Health technology assessment of chimeric antigen receptor (CAR) T-cell therapies for cancer

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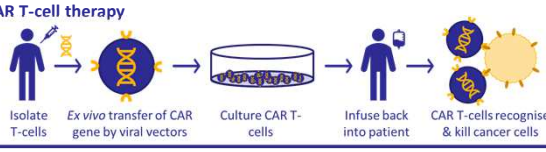
Introduction

- Chimeric antigen receptor (CAR) T-cell therapy involves genetically engineering a patient's T-cells to produce CARs which, when infused back into the patient, can recognise and kill cancer cells expressing the antigen on their cell surface (**Figure 1**).
- Axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah) are CAR T-cell therapies licensed for the treatment of rare cancers (prevalence ≤1:2,000 in EU or <200,000 people in US)[1,2].
- HTA organisations may use specialised criteria to assess drugs for rare cancers and other rare diseases. For example, the National Institute for Health and Care Excellence (NICE; England) Highly Specialised Technology (HST) Programme assesses drugs for ultra-rare diseases (prevalence ≤1:50,000)[3]. Cancer treatments can also be recommended by NICE within the Cancer Drugs Fund (CDF)[4].

Figure 1: CAR T-cell therapy



Objectives and Methods

The objectives and methods are summarised in **Figure 2**.

Figure 2: Objectives and methods

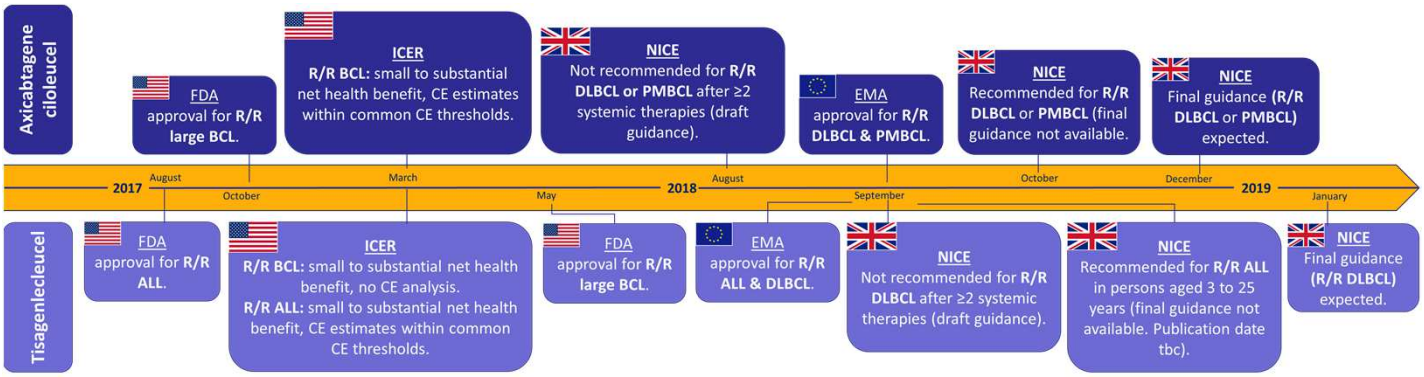
Identify HTAs of licensed CAR T-cell therapies in key European markets (England, France, and Germany) and the US. → Review the HTA outcomes and key considerations/ criteria used to assess CAR T-cell therapies. → Understand the HTA challenges and opportunities facing CAR T-cell therapies and other innovative gene therapies.

- Searches conducted 9th October 2018:
  - National Institute for Health and Care Excellence (NICE; England) (https://www.nice.org.uk/);
  - National Authority for Health (HAS; France) (https://www.has-sante.fr/);
  - Federal Joint Committee (G-BA; Germany) (https://www.g-ba.de/);
  - Institute for Clinical and Economic Review (ICER; US) (https://icer-review.org/);
  - PubMed, Embase, Cochrane Library, EconLit, and ISPOR Scientific Presentations Database.

Results

- Draft guidance documents from NICE were identified for **1)** axicabtagene ciloleucel in relapsed/ refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL)[5] and **2)** tisagenlecleucel for R/R DLBCL[6].
- A positive recommendation from NICE was identified for tisagenlecleucel in R/R acute lymphoblastic leukaemia (ALL) in persons aged 3 to 25 years. Details of the appraisal were unavailable at time of writing.
- A combined assessment of CAR T-cell therapies was conducted by ICER[7].
- HTA conclusions, as of October 2018, from NICE and ICER are summarised in **Figure 3**.
- No HTAs by HAS or the G-BA were identified.
- Supplementary database searching identified two publications for R/R ALL:
  1. An exploratory mock NICE appraisal of CAR T-cell therapy[8].
  2. A cost analysis of implementing a managed entry agreement (MEA) for a hypothetical CAR T-cell therapy from a National Health Service (NHS) England perspective[9].

