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Cost-Effectiveness of First-Line Versus Second-Line Use of Daratumumab in Older, Transplant-Ineligible Patients With Multiple Myeloma

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abstract

PURPOSE The MAIA trial found that addition of daratumumab to lenalidomide and dexamethasone (DRd) significantly prolonged progression-free survival in transplant-ineligible patients with newly diagnosed multiple myeloma, compared with lenalidomide and dexamethasone alone (Rd). However, daratumumab is a costly treatment and is administered indefinitely until disease progression. Therefore, it is unclear whether it is cost-effective to use daratumumab in the first-line setting compared with reserving its use until later lines of therapy.

METHODS We created a Markov model to compare healthcare costs and clinical outcomes of transplant-ineligible patients treated with daratumumab in the first-line setting compared with a strategy of reserving daratumumab until the second-line. We estimated transition probabilities from randomized trials using parametric survival modeling. Lifetime direct healthcare costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated for first-line daratumumab versus second-line daratumumab from a US payer perspective.

RESULTS First-line daratumumab was associated with an improvement of 0.52 QALYs and 0.66 discounted life-years compared with second-line daratumumab. While both treatment strategies were associated with considerable lifetime expenditures ($1,434,937 *v* $1,112,101 in US dollars), an incremental cost of $322,836 for first-line daratumumab led to an ICER of $618,018 per QALY. The cost of daratumumab would need to be decreased by 67% for first-line daratumumab to be cost-effective at a willingness-to-pay threshold of $150,000 per QALY.

CONCLUSION Using daratumumab in the first-line setting for transplant-ineligible patients may not be cost-effective under current pricing. Delaying daratumumab until subsequent lines of therapy may be a reasonable strategy to limit healthcare costs without significantly compromising clinical outcomes. Mature overall survival data are necessary to more fully evaluate cost-effectiveness in this setting.

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INTRODUCTION

Multiple myeloma is the second most common hematological malignancy in the United States.[1] Patients with myeloma that are ineligible for autologous stem-cell transplantation as a result of age or comorbidities are managed with multiagent regimens, which traditionally include immunomodulatory drugs, alkylating agents, proteasome inhibitors, and/or glucocorticoids.[2,3] Although multiple myeloma is generally an incurable disease, these regimens have led to meaningful responses in the transplant-ineligible population, with a median overall survival (OS) of approximately 5 years from the time of diagnosis.[4]

The addition of daratumumab, a novel CD38-targeted monoclonal antibody, to standard-of-care regimens has been shown to significantly prolong progression-free survival (PFS) in patients with relapsed or refractory (R/R) multiple myeloma.[5-7] Given the promising activity seen in R/R patients, daratumumab has recently undergone testing in the first-line setting.[8-10] The phase III MAIA trial randomly assigned transplant-ineligible patients with newly diagnosed multiple myeloma to daratumumab, lenalidomide, and dexamethasone (DRd) or lenalidomide and dexamethasone alone (Rd).[8] After a median follow-up of 28 months, DRd was found to reduce the risk of disease progression by 44% compared with Rd, with estimated 30-month PFS rates of 70.6% and 55.6%, respectively.[8] Patients in both groups received treatment until disease progression or toxicity, with 67.6% of patients in the DRd arm still on treatment at the time of data cutoff.[8] Based on such clinical trial data, daratumumab-containing triplet regimens are now category 1 National Comprehensive Cancer Network recommendations for the treatment of newly

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The phase III MAIA trial found that addition of daratumumab, a CD38-targeted monoclonal antibody, to lenalidomide and dexamethasone prolonged progression-free survival in transplant-ineligible patients with previously untreated multiple myeloma. However, daratumumab is a costly drug, priced at nearly $6,500 per infusion; as a result, it is unclear whether it provides sufficient value in this clinical setting. This study sought to assess the cost-effectiveness of using daratumumab in the first-line setting for transplant-ineligible patients, compared with waiting until the second-line.

Knowledge Generated

First-line use of daratumumab was not cost-effective compared with second-line use, with an incremental cost-effectiveness ratio of $618,018 in US dollars per quality-adjusted life-year. The price of daratumumab would need to be decreased by at least 67% for first-line daratumumab to be cost-effective.

Relevance

This study suggests that significant price reduction would be required for daratumumab to provide sufficient value in the first-line setting for transplant-ineligible patients with multiple myeloma.

diagnosed and R/R disease and represent the new standard-of-care.[11]

Although the addition of daratumumab to Rd in the MAIA trial significantly prolonged PFS, this treatment is associated with significant cost. Daratumumab itself is priced at nearly $6,500 in US dollars (USD) per infusion, and the total cost of treatment with regimens such as DRd can be substantial, particularly when considering the potential for prolonged treatment duration as well as the high cost of lenalidomide and other novel myeloma therapies.[12-14] Therefore, we hypothesized that use of daratumumab in the first-line setting for transplant-ineligible patients with multiple myeloma would not be a cost-effective treatment strategy when compared with reserving its use until the second-line.

