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Original Article

Cost-Effectiveness of Post-Autotransplant Lenalidomide in Persons with Multiple Myeloma

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Abstract. Considerable data indicate post-transplant lenalidomide prolongs progression-free survival and probably survival after an autotransplant for multiple myeloma (MM). However, optimal therapy duration is unknown, controversial and differs in the EU and US. We compared outcomes and cost-effectiveness of 3 post-transplant lenalidomide strategies in EU and US settings: (1) none; (2) until failure; and (3) 2-year fixed duration. We used a Markov decision model, which included six health states and informed by published data. The model estimated the lenalidomide strategy given to failure achieved 1.06 quality-adjusted life years (QALYs) at costs *per* QALY gained of €29,232 in the EU and $133,401 in the US settings. Two-year fixed-duration lenalidomide averted €7,286 *per* QALY gained in the EU setting and saved 0.84 QALYs at $60,835 *per* QALY gained in the US setting. These highly divergent costs *per* QALY in the EU and US settings resulted from significant differences in post-transplant lenalidomide costs and 2nd-line therapies driven by whether post-transplant failure was on or off-lenalidomide. In Monte Carlo simulation analyses which allowed us to account for the variability of inputs, 2-year fixed-duration lenalidomide remained the preferred strategy for improving healthcare sustainability in the EU and US settings.

Keywords: Lenalidomide, Multiple myeloma.

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Introduction. High-dose chemotherapy, typically with melphalan followed by a haematopoietic cell autotransplant, is the global *standard-of-care* in persons < 65-70 years with multiple myeloma (MM).[1-5] Substantial data indicate post-transplant lenalidomide prolongs post-transplant progression-free survival (PFS) and probably survival without reducing *quality-of-life* (QoL) or increasing interval-to-progression after starting subsequent anti-MM therapy/ies.[6-15] Based on these data, post-transplant lenalidomide is approved in the EU and US by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA).

Precisely how long to continue lenalidomide post-transplant is controversial. Two considerations, besides therapy-outcome and cost, affect this calculus. First, some data, albeit controversial, suggest an increased risk of new cancers in persons receiving continuous post-transplant lenalidomide leading some experts, especially in the EU, to recommend giving post-transplant lenalidomide for 1 or 2 years.[8] In contrast, the strategy in

the US is to give post-transplant lenalidomide until failure. These strategies are not compared in randomized trials, so there is no evidence-based way to decide which is better.

The 2nd consideration is cost. On 1st examination giving continuous post-transplant lenalidomide seems more expensive than the no or fixed duration lenalidomide strategies. However, this conclusion fails to consider other critical confounding issues. Because high-dose chemotherapy with autotransplant is not curative, most, if not all, recipients relapse or progress. Their subsequent anti-MM therapy will depend on circumstances of therapy failure. For example, persons failing whilst receiving post-transplant lenalidomide are likely to be treated with drugs other than lenalidomide. In contrast, a person failing after no or after stopping fixed duration post-transplant lenalidomide is likely to receive lenalidomide-based therapies. Consequently, a critical economic analysis must consider the cost not only of post-transplant lenalidomide but also costs of drugs used to treat therapy failure and their anticipated clinical outcomes.

We compared consequences of 3 potential post-transplant interventions: (1) no intervention; (2) 2-year fixed-duration lenalidomide; and (3) lenalidomide until failure (relapse or progression). These strategies were compared in EU and US cost settings. Our analysis considered not only clinical outcomes such as interval from autotransplant to first progression or death from any cause (PFS1), the interval from autotransplant to second progression or death (PFS2) and interval from the start of rescue therapy to second progression or death (2nd PFS), survival and costs but also costs of subsequent therapy/ies.

Methods.

Decision problem and scope. We interrogated the problem of assessing the *cost-for-value* of 2-year fixed-duration or continuous post-transplant lenalidomide in persons with MM by comparing these strategies with no post-transplant intervention. The economic assessment is conducted from the perspective of the third-party payers in the EU and US.

Model details. We used a 6-state Markov model, which allowed us to follow the monthly evolution of subjects from progression-free on-lenalidomide to progression-free off-lenalidomide, 1st subsequent therapy, 2nd subsequent therapy and death (**Figure 1**). We modelled subjects with a median age of 58 years based on data from randomized trials included in the meta-analysis providing baseline PFS1.[6] Subjects should have had a partial or complete response 90 days after their autotransplant.

The progression rate in subjects receiving no post-transplant lenalidomide was assessed in two-time

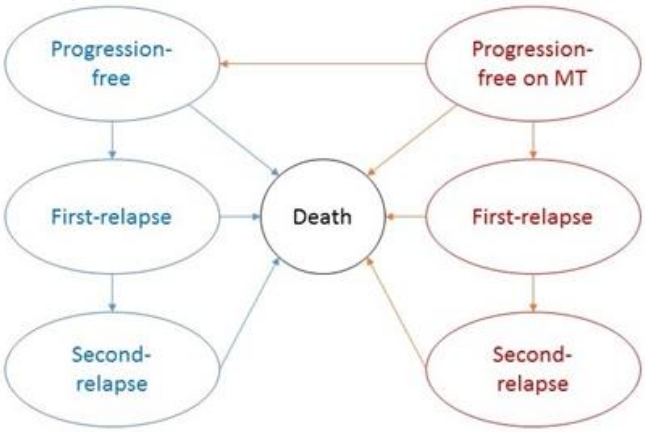

Figure 1. Markov model. MT = maintenance therapy (post-transplant lenalidomide)

intervals based on PFS1 curves reported in a meta-analysis.[6] An exponential parametric assumption was made to allow model reproducibility.

The rate of progression in subjects on post-transplant lenalidomide was estimated by adapting the hazard ratio reported by the above intention-to-treat meta-analysis[6] since we considered the possibility post-transplant lenalidomide might be stopped because of an adverse event(s) (**Table 1**),[6,16,18-23,25,26] progression or planned interruption because of a 2-year fixed-duration post-transplant lenalidomide strategy.

