How should we evaluate the cost-effectiveness of CAR T-cell therapies?

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Highlights

In this article we describe the key features of chimeric antigen receptors (CAR) T-cell therapies set to revolutionise oncology and describe the challenges that lie ahead. We show

- The opportunity cost of CAR T-cell therapy and what is forgone as a consequence of adopting CAR T-cell therapy.
- The challenges in evidence generation and uncertainty that make it difficult to produce the robust estimates of health and economic impact.
- The reimbursement mechanisms in response to highly specialised technologies, allowing the NHS to better understand the emerging therapy.

How should we evaluate the cost-effectiveness of CAR T-cell therapies?

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Recent approvals of pioneering chimeric antigen receptors (CAR) T-cell therapies, axicabtagene ciloleucel (Yescarta®) and tisagenlecleucel (Kymriah®), have resulted in considerable interest in the budgetary impact, clinical effectiveness and cost-effectiveness of these technologies. Traditional approaches of appraising new technologies in the UK would mean several promising highly specialised technologies such as CAR T-cell therapies would not gain approval. This article provides insights into the opportunity costs and challenges associated with CAR T-cell therapies, and describes the reimbursement models developed to ensure market access for CAR T-cell therapies.

In 2017, NICE's evaluation guide to the Process and Methods of Technology Appraisal (TA) proposed a threshold of £100,000-£300,000 per QALY for the evaluation of highly specialised technologies (HSTs)(1). The proposal was accompanied with a budget of £20 million per year (2), for each technology evaluated under the technology appraisal (TA) and highly specialised technologies (HST) guidance. The budget is set to signal the need for commercial discussions between the company and NHS England to keep prices low.

Axicabtagene ciloleucel was the first CAR T-cell therapy to be approved for adults living with certain types of non-Hodgkins lymphoma (3). In August 2018, NICE recommended against its use (4) on the basis that the cost-effectiveness estimates of Yescarta compared with salvage chemotherapy exceeded £100,000 per QALY gained, with a high degree of uncertainty in the estimates. Within weeks of reaching this decision, NHS England negotiated a confidential deal with the manufacturer of Axicabtagene ciloleucel (Kite, a Gilead Company, Santa Monica, CA), that allowed 200 adults with lymphoma to access Axicabtagene ciloleucel through the Cancer Drug Fund (CDF) (5).

The use of tisagenlecleucel (Novartis, Basel, Switzerland) in paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL), was approved by NICE in December 2018 (6). The estimated incremental cost-effectiveness ratio (ICER) for tisagenlecleucel ranged from £29,501 to £44,299 per QALY gained, and was dependant on the choice of overall survival extrapolations and length of follow-up in the tisagenlecleucel studies. Tisagenlecleucel was funded on the basis it would be funded by the CDF while more data were collected.

If future cell and gene therapies have incremental cost-effectiveness ratios beyond the conventional £20,000-£30,000per QALY, what is the drawback? The real concern here is that the cost of these therapies is unsustainable and presents an opportunity cost dilemma to the NHS. For example, the opportunity cost for 200 patients treated with a single dose of CAR T-cell therapy is likely to be up to £56m, which would for example otherwise enable us to treat around 630 patients for lung cancer, the most common cause of cancer death, accounting for around a fifth (21%) of all cancer deaths (7) (Table 1). Similarly, the opportunity cost to treat 200 patients with a single dose of CAR T-cell

therapy could otherwise be spent on 4,435 patients undergoing coronary artery bypass grafting (CABG) to treat coronary heart disease (CHD), the most common type of heart and circulatory disease, and one of England's leading causes of death and single biggest cause of premature death (8).

Table 1: Trade-off between the cost of an autologous CAR T-cell therapy and life-extending lung cancer treatment Pembrolizumab (Keytruda) and CABG procedure

Parameter	Treatment		
	CAR T-cell	Pembrolizumab (Keytruda)	Coronary artery bypass grafting (CABG) procedure
Indication	Relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL)	Untreated metastatic squamous non-small-cell lung cancer	Bilateral internal mammary artery (BIMA) conduit for CABG
Cost per patient per course of treatment (£)	282,000 (6)	89,420* (9)	12,717 (10)
No of patients that can be treated per year with an annual budget of £56.4 million	200 (5)	630	4,435

* 200mg administered every 3 weeks by intravenous infusion for 1-year (list price £5,260 per infusion).

