National Essential Medicine List

Tertiary Medication Review Process

Rapid review of Economic Evaluation literature and a basic cost effectiveness analysis: Bortezomib as induction for Multiple Myeloma for transplant eligible population

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1. Introduction

Multiple myeloma (MM) is a malignant clonal bone marrow plasma cell tumor with excessive monoclonal protein production leading to bone destruction and marrow failure. MM remains an incurable disease and to prolong progression-free survival (PFS) and overall survival (OS), the goal of frontline treatment is to maximize depth of tumor reduction which is often pursued with autologous stem cell transplant (ASCT), a standard of care for eligible patients. Induction therapy before transplantation can influence post-transplant results. Therefore, best frontline treatment for transplant-eligible patients should be based on best available evidence to guide therapy.

The effectiveness of bortezomib for induction treatment prior to ASCT in multiple myeloma (MM) patients has been demonstrated in several randomized, open-label phase III trials. As with many new therapies, the cost of using bortezomib as induction therapy prior to ASCT is higher compared to the conventional chemotherapies. The objective of this report is to assess the cost-utility of adding bortezomib to the current induction therapies and aid in further decision making.

2. Methodology

The methodology and format applied is adapted from the proposed HTA methods guide. Due to time and resource constraints, this report will incorporate some aspects of both the rapid review and the basic CEA. Any major deviations to the proposed guide will be highlighted throughout the report.

Analytical question

Intervention	Bortezomib
Comparator	Thalidomide plus dexamethasone
Indication	Induction therapy for Multiple Myeloma (MM) prior to ASCT
Population	Newly diagnosed transplant eligible patients < 65years
Level of care	Tertiary
Prescriber	Specialist Oncologist, Clinical Hematologist

Summary of other HTA agency decisions

The table reflects the list of HTA reports that were reviewed. Any recommendations which were not specific to the indication above, i.e. induction prior to ASCT in transplant eligible populations were excluded.

Table 1: Summary of Health Technology Assessment (HTA) agency decisions

Name	Included	Comment
NICE – National Institute for Health Care Excellence	Y	Summarised in table xx below
Canadian Agency for Drugs and Technologies in Health (CADTH)	Y	Summarised in table xx below
Scottish Medicines Consortium (SMC)	Y	Summarised in table xx below
Australian Government Department of Health	N	Review was a cost minimization analysis
Health Intervention and Technology Assessment Program (HITAP)	N	Review for relapsed refractory multiple myeloma
European network for Health Technology Assessment (EUnetHTA)	N	No reviews for multiple myeloma
International HTA Database	N	The other reviews excluded as comparators, indication and setting were not appropriate for this report.
All Wales Therapeutics and Toxicology Centre (AWTTC), secretariat of the All Wales Medicines Strategy Group (AWMSG)	Y	AWMSG aligned with NICE. (To avoid duplication, AWMSG would not usually appraise a medicine if NICE intends to appraise the same medicine for the same indication within 12 months of the date of marketing authorisation.)

An applicability checklist was done for the HTA reports reviewed. Due to time and resource constraints, the HTA reports were not critically appraised. Given that these HTA agencies have established high quality economic evaluation methods in place, the critical appraisal of the reports was not deemed essential due to the time and resource constraints. However, the recommendations made by the agencies have been considered in compiling this report.

Table 2: Context applicability checklist

	NICE		**pCODR**		**SCM**	
	Yes/No/Unsure	**Score *("yes" = 1 point)***	**Yes/No/Unsure**	**Score *("yes" = 1 point)***	**Yes/No/Unsure**	**Score *("yes" = 1 point)***
Is the population similar to South African patients?	Y	1	Y	1	Y	1
Is the technology administered in a similar way as in the South African public sector?	y	1	Y	1	Y	1
Is the comparator similar to the comparator defined in the Technical Report	Y	1	Y	1	Y	1
Is the clinical management of patients indicated for the technology being assessed similar to the South African public sector?	Y	1	Y	1	Y	1
Is the health system context similar to the South African public sector	U	0	U	0	U	0
Are there significant differences in costs and costs structures compared to the South African public sector?	U	0	U	0	U	0
	Total score	**4 /6**	***Total score***	**4 /6**	***Total score***	**4 /6**

