Analysis of the ASCO Value Framework net health benefit score as a tool for assessing novel therapies in relapsed/refractory multiple myeloma (RRMM)

David M.W. Cork, Lucy Nelson, Alistair S. Curry
SIRIUS Market Access Ltd., London, UK. email: info@siriusmarketaccess.com

PRM13

Introduction

New agents in oncology continue to be scrutinised as payers consider innovative medicines with premium pricing. Several novel therapies are entering the market to treat patients with relapsed/refractory multiple myeloma (RRMM). These include the proteasome inhibitors carfilzomib and ixazomib, and elotuzumab, an anti-SLAMF7 monoclonal antibody. The introduction of several novel RRMM therapies has spurred many assessments; the Institute for Clinical and Economic Review assessed the introduction of carfilzomib (C), elotuzumab (E), or ixazomib (I) in combination with lenalidomide/dexamethasone (Ld)[1].

Here, the ASCO Value Framework is analysed as a tool for assessing the clinical value of novel therapies in RRMM with consideration given to the impact of trial design and maturity of data upon the net health benefit score. This analysis does not include the drug acquisition cost or patient co-payment elements of the ASCO Value Framework which will be highly variable depending on location.

Methods

The ASCO Value Framework is intended to assess the relative value of cancer treatment regimens that have been studied head-to-head in clinical trials.[2] Points are awarded for the clinical benefit and deducted for additional toxicity compared with the comparator. The ASCO Value Framework will form the basis of a software tool that can be used by physicians to assist decision making with their patients. It is not intended to inform policy decisions

The calculations for each component score and the net health benefit in the ASCO value framework are detailed in Table 1.

Table 1 Scoring criteria of the ASCO value framework

Clinical benefit score	
Hazard ratio for death	1 - HR for death x 100
Median overall survival	Percentage difference in OS between two regimens multiplied by 100
HR for disease progression	1 – HR for disease progression x 100 x 0.8
Median PFS	Percentage difference in PFS between two regimens multiplied by 100 * 0.8
Toxicity score	
Assign a toxicity score for each adverse event for each regimen: Grade 1 or 2 < 10% = 0.5 points Grade 1 or 2 ≥ 10% = 1.0 point Grade 3 or 4 < 5% = 1.5 points Grade 3 or 4 ≥ 5% = 2.0 points	Calculate the total number of points for each regimen and then calculate the percentage difference in the toxicity of the two regimens (excluding laboratory results only). Multiply this score by 20. If the test regimen is more toxic than the comparator then subtract the score from the clinical benefit., if less toxic, add the score.
Bonus points	
Tail of the curve	Identify time-point where OS (or PFS) is double the median. If this is more than 50% greater for test regimen than comparator award 20 points.
Palliation	If there is a statistically significant improvement in cancer related symptoms award 10 points.
QoL	If there is a statistically significant improvement in QoL with the test regimen over the comparator award 10 points.
Treatment free interval	If there is a statistically significant improvement in treatment-free interval then multiply the percentage difference by 20 and award that number of points.
Net health benefit	
Clinical benefit +/- toxicity score + bonus points	

Methods (continued)

The ASCO Value Framework was used to calculate clinical benefit and toxicity versus Ld using published trial data for CLd (ASPIRE)[3], ELd (ELOQUENT-2)[4], and ILd (TOURMALINE-MM1)[5]. Bonus points were awarded for outcomes including statistically significant improvements in QoL. Component scores were combined to calculate net health benefit.

Table 2 provides an overview of the ASPIRE, ELOQUENT-2, and TOURMALINE-MM1 trials which compared CLd, ELd, or ILd, respectively, to Ld and Table 3 presents key efficacy results.

Table 2: Trial design and baseline characteristics of ASPIRE, ELOQUENT-2, and TOURMALINE-MM1

	ASPIRE CLd (N=396)	ELOQUENT-2 ELd (N=321)	TOURMALINE-MM1 ILd (N=360)
Blinding	Randomized, open-label phase 3 study, due to the need for IV administration of carfilzomib.	Randomized, open-label phase 3 study, due to the need for IV administration of elotuzumab.	Randomized, double-blind, placebo-controlled phase 3 study.
Median age, years (range)	64 (38–87)	67 (37–88)	66 (38–91)
Male sex, n (%)	215 (54)	192 (60)	207 (58)
ECOG performance status 0 / 1 / 2 / missing, n (%)	165 (42) / 191 (48) / 40 (10) / 0	159 (50) / 138 (43) / 24 (8) / 0	180 (50) / 156 (43) / 18 (5) / 6 (2)
1 prior line*	184 (47)	151 (47)	224 (62)
Prior bortezomib, n (%)	261 (66)	219 (68)	248 (69)
Refractory to prior bortezomib, n (%)	60 (15) Bortezomib non-responsive	72 (22) Bortezomib-refractory	22 (6) Bortezomib-refractory (protocol exclusion criterion)
Prior lenalidomide, n (%)	79 (20)	16 (5)	44 (12)
Refractory to prior immunomodulatory drugs, n (%)	85 (22)	30 (9)	41 (11)

*TOURMALINE, based on relapse or progression only) / 1 prior regimen (ASPIRE, ELOQUENT-2), n (%)

