Cost Offsets in the Treatment Journeys of Patients With Relapsed/Refractory Multiple Myeloma

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ABSTRACT

Purpose: Multiple new regimens are available for the treatment of relapsed/refractory multiple myeloma (RRMM). In this context, it is increasingly important to understand the differential costs of regimens used to treat RRMM.

Methods: A treatment journey for RRMM during a 12-month period of therapy was developed to reflect real-world clinical practice based on current treatment guidelines and input from hematologists/oncologists. The journey incorporated prescreening visits, laboratory tests, regimen-specific premedication, treatment-related costs, medical costs, and indirect costs. A cost model was constructed from the standard RRMM treatment pathway to compare overall, direct, and indirect costs across therapies over a 12-month period from initiation of second-line therapy and to determine cost offsets (incremental costs) associated with use of ixazomib-based therapy versus comparator regimens. According to the clinical input, the standard pathway was modified for patients with high unmet need to determine specific cost offsets in these subgroups.

Findings: Total costs ranged from $93,683 for bortezomib-cyclophosphamide-dexamethasone to $315,296 for daratumumab-bortezomib-dexamethasone. Drug cost comprised the highest proportion (83%–98%) of total costs of second-line therapy across regimens, which were generally highest for regimens based on recently approved agents. Indirect costs were higher for regimens that required more frequent or longer durations of drug administration, and lower for all-oral regimens. Costs were reduced among frail patients because of the use of adjusted dosing, whereas indirect costs were increased for regimens that required a greater number of clinic visits among patients with barriers to physician access.

Implications: Cost model analyses highlight the differential direct and indirect costs associated with multiple regimens for the treatment of RRMM, including many recent new regimens. The results indicate the lower treatment burden and indirect costs associated with administering all-oral regimens compared with regimens that require frequent and/or lengthy subcutaneous or intravenous infusions. Understanding comparative costs associated with the treatment journeys of different patients with RRMM may help inform payer and patient therapeutic choices. (*Clin Ther*. 2019;41:477–493)

Key words: cost offsets, direct costs, indirect costs, multiple myeloma, oral therapies.

INTRODUCTION

The treatment landscape for multiple myeloma (MM), and in particular for relapsed/refractory MM (RRMM), has evolved rapidly in recent years, with

Accepted for publication January 14, 2019
https://doi.org/10.1016/j.clinthera.2019.01.009
0149-2918/$ - see front matter

multiple new agents receiving regulatory approval.[1] In addition to the first-in-class proteasome inhibitor bortezomib and the second-generation agent carfilzomib, the first oral proteasome inhibitor ixazomib has been approved for the treatment of RRMM by the US Food and Drug Administration and is approved in 48 countries worldwide. Three immunomodulatory drugs − thalidomide, lenalidomide, and pomalidomide − are also available for the treatment of MM, in addition to approved agents with other mechanisms of action such as the histone deacetylase inhibitor panobinostat and the monoclonal antibodies elotuzumab and daratumumab.[1] The introduction of these new agents has contributed to substantial improvements in patient outcomes. Although health benefits may offset some of the costs of care by delaying disease progression and its associated morbidities,[2] these new drugs are associated with high costs at both the societal and individual levels,[3–5] particularly when used in combination therapy and for prolonged periods of time, per the evolving management paradigms in MM.[6]

In this context, it is increasingly important to understand the differential costs of regimens used to treat RRMM. Previous studies have analyzed pharmacy and medical costs associated with the use of some of the available regimens for RRMM[7,8]; however, a broader analysis covering the total costs across the entire treatment journey associated with recently approved regimens has not been reported to date. Specifically, in addition to understanding the direct costs of these newer regimens, it is also particularly important to understand the patient and caregiver burden of treatment,[9] and the indirect costs associated with receiving treatment for RRMM. Patients with MM are living longer due to the availability of new therapies[10] and have a greater range of treatment options for use across their lengthening disease course. Thus, quality of life (QoL),[9] the indirect burden of treatment,[9] and the associated costs to patients and caregivers[11,12] are becoming increasingly relevant factors when considering treatment choices. Furthermore, MM is a heterogeneous disease, and some subgroups of patients with RRMM have high unmet needs; for example, patients with comorbidities or ongoing toxicities from previous therapies, frail patients, and patients with logistic or geographic restrictions may face limitations with respect to their treatment options and may incur additional costs associated with their care as a consequence of these factors. Thus, it is important to consider how differences in the treatment pathway affect these patients and the costs associated with their treatment.

The objectives of this study were to determine the costs associated with treating RRMM with second-line therapies and to determine cost offsets (incremental costs) associated with the use of ixazomib-based therapy versus comparator regimens, overall and in subgroups of patients with high unmet needs.

METHODS

Development of a Treatment Journey

A treatment journey for RRMM during a 12-month period of therapy was developed to reflect real-world clinical practice based on current treatment guidelines and input from hematologists/oncologists.[13–19] The journey incorporated prescreening visits, laboratory tests, regimen-specific premedication, treatment-related costs, medical costs, and indirect costs (see Supplemental Figure 1 in the online version at doi: 10.1016/j.clinthera.2019.01.009).

From a comprehensive review of the literature and validation of findings from the literature review by a group of nine hematologists/oncologists practicing in North America, South America, and Europe, the following subgroups of patients with MM were identified to have high unmet needs: patients with renal disease, cardiac disease, diabetes, high-risk biomarkers, grade $\geq$2 peripheral neuropathy (PN), poor venous access, barriers to physician access, disease that has become refractory or has relapsed within 6 months, frail patients, and patients receiving third- or fourth-line treatment. The standard treatment journey for patients with RRMM was modified according to the specific treatment requirements of these different patient subgroups.

Regimens of Interest

Comparator regimens used to treat RRMM as second- or third-line therapy were initially identified and validated based on discussions with hematologists/oncologists and a review of clinical studies. The analysis focused on second- or third-line therapy to study a relatively homogenous patient population, and because the most recently approved agents (ixazomib, elotuzumab, and daratumumab)

have been approved by the Food and Drug Administration for use as second-line therapy or beyond in patients with RRMM. The following regimens were included in the cost model: lenalidomide-dexamethasone (Rd), bortezomib-dexamethasone (Vd), bortezomib-lenalidomide-dexamethasone (VRd), bortezomib-cyclophosphamide-dexamethasone (VCd), pomalidomide-dexamethasone (Pom-dex), carfilzomib plus dexamethasone (Kd), melphalan-prednisone-thalidomide (MPT), bortezomib-melphalan-prednisone (VMP), KRd, ixazomib-Rd (IRd), elotuzumab-Rd (ERd), daratumumab-Vd (DVd), and panobinostat-Vd (PaVd). Note that some of these regimens were not approved at the cut-off date for model inputs but have been subsequently approved. Regimen details and the recommended prophylaxis (based on clinical trial usage, prescribing information, and clinical experience) are summarized in Supplemental Table I (available in the online version at doi: 10.1016/j.clinthera.2019.01.009).

Cost Model

We constructed a model to determine the costs associated with treating patients with RRMM in the second-line setting with the various regimens currently approved or widely used within the United States. Because specific subgroups of patients with RRMM may require additional considerations in their management and treatment, we applied our cost model to different subgroups of patients with RRMM with high unmet needs to determine whether there were any differential costs for these subgroups. The model aimed to provide a comprehensive framework for evaluating costs across different regimens available for the treatment of RRMM but also among different patient subgroups with specific needs along their treatment journey.

The cost model assumed continuous treatment for a fixed duration of 12 months and included direct and indirect costs incurred at the initiation of second-line therapy, during second-line therapy, and for a subsequent line of therapy among patients who discontinued second-line therapy because of disease progression or adverse events (AEs). The direct and indirect cost categories considered at each of these stages are described in Table I. Aggregated costs were calculated by multiplying the number or frequency of each input item with the associated item cost. Each cycle of therapy during second-line treatment was assumed to have a duration of 28 days.