The relative risk of relapse or progression in subjects stopping lenalidomide for reasons other than relapse or progression was returned to 1 if post-transplant lenalidomide duration was < 12 months, whereas it was decreased progressively as post-transplant lenalidomide duration lengthened beyond 12 months (**Table 1**) as reported in a retrospective study[16] and a randomized trial.[34] Probabilities of 2nd and 3rd progression were obtained from recent clinical trials (**Table 1**). The fatality rate was estimated to be 12, 40 and 60 per cent at 1st, 2nd and 3rd failure.[24]

We assumed subjects relapsing or progressing post-transplant would next receive a therapy based on carfilzomib or daratumumab. Lenalidomide triplets were allowed for subjects failing off post-transplant lenalidomide. A 1:1 ratio was assumed in assigning subjects to a daratumumab- or carfilzomib-based treatment. Nighty per cent of subjects with a 1st relapse or progression were assumed to receive a 2nd therapy, and 80% of subjects with a 2nd relapse to receive a 3rd line therapy.[17] Subjects were assigned 1:1 to a pomalidomide-based or a daratumumab- or carfilzomib-based therapy according to prior therapy. The modelled strategies were reported in **Supplementary Table 1**.

Utilities. Utilities were adapted from a study mapping EORTC QLO-30 and an MM-specific *quality-of-life* (QoL) questionnaire to EQ5D-based utilities.[25] We also considered the impact of being on-therapy, including

Table 1. Input clinical values of the model.[6,16,18-23,25,26]

	Value
Clinical variable	
Monthly rate of progression without maintenance[6]	3% (< 36 months) 2.5% (>= 36 months)
Relative risk of progression on MT[6]	0.3
Relative risk of progression off MT[16] Maintenance duration < 12 months Maintenance duration 13-24 months Maintenance duration 25-36 months Maintenance duration >36 months	 1 0.6 up to month 36 0.5 up to month 48 0.4 up to month 60
Fatality portion at 1st progression	12%
Monthly rate of MT interruption unrelated to progression[6,16]	2% (< 12 months) 1.5% (> 12 months)
Monthly rate of progression on second-line therapy DVD or KD[19,21] DRD or KRD[18,20]	 3% 2%
Fatality portion at 2nd progression	40%
Monthly mortality on third line therapy[22,23]	4%*60%
Health utility	
Progression-free[25]	0.83
Progression-free 2nd line[25]	0.68
Progression-free 3rd line[25]	0.47
Treatment disutility[26]	-0.07

Note: MT = maintenance therapy (post-transplant lenalidomide).

Table 2. Input cost values of the model.

Monthly drug cost[27-33]	**US**	**Ratio**	**EU**	**Ratio**
Lenalidomide	$13,660	1.00	€6,085	1.00
KRD	$33,913	2.48	€24,087	3.95
KD	$20,253	1.48	€17,053	2.80
DVD	$22,421	1.64	€12,415	2.04
DRD	$31,203	2.28	€17,377	2.85
PomVD	$18,566	1.35	€9,934	1.65
Other healthcare costs				
Baseline medical costs[31-33] - Progression-free - Progressed	 $250 $450		 €250 €450	
Management of adverse events (prophylaxis & treatment)[28-33] - non IMID-based treatment - IMID-based treatment	 $143 $355		 €75 €150	

Note: "progression" includes: relapse, progression or death *70Kg weight patient 1.70 sq mt.

post-transplant lenalidomide.[25]

Costs. Costs were considered in EU and US settings. We used a third payer perspective and included only direct medical costs given in 2018 EU and US euros and dollars. Anti-MM therapies were valued according to *ex-factory* drug costs for EU and wholesale US cost (**Table 2**).[27-33] A 3 per cent additional cost was considered for parenteral drugs.[31-33] Theoretical drug costs were reduced by 10 per cent because of treatment schedules and therapy-free months between progression and start of subsequent therapy/ies (**Table 2**). Post-transplant lenalidomide's monthly cost was calculated for a 21 of 28-day schedule at 10 mg *per* day.

Analyses. Mean costs and mean effectiveness were calculated as discounted costs and discounted *quality-adjusted years-of-life* (QALYs) associated with each clinical state. Analysis of life years and costs was limited to a 20-year time horizon which is ≥ twice the median survival reported for persons not receiving post-transplant lenalidomide.[6] According to international

guidelines, life years and costs were discounted by 3 per cent per year.[15] First-order sensitivity analyses were run for all input co-variates and for ratios amongst co-variates. Furthermore, scenario analyses explored extreme ranges for key variables. Second-order sensitivity analysis was run for each paired comparison; 10,000 Monte Carlo simulations were run by sampling log-normal distributions for hazard ratios, beta distributions for utilities, and gamma distributions for cost.

Results.

Model validation. The model forecasted 70%, 52%, and 29% of persons assigned to continuous lenalidomide remained on-therapy after 12, 24 and 48 months. The median therapy duration was 25 months, and the mean duration of therapy 30 months in a 79-month time horizon (39 months in a 20-year horizon). Corresponding rates in a meta-analysis were 70%, 54% and 15% and the mean post-transplant therapy duration 28 months at a median follow-up of 79 months.[6] The model also forecasted mean lenalidomide duration in the 2-year fixed-duration cohort was 18 months like that reported for Arm A1 in the GMMG-MM5 randomized trial.[34]

The model predicted median PFS1 like data from the meta-analysis for no intervention and continuous lenalidomide strategies, 23 and 52 months.[6] Notably, the model did not over-estimate long-term outcomes, which was an 80-month PFS of 31% and survival of 67% for persons receiving continuous lenalidomide. The model also forecasted a 5-year PFS of 36% and survival of 76% for persons receiving 2-year fixed-duration lenalidomide like data from the GMMG-MM5 trial (arms A1 and A2).[34]

