IMPACT OF PRO DATA ON IQWIG BENEFIT RATINGS IN ONCOLOGY

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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 in a category 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).

All 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

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Overall benefit rating not corresponding to mortality rating in subgroups

- 111 subgroups' overall benefit rating directly corresponded to the mortality rating, of which in 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

37

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

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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-severe symptoms, or the decision was clearly influenced by the better safety profile of the drug.

IQVIA 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 due to immature or statistically nonsignificant difference. However, based on positive PRO data, IQWiG's overall benefit rating ranged from considerable to non-quantifiable. E.g. while mortality data was not available for Xalkori© (crizotinib), IQWiG recognized a considerable benefit in the addendum for both morbidity (improvement of symptoms and deterioration of symptoms of dyspnoea, cough and pain as measured through EORTC QLQ-C30 and EORTC QLQ-LC13) and HRQoL (all single EORTC QLQ-C30 scales except cognitive function), leading to a considerable overall benefit rating.

In 4 other cases, PRO data improved the 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. E.g. in the assessment of Alecensa© (alectinib), the added benefit was largely attributed to a reduction of several side effects, and the EORTC QLQ-C30 results for the morbidity outcome confirmed these results.

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.

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/serious and non-severe/non-serious adverse events and one negative effect in the endpoint category of non-severe/non-serious adverse events. However, as there was an 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, 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.

Figure 1. Flow for identifying subgroups where PRO data had an impact on IQWiG's overall benefit rating

Drug	Generic name	Year	Indication	Subgroup	IQWiG Benefit rating	Mortality rating	Morbidity: Highest PRO rating	Morbidity: Lowest PRO rating	Morbidity: Highest non-PRO rating	Morbidity: Lowest non-PRO rating	HrQoL: Highest PRO rating	HrQoL: Lowest PRO rating	Adverse Events: Highest benefit	Adverse Events: Lowest benefit	G-BA benefit rating
Kadcyla©	Trastuzumab emtansine	2014	Breast cancer	Prev. therapy with anthracyclines, taxanes & trastuzumab	Major additional benefit	+	No data		No data		+		+	-	↓
Xtandi©	Enzalutamide	2015	Pre-chemo mCRPC	<75 years	Considerable additional benefit	+	Data not accepted		+	+	+		+	-	=
Keytruda©	Pembrolizumab	2016	Melanoma	Treatment-naïve, BRAF V600 wild type tumour	Considerable additional benefit	+			No data		+		+		=
Jakavi©	Ruxolitinib	2014	Myelofibrosis	N/A	Considerable additional benefit	+	+				No data				=
Xalkori©	Crizotinib	2013	NSCLC	Chemo-eligible	Considerable additional benefit		+		No data		+	+		-	=
Tecentriq©	Atezolizumab	2017	Uroethial carcinom	After chemo	Considerable additional benefit		+		No data		+		+	-	↓
Opdivo©	Nivolumab	2016	RCC	Prev. treated; intermediate MSKCC score	Considerable additional benefit		+	+	No data		No data		+		Different subgroup
Giotrif©	Afatinib	2014	NSCLC	<65 years, with L858R mutation	Minor additional benefit		+	-	No data		+	-			Different subgroup
Tecentriq©	Atezolizumab	2017	NSCLC	After chemo	Non-quantifiable benefit		+		No data				+	-	Different subgroup
Alecensa©	Alectinib	2018	NSCLC	N/A	Non-quantifiable benefit		+	-	No data				+	-	=
Jakavi©	Ruxolitinib	2015	Polycythaemia vera	N/A	Non-quantifiable benefit		+				+			-	↑
Cyramza©	Ramucirumab	2016	Colorectal cancer	Males	Lesser benefit			-	No data			-		-	Different subgroup

Legend	
Rating for overall benefit, mortality, morbidity and HrQoL	Lesser benefit
	No additional benefit
	Non-quantifiable benefit
	Minor additional benefit
	Considerable additional benefit
	Major additional benefit
Rating for Adverse Events	Greater harm: major
	Greater harm: considerable
	Greater harm: minor
	Greater harm: non-quantifiable
	No greater/lesser harm
	Lesser harm: considerable
	Lesser harm: major
+	Outcome as positive decision driver
-	Outcome as negative decision driver
↑	G-BA benefit rating higher than IQWiG
=	G-BA benefit rating same as IQWiG
↓	G-BA benefit rating lower than IQWiG

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

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.

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