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ORIGINAL RESEARCH

The Cost Impact of Lenalidomide for Newly Diagnosed Multiple Myeloma in the EU5

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ABSTRACT

Introduction: Lenalidomide is an active agent that was approved for use in the EU in 2015 as a first-line therapy for previously untreated, non-transplant eligible multiple myeloma patients. Our objective was to assess the cost impact of lenalidomide when selected as a first-line treatment for transplant-ineligible patients in France, Germany, Italy, Spain, and the United Kingdom (EU5).

Methods: We developed a cost-impact model of the total costs associated with newly diagnosed multiple myeloma over 5 years in the EU5 based on treatment duration and time to progression (TTP) (taken from trial data). We compared a baseline scenario (of current lenalidomide uptake) with two alternative future scenarios. Future Scenario A used an increased uptake of first-line lenalidomide: up to 50% in Year 5. Future Scenario B was similar to the baseline, but included a 20% increased uptake of the triple therapy regimen, carfilzomib, lenalidomide, and dexamethasone (KRd) at second line.

Results: Compared to alternative first-line care pathways, lenalidomide provides a time to progression advantage of up to 5.1 months. In the baseline scenario, the costs per patient were €40,692 in Year 1. Future Scenario A showed an additional expenditure of €867 per patient in Year 1, increasing to €3358 per patient by Year 5, a 2.1% and 8.2% increase from baseline, respectively. However, lenalidomide use was associated with a lower monthly hospitalisation per-patient cost (€813) compared with bortezomib (€1173) and thalidomide (€1532). Future Scenario B was associated with a 29% increase in cost.

Conclusions: Compared to other first line therapies, lenalidomide delays time to

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progression resulting in associated savings across a patient's treatment pathway and overall is likely to result in a limited impact on budget. Lenalidomide should, therefore, be considered as a first treatment option for multiple myeloma patients ineligible for transplant.

INTRODUCTION

Multiple myeloma is an incurable haematologic cancer, accounting for 1% of all cancers and approximately 10% of all haematologic malignancies [1]. The treatment paradigm of induction followed by maintenance to progression has now been clearly demonstrated to increase progression-free survival (PFS) and overall survival (OS). However, myeloma management is complicated because nearly all patients relapse and become refractory [2]. Clinicians must consider several factors when making treatment decisions: patient preference and access to treatment, age, comorbidities and frailty [3].

Lenalidomide is an efficacious multiple myeloma treatment previously licensed for use in relapsed and refractory disease. It was licensed in the EU as a first-line therapy in 2015, and in light of data from the FIRST study [3, 4], it is likely to become the standard of first-line care for patients with multiple myeloma. In patients with newly diagnosed transplant-ineligible multiple myeloma, continuous lenalidomide–dexamethasone was superior to melphalan, prednisone, and

thalidomide (MPT) (72 weeks) for all primary and secondary efficacy endpoints, including OS, at the time of final analysis of primary endpoint, PFS. OS at 4 years was 59% with continuous lenalidomide–dexamethasone, 56% with 18 cycles of lenalidomide–dexamethasone, and 51% with MPT [5]. Further analysis showed that median OS was 58.9, 56.7, and 48.5 months for patients treated with continuous lenalidomide–dexamethasone, 18 cycles of lenalidomide–dexamethasone, and MPT, respectively; for continuous lenalidomide–dexamethasone, this represents a 10.4-month improvement in OS compared with those receiving MPT [6]. The increased survival benefit with lenalidomide was confirmed by Weisel et al., who conducted a network meta-analysis of survival in randomised controlled myeloma trials; lenalidomide was associated with a significant progression-free and overall survival advantage versus other first-line treatments (bortezomib, melphalan, and prednisone [VMP] and MPT) [7]. In addition to its favourable efficacy and acceptable toxicity profile, lenalidomide is an oral therapy requiring fewer hospital visits for treatment administration compared with alternative subcutaneous or intravenous agents [8–10], making this a more acceptable and better tolerated class of drugs.