Second PFS was estimated to be 23 and 36 months for persons failing on- or off-lenalidomide, respectively. Similarly, median survival after the first failure was estimated as 45 and 60 months, respectively. These survival rates are like those reported in the GMMG-MM5 trial and in a recent pooled analysis of randomized trials, including continuous post-transplant lenalidomide.[34,39] Finally, the model estimated median survival after 2nd failure of 28 months. Median PFS2 was 84 months for continuous lenalidomide, 82 months for 2-year fixed duration lenalidomide and 63 months for no post-transplant therapy. These figures are higher than reported by the McCarthy meta-analysis because of the assumption currently available highly effective 2nd-line therapies are prescribed.[6]

Baseline analysis. At baseline analyses, continuous and 2-year fixed-duration post-transplant lenalidomide prolonged median survival from 97 to 119 and 113 months, indicating a 6-month advantage for the continuous strategy compared with fixed-duration. Mean life-years and quality-adjusted life-years for the three strategies are displayed in **Table 3**: continuous post-transplant lenalidomide prolonged mean survival by 21.5 months and fixed-duration by 16.0 months. After

Table 3. Base-case cost-effectiveness analysis

Undiscounted	**No maintenance**	**Two-year lenalidomide**	**Continuous lenalidomide**
Life months	97.5	113.5	119.0
		+16.0	+21.5
Quality-adjusted months	67.2	79.9	84.4
		+12.7	+17.2
Costs EU	1 073 349	1 088 054	1 128 805
Incremental cost		14 705	55 456
Costs US	1 678 162	1 762 767	1 872 859
Incremental cost		84 605	194 698
Discounted 3%/year			
Life months	82.6	94.9	98.9
Gained		+12.4	+16.4
Quality-adjusted months	57.6	67.7	70.3
Gained		+10.1	+12.7
Quality-adjusted years	4.80	5.64	5.85
Gained		+0.84	+1.06
Costs EU	878 077	871 944	902 882
Incremental cost		-6 133	+30 938
Costs US	1 372 141	1 423 344	1 513 324
Incremental cost		+51 203	+141 183
ICUR EU	dominated	-7 286	29 232
ICUR US	-	60 835	133 401

adjusting for quality of life, the two strategies' gain was 17.2 and 12.7 quality-adjusted months, respectively.

Discounting of future life years further reduced the gain of post-transplant strategies to 12.7 and 10.1 months, respectively, which is about a 40% decrease of the gain. Cumulative health-care costs for managing post-transplant MM ranged from €1,073,349 to €1,128,805 in EU and from $1,678,162 to $1,872,859 in US in the 20 year time horizon chosen for the analysis. Breakdown of costs (**Supplementary Figure 1**) reported that 16% (EU) and 22% (US) of the overall healthcare costs of the continuous post-transplant lenalidomide strategy were from to costs of lenalidomide. The same rates were 10% (EU) and 15% (US) for 2-year fixed duration lenalidomide. 3rd-line therapies accounted for 17-20% of overall costs, whereas 2nd-line therapies accounted for 59-77% of overall costs. By avoiding some1st failures, 2-year fixed duration strategy saved $146,045 (€88,112) and continuous lenalidomide saved $194,705 (€117,010). Continuous lenalidomide avoided > $200,000 (€120,000) of further therapy costs, but this is 54% and 73% of the post-transplant lenalidomide drug cost. Fixed-duration post-transplant lenalidomide avoided > $150,000 dollars and > €110,000 in the US and EU settings. These are 62% and 104% of the drug cost for post-transplant lenalidomide. Consequently, post-transplant lenalidomide's resulting incremental cost was especially favourable for the 2-year fixed-duration strategy and even more favourable in the EU setting because the largest part of post-transplant costs was offset by avoided 2nd-line costs.

Future healthcare costs discounting further reduced incremental costs of 2-year fixed-duration post-transplant lenalidomide because more subjects assigned to this strategy receive higher-cost drug triplets at 1st failure. Consequently, in the EU setting, 2-year fixed-duration post-transplant lenalidomide reduced net healthcare cost and avoided €7,286 in costs for every QALY saved. In contrast, continuous post-transplant lenalidomide achieved 1 QALY at the cost of €29,232. In the US setting, 2-year fixed-duration post-transplant lenalidomide increased discounted healthcare costs by $60,835 *per* QALY saved, whereas continuous post-transplant lenalidomide achieved each QALY at the cost of $133,401.

Sensitivity analyses. We tested the results' sensitivity to different time horizons and multiple input co-variates (**Figure 2**). Results were highly sensitive to the time horizon, the monthly cost of lenalidomide, and the cost of 2nd-line and subsequent therapy/ies. However, 2-year fixed-duration lenalidomide maintained a favourable incremental cost *per* QALY gained < €50,000 in the EU setting even in persons with a low risk of early relapse or progression, such as individuals achieving a complete post-transplant response.[38,40] Similarly, in the US setting, 2-year fixed-duration lenalidomide maintained an incremental cost *per* QALY gained < $150,000 despite extreme-range sensitivity analysis.

Relative costs were the major driver of the incremental cost *per* QALY saved: the higher the ratio between 2nd-line lenalidomide-based therapies *versus* post-transplant