Medical and Laboratory Costs

The model assumed one prescreening outpatient medical visit at initiation of second-line therapy, two outpatient medical visits during the first cycle, and one routine outpatient medical visit during each subsequent cycle of second-line therapy to monitor patient health and response. Multiple prescreening laboratory tests were assumed for each regimen at the initiation of second-line therapy. Regimen-specific tests were also accounted for, such as one transthoracic echocardiogram before initiating therapy for carfilzomib-based regimens according to common practice. Subgroup-specific laboratory tests were also assumed in some cases. For example, the model for the cardiac disease subgroup assumed a transthoracic echocardiogram at treatment initiation for all regimens, and every 3 cycles for carfilzomib-based regimens during treatment. Laboratory tests that occurred during second-line therapy, specifically complete blood counts and chemistry panels, were also accounted for. These laboratory tests were assumed to occur more frequently for injectable regimens than for oral regimens, based on information gathered from interviews with physicians, pivotal trials, and guidelines for the treatment of MM. Because cytogenetic testing is not routinely performed at relapse in the community setting, although in centers where this is routinely conducted on disease progression (rather than based on choice of therapy) the cost impact of repeat cytogenetic testing would be similar for all the various treatment regimens (and thus would not affect cost offset estimates), it was not included in the model for any of the regimens. Medical and laboratory costs were derived from the American Medical Association's 2015 CPT (Current Procedural Terminology) Code/Relative Value Search and Clinical Diagnostic Fee Schedule (see Supplemental Table II). All costs were inflated to 2017 dollars by using the medical care component of the consumer price index. In addition, administration costs were included and were determined by multiplying the number of administrations required for each regimen by the corresponding cost of a chemotherapy administration (either intravenous or subcutaneous) according to the CPT code obtained from the American Medical Association database. Hydration costs were obtained

Table I. Description of cost categories considered at each stage of the second-line relapsed/refractory multiple myeloma treatment journey.

Stage of Treatment Journey	Direct Cost Categories	Indirect Cost Categories
Initiation of second-line therapy	Prescreening outpatient visit	Productivity loss to patient
	Medical visit	Transportation
	Laboratory tests	Travel
		Relocation
		Caregiving
During second-line therapy	Drug-related costs	Productivity loss to patient
	Regimen	Transportation
	Prophylaxes	Travel
	Other medications	Relocation
	Drug administration	Caregiving
	Hydration	
	Medical costs	
	Monitoring comorbidities	
	Routine medical visit	
	Monitoring AEs	
	Treating AEs	
	Additional costs of first cycle	
Subsequent line of therapy	Initiation of subsequent line	
	Medical, drug, productivity, transportation, and caregiving costs associated with subsequent line of therapy	

AE = adverse event.

in the same way and were included for Kd and KRd (based on how the regimen was administered in pivotal trials). Additional infusion hours were also included for ERd and DVd to account for the administration of these monoclonal antibodies.

Drug Costs

Treatment regimen costs were calculated by assuming a 28-day cycle, with cost adjustments made for regimens delivered that used different cycle lengths (eg, the cost for 21-day regimens were standardized to 28 days by calculating a per-day cost for the regimen and multiplying by 28). All drug-related costs (including those for premedication, prophylaxes, and the wholesale acquisition costs for the comparator regimens) were extracted from the US Red Book.[20] Costs of comparator regimens are shown in Supplemental Table I, and those for premedication and prophylaxes are shown in Supplemental Table III.

Adverse Events

The incidence of AEs associated with each comparator regimen was obtained from prescribing information and pivotal trials, and the costs of incident AEs were obtained from international published literature on the treatment of cancer (see Supplemental Table IV).[7,21–28] AEs of grade 3 or higher only were considered for all regimens. For each AE, the incidence was multiplied by the respective incident cost identified from the literature. All costs were inflated to 2017 dollars, using the medical care component of the consumer price index.

Indirect Costs

Indirect costs included costs arising from loss of productivity, transportation, or caregiving services associated with outpatient medical visits at initiation and during therapy — the model assumed 3 h for each visit, including for each intravenous or subcutaneous injection, to account for time spent traveling to/from

the clinic, in addition to time in the clinic, with additional infusion time assumed for regimens that contained monoclonal antibodies. For indirect costs (see Supplemental Table V), the model assumed productivity losses based on 3 h lost from work for each medical visit, with the hourly wage for patients estimated as the US mean wage of all jobs, adjusted for MM prevalence and employment per age group. Transportation costs were estimated based on round-trips[29] for prescreening medical visits and laboratory tests at initiation of second-line therapy, plus one round-trip for an outpatient visit during each cycle of treatment, and one round-trip per drug administration. Caregiving costs were estimated based on 3 h of time for a caregiver for each medical visit, and using the US mean wage of a home health aide. Total productivity costs, travel costs, and caregiving costs varied across types of regimen (eg, oral versus intravenous administration), the number of administration visits per cycle as defined by information from pivotal trials, and duration of infusion (as applicable).

Subsequent Line of Therapy

Discontinuation rates for comparator regimens were derived from pivotal trials and ranged from 9% (Pom-dex) to 35% (MPT) (see Supplemental Table VI).[30–46] Duration of treatment for patients who discontinued therapy was assumed to be half of the overall period (ie, 6 months of the 12-month period). Subsequent therapy was assumed to be a weighted average of multiple regimens – Pom-dex (38%), Kd (31%), KRd (10%), VCd, VRd, Vd, and Rd (each 4%), and other regimens (ie, PomKd) that were not considered in our study (5%; proportionally reassigned to the other regimens under study) – based on internal market research at Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The same weighted average was assumed across all regimens in the model. Costs for initiation of and treatment during the subsequent line of therapy were calculated according to this weighted average. Specific direct and indirect costs associated with initiation of and treatment with the subsequent line of therapy are summarized in Supplemental Table VII.

RESULTS

Total Costs of Treatment Regimens

The total cost summaries for a 12-month treatment period for each of the regimens are shown in Table II. Drug cost represents the primary cost component of the total cost of second-line therapy across all regimens, ranging from 83%, 84%, and 85% of the regimen costs for Vd, VCd, and VMP, respectively, to 96%, 96%, and 98% of the regimen costs for Rd, Pom-dex, and IRd, respectively, with the percentage varying depending on overall regimen drug costs and the other costs associated with each regimen. Similarly, drug cost represents between 62% (MPT) and 90% (Pom-dex) of the total annual cost, which takes into account the cost of initiation of second-line therapy, cost of second-line therapy, and cost of subsequent therapy.

Figure 1A and 1B illustrate the differences between regimens for overall total costs, including and excluding drug costs, respectively, over a 12-month period. Total costs were generally highest for regimens based on recently approved agents, including DVd, Kd, KRd, ERd, PaVd, and IRd, compared with older doublet or triplet regimens such as VCd, VMP, Vd, MPT, and Rd. Total costs excluding drug costs appeared highest with regimens with substantial rates of discontinuation because of AEs, such as MPT, and with triplet regimens in which one or more of the agents was administered by intravenous or subcutaneous infusion, such as DVd, KRd, PaVd, and ERd. Overall, in comparison with other new or recently approved doublet or triplet regimens, IRd appeared less expensive than Kd, KRd, ERd, and DVd, driven by its lower administration costs, lower AE-related costs, and lower indirect costs.

Direct costs for a 28-day cycle of each regimen, excluding drug costs, are presented in Figure 1C. Direct medical costs, including medical visits, laboratory tests, administration costs, and costs for prophylaxes, were $140.97 for the all-oral regimens IRd, Rd, and Pom-dex (costs per 28-day cycle comprise 1 routine outpatient visit, 2 complete blood count tests, 2 chemistry blood panels, and prophylaxis; 12-month cost: $1691.61). Direct costs were higher for bortezomib-containing regimens, such as Vd ($707.75; 12-month cost: $8493.01), VRd ($708.29; 12-month cost: $8499.50), and VCd ($561.72; 12-month cost: $6740.69), compared with all-oral regimens, driven by higher administration and laboratory test costs. Similarly, compared with all-oral regimens, direct costs were higher for regimens that contained new drugs requiring clinic administration, such as Kd ($1009.65; 12-month

Table II. Summary of total costs for regimens of interest for treatment of relapsed/refractory multiple myeloma across a 12-month period, based on cost model.

