The importance of different endpoints in oncology-related Health Technology Assessments : Results of a review of decisions in Germany

Hardtstock F.[1], Kocaata Z.[1], Wilke T.[1]

[1] Ingress-Health HWM GmbH, Alter Holzhafen 19, 23966 Wismar, Germany.

Background

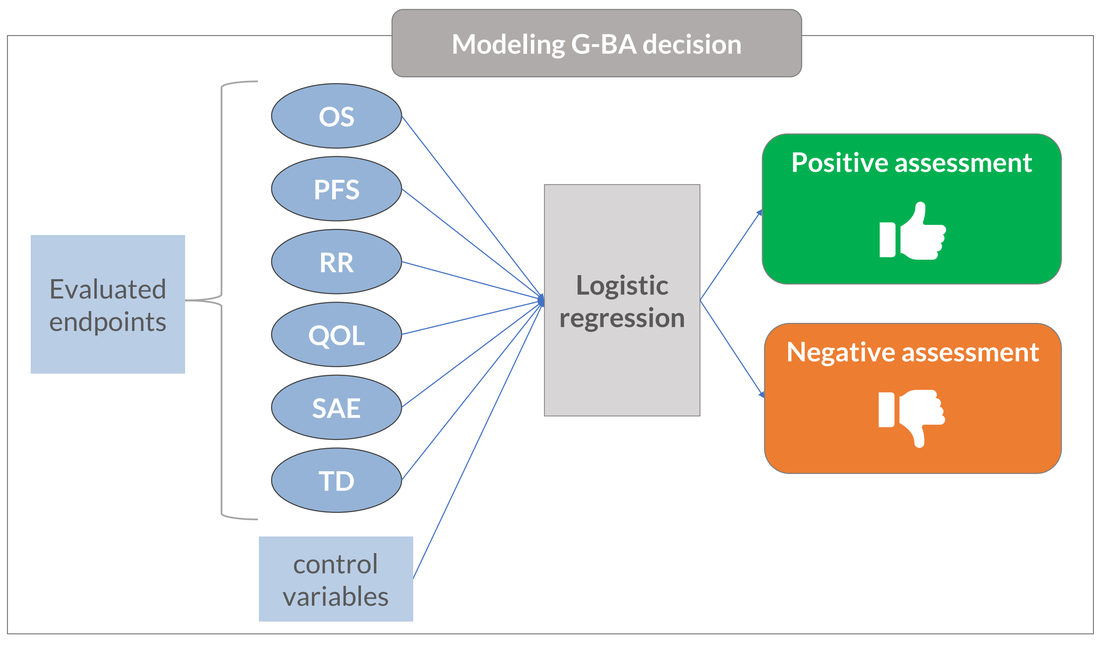
Choosing meaningful endpoints is vital for assessing the efficacy and safety of therapies – especially in oncology-related health technologies, where unmet patient needs are high. Moreover, even if the German G-BA obviously prefers overall survival (OS) and health-related quality of life (HrQoL) as main oncology-related endpoint it is unknown whether other endpoints play a role in driving a G-BA assessment. Therefore, this study aimed to analyze oncology-related health technology assessments (HTAs) in Germany in terms of assessment of different endpoints and their association with G-BA's decisions.

Methods

Data sources and coverage

- All oncology-related HTAs as available in G-BA records were hand-collected (**INGRESS HTA databank**) for the period 10/2010–03/2019.
- The data set included information on **general dossier characteristics, HTA decision (the extent of added benefit and quality of evidence), clinical evidence, real-world evidence, observational data and evaluated endpoints** [overall survival (OS), progression-free survival (PFS), response rate (RR), quality of life (QOL), serious adverse events (SAE) and therapy discontinuation (TD)]

Figure 1. Model representation



Analysis

- **Multivariate logistic regression** was performed, alongside alternative model specifications [(i) logistic regressions without controls, (ii) logistic regression with stepwise elimination of all variables with p>0.10, and (iii) probit regression] (See **Figure 1**).
- **Dependent variable** was a binary variable, taking the value:
  - **1 (one)** if the G-BA HTA resulted in *positive assessment* (large, considerable, minor, not quantified added benefit)
  - **0 (zero)** if the G-BA assessment resulted in *negative assessment* (no added benefit, benefit less than alternative)
- **Independent variables** were a series of binary variables on whether:
  - Evaluated endpoints were **OS, PFS, RR, QOL, SAE, TD;**
  - **First-line therapies (vs. other therapy lines), orphan drugs, mutation-specific assessment** were elements included in the HTAs;
  - **Randomized controlled trials, real-world evidence, indirect treatment comparison, patient preferences** were presented.
- In addition, a continuous variable on the year of assessment was included as independent variable.

Results

Descriptive characteristics of oncology-related HTA submissions

- The dataset included 153 distinct HTAs.
- Majority of the HTAs were completed in recent years; namely from 2015 onwards (79.1%).
- Around 30.1% of the studied HTAs were on orphan technologies.
- The HTAs were on 16 different cancer indications with the most common ones being: blood and bone marrow cancers (24.1%), lung cancer (16.3%) and skin cancer (14.3%).
- The majority of HTAs were evaluated positively by the G-BA (73.9%).
- In terms of evaluated endpoints, 68.0% of the HTAs presented evidence on OS, followed by PFS (54.3%), RR (41.8%), QOL (24.8%), TD (18.3%) and SAE (10.5%)

Results of the regression analyses

- Controlling for the year of submission, indication-related characteristics as well as controls related to presented evidence, **OS and QOL** were significantly associated with a positive G-BA assessment **(OR=8.01, p<0.01 and OR=9.97, p<0.05, respectively)** at 5% significance level.
- Conversely, no significant effects of **PFS (OR=0.40, p>0.1), RR (OR=3.34, 0.05<p<0.1), SAE (OR=3.00, p>0.1)** as well as **TD (OR=0.58, p>0.01)** on ultimate G-BA decision were found.
- Dropping control variables from the main regression yielded similar results, whereby **OS (OR= 6.77, p<0.01) and QOL (OR=5.10, p<0.05)** were significant predictors of a positive G-BA assessment.
- To ensure that significant effects are not derived due to a specific combination of independent variables of choice in regressions, stepwise elimination of covariates were considered and resulted in **significant OS and QOL effects (OR=7.28, p<0.01 and OR=8.55, p<0.01, respectively).**
- The robustness of the main model against changes in functional forms were confirmed in a probit model, where **marginal effects of OS (3.38, p<0.01)** and **QOL (3.73, p<0.05)** were found to be significantly associated with a positive G-BA decision.

Table 1. Regression output (standard errors in parenthesis; * p<0.10, ** p<0.05, *** p<0.01)

	Main model	Other model specifications		
DEPENDENT VARIABLE: I(Positive assessment = 1)	Logistic regression with controls	Logistic regression without controls	Logistic regression after stepwise elimination	Probit regression with controls
Overall survival	**8.011*** (4.968)**	**6.772*** (3.079)**	**7.275*** (3.896)**	**3.327*** (1.126)**
Progression-free survival	0.399 (0.270)	1.101 (0.549)		0.589 (0.220)
Response rate	3.344* (2.330)	2.390 (1.280)		1.935* (0.757)
Quality of life	**9.969** (9.538)**	**5.097** (4.117)**	**8.552*** (7.105)**	**3.727** (1.936)**
Serious adverse events	2.995 (3.748)	0.554 (0.556)		2.199 (1.510)
Treatment discontinuation	0.575 (0.605)	1.