METHODS

Patients and Intervention

We constructed a cost-effectiveness model to compare the strategy of using daratumumab in the first-line setting with reserving daratumumab until the second-line. Patients entering our model mirrored the cohort enrolled in the MAIA trial comparing DRd with Rd alone.[8] Patients were a median age of 73 years, 14.3% of patients had a high-risk cytogenetic profile, and all patients were ineligible for stem-cell transplantation as a result of age (> 65 years) or comorbidities.

Model Construction

Our analysis was based on a Markov model (Fig 1, Data Supplement, online only). Individuals entered the model with newly diagnosed multiple myeloma and received either DRd or Rd.[8] Individuals who progressed in the DRd arm subsequently received carfilzomib and dexamethasone (Kd),[7] while those progressing in the Rd arm subsequently received daratumumab, carfilzomib, and dexamethasone (DKd).[7] Third and later lines of therapies were identical between the DRd and Rd arms, including pomalidomide and dexamethasone (Pd)[15] and selinexor and dexamethasone (Sd)[16] as third-line and fourth-line therapies, respectively. Dosing and administration schedules for each line of treatment were based on the respective clinical trial.[7,8,15,16] Patients who progressed following treatment with Sd entered a best supportive care health state before death.

We used a 1-month Markov cycle and estimated the cost and utility associated with each treatment strategy over a lifetime horizon. The outputs of the model were used to calculate an incremental cost-effectiveness ratio (ICER), which represents the cost in 2020 USD for each additional quality-adjusted life-year (QALY) gained as a result of treatment. Both cost and utility were discounted at a rate of 3% annually.[17] Our analysis was conducted from a US payer perspective with a willingness-to-pay threshold of $150,000 (USD) per QALY.[18] The Markov model was constructed using TreeAge Pro (TreeAge Software, Williamstown, MA), and additional statistical analyses were performed using R[19] and STATA (StataCorp, College Station, TX). Model validation was performed following the International Society for Pharmacoeconomics and Outcomes Research guidelines[20] (Data Supplement).

Transition Probabilities

Base-case estimates for transition probabilities are provided in Table 1. Monthly transition probabilities for disease progression were derived from the respective clinical trial using standard extrapolation techniques.[21,22] Briefly, individual patient level data were recreated from the PFS Kaplan-Meier curves and at-risk tables of each trial. These recreated survival data were then fit to several parametric functions (Exponential, Weibull, Gompertz). For DRd, DKd, Pd, and Sd, we selected the appropriate parametric distribution based on statistical measures of goodness-of-fit (Akaike information criterion and Bayesian information criterion) and clinical experience (Data Supplement).