Costs, US$	Doublet Regimens				Triplet Regimens (1 New Agent)			Triplet-Regimens (>1 New Agent)					
	Rd	Vd	Kd	Pom-dex	VCd	MPT	VMP	IRd	VRd	KRd	ERd	DVd	PaVd
Initiation of therapy	$739	$739	$879	$739	$739	$739	$739	$739	$739	$879	$739	$739	$739
Overall cost of regimen	$140,814	$81,803	$265,140	$161,825	$79,876	$89,291	$87,103	$238,463	$202,429	$270,884	$273,816	$290,598	$188,391
Drug cost	$135,817	$68,114	$245,529	$154,688	$67,050	$80,072	$73,654	$233,320	$187,176	$250,868	$256,656	$269,059	$172,541
Administration	$6	$4931	$9306	$6	$4037	$4945	$4549	$6	$4937	$9061	$6892	$9518	$4931
Medical costs	$1595	$2704	$2085	$1690	$2376	$1467	$2580	$1595	$2704	$2033	$2028	$2794	$2704
AE-related costs	$2550	$1106	$2538	$4543	$2879	$2033	$1707	$2697	$2665	$3393	$3313	$1721	$3268
Indirect costs	$845	$4946	$5681	$898	$3533	$774	$4614	$845	$4946	$5528	$4927	$7506	$4946
Cost of subsequent line of therapy	$21,563	$23,958	$16,117	$9366	$13,068	$38,116	$16,009	$21,563	$23,958	$21,563	$21,563	$23,958	$23,958
Total cost	**$163,116**	**$106,500**	**$282,136**	**$171,930**	**$93,683**	**$128,146**	**$103,851**	**$260,765**	**$227,126**	**$293,325**	**$296,118**	**$315,296**	**$213,089**

AE = adverse event; DVd = daratumumab-bortezomib-dexamethasone; ERd = elotuzumab-lenalidomide-dexamethasone; IRd = ixazomib-lenalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; MPT = melphalan-prednisone-thalidomide; PaVd = panobinostat-bortezomib-dexamethasone; Pom-dex = pomalidomide-dexamethasone; Rd = lenalidomide-dexamethasone; VCd = bortezomib-cyclophosphamide-dexamethasone; Vd = bortezomib-dexamethasone; VRd = bortezomib-lenalidomide-dexamethasone.

cost: $12,115.75), KRd ($1010.19; 12-month cost: $12,122.24), ERd ($795.00; 12-month cost: $9539.99), DVd ($1122.63; 12-month cost: $13,471.61), and PaVd ($707.75; 12-month cost: $8493.01).

AE management costs per 28-day cycle are summarized in Figure 2. On average, AE-related costs were estimated to be $243.37 per 28-day cycle (12-month cost: $2920.42), with lower costs associated with Vd ($103.58; 12-month cost: $1242.91) and higher costs associated with Pom-dex ($395.58; 12-month cost: $4747.00) and PaVd ($306.02; 12-month cost: $3672.20). Pneumonia was among the most expensive AE across all regimens (cost per incidence: $15,294.82; see Supplemental Table IV), and the higher rates of this AE, possibly associated with the populations in which the regimens were studied, and its management drove the high monthly AE management costs associated with Pom-dex and PaVd.

Indirect costs per 28-day cycle of each regimen are presented in Figure 1D. Indirect costs were higher for regimens that required more frequent or longer durations of drug administration, such as DVd ($702.78; 12-month cost: $8433.33), Kd, and KRd ($511.26; 12-month cost: $6135.06), and lowest for the all-oral regimens IRd, Rd, and Pom-dex ($78.19; 12-monthly cost: $938.30).

Patient Subgroups

Cost offsets were evaluated in specific subgroups of patients with RRMM with high unmet need, prioritized according to patient-related and disease-related factors. In frail patients, adjustments were made to the patient treatment pathway and the cost model to take account of the ability and frequency with which these patients can and need to visit the clinic, the impact of frailty on treatment decisions, including the anticipated lower tolerability of therapies, and the adjustments required to therapy dosing for frail patients. As shown in Figure 3, these adjustments resulted in differences in cost elements for frail patients, with dose adjustment, particularly the use of weekly bortezomib, affecting the annual treatment costs (DVd: reduction of $88,364; Vd: reduction of $31,899; VCd: reduction of $23,303; VRd: reduction of $18,671).

Costs were also evaluated in the subgroup of patients with barriers to physician access, for whom distance from hospital may be an important consideration. Direct costs are unaffected in this subgroup (Figure 4A). Additional costs were determined from the assumption that patients with barriers to physician access require 1 additional hour per visit and administration, travel costs based on a round-trip of 70 miles (rather than 35 as assumed for the standard RRMM treatment pathway), and overnight stays (for those treatments administered on 2 consecutive days). This is reflected in the increased indirect costs per 28-day cycle seen in this subgroup of patients with those regimens that required a greater number of clinic visits for consultations and to receive treatment (Figure 4B).

Increases in the direct and indirect costs of treatment with certain regimens were seen in the subgroup of patients with preexisting cardiac disease. Specifically, K-based regimens required additional monitoring (additional visit and tests) compared with the standard patient treatment pathway, which resulted in an increase to the direct ($197.63; Figure 4C), indirect ($24.06; Figure 4D), and AE management costs ($21.41 for KRd and $19.59 for Kd) per cycle. Total direct costs per 28-day cycle of treatment with KRd and Kd in patients with preexisting cardiac disease were $1207.82 and $1207.28, respectively, and total indirect costs per 28-day cycle with both regimens were $535.31. Minor increases in the costs associated with IRd in these patients were associated with an additional echocardiogram (which was assumed across all regimens in the model for the cardiac disease subgroup) at baseline ($139.24) and once every 3 months during second-line therapy, and additional AE management costs for cardiac failure ($1.83 per 28-day cycle), to result in total direct and indirect costs of $140.97 and $78.19, respectively, per 28-day cycle.

Minor differences in the overall treatment cost were observed for the subgroups of patients with PN, renal disease, and diabetes relative to the standard treatment journey based on the need for an additional clinic visit and/or laboratory testing and associated indirect costs. For other subgroups of patients with high unmet need for which the standard RRMM treatment pathway was modified, no differences in the total overall cost of treatment were observed compared with the standard treatment journey for RRMM.