Table 3. Methodological applicability checklist

	NICE		**pCODR**		**SCM**	
	Yes/No/Unsure	**Score** *("yes" = 1 point)*	**Yes/No/Unsure**	**Score** *("yes" = 1 point)*	**Yes/No/Unsure**	**Score** *("yes" = 1 point)*
Is the type of economic evaluation a cost utility analysis?	Y	1	Y	1	Y	1
Are health effects reported directly from patients and/or carers?	N	0	N	0	N	0

	NICE		pCODR		SCM	
	Yes/No/Unsure	**Score** *("yes" = 1 point)*	**Yes/No/Unsure**	**Score** *("yes" = 1 point)*	**Yes/No/Unsure**	**Score** *("yes" = 1 point)*
Is the value of health effects expressed in terms of Quality Adjusted Life years?	Y	1	Y	1	Y	1
Is the analysis over a time horizon that captures all relevant differences in costs and effects between the intervention and comparator?	Y	1	Y	1	Y	1
Are costs reported from the perspective of a 3rd-party payer (e.g. public sector)	Y	1	Y	1	Y	1
Are costs and effects discounted at an annual rate of 5%?	N	3.5%	U	0	u	0
	Total score	4/6	*Total score*	4/6	*Total score*	4/6

Table 4. Summary Table: HTA reports

	HTA report 1	HTA report 2	HTA report 3
Country + HTA agency	NICE	pan-Canadian Oncology Drug Review	Scottish Medicines Consortium (SMC)
Year	2013	2013	2013
Indication	Newly diagnosed multiple myeloma eligible for ASCT	Multiple myeloma induction and maintenance	Newly diagnosed multiple myeloma eligible for ASCT
Intervention	bortezomib, thalidomide and dexamethasone induction	bortezomib to vincristine, doxorubicin and dexamethasone (VAD) induction and bortezomib maintenance	bortezomib, dexamethasone and thalidomide
Comparator	thalidomide and dexamethasone	Not specified	TD
Modelling approach	state-transition Markov model	Not specified	Markov
Type of analysis	CUA	CUA	CUA
Results	Estimates varied depending on the source of the long term survival MRC Myeloma VII data - £17,800 per QALY gained. Alvares - £22,700 per QALY NMSG 5/94 data - £39,600 per QALY	$182,619 / QALY gained	£23,077/QALY
Major areas of uncertainty	Overall survival and PFS estimates Comparator used not standard of care in the UK	- Quality of evidence used (abstracts) - Inappropriate comparators – underestimates the incremental costs -Modelling for long term outcomes - drug wastage	-Comparator used not standard of care in Scotland - exclusion of >65 - use of studies with maintenance therapies not reflective of standard care : -implications on OS, PFS, TTP - time horizon
Ethical, social, legal issues	No equality issues relevant to the Committee's recommendations were raised.	None mentioned	Although the modelling approach was subject to uncertainties, the recommendation was based on the need to bridge a gap in treatment
Recommendation	Recommended	Recommended	Recommended
Context applicability score /6	4/6	4/6	4/6
Methods applicability score /6	4/6	4/6	4/6

Table 5. Summary Table: Published economic evaluations.

There are several reviews on the clinical effectiveness of bortezomib containing regimens in the multiple myeloma setting. This report has narrowed the search to include only studies which reviewed the cost effectiveness of bortezomib, thalidomide and dexamethasone as induction in newly diagnosed transplant eligible patients.