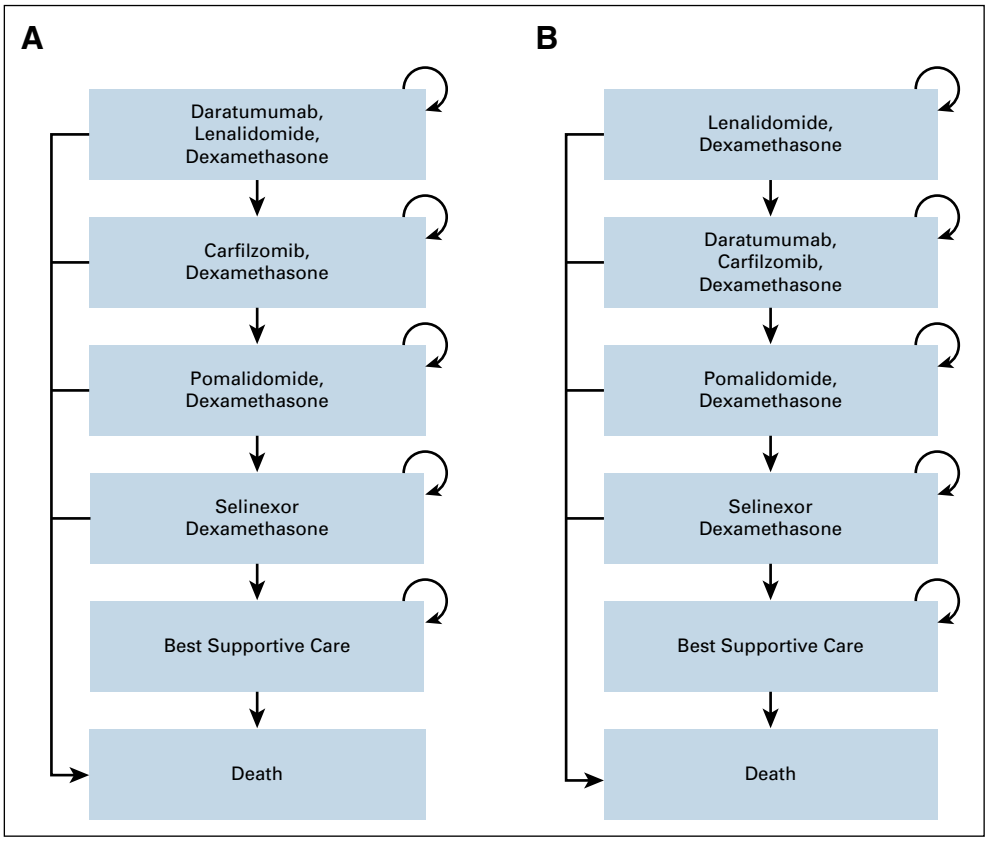

FIG 1. Treatment sequences used in the Markov model. (A) Treatment sequence for individuals who receive daratumumab in the first-line setting. (B) Treatment sequence for individuals who receive daratumumab in the second-line setting.

Progression rates for Rd and Kd were calculated based on the reported hazard ratios (HRs) from the MAIA and CANDOR trials, respectively.[7,8]

We also incorporated discontinuation of treatment as a result of adverse events (AEs) in our model, with transition probabilities derived from the literature. For patients on DRd, we separately modeled discontinuation of lenalidomide alone, as a significant proportion of patients in the MAIA trial discontinued lenalidomide while continuing daratumumab and/or dexamethasone.[8] For first-line regimens, discontinuation as a result of AEs was highest during the first 6 months of treatment, accounting for the greater frequency of severe AEs within that timeframe.[2] Transition probabilities for death during each line of treatment were estimated by combining an age-matched background mortality rate from US Life Tables[23] with data regarding fatal treatment-related AEs from each clinical trial.[7,8,15,16] Finally, the probability of death from the best supportive care health state was estimated based on mortality data for relapsed or refractory myeloma patients.[24]

Costs

Costs incorporated in the model are outlined in Table 2. The cost of intravenous (IV) medications, including daratumumab and carfilzomib, was 106% of the average sales price.[12] We assumed a total body surface area of 1.7 m^2 and accounted for drug wastage by rounding up to the next full single-use vial size available for each dose administered.[25,26] Costs of drug administration were based on the 2020 Centers for Medicare & Medicaid Services Physician Fee Schedule,[27] with the length of drug infusion based on US Food and Drug Administration package inserts.

The costs of oral medications, including lenalidomide, pomalidomide, and selinexor, were derived from the Medicare Plan-Finder tool using methodology from Memorial Sloan Kettering's Drug Pricing Lab[28,29] (Data Supplement). Recent studies have demonstrated that the majority of patient cost-sharing for oral cancer therapies is covered by pharmaceutical patient-assistance programs[30,31]; therefore, we did not include patient out-of-pocket costs in our oral treatment calculations. Rather, our modeled costs reflect what Medicare and Part D prescription plans reimburse when filling these oral medications.

Patients were assumed to receive monthly routine follow-up, which consisted of a physician office visit and standard laboratory tests.[32,33] We also incorporated the cost of severe AEs in our model, including cytopenias and infection; each grade $\geq$ 3 AE was assumed to result in an inpatient admission, with costs based on Medicare diagnosis-related

