being investigated in an ongoing phase III trial (CASTOR).
- In the CASTOR phase III clinical trial, MM patients who had received at least one prior line of therapy, were randomized to DVd or bortezomib plus dexamethasone (Vd). DVd showed significant improvements in progression-free survival (hazard ratio = 0.39; 95% confidence interval [CI], 0.28 to 0.53; p<0.001) compared to patients receiving Vd (Palumbo et al., NEJM, 2016).
- Based on results of the CASTOR trial, a decision-analytic model was developed to explore the cost-effectiveness of DVd versus Vd in patients who had received at least one prior line of therapy and in a subgroup of patients with only one prior line of therapy (i.e. patients treated at first relapse).

METHODS

- The model structure (Figure 1) took the form of a partitioned survival analysis with three health states: progression-free survival (PFS), progressive disease, and death. PFS is estimated as the time under the PFS curve, overall survival (OS) is estimated as the time under the OS curve, and time spent with progressive disease is calculated as OS minus PFS.

Figure 1. Model Structure

- A range of parametric survival functions were fitted to patient-level PFS data from the CASTOR trial with (1) selection based on the Akaike and Bayesian information criteria and (2) priority given to the external validity of extrapolations with conservative survival projections.
- Diagnostic plots were used to assess the validity of the proportional hazards assumption between DVd and Vd and additional support of goodness-of-fit for parametric curves.
- Due to the limited number of data events and the follow-up time of the trial at the time of this analysis, overall survival (OS) was not estimated via parametric extrapolation of trial data but rather by its relationship to PFS, based on a retrospective analysis of approximately 23,000 MM patients (Felix et al., BMC Cancer, 2013) where an additional 2.45 months of median OS was associated with each additional month of median PFS gained.
- OS was operationalized by assuming the intercept and scale parameters as the best-fit parametric PFS functions, and solving for a regression covariate that would result in the estimated median OS from the median of the best-fit PFS curve and Felix et al. (2013) adjustment.
- Cost inputs are summarized in Table 1, where drug costs were taken from wholesale acquisition costs (Red Book, September 2017). Dosing information was extracted from the CASTOR trial, including recommended dosing amounts, cycle schedule, and relative dose intensity. Drug-administration costs and health-state costs were sourced from published literature.
- Subsequent therapy utilization patterns were sourced from Farr et al. (2011) and the Institute for Clinical and Economic Multiple Myeloma Review (2016), where 80% of patients received subsequent therapy for an average of 124 days.
- Utility weights were based on a published regression equation (NICE TA427, 2017) informed by baseline patient characteristics specific to the model population being analyzed (overall trial population or the subgroup of patients treated at first relapse), and treatment-specific best response, average number of hospitalizations, and incidence of Grade 3/4 adverse events from the CASTOR trial (Table 2).
- Cost-effectiveness was estimated over a lifetime horizon, with costs and outcomes discounted at 3% per annum.
- Incremental cost-effectiveness ratios were calculated, specifically the incremental cost per quality-adjusted life-year (QALY) gained and the incremental cost per life-year gained.
- One-way and probabilistic sensitivity analyses (PSA) were conducted, as well as scenario analyses around parametric curve selection.
- All analyses were performed for the overall trial population and for the subgroup of patients with a first relapse.

Table 1. Cost Inputs

Input	DVd	Vd	Source
Drug acquisition cost per administration			
Daratumumab*	$5,892	N/A	Estimated from WAC (Red Book, September 2017), patient characteristics, recommended dosing, and relative dose intensity from CASTOR
Bortezomib	$1,603	$1,603	
Dexamethasone	$0.50	$0.50	
Administration costs			
Initial IV infusion hour	$140		CMS (2017)
Subsequent IV infusion hours	$66		
Health state costs			
Progression-free cost per month	$200		Jakubowiak et al. (2016)
Progressive disease cost per month	$472		
Other resource use			
Physician visit	$45		Jakubowiak et al. (2016)
Serum-free light chain assay	$20		
Adverse event costs			
Neutropenia	$9,108		Jakubowiak et al. (2016)
Anemia	$6,077		
Thrombocytopenia	$5,321		
Lymphopenia	$9,108		
Peripheral sensory neuropathy	$1,810		
Pneumonia	$1,263		
Hypertension	$2,603		

*Based on average patient weight in CASTOR Trial (78 kgs)
CMS = Centers for Medicare and Medicaid Services; DVd = daratumumab plus bortezomib and dexamethasone; IV = intravenous; N/A = not applicable; Vd = bortezomib and dexamethasone; WAC = wholesale acquisition costs.
All costs were inflated to May 2017 USD using the medical component of the Consumer Price Index (US Bureau of Labor, 2017).