	Economic evaluation 1	Economic evaluation 2	Economic evaluation 3
Author	Kouroukis et al*	Mucha et al†	Van Beurden-Tan et al‡
Year	2013	2014	2014
Publication type	Abstract	Abstract	Abstract
Context (country and health system)	Canada	Poland	Germany
Indication Treatment setting	Induction treatment prior to SCT	Induction treatment in patients eligible for ASCT	Induction treatment prior to SCT
Intervention	BTZ	VTD	VTD
Comparator	non-BTZ treatment	TD	TD
Economic evaluation type	CUA	CUA	CUA
Modelling approach	Markov	Markov	Markov
Discount rate for outcomes	5	3.5	3
Discount rate for costs	5	5	3
Time horizon	50 years	Lifetime	Lifetime
Data source for treatment effects	IFM2005-01 trial	PETHEMA trial	PETHEMA trial
Data source for utility	Van Agthoven et al	Van Agthoven et al	Not reported
Results ICER	$99,200/QALY Threshold of $100,000/QALY.	$24,751/QALY. Threshold of $35,278/QALY.	€30,655 per QALY gained. Threshold of €35,000 / QALY gained
Model health states	Progress free Progressive disease Death	First-line Second line Third line Subsequent line Death	First-line Second line Third line Fourth-line Death

* Kouroukis et al. Cost-Utility Of Bortezomib In Induction Treatment Prior To Autologous Stem-Cell Transplantation (ASCT) In Previously Untreated Multiple Myeloma Patients In Canada. *Blood* (2013) 122 (21): 1735.

† Mucha J, Walczak J, Tronczynski K, Skrzekowska-Baran I. Bortezomib-based regimens used as induction in newly diagnosed multiple myeloma (ndMM) patients eligible for stem cell transplantation (SCT) the cost-utility analysis. *Value Health.* 2014;**17**(3):A229.

‡ Van Beurden-Tan C, Rosinol L, Diels J, et al. Cost-effectiveness of induction treatment with bortezomib added to thalidomide and dexamethasone in newly diagnosed multiple myeloma patients eligible for autologous stem cell transplantation in Germany. *Value Health.* 2013;**16**(7):A409–A410.

3. Perspective of costs

The setting for this study is the South African public health sector and the evaluation takes the perspective of the public health sector payer. Only direct costs to the public health sector are considered and indirect costs such as loss of productivity are not included.

Chemotherapy drug costs

The cost of Bortezomib (Miblex®) used was the proposed state price from manufacturer (R2 500 incl vat). All pharmaceutical costs for the intervention and comparator are shown in the table below.

	Bortezomib	**Source**	**Thalidomide**	**Source**	**Dexamethasone**	**Source**
Pharmaceutical formulation	*IV*	*SAHPRA PI*	Capsule	*SAHPRA PI*	IV	*SAHPRA PI*
Method of administration	*SC or IV*	*SAHPRA PI*	Oral	*SAHPRA PI*	IV	*SAHPRA PI*
Strength	*3.5mg*	*SAHPRA PI*	50mg	*SAHPRA PI*	4	*SAHPRA PI*
Average dose/s and dosing schedule/s	Day 1, 8 and 15	Expert opinion	Daily	PETHEMA trial	40mg once a week	Expert opinion
Average daily dose	*1.6mg/m^2 SC*	Expert opinion	100mg/ day	Expert opinion – maximum tolerated dose	40mg/day once a week	Expert opinion
Acquisition cost incl vat (pack size)	R2 500 (1 x 3.5mg)	Proposed contract price	R1 480.00 (50mg X 28 capsules)	Contract price	R5.26 (1x4mg)	Contract price
Cost of treatment/ cycle	R7 500	Calculated value	R2 960.00	Calculated value	R157.80	Calculated value
Average length of a course of treatment	6 cycles	Calculated value	6 cycles	Calculated value	6 cycles	Calculated value
Cost of a course of treatment	R45 000.00	Calculated value	R17 760.00	Calculated value	R946.80	Calculated value
(Anticipated) average interval between courses of treatment	28 days	Calculated value	28 days	Calculated value	28 days	Calculated value
(Anticipated) number of repeat courses of treatment	No repeat – once off induction cost prior to stem cell transplant					

Costs of treating adverse effects.

Bortezomib trials have shown that the IV formulation increases the risk of neuropathy and varicella zoster reactivation. However, use of the SC formulation substantially reduces the risk of adverse effects. Based on expert opinion, the only additional costs would be the cost of anti-emetic. A 5HT-3 antagonist (ondansetron) would be used orally on day 1, 8 and 15 when the bortezomib is administered.

