the value of cancer therapies based on clinical benefit, toxicity, and QoL, while cost is used to provide "context."[2] There are meaningful differences in benefit between regimens that need to be considered when assessing value. For example, only carfilzomib-based regimens have demonstrated superior OS benefit and clinically meaningful improvements in QoL through the robust phase-3 clinical trials ASPIRE and ENDEAVOR.[3-5] If value and not just cost is the focus, then cost per outcome associated with these regimens would be more meaningful to decision makers than cost alone.

Key limitations to this study include the following:

1. Patient-relevant benefits of OS and improved QoL during the course of therapy were not considered in this assessment.
2. This analysis penalizes regimens with longer progression-free survival (PFS) compared with regimens with inferior PFS by adjusting the 1-year cost upward to account for the greater PFS and correspondingly lower use of subsequent therapies.
3. In order to calculate average cost per patient, the cost for the entire treatment period should be considered rather than limiting the time frame to 1 year. If cost per patient during the first 2-3 years were estimated, different estimates and rankings would be generated due to differences in treatment schedules for these regimens (e.g., in the carfilzomib plus lenalidomide plus dexamethasone regimen, carfilzomib is stopped after 18 cycles, so the cost is lower after that time period).
4. The cost calculation only considers discontinuation due to progression, whereas there are many other reasons for discontinuation.
5. Duration of therapy is assumed to be the time to progression. However, in certain pivotal trials the planned duration of therapy may be shorter than time to progression.
6. Considerable heterogeneity across pivotal trials was not considered. For example, the median number of previous therapies in the POLLUX trial was 1 as opposed to 2 in other trials. Planned duration of therapy, outcomes, subsequent regimens, and cost would change based on factors such as previous treatment history and refractoriness to therapies.
7. To calculate the cost of subsequent therapy for patients who progressed within 1 year, the authors multiplied the cost of 1 year of subsequent therapy with the probability of progression. It is not clear if administration, monitoring, and comedication costs for subsequent therapies were included in these calculations.
8. Hospitalization rates and associated costs were not considered in the calculation of overall cost.
9. The authors have misreported the number of administrations per cycle for daratumumab plus bortezomib plus dexamethasone in Table 1 as 3 administrations for the first 2 cycles, rather than 3 for the first 3 cycles as described in the daratumumab prescribing information. Omitting an administration of daratumumab would underestimate the cost of that regimen.

Rohan Medhekar, MPharm, PhD
Senior Manager, Global Health Economics
Amgen, Thousand Oaks, CA
rmedheka@amgen.com

Sandhya J. Sapra, BPharm, PhD
Director, Global Health Economics
Amgen, Thousand Oaks, CA

Istvan Majer, PhD
Senior Manager, Global Health Economics
Amgen (Europe) GmbH
Rotkreuz, Zug, Switzerland

David J. Harrison, PhD
Executive Director, Global Health Economics
Amgen, Thousand Oaks, CA

Christina Tekle, PhD
Medical Director
Amgen, Thousand Oaks, CA

DISCLOSURES

No funding was involved in the writing of this letter. Medhekar, Sapra, Majer, Harrison, and Tekle are employees of and stockholders in Amgen.

REFERENCES

1. Hollmann S, Moldaver D, Goyert N, Grima D, Maiese E. A U.S. cost analysis of triplet regimens for patients with previously treated multiple myeloma. *J Manag Care Spec Pharm.* 2019;25(4):449-59. Available at: https://www.jmcp.org/doi/full/10.18553/jmcp.2019.25.4.449.

2. Schnipper L, Davidson N, Wollins D, et al. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. *J Clin Oncol.* 2015;33(23):2563-77.

3. Siegel D, Dimopoulos M, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol.* 2018;36(8):728-34.

4. Dimopoulos M, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017;18(10):1327-37.

5. Ludwig H, Moreau P, Dimopoulos M, et al. Health-related quality of life in the ENDEAVOR study: carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed/refractory multiple myeloma. *Blood Cancer J.* 2019;9(3):23.

