LATEST ADVANCES IN
CAR-T CELL MANUFACTURE
& CLINICAL DEVELOPMENTS

SPOTLIGHT

INTERVIEW

Pricing Models and Strategies to make CAR-T Therapy Affordable

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Q The Institute for Clinical and Economic Review (ICER) recently published a report on the cost-effectiveness of tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta), the two approved CAR-T therapies with price tags over $350,000. Could you provide some of the key findings from the study?

DO: We extrapolated data from the clinical trials of the 2 CAR-T therapies on event-free and overall patient survival, in order to estimate the gains in life expectancy and quality of life that would be

seen with these therapies when compared to standard chemotherapy approaches. The results obtained were quite impressive. It indicated that CAR-T therapy would extend life by an average of 4 years and 8 years for adult and pediatric populations, respectively. In comparison to what is typically seen for new chemotherapies, this is quite a substantial gain.

However, the costs associated with CAR-T therapy are very high and would likely be higher than most chemotherapy therapeutic regimens. But because the gains in survival were so large this translated into cost-effectiveness results that were within or below common thresholds for cost effectiveness in the US. The thresholds that we focus on in the US are between 100,000 and 150,000 US dollars per quality-adjusted life year (QALY) gained.

There are 2 very important cautions to these results. One of them is that, while we saw a survival advantage, this was based on early survival data from these trials obtained at the time we did the analysis. For Kymriah the median follow-up was only about 8 months and for Yescarta, it was less than 2 years. Therefore, while the information at this point is very promising, if that survival advantage were to erode in any way over time as the data becomes more mature then obviously the cost-effectiveness would look less favorable.

The second caution is something specific to ICER's approach to assessing value in that we look not only at the lifetime cost-effectiveness, but also at the potential impact on the health system. We identified that, for Yescarta in the adult population, because it's a relatively large group, there is likely to be a significant budget impact if all candidates have the therapy available to them. We also recognize that these 2 therapies are part of a coming wave of CAR-Ts, so they're not only being tested themselves in other indications but we have other CAR-Ts from other manufacturers being put into the mix as well. So there is a budget issue that is coming. And it's going to need to be managed.

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Q Do you think introducing cost-saving measures in other areas of cancer research could help increase the capacity of health care budgets to pay for new innovations such as CAR-T?

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DO: We've identified this as something that's of interest to us, to try and hear from stakeholders about what sort of inefficiencies in the current system for treating leukemias and lymphomas could be addressed to try and make headroom in budgets to pay for innovative new therapies.

The American Society of Clinical Oncology (ASCO) has put forward several Choosing Wisely recommendations that have the potential to be cost-saving in the treatment of leukemias and lymphomas. One of them is to limit the use of PET or PET-CT scans. In some settings there might be overuse of PET scans or PET-CT scans to detect cancer recurrence. The recommendation is not to routinely use these scans for follow-up visits to detect cancer recurrence in asymptomatic patients who have completed initial treatment, unless high-level evidence suggests that such imaging will change the outcome.

Another example would be the overuse of white cell stimulating factors like filgrastim. ASCO recommends avoiding the use of these factors for primary prevention of febrile neutropenia in patients whose risk for this complication is less than 20%.

We would always be interested in understanding whether the current state of treatment has inefficiencies in it that could be addressed to help pay for new innovations.

Q Novartis has introduced an outcome-based pricing arrangement to allow for payment only if the patients respond to Kymriah by end of the first month of treatment. What are your thoughts on such performance-based reimbursement models?

DO: We are in support of performance-based contracting, or outcome-based pricing agreements, because we do feel they have the potential to cement the value proposition for high value treatments.

When we get concerned is when we feel a manufacturer is trying to promote the use of this kind of agreement to distract the conversation away from value in the first place. That's not the case here because we have already determined that these 2 therapies are of high value based on early data.

However, there are some considerations we need to think about. In general, these agreements must be relatively simple to administer and monitor

because it won't work for any payer if tracking an agreement becomes too burdensome.