Within the EU, a lenalidomide doublet regimen will be standard of care for elderly patients and those ineligible for autologous stem cell transplantation, whilst triple therapy regimens combining an immunomodulatory drug and steroid with either a proteasome inhibitor or a monoclonal antibody are anticipated to become new standards of care in the next 5 years for younger, transplant eligible patients [3, 11–14].

In an era of increasingly cost-conscious health systems, economic information,

including resource use, plays an important role in market access decision making for innovative medicines. The objective of our study was to assess the cost impact of lenalidomide when selected as a first-line treatment for newly diagnosed multiple myeloma patients in the EU5 (France, Germany, Italy, Spain, and the United Kingdom) versus current treatment options. We hypothesised that lenalidomide is likely to have a marginal incremental cost burden in the EU5 at first-line; the increase in OS and reduced administration costs compared to other first-line therapies will delay those costs incurred by subsequent treatment choices at second and third-line.

METHODS

Lenalidomide Efficacy

To demonstrate the average time to progression of an entire multiple myeloma care pathway, treatment sequences that included lenalidomide-based therapy in first line were compared with treatment sequences that included thalidomide- or bortezomib-based regimens as first-line options.

Lenalidomide First-Line Uptake in the EU5

We developed a cost-impact model to estimate the total costs associated with newly diagnosed multiple myeloma over 5 years in the EU5. We based this model on treatment duration and time to progression data from several trials; these outcomes also allowed us to model the efficacy of multiple myeloma treatments. This research is based on previously conducted studies; it does not involve any new studies involving human or animal participants, as conducted by any of the authors. The current

EU standard of care for multiple myeloma in autologous stem cell transplant-ineligible patients at first-line is MPT or VMP, as advised by the European Society of Medical Oncology (ESMO) [1]. The model included drug, administration, and hospitalisation costs of first-line treatment and two more additional lines of post-progression treatment for lenalidomide-, thalidomide-, and bortezomib-based regimens, as well as the costs of fourth-line pomalidomide-based regimens, based on expected clinical practice. We sourced hospitalisation costs from a retrospective chart review of Dutch patients with relapsed/refractory multiple myeloma [10]. We adapted these costs to the first-line setting by adjusting for the duration of treatment (DoT) and the time to progression (TTP) as reported in the clinical trials of each regimen (shown in Table 1). It is worth noting that DoT data may also include treatment-free intervals associated with some treatments. The model has been designed using TTP data; time to next treatment data were not available within the trials because of the variability in starting a new treatment line.

Drug costs were calculated according to drug prices and dosing (i.e., the number of doses per month multiplied by the total mg per dose multiplied by the cost per mg). Weighted averages were used to calculate listed drug prices across the EU5. Monthly costs within the line of treatment were equated to the sum of hospital-based costs (visits, admission, procedures, concomitant medication) as published by Gaultney et al. [10]. Hospital costs in the first-line treatment setting were not described by Gaultney et al.; therefore, hospital costs in the second-line treatment setting were adjusted to TTP and applied to first-line use, assuming the same monthly cost during treatment time.

Table 1 Duration of treatment and efficacy of each regimen in each line

Line	Treatment	Duration of treatment (months)	Progression-free survival (months)	Time to progression (months)[a]	Source
1	Thalidomide	15.4	21.2	23.9	FIRST trial [5]
	Bortezomib	10.6	21.7	24.0	VISTA trial [15]
	Lenalidomide	18.4	25.5	32.5	FIRST trial [5]
2	Thalidomide	6.4	7.3	8.0	Kropff et al. [16]
	Bortezomib	7.0	8.1 (DoR)	7.0	Richardson et al. [17]
	Lenalidomide	12.5	14.1	17.1	Stadtmauer et al. [18]
3	Thalidomide	6.4	7.3	7.0	Kropff et al. [16]
	Bortezomib	4.9	7.8 (DoR)	4.9	Richardson et al. [17]
	Lenalidomide	9.2	9.5	10.6	Stadtmauer et al. [18]
4[b]	Pomalidomide	2.9	4.6	3.6	MM-008 trial CSR

CSR clinical study report, *DoR* duration of response

[a] Time to progression given as median

[b] Pomalidomide-based regimens assumed to be used exclusively after third line

We compared a baseline scenario (of current lenalidomide uptake) with two alternative future scenarios. The baseline scenario reflected the estimated current uptake of first-line lenalidomide (i.e., 11% of the market). For Future Scenario A, we assumed a steadily increasing uptake of first-line lenalidomide: up to 50% in Year 5. The baseline 11% market share for lenalidomide was taken from bortezomib-based and thalidomide-based regimens so that, proportionally, the relative market share of these two comparators remained the same. Table 2 shows the baseline scenario and assumed market share of therapies at first line. Table 3 shows the market share overrides after first-line therapies for Future Scenario A.