Ondansetron

Pharmaceutical formulation	Capsule
Method of administration	Oral
Available strength	4mg
Average dose/s and dosing schedule/s	8mg day 1, 8 , 15 , prior to Bortezomib
Average daily dose	8 mg
Acquisition cost incl vat (pack size)	R16.89
Cost of treatment/ cycle	R101.34

Costs of administration

No additional costs of administration of bortezomib were given – it was assumed that this would not be substantial as it is given as SC.

Costs of stem cell transplant

The costs of a stem cell transplant were not included in the analysis. The cost of stem cell transplant is the same, irrespective of the choice of intervention and it was assumed that excluding these costs from the analysis would not affect the decision-making process. All patients are receiving the induction therapy prior to stem cell transplant and being transplant eligible is a pre-requisite to receiving the bortezomib.

4. Outcomes and health effects

Response rates

The post induction response rates considered were complete response, very good partial response, partial response or stable disease. Progressive disease and death were not included in the model as the decision making is determined largely by the impact of those achieving at least a partial response. Excluding these responses was assumed to not undermine the base case cost effectiveness results.

Induction therapy increases the depth of response and provides an additive benefit on the post-transplant response rate and overall survival. To avoid creating a complicated model, response rate post-transplant was categorised only as complete and not complete response. The post-transplant response rates were further analysed based on the response rate post induction.

Overall survival

It is important to note that overall survival results may be confounded by consolidation and maintenance treatments and that the approval for the bortezomib is only for the induction phase, hence variations in the real world outcomes might result in possible lower overall survival. The impact of overall survival will be accounted for in the sensitivity analysis.

Effects

Although the chemotherapy regimens used are different to the base case , the van Agthoven et al. results have been used with similar economic evaluations. It is assumed that the value assigned to the health state by the patient is based mainly on the response received and not on the type of chemotherapy received.

Table 6: Summary of health outcomes and effects model parameters

Post-induction	TD	VTD	Reference
CR	0.35	0.14	PETHEMA trial[§]
VGPR	0.25	0.15	
PR	0.25	0.33	
SD	0.06	0.12	
Achieving CR post-transplant based on pre-transplant response			
CR	0.38	0.37	Derived from PETHEMA trial and Lalit et al,2014[**]
VGPR	0.38	0.37	
PR	0.33	0.32	
SD	0.087	0.085	
Not achieving CR post-transplant based on pre-transplant response			
CR	0.62	0.63	Lalit et al,2014
VGPR	0.62	0.63	
PR	0.67	0.68	
SD	0.913	0.915	
Other parameters			
Overall survival	0.74	0.65	PETHEMA trial
Utility value of CR post-transplant	0.81	0.81	van Agthoven et al. [††]
Utility value of not achieving CR post-transplant	0.81	0.81	
Life years	5.06	6.38	Van Beurden-Tan et al[‡‡]

[§] Rosiñol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized Phase 3 PETHEMA/GEM study. Blood. 2012;120(8):1589–1596

[**] Recalculated based on CR rates post-transplant from PETHEMA and the response rates post-transplant based on pre-transplant status from Lalit et al.
Lalit Kumar, Nida Iqbal, Anjali Mookerjee, Rakesh Kumar Verma, Om D. Sharma, Atul Batra, Raja Pramanik & Ritu Gupta. (2014). Complete response after autologous stem cell transplant in multiple myeloma. Cancer Medicine. 3(4): 939–946

[††] van Agthoven M, Segeren CM, Buijt I, Uyl-de Groot CA, van der Holt B, Lokhorst HM, et al. A cost–utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma: a prospective randomised phase III study. Eur J Cancer. 2004;40:1159–69.

