LIMITATIONS AND EXPECTED CHALLENGES OF CAR-T ECONOMIC EVALUATION

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OBJECTIVES:

Provide an overview of Chimeric Antigen Receptor T (CAR-T) cells clinical trials under development, analyze the methodology of the CAR-T health technology assessments (HTA) appraisals currently published, and identify challenges related to CAR-T cells compared to existing treatments that may impact the cost-effectiveness analysis (CEA).

METHODS:

A search of phase 2 and 3 CAR-T cells clinical trials under development was performed on ClinicalTrials™ database[1] (on August 2018).
Secondly, a targeted literature review on PubMed and HTA Accelerator ™ (online platform summarizing HTA assessment reports published by HTA bodies worldwide) was conducted to identify publicly available information from HTA appraisals related to curative and innovative therapies.
As a final step, a comparison of methodologies and issues raised in these HTA appraisals were analyzed.

RESULTS:

A total of 175 clinical CAR-T cells trials were identified, with a majority of trials performed in hematology. Target populations of CAR-T cells trials mainly focused on adults and seniors. Most of these trials are based on a small sample size (n≤50). A majority of current CAR-T cells trials are in their early stages of development (between phases 1 and 2) **[Figure 1]**.

Two CAR-T cells therapies have recently been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA)[2,3,4,5], and two CEAs reports have been published[6,7]. In both studies, a payer perspective and a lifetime horizon were chosen, but different modelling structures and assumptions related to data extrapolation were used. Despite a significant health gain (*4.12 to 11.95 Life Years (LY)*) and an incremental cost-effectiveness ratio (ICER(1)) which fell above the range normally considered cost-effective (*45,871-136,078 $/QALY and 49,994-49,995 £/QALY*), HTA bodies raised concern around uncertainty surrounding survival data extrapolation, mainly due to the lack of long-term data and the phase 2 study design **[Figure 2]**. In addition, given the specific cycle of administration for CAR-T cells, a lack of experience of using the treatment, the absence of a regulatory framework, valorization of costs and extrapolation of clinical data remain uncertain.
For now, the National Institute for Health and Care Excellence (NICE) is the first European HTA body that issued pre-appraisals for two CAR-T cells: YESCARTA® and KYMRIAH®. In its draft guidance, the NICE has recommended YESCARTA® has a treatment option in the Cancer Drugs Fund for treating diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) after two or more systemic therapies. This was approved on August, 2018[8], i.e. one month before National Health Service (NHS) rejected use of KYMRIAH® for treating adults with relapsed or refractory DLBCL[9]. However, the NICE approved KYMRIAH® for treating B-cells Acute Lymphoblastic Leukemia (B-ALL) for patients aged from 3 to 25 years. Assessment of long-term impact of CAR-T cells therapies remain uncertain and may be a major concern for HTA bodies, given the expected budget impact for payers due to the high drug price.

The main challenges of CAR-T cells market access are summarized in **[Figure 3]**. Manufacturers will have to make sure to collect real life data to anticipate new evaluations.

Figure 1 An overview of currently approved and upcoming CAR-T cells trials[1]

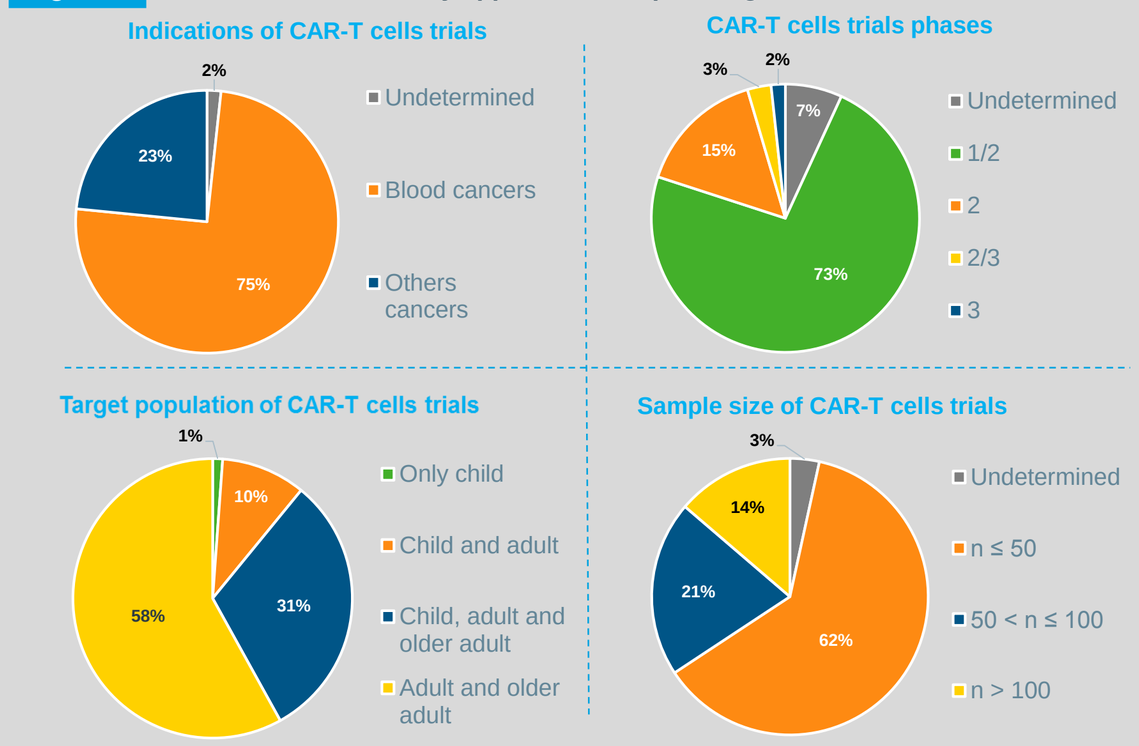
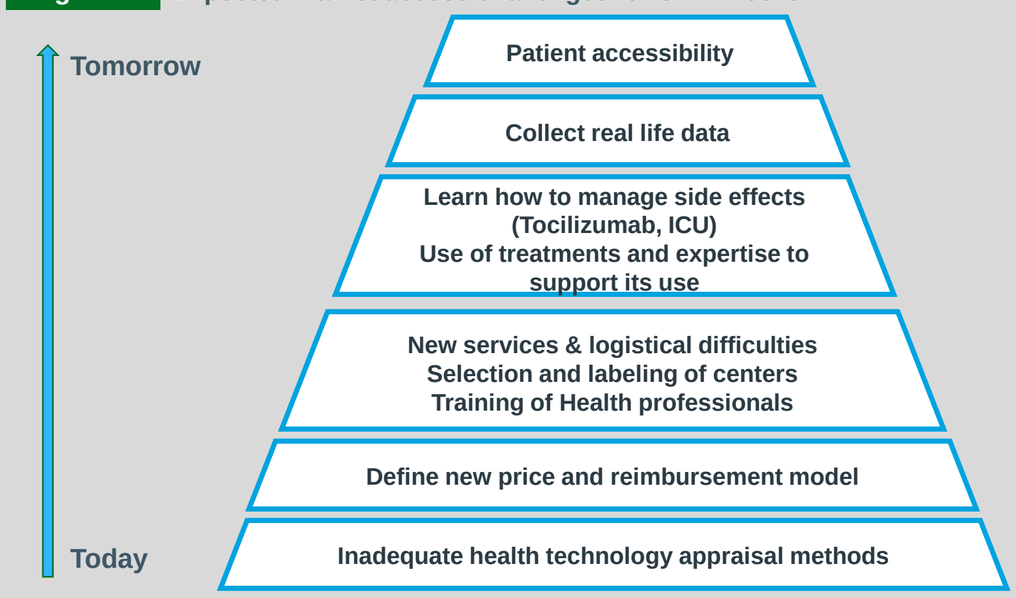