To address challenges of affordability, flexible reimbursement models have been introduced in England to reduce the risk of therapies hitting the market and limiting patient access. These are often embedded with a simple discount, but may comprise more complex models such as performance based models based upon pre-specified clinical outcomes being met (11, 12) and annuity models. Performance based models, also known as an outcomes based models, facilitate patient access to new therapies, enabling payers to manage their overall budgets and limit the financial losses as a consequence of treatment failure (13). This model has many variations, including a money back guarantee, a confidential discount and a managed access agreement (MAA). The MAA is an agreement between the payer and manufacturer, specifying the type of data to be collected while treating patients. The data includes, but is not limited to quality-based measures, clinical

outcomes, and patient satisfaction (6, 14). Annuity models allow the cost of therapies to be spread over a specified period, allowing the potential to reward innovation and to better align costs with the time period over which benefits are delivered to the patient. The aim is to reduce the up-front budget impact to the payer and reduce the initial cost of treatment (15). Implementation of performance based models with MAA have been linked to tisagenlecleucel and axicabtagene ciloleucel in England, though the exact details are not accessible due to the confidentiality issues. While, the aim of these models is to facilitate management of budgets and limit the impact of treatment failure, both models require data collection and monitoring over time, which can impose a burden on health services.

Similarly, how other countries in Europe will manage their budgets with the high-cost of CAR T-cell therapies is unclear. Germany have agreed to a performance based deal (16) but we do not currently know how Germany will assess the CAR T-cell therapies as the healthcare system traditionally waivers the MAA (17). Italy, on the other hand is not new to performance based models, particularly for oncology drugs, and has unveiled a model that involves payment in instalments based on patient response to treatment (18). Payments will be made at the time of infusion, after six months, and after 12 months. If the treatment is unsuccessful at any point in the 12-month period, hospitals will not have to make any subsequent payments(19). Additionally, in France Kymriah and Yescarta have been available for prescription through the early access program known as the l'Autorisation Temporaire d'Utilisation (ATU) and is being used for gathering real-world data that will be used during pricing negotiations (17). Finally, while most commercial insurers in the U.S. do cover CAR T-cell therapies, they do so on an individual basis, writing single-patient agreements each time. The staggering prices have led insurers to exercise coverage at a decreased rate, due to high-prices and the cost of aftercare (20).

Challenges around the clinical effectiveness of cell and gene therapies are that data are typically captured over shorter time periods (21), with a small number of patients and hampered by poorly understood study endpoints (22). Moreover, there are difficulties in identifying the appropriate comparator to measure these therapies against (23) and there is limited experience of safety evidence that might occur years after the treatment. These uncertainties make it difficult to produce estimates of health and economic impact that are the core of any assessment of value (24).

In brief, the increase in spending on cell and gene therapies poses an ongoing risk to the NHS that may not be sustainable with larger patient populations. To ensure all potential risks have been captured, NHS England will need to work closely with manufacturers to address concerns around evidence generation and pricing. However, the introduction of new reimbursement models mean

NHS England has greater flexibility to address the affordability, though reimbursement models will need to be determined from the onset to account for the budgetary impact.

Abbreviations

CAR T-cell: chimeric antigen receptors T-cell therapies
HST: Highly specialised technologies
NICE: National Institute for Health and Care Excellence
ICER: Incremental cost-effectiveness ratio
QALY: Quality-adjusted life-year
TA: Technology Appraisal
CDF: Cancer Drug Fund
ALL: Acute lymphoblastic leukaemia
BIMA: Bilateral internal mammary arteries

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Author statements

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The authors declare that they have no competing interests.

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References

1. National Institute for Health and Care Excellence (NICE). Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes [Internet]. April 2017 [cited September 2019]. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf.
2. National Institute for Health and Care Excellence. NICE gets go-ahead to fast-track more drug approvals [Internet]. March 2017 [cited 22 September 2019]. Available from: https://www.nice.org.uk/news/article/nice-gets-go-ahead-to-fast-track-more-drug-approvals.
3. Gilead. Kite's Yescarta (Axicabtagene Ciloleucel) Becomes First CAR T Therapy Approved by the FDA for the Treatment of Adult Patients With Relapsed or Refractory Large B-Cell Lymphoma After Two or More Lines of Systemic Therapy [Internet]. 18 October 2017 [cited September 2017]. Available from: https://www.gilead.com/news-and-press/press-room/press-releases/2017/10/kites-yescarta-axicabtagene-ciloleucel-becomes-first-car-t-therapy-approved-by-the-fda-for-the-treatment-of-adult-patients-with-relapsed-or-refrac.
4. National Institute for Health and Care Excellence. Appraisal Consultation Document. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [internet]. August 2018 [cited September 2019]. Available from: https://www.nice.org.uk/guidance/ta559/documents/appraisal-consultation-document.
5. NHS England. NHS England strikes deal for ground breaking cancer treatment in a new European first [Internet]. 5 October 2018 [cited October 2019]. Available from: https://www.england.nhs.uk/2018/10/nhs-england-strikes-deal-for-ground-breaking-cancer-treatment-in-a-new-european-first/.
6. National Institute for Health and Care Excellence. Technology Apprasial Guidance.Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [TA554] [Internet]. 21 December 2018 [cited September 2019]. Available from: https://www.nice.org.uk/guidance/ta554/resources/tisagenlecleucel-for-treating-relapsed-or-refractory-bcell-acute-lymphoblastic-leukaemia-in-people-aged-up-to-25-years-pdf-82607021872837.
7. Cancer Research UK. Cancer mortality for common cancers [Internet]. 2017 [cited 22 September 2019]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared.
8. British Heart Foundation. England Factsheet, Heart and Circulatory Diseases (Cardiovascular Disease; CVD) [Internet]. December 2019 [cited January 2019]. Available from file://ad.ucl.ac.uk/homep/rmjdnvp/DesktopSettings/Desktop/bhf-cvd-statistics-england-factsheet.pdf.
9. National Institute for Health and Care Excellence. New lung cancer treatment option approved by NICE [Internet]. 8 August 2019 [cited 22 September 2019]. Available from: https://www.nice.org.uk/news/article/new-lung-cancer-treatment-option-approved-by-nice.
10. Gray AM, Murphy J, Altman DG, Benedetto U, Campbell H, Flather M, et al. One-year costs of bilateral or single internal mammary grafts in the Arterial Revascularisation Trial. Heart (British Cardiac Society). 2017;103(21):1719-26.
11. Kusel J, Spoors J. Recent trends in the pricing of high-cost pharmaceuticals. British Journal of Healthcare Management. 2016;22(5):267-77.