Scenario Estimating Potential Impact of Triple Therapy

Future Scenario B was identical to baseline scenario, but we also assumed a 20% increased uptake of carfilzomib-based triple therapy (KRd) at second-line. Furthermore, a small percentage of patients in both future scenarios were assumed to receive a re-treatment. For example, VMP after first-line

Table 2 Assumed market share of therapies in first-line setting

Treatment regimen	Model scenario market shares					
	Baseline scenario (%)	Future Scenario A				
		Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
Thalidomide	25	19	17	16	15	14
Bortezomib	64	53	48	44	40	36
Lenalidomide	11	28	35	40	45	50

Table 3 Market share overrides after first-line for Future Scenario A

Treatment regimen	Model scenario market shares[a]					
	After first-line			After second-line		
	THAL (%)	BORT (%)	LEN (%)	THAL (%)	BORT (%)	LEN (%)
Thalidomide	7	14	17	4	21	36
Bortezomib	37	25	71	30	13	58
Lenalidomide	56	61	12	66	66	6

BORT bortezomib, *LEN* lenalidomide, *THAL* thalidomide

[a] Pomalidomide-based regimens assumed to be used exclusively after third line; some patients were assumed to receive a re-treatment, e.g., MPT after first-line MPT

VMP; there is a precedent for this in clinical practice with bortezomib-based regimens [19]. Table 2 shows the baseline scenario and assumed market share of therapies at first-line and Table 3 shows the market share overrides for Future Scenario A. Table 4 shows the market share overrides after first-line therapies for Future Scenario B.

Table 4 Market share overrides after first-line for Future Scenario B

Treatment regimen	Model scenario market shares[a]						
	After first-line			After second-line			
	THAL (%)	BORT (%)	LEN (%)	THAL (%)	BORT (%)	LEN (%)	CAR (%)
Thalidomide	5	11	17	4	21	36	39
Bortezomib	26	20	63	30	13	58	61
Lenalidomide	39	39	10	66	66	6	0
Carfilzomib	30	30	10	0	0	0	0

BORT bortezomib, *CAR* carfilzomib, *LEN* lenalidomide, *THAL* thalidomide

[a] Pomalidomide-based regimens assumed to be used exclusively after third-line; some patients were assumed to receive a re-treatment, e.g. thalidomide after first-line thalidomide

RESULTS

Compared with alternative first-line care pathways, our model results demonstrated that first-line lenalidomide provides a time to progression advantage of up to 5.1 months over a patient's lifetime (when averaging all treatment pathways), as is shown in Fig. 1.

In the baseline scenario, the annual costs per patient were €40,692 in Year 1. In Future Scenario A, we replaced the current first-line standard of care with lenalidomide; in Year 1, this resulted in an additional expenditure of €867 per patient, which represents a 2.1% increase from the baseline scenario. By Year 5, the additional expenditure in Future Scenario A increased to €3358 per patient, an 8.2% increase from baseline. The cost per patient of using lenalidomide at first-line in the EU5 is shown in Fig. 2. Lenalidomide-treated patients had higher monthly drug costs per patient (€5388) compared with patients receiving bortezomib (€3381) or thalidomide (€1742). However, lenalidomide use was associated with a lower monthly hospitalisation cost per patient (€813) compared with bortezomib (€1173) and thalidomide (€1532). Monthly hospitalisation costs were calculated on the basis of "total cost in line of therapy"—this value was derived from the monthly costs within the line of treatment multiplied by the TTP for each treatment arm. Monthly costs within the line of treatment were

the sum of hospital based costs published by Gaultney et al. [10].