The Authors Respond

We are glad to have the opportunity to respond to the concerns noted in the previous letter from Medhekar et al. First, we must mention that the purpose of our study, as stated in our published article,[1] was to estimate the 1-year direct costs of triplet regimens used for the treatment of patients with previously treated multiple myeloma (MM). This warrants emphasizing, since the economic value of daratumumab-based triplet

TABLE 1 Key Values

	Values	Location in Published Study[1]
Monthly DVd drug acquisition costs per patient	$12,516	Table 3
Yearly DVd drug acquisition cost per patient	$150,192	*Calculated from Table 3* (12 × 12,516)
Cost cycle A (DVd)	$26,311	Table 1
Cost cycle B (DVd)	$13,054	Table 1
Cost cycle C (DVd)	$6,628	Table 1
Length of cycle A (DVd)	21 days	Table 1
Length of cycle B (DVd)	21 days	Table 1
Length of cycle C (DVd)	28 days	Table 1
Patients on DVd at 12 months	57.60%	Table 1

Note: Multiplying the cost of cycle a, b, and c, by 3, 5, and 7 (the number of times each cycle type occurs over a 1-year time horizon) yields $190,599. Application of the half-cycle corrected 1-year PFS estimate ($190,599 × [1 + 0.576) ÷ 2]) yields $150,192.

DVd = daratumumab + bortezomib + dexamethasone; PFS = progression-free survival.

regimens for relapsed/refractory multiple myeloma (R/R MM) has been demonstrated previously,[2] so it was not the focus of our study. We agree that determination of value is important, but it is also important to ensure that budget is allocated to allow access to effective treatments.

In claiming overall survival (OS) superiority of carfilzomib regimens per the ASPIRE and ENDEAVOR trials,[3,4] Medhekar et al. ignore that the OS analyses for daratumumab regimens in the CASTOR or POLLUX trials have yet to be completed[5,6]: insufficient deaths have occurred to date to trigger the a priori defined threshold. Medhekar et al. also do not acknowledge that clinically meaningful quality of life (QoL) improvement with carfilzomib + lenalidomide + dexamethasone (KRd) was lost at 18 weeks or that there was sustained QoL from cycle 3 and beyond with daratumumab + lenalidomide + dexamethasone (DRd).[7,8]

We disagree with Medhekar et al. that our analysis penalizes regimens with longer progression-free survival (PFS). Whether PFS or OS, survival is a major clinical objective, but treating longer also costs more. Interestingly, Medhekar et al. did not mention that DRd had the greatest 1-year PFS, but KRd was the most costly option. Longer time horizons to accommodate decreases in dosing frequency might be helpful.[9] However, payers plan budgets based on annual case-mix estimates, not patient trajectories.

Treatment may be discontinued for many reasons; however, progression was the main reason for discontinuation in the trials. Data for other causes were inconsistent. Medhekar et al. stated that we assumed only progression to be the marker of treatment duration. To the contrary, duration was either progression or the U.S. Food and Drug Administration (FDA) approved duration, whichever came first. Regarding heterogeneity, Medhekar et al. overlooked our rationale for the included regimens: all regimens were FDA-approved and equally recommended by the National Comprehensive Cancer Network MM guidelines for previously treated patients.[10]

A number of questionable challenges to our cost estimation methodology in Medhekar et al.'s letter must be noted. Absent real-world data, subsequent therapy costs beyond 1 year were calculated conservatively using established methods.[11] Hospitalization costs (inpatient/outpatient) were considered as part of managing adverse events grade ≥ 3 using literature. Other hospitalizations were excluded because data for all comparators were not available.

The claim that we underreported daratumumab administrations and thus underestimated the cost of daratumumab + bortezomib + dexamethasone (DVd) is not accurate, as there were no modeling errors—3 administrations of daratumumab were considered in each of the first 3 cycles. Table 1 highlights the values presented in the study and demonstrates that the modeled DVd drug acquisition costs of $150,192 are consistent with the label. Since these values are present in the study, had Medhekar et al. attempted to calculate the values, it would have been apparent that costs were not underestimated.