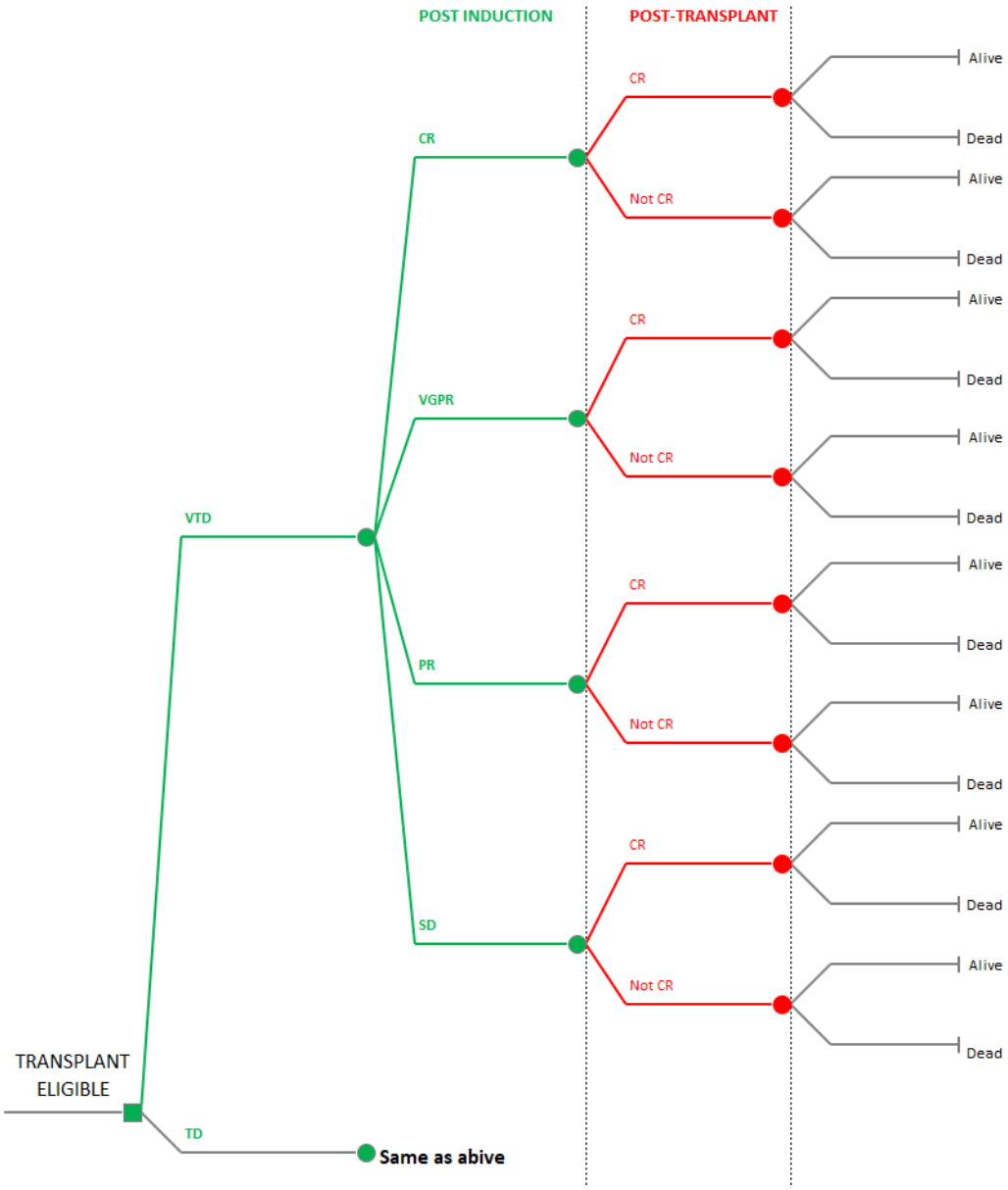
‡‡ Van Beurden-Tan C, Rosinol L, Diels J, et al. Cost-effectiveness of induction treatment with bortezomib added to thalidomide and dexamethasone in newly diagnosed multiple myeloma patients eligible for autologous stem cell transplantation in Germany. Value Health. 2013;16(7):A409–A410

5. Results

A decision tree model was used to determine the cost utility of combination bortezomib, thalidomide and dexamethasone compared to thalidomide and dexamethasone. The limitation of using a decision tree in this setting is the inability to account for transition probabilities, which are best represented on a Markov model. However, the reports from NICE and CADTH highlighted the possibility of an inaccurate estimation of the transition probabilities used in the Markov models and this could not have been prevented due to the lack of data with a better fit. Given the possibility of deriving inaccurate transition probabilities and the need for more time and resources in generating the transition models, it was assumed the results obtained from a decision tree would be adequate for decision making.