Figure 3: Timeline of regulatory and HTA decisions for axicabtagene ciloleucel and tisagenlecleucel



ALL, acute lymphoblastic leukaemia; BCL, B-cell lymphoma; CE, cost-effectiveness; DLBCL, diffuse large BCL; PMBCL, primary mediastinal BCL; R/R, relapsed/ refractory; TBC, to be confirmed.

UK

Axicabtagene ciloleucel

- NICE considered both clinical and cost-effectiveness (CE) estimates to be associated with substantial uncertainty due to the use of single arm clinical data for R/R DLBCL and PMBCL[5]. End-of-life (EoL) criteria (life expectancy <24 months and extension of life >3 months) were met but all CE estimates were above the £50,000/ quality-adjusted life year (QALY) gained threshold. Not eligible for inclusion in the CDF in draft guidance.

Tisagenlecleucel

- Single arm data of short duration was a source of uncertainty for R/R DLBCL[6]. CE estimates, incorporating a PAS confidential discount, ranged from £47,500-94,000/ QALY gained, above the £20,000-30,000/ QALY range NICE normally consider cost-effective. In draft guidance, EoL criteria were not met and ineligible for inclusion in the CDF.
- Recommended for R/R ALL in patients aged 3 to 25 years following commercial agreement between the manufacturer and NHS England. At time of writing, no details of the appraisal have been published.

US

Axicabtagene ciloleucel

- ICER's base case CE estimate in R/R BCL was $136,078 vs. standard of care[7]. Payment was made at infusion and CE estimates exceeded $150,000 per QALY gained in some sensitivity analyses. Based on an estimated 5,902 eligible patients, the $915 million budget impact (BI) threshold was exceeded at all except the price to achieve a CE estimate of $50,000/ QALY gained. A pricing discount of 11-28% would be required to reach the CE threshold prices of $100,000 and $150,000/ QALY gained.

Tisagenlecleucel

- ICER's base case CE estimate in R/R ALL was $45,871 vs. standard of care[7]. Payment was made for responders at one month and results were robust through sensitivity analysis, remaining less than $150,000 per QALY gained in all analyses. Based on an estimated 400 eligible patients, the BI threshold was not exceeded at any modelled price.
- CE analysis in R/R BCL was not performed due to a lack of available data for cost-effectiveness modelling.

Conclusions

- NICE used hypothetical data for a CAR T-cell therapy in a mock HTA appraisal[8]. This appraisal highlighted uncertainty in the evidence base from single-arm trials as a major HTA challenge, which has been highlighted by both NICE and ICER during subsequent assessments.
- Clinical uncertainty was also highlighted as an issue in implementing a performance-based MEA for a hypothetical CAR T-cell therapy in England. Increased monitoring would be required to compensate for greater clinical uncertainty and to inform the performance-based reimbursement, resulting in increased costs and administrative burden[9].
- Although innovation was acknowledged in NICE assessments, this did not strongly influence decision-making. HTA processes may need to adapt for assessment of innovative technologies such as CAR T-cell therapy.
- Furthermore, innovative pricing and reimbursement schemes are likely to be essential for securing access to these treatments. The ICER assessment of CAR-T therapies highlighted the effect of pricing arrangements on net budget impact. These innovative schemes may be particularly important to allow management of combined budget impact where a treatment is used across multiple indications.

References:
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2) EMA (2018). Find medicines. Accessed 17th September 2018.
3) NICE (2017). Interim process and methods of the highly specialised technologies programme.
4) NICE [PGM9 addendum] (2018). Final amendments to NICE TA methods guide to support CDF arrangements.
5) NICE [IS1115] (2018). Axicabtagene ciloleucel for DLBCL and PMBCL after 2 or more systemic therapies.
6) NICE [ID1166] (2018). Tisagenlecleucel for R/R DLBCL after 2 or more systemic therapies.
7) ICER (2018). CAR T-cell therapy for B-cell cancers: effectiveness and value.
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