Table 3: Efficacy results from ASPIRE, ELOQUENT-2, and TOURMALINE-MM1

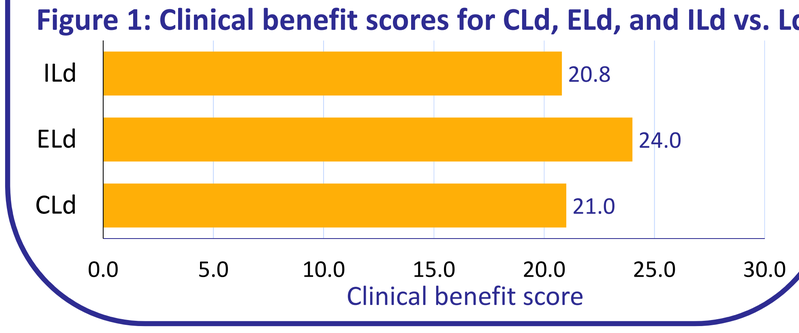
	ASPIRE (N=396)		ELOQUENT-2 (N=321)		TOURMALINE-MM1 (N=360)	
	CLd	Ld	ELd	Ld	ILd	Ld
Hazard ratio for death	0.79 (95% CI 0.63-0.99; p= 0.004)		-		-	
Median OS (months)	-	-	-	-	-	-
Hazard ratio for progression	0.69 (0.57-0.83; p = 0.0001)		0.70 (0.57-0.85; p = 0.0004)		0.74 (0.59-0.94;p = 0.012)	
Median PFS (months)	26.3	17.6	19.4	14.9	20.6	14.7

Results

Clinical benefit score

- The clinical benefit of CLd vs. Ld was calculated based on the hazard ratio (HR) for death in the ASPIRE trial: 0.79.
- The HR for death vs. Ld is not available in the trial publications for either ELd or ILd.
- The clinical benefits of ELd and ILd were therefore calculated using the HR for progression: ELd: 0.70, ILd: 0.74
- The clinical benefit of each regimen vs. Ld is shown in Figure 1.

Figure 1: Clinical benefit scores for CLd, ELd, and ILd vs. Ld

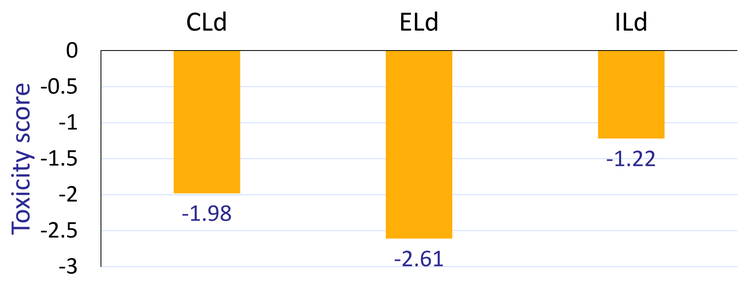


Results (continued)

Toxicity score

- The toxicity score is calculated based on the rate and severity of adverse events (AEs) for the test regimen and the comparator regimen in each clinical trial.
- AEs present in ≥20% of one trial arm were reported for ASPIRE, AEs present in ≥20% of one trial arm and other AEs of interest were reported for TOURMALINE-MM1, and AEs present in ≥25% of one trial arm were reported for ELOQUENT-2.
- The toxicity scores for each regimen are presented in Figure 2.

Figure 2: Toxicity scores for CLd, ELd, and ILd vs. Ld



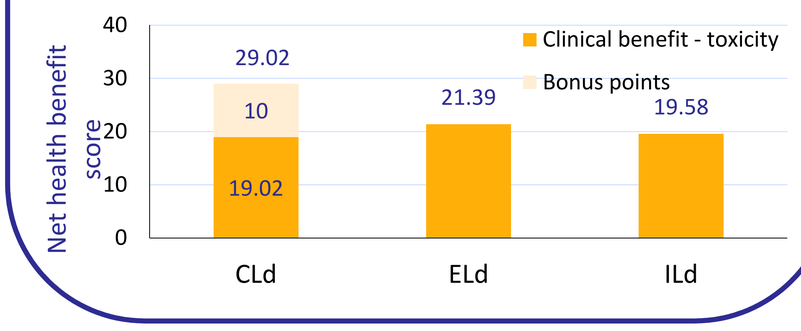
Bonus points

- Data were not mature enough in all three trials to demonstrate the benefits required for the award of bonus points for tail of the curve, palliation, or treatment free interval.
- The 10 point QoL bonus was awarded to CLd because of a statistically significant improvement in HRQoL compared to Ld demonstrated in the open label ASPIRE trial, measured using the EORTC QLQ-C30.

Net health benefit

- The net health benefit is calculated by combining the clinical benefit, toxicity, and bonus point scores for each regimen.
- Net health benefit scores are presented in Figure 3.

Figure 3: Net health benefit of CLd, ELd, and ILd vs. Ld



Conclusions

- The ASCO Value Framework demonstrates clear health benefits for CLd, ELd, and ILd compared with Ld for the treatment of patients with RRMM.
- Toxicity scores were heavily influenced by AE publication criteria and each drug added minimal toxicity to Ld.
- The greater net health benefit of CLd largely resulted from 10 bonus points for QoL. However, QoL data from ASPIRE (open-label, non-blinded design, mature data) is incomparable with the placebo-controlled, double-blinded TOURMALINE-MM1 trial and immature ELOQUENT-2 data.
- Net health benefit scores should be interpreted with caution, being strongly influenced by trial design, maturity of data, and publication criteria.
- As the ASCO Value Framework is developed further, QoL bonus points could be adapted to reflect trial design and consider the importance of double-blinded placebo-controlled trials in assessing QoL.

References

1. Midwest Comparative Effectiveness Public Advisory Council (ICER). Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks- Final Evidence Report and Meeting Summary. Institute for Clinical and Economic Review, June 9, 2016
2. Schnipper LE, et al. J Clin Oncol. 2016;34(24):2925-34.
3. Stewart AK, et al. N Engl J Med. 2015;372(2):142-52.
4. Lonial S, et al. N Engl J Med. 2015;373(7):621-31.
5. Moreau P, et al. N Engl J Med. 2016;374(17):1621-34

SIRIUS MARKET ACCESS