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CLINICAL TRIALS AND OBSERVATIONS

*Comment on Yamamoto et al, page 594*

# Cost-effectiveness: maximizing impact by meticulous data

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**In this issue of *Blood*, Yamamoto et al[1] report that treatment with first-line daratumumab in combination with bortezomib, thalidomide, and dexamethasone (Dara-VTd) or lenalidomide, bortezomib, dexamethasone (Dara-RVd) resulted in increased quality adjusted life years (QALYs) and lower costs compared with deferring daratumumab treatment to the second line in combination with carfilzomib and dexamethasone (Dara-Kd).**

Cost-effectiveness analysis provide insight in the relation between input (scarce resources) and outcomes (ie, health benefits for patients) and guide reimbursement decisions. Currently, we are in the privileged situation of rapid drug development in the field of multiple myeloma (MM), which challenges the methodology of cost-effectiveness analyses.

When treatment options are rapidly increasing, cost-effectiveness analyses should expand their focus from a comparison between discrete treatments to include a comparison of treatment sequences.[2] This will also create a better base for price negotiations: "value-based" instead of "one price fits all" with the ultimate goal of ensuring global accessibility to treatments.

Evidence from cost-effectiveness analysis should be available timely for reimbursement decisions, price negotiations, and even clinical decision-making between treatments with comparable efficacy. Trials are currently not designed to provide timely evidence for cost-effectiveness analysis and need modification. Due to the rapid development in MM, at the time mature data on progression-free survival (PFS) and overall survival (OS) become available, the outcomes of clinical studies are often outdated (ie, the comparator treatment might not reflect standard of care anymore). Therefore, cost-effectiveness analyses require not only that the cost data be collected simultaneously with the clinical data but also that earlier surrogate endpoints for PFS and OS be gathered.

Yamamoto and colleagues found relevant additional information by modeling sequences of treatments. With a 5-year horizon, the use of first-line daratumumab in induction regimens was far above current willingness-to-pay thresholds. However, the authors elegantly showed that the higher costs of adding daratumumab in the first line are negated by lower costs for second-line treatment (ie, higher costs for the comparator sequences, including daratumumab continuously in second-line) and, from a 10-year time horizon, even cost-saving. Moreover, the authors address the endpoint problem by using minimal residual disease (MRD) as a surrogate for PFS, using data from the IFM 2009 trial to inform this relation.[3] The advantage of their approach is that decision makers have access to cost-effectiveness estimates at the moment that decisions regarding reimbursement need to be made (ie, shortly after European Medicines Agency/Food and Drug Administration approval).

Although major hurdles were addressed by their approach, several steps are still required for optimizing future cost-effectiveness analyses.

Cost-effectiveness analyses are comparing alternatives and labeling treatment cost-effective, or cost saving should always be seen in relation to the comparison that is made. So, the conclusion of the work of Yamamoto and colleagues should actually be that adding daratumamab to first-line treatment is cost saving, compared waiting for second-line therapy, for the following sequences: Dara-RVd–Kd compared with RVd–Dara-Kd, both followed by elotuzumab, pomalidomide, and dexamethasone as third-line treatment and panobinostat, bortezomib, and dexamethasone as fourth-line treatment. The assumed second-line treatment and the patient population are crucial for both outcomes and costs, as stated by the authors. This is illustrated by the data of Patel and colleagues showing that daratumumab given with first-line therapy was not cost-effective in non-transplant–eligible patients with MM.[4] Besides a difference in population (ie, non-transplant vs transplant eligible), daratumumab was used until progression in both first- and second-line treatment in the Patel study, whereas Yamamoto and colleagues used a fixed duration of daratumumab in first-line treatment and until progression in second-line, which impacted cost-effectiveness. Providing data from other drug combinations is of interest from a global perspective. For example, given the efficacy of Dara-Rd as a second-line regimen, studies including this regimen are relevant from a cost-effective perspective and may be of value in facilitating accessibility to treatment, especially in low- and middle-income countries.[5,6]

The use of MRD as surrogate endpoint for PFS and OS is key for timely analyses but

requires extrapolation of currently available data over a long period. Therefore, follow-up of the current study is needed to confirm that the presented results are achieved in practice. Such a dynamic assessment of the cost-effectiveness of treatments, implementing continuous updates of new evidence and insights, might be a valuable approach to ensure rapid access to promising new treatments while ensuring affordable healthcare.

Cost-effectiveness analysis uses QALYs that combine length and quality of life (QoL). In the analysis of Yamamoto and colleagues, length of life is similar (0.1), meaning QALY gains are driven by differences in QoL. Ideally, QoL values should be treatment specific; however, QoL data are often lacking, as in this study. Instead, the data were derived from the literature (ie, representing older regimens in UK patients).[7] Moreover, the assumption of higher QoL during maintenance therapy is crucial. In fact, the conclusion of the authors, that the key driver of QALYs gained is first-line PFS, only holds if their assumption (ie, that QoL during first-line PFS is substantially better than QoL for second-line PFS) is correct. Given the relevance, the collection of QoL data should be a research priority in future trials.

In conclusion, Yamamoto and colleagues add to the field of cost-effectiveness analyses in MM by broadening the study to include sequential treatments and by using MRD as an endpoint. This is of utmost importance because in many parts of the world, ensuring (financial) access to novel treatments leading to a longer and valuable life is limited by financial constraints.[8] Timely cost-effectiveness evidence should help with the optimal use of scarce resources and price negotiations, improving access for individual patients. Nevertheless, such analyses are only as good as the data underlying them. Often, assumptions must be made that substantially affect outcomes. Thus, it is critical that dynamic assessments using different endpoints over time and solid MRD and QoL data are collected during clinical trials and population-based registries.

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**IMMUNOBIOLOGY AND IMMUNOTHERAPY**

*Comment on Diorio et al, page 619*

# The uncut version: base-edited allo-CAR T cells

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**In this issue of *Blood*, Diorio et al[1] harness base editing technology to develop a potent and complex gene-edited CD7-specific chimeric antigen receptor (CAR) T-cell product for off-the-shelf use in patients with T-cell leukemia and other CD7$^+$ malignancies. Their manufacturing platform showcases the potential of base editing for future progress toward safer and more accessible CAR T-cell therapies.**

After the success of personalized CAR T-cell therapy in B-cell malignancies, the field expanded to develop CAR technology for other malignant diseases. With some CAR T-cell products moving toward use earlier in treatment, there is an increasing interest in overcoming the logistic hurdles involved in personalized cell manufacturing by establishing allogeneic off-the-shelf solutions.[2] Herein, gene silencing with programmable nucleases (eg, via Zinc finger nucleases, TALEN, CRISPR-Cas9) has become an essential tool to facilitate engineering of T cells with the desired attributes.

Conventional programmable nucleases allow gene silencing by forcing DNA double-stranded breaks (DSBs) at coding regions of the targeted gene. Repeated cuts and error prone DNA repairs promote small insertions and deletions that induce frameshift mutations and disrupt protein expression. Despite achieving highly efficient gene knockouts, repetitive cutting by nucleases can induce genetic rearrangements such as inversions, larger deletions, and even complete loss of chromosomes.[3] To overcome the challenges of safe allogeneic CAR (allo-CAR) T-cell therapy, multiple genetic modifications will be required to eliminate the risk of graft-versus-host disease and allogeneic cell immunogenicity, which limit CAR T-cell persistence and antitumor efficacy.[4] However, simultaneous targeting of multiple genes with nuclease-assisted gene disruption can create myriad translocations and genetic rearrangements with unknown long-term consequences.