TABLE 1. Model Clinical Parameters

Result or Transition	Estimate	Range	Study or Data Source
PFS for DRd	Weibull: $\lambda = 0.0194709$, $\kappa = 0.8385565$	—	Facon et al[8]
HR for DRd (Rd as reference)	0.56	0.43-0.73	Facon et al[8]
PFS for DKd	Weibull: $\lambda = 0.0415401$, $\kappa = 0.845898$	—	Dimopoulos et al[7]
HR for DKd (Kd as reference)	0.63	0.46-0.85	Dimopoulos et al[7]
PFS for DVd	Exponential: $\lambda = 0.0265072$	—	Mateos et al[39]
HR for DVd (Vd as reference)	0.22	0.15-0.32	Mateos et al[39]
PFS for Pd	Exponential: $\lambda = 0.102912$	—	Attal et al[15]
PFS for Sd	Weibull: $\lambda = 0.0960114$, $\kappa = 1.404122$	—	Chari et al[16]
Proportion of first-line discontinuation events as a result of AE that occur within first 6 months of treatment	37.3%	18.7%-55.6%	Benboubker et al[2]
Probability of treatment discontinuation as a result of AE			
DRd	7.4%	3.7%-11.1%	Facon et al[8]
Rd	16.2%	8.1%-24.3%	Facon et al[8]
Lenalidomide only, DRd arm	13.5%	6.8%-20.3%	Facon et al[8]
DKd	22.4%	11.2%-33.6%	Dimopoulos et al[7]
Kd	24.8%	12.4%-37.2%	Dimopoulos et al[7]
DVd	10.0%	5.0%-15.0%	Mateos et al[39]
Vd	9.0%	4.5%-13.5%	Mateos et a[39]
Pd	12.8%	6.4%-19.2%	Attal et al[15]
Sd	18.0%	9.0%-27.0%	Chari et al[16]
Probability of treatment mortality as a result of AE			
DRd	6.9%	3.5%-10.4%	Facon et al[8]
Rd	6.3%	3.2%-9.5%	Facon et al[8]
DKd	1.6%	0.8%-2.4%	Dimopoulos et al[7]
Kd	0.0%	—	Dimopoulos et al[7]
DVd	2.0%	1.0%-3.0%	Palumbo et a[57]
Vd	0.8%	0.4%-1.2%	Palumbo et a[57]
Pd	1.3%	0.7%-2.0%	Attal et al[15]
Sd	1.6%	0.8%-2.5%	Chari et al[16]
Probability of death from BSC, monthly	20.6%	10.3%-30.9%	Kumar et al[24]
Probability of background death	—	—	Arias et al[23]
Discount rate	3%	1.5%-6%	Sanders et al[17]
Median starting age of cohort	73	65-81	Facon et al[8]

Abbreviations: AE, adverse event; BSC, best supportive care; DKd, daratumumab, carfilzomib, and dexamethasone; DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; HR, hazard ratio; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; Rd, dexamethasone; Sd, selinexor and dexamethasone; Vd, bortezomib and dexamethasone.

group-based payments[34] (Data Supplement). Finally, the costs of end-of-life care were based on prior work.[35] All costs were converted to 2020 USD using the personal consumption expenditure – health index.[36]

Utilities

Our utility values were based on a study by Hatswell et al, which used metaregression to synthesize quality-of-life measurements for multiple myeloma patients from several studies across multiple lines of therapy.[37] In our base case, first-line therapy was associated with a utility of 0.659, second-line therapy had a utility of 0.620, third-line therapy had a utility of 0.606, and fourth-line therapy and best supportive care were assigned a utility of 0.494. QALYs were calculated by weighting patient survival based on utility estimates for each health state.

TABLE 2. Model Costs and Utilities

Model Parameter	Baseline (US$)	Range (US$)	Study or Data Source
Daratumumab, 16 mg/kg, per dose	6,497.40	—	J9145
Carfilzomib, 56 mg/m^2, per dose	3,757.90	—	J9047
Bortezomib, 1.3 mg/m^2, per dose	957.08	—	J9044
Dexamethasone, 20mg, per dose	5.84	—	J8540
Lenalidomide 25mg, 21 capsules, monthly	15,462.00	—	CMS Plan-Finder, DrugPricing Lab[29]
Pomalidomide 4mg, 21 capsules, monthly	17,672.29	—	CMS Plan-Finder, DrugPricing Lab[29]
Selinexor 20mg, 32 capsules, monthly	21,423.86	—	CMS Plan-Finder, DrugPricing Lab[29]
Routine office visit	113.68	106.46-153.71	CPT 99215
Chemotherapy IV infusion, first hour	142.55	122.39-189.18	CPT 96413
Chemotherapy IV infusion, additional hour	30.68	27.00-39.38	CPT 96415
Chemotherapy IV infusion, additional sequence	69.29	59.80-90.99	CPT 96417
Pre-infusion medication	12.30	—	Barnes et al[58]
Chemotherapy, SQ injection	80.12	69.07-105.81	CPT 96401
Complete blood count	7.77	—	CPT 85025
Comprehensive metabolic panel	10.56	—	CPT 80053
Serum electrophoresis	10.74	—	CPT 84165
Serum-free light chains	13.60	—	CPT 83883
Hospice	9,893.73	4,946.87-14,840.60	Fiala et al[35]

Utilities	QALY	Range	Study or Data Source
First-line treatment	0.659	0.591-0.734	Hatswell et al[37]
Second-line treatment	0.620	0.590-0.650	Hatswell et al[37]
Third-line treatment	0.606	0.561-0.630	Hatswell et al[37]
Fourth-line treatment, BSC	0.494	0.403-0.570	Hatswell et al[37]

Abbreviations: BSC, best supportive care; IV, intravenous; QALY, quality-adjusted life-year; SQ, subcutaneous.

