# Unlocking access to CAR-T in Europe: progress and growing pains

## CAR-Ts pose a unique challenge for healthcare systems, exacerbated by uncertainty around their long-term, real-world value

By Philippe Coune, Anna Lenard and Héctor Castañón

**When chimeric antigen receptor (CAR)-T cell therapy first arrived, *Time Magazine* called it 'cancer's newest miracle cure'. Certainly, the therapy – which uses a patient's own genetically altered T cells to treat cancers such as lymphoma, multiple myeloma and leukaemia – heralded a medical breakthrough. Hard-to-treat conditions with no prior curative alternative and very low rates of survival, such as relapsed or refractory diffused large B-cell lymphoma (r/r DLBCL), suddenly had a highly effective treatment available, seemingly even a 'cure'.**

But ever since the first two CAR-Ts were approved in Europe in 2018 – Kymriah and Yescarta – the focus has been on price and logistics as much as therapeutic value. With their highly complex treatment procedures and high price tags, CAR-Ts posed a unique challenge for healthcare systems, exacerbated by uncertainty around their long-term, real-world value.

Industry and healthcare systems collaborated to find solutions. Novel outcomes-based reimbursement schemes were installed to address the uncertainty on long-term value. For example, in France and the UK, reimbursement was on the condition of collecting additional data and subject to future reassessments. Elsewhere, rebates (Germany) or staged payments (Italy and Spain) were linked to individual patient outcomes. Moreover, CAR-T specific processes and infrastructure to allow patient identification, referral and treatment in authorised treatment centres have been established.

### Six years of progress reinforce the benefit

Since then, substantial real-world evidence has accumulated for these first CAR-T indications. For instance, outcomes in r/r DLBCL have been shown to align with clinical trial results, even in a broader patient population.

Much has been learned to allow for these real-world outcomes. Healthcare professionals involved in patient management have acquired extensive experience in the resolution of adverse reactions. Through stakeholder coordination, product manufacturing and delivery times have been highly optimised, reducing turnaround time from over a month to less than three weeks, helping to improve CAR-T effectiveness and patient outcomes.

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The progress in this period has been exceptional. However, hurdles remain to broad patient access – and in a rapidly changing environment, these hurdles may be increasing.

### Hurdles to patient access

It is estimated that 29-71% of medically eligible r/r DLBCL patients across France, Germany, Italy and Spain are not treated with a licensed CAR-T.

Hurdles can be broadly divided into three categories: patient identification and referral, reimbursement restrictions and processes, and capacity challenges.

*Patient identification and referral*

In referring hospitals, specific knowledge of the benefits and eligibility criteria for CAR-T may be limited, which leaves patients unreferred. Even when patients are identified, referral is not always straightforward due to the lack of clear and well-defined referral pathways.

The limited geographic coverage of authorised treatment centres, requiring patients to travel long distances, may also hinder referral.

*Reimbursement restrictions and processes*

Some patients are prevented from accessing CAR-T through reimbursement restrictions beyond the EMA approved indication. For example, patient eligibility criteria have been restricted in Germany and Spain based on the selection criteria applied in the registrational trials. In Italy, in addition to the registrational trial criteria, a maximum patient age of 70 years (later increased to 75) was defined. Meanwhile, lengthy and complex bureaucratic approval processes may be disincentivising referrals and delaying access. Spain and the UK have put in place centralised assessments to help control CAR-T requests, adding an extra layer of bureaucracy, which can lead to delays.

