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™ database1 (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)2-5, and two CEAs reports have been published6-7. 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 bases 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, 20188, i.e. one month before National Health Service (NHS) injected use of KYMRIAH® for treating adults with relapsed or refractory DLBCL9. 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.

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.


Figure 1
Indications of CAR-T cells trials
a) Unallocated
b) Hematological

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

<table>
<thead>
<tr>
<th>Type of model</th>
<th>NICE</th>
<th>YESCARTA®</th>
<th>KYMRIAH®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term decision tree and long-term semi-Markov partitioned survival model</td>
<td>Curative</td>
<td>Bridge to HICST</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3
Expected market access challenges for CAR-T cells

Tomorrow
Patient accessibility
Collect real life data
Learn how to manage side effects (Tocilizumab, ICU)
Use of treatments and expertise to support its use
New services & logistical difficulties
Selection and labeling of centers
Training of Health professionals
Define new price and reimbursement model
Inadequate health technology appraisal methods

Today

References:

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