Chimeric Antigen Receptor T-Cells (CAR-Ts): Are Ongoing Clinical Trials Designed to Meet Evidence Needs of Key European Health Technology Assessments (HTAs)?

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Background

- Cell therapies represent the largest number of active agents in development in the immune-oncology field overall[1]
- Chimeric antigen receptor t-cells (CAR-Ts) are innovative therapies requiring reprogramming of a patient's own T-cells to express a chimeric antigen receptor (CAR) on their surface. These CAR-Ts are then reinjected into the patient to elicit robust T-cell activation and killing of tumor cells bearing the target antigen
- Tisagenlecleucel and axicabtagene ciloleucel were the 2 first CAR-Ts approved in Europe by the European Medicines Agency (EMA) in 2018[2,3]
- Tisagenlecleucel is indicated in patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in post-transplant relapse, or in second or later relapse (R/R ALL) and adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) after 2 or more lines of systemic therapy[2]
- Axicabtagene ciloleucel is indicated in adult patients with R/R DLBCL and relapsed or refractory primary mediastinal large B-cell lymphoma (R/R PMBCL) after 2 or more lines of systemic therapy[3]
- Following EMA approval, both these products have been assessed by various national health technology assessment bodies (HTABs) in Europe
- Multiple CAR-T products are now in phase 1/2 to phase 3 clinical trials for a variety of indications
- Although CAR-Ts may display exceptional efficacy or curative potential, they are also associated with a high economic impact, which can raise the evidentiary demands of HTABs appraising new CAR-Ts

Objectives

To review available tisagenlecleucel and axicabtagene ciloleucel assessments by HTABs in core European countries and compare their evidence expectations with the design of ongoing CAR-T trials to understand if they could generate the supporting evidence sought by these key HTABs

Methods

- National HTA decisions in 5 European countries (France, Germany, Italy, Spain, and the United Kingdom) for tisagenlecleucel and axicabtagene ciloleucel in hematological cancers were reviewed to assess appraisal outcomes, cited evidence gaps, and future data needs
- All ongoing phase 1/2 to phase 4 clinical trials for any CAR-T were identified from clinicaltrials.gov. CAR-T monotherapy trials in hematological malignancies were selected from identified trials and their salient features, including design, endpoints, and comparators, were extracted and benchmarked against evidence requirements articulated by HTABs in their appraisals

Results

Health technology assessment (HTA) decisions

- Reviewed HTA decisions (n=14) showed that to date, 6 HTABs across the 5 European countries have approved tisagenlecleucel and 3 have approved axicabtagene ciloleucel
- Availability of a comparator arm and inclusion of survival endpoints as primary outcomes in clinical trials were key evidence requirements cited in these decisions (Table 1)
- Approvals were given based on evidence from single-arm trials
- All the reviewed HTAB decisions mandated collection of additional data to mitigate the lack of comparative trial data and the uncertainty about long-term benefits. The National Institute for Health and Care Excellence (NICE) stated that collecting more data on overall survival (OS) and progression-free survival (PFS) for tisagenlecleucel will reduce the uncertainty in the evidence
- While the information on outcome-based agreements was not always publicly available, 3 countries were identified as having negotiated specific schemes for tisagenlecleucel and axicabtagene ciloleucel

"There is a high degree in uncertainty in the estimates of overall survival for tisagenlecleucel because of the length of follow-up in the tisagenlecleucel studies and that this was an important source of uncertainty in the economic model. Further data on overall survival would likely resolve these uncertainties."
NICE Tisagenlecleucel in R/R ALL[4]

"Although the trial showed axicabtagene ciloleucel to be effective at increasing response rate, progression-free survival, and overall survival, the immaturity of the data and the lack of data comparing it with other treatments makes the magnitude of the benefit uncertain."
NICE axicabtagene ciloleucel R/R DLBCL[5]

"Precise quantification of the clinical benefit is difficult due to the absence of head-to-head data. There is a need for data on a larger number of patients and with a longer follow-up than currently available (median follow up of 15.1 months) to ensure the maintenance of the response and the impact on overall survival."
TC, Axicabtagene ciloleucel in R/R DLBCL[7]

"In the data cuts available for the benefit assessment, the very short median follow-up time and incomplete recruitment of patients give rise to strong uncertainties. In addition, there are no data cuts for the intent-to-treat population, including patient characteristics and overall survival. Overall, from a legal point of view, there is an unquantifiable added benefit."
G-BA, Tisagenlecleucel in R/R ALL[6]

"It remains to be determined whether the results of efficacy translate into a better overall survival and the potential impact on the evolution of the disease. A post-authorization study will be carried out to obtain long-term safety data."
AEMPS, Tisagenlecleucel in R/R ALL[8]