In Future Scenario B, we modelled a 20% uptake of the novel triplet combination KRd at second line; we estimated that the impact on the budget will represent an additional 29% increase over the current baseline scenario. In contrast, modelling a future care pathway with increasing first-line lenalidomide resulted in a budget impact of only 8% over the current baseline, as shown in Fig. 3.

DISCUSSION

Our results show that the availability of lenalidomide at first-line has a relatively small impact on budget, i.e., an 8% increase. This increase should be considered both within the context of the increased benefit expected for patients in terms of TTP and OS, and when compared to the potential impact of introducing triple combination therapy with a novel agent as first-line salvage for the 20% of patients we estimated to be fit enough to receive this treatment later in their treatment pathway (29% increase in budget impact). Not all patients are eligible for triple therapy during subsequent lines of treatment; this is especially relevant in the context of an increasingly elderly population. Although there are no direct, randomised data comparing Rd and VMP, lenalidomide is expected to be more
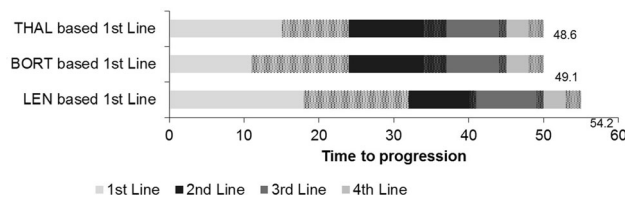

Fig. 1 Treatment efficacy (DoT, TTP, months). *BORT* bortezomib, *DoT* duration of treatment, *LEN* lenalidomide, *THAL* thalidomide, *TTP* time to progression.

Cross-hatching represents the time spent off-treatment before progression. This varies between treatments because they have either a fixed DoT or a dose intervention
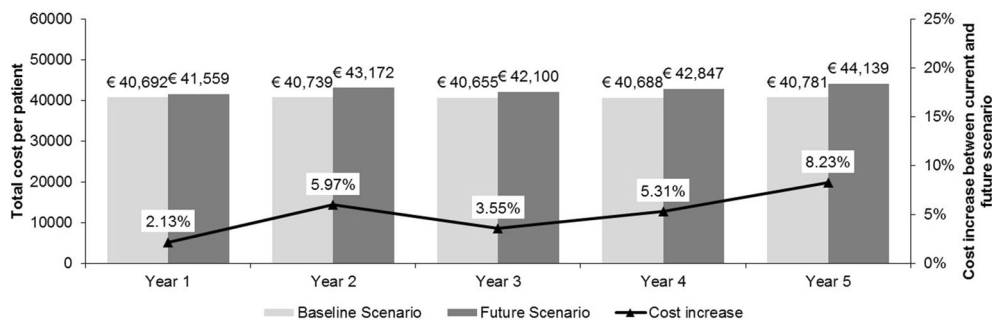
Fig. 2 Annual cost per patient receiving first-line lenalidomide in the EU5 for Future Scenario A. *EU5* France, Germany, Italy, Spain, and the United Kingdom
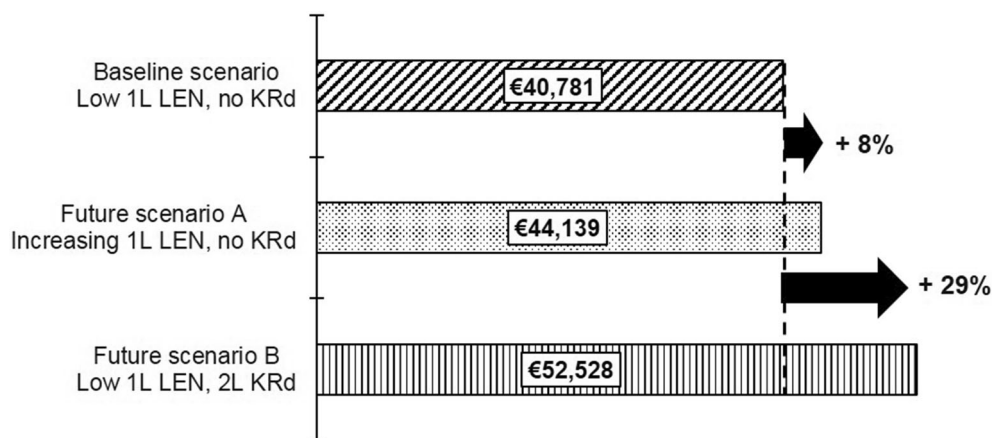
Fig. 3 Per-patient costs in Year 5 of baseline and future scenarios in the EU5. *1L* first-line, *2L* second-line, *EU5* France, Germany, Italy, Spain, and the United Kingdom, *LEN* lenalidomide, *KRd* carfilzomib, lenalidomide, and dexamethasone

