HTA168: DATA MATURITY AND TREATMENT POSITIONING TO SUPPORT REIMBURSEMENT: THE CASE FOR SILTUXIMAB (SYLVANT®) IN AUSTRALIA

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1 Background

Idiopathic Multicentric Castleman disease (iMCD) is a subcategory of MCD, a rare lymphoproliferative disorder characterised by systemic enlargement of the lymph nodes and related lymphatic tissues. Irrespective of the higher incremental cost-effectiveness ratios (ICERs) that are associated with rarer diseases, it is challenging to meet willingness to pay thresholds for rare diseases without a severity modifier. Following stakeholder engagement in Australia, this cost-effectiveness analysis successfully demonstrated that public investment in siltuximab for the treatment of iMCD would deliver positive outcomes in a small group of patients.

Aim

To assess the cost-effectiveness, from the perspective of the Australian public healthcare system, of siltuximab (Sylvant®) with best supportive care (BSC) (SIL/BSC) compared with placebo plus BSC (PLB/BSC) in patients with iMCD with the availability of 6-year follow-up data (mature data).

2 Methods

A health state semi-Markov model was constructed to estimate the costs and QALYs of the target population based on individual patient data from the MCD2001 study. The model included transition probabilities varying over time (particularly in treatment failure via tunnel substates), adjustment for trial crossover and incorporation of longer-term data (an additional 4.91 years of follow-up data). Model validation included comprehensive reviews by two experienced academic modelers and several Australian clinical expert opinions. The model consisted of four health states: (1) Stable Disease (i.e., no treatment failure (TF) without response (NR)), (2) Responder (no TF with response (R)), (3) Post treatment failure (pTF), and (4) death (D) (Fig. 1). When TF occurred, patients moved to the pTF state and received subsequent therapies or BSC alone. Response to subsequent therapies was not assessed. The model projected that SIL/BSC treatment resulted in a longer time to TF, due to comparatively more patients responding (R state), and fewer patients experienced TFs from the NR state. Costs and quality adjusted life years (QALYs) for each treatment were accumulated based on the mean time spent in each health state, from which the ICER (cost/QALY) was determined which is the primary economic consideration for the Pharmaceutical Benefits Advisory Committee (PBAC). Probabilistic sensitivity analysis was undertaken, and the HTA was performed from an Australian public healthcare system approach. All outcomes were discounted by 5% per annum beyond the first year, in line with Australian guidelines.

Input into the clinical parameters of the model was provided by Australian clinical experts. Following advice from the PBAC, the time horizon of the model was shortened to 20-years.

Key input parameters used to build the model are displayed in Table 1. The approach to extrapolate time-to-event data included an assessment of log-cumulative hazard and residual plots to assess whether proportional hazards (or accelerated failure time) could be assumed. If plots were not parallel, then independent functions were fitted to each arm. Alternatively, if plots showed non-straight lines, consideration was given to other flexible modelling techniques including fitting standard parametric models such as exponential, Weibull, lognormal, log-logistic, Gompertz and generalised gamma.

From these extrapolation methodologies, in the base case, an exponential model and Lognormal model of TTF was used among patients who responded and those who did not respond with SIL/BSC, respectively (providing the lowest AICs, and best visual fit). Similarly, a generalised gamma model was used for non-responding patients treated with PLB/BSC.

Model utilities are presented in Table 2.

Participants

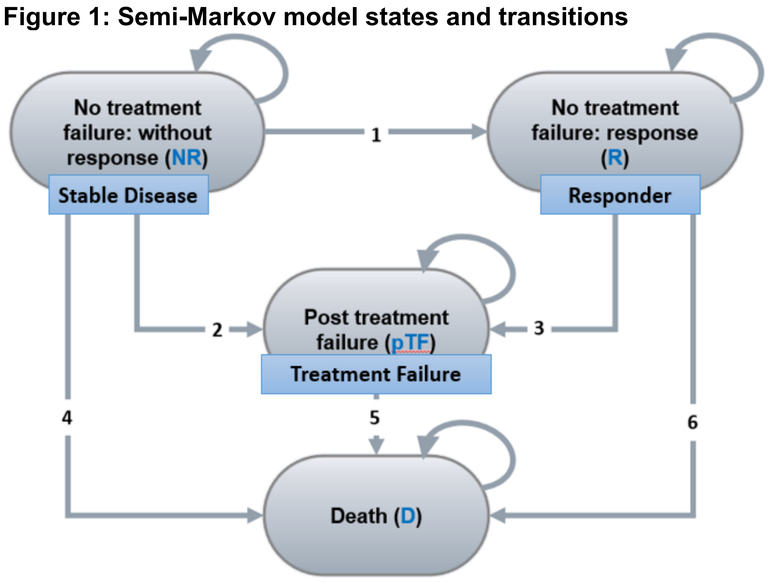
Individual patient data from the sole randomised controlled trial (RCT; double blind, placebo-controlled, multicentre trial), MCD2001, and its corresponding long-term follow up study, MCD2002, was the population on which the modeling was based. Patients in the study had symptomatic iMCD and were either newly diagnosed or previously treated for the disease (most patients had prior corticosteroid treatment).

The main outcome of interest was the incremental cost effectiveness ratio (cost per QALYs gained).

3 Results

Response and overall survival shows that SIL/BSC has superior efficacy and similar safety compared with PLB/BSC with the model demonstrating siltuximab's cost-effectiveness with an ICER of A$84,935 per QALY gained (Table 3).