12. Ramsey S. Drug pricing should depend on shared values. Nature. 2017;552(7685):S78.
13. Cook FS, T. Werner, M. Regenerative Medicine is Here: New Payment Models Key To Patient Access [Internet]. July 2018 [cited September 2019]. Available from: https://invivo.pharmaintelligence.informa.com/IV005371/Regenerative-Medicine-Is-Here-New-Payment-Models-Key-To-Patient-Access.
14. National Institute for Health and Care Excellence. Cancer Drugs Fund, Managed Access Agreement. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA559] [Internet]. 23 January 2019 [cited September 2019]. Available from: https://www.nice.org.uk/guidance/ta559/resources/axicabtagene-ciloleucel-for-treating-diffuse-large-bcell-lymphoma-and-primary-mediastinal-large-bcell-lymphoma-after-2-or-more-systemic-therapies-pdf-82607030270917.
15. Slocomb TW, M. Haak, T. Valluri, S. Rader, B. New Payment And Financing Models For Curative Regenerative Medicines [Internet]. 24 July 2017 [cited September 2019]. Available from: https://invivo.pharmaintelligence.informa.com/IV005132/New-Payment-And-Financing-Models-For-Curative-Regenerative-Medicines.
16. Bruce F. Novartis Strikes Kymriah Outcome-Based Deal With German Insurers [Internet]. 14 March 2019 [cited 22 September 2019]. Available from: https://pink.pharmaintelligence.informa.com/PS124927/Novartis-Strikes-Kymriah-OutcomeBased-Deal-With-German-Insurers.
17. Privolnev Y, Webster R. CAR T-Cell Therapies In The EU5: What Can We Expect From Payers? [Internet]. 24 January 2019 [cited 22 September 2019]. Available from: https://www.cellandgene.com/doc/car-t-cell-therapies-in-the-eu-what-can-we-expect-from-payers-0001.
18. Schofield I. Italy Unveils New Payment Model For Novartis's CAR-T Kymriah [Internet]. 19 August 2019 [cited 22 Septemebr 2019]. Available from: https://pink.pharmaintelligence.informa.com/PS140701/Italy-Unveils-New-Payment-Model-For-Novartiss-CART-Kymriah.
19. Grubert N. Italy announces a new reimbursement model for the first CAR-T-cell therapy [Internet]. 8 August 2019 [cited 22 September 219]. Available from: https://www.linkedin.com/pulse/italy-announces-new-reimbursement-model-first-therapy-neil-grubert.
20. Andrews M. Kasier Health News. Italy announces a new reimbursement model for the first CAR-T-cell therapy [Internet]. 17 July 2018 [cited 22 September 2019]. Available from: https://khn.org/news/staggering-prices-slow-insurers-coverage-of-car-t-cancer-therapy/.
21. Abou-El-Enein M, Hey SP. Cell and Gene Therapy Trials: Are We Facing an 'Evidence Crisis'? EClinicalMedicine. 2019;7:13-4.
22. Solaski B, Yin P. 4 Barriers To Cell And Gene Therapy Development For Rare Diseases — And How To Overcome Them [Internet]. 27 September 2018 [cited 22 September 2019]. Available from: https://www.cellandgene.com/doc/barriers-to-cell-and-gene-therapy-development-for-rare-diseases-and-how-to-overcome-them-0001.
23. Goldsmith J, Kempf L, Blumenrath S. From Drug Development to Approval [Internet]. April 2018 [cited Septemeber 2019]. Available from: https://globalforum.diaglobal.org/issue/april-2018/the-challenge-of-rare-diseases-from-drug-development-to-approval/.
24. Jonsson B, Hampson G, Michaels J, Towse A, von der Schulenburg JG, Wong O. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. The European journal of health economics : HEPAC : health economics in prevention and care. 2019;20(3):427-38.