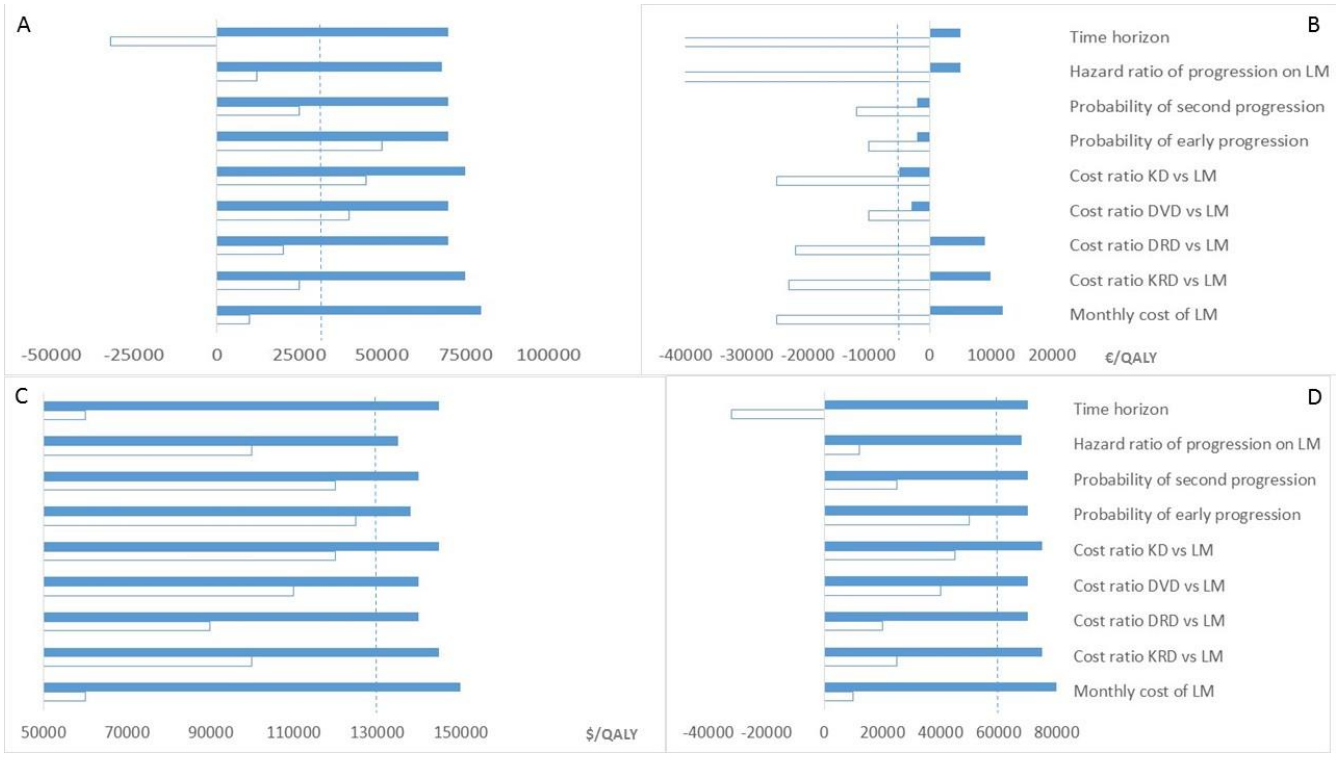

Figure 2.

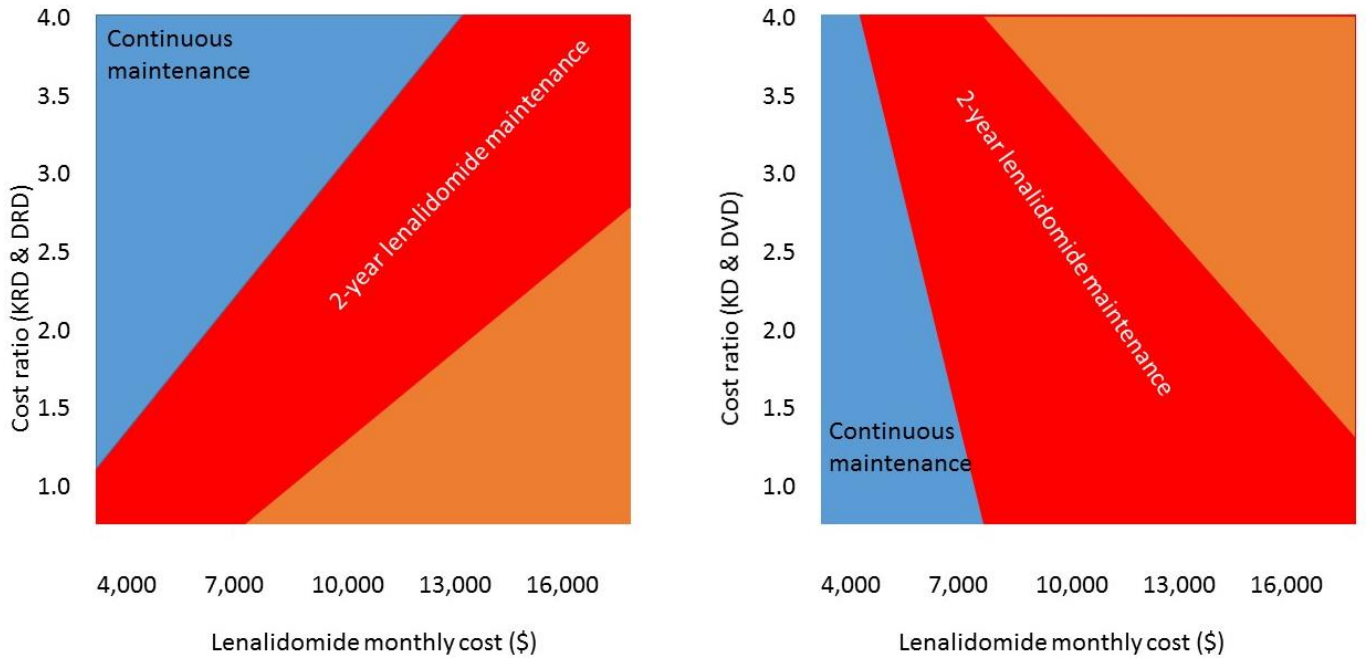

Figure 3.

lenalidomide, the greater the economic benefit of post-transplant lenalidomide. For cost ratios of carfilzomib, lenalidomide, dexamethasone (KRD) > 4.1 and daratumumab, lenalidomide, dexamethasone (DRD) > 3.0 continuous post-transplant lenalidomide was cost saving in the EU setting. Similarly, for cost ratios of DRD > 2.8 and KRD > 3.1, 2-year fixed-duration lenalidomide was cost-saving in the US setting.