The model assumed that a patient enters once deemed eligible for transplant. The patient would then be given either VTD or TD as part of induction. The patient may have complete response, very good partial response, partial response or stable disease. Thereafter the patient would receive a transplant and then either die or survive.

The patients in the model will not receive any consolidation or maintenance chemotherapy. From expert opinion, there are several permutation of subsequent treatment options which include more chemotherapy, enrolment in clinical trials or supportive care. This decision making is also not solely dependent on the induction therapy. To avoid complicating the model, and to reduce the possibility of introducing further uncertainty into the model, it was therefore assumed that there would be no further lines of treatment following stem cell transplant.


POST INDUCTION
POST-TRANSPLANT
TRANSPLANT ELIGIBLE
VTD
TD
Same as abive
CR
VGPR
PR
SD
CR
Not CR
Alive
Dead

As with most novel agents, the addition of Bortezomib will result in both an incremental cost and incremental effect, with an ICER of R33 784.90 / QALY gained. This is below the threshold of R38 500/QALY and hence would be deemed cost effective.

	Total cost	Total effect	Incremental cost	Incremental effect	ICER
Thalidomide + dexamethasone	R 13 856.84	1.61	-	-	-
Bortezomib + Thalidomide + dexamethasone	R 58 526.50	2.93	R 44 669.66	1.32	R 33 784.90

6. Sensitivity analysis

Sensitivity analyses was done to assess the robustness of the model.

Wastage

The model assumes that each patient receives one vial of bortezomib. Each vial contains 3.5mg and an average patient receives 2.768 at a dose of 1.6mg/m2. There was no sensitivity for wastage given that approximately 0.732mg is wasted with each dose administered.

Vial sharing

Given the wastage and the extended stability of 15 days per vial, here is a possibility of vial sharing. Although this was not modelled in the sensitivity analyses as the practicality given the patient numbers is uncertain, where vial sharing is possible, there is a significant reduction in ICER to R15 747.86/QALY gained.

	Total cost	**Total effect**	**Incremental cost**	**Incremental effect**	**ICER**
TD	R 13 856.84	1.61	-	-	-
VTD	R 34 678.32	2.93	R 20 821.48	1.32	R 15 747.86

The costs of bortezomib, outcome and effect parameters were varied as follows:

