Predictors of Utility over Time among Patients with Treatment-Naïve Advanced Melanoma from the Phase 3 CheckMate 066 Trial

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Abstract

Objective: The aim was to assess predictors of health-related quality of life over time to estimate utilities for patients with treatment-naive advanced melanoma in the randomized CheckMate 066 trial comparing nivolumab versus dacarbazine (DTIC) for use in a cost-effectiveness model (CEM).

Methods: The EQ-SD was administered at baseline and every 6 weeks in CheckMate 066 and was used to generate index utility scores using the UK time trade off (TTO) method. Covariates were based on a combination of prior analyses of large trial datasets, including patient demographic and clinical characteristics, quantitative metrics of HRQoL, qualitative/clinical plausibility, and reliance to the CEM. Several longitudinal mixed linear models were explored using different covariance sets.

Results: This analysis included 288 patients and 1,125 visits where the EQ-SD was administered. Baseline utility score was 0.75 for nivolumab patients, 0.69 for dacarbazine, and 0.72 across all patients. The final model included baseline utility (to adjust for imbalance between treatment arms), progression status, treatment arm, days until death or end of follow-up (>30 days), and treatment arm. Parameter estimates in the model were 0.603 for baseline utility (p = 0.001), -0.074 for progression status (p = 0.001), -0.022 for >30 days until death (p = 0.001), and 0.036 for treatment arm (DTIC vs. nivolumab) (p = 0.008). When implemented in the CEM, the utility estimate for pre-progression and post-progression status were 0.852 and 0.728, respectively (nivolumab as the treatment arm). A decrement for the month proceeding death is applied using the estimate for >30 days until death or end of follow-up (p = 0.022).

Conclusions: Results showed that baseline utility, progression, <30 days until death or end of follow-up, and treatment arm are predictors of utility over time, which is consistent with prior work in melanoma. As data mature, these analyses will be replicated in this and other nivolumab trials.

Introduction

- Survival, progression, and health-related quality of life (HRQoL) are the central outcome measures in health technology assessment of oncology treatments.
- Health states used in economic evaluations in oncology typically center on progression status with the key measure of effectiveness being quality-adjusted survival.
- A cost-effectiveness model (CEM) comparing nivolumab and DTIC-1 agent used to treat advanced melanomas, to competing treatments, including DTIC, has been developed.
- The CEM includes three health states: pre-progression, post-progression, and death, and employs a partitioned survival analysis approach in which progression and survival are modeled separately. Survival extrapolations in the CEM are stratified by response status at landmarks (landmarks), one of the key endpoints in the nivolumab clinical trials.
- The CEM evaluates the implications of treatments with nivolumab over a long time horizon, so it is important to understand how utility changes over time.

Methods

- In CheckMate 066, comparing nivolumab vs. DTIC, the EQ-SD was administered during each 6-week cycle, with initial assessments taken at randomization. During the follow-up (off-treatment) phase, EQ-SD assessments continued to be taken every three months for the next 12 months.
- EQ-SD responses were used to generate index utility scores using the UK time trade off (TTO) method.
- The SAS PROC MIXED was used to estimate longitudinal mixed linear models of utility over time. This mixed linear model has a random intercept for each patient and an random slope for each patient’s time-variant parameter for treatment status.
- Askale Information Criteria (AIC), as well as statistical significance, qualitative assessment/critical plausibility, and relevance to the economic modeling efforts were considered when comparing models and parameters. Three models were selected for the final analysis and are presented here.

Table 1. Number of visits where an EQ-SD was administered

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean Number of Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>180</td>
<td>10.5</td>
</tr>
<tr>
<td>DTIC</td>
<td>139</td>
<td>13.2</td>
</tr>
</tbody>
</table>

Table 2. Mean EQ-SD at Visit 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean Utility</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>167</td>
<td>0.75</td>
<td>0.23</td>
</tr>
<tr>
<td>DTIC</td>
<td>170</td>
<td>0.69</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Figure 1 describes the process by which the longitudinal models were selected and summarizes the significant predictors. More detail for each model is provided in the tables that follow.

Figure 1. Summary of Model Selection & Results

- Model 1
  - Age
  - Sex
  - Progression status (pre/post)
  - Days until death or end of follow-up (>30 days)
  - Treatment arm
  - Treatment arm
- Model 2
  - Age
  - Sex
  - Days until death or end of follow-up (>30 days)
  - Treatment arm
- Model 3
  - Age
  - Sex
  - Progression status (pre/post)
  - Days until death or end of follow-up (>30 days)
  - Treatment arm

Results

- Table 2 shows that including response status at landmark (LM), combined with the time-varying progression status in Model 2 does not improve the precision of the model.
- Further, the inclusion of the landmark/progression status variable reduces the sample size substantially from 1020 to 334 observations due to the number of patients who are censored before the landmark point.

Table 4. Model 2

<table>
<thead>
<tr>
<th>Effect</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.59</td>
<td>0.03</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.0000</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>-0.003</td>
<td>0.00</td>
<td>0.0000</td>
</tr>
<tr>
<td>Days Left: 30 or less</td>
<td>-0.035</td>
<td>0.016</td>
<td>0.0000</td>
</tr>
<tr>
<td>Days Left: &gt;30</td>
<td>-0.016</td>
<td>0.017</td>
<td>0.2320</td>
</tr>
<tr>
<td>Days Left: &gt;60</td>
<td>-0.015</td>
<td>0.016</td>
<td>0.2366</td>
</tr>
<tr>
<td>Days Left: &gt;90</td>
<td>0.009</td>
<td>0.018</td>
<td>0.3625</td>
</tr>
<tr>
<td>Days Left: &gt;120</td>
<td>0.009</td>
<td>0.018</td>
<td>0.3625</td>
</tr>
<tr>
<td>Days Left: &gt;180</td>
<td>0.022</td>
<td>0.043</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

Conclusion

- These analyses showed that baseline utility, progression status, and time to death were significant predictors of utility over time, which is consistent with prior analyses in advanced melanoma.
- Due to the preliminary nature of the available data at this time, these analyses should be revisited as data mature.

Limitations

- Data from CheckMate 066 are relatively immature. The available EQ-SD observations are concentrated in the first 6 months of study follow-up.
- As a proxy for time to death, the number of days left until end of follow-up or death was used, which includes patients who were censored potentially underestimating the predicted effect.
- The residual treatment effect observed for the treatment arm parameter in Model 3 for both trials is assumed to be attributable to different adverse events (AEs) profiles across treatment arms. It was not possible to incorporate specific AEs into the longitudinal models due to the relatively low number of AEs within each type of event and the need to have a proximal and preceding EQ-SD assessment.

Conclusions

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- Due to the preliminary nature of the available data at this time, these analyses should be revisited as data mature.