Two-way sensitivity analysis display chances for post-transplant strategies to be cost-effective (incremental cost < $100,000 *per* QALY) derive from the interplay between lenalidomide monthly cost and the cost ratio of 2nd-line therapies (**Figure 3**). Therefore, continuous lenalidomide is potentially cost-effective for lower monthly lenalidomide cost and higher KRD and DRD cost ratios, as happens in the EU setting. In contrast, 2-year fixed duration lenalidomide may be cost-effective even at higher lenalidomide cost and lower KRD and DRD cost ratios, as in the US setting.

Our study tested different post-transplant strategies in cohorts of subjects in whom individual probabilities of post-transplant failure are unknown and for whom we have only estimated with reasonably wide 95 per cent confidence intervals. However, different persons in these cohorts have different probabilities of post-transplant failure. If these probabilities could be accurately predicted on the subject-level, it would be possible to predict the most cost-effective strategy for that person. Monte Carlo simulation analysis (10,000 runs) allowed us to simultaneously assess multiple input variables' effect on the results and track several individual outcomes as displayed by the scatterplots in **Supplementary Figure 2**. Continuous post-transplant lenalidomide had a 62% probability of achieving a QALY at a cost < €50,000 in the EU setting, whereas in the US, the probability of achieving one QALY at < $100,000 was only 42%. 2-year fixed-duration lenalidomide had an 81% probability of achieving a QALY at a cost < €50,000 in the EU setting and a 69% probability of achieving a QALY at a cost < $100,000 in the US setting.

Scenario analyses. We tested the sensitivity of the results to extreme variations of five input variables in order to test the variability of the results according to different settings, namely patient age and therapeutic choices for second and third line. Based on different survival rates in patients younger than 50 years,[45] we modelled patients younger than 50 years by decreasing fatality rates by 50% and patients older than 65 years by increasing fatality rates by 50%. **Table 4** shows that, as expected, both continuous post-transplant lenalidomide maintenance and two-year lenalidomide have a markedly better cost-utility in younger patients: despite a better cost-utility profile of two-year maintenance, continuous lenalidomide maintenance was also cost-saving in this clinical subgroup.

We also tested extremely low (20%) and extremely high (80%) shares of KRD, KD and pomalidomide in the second and third line. **Table 4** shows that the two maintenance strategies might report a better cost-utility in case of a lower carfilzomib share in the second line and a lower pomalidomide share in the third line.

Finally, we tested whether a strongly shorter PFS2 after lenalidomide might change the results: a PFS2 of 18 months, corresponding to a monthly rate of progression of 0.04 ameliorates the cost-utility profile of both the maintenance strategies. Therefore, continuous

Table 4. Scenario analysis.

	No maintenance		Two-year lenalidomide		Continuous lenalidomide	
Age-adjusted fatality rates	-50%	+50%	-50%	+50%	-50%	+50%
Quality-adjusted months	69.3	51.9	78.3	62.4	80.7	65.4
Costs EU	1 154 320	736 579	1 120 106	744 010	1 140 941	779 754
Costs US	1 809 152	1 148 818	1 815 427	1 221 927	1 889 298	1 319 617
ICUR EU (€/QALY)			-45 619	8 493	-14 083	38 378
ICUR US ($/QALY)			8 367	83 553	84 364	151 821
Monthly progression after lenalidomide	0.02	0.04	0.02	0.04	0.02	0.04
Quality-adjusted months	57.6	57.6	68.9	66.6	72.1	69.7
Costs EU	878 077	878 077	898 262	875 666	935 389	885 170
Costs US	1 372 141	1 372 141	1 460 895	1 402 948	1 559 690	1 488 030
ICUR EU (€/QALY)			21 435	-3 215	47 430	7 034
ICUR US ($/QALY)			94 252	41 076	155 212	114 931
KRD share (2nd line)	20%	80%	20%	80%	20%	80%
Quality-adjusted months	57.6	57.6	67.7	67.7	70.3	70.3
Costs EU	811 743	944 410	821 474	922 413	856 807	948 956
Costs US	1 345 350	1 398 931	1 402 960	1 443 727	1 494 715	1 531 932
ICUR EU (€/QALY)			11 562	-26 135	42 580	4 295
ICUR US ($/QALY)			68 448	53 223	141 132	125 670
KD share (2nd line after lenalidomide)	20%	80%	20%	80%	20%	80%
Quality-adjusted months	57.6	57.6	67.7	67.7	70.3	70.3
Costs EU	847 689	908 464	866 128	877 760	895 643	910 120
Costs US	1 361 262	1 383 019	1 420 625	1 426 062	1 509 940	1 516 707
ICUR EU (€/QALY)			21 908	-36 480	45 311	1 565
ICUR US ($/QALY)			70 530	51 140	140 483	126 319
Pomalidomide share (3rd line)	20%	80%	20%	80%	20%	80%
Quality-adjusted months	57.6	57.6	67.7	67.7	70.3	70.3
Costs EU	878 076	878 076	843 498	900 389	875 251	930 512
Costs US	1 372 140	1 372 140	1 413 160	1 433 527	1 503 432	1 523 215
ICUR EU (€/QALY)			-41 083	26 510	-2 669	49 546
ICUR US ($/QALY)			48 737	72 935	124 055	142 748

lenalidomide might still be a cost-effective option in those patients for whom a shorter PFS2 is expected.

Discussion. In persons with MM receiving an autotransplant, giving post-transplant lenalidomide until relapse or progression prolongs median PFS and survival by about 2 years.[6] Put otherwise, about 5 persons need to receive post-transplant lenalidomide for 2 years to avoid one relapse or progression over a 5-year horizon. Achieving this gain involves the cost of post-transplant lenalidomide and subsequent therapy/ies.[31,32,41] However, analyzing the cost of post-transplant lenalidomide is complex. Issues include: (1) numbers needed to treat to avoid failure; (2) duration; and (3) post-failure outcomes and interventions.