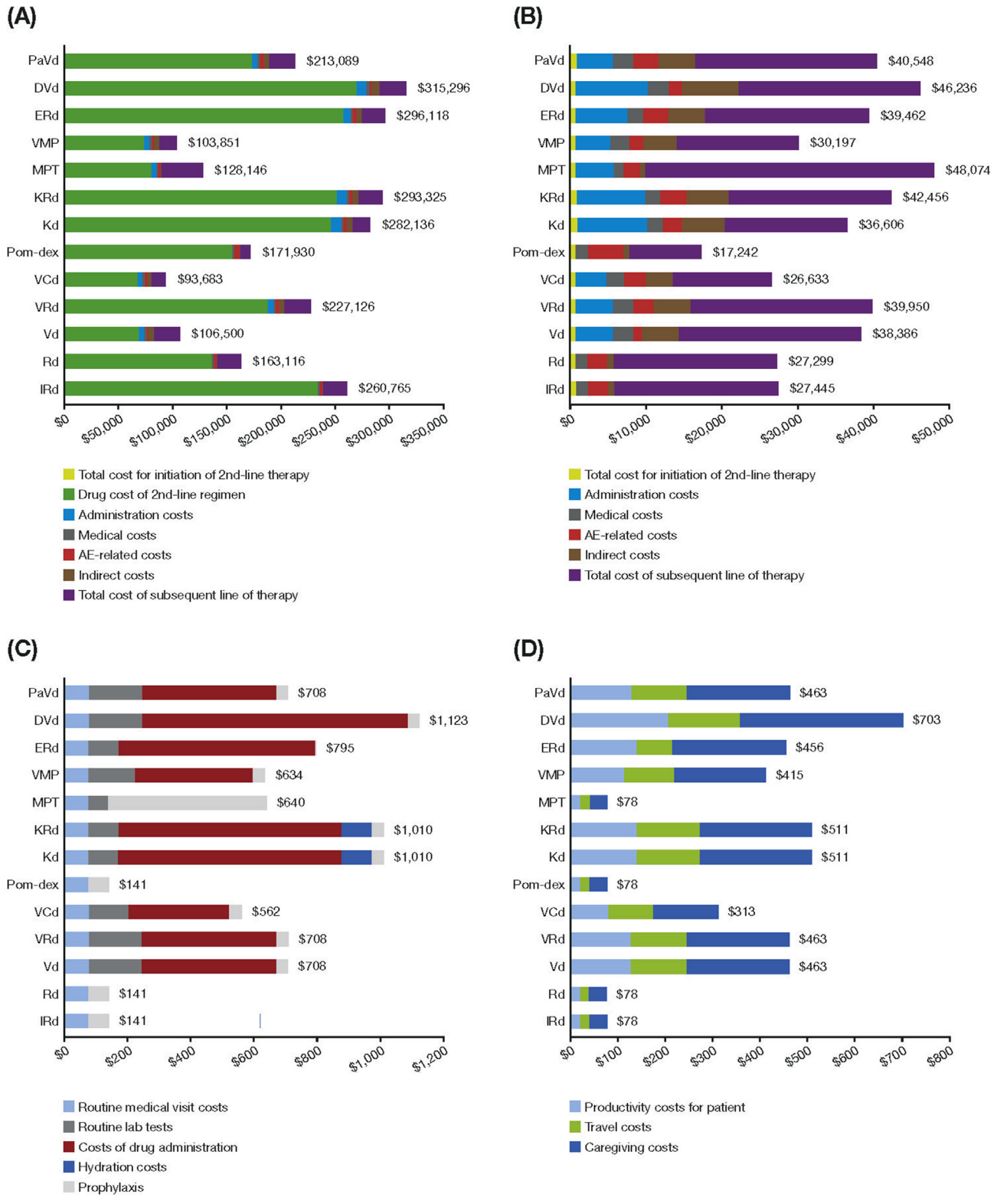

Figure 1. Cost summary per regimen over a 12-month period for (A) all costs, (B) costs that exclude drug costs, (C) direct costs that exclude drug costs, and (D) indirect costs per 28-day cycle by treatment regimen.

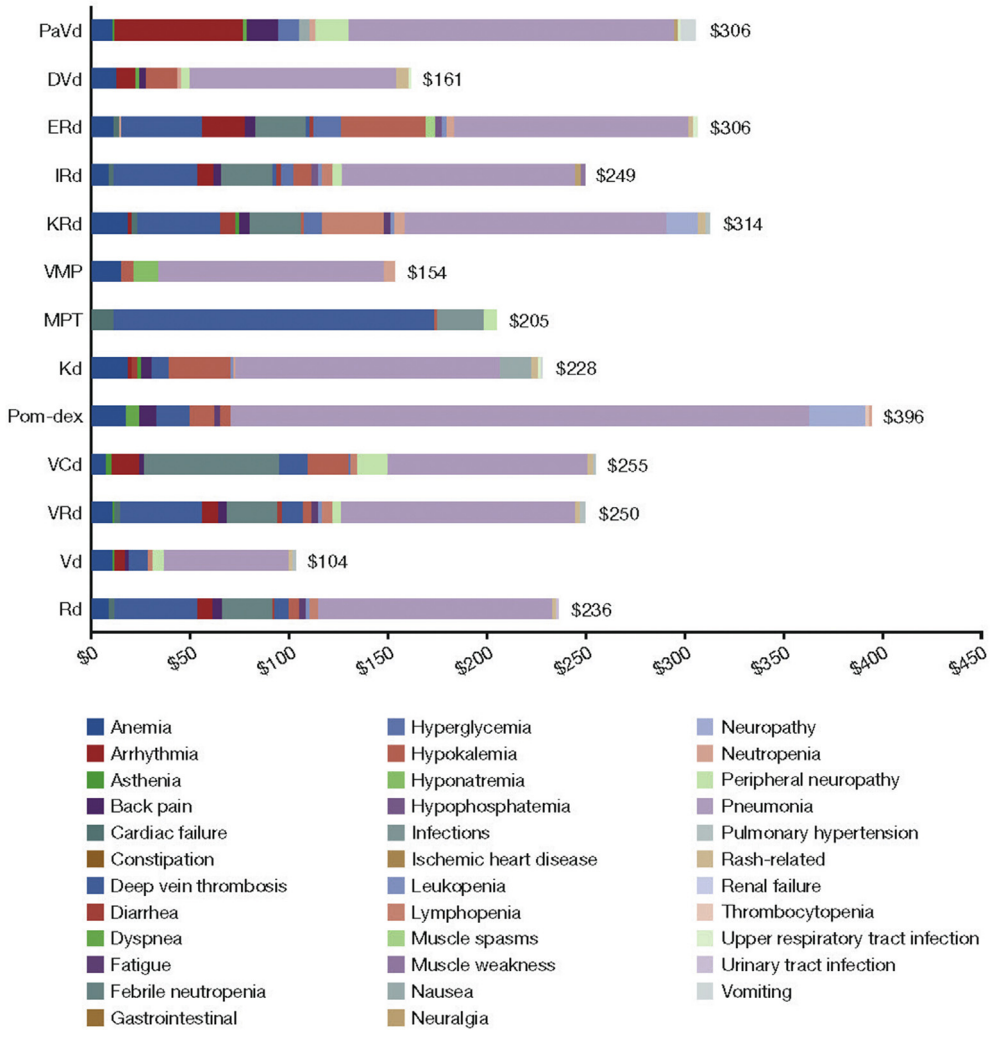

Figure 2. Adverse event management costs per 28-day cycle by treatment regimen. (DVd = daratumumab-bortezomib-dexamethasone; ERd = elotuzumab-lenalidomide-dexamethasone; IRd = ixazomib-lenalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; MPT = melphalan-prednisone-thalidomide; PaVd = panobinostat-bortezomib-dexamethasone; Pom-dex = pomalidomide-dexamethasone; Rd = lenalidomide-dexamethasone; VCd = bortezomib-cyclophosphamide-dexamethasone; Vd = bortezomib-dexamethasone; VMP, bortezomib-melphalan-prednisone; VRd = bortezomib-lenalidomide-dexamethasone.)

(AE = adverse event; DVd = daratumumab-bortezomib-dexamethasone; ERd = elotuzumab-lenalidomide-dexamethasone; IRd = ixazomib-lenalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; MPT = melphalan-prednisone-thalidomide; PaVd = panobinostat-bortezomib-dexamethasone; Pom-dex = pomalidomide-dexamethasone; Rd = lenalidomide-dexamethasone; VCd = bortezomib-cyclophosphamide-dexamethasone; Vd = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VRd = bortezomib-lenalidomide-dexamethasone.).