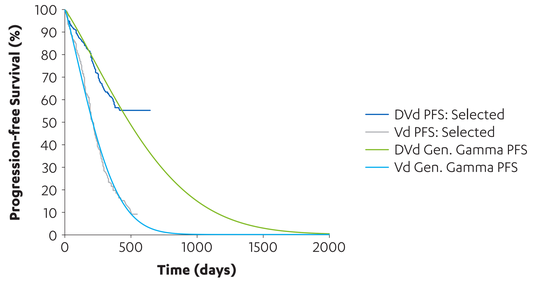
Table 2. Hospitalization and Grade 3/4 Adverse Event Inputs

Input	DVd	Vd
Hospitalization	58%	42%
Mean length of hospital stay (days)	9.9	7.3
Grade 3/4 adverse events		
Neutropenia	13%	4%
Anemia	14%	16%
Thrombocytopenia	45%	33%
Lymphopenia	9%	3%
Peripheral sensory neuropathy	5%	7%
Pneumonia	8%	10%
Hypertension	7%	1%

Source: CASTOR clinical study report for hospitalization data. Palumbo et al. (2016) for adverse event incidence.
Note: Grade 3/4 adverse events occurring in ≥5% of patients in either treatment arm were considered.

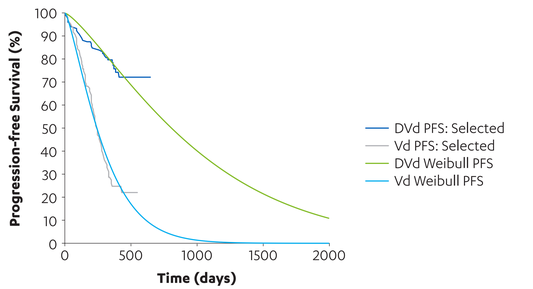
RESULTS

- The best-fit, clinically plausible parametric function for the overall trial population was the generalized gamma (Figure 2a) and for the subgroup of first relapse patients, the Weibull (Figure 2b).



DVd = daratumumab plus bortezomib and dexamethasone; PFS = progression-free survival; Vd = bortezomib and dexamethasone.

Figure 2a. Progression-free Survival Kaplan-Meier and Best-fit Parametric Curve in the Overall Trial Population



DVd = daratumumab plus bortezomib and dexamethasone; PFS = progression-free survival; Vd = bortezomib and dexamethasone.

Figure 2b. Progression-free Survival Kaplan-Meier and Best-fit Parametric Curve in the Subgroup of First Relapse Patients

- All results are presented as discounted values (Table 3).

Table 3. Results

	Overall Trial Population		Subgroup: First Relapse	
Outcome	**DVd**	**Vd**	**DVd**	**Vd**
Mean PFS (years)	1.50	0.67	2.56	0.80
Mean life-years	3.50	1.58	5.74	1.90
QALYs	2.88	1.26	4.78	1.55
Costs (lifetime)				
Drug acquisition	$231,528	$68,809	$311,355	$69,875
Administration	$7,902	$4,366	$9,930	$4,483
Other medical	$22,225	$11,264	$32,468	$12,757
Total	*$261,655*	*$84,439*	*$353,753*	*$87,115*
ICER*				
QALY gained	$109,903		$82,617	
Life-year gained	$92,398		$69,415	

*Drug costs were updated since development of the abstract to incorporate an assumption of no drug wastage, which slightly modified the ICERs.
DVd = daratumumab plus bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PFS = progression-free survival; Vd = bortezomib and dexamethasone; US = United States.
Notes: All results are presented as discounted (3% per annum) in 2017 US dollars.
The CASTOR trial is a parallel study to the POLLUX trial of daratumumab plus lenalidomide plus dexamethasone; cost-effectiveness is reported separately.