Post-transplant maintenance's optimal duration is unknown: direct and indirect data from prospective studies report a prolonged failure-free period after stopping post-transplant lenalidomide in persons receiving it failure-free for > 2 years.[16,34,39] These data suggest a fixed-duration strategy of post-transplant lenalidomide might be as effective at a lower cost compared with continuous post-transplant lenalidomide. Because of this possibility, we compared the cost-effectiveness of different post-transplant strategies: (1) no intervention; (2) continuous post-transplant lenalidomide; and (3) 2-year fixed-duration lenalidomide. The model was based on simplified modelling of failure rates and costs but calibrated to provide survival rates and mean post-transplant lenalidomide durations like published randomized trials.[6,34]

Outputs of our model indicate continuous lenalidomide is cost-effective in the EU setting but costs more than $100,000 *per* QALY in the US setting. 2-year fixed-duration lenalidomide significantly prolonged PFS and quality-adjusted survival at an acceptable cost *per*

life-year gained in EU and US settings. In the EU setting, 2-year fixed-duration lenalidomide reduced overall healthcare costs in the baseline 20-year horizon. Different costs between the EU and US settings resulted predominately from cost ratios for 2nd-line and subsequent therapy/ies compared with post-transplant lenalidomide cost.[42]

Sensitivity analyses of the model highlighted some interesting issues. First, economic advantages driven by the lower rate of failure while receiving post-transplant lenalidomide were more evident in shorter time horizons. In the long-term, advantages were partially balanced by the healthcare costs for subsequent therapy/ies. Second, the incremental cost *per* QALY gained by post-transplant lenalidomide *versus* no intervention was highly dependent on subsequent therapy/ies costs. Higher costs for therapies containing lenalidomide or pomalidomide in persons failing after stopping post-transplant lenalidomide favoured giving post-transplant lenalidomide whereas higher costs for subsequent therapy(ies) without lenalidomide or pomalidomide in persons failing while receiving lenalidomide were against post-transplant lenalidomide (**Figure 2, Figure 3**). Third, there was an increase in the *cost-for-benefit* ratio of post-transplant lenalidomide as the rate of 2nd failure increased in persons previously failing off-lenalidomide. We also tested other lenalidomide fixed-durations, including 1- and 3-year fixed-durations with no substantial change in our conclusions.

Our analysis focused on cost-effectiveness, typically expressed as cost *per* QALY. However, this widely accepted approach does not consider the economic value of a quality life saved, termed the value of a statistical life (VSL), which is about €225,000 ($250,000) per year. In our analysis, lenalidomide given until failure saves more lives than 2-year fixed-duration lenalidomide but at a considerable cost *per* QALY saved. The 2-year fixed duration strategy in the EU saves substantial health care costs. In the US setting, it results in substantially less cost *per* QALY. Neither calculation is adjusted for VSL saved, which may be an important offset to some patients, families, physicians, policy-makers, and societies.

Our study has several limitations. 1st, the results have no universal value because they depend on the time horizon adopted and country-specific drug costs.[43] 2nd, our analyses used a 3rd- party payer perspective but did not consider indirect costs from productivity loss, a relevant social burden for young persons with MM.[44] 3rd, unit costs of treatments resembled *ex-factory* costs and not true acquisition costs. This could result in relevant mismatches. Finally, we did not cover model costs of palliative and end-of-life care.

Conclusions. Our modelling indicates the most favourable *value-for-cost* of post-transplant lenalidomide in persons with MM is associated with a 2-year fixed-duration strategy. However, continuous lenalidomide maintenance showed an acceptable cost-utility in younger patients and in those for whom a shorter PFS2 is expected. Definite conclusions require validation in controlled clinical trials, which consider safety, efficacy, and cost.

We compared our results with other published clinical and economic outcomes of continuous post-transplant lenalidomide (**Supplementary Figure 2** and **Table 2**). These studies used partitioned survival but considered different health states and comparators. All studies included survival data from the CALBG 100104 study, whereas 2 studies included data from the IFM trial or other studies (**Supplementary Table 3**). Time horizons were also different, ranging from 10 years to a lifetime. Consequently, incremental life-years gained ranged from 1 to 3.64 years. Overall incremental costs ranged from €147,707 to $476,690 and incremental cost *per* QALY from €30,709 to €277,456.

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Supplementary Data:

Supplementary Table 1. Distribution of therapy choices for second and third line: carlfizomib, lenalidomide, dexamethasone (KRD), daratumumab, lenalidomide, dexamatheasone (DaraRD), daratumumab, bortezomib, dexamethasone (DaraVD), carlfizomib, dexamethasone (KD), pomalidomide, bortezomib, dexamethasone (pomVD), pomalidomide, cyclophosphamide, dexamethasone (PomCD).

Treatments	KRD	DaraRD	KD	DaraVD	PomVD	PomCD
2nd line after lenalidomide maintenance			50%	50%		
2ns line without lenalidomide	50%	50%				
3rd line after KRD				50%		50%
3rd line after DaraRD			50%		50%	
3rd line after KD				50%		50%
3rd line after DaraVD			50%			50%

Supplementary Table 2. Literature search strategy.

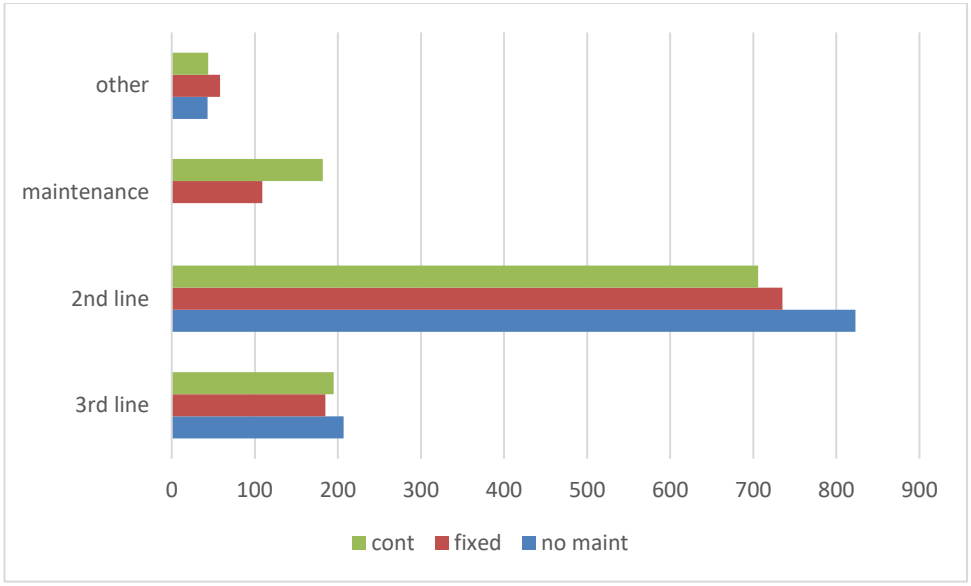
Search equation EMBASE	Search description
1. 'myeloma'/exp 2. 'transplantation' 3. maintenance 4. 1 AND 2 AND 3	Major search module
5. [english]/lim 6. 4 AND 5	Limitations (language)
7. cost effectiveness 8.	Search for economic evaluations
9. lenalidomide AND 'cost effectiveness' AND myeloma AND transplant	