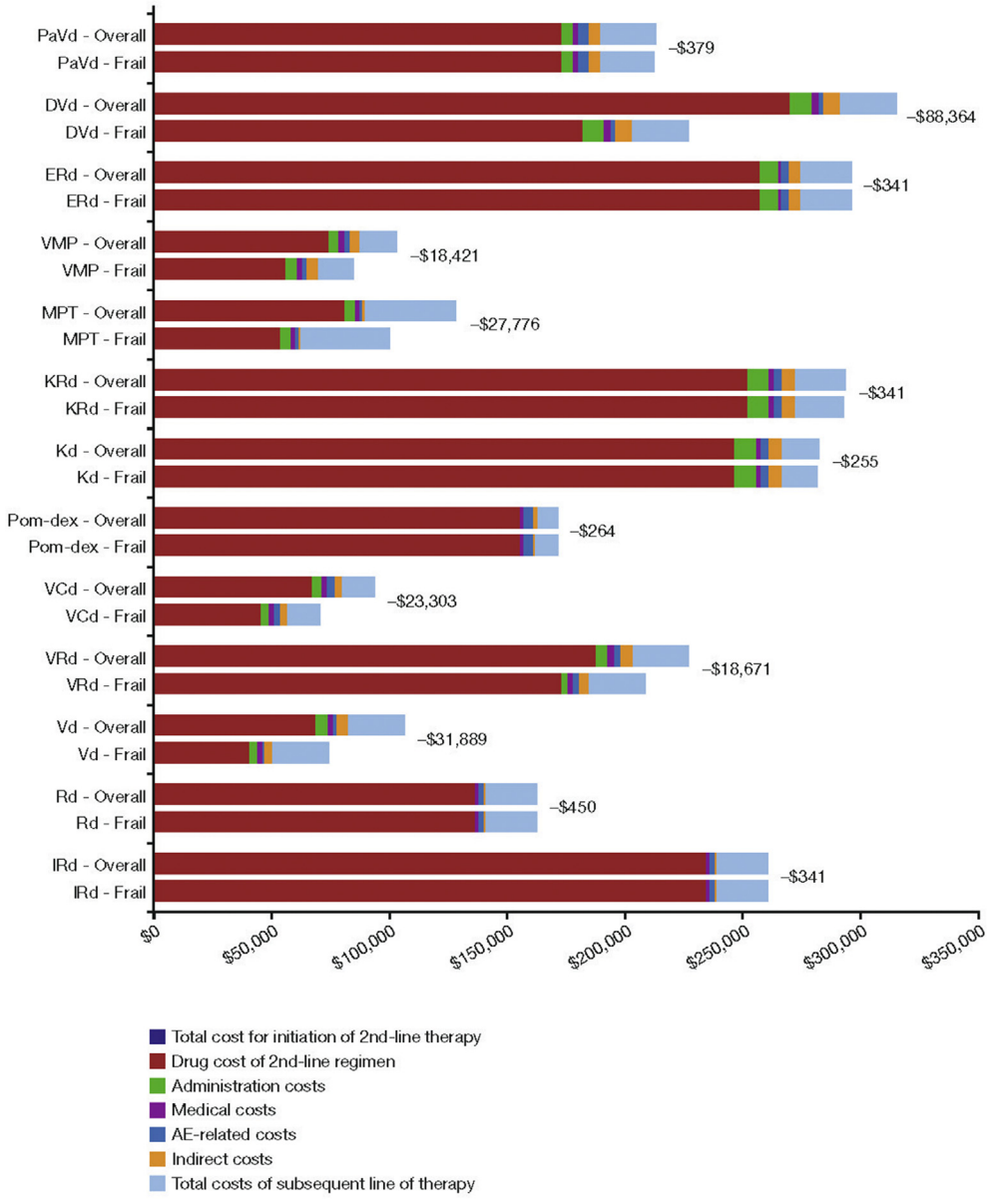

Figure 3. Annual differences in cost elements between the frail subgroup model and the overall cost model; cost offsets in frail patients are shown for each regimen. (AE = adverse event; DVd = daratumumab-bortezomib-dexamethasone; ERd = elotuzumab-lenalidomide-dexamethasone; IRd = ixazomib-lenalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; MPT = melphalan-prednisone-thalidomide; PaVd = panobinostat-bortezomib-dexamethasone; Pom-dex = pomalidomide-dexamethasone; Rd = lenalidomide-dexamethasone; VCd = bortezomib-cyclophosphamide-dexamethasone; Vd = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VRd = bortezomib-lenalidomide-dexamethasone.)

DISCUSSION

The findings of this analysis, based on a modelled, guideline-defined RRMM treatment journey,[13–19] found that among the multiple treatment options for patients in this setting, triplet regimens that incorporated combinations of 2 new agents are associated with the highest annual costs (>$200,000), primarily because of the cost of the agents themselves. However, excluding the acquisition costs of these drugs, the differences in the total cost of the treatment journey between regimens were driven primarily by administration costs, AE-related costs, and indirect costs. Consequently, the all-oral regimens were estimated to have lower total costs than Kd, KRd, ERd, and DVd, because the latter regimens require intravenous or subcutaneous infusion and, in all cases except Kd, are associated with greater direct costs of AE management related to their safety profiles. In the TOURMALINE-MM1 (A Phase III Study Comparing Oral Ixazomib Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma) Phase III study,[38] the triplet IRd regimen was found to be associated with limited additional toxicity compared with the doublet placebo plus Rd regimen. This is reflected because AE-related costs and costs of subsequent therapy of these 2 regimens are similar in this cost model. For other regimens, this cost model analysis clearly highlights that elevated rates of AEs that are costly to manage, such as pneumonia,[7] febrile neutropenia,[7] deep vein thrombosis,[7] and renal failure, can result in higher non−drug-related direct costs.

An, important aspect of this cost model is that it considers indirect costs, that is, the burden on patient productivity and caregivers. Thus, the findings of the model highlight the patient and the caregiver impact with respect to the burden of treatment with each regimen. The model clearly indicates that all-oral regimens such as the triplet IRd and the doublets Rd and Pom-dex are associated with substantially lower indirect costs to patients because of the lower burden of outpatient clinic visits. For the other regimens, which require more frequent or longer durations of drug administration via subcutaneous or intravenous infusion, outpatient clinic visits are associated with higher indirect costs because of loss of productivity for the patient, travel costs to receive treatment, and the costs of caregiver support for these visits. Such logistic, geographic, and economic aspects of MM treatment were found to have a marked impact on patients' health-related QoL and to add to the burden of treatment, potentially affecting patients' ability to remain on long-term treatment.[9,11,12] Our model currently does not consider QoL, but this represents an area of potential interest for further research because QoL end points are being used increasingly in ongoing clinical trials in MM especially with new therapeutic agents.[47] This indirect cost profile of treatment for patients can contribute to the financial difficulty of undergoing therapy.[12] However, for oral therapies, although indirect costs are lower, it is also important to consider direct costs to patients − a recent analysis has found that these costs can be substantially reduced by a specialty pharmacy helping patients in securing funding and co-pay assistance.[48]

For the subgroup of patients with barriers to physician access, the indirect cost profile of treatment in our model was of particular relevance. Among these patients, distance to the hospital can be an important consideration, especially for patients who have the burden of visiting multiple clinics to receive treatment, consultations, and for other medical visits, and oral regimens may consequently be preferred in this subgroup. Oral regimens also appear preferable from the perspective of indirect costs in this subgroup, among whom the need for longer visits, journeys, and possibly overnight stays resulted in greater increases in indirect costs for intravenously or subcutaneously administered regimens. However, compliance with self-administered oral therapies is an important consideration from the physician perspective,[49] and additional monitoring to ensure treatment compliance may be required, not only in this subgroup of patients but more generally. Although pill diaries and journals are routinely used in the clinical trial setting with oral medications, we did not find evidence for the use of such techniques in routine clinical practice. In addition, although the cost model was not substantially affected by the presence of comorbidities, it is important to emphasize that comorbidities are important clinical considerations in the selection of treatment options for patients with RRMM. Some subgroups have an unmet need for additional options because of their