- In the overall trial population, the mean PFS was estimated to be 1.50 and 0.67 years for DVd and Vd, respectively. DVd resulted in an average of 1.92 additional life-years (3.50 life-years – 1.58 life-years) and 1.62 additional QALYs (2.88 QALYs – 1.26 QALYs) over Vd.
- Costs increased for DVd; the majority were related to drug acquisition of daratumumab and to longer time on treatment due to a longer PFS period. Incremental cost-effectiveness ratios in the overall trial population were $92,398 per life-year gained and $109,903 per QALY gained.
- Overall, survival (life-years), PFS, and QALYs were greater in the first relapse subgroup for both DVd and Vd than in the overall trial population. Mean PFS was estimated to be 2.56 and 0.80 years for DVd and Vd, respectively. DVd resulted in an average of 3.84 additional life-years (5.74 life-years – 1.90 life-years) and 3.23 additional QALYs (4.78 QALYs – 1.55 QALYs) over Vd.
- Incremental cost-effectiveness ratios in the first-relapse subgroup were $69,415 per life-year gained and $82,617 per QALY gained.
- One-way and scenario analyses indicated the most sensitive parameters to be PFS distribution, the relationship between PFS and OS, discount rates, utility weights, and drug-acquisition costs.
- The PSA was summarized in the form of scatter plots and cost-effectiveness acceptability curves (not shown).

LIMITATIONS

- At the time of this analysis, OS was not mature, therefore, an assumption for OS was utilized from the literature.
- Information on subsequent therapies was limited at the time of the analysis due to few patients initiating subsequent therapy, therefore, an assumption of subsequent therapies were based on the literature.
- Drug acquisition costs were based published WAC price, which does not contain discounts, price concessions, or chargebacks extended to wholesalers or other end users.
- The health state preferences utilized in this analysis may be not be representative of all multiple myeloma patients.

CONCLUSIONS

- **Based on the range of plausible cost-effectiveness ratio thresholds ($183,000-$264,000 per life-year gained and $109,000-$297,000 per QALY gained) reported in the 2003 cost-effectiveness decision rules for the US (Braithwaite et al., Med Care, 2008), this analysis suggests that DVd is cost-effective compared to Vd in the treatment of previously treated MM.**

- **Janssen does not endorse the use of cost-per-QALY or cost-per-life-year-gained analysis as the sole or primary basis of decision making**

REFERENCES

CMS (Centers for Medicare and Medicaid Services). Physician fee schedule search. Updated April 10, 2017. Available at: http://www.cms.gov/apps/physician-fee-schedule. Accessed April 20, 2017.

Farr AM, Stott-Miller M, Varker H, Spencer D, Shah M, Chen C. Treatment Sequencing Patterns Associated with Elderly Patients with Relapsed/Refractory Multiple Myeloma (MM) in the US Community Setting. *Blood*. 2016;126(23):5392.

Felix J, Aragao F, Almeida JM, Calado FJM, et al. Time-dependent endpoints as predictors of overall survival in multiple myeloma. *BMC Cancer*. 2013;13:122.

Institute for Clinical and Economic Review. Treatment options for relapsed or refractory multiple myeloma: effectiveness, value, and value-based price benchmarks. Final evidence report and meeting summary. 2016.

Jakubowiak AJ, Campioni M, Benedict A, et al. Cost-effectiveness of adding carfilzomib to lenalidomide and dexamethasone in relapsed multiple myeloma from a US perspective. *J Med Econ*. 2016;19(11):1061-1074.

NICE. Pomalidomide for multile myeloma previously treated with lenalidomide and bortezomib. Technology appraisal guidance [TA427]. Published January 11, 2017. Available at: https://www.nice.org.uk/guidance/ta427. Accessed April 20, 2017.

Palumbo A, Chanan-Khan A, Weisel K, et al., for the CASTOR Investigators. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:754-66.

Red Book Online [database on the Internet]. Ann Arbor, MI: Truven Health Analytics;2017. Available at: http://www.micromedexsolutions.com/. Subscription required to view. Accessed April 20, 2017.

US Bureau of Labor Statistics. Consumer price index - all urban consumers. Item: medical care. Available at: http://data.bls.gov. Accessed June 16, 2017.

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