Supplementary Table 3. Retrieved studies.

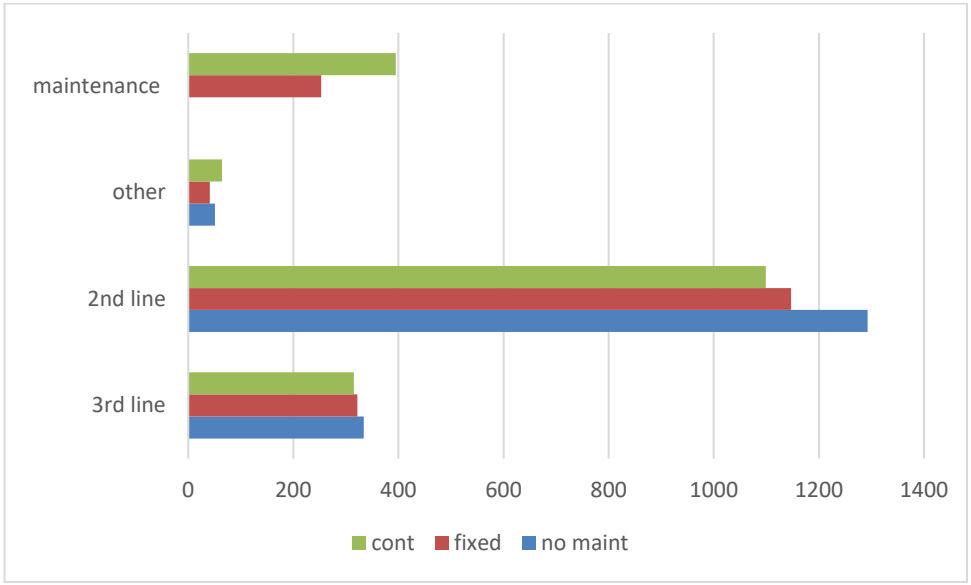
	Olry de Labry Lima[35]	Uyl de Groot[37]	Zhou[36]
Country, year	Spain, 2019	The Netherlands, 2018	US, 2018
Perspective	National Health System	na	na
Decision model	PSM	PSM	PSM
Cycle duration	na	na	28 days
Health states	PF, progression, progression after following line, death	PF (on & off treatment), post-progression (before, on and after 2nd line therapy), death	PF on treatment, PF off treatment, progressed, death
Lenalidomide schedule	10 mg→15mg continuous administration (CALBG)	21/28 day cycles	
Duration of lenalidomide treatment	According to CALGB 100104.	na	Pooled from the 3 trials
Comparator	No maintenance	No maintenance	No maintenance or bortezomib maintenance
Efficacy data	CALGB 100104 and IFM 2005-02	pooled meta-analysis of the 3 trials	CALGB 100104 (adjustments for crossover).
Estimation of long-term survival	Parametric models	Parametric models	Parametric models for OS and PFS + natural mortality rates in the USA.
Adverse events considered	Grade 3-4	na	na
Secondary primary malignancies	considered	na	na
Utilities	EQ5D estimation from EORTC-Q30: PF 0.833, 1st relapse 0.679, 2nd relapse 0.474	real-world setting captured in the Connect MM Disease Registry	na
Healthcare resource utilization source	National unit costs, local pattern of utilization (Andalusia)	EU5 real-world study (Ashcroft J, et al. 2018)	na
Second-line therapies	KD 70%; DaraVd 30% (MT) KRD 50%, Rd 50% (noMT)	na	na
Monthly lenalidomide cost	€8,165	na	na
Monthly cost for 2nd line therapy	€20,552 (MT) €9,950 (no MT)	na	na
Financial year	2017	2016	2018
Time horizon	10 years	lifetime	lifetime
Discount	0%	na	na
Incremental LY	1.01 (CALBG)	2.79	3.64
Incremental QALY	1.11 (CALBG) 0.14 (IFM)	2.26	2.99
Incremental cost	€307,571 (CALBG)	€147,707- €77,462	$476,690
ICUR	€277,456 CALBG €1,502,780 IFM	€30,709 (10 mg)	$159,240

Abbreviations: PSM = partitioned survival model; Y = yes; MT = maintenance therapy; LY = life years

