OBJECTIVES

IQWiG is one of the few health technology assessment (HTA) agencies that specifically assesses patient reported outcomes (PROs). PROs are reviewed as part of patient-relevant morbidity and health-related quality of life (HRQoL) outcomes. Additionally, IQWiG also assesses the mortality and safety outcomes, with mortality considered as the most important endpoint in oncology. The overall benefit rating typically aligns with the mortality rating in IQWiG’s HTA recommendations. Looking forward, our objective is to understand whether PROs can influence IQWiG’s benefit rating recommendation for oncology drugs.

METHODS

Oncology HTAs from January 2011 to May 2018 were identified using IQVIA’s proprietary database HTA Accelerator. For each subgroup in the identified HTAs, the outcome ratings and the overall benefit rating were collected. For categories where multiple outcomes were assessed (morbidity, HRQoL and safety), the highest and lowest ratings were noted. If the highest and lowest rating in a category were the same, they were noted separately. If only one outcome was available, the same rating was noted for the highest and lowest rating. For morbidity, ratings for PRO and non-PRO measures were noted separately. For the subgroups where IQWiG’s overall benefit rating diverged from its rating of the mortality outcome, we assessed whether IQWiG considered PRO data as a decision driver. For identified cases where PRO data was a decision driver, the impact of each outcome on the overall benefit rating was further examined.

RESULTS

Since 2011, IQWiG has published 143 oncology assessments, of which 66 were full benefit assessments and 77 assessments were abbreviated assessments of orphan drugs. In these 66 full benefit assessments, IQWiG assessed the benefit of new technologies in 148 subgroups. Data was not submitted or accepted in almost half of these subgroups (72 subgroups).

PRO data as drivers of overall benefit rating

- 148 subgroups in IQWiG full benefit assessments for oncology
- 143 IQWiG benefit assessments in oncological indications, of which 66 were full benefit assessments
- 148 subgroups were assessed in the full benefit assessments

Overall benefit rating not corresponding to mortality rating in subgroups

- 111 subgroups’ overall benefit rating directly corresponded to the mortality rating of which 72 cases received no added benefit due to IQWiG’s rejection of the whole evidence package
- 37 subgroups’ overall benefit rating was higher (23) or lower (14) than the mortality rating

PRO data as drivers of overall benefit rating

- 11 times PRO data positively influenced the overall benefit rating
- In one case the PRO data negatively influenced the overall benefit rating

PROs can influence IQWiG’s overall benefit rating by 1 or 2 levels compared to what would be expected based on the mortality rating, improvement in PRO data was often associated with lesser harm from adverse events.

In 5 cases, G-BA agreed with IQWiG’s overall benefit rating for these subgroups. In Xtandi® (enzalutamide) for example, IQWiG noted positive effects in mortality, severe symptoms, HRQoL, severe/more serious and non-severe adverse events and one negative effect in the endpoint category of non-serious/non-serious adverse events. However, as there was a negative effect modification observed in mortality, IQWiG rated the benefit of Xtandi® in pre-chemo metastatic castration resistant prostate cancer (mCRPC) patients <75 years as considerable due to which G-BA agreed. The 3 cases where G-BA gave a higher or lower benefit rating than IQWiG were not driven by a difference in opinion of the PRO data. In the other 4 cases, G-BA used different subgroups.

In the 111 subgroups where the benefit rating responded directly to the mortality rating, IQWiG rejected the whole evidence package (including PROs), which in 72 cases (49% of all subgroups) resulted in a no added benefit rating. The most common reason for IQWiG to dismiss the evidence package was the comparator used in the clinical trial.

CONCLUSIONS

While overall survival remains the most important decision driver in oncology, PROs were observed to be a differentiating factor in 15% of IQWiG oncology assessments where data was submitted or accepted. Positive PRO data can lead to a favourable benefit rating, especially in cases where survival outcomes are immature or statistically insignificant. In most cases, G-BA agrees with IQWiG’s favourable assessment of PROs.