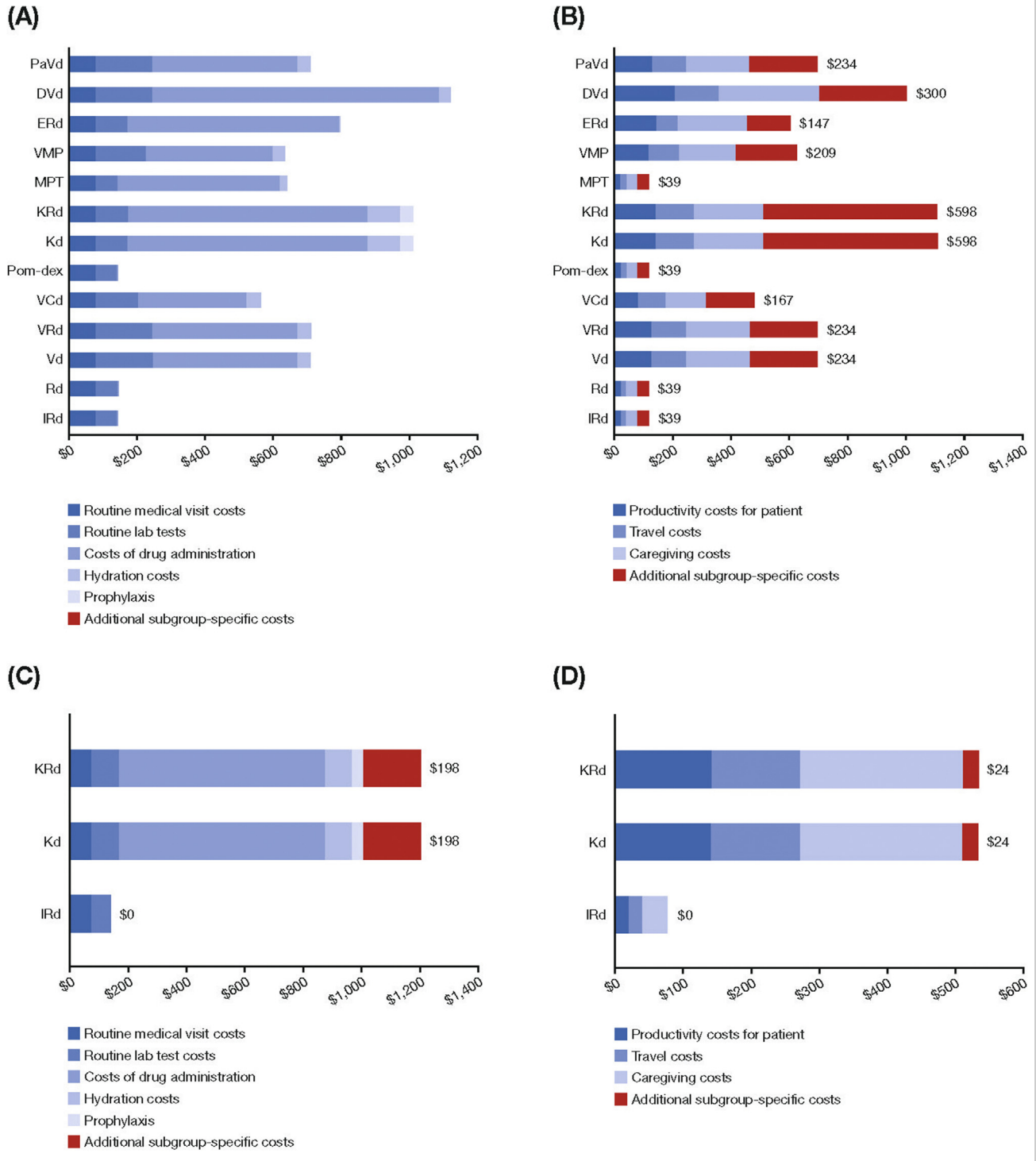

Figure 4. (A) Direct and (B) indirect costs of treatment, per 28-day cycle, in patients with barriers to physician access, by regimen. Additional indirect treatment costs (red bars) reflect the estimated requirement for 1 additional hour per visit and administration, travel costs based on a round-trip of 70 miles, and overnight stays for treatments administered on 2 consecutive days. (C) Direct and (D) indirect costs

comorbidities potentially precluding them from receiving a number of the currently available regimens.[50] In addition, although not considered in the present study, patient preferences must also be considered when selecting RRMM treatment options, for example, for oral versus intravenous administration; this is an area for further research.

Additional costs in patients with preexisting cardiac disease were seen primarily for carfilzomib-based regimens, which have been associated with a higher risk of cardiovascular AEs; thus, patients with cardiac disease require careful monitoring during carfilzomib treatment.[50–52] Similarly, additional costs in patients with PN were seen for bortezomib-based regimens, because PN is a key AE associated with bortezomib,[53] and additional costs in patients with renal disease were required for lenalidomide-based regimens because of the increased complexity of managing patients treated with such regimens and potentially increased AEs in this subgroup.[54]

Limitations

Our cost model analysis has a number of limitations. In particular, the rapidly evolving treatment landscape for RRMM, changes in clinical practice and guidelines, and the recent presentation and subsequent publication of new data on new agents and regimens, notably daratumumab,[55,56] has meant that some of the latest data from clinical studies are not captured in our model, the construction of which took place before these data were available. The regimens included in the model were selected at the time of model development, from discussions with hematologists/oncologists and a review of clinical studies available at the time, and no new information that became available after this time was incorporated (with the exception of updated data on AEs associated with DVd published in the CASTOR [Addition of Daratumumab to Combination of Bortezomib and Dexamethasone in Participants With Relapsed or Refractory Multiple Myeloma] trial, because the existing AE data on DVd were deemed inconsistent). Thus, the daratumumab plus Rd regimen was not considered in the model, because the pivotal trial for this regimen (POLLUX; A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma) was not reported until after model development. Furthermore, some regimens that were considered in the cost model may not be used as widely as others. For example, based on feedback from clinicians, geographical preference may play a role in how commonly PaVd is used across the United States. Moreover, with respect to the assumption for subsequent therapy after second-line treatment, information about the mix of therapies used to treat RRMM may have changed since the model was developed. However, the same weighted average of therapies was used across all regimens in the model; thus, the cost of subsequent lines of therapy is assumed to be the same across regimens (varying only according to discontinuation rates). Thus, this should not impact the cost for each regimen differentially.

Another limitation that may be perceived is that this analysis does not incorporate the differential efficacy of the various regimens as second-line treatment for RRMM. However, this cost offset analysis, by its nature, is intended only to provide comparative costs for the regimens included to help inform therapeutic choices. Relative efficacy also represents a critical, separate consideration in treatment selection. In the context of limited head-to-head Phase III clinical trials, a number of network meta-analyses have been reported recently for RRMM treatment options; the findings suggest daratumumab-based regimens as a preferred option based on clinical trial efficacy data alone, with the triplet regimens IRd, KRd, and ERd also offering substantial clinical benefit.[57–61] These findings, along with safety profile, costs, and various other factors

of treatment, per 28-day cycle, in patients with preexisting cardiac disease, in select regimens. (DVd = daratumumab-bortezomib-dexamethasone; ERd = elotuzumab-lenalidomide-dexamethasone; IRd = ixazomib-lenalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; MPT = melphalan-prednisone-thalidomide; PaVd = panobinostat-bortezomib-dexamethasone; Pom-dex = pomalidomide-dexamethasone; Rd = lenalidomide-dexamethasone; VCd = bortezomib-cyclophosphamide-dexamethasone; Vd = bortezomib-dexamethasone; VMP = bortezomib-melphalan-prednisone; VRd = bortezomib-lenalidomide-dexamethasone.)

should all be considered when selecting treatment options for RRMM; for example, prior regimens used in first-line therapy and the duration of treatment/response with these regimens may have an impact on the efficacy — and in some cases the safety profile/tolerability — of second-line treatment options for RRMM, and thus form another important consideration.

In addition, data on a number of the regimens included in our cost model are not available specifically for the setting of second-line treatment of patients with RRMM. Thus, in some cases, the model inputs incorporate information associated with treatment at later lines of therapy and in populations with different disease and prior therapy characteristics than the one under study. Our model is based on clinical trial data and assumes continuous treatment for a period of 12 months unless patients discontinue because of toxicity; in the real-world setting, treatment patterns for the regimens considered in our model may differ markedly between those observed in clinical trials.[62,63] Indeed, duration of therapy longer than 12 months and the use of autologous stem cell transplant in the relapse setting would substantially affect the costs of care, and it is a limitation of our treatment journey model that this more extensive and comprehensive analysis was beyond the scope of the present project. Nevertheless, rather than analyzing total absolute costs of second-line treatment, our model provides valuable information in determining the relative cost offsets between regimens over a 12-month continuous treatment period. With respect to AEs, a preselected comprehensive list was discussed with clinicians and included in the study. This list may have excluded specific AEs that were associated with certain regimens. For instance, hematologic AEs were considered separately rather than collectively in the model. As such, the cost of AEs associated with MPT may appear to be lower than expected, given collective hematologic AEs only were reported for this regimen and thus not included in the model. Another limitation of our model, with respect to indirect costs, is that caregiving costs were based on cost per hour and did not include additional costs such as parking costs. Caregiving costs may therefore be underestimated for patients treated in larger city centers, where parking costs may be more substantial.

Therefore, when considering these limitations, the total treatment cost derived using our model may not necessarily reflect the cost burden in real-world practice. Nevertheless, our model provides a means of comparing overall treatment costs across multiple different regimens using a comprehensive, standardized approach; our assumptions help with developing a comparative model, which would otherwise not be feasible, considering the heterogeneity in real-world practice. Our findings provide important information about differential direct costs and indirect cost burdens of these treatment regimens for patients with RRMM. Furthermore, these findings highlight the differential burden on the health care system of current routine management practices associated with intravenous/subcutaneous versus oral drug administration and may provide the stimulus for a discussion about the necessity of such practices, with the aim of reducing costs and burden while maintaining optimal patient care.

CONCLUSIONS

In conclusion, our cost model analyses highlight the differential direct and indirect costs associated with multiple regimens for the treatment of RRMM, including many recent new regimens. The results indicate the lower treatment burden and indirect costs associated with administering all-oral regimens compared with regimens that require frequent and/or lengthy subcutaneous or intravenous infusions.[64] These findings represent one of a number of important considerations when selecting treatment options for RRMM and, together with efficacy, safety profile, and various other factors, may help inform payer and patient therapeutic choices.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of Patrick Lefebvre and Jonathan Fortier of Analysis Group to the analyses reported in this article. The authors also acknowledge Steve Hill of FireKite, an Ashfield company, part of UDG Healthcare plc, for writing support during the development of this article, which was funded by Millennium Pharmaceuticals Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and complied with Good Publication Practice 3 ethical guidelines (Battisti et al. *Ann Intern Med*. 2015;163:461–464).