Ongoing trials in CARTs

- Of 38 CAR-T trials meeting inclusion criteria, 35 (92%) were phase 1/2 or phase 2 single-arm studies (n=3−500 participants); 3 (8%) were phase 3 head-to-head studies (n=220−381 participants).
- Overall response rate (ORR) was the most common primary endpoint (26 trials; 68%), followed by adverse events/toxicity (13 trials; 34%).
- OS was being measured in 25 (66%) trials and PFS in 26 (68%), mostly as secondary endpoints. Only the 3 phase 3 trials included a comparator arm and measured OS or PFS as a primary endpoint, thereby meeting both the stated evidence requirements of HTABs
- Quality of life (QoL) was measured in 11 (29%) of the trials. The EuroQol-5 Dimensions (EQ-5D) was the most common instrument (n=8), followed by the cancer-specific European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) (n=6), and the Short Form-36 (SF-36) (n=1) for general health status. Two trials did not specify the instrument used and the myeloma-specific QLQ-MY20 was used in 4 of the 6 trials that used the EORTC instrument.

REFERENCES:
1. Tang J, Pearce L, O'Donnel-Torney J, et al. *Nat Rev Drug Discovery*. 2018;17:783-784. **2.** EMA. Tisagenlecleucel EPAR. September 2018; **3.** EMA. Axicabtagene ciloleucel EPAR. September 2018. **4.** NICE. TA554 tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years, 21 December 2018 (accessed 2/9/2019). **5.** NICE. TA567, axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115] committee papers (accessed 2/9/2019). **6.** G-BA. medicinal products directive / annex XII: tisagenlecleucel (DLBCL), 7 March 2019 (accessed 27 August 2019). **7.** Transparency Commission. Axicabtagene ciloleucel (DLBCL and PMBCL), 5 December 2018 (accessed 27 August 2019). **8.** AEMPS therapeutic positioning report, tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years, 25 February 2019 (accessed 27 August 2019).

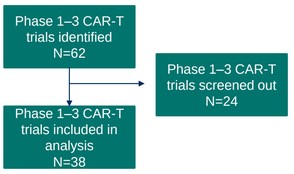
Results (cont.)

Table 1. Summary of Key HTA Assessment Outcomes per Country

	Tisagenlecleucel	Axicabtagene ciloleucel
England	▪ Recommended by NICE in Dec 2018 and March 2019 in 2 indications: R/R DLBCL in adults and R/R ALL in people aged up to 25 ▪ In R/R DLBCL, considered a life-extending treatment at the end of life and included in the CDF ▪ In R/R ALL, not considered a life-extending treatment at the end of life but included in the CDF ▪ Cited lack of comparative trial data for uncertainty in benefit ▪ Managed access agreement and a confidential commercial access arrangement implemented	▪ Recommended by NICE in January 2019 in R/R DLBCL and R/R PMBCL ▪ Considered a life-extending treatment at the end of life and included in the CDF ▪ Lack of comparative trial data cited as a shortcoming ▪ Managed access agreement and a confidential commercial access arrangement implemented
France	▪ Approved by HAS in December 2018 after being approved for an early access program (ATU) in July 2018 in 2 indications: R/R DLBCL in adults and R/R ALL in people aged up to 25 ▪ Granted SMR important and ASMR IV in R/R DLBCL ▪ Granted SMR important and ASMR III in R/R ALL ▪ Mandatory data collection via a registry for CAR-T products and reassessment by HAS required every year ▪ Lack of comparative and tolerability trial data and QoL data cited as shortcomings	▪ Approved by HAS in December 2018 for R/R DLBCL and R/R PMBCL after being approved for early access program (ATU) in July 2018 ▪ Granted SMR important and ASMR III ▪ Mandatory data collection via a registry for CAR-T products and reassessment by HAS required every year ▪ Lack of comparative and tolerability trial data and QoL data cited as shortcomings
Germany	▪ Approved by the G-BA in July 2019 in 2 indications: R/R DLBCL in adults and R/R ALL in people aged up to 25 ▪ Granted orphan status in both indications; therefore, additional benefit granted by default ▪ Extent of benefit rated "unquantifiable" with submitted evidence (no comparative trial data, lack of QoL data) ▪ Current decisions will be reviewed by March 2020 ▪ Outcomes-based agreement implemented (pay-for-performance)	▪ Approved by G-BA in February 2019 in R/R DLBCL and R/R PMBCL ▪ Granted orphan status in both indications; therefore, additional benefit granted by default ▪ Extent of benefit rated "unquantifiable" with submitted evidence (no comparative trial data, lack of QoL data) ▪ Current decision will be reviewed by May 2022 ▪ Outcomes-based agreement implemented
Italy	▪ Approved by AIFA in Aug 2019 in 2 indications: R/R DLBCL in adults and R/R ALL in people aged up to 25 ▪ Restricted for use in centers of excellence only ▪ Outcomes-based agreement put in place (payment by results	Appraisal in progress as of Sep 2019
Scotland	▪ Approved by SMC in Feb 2019 in R/R ALL in people aged up to 25 ▪ Rejected by SMC in Mar 2019 for R/R DLBCL in adults ▪ Resubmission evaluated in Aug 2019 and approved in Sep 2019 ▪ Lack of comparative data, confounding of the treatment effect due to bridging therapy, and short follow-ups were cited as shortcomings	▪ Rejected by SMC in Feb 19 for R/R DLBCL and R/R PMBCL ▪ Resubmission to be evaluated third quarter of 2019
Spain	▪ Approved by the Spanish health ministry in February 2019 in 2 indications: R/R DLBCL in adults and R/R ALL in people aged up to 25 ▪ Restricted for use in centers of excellence only ▪ Lack of comparative trial data cited; long-term data are necessary to confirm the benefits observed	No publicly available information was found at the time of the search