In particular with regards to the Novartis outcome-based pricing arrangement, I don't know if basing such arrangements on one-month remission rate is really appropriate because results from the Kymriah clinical trials showed that about a quarter of patients experienced relapse of symptoms after the one-month point. Most evidence-based organizations have raised similar concerns, and at our own public meeting one of the key policy recommendations was to use a more durable measure of response and at a later time point. For instance, one-year outcome would be more clinically meaningful than response assessed at one month. The specific outcomes need to be defined in a way that allows for consistent, accurate assessment across centers to ensure confidence in the outcomes for both manufacturers and insurers.

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Q Based on the study findings, ICER has provided some recommendations to help ensure access to CAR-T therapies. Could you elaborate on these?

DO: Many of the recommendations we have put forward are in fact tied in some way to pricing. We discuss not only the possibility of outcome-based arrangements such as those we just talked about between manufacturers and individual payers, but also make some recommendations for manufacturers to consider tying the pricing of their therapy generally to performance.

When launching novel therapeutics like CAR-T therapy that are approved with limited clinical evidence, manufacturers should consider one of two options: a lower than expected launch price with the potential for increase should substantial clinical benefits be confirmed; or a higher initial price tied to requirement for refunds or rebates if real-world evidence fails to confirm high expectations. It could be done on a list price basis, it doesn't necessarily have to be done as part of an agreement with any individual payer.

Something that's very specifically an issue in the US, and we also mention in our report, is the notion of hospital mark-up. Hospitals in the US typically use a buy and build approach when integrating expensive therapy for treatment in their institutional settings. With the buy and build

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approach oftentimes comes a very high mark-up that is tied in some way to the list price of the therapy.

The recommendation from discussion at ICER's public meeting is that hospital mark-up for CAR-T therapies should reflect the expected additional cost for care delivered in the hospital, rather than a percentage of the drug cost, to avoid perverse incentives in choosing the treatment location. A fixed administrative fee to cover the expense associated with innovative therapies that does not differ by therapy or setting would be preferable.

Q Where do you see the biggest opportunities to impact the cost of CAR-T therapies so that it becomes an affordable modality for global healthcare systems?

DO: There have been discussions on the high cost of goods and services, and the manufacturing costs associated with these therapies. We have not seen enough information about what those costs actually are to understand how closely they are linked to the prices themselves.

We conclude that the CAR-T prices as they currently exist are aligned with value to the patient, at least at this point, but we are also sounding an alert around health system affordability. There are several ways that prices can be modified to reflect the affordability concerns. One way could be to price the therapies differently by indication. This is something that Novartis has also mentioned publicly as a possibility and we are also talking about the idea of possibly adjusting pricing as evidence emerges.

Yet another possibility is the idea of an annuity-based payment, where payers are paying in instalments over time rather than paying the high upfront cost. It is obviously much more feasible in a system like the National Health System in the UK where there is a single payer. It's much more difficult in the US because of the issue of what some call "divided benefits." Let's say everything works well, patient is essentially cured, that patient then moves on to another payer and receives all the clinical benefit of being cured but that second payer isn't paying anything for the treatment. That is a big issue and nobody really has a great understanding of how to solve that in the US.

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In terms of manufacturing these products, reducing the cost of goods would also be significant. CAR-T therapy is obviously a labor-intensive

type of therapy, where you have to harvest the T-cells, process them and infuse them back into the patient. I think there can be a lot of learnings taken from how efficient processing, harvesting and infusing stem cells has become. Stem cell transplant can essentially be a model on how to make the manufacturing process as efficient as possible. But again, the prices as they are currently listed are not really tied to the manufacturing costs. If manufacturing costs become much more efficient but the pricing doesn't change, we're essentially just talking about excess profit.

There's enormous promise around CAR-T therapies and we heard some quite compelling patient testimonials at our meetings. We do want to try and support this kind of innovation, especially if prices based on current evidence are aligned with the value to the patient. That's what ICER and other HTA organizations around the world are focused on. We hope that not only the promise of these therapies continues to play out, but also that the attention we have raised around the affordability issues they will bring leads to some very productive conversations about how to address them.

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