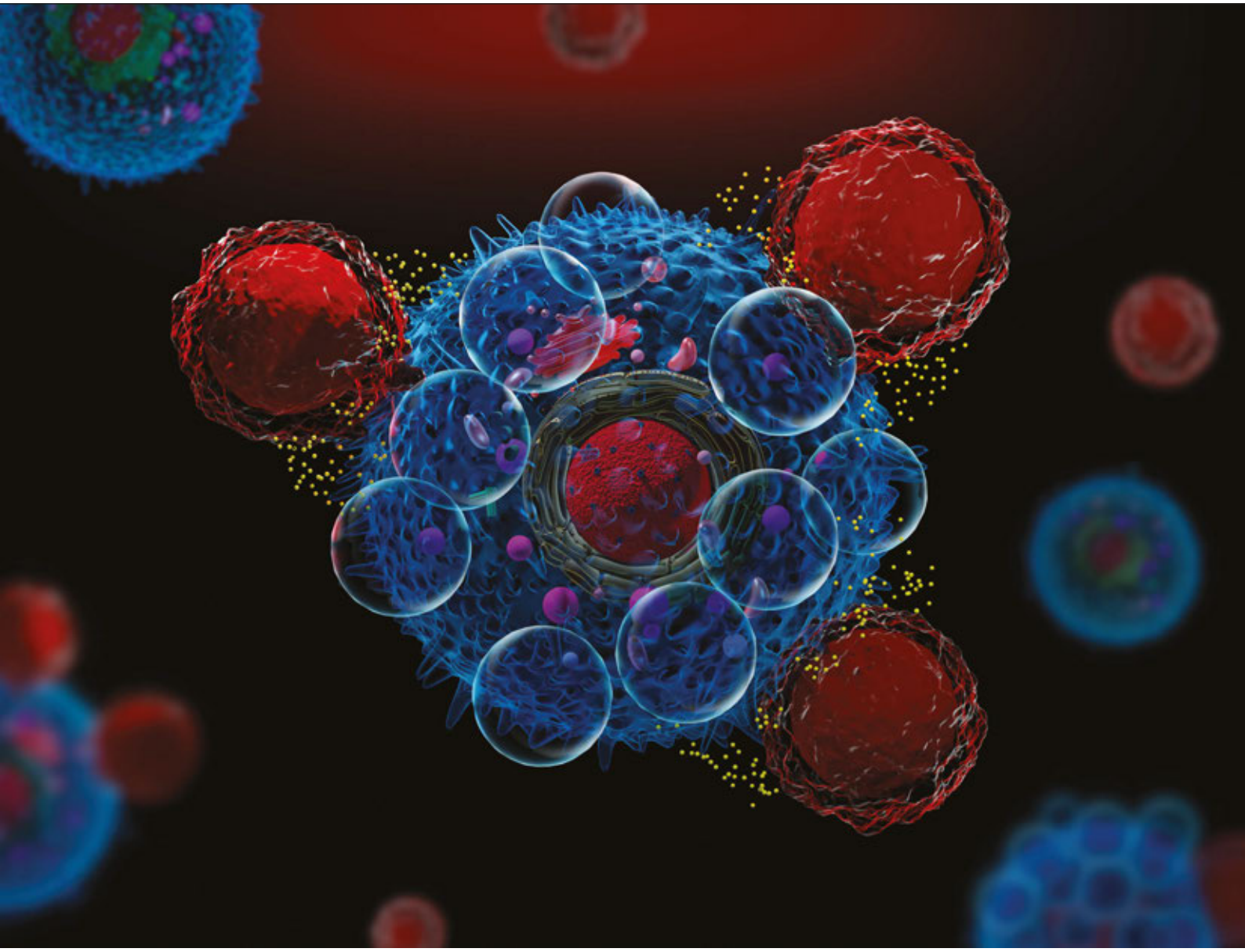
*Capacity challenges*

Despite an increasing number of CAR-T authorised treatment centres, capacity bottlenecks remain. Apheresis slots are a particular bottleneck. The numbers of haematologists, nurses and ICU beds are also important limitations, which require further growth as patient numbers increase.

### One roadmap for the future

The CAR-T environment is evolving rapidly, which will only intensify these challenges. Six CAR-Ts are now approved, with hundreds of clinical trials currently being conducted in earlier lines of treatment and various new malignancies.

With healthcare systems under considerable budget constraints, pricing pressures will increase on CAR-T manufacturers and more stringent evidence requirements may be implemented to grant reimbursement. This poses a challenge to a sustainable CAR-T price that reflects the curative potential of the technology and



high manufacturing costs. In the long term, such pressures may make bringing these innovations to patients more challenging.

For example, in Germany, Yescarta originally had a shortened AMNOG evaluation based on its orphan drug status. It now faced a full re-examination after reaching a revised sales threshold. The full assessment process requires comparative data and resulted in a downgrade to 'no proven added benefit' in one indication, triggering price re-negotiations. Similarly, in France, both Abecma and Carvykti received an ASMR-V (no added benefit) rating in the initial assessment for multiple myeloma because they lacked a comparison arm in their trial. This rating significantly restricts their price potential and reimbursement possibilities.

To address this challenge, CAR-T manufacturers should aim to enhance the perceived value of CAR-Ts, start payer engagement early to ensure the clinical trials satisfy the requirements of payers and HTA bodies, and be ready to strike a balance between payers' needs to control budget impact and finding a sustainable price.

Meanwhile, an increasing number of treatment options – not just CAR-Ts, but other therapies for the same indications, such as bi-specifics and antibody-drug conjugates – will make patient identification harder.

Treatment guidelines that are easy to follow will be required and revised frequently to match the latest treatment landscape.

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Moreover, as more CAR-Ts become available, treatment capacity will have to increase, ensuring enough apheresis slots, healthcare professional availability and ICU beds to accommodate patients who need to stay in centres for up to three weeks after infusion. There is the potential to offload certain tasks to non-treatment centres – for example, apheresis-only centres have been established in Spain.

In the six years since the first CAR-T approvals in Europe, significant progress has been made. CAR-T manufacturers and healthcare systems have collaborated to answer complex questions: how to reimburse a one-time treatment with long-term uncertainty; how to appropriately identify patients and manage treatment; and how to improve manufacturing and boost capacity. In a rapidly evolving treatment landscape with increasing access hurdles, all stakeholders must continue collaborating to find new solutions and crucially policymakers should step in to define adoption targets. These targets will inform and drive adequate resource allocation, ensuring that as many eligible patients as possible benefit from these life-saving medicines.

*References are available on request.*

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