CAR-Ts cell therapy: implications of recent Yescarta and Kymriah announcements for manufacturers and assessment agencies

With NICE’s rejection of Gilead’s Yescarta for treating DLBCL and NHS England’s announcement that a deal has been agreed with Novartis to fund Kymriah for childhood ALL, what are the key areas to watch for CAR-T manufacturers and for other assessment agencies?
Many people will have seen the news that NICE has rejected Gilead’s CAR-T therapy, Yescarta, for treating DLBCL.¹ This was followed little more than a week later by an exceptional announcement from NHS England that a deal has been reached with Novartis to fund Kymriah for the treatment of childhood ALL through the Cancer Drugs Fund.²

The draft guidance on Yescarta in DLBCL³ presented a complex array of reasons for the decision to reject the product for funding. We also look forward to analyzing in detail the decision on Kymriah, once this has been formally published by NICE.

In the meantime, senior members of our team have highlighted five key areas to watch for future developments.

“CENTER OF EXCELLENCE” MODELS

In the US, payers and providers use centers of excellence as a core element in providing high-quality care; for example, Blue Cross Blue Shield’s Blue Distinction Specialty Care Program.⁴ This is forming up as an obvious approach to rolling out CAR-T therapies, starting with certified centers from clinical trials, and expanding through the existing network of accredited centers used by each payer.

NHS England’s submission within the NICE appraisal for Yescarta very clearly signaled a similar intent, but with an additional layer to consider of the costs involved with the new service specification to be developed. Partly due to the very limited experience from commercial clinical trials within Europe, manufacturers need to prepare for payers and health systems taking a slow and cautious approach to roll-out, with initially a very limited geographic footprint of CAR-T centers, to address uncertainty on care quality and also to contain costs.

Manufacturers should think about how their knowledge can be folded into risk-sharing agreements to support care quality and gather real-world data on outcomes. The costs of travelling and lodging for patients and their carers who live far from designated treatment centers may need to be considered in HTA. Finally, manufacturers should prepare to understand and engage with the implications of a sustained period of constrained capacity – including issues of equity across patients eligible for treatment.
SAFETY

We saw detailed discussion of adverse events in the NICE appraisal consultation document for Yescarta: cytokine release syndrome and neurotoxicity in particular. Detailed scrutiny of adverse events would normally be left to the appropriate regulatory agencies (i.e., the EMA). However, within HTA, there is real concern not only about the rate and type of adverse events per se, but also their immediate implications for service delivery, such as the need for extensive training of NHS personnel at several levels and – at least in the near term – reserving intensive care capacity close to the patient for urgent response to the most serious adverse events.

Manufacturers need to explore the significance of this issue within health system capacity, and think about how budget holders at different levels are affected. In some countries, this may become an additional headwind for manufacturers in pricing and access negotiations. Manufacturers should plan to rapidly present new evidence and advance provider understanding, as clinical trial and commercial experience builds and knowledge of optimal adverse event management strategies matures.

PAYMENT MODELS AND RISK-SHARING AGREEMENTS

Novartis’ initial proposals for Kymriah in the US indicated that innovative pricing models would be a key strategy to address some of the challenges on uncertainty of value for CAR-T therapy. However, the value-based scheme proposed for Kymriah in the US hit significant implementation obstacles, while Kite/Gilead does not appear to have offered any innovative pricing schemes in the US and proposed only a simple discount in the UK. Novartis has reiterated its commitment to explore value-based pricing deals with European payers and the recent NHS England announcement on Kymriah suggests the company has pursued a more creative and collaborative approach to secure access in the UK.

Upcoming P&R processes will reveal whether payers in other countries have a similar appetite for innovative payment approaches and how both manufacturers will adapt their strategies accordingly.

HEALTH ECONOMICS AND OUTCOMES RESEARCH MODELING

In the assessment of Yescarta, NICE’s Evidence Review Group noted that modeling had previously been undertaken by the Institute for Clinical and Economic Review (ICER) in the US, and specifically requested a comparison of the manufacturer’s proposed approach submitted to NICE and the independent work of ICER. In the process of addressing this question, Kite/Gilead criticized the ICER methodology.

We expect NICE’s assessment of Kymriah to be published soon, but we also expect to see ICER assess Celgene’s lisocabtagene maraleucel in 2019. This will generate an ongoing, multi-country, multi-agency, multi-product pattern of assessments, almost surely referencing one another in a way probably not seen before.
MANUFACTURING AND DELIVERY

Novartis and Kite/Gilead began with similar challenges on manufacturing and logistics, but now find themselves in quite different situations.

Kite appears to have successfully prepared for and up-scaled from manufacturing for US-focused clinical trials to an operation capable of commercial supply with a broader geographic footprint. Kite established a new plant in California, close to LAX airport, which has since achieved consistently low manufacturing turnaround times and appears able to supply EU markets from the US until technology transfer is complete for its new facility under construction in the Netherlands, at Schiphol airport. Novartis acquired an existing cell therapy production facility site in New Jersey (a former Dendreon site for Provenge).

Novartis turnaround times have been longer, with greater variability and some significant manufacturing problems have been encountered in clinical trials. Novartis will rely on gene therapy CMOs in France and Germany to supply CAR-T therapies for Europe until it has established a new plant in Switzerland, expected to be operational in 2020.

The success rate and turnaround time in manufacturing will affect treatment decisions, the economics of CAR-T therapy, and payment models that need to be considered. In particular, with long or highly variable turnaround times, bridging therapies may be needed for higher-risk patients. In this area, Kite/Gilead currently appears to have the advantage over Novartis.

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