Sensitivity Analysis

We incorporated sensitivity analyses to assess uncertainty in our model. During one-way sensitivity analyses, individual model parameters were varied across the ranges outlined in Tables 1 and 2 to determine their impact on the ICER. HRs and utility values were varied across their 95% CIs; other transition probabilities, including treatment discontinuation and mortality as a result of AEs, were varied within a 50% range. During probabilistic sensitivity analysis, each parameter was estimated using a distribution and we performed 10,000 Monte Carlo simulations, each time randomly sampling from the distribution of model inputs. Costs were described by γ distributions, median starting age by a normal distribution, and probabilities and utilities by β distributions.

We also incorporated four scenario analyses. In the first, we modeled the use of subcutaneous (SQ) daratumumab, rather than IV.[38] Since Medicare reimbursement rates for SQ daratumumab are not yet available, we conservatively assumed that the cost of each SQ daratumumab dose was identical to IV daratumumab. However, SQ does have shorter chair time, and our model therefore accounted for a lower cost of drug administration with SQ daratumumab compared with IV.[27] In the second scenario analysis, we assumed that a small percentage of patients (between 10% and 30%) would elect for best supportive care after progressing from second-line or third-line treatment, rather than receiving additional therapy with Pd and/or Sd. In the third scenario analysis, we included daratumumab, bortezomib, and dexamethasone (DVd) or bortezomib and dexamethasone (Vd) as the second-line treatments in the model rather than DKd or Kd, using updated data from the CASTOR trial (Data Supplement).[39] Since the relative efficacy of DVd versus DKd is not yet known, this scenario allowed us to ensure that our results remained consistent, regardless of the specific proteasome inhibitor used in the second-line setting. In our final scenario analysis, we assumed that the utility of first-line treatment with DRd was 20% higher than Rd alone (ie 0.791 compared with 0.659). Although preliminary data from the MAIA trial suggest similar utility values between both treatment arms,[40] this scenario allowed us to be as conservative as possible when estimating the cost-effectiveness of first-line daratumumab.

RESULTS

Base-Case Analysis

In our base-case analysis, use of daratumumab in the first-line setting was associated with an improvement of 0.52 QALYs and 0.66 discounted life-years (LYs) compared with reserving daratumumab until the second-line (4.87 *v* 4.34 QALYs and 7.47 *v* 6.80 LYs, respectively). However, first-line daratumumab was also associated with significantly greater lifetime individual healthcare costs ($1,434,937 *v* $1,112,101), leading to an ICER of $618,018 per QALY (Table 3).

Sensitivity Analysis

Our model was most sensitive to the HR for DRd relative to Rd (Fig 2). Increasing the HR from 0.56 to 0.73, which resulted in 4.87 versus 4.70 QALYs for first-line and second-line daratumumab, respectively, increased the ICER to $2,148,959 per QALY. On the other hand, decreasing the HR to 0.43, which resulted in 4.87 versus 4.02 QALYs, respectively, decreased the ICER to $364,780 per QALY. Other model parameters that had a significant impact on our estimated ICER included the median starting age of the cohort, the probability of DRd treatment discontinuation as a result of AEs, and the utility of first-line treatment. Of note, all ICERs during one-way sensitivity analyses remained above the willingness-to-pay threshold of $150,000 per QALY. Threshold analysis showed that the cost of daratumumab would need to be decreased by approximately 67%, 74%, and 81% for first-line daratumumab to be cost-effective at willingness-to-pay thresholds of $150,000 per QALY, $100,000 per QALY, and $50,000 per QALY, respectively. During probabilistic sensitivity analyses, 98% of iterations produced ICERs above the willingness-to-pay threshold of $150,000 per QALY (Fig 3).

In our first scenario analysis, incorporating SQ daratumumab rather than IV modestly reduced the ICER to $610,384 per QALY. In our second scenario analysis, we assumed that a fixed percentage of patients would receive BSC after progressing from second- or third-line treatment, rather than receiving additional therapy. This adjustment did not significantly change our results, with ICERs of $612,236 per QALY and $601,879 per QALY when modeling 10% and 30% of patients electing for best supportive care, respectively. In the third scenario analysis, we incorporated DVd and Vd as the second-line treatments in our model, rather than DKd and Kd. Here, use of daratumumab in the first-line setting was associated with an incremental cost of $539,070 ($1,369,665 *v* $830,595), an incremental effectiveness of 0.49 QALYs (4.68 *v* 4.18 QALYs), and an ICER of $1,096,715 per QALY compared with reserving daratumumab until the second-line. In the final scenario analysis, we assumed that use of daratumumab in the first-line setting provided a significant quality-of-life benefit. Even with this conservative assumption, first-line daratumumab was not found to be cost-effective, with an ICER of $231,387 per QALY.