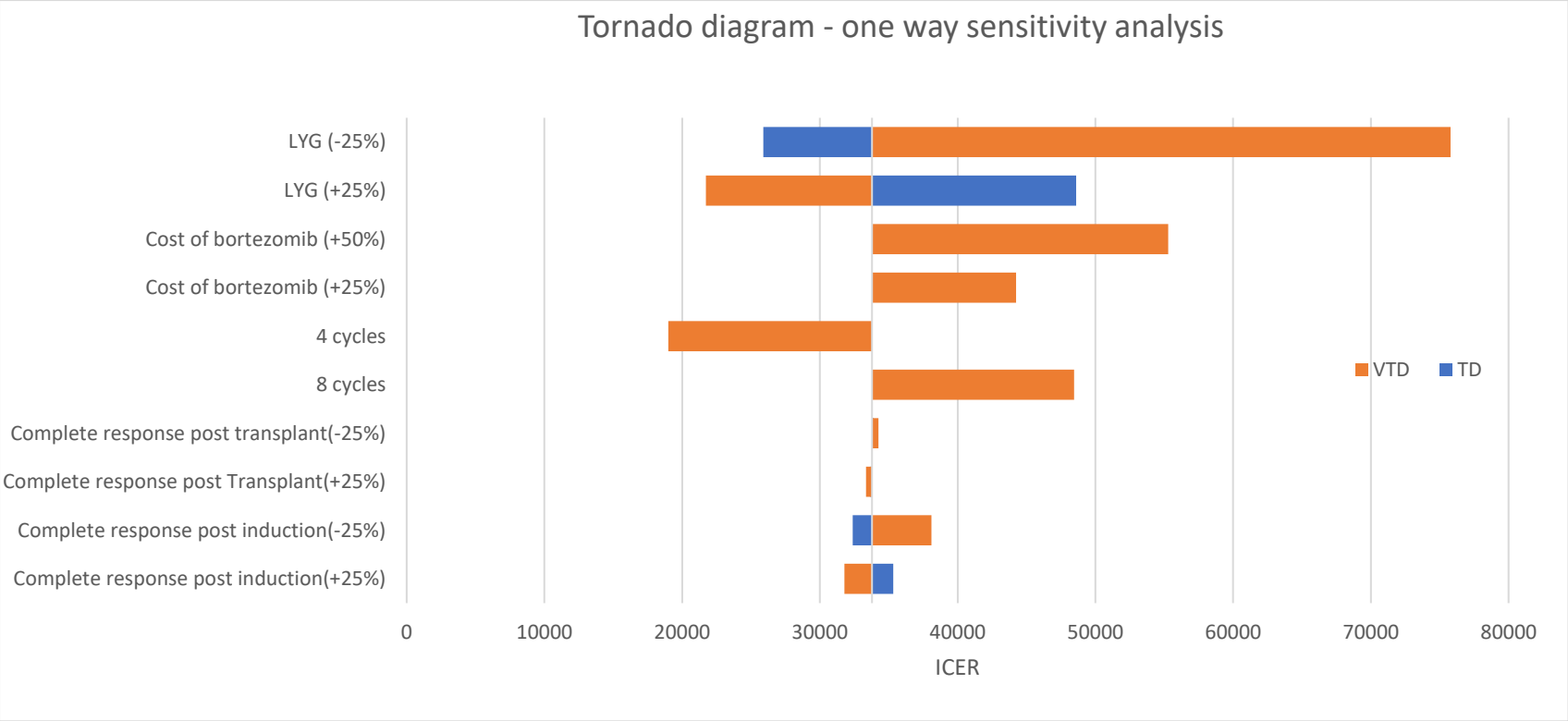
- Response rate and life years gained: varied by +/- 25%.
- The number of cycles: varied by +/-2.
- The cost of bortezomib: varied by +25% and +50%. The current quotations of Bortezomib received varied from R2500 to R2 875.

The Table below shows a tabular presentation of the sensitivity results.

VTD				ICER (R/QALY)		
Parameter	**Baseline**	**Upper value**	**Lower value**	**Upper value**	**Lower value**	**Range**
CR post induction	0.35	0.4375	0.2625	R 31 777.38	R 38 099.79	R 6 322.40
CR post-transplant	0.26	0.32	0.19	R 33 350.26	R 34 262.14	R 911.88
Life years	6.38	7.975	4.785	R 21 721.50	R 75 783.08	R 54 061.58
Cost of bortezomib	R 63 706.00	R 79 632.50	R 95 559.00	R 44 242.25	R 55 288.95	R 11 046.70
Number of cycles	6	8	4	R 48 445.74	R 18 999.22	R 29 446.51

TD				ICER (R/QALY)		
Parameter	**Baseline**	**Upper value**	**Lower value**	**Upper value**	**Lower value**	**Range**
CR post induction	0.14	0.175	0.105	R 35 317.54	R 32 382.63	R 2 934.91
CR post-transplant	0.13	0.1625	0.0975	R 33 654.28	R 33 917.08	R 262.81
Life years	5.06	6.325	3.795	R 48 607.85	R 25 889.81	R 22 718.04

The results from the one-way deterministic sensitivity analysis are shown on the tornado plot below. The uncertainties around life years gained and complete response rate can result in an ICER of more than R70 000/QALY gained and R50 000/QALY gained, respectively.