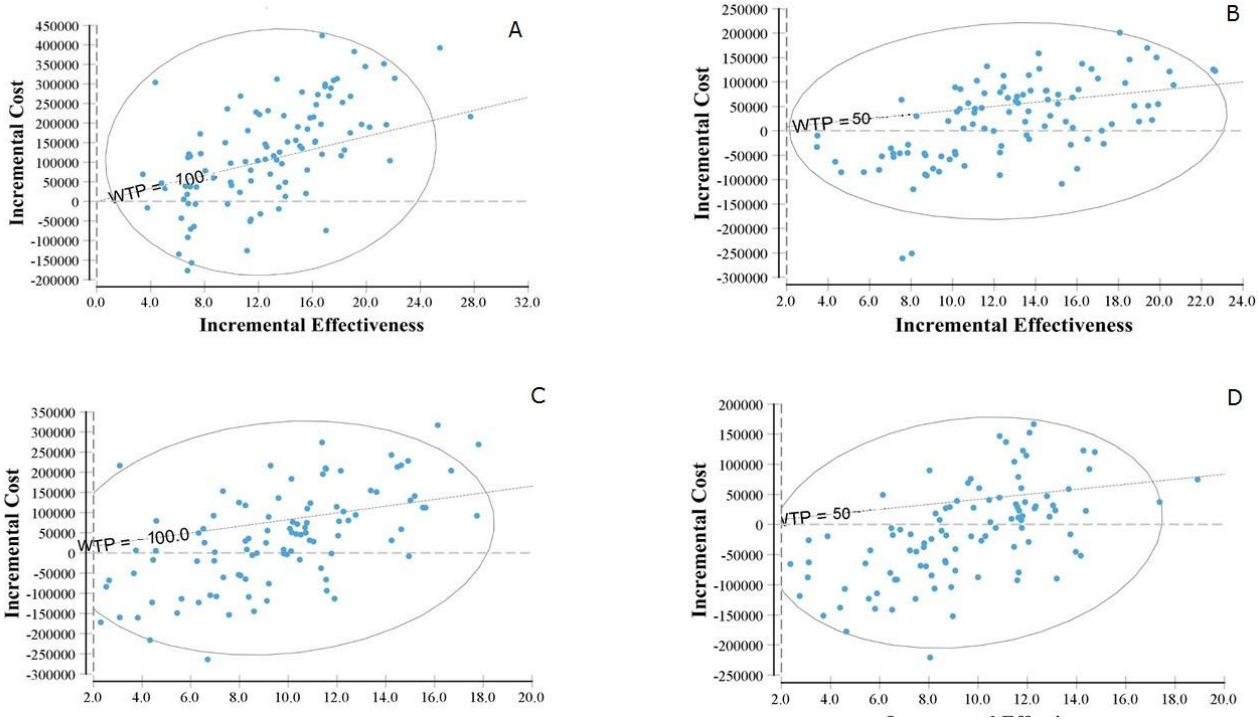
A.



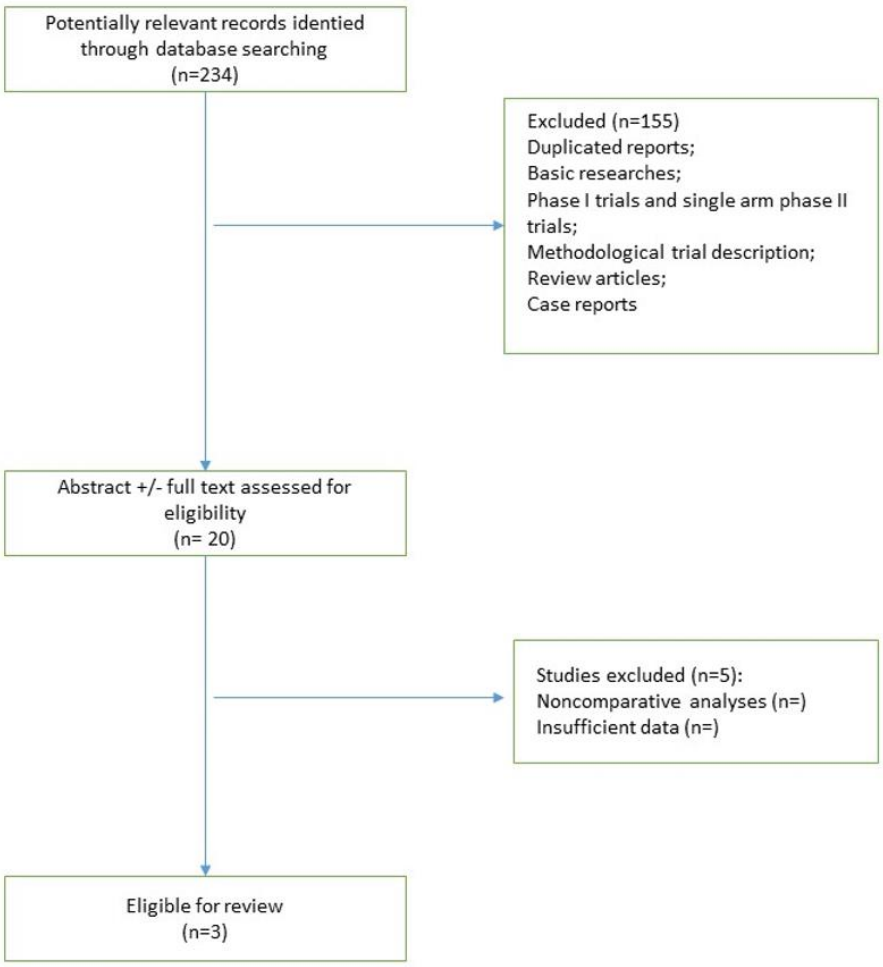
B.



Supplementary Figure 1. Breakdown of costs in the EU setting (panel A) and in the US setting (panel B). X-axis shows thousand euros in panel A and thousand dollars in panel B.
Abbreviations: continuous lenalidomide maintenance: "cont"; 2-year fixed-duration lenalidomide maintenance: "fixed"; no post-transplant maintenance: "no maint".



Supplementary Figure 2. Monte Carlo simulation of the decision model outputs. Incremental cost and incremental effectiveness (quality-adjusted months) of continuous or fixed-duration lenalidomide maintenance versus no maintenance are reported: each simulation is represented by a dot. Continuous lenalidomide maintenance versus no maintenance is reported in panels A (US setting) and B (EU setting). Two-year fixed duration maintenance versus no maintenance is reported in panels C (US setting) and D (EU setting). Willingness to pay (WTP) for an additional QALY in thousand dollars or thousand euros is plotted. The higher is the number of dots plotted above the WTP line, the less cost-effective was the maintenance strategy assessed.



Supplementary Figure 3. PRIMSA flow-chart.