effective than current first-line therapies, as suggested by the FIRST trial results and supported by the indirect comparison of treatments conducted by Weisel et al. [5–7]. Using lenalidomide, therefore, delays the time to subsequent therapy because of its improvement in time to progression compared to other first-line therapies, but we are aware that the duration of treatment may vary across countries, which may further affect treatment efficacy. The reduction in requirement for subsequent therapy reduces costs for administration and hospitalisation due to toxicities; this contributes to off-setting the increased drug cost of lenalidomide use. Our results also show that reserving lenalidomide

for a later line such as combination with a novel triple therapy combination (KRd) will increase the budget by 29% compared to the current baseline scenario.

Our findings agree with those from Arikian et al., who used US healthcare data to show that, for the first 3 years of treatment, patients who initiated lenalidomide-based treatments had lower mean monthly total costs compared to those who initiated on bortezomib-based treatments [8]. Arikian et al. also demonstrated that the cumulative cost of first-line lenalidomide was approximately $120,000 (€109,000) lower than for first-line bortezomib [8]. These findings further support our recommendation that the most beneficial way

to use lenalidomide for patients with newly diagnosed multiple myeloma is at first-line thus capitalising on its increased time to progression/OS and cost impact compared to other choices of first-line treatment.

Our results suggest that compared to other first-line therapies, appropriately selecting patients to receive first-line lenalidomide would have a reduced cost impact, as well as better OS and tolerability. Many of these patients, who are too frail to tolerate triplet combinations upfront, are unlikely to become more suitable upon relapse.

The costs of managing toxicity both to the patient and the healthcare system should also be carefully considered. Myelosuppression, which occurs more frequently with triplet therapies, does have a significant cost impact when treatment with blood products or growth factors is required. One limitation of this study is that it did not assess the costs associated with patient side-effects from treatment. As these data were not available for all comparators, we only assessed the impact on hospitalisation. However, given the relatively similar side-effect profiles between the treatments, this was not believed to significantly affect the conclusions of the model. Another limitation of our study is that data are taken from a variety of sources in order to estimate the likely economic impact of future treatment scenarios. In particular, data for hospitalisation were taken from a retrospective analysis, which increases the risk of bias or confounding.

Further research to evaluate the complete direct and indirect costs of multiple myeloma treatment across all treatment lines would further improve the understanding of the economic impact of this disease. As yet, there are no available real-world data to guide patient selection for therapies to improve both long-term patient outcomes and reduce the impact on EU5 healthcare systems.

Conducting cost-impact analyses may be advantageous for understanding the budget impact implications of new and/or expensive oncology therapies and patient pathways, particularly within disease areas where there are multiple potential sequences of treatments that could present a viable option for patients. Selecting the most appropriate treatment up-front is likely to be even more important in the future, when new, more expensive treatment regimens for relapsed multiple myeloma become available. This will help reduce and optimise the burden to healthcare systems and ensure that these treatments are available to the patients who would benefit the most. Arikian et al. have demonstrated the economic benefits of delaying first progression in multiple myeloma in the US healthcare setting [8]; it is limiting to multiple myeloma patients that this is not an option in the EU. Further research on the benefit to both patients and the healthcare system of delaying first progression is, therefore, also warranted.

CONCLUSION

Using lenalidomide in the first-line setting delays the time to subsequent therapy compared to other first-line treatments. It offers substantial cost offsets due to the reduced requirement for subsequent therapy, lowering the costs associated with administration and hospitalisation.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. All data generated or analysed during this study are included in this published article/as supplementary information files.

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