Key: AEMPS – Agencia Española de Medicamentos y Productos; AIFA – Agenzia Italiana del Farmaco; ALL – acute lymphoblastic leukemia; ASMR – added medical benefit; ATU – autorisation temporaire d'utilization; CDF – Cancer Drug Fund; DLBCL – diffuse large B-cell lymphoma; GBA – Gemeinsamer Bundesausschuss; HAS – Haute Autorité de Santé; NICE – National Institute for Health and Care Excellence; PMBCL – primary mediastinal large B cell lymphoma; QoL – quality of life; R/R – relapsed refractory; SMC – Scottish Medicines Consortium; SMR – medical benefit

Figure 1. Summary of Ongoing Clinical Trials in CAR-Ts



Reason for Exclusion	N
Endpoints: No measure of efficacy	14
Indication: Not a hematological malignancy	9
Intervention: Combination therapy	1
Total	24

Meet HTA Expectations
- RCT
- OS or PFS as primary endpoint

3 Clinical Trials
- All 3 are phase 3, head-to-head trials against SOC in the respective indications that include either OS (n=1) or PFS (n=2) as a primary endpoint
- Indications: MM, NHL, and ALL

Partially Meet HTA Expectations
- Single-arm trial
- OS as a secondary endpoint
- N≥50

16 Clinical Trials
- Equal number of phase 2 (n=8) and phase 1/2 (n=8) single-arm trials with ≥50 participants
- The primary or co-primary endpoints are ORR (n=12), AEs (n=4), MRD (n=1), and CR (n=1)
- QoL endpoints are included in 7 trials, whereas the remaining 9 trials do not have any QoL endpoints
- Indications: ALL, CLL, DLBCL, FL, MCL, MM, NHL

Do Not Meet HTA Expectations
- Single-arm trial
- No OS endpoint

19 Clinical Trials
- All are single-arm phase 1/2 (n=15) or phase 2 (n=4) trials
- The primary or co-primary endpoints are ORR (n=14), AEs (n=8), and DLTs (n=2)
- QoL endpoints are not included in the majority (n=18) of these trials and only 1 trial includes a QoL endpoint
- Indications: ALL, MM, NHL, CLL, DLBCL, and MCL

Key: AE – adverse event; ALL – acute lymphoblastic leukemia; BCMA – B-cell maturation antigen; CLL – chronic lymphocytic leukemia; CR – complete response; DLBCL – diffuse large B-cell lymphoma; DLT – dose-limiting toxicity; FL – follicular lymphoma; HTA – health technology assessment; MM – multiple myeloma; MRD – maximum recommended dose; NHL – non-Hodgkin Lymphoma; ORR – overall response rate; OS – overall survival; MCL – mantle cell lymphoma; QoL – quality of life; RCT – randomized controlled trial; R/R – relapsed or refractory; RRMM – relapsed or refractory multiple myeloma; SOC – standard of care

Conclusions

- Our assessment suggests that only a minority of ongoing clinical trials for CAR-Ts in hematological cancers are currently designed to generate comparative efficacy evidence matching existing HTAB expectations in 5 key European countries
- Some ongoing single-arm phase 2 trials may support conditional reimbursement; however, with the increasing number of CAR-Ts and appraisals, HTAB decisions will likely evolve to require more robust survival and comparative data before expanding patient access to these therapies

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