Policy

Paying for patient-specific therapy: à la CAR-T

CAR-T therapies represent a huge leap forward in the treatment of cancer

Using the body's own defence mechanisms to overcome cancer is hardly a new idea, beginning with the pioneering work of William Coley in the late 19th century. Advances in the use first of immune checkpoint inhibitors (CTLA4 and PD-1) and more recently adoptive cell transfer techniques, have given new prominence to immunotherapy. Among immunotherapies, chimeric antigen receptor (CAR)-T cell treatments have gained increasing prominence over the last 2–3 years. For some patients, CAR-T therapy can offer prolonged periods of disease-free remission and extended survival.

To date, two CAR-T therapies have been approved for use by the FDA and EMA:

Kymriah (tisagenlecleucel) for either adults with relapsed or refractory diffuse B-cell lymphoma or children/young adults up to 25 years old with relapsed or refractory acute lymphoblastic leukaemia.

Yescarta (axicabtagene ciloleucel) following failure to respond to two previous therapies in various B-cell lymphomas – including diffuse B-cell lymphoma.

After culturing of patient-specific cells, treatment is given as a one-off infusion. Early indicators show that response rates to CAR-T therapy are high and prolonged, but limitations in the clinical trial dataset present challenges for payers and policy makers.

Demonstrating effect: the search for cure

Curative effect is the hope of every oncologist and patient. The most common measure of survivorship is disease free survival at 3–5 years post-treatment. Many therapeutic choices – surgical resection, stem cell transplant, solid organ transplant – are deemed valuable by default; there is minimal oversight or input from payers/policy makers in the considerations of these approaches since they are nominally curative and do not require expensive pharmaceutical treatments.

The CAR-T therapies blur the lines of treatment – being neither truly a surgical intervention nor a pharmaceutical product. They are highly complex and applied in rare diseases where survival has been historically very poor. This leads to an impressive but, never-the-less, limited set of data with small patient numbers, relatively short follow up, and minimal data on rates and types of subsequent treatment requirement.

The evidence reflects the challenge of innovation – very promising early clinical results allow regulatory review and approval but leave gaps in terms of the understanding of long-term outcomes and impact in the real world.

	Kymriah				Yescarta
	ELIANA	**ENSIGN**	**B2101J**	**JULIET**	**ZUMA-1**
	n=75	**n=58** (42 for overall remission rate)	**n=59**	**n=93**	**n=108**
Source	Maude, Laetsch (2018)	Company data	Maude, Grupp (2018)	Schuster (2019)	Locke (2019)
Overall remission rate (proportion of patients [95% CI])	81 (71–89)	69 (53–82)	93 (NR)	52 (41–62)	82
Median overall survival: m (95% CI)	NE	23.8 (9 to NE)	NR	22.2	NR (12.8 to NE)
Survival at 12 m: proportion of patients (95% CI)	76 (63 to 86)	63 (46 to 76)	79 (69 to 91)		

Illustrative data from CAR-T clinical trials programmes

Establishing value

The major concern of payers and health services are the costs associated with CAR-T therapy: a high initial price for therapy coupled with costs associated with hospitalisation and careful long-term patient management.

While initial costs are high, these are balanced by projected outcomes:

- High response rates
- Durable and long-term disease-free periods
- Limited need for long-term chronic care

Regulators have allowed rapid evaluation of the evidence and built new approaches to allow breakthrough products (like CAR-T) to be used more quickly and on less certain evidence. Against this backdrop, there remains significant uncertainty within the long-term outcomes for CAR-T patients.

While the intrinsic value of cure is evident, the uncertainty inherent in extrapolation of non-comparative and short-duration clinical trials to the long-term real-world setting presents questions for payers and for the pharmaceutical industry.

Payers have sought to allow conditional access in early indications (such as through the Cancer Drugs Fund in England and Wales) while manufacturers have offered alternative payment mechanisms and offers to support funding.

Others, such as Canada, have allowed review of CAR-T as a surgical intervention/device, lowering the expectation for data and, perhaps, better reflecting the nature of the technology.

Who pays and how?

Given the potential lifelong effect of treatment, the "sticker price" of CAR-T therapies is notably high. High manufacturing costs and complex management of the supply chain contribute to the costs of delivery of CAR-T therapy.

This raises two questions:

- How to accommodate/reward manufacturers in outcomes-based payment schemes in the few cases where treatment fails?
- How to manage the per patient and overall high budget impact?

On the first question, there are many examples of proposed outcomes-based payment schemes that may be particularly relevant. In recent years, outcomes-based schemes have been unpopular with payers given the complexity of gathering evidence on outcomes, flawed financial structures and administrative burden. Never-the-less, the patients in the case of CAR-T therapies are limited in number and, given the nature of their initial disease, closely followed clinically. Furthermore, initial response to CAR-T seems to be a reasonable indicator of long-term success.

Establishing an appropriate access scheme requires a clear, well-documented and structured approach considering all alternatives and gathering input from all relevant stakeholders:

Topic	Meaning	
Consistency with brand strategy (local and global)	What impact will the access scheme have on current indications?	Internal
Long term strategy	What will be the effect of the scheme on new and current indications in the long term?	
Competitive dynamics	How will the scheme impact the current market in the indication and other indications? How will competitors respond to the introduction of the scheme	
Financial impact	How will the scheme affect revenue streams? What will be the cost of developing and implementing a scheme?	
HTA impact	Does the scheme meet the need in terms of ICER and HTA strategy?	
Resource requirements (internal)	What is the burden of scheme development and implementation for the manufacturer?	
Resource requirements (external)	What is the burden of scheme development and implementation for the NHS and other stakeholders	External
Time horizons	How will the scheme impact (A) HTA submission deadlines, (B) access scheme proposal deadlines, and (C) launch of the product and scheme implementation?	
Clinical feasibility	How will the scheme be perceived by clinicians? Can the correct outcome measures for the scheme be used and collected effectively? Will there be gaming of the system by prescribers?	
Operational feasibility	How will the scheme work on the ground? Will the scheme prove burdensome from the perspective of (A) the manufacturer and (B) the health service, and (C) other organisations?	
Data transfer and administration	How will data be collected and shared efficiently between stakeholders and the manufacturer?	
Privacy issues (data protection)	How will the access scheme comply with the Data Protection Act?	
Attractiveness to stakeholders	How will the scheme be perceived by registered interests i.e. patients/PAG/prescribers and pharmacists/commissioners/payers?	

A framework for evaluating alternative pricing/access schemes

Managing the budget impact, and in particular the effect of an annual planning cycle, presents additional challenges. Manufacturers have already suggested many alternatives – including annuity-based compensation that can spread the cost of therapy over several years. Health services globally will need to be flexible in order to meet manufacturers part way.

Options for alternative payment approaches include:

- National level fixed or capped budgets: giving annual budget certainty but allowing patient access
- Annuity-based approaches and future payment schedules
- Service-based payment
- Shared manufacturing capability and cost

Other possibilities include extending data exclusivity or establishing further tax and/or R&D incentives for a trade-off in list pricing.

Conclusion

CAR-T therapies represent a huge opportunity for enhanced patient outcomes – and the hope of cure for some.

Establishing a clear understanding of the value of CAR-T and then using a structured approach to engage with key stakeholders to manage the introduction and budget will be critical in launching CAR-T.

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