Modeled Clinical Outcomes

In addition to calculating the cost and effectiveness of each treatment strategy, we also used our base-case model to estimate long-term clinical outcomes for patients. Median non–future-discounted OS was 7.50 years (interquartile range [IQR], 3.75-13.17) in the first-line daratumumab arm, compared with 6.75 years (IQR 3.58-11.33) in the delayed daratumumab arm (Data Supplement). The median duration of daratumumab exposure was significantly longer when used in the first-line setting compared with the second-line setting (53 months [IQR 18-119] *v* 17 months [IQR 7-35], respectively). Furthermore, the median duration of lenalidomide exposure was 46 months (IQR 17-89) for patients who received DRd, compared with 24 months (IQR 9-52) for patients who received Rd.

DISCUSSION

The MAIA trial demonstrated that addition of daratumumab to lenalidomide and dexamethasone in the first-line treatment of transplant-ineligible multiple myeloma significantly decreases the risk of disease progression.[8] However, since daratumumab is a high-cost treatment that is administered indefinitely until disease progression, its use in earlier lines of therapy can result in substantial cumulative healthcare expenditure compared with delaying its use to subsequent lines of therapy. Our model suggests that use of daratumumab in the first-line setting is unlikely to be cost-effective compared with reserving its use until the second-line, with an ICER of $618,018 per QALY. As a first-line therapy, our sensitivity analysis suggests that the price of daratumumab would need to be decreased substantially before it would meet commonly

TABLE 3. Base-Case Cost-Effectiveness Analysis

Strategy	Costs (USD)	Incremental Costs (USD)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER (USD/QALY)	ICER 95% CI (USD/QALY)
Baseline Model						PSA Model
First-line daratumumab	1,434,937	322,836	4.87	0.52	618,018	185,202 to Dominated
Second-line daratumumab	1,112,101	—	4.34		—	

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; USD, US dollars.