Table 1. Outcome rating and overall benefit rating of subgroups where the overall benefit rating differed from the mortality rating and PRO data was identified as a decision driver

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Name</th>
<th>Year</th>
<th>Indication</th>
<th>Subgroup</th>
<th>IQWiG Benefit rating</th>
<th>Mortality rating</th>
<th>Morbidity rating</th>
<th>Safety rating</th>
<th>G-BA benefit rating</th>
<th>Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casparglu®</td>
<td>Truxalumab eretemaban</td>
<td>2014</td>
<td>Breast cancer</td>
<td>5 years</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Xar txt®</td>
<td>Enzalutamide</td>
<td>2015</td>
<td>mCRPC</td>
<td>&lt;75 years</td>
<td>Data not accepted</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Keytruda®</td>
<td>Pembrolizumab</td>
<td>2016</td>
<td>Melanoma</td>
<td>Treatment-naive, BRAF V600 wild type tumour</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Jakobi®</td>
<td>Ruxolitinib</td>
<td>2014</td>
<td>Myelodysplasia</td>
<td>N/A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kalkort®</td>
<td>Crizotinib</td>
<td>2013</td>
<td>NSCLC</td>
<td>Chemo-naive</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Xofigo®</td>
<td>Alcensa</td>
<td>2017</td>
<td>Alectinib</td>
<td>After chemo</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Opdivo®</td>
<td>Nivolumab</td>
<td>2016</td>
<td>RCC</td>
<td>Treatment-naive intermediate NSCLC score</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gilead®</td>
<td>Ataluren</td>
<td>2014</td>
<td>NSCLC</td>
<td>&lt;55 years, with L1057R mutation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tecentriq®</td>
<td>Alectinib</td>
<td>2017</td>
<td>NSCLC</td>
<td>&lt;85 years, with L858R mutation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alcensa®</td>
<td>Alectinib</td>
<td>2018</td>
<td>NSCLC</td>
<td>N/A</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Jakobi®</td>
<td>Ruxolitinib</td>
<td>2015</td>
<td>Polycythaemia vera</td>
<td>N/A</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cyremz®</td>
<td>Ramucirumab</td>
<td>2015</td>
<td>Colorectal cancer</td>
<td>Males</td>
<td>No data</td>
<td>No data</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

In most cases (111 subgroups), the overall benefit rating directly corresponded to the mortality rating. In 37 subgroups, the overall benefit rating was higher (23 subgroups) or lower (14 subgroups) than the mortality rating (figure 1).

In 12 of the 37 subgroups, IQWiG noted PRO data from the morbidity and/or HRQoL categories as one of the decision drivers for the overall benefit rating (table 1). In the other 25 subgroups, PROs were not considered as a decision driver by IQWiG for various reasons, e.g. data was non-significant, change was observed only in non-serious symptoms, or the decision was clearly influenced by the better safety profile of the drug.

IQWiG analysis showed that PRO data improved the overall benefit rating in 11 subgroups (7% of all subgroups). In 7 of these cases, mortality was rated as no added benefit or greater harm: minor/major. This resulted in a decreased overall benefit rating by IQWiG. Furthermore, while G-BA did not analyze gender-specific subgroups, it agreed with IQWiG’s assessment on the negative effects regarding morbidity, HRQoL, and adverse events.

Only in one case did the negative impact of PRO data lead to a lower overall benefit rating. Cyramza® (ramucirumab) did not demonstrate a mortality benefit in men with colorectal cancer and IQWiG rated the morbidity, HRQoL, and adverse events as less benefit/greater harm. This resulted in a decreased overall benefit rating by IQWiG. Furthermore, while G-BA did not analyze gender-specific subgroups, it agreed with IQWiG’s assessment on the negative effects regarding morbidity, HRQoL, and adverse events.

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