From the title and throughout the text, our study is specified as a cost analysis—a perspective and approach that seemed to disconcert Medhekar et al. Their presumptive statements and categorical positions only strengthen our confidence in our study and resolve to support payers with objective evidence to support budgetary planning.

Sarah Hollmann, MBiotech
Cornerstone Research Group
Burlington, Ontario, Canada

Daniel Moldaver, PhD
Cornerstone Research Group
Burlington, Ontario, Canada

Nik Goyert, MA
Cornerstone Research Group
Burlington, Ontario, Canada

Daniel Grima, MSc
Cornerstone Research Group
Burlington, Ontario, Canada

Eric M. Maiese, MHS, PhD
Janssen Scientific Affairs
Horsham, PA
emaiese@ITS.JNJ.com

DISCLOSURES

No additional funding was received for the writing of this letter. The published study referred to in this letter was funded by Janssen Scientific Affairs, which employs Maiese and funded Cornerstone Research Group, a health economic consulting group, to conduct the study. Grima is a founding partner of Cornerstone Research Group, which employs Hollmann, Goyert, and Moldaver.

REFERENCES

1. Hollmann S, Moldaver D, Goyert N, Grima D, Maiese EM. A U.S. cost analysis of triplet regimens for patients with previously treated multiple myeloma. *J Manag Care Spec Pharm*. 2019;25(4):449-59. Available at: https://www.jmcp.org/doi/full/10.18553/jmcp.2019.25.4.449.

2. Maiese EM, Graham CN, Hawe E, Le Moine J-G, Abraham I, Senbetta M. Cost-effectiveness of daratumumab plus lenalidomide plus dexamethasone versus lenalidomide plus dexamethasone for treatment of patients with multiple myeloma who have received at least one prior therapy: an analysis of the Pollux trial [abstract]. *Blood*. 2017;130(Suppl 1):4711. Available at: www.bloodjournal.org/content/130/Suppl_1/4711.powerpoint. Accessed August 6, 2019.

3. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-52.

4. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(10):1327-37.

5. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. *Haematologica*. 2018;103(12):2079-87.

6. Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. *Haematologica*. 2018;103(12):2088-96.

7. Stewart AK, Dimopoulos MA, Masszi T, et al. Health-related quality-of-life results from the open-label, randomized, phase III ASPIRE trial evaluating carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in patients with relapsed multiple myeloma. *J Clin Oncol*. 2016;34(32):3921-30.

8. Perrot A, Facon T, Plesner T, et al. Faster and sustained improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) patients ineligible for transplant treated with daratumumab, lenalidomide, and dexamethasone (D-Rd) versus Rd alone: MAIA [abstract]. *J Clin Oncol*. 2019;37(15 Suppl):8016. Available at: https://abstracts.asco.org/239/AbstView_239_264205.html. Accessed August 6, 2019.

9. Jakubowiak AJ, Campioni M, Benedict A, et al. Cost-effectiveness of adding carfilzomib to lenalidomide and dexamethasone in relapsed multiple myeloma from a U.S. perspective. *J Med Econ*. 2016;19(11):1061-74.

10. National Comprehensive Cancer Network. Clincal Practice Guidelines in Oncology: Multiple Myeloma. Version 2.2017. Retrieved October 28, 2016. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed August 6, 2019.

11. Ollendorf D, Chapman R, Khan S, et al. Treatment options for relapsed or refractory multiple myeloma: effectiveness, value, and value-based price benchmarks. Evidence report. Institute for Clinical and Economic Review. May 5, 2016. Available at: https://icer-review.org/wp-content/uploads/2016/05/MWCEPAC_MM_Evidence_Report_050516-002.pdf. Accessed August 6, 2019.