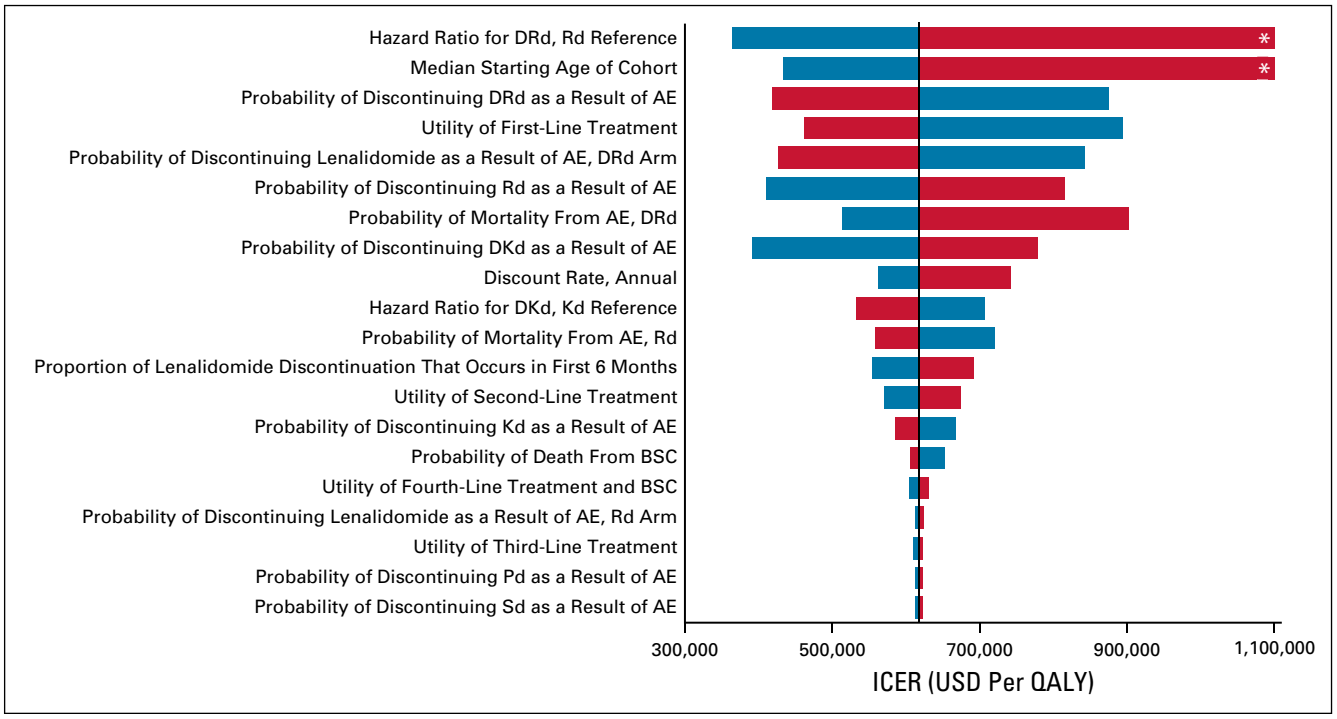

FIG 2. One-way sensitivity analysis. All model parameters with ranges in Tables 1 and 2 were varied during one-way sensitivity analyses. However, only parameters that produced greater than a $10,000/QALY change when evaluated across their entire range are included in the Tornado diagram. Blue represents the lower value in the range, whereas red represents the higher value. *ICER exceeds $1.1M(USD)/QALY. AE, adverse event; BSC, best supportive care; DKd, daratumumab, carfilzomib, and dexamethasone; DRd, daratumumab, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; Kd, carfilzomib and dexamethasone; QALY, quality-adjusted life-year; Rd, lenalidomide and dexamethasone; USD, US dollars.

accepted thresholds for cost-effectiveness for both cancer treatments and therapies for other diseases.[17,18]

Our model has several notable strengths. First, the majority of inputs used to populate the model were derived from large, randomized, phase III clinical trials.[7,8,15,39] Second, we incorporated contemporary multiagent regimens to reflect the most recent advances in the treatment of multiple myeloma, including the use of daratumumab, carfilzomib, bortezomib, and pomalidomide in the relapsed or refractory setting.[7,39] Third, our model incorporates treatment discontinuation because of AEs, including isolated lenalidomide discontinuation in the first-line setting,[8] as well as the costs associated with drug toxicity.

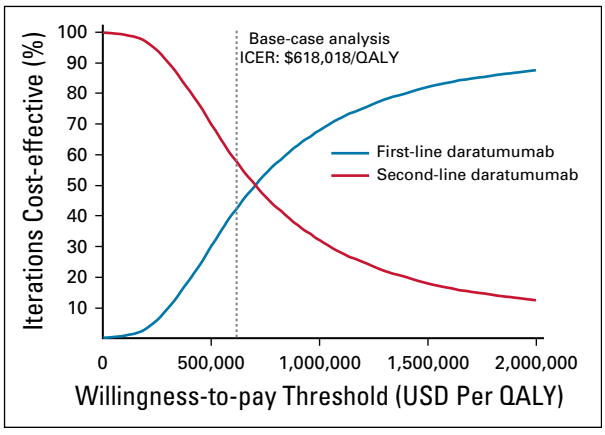

FIG 3. Cost-effectiveness acceptability curve. The results of the probabilistic sensitivity analysis are based on 10,000 iterations of the Markov model. QALY, quality-adjusted life-year; USD, US dollars.

To our knowledge, this is the first cost-effectiveness analysis of daratumumab in the first-line setting. Prior studies have assessed the economic value of daratumumab-containing regimens in patients with R/R myeloma; although the reported ICERs from these studies vary, many suggest that the addition of daratumumab to standard doublet regimens is unlikely to be cost-effective.[13,14,41] Zhang et al,[13] for instance, used clinical data from the POLLUX and CASTOR trials to evaluate the inclusion of daratumumab with lenalidomide- and bortezomib-containing regimens for R/R patients and calculated ICERs of $1,369,062 per QALY and $284,180 per QALY, respectively. The high cost of daratumumab-containing regimens is driven only in part by the acquisition cost of daratumumab; an equally important factor is the treat until progression approach for these combination therapies, which include other high-cost drugs such as lenalidomide and carfilzomib.

It is notable that in our base-case model, even the more cost-effective strategy of delaying daratumumab until the second-line setting results in average direct healthcare costs of over $1.1 million per patient. Prior studies have

brought attention to high costs associated with myeloma, which is only expected to worsen with the increased use of novel targeted therapies and the inclusion of triplet and/or quadruplet regimens as standard-of-care.[14,42-45] Apart from direct price reductions, strategies to curb the costs of multiagent regimens include the possibility of shorter courses of therapy or the possibility of dose reduction and/or treatment discontinuation in patients that achieve minimal residual disease–negative status.[42] Future trials that assess the safety of these approaches will be critical to develop more cost-effective treatment strategies for multiple myeloma.