7. Budget impact

There are currently approximately 200 multiple myeloma patients in the public sector. Of those, 60 are transplant eligible and 140 are transplant ineligible. Given the current need for more effective induction therapy for transplant eligible multiple myeloma patients, it is assumed that there will be a rapid uptake of bortezomib. The net budget impact varies from R1 368 241.20 to R2 736 482.40 for 50% to full coverage, respectively.

Projected budget of bortezomib based induction.

VTD	100% coverage (n=60)	90% coverage (n=54)	80% coverage (n=48)	70% coverage (n=42)	60% coverage (n=60)	50% coverage (n=30)
4 cycles	R2 572 593.60	R2 315 334.24	R2 058 074.88	R1 800 815.52	R1 543 556.16	R1 286 296.80
6 cycles	R3 858 890.40	R3 473 001.36	R3 087 112.32	R2 701 223.28	R2 315 334.24	R1 929 445.20
8 cycles	R5 145 187.20	R4 630 668.48	R4 116 149.76	R3 601 631.04	R3 087 112.32	R2 572 593.60

Current budget

TD	100% coverage (n=60)	90% coverage (n=54)	80% coverage (n=48)	70% coverage (n=42)	60% coverage (n=60)	50% coverage (n=30)
4 cycles	R748 272.00	R673 444.80	R598 617.60	R523 790.40	R448 963.20	R374 136.00
6 cycles	R1 122 408.00	R1 010 167.20	R897 926.40	R785 685.60	R673 444.80	R561 204.00
8 cycles	R1 496 544.00	R1 346 889.60	R1 197 235.20	R1 047 580.80	R897 926.40	R748 272.00

Net budget impact

VTD	100% coverage (n=60)	90% coverage (n=54)	80% coverage (n=48)	70% coverage (n=42)	60% coverage (n=60)	50% coverage (n=30)
4 cycles	R1 824 321.60	R1 641 889.44	R1 459 457.28	R1 277 025.12	R1 094 592.96	R912 160.80
6 cycles	R2 736 482.40	R2 462 834.16	R2 189 185.92	R1 915 537.68	R1 641 889.44	R1 368 241.20
8 cycles	R3 648 643.20	R3 283 778.88	R2 918 914.56	R2 554 050.24	R2 189 185.92	R1 824 321.60

8. Conclusion

The model presented to aid decision making has underlying uncertainties and the impact has been shown through the sensitivity analyses. Economic models that have been built to aid in decision making for a similar population and intervention have also highlighted the uncertainties around the modelling approaches due to lack of data that accurately matches the given setting. Given the consistency of clinical benefits associated with using bortezomib as part of the induction regimen, decisions making has mostly been based on bridging the gap and an unmet clinical need with a possibility of cost-effectiveness.

A real-world Australian study of patients who received upfront bortezomib between 2012 and 2015 has shown a significant reduction in annual costs for those who received bortezomib compared to the control population. Although the actual treatment details are not specified, this portrays the possibility of costs reduction with upfront bortezomib.

	Patients treated with bortezomib (n = 70)		Historical controls (n = 70)	
	Median	Mean (SD)	Median	Mean (SD)
Hospital admissions	$4950·0	$5935·1 (6626·3)	$9270·0	$9953·0 (9468·0)
Outpatient visits	$5282·9	$6681·6 (11571·1)	$4388·6	$7029·0 (11642·0)
Investigations	$9488·2	$9428·9 (4411·7)	$11802·1	$11577·3 (6902·4)
Drugs	$256·8	$1031·3 (1637·2)	$278·3	$1968·9 (2252·3)
Total yearly cost (all-inclusive)	$19727·3	$23125·9 (14924·7)	$30125·9	$28962·8 (18481·3)
Total yearly cost (excl. drug costs)	$19448·8	$22094·6 (14771·5)	$27583·0	$26993·9 (17231·3)

If bortezomib is funded, there should be a strict restriction on use and it is recommended that a real world analysis of these patients is done to give a true reflection of the costs and the actual benefits within South Africa.