Figure 2 Comparison of CAR-T cells economic evaluation by the NICE and the ICER(2)

	ICER(2)[6]		NICE[7]	
	YESCARTA®	KYMRIAH®	Curative	Bridge to HSCT
Type of model	Short-term decision tree and long-term semi-Markov partitioned survival model		Curative intent model based on a simple three-state (alive and event free, alive post event, dead) partitioned survival model	Short-term decision tree and long-term semi-Markov partitioned survival model
Population	Adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma who are ineligible for auto-SCT	Patients ages 0-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL)	Children and young adults with two or more relapses or refractory ALL.	
Perspective	Third-party payer		NHS/PSS	
Choice of comparator	Chemotherapy	Clofarabine	Clofarabine	
CAR-T payment strategy	Payment at infusion	Only for responders at one month	Payment for performance	
Time horizon	Lifetime time horizon		Lifetime horizon	
Costs and outcomes discount rate	3%	3%	3.5%	3.5%
Extrapolation methods	After 5 years, survivors experienced a mortality risk profile consistent with that of a long-term survivor, after adjustments were made for excess mortality. OS equals general population survival and PFS remain constant for responders. After the 5-year time horizon, patients in the 'alive and not responding to treatment' state will be assumed dead.		Alternative scenarios are considered to compare the implications of different methods for the extrapolation of the results.	
Costs to be considered	The model included costs of : hospital stays, therapies administration during hospitalization and grade 3/4 AEs. A hospital mark-up was added for each hospital-administered treatment ($100,000 per treatment).		The resource use and costs incorporated within each separate model were based on the following components: treatment acquisition costs, administration and monitoring costs, adverse events, HSCT, long-term costs.	
ICER(1) results (base case)	4.12 LY, 3.40 QALY 112,168$/LY, 136,078$/QALY	7.91 LY, 7.18 QALY 41,642$/LY, 45,871$/QALY	11.95 LY, 10.07 QALY 449,128£, 49,994 £/QALY	8.83 LY, 7.46 QALY, 583,362£, 49,995 £/QALY

Figure 3 Expected market access challenges for CAR-T cells



CONCLUSION:

Many CAR-T cells clinical trials are currently ongoing in different therapeutic areas. Among available CAR-T cell CEAs, the same challenges seem to be encountered. Majority of trials are single arms, with a small sample size and a limited follow-up limiting comparability of data and adding a large uncertainty around data extrapolation. Valorization of resources is also difficult given the limited experience of use.

Abbreviations: Auto-SCT: Auto-Stem Cell Transplant; B-ALL: B-cells Acute Lymphocytic Leukemia; CAR-T: Chimeric Antigen Receptor T; CEA: Cost-Effectiveness Analysis; CEESP: Committee on Economic Evaluation and Public Health; DLBCL: Diffuse Large B-Cell Lymphoma; EMA: European Medicines Agency; FDA: Food and Drug Administration; HSCT: Hematopoietic Stem Cell Transplantation Target; HTA: Health Technology Assessment; ICER(1): Incremental Cost-Effectiveness Ratio; ICER(2)): Institute for Clinical and Economic Review; ICU: Intensive Care Unit; LY: Life Year; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PMBCL: primary mediastinal B-cell lymphoma; QALY: Quality-Adjusted Life-Year;

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