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

E.M. Maiese,[1] C.N. Graham,[2] E. Hawe,[3] J-G. Le Moine,[3] I. Abraham,[4] M. Senbetta[1]

[1]Janssen Scientific Affairs LLC, Horsham, PA, USA; [2]RTI Health Solutions, Research Triangle Park, NC, USA; [3]RTI Health Solutions, Manchester, UK; [4]University of Arizona, Tucson, AZ, USA

BACKGROUND

- The safety and efficacy of daratumumab, a CD38-directed cytolytic monoclonal antibody, in combination with lenalidomide and dexamethasone (DRd) is being investigated in an ongoing phase III trial (POLLUX).
- In the POLLUX phase III clinical trial, MM patients who had received at least one prior line of therapy, were randomized to DRd or lenalidomide plus dexamethasone (Rd). DRd showed significant improvements in progression-free survival (hazard ratio = 0.37; 95% confidence interval [CI], 0.27 to 0.52; p<0.001) compared to patients receiving Rd (Dimopoulos et al., NEJM, 2016).
- Based on results of the POLLUX trial, a decision-analytic model was developed to explore the cost-effectiveness of DRd versus Rd 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 POLLUX 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 DRd and Rd 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 POLLUX 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 POLLUX 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	DRd	Rd	Source
Drug acquisition cost per administration			
Daratumumab*	$5,626	N/A	Estimated from WAC (Red Book, September 2017), patient characteristics, recommended dosing, and relative dose intensity from POLLUX
Lenalidomide	$464	$513	
Dexamethasone	$1	$1	
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		
Febrile neutropenia	$24,793		
Lymphopenia	$9,108		
Diarrhea	$1,880		
Fatigue	$2,160		
Pneumonia	$1,263		

*Based on average patient weight from POLLUX Trial (74 kgs).
CMS = Centers for Medicare and Medicaid Services; DRd = daratumumab plus lenalidomide and dexamethasone; IV = intravenous; N/A = not applicable; Rd = lenalidomide 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).

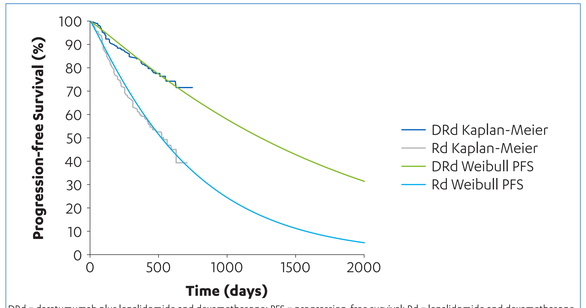
Table 2. Hospitalization and Grade 3/4 Adverse Event Inputs

Input	DRd	Rd
Hospitalization	61%	45%
Mean length of hospital stay (days)	5.2	5.9
Grade 3/4 adverse events		
Neutropenia	51.9%	37.0%
Anemia	12.4%	19.6%
Thrombocytopenia	12.7%	13.5%
Febrile neutropenia	5.7%	2.5%
Lymphopenia	5.3%	3.6%
Diarrhea	5.3%	3.2%
Fatigue	6.4%	2.5%
Pneumonia	7.8%	8.2%

Source: POLLUX clinical study report for hospitalization data. Dimopoulous 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 Weibull (Figure 2a) and for the subgroup of first relapse patients, the exponential (Figure 2b).



DRd = daratumumab plus lenalidomide and dexamethasone; PFS = progression-free survival; Rd = lenalidomide and dexamethasone.

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

DRd = daratumumab plus lenalidomide and dexamethasone; PFS = progression-free survival; Rd = lenalidomide 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	**DRd**	**Rd**	**DRd**	**Rd**
Mean PFS (years)	4.12	1.84	5.02	2.09
Mean life-years	8.43	4.19	9.51	4.68
QALYs	7.12	3.46	8.06	3.89
Costs (lifetime)				
Drug acquisition*	$903,896	$284,161	$1,082,837	$318,094
Administration	$9,454	$649	$11,063	$625
Other medical	$46,787	$26,130	$50,832	$28,336
Total	*$960,137*	*$310,940*	*$1,144,732*	*$347,056*
ICER*				
QALY gained	$177,456		$190,985	
Life-year gained	$153,073		$165,134	

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

- In the overall trial population, the mean PFS was estimated to be 4.12 and 1.84 years for DRd and Rd, respectively. DRd resulted in an average of 4.24 additional life-years (8.43 life-years – 4.19 life-years) and 3.66 additional QALYs (7.12 QALYs – 3.46 QALYs) over Rd.
- Costs increased for DRd; 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 $153,073 per life-year gained and $177,456 per QALY gained.
- Overall, survival (life-years), PFS, and QALYs were greater in the first relapse subgroup for both DRd and Rd than in the overall trial population. Mean PFS was estimated to be 5.02 and 2.09 years for DRd and Rd, respectively. DRd resulted in an average of 4.83 additional life-years (9.51 life-years – 4.68 life-years) and 4.17 additional QALYs (8.06 QALYs – 3.89 QALYs) over Rd.
- Incremental cost-effectiveness ratios in the first-relapse subgroup were $165,134 per life-year gained and $190,985 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 DRd is cost-effective compared to Rd 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**

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