Chimeric antigen receptor T-cell (CAR-T) therapy is a transformative therapy that involves patients' own immune cells being collected, engineered, and infused back to attack cancer cells. In 2017, two CAR-T therapies were approved by the US Food and Drug Administration (FDA): axicabtagene ciloleucel for the treatment of adults with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) and tisagenlecleucel for the treatment of pediatric B-cell acute lymphoblastic leukemia (B-ALL). These therapies have recently undergone cost-effectiveness evaluations by the US Institute for Clinical and Economic Review (ICER) and the UK National Institute for Health and Care Excellence (NICE). We reviewed and compared these assessments, focusing on extrapolation of overall survival (OS), to explore which model was most suitable and accurate in predicting long term OS.

Methods

We identified one ICER evaluation that included two populations and three NICE technology assessment (TAs) of the cost-effectiveness of CAR-T therapies, axicabtagene ciloleucel (R/R DLBCL) and tisagenlecleucel, which are presented in Table 1. Following review of OS methods in each evaluation, we performed a targeted search of updated trial data and compared the original experimental OS to the latest trial data.

Table 1: Overview of NICE and ICER CAR-T therapy valuations

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>NICE TA554</th>
<th>NICE TA556</th>
<th>NICE TA677</th>
<th>ICER DLBCL</th>
<th>ICER B-ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>R/R DLBCL in people aged up to 25 years; unicor cells followed parametric curve from time of infusion</td>
<td>R/R DLBCL in adults after two or more systemic therapies</td>
<td>R/R DLBCL in adults after two or more systemic therapies</td>
<td>R/R DLBCL in adults after two or more systemic therapies</td>
<td>R/R B-ALL in people aged up to 25 years</td>
</tr>
<tr>
<td>Trial</td>
<td>ELIANA, ENDEavour, B2101J</td>
<td>ZUMA-1</td>
<td>JULIET</td>
<td>ZUMA-1</td>
<td>JULIET</td>
</tr>
<tr>
<td>Intervention</td>
<td>Tisagenlecleucel</td>
<td>Axicabtagene ciloleucel, Tisagenlecleucel</td>
<td>Tisagenlecleucel</td>
<td>Axicabtagene ciloleucel, Tisagenlecleucel</td>
<td>Tisagenlecleucel</td>
</tr>
<tr>
<td>Comparators</td>
<td>Salvage chemotherapy, excluding platinaptein</td>
<td>Salvage chemotherapy, excluding platinaptein</td>
<td>Salvage chemotherapy</td>
<td>Salvage chemotherapy, excluding platinaptein</td>
<td>Salvage chemotherapy</td>
</tr>
<tr>
<td>Final recommendations</td>
<td>Recommended for CDF</td>
<td>Cost effective, but highly uncertain</td>
<td>Cost effective, but highly uncertain</td>
<td>Cost effective, but highly uncertain</td>
<td>Cost effective, but highly uncertain</td>
</tr>
</tbody>
</table>

Key: R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drug Fund; R/R DLBCL, relapsed/refractory diffuse large B-cell lymphoma; ICER, Institute for Clinical and Economic Review; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Results

We identified a newer data cut of ZUMA-1 after the NICE and ICER assessments. Table 3 compares the key OS extrapolation results reported in the health technology assessments (HTAs), with the latest data cut available. Using digitized data, Figure 1 shows the overlay of original and newer Kaplan–Meier data, as well as the preferred extrapolations in the HTAs. The company base case OS extrapolation approach in NICE TA559 (a log-logistic mixture cure model with an estimated cure fraction of 50%) appears to predict the latest available Kaplan–Meier data better than the ERG-preferred curve and the curves chosen by ICER.

Different approaches, including mixture cure models, spline models and the use of general population mortality after a cutoff time have been used in recent NICE TAs and US ICER assessments for extrapolation of OS for CAR-T therapies. Mixture cure models seem to be a potentially suitable and promising method and have predicted Kaplan–Meier data available from a newer trial data cut more accurately than other methods. In the recent ICER guidance on assessing high impact single and short-term therapies, ICER has made cure proportion modeling (including mixture and non-proportion cure models) the standard reference case when relevant and suggests addressing uncertainty by providing alternative survival modeling approaches.

Discussion

We identified a newer data cut of ZUMA-1 after the NICE and ICER assessments. Table 3 compares the key OS extrapolation results reported in the health technology assessments (HTAs), with the latest data cut available. Using digitized data, Figure 1 shows the overlay of original and newer Kaplan–Meier data, as well as the preferred extrapolations in the HTAs. The company base case OS extrapolation approach in NICE TA559 (a log-logistic mixture cure model with an estimated cure fraction of 50%) appears to predict the latest available Kaplan–Meier data better than the ERG-preferred curve and the curves chosen by ICER.

Figure 1: Comparison of OS extrapolations vs trial Kaplan–Meier data over 5 years for axicabtagene ciloleucel in DLBCL evaluations

References