S. Ailawadhi and M.S. Duh conceived and/or designed the work; M. DerSarkissian, M.S. Duh, M.-H. Lafeuille, and G. Posner acquired data; S.

Ailawadhi, M. DerSarkissian, M.-H. Lafeuille, and G. Posner analyzed data; S. Ailawadhi, M. DerSarkissian, M.S. Duh, M.-H. Lafeuille, and G. Posner interpreted the results; all authors drafted/reviewed and revised the manuscript; all authors approved the final manuscript. Apart from the listed authors, no representatives of the sponsor were involved in the analyses or the writing of this manuscript.

CONFLICTS OF INTEREST

This work was funded by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. S. Ailawadhi is a Consultant for Takeda, Amgen, and Novartis and has received research funding from Pharmacyclics. M. DerSarkissian, M.S. Duh, M.-H. Lafeuille, and G. Posner are employees of Analysis Group, Inc, which has received research funds from Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. S. Ralston is an employee of Sirius Market Access, which has received research funds from Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. E. Zagadailov and A. Ba-Mancini are employees of Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. R. Rifkin has attended advisory boards for Amgen (Onyx), Celgene, and Takeda. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary Table S1. Treatment regimens and associated costs for RRMM included in the cost model.

Regimen	Drugs	Cycle length	Unit cost[a] per day of treatment	Cycle cost per agent	Cycle cost	28 days equivalent costs
Rd[1]	**Lenalidomide** 25 mg per day on days 1—21 of each 28-day cycle	28 days	$597.22	$12,541.59	$12,561.69	**$12,561.69**
	Dexamethasone 40 mg per day on days 1, 8, 15 and 22 of each 28-day cycle		$5.03	$20.11		
Vd[2]	**Bortezomib**: 1.3 mg/m^2 twice weekly (on days 1, 4, 8, and 11) for 2 out of 3 weeks (21-day cycle)	21 days	$1190.80	$4763.20	$4783.31	**$6377.75**
	Dexamethasone: 40 mg on days 1, 4, 8, and 11		$5.03	$20.11		
VRd[3]	**Bortezomib**: 1.3 mg/m^2 on days 1, 4, 8, and 11 of 21 day cycle	21 days	$1190.80	$4763.20	$13,144.37	**$17,525.82**
	Lenalidomide: 25 mg/day on days 1 through 14		$597.22	$8361.06		
	Dexamethasone 40 mg per day on days 1, 4, 8 and 11 of each 21-day cycle		$5.03	$20.11		
VCd[4]	**Bortezomib**: 1.5 mg/m^2 weekly (on days 1, 8, 15, and 22)	28 days	$1374.00	$5496.00	$5944.16	**$5944.16**
	Cyclophosphamide: 300 mg/m^2, weekly (on days 1, 8, 15, and 22)		$107.01	$428.05		
	Dexamethasone: 40 mg weekly (on days 1, 8, 15, and 22)		$5.03	$20.11		
Pom-dex[5]	**Pomalidomide**: 4 mg per day on days 1—21 of each 28-day cycle	28 days	$640.47	$13,449.80	$13,469.91	**$13,469.91**
	Dexamethasone: 40 mg per day on days 1, 8, 15, and 22 of each 28-day cycle		$5.03	$20.11		
Kd[6]	**Carfilzomib**: 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16 in 28-day cycles	28 days	$3680.13	$22,080.80	$22,095.88	**$22,095.88**
	Dexamethasone: 20 mg/day on days 1, 2, 8, 9, 15, and 16 in 28-day cycles		$2.51	$15.08		

Supplementary Table S1. (*Continued*)

Regimen	Drugs	Cycle length	Unit cost[a] per day of treatment	Cycle cost per agent	Cycle cost	28 days equivalent costs
MPT[7]	**Melphalan**: 4 mg/m^2 on days 1 through 7	28 days	$45.28	$316.97	$8088.08	**$8088.08**
	Prednisone: 40 mg/m^2 on days 1 through 7		$0.53	$3.70		
	Thalidomide: 100 mg/day continuously		$277.41	$7767.41		
VMP[8]	**Bortezomib**: 1.3 mg/m^2 on days 1,4,8,11,22,25,29,32	42 days	$1190.80	$9526.40	$9937.11	**$6624.74**
	Melphalan: 9 mg/m^2 on days 1 through 4		$101.88	$407.53		
	Prednisone: 60 mg/m^2 on days 1 through 4		$0.79	$3.17		
KRd[9]	**Carfilzomib**: 27 mg/m^2 on days 1, 2, 8, 9, 15, and 16 in 28-day cycles	28 days	$1774.35	$10,646.10	$23,202.77	**$23,202.77**
	Lenalidomide: 25 mg/day on days 1 through 21		$597.22	$12,541.59		
	Dexamethasone: 20 mg/day on days 1, 2, 8, 9, 15, and 16 in 28-day cycles		$2.51	$15.08		
IRd[10]	**Ixazomib**: 4 mg on days 1, 8, and 15 in 28-day cycles	28 days	$3006.00	$9018.00	$21,579.69	**$21,579.69**
	Lenalidomide: 25 mg/day on days 1 through 21		$597.22	$12,541.59		
	Dexamethasone: 40 mg/day on days 1, 8, 15, and 22		$5.03	$20.11		
ERd[11]	**Elotuzumab**: 10 mg/kg on days 1, 8, and 15 in 28-day cycles	28 days	$3725.46	$11,176.37	$23,738.06	**$23,738.06**
	Lenalidomide: 25 mg/day on days 1 through 21		$597.22	$12,541.59		
	Dexamethasone: 28 mg plus 8 mg IV on Elo dosing days, or 40 mg once weekly		$5.03	$20.11		
DVd[12]	**Daratumumab**: 16 mg/kg IV: weekly ×10, q3w until end of Vd, then q4w until disease progression	21 days	$4703.77	$14,111.30	$18,894.61	**$25,192.81**
	Bortezomib: 1.3 mg/m^2 twice weekly (days 1, 4, 8, and 11) for 2 out of 3 weeks (21-day cycle)		$1190.80	$4763.20		

(*continued on next page*)

Supplementary Table S1. (*Continued*)

Regimen	Drugs	Cycle length	Unit cost[a] per day of treatment	Cycle cost per agent	Cycle cost	28 days equivalent costs
	Dexamethasone 40 mg per day on days 1, 4, 8 and 11 of each 21-day cycle		$5.03	$20.11		
PaVd[13]	**Panobinostat**: 20 mg, on days 1, 3, 5, 8, 10, and 12	21 days	$1222.22	$7333.34	$12,116.65	**$16,155.53**
	Bortezomib: 1.3 mg/m^2 on days 1, 4, 8, and 11		$1190.80	$4763.20		
	Dexamethasone: 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12		$2.51	$20.11		

[a] Source of costs: Truven Health Analytics, Micromedex Solutions. Red Book, http://sites.truvenhealth.com/redbook/online/. Accessed on February 13, 2017.

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Supplementary Table S2. Summary of medical and laboratory costs used in the cost model.

Count and item name	CPT code	Cost ($)
Medical visits		
1 outpatient visit	99213	77.01
Laboratory tests		
1 complete blood count	85025	11.20
1 blood testing-chemistry panel	82565; 84520; 82310	20.50
1 blood testing-FREELITE® test	83883	19.58
1 blood testing-immunofixation	86334	32.18
1 blood testing-serum protein electrophoresis	84165	15.47
1 bone testing - X-rays	77075	92.58
1 bone marrow aspirate	38220	65.81
1 bone marrow biopsy	38221	81.32
1 serum albumin	82040	7.13
1 serum lactate dehydrogenase	83615	8.69
1 serum β2 microglobulin	82232	23.30
1 urine testing - immunofixation	86335	42.28
1 urine testing - protein electrophoresis	84166	25.69
Pre-screening laboratory tests, carfilzomib regimens		
1 transthoracic echocardiogram	93307	139.24
1 natriuretic peptide	83880	234.99
1 troponin serum level	84484	141.64
1 hemoglobin A1c	83036	13.98

Supplementary Table S3. Summary of prophylaxes, pre-medication, and administration costs used in the model.