Figure 1: Semi-Markov model states and transitions



NR stable disease, *R* responder, *pTF* post treatment failure, *D* death

Table 1. Description of key input parameters

	Parametric Function	Parameter	Value
TTF			
CR/PR patients – SIL/BSC ('R')	Exponential	rate	0.000099
Patients without response – SIL/BSC ('NR')	Lognormal	meanlog	5.907
		sdlog	1.449
Patients without response in PLB/BSC ('NR')	Generalised gamma	mu	4.543
		sigma	1.019
		Q	-1.578
OS			
SIL/BSC	Exponential	rate	0.000083
PLB/BSC	Exponential	rate	0.000352

CR complete response, PR partial response, BSC best supportive care, NR stable disease, R responder, OS overall survival, *SIL/BSC* siltuximab plus BSC, *PLB/BSC* placebo plus BSC

Table 2. Utility Inputs

Parameter	Mean	SE
Baseline utility of iMCD	0.7034	0.0252
Utility increment for responders	0.0352	0.0160
Utility decrement post-treatment failure	0.1801	0.0648
Utility increment due to treatment:		
SIL/BSC	0.0819	0.0310

BSC best supportive care, iMCD idiopathic Multicentric Castleman's disease, SE standard error, *SIL/BSC* siltuximab plus BSC

The results were sensitive to the censoring of patients following crossover compared to ITT, the time horizon, duration of treatment cycle (i.e., whether 3-weekly (licensed) or 6-weekly administration – the latter was adopted by some patients in MCD2002), method of overall survival (OS) extrapolation, utility weights and discount rates applied.

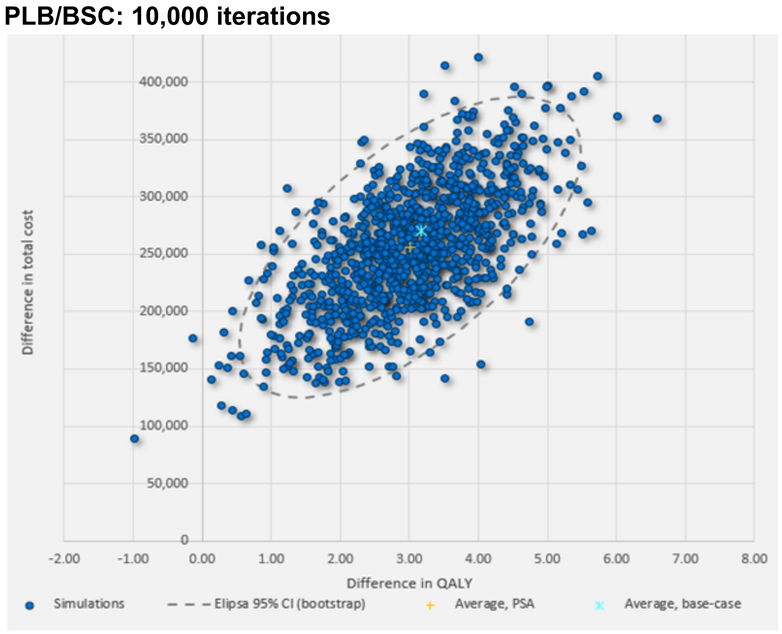
Table 3. Results for health outcomes and total costs – base case, over a 20-year time horizon.

	SIL/BSC	PLB/BSC	Change (Δ)
Health effects (discounted)			
Life Years	10.12	5.62	4.50
Life Years with tumour & symptomatic response	2.52	0.00	2.52
Life Years without treatment failure	3.87	1.41	2.46
QALY	**6.37**	**3.19**	**3.18**
Costs from the perspective of public payer (discounted) A$			
Siltuximab	$228,911	$0	$228,911
Premedication, administration & monitoring	$6,875	$0	$6,875
Concomitant therapy (excl. BSC)	$0	$0	$0
BSC: drugs	$30,713	$15,025	$15,688
Subsequent treatments	$7,717	$9,003	-$1,286
BSC: visits, tests & hospitalisations	$101,091	$64,525	$36,566
End-of-life cost	$14,864	$31,836	-$16,973
Adverse events	$632	$300	$331
Total cost	**$390,803**	**$120,689**	**$270,113**
Incremental cost-utility ratio	**$ 84,935/QALY**		

BSC best supportive care *SIL/BSC* siltuximab plus BSC *PLB/BSC* placebo plus BSC

The probabilistic sensitivity analysis, using 10,000 Monte Carlo simulations, demonstrated SIL/BSC had a 72.1% probability of being cost-effective compared to PLB/BSC alone, at a willingness-to-pay threshold of A$100,000 per QALY gained (Figure 2).

Figure 2: Cost-effectiveness plane for SIL/BSC compared with PLB/BSC: 10,000 iterations



4 Limitations

In 2014, the initial HTA consideration of siltuximab by the Canadian Agency for Drugs and Technologies in Health (CADTH) criticised the ICER as being highly uncertain; a key reason identified was the lack of maturity of the OS data, with only 1 year of data available at the time. This model was heavily informed by the randomised study MCD2001 and its follow-up MCD2002 with now 6 years of follow-up data. However, improvements included the derivation of OS for the PLB/BSC population by incorporating evidence from several retrospective/natural history publications and allowing for patient crossover. This raises some universal limitations, applicable to most HTA economic evaluations, including the lack of longer-term data and the number of OS years extrapolated in rare diseases.

5 Conclusions

Compared to BSC alone, SIL/BSC was considered to be a cost-effective public investment in the treatment of a small group of iMCD patients at a willingness-to-pay threshold of $A100,000 per QALY gained. This higher-than-average threshold was considered appropriate for this rare disease.