Our results, combined with a number of prior cost-effectiveness studies that have demonstrated high ICERs for cancer drugs,[13,26,46] reinforce the need for alternative pricing schemes in oncology, such as indication-specific pricing,[47] value-based pricing,[48] or a subscription model.[49] A number of other countries have regulatory bodies, such as the National Institute for Health and Care Excellence in the United Kingdom, that oversee the approval and reimbursement of drugs based on the demonstrated economic value. By contrast, legal statutes in the United States compel its largest insurer, Medicare, to cover all approved cancer therapies, limiting negotiations with pharmaceutical companies.[50] As a result, the pricing of cancer drugs in the United States is often unrelated to their novelty or their relative improvement in OS, quality of life, or surrogate end points.[51] As the costs of cancer drugs continue to increase, there is a commensurate need for updated policy that can more rationally align the costs of novel therapeutics with their proven clinical efficacy.

Although our model has important strengths, there are limitations to consider. First, our model does not feature other first-line daratumumab-containing regimens that have been evaluated for patients with transplant-ineligible disease, including daratumumab, bortezomib, melphalan, and prednisone (Dara-VMP).[9] However, since Dara-VMP is rarely used in the United States, we chose to include DRd as the first-line daratumumab regimen in our model as it represents the more relevant treatment strategy for the US patient population. Second, we recognize that there are compelling triplet combinations, such as VRd[3] or VRd-lite,[52] that could have been used as the first-line comparator in our model, rather than Rd alone. However, direct comparisons between DRd and VRd or VRd–lite are not currently available, and we chose to avoid indirect comparisons across clinical trials as these methods rely on assumptions that would weaken the validity of our model. Furthermore, since VRd is more efficacious than Rd and the added costs of bortezomib are incurred only for a fixed-duration,[3] it is likely that use of VRd in our model rather than Rd would make first-line daratumumab even less cost-effective. Third, our study does not include elotuzumab- or isatuximab-based regimens in the relapsed or refractory setting, as the randomized trials that studied these treatments included very few patients who had previously received daratumumab.[15,53,54]

Fourth, modeling the cost of treatment with multiagent regimens relies on accurate data regarding discontinuation of treatment for reasons unrelated to disease progression. For instance, a significant portion of patients in the DRd arm of the MAIA trial discontinued lenalidomide but continued on daratumumab and dexamethasone[8]—such events would significantly alter the cumulative cost of treatment for these patients as lenalidomide acquisition costs are considerable. Our model estimates treatment discontinuation for each line of treatment using data from the respective clinical trial[7,8,15,16]; however, without individual patient data, there is uncertainty regarding the temporal pattern of discontinuation as well as the probability of discontinuation in the post-trial period. Fifth, our model incorporated data from multiple clinical trials, each with a slightly different patient population, to estimate a lifetime horizon. Although we validated our model with regard to PFS in each line of therapy, we were unable to externally validate the modeled OS curves as a result of limited long-term survival data for patients that receive daratumumab in early treatment lines. As such information becomes available, it will be important to assess the concordance of our modeled outcomes with long-term clinical trial and real-world data.[20]

Finally, the MAIA trial included a heterogenous patient population, with differences in mortality risk at the individual patient level.[8] Although the ICER reported in our study suggests that first-line daratumumab is unlikely to provide sufficient value for most transplant-ineligible patients, there may be specific populations that benefit from the inclusion of daratumumab in early lines of therapy. For example, patients with high-risk cytogenetics (del17p, t[14:16], or t[4:14]) often experience early disease progression; for these individuals, the use of a triplet combination in the first-line setting may be appropriate as it may not be feasible to save these regimens for later treatment lines.[55] An important consideration is whether VRd could be used in these individuals rather than DRd, given the lower cost of treatment. Despite indirect comparisons suggesting that DRd may provide the best balance between efficacy and toxicity,[56] direct comparison trials between VRd and DRd will be necessary to better inform this treatment decision.

In conclusion, for older adults with multiple myeloma who are ineligible for transplant, our study suggests that the more cost-effective strategy is reserving daratumumab for second-line use. Significant price reductions or establishing the efficacy of a fixed duration of therapy would likely be necessary to make daratumumab cost-effective as a first-line therapy. Mature OS data for patients who receive first-line daratumumab are necessary to more fully evaluate cost-effectiveness in this setting.

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Cost-Effectiveness of First-Line Versus Second-Line Use of Daratumumab in Older, Transplant-Ineligible Patients With Multiple Myeloma

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