Pre-Medication/Prophylaxes	Dosage	Cost per unit ($)
Enoxaparin	40 mg	$17.82
Valacyclovir	500 mg	$2.75
Aspirin	81 mg or 325 mg	$0.02
Acyclovir	400 mg	$0.66
Dexamethasone	4 mg	$0.11
Sulfamethoxazole /trimethoprim	400/80 mg	$0.13
Pre-medication	Methylprednisolone 50 mg	$4.45
	Diphenhydramine 50 mg	$0.06
	Acetaminophen 1000 mg	$0.35

Administration costs	**CPT code**	**Cost ($)**
1 chemotherapy administration for each chemotherapy infusion (subcutaneous)	96409	79.67
1 chemotherapy administration for each chemotherapy infusion (intravenous)	96409	117.52
1 hydration administration	96361	15.89
Additional infusion hour	96415	29.98

Supplementary Table S4. Summary of AE costs per incidence used in the cost model.

AE	Cost per incidence ($)	AE	Cost per incidence ($)
Anemia	997.84	Leukopenia	2063.16
Arrhythmia	660.16	Lymphopenia	2063.16
Asthenia	821.68	Muscle spasms	821.68
Cardiac failure	2191.91	Muscle weakness	821.68
Constipation	220.43	Nausea	1227.49
Deep vein thrombosis	32,545.12	Neuralgia	27.67
Diarrhea	3138.19	Neuropathy	27.67
Dyspnea	590.33	Neutropenia	171.09
Fatigue	821.68	Peripheral neuropathy	1167.78
Febrile neutropenia	13,614.91	Pneumonia	15,294.82
Gastrointestinal	181.80	Pulmonary hypertension	9616.62
Hyperglycemia	342.27	Rash-related	150.74
Hypokalemia	287.41	Renal failure	5755.16
Hyponatremia	143.60	Thrombocytopenia	171.09
Hypophosphatemia	143.60	Upper respiratory tract infection/Pulmonary-related	369.73
Infections	2207.46	Urinary tract Infection	120.57
Ischemic heart disease	2191.91	Vomiting	1227.49

Supplementary Table S5. Summary of indirect costs — productivity loss, transportation, caregiving costs — used in the cost model.

Indirect cost	Rate/unit cost	Cost ($)
Productivity costs — hours lost (regimen)	**Wage per hour***	**Cost of income ($)**
3 (Rd, Pom-dex, MPT, IRd)	6.69	20.07
19 (Vd, VRd, PaVd)	6.69	127.11
21 (Kd, KRd, ERd)	6.69	140.49
12 (VCd)	6.69	80.28
17 (VMP)	6.69	113.73
31 (DVd)	6.69	207.39
Transportation costs — round-trips taken (regimen)	**Cost per trip†**	**Cost ($)**
1 (Rd, Pom-dex, MPT, IRd)	18.52	18.52
6 (Vd, VRd, PaVd, VMP)	18.52	111.12
5 (VCd)	18.52	92.60
7 (Kd, KRd)	18.52	129.64
4 (ERd)	18.52	74.08
8 (DVd)	18.52	148.16
Caregiving costs — hours served (regimen)	**Rate per hour‡**	**Cost ($)**
3 (Rd, Pom-dex, MPT, IRd)	11.19	33.57
19 (Vd, VRd, PaVd)	11.19	212.61

Supplementary Table S5. (*Continued*)

Indirect cost	Rate/unit cost	Cost ($)
12 (VCd)	11.19	134.28
17 (VMP)	11.19	190.23
21 (Kd, KRd, ERd)	11.19	234.99
31 (DVd)	11.19	346.89

*US mean wage of all jobs. †Based on round-trips[14] for pre-screening medical visits and laboratory tests at initiation of second-line therapy, plus one round-trip for an outpatient visit during each cycle of treatment and one round-trip per drug administration. ‡Using the US mean wage of a home health aide.

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Supplementary Table S6. Regimen discontinuation rates used in the cost model.

Regimen	Discontinuation rate due to AEs	Regimen	Discontinuation rate due to AEs
Rd	20%	VMP	15%
Vd	22%	KRd	20%
VRd	22%	IRd	20%
VCd	12%	ERd	20%
Pom-dex	9%	DVd	22%
Kd	15%	PaVd	22%
MPT	35%		

Supplementary Table S7. Direct and indirect costs associated with initiation and administration of a subsequent line of therapy used in the cost model; based upon a weighted average of the following regimens: Pom-dex (38%), Kd (31%), KRd (10%), VCd, VRd, Vd, and Rd (each 4%), and other treatments (5%; proportionally reassigned to the subsequent lines of therapy shown above).

Cost type	Cost category	Specific costs	Cost ($)
Initiation of subsequent line of therapy			
Direct costs	Pre-screening visit	Medical visit	77.01
		Laboratory	505.82
		Premedication	0.00
Indirect costs		Productivity loss	60.25
	Transportation	Travel	55.56
		Caregiving	100.73
Total			799.36

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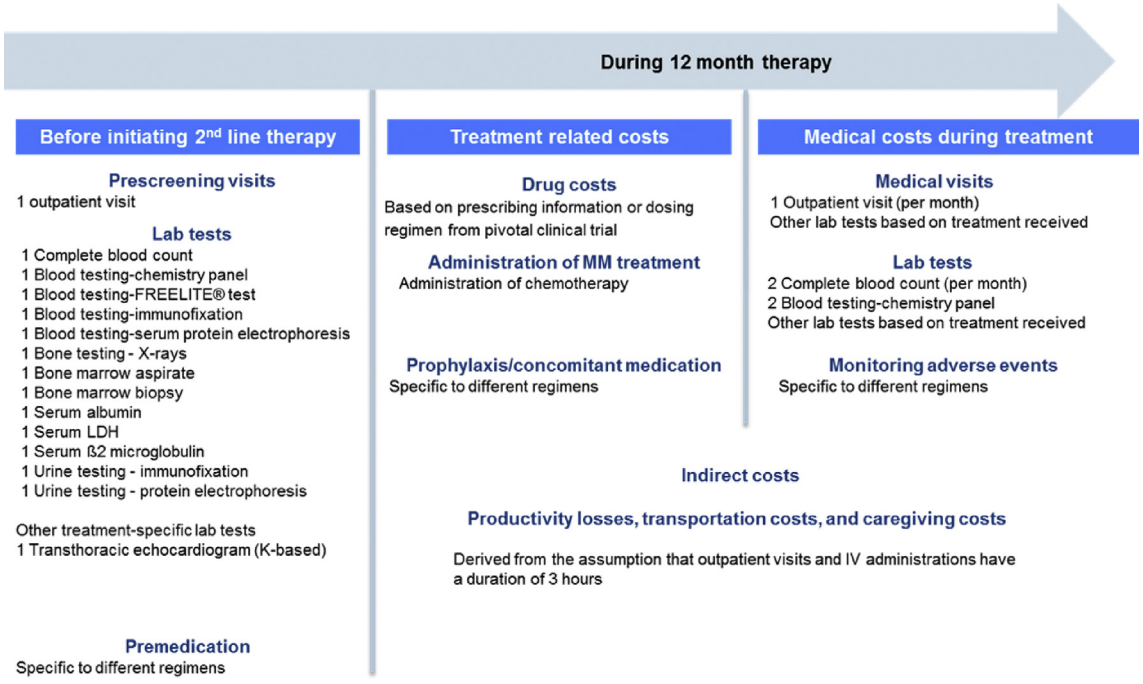
Supplementary Table S7. (*Continued*)

Cost type	Cost category	Specific costs	Cost ($)
Costs during subsequent line of therapy, excluding drug costs			
Direct costs	Drug-related	Prophylaxes	21.09
		Administration	353.48
		Hydration	41.15
	Medical	Routine visit	165.67
	AE	AE treatment	301.34
	Additional first-cycle costs		118.16
Indirect costs		Productivity loss	85.31
	Transportation	Travel	79.46
		Caregiving	142.64
Total			1308.30



Supplementary Figure S1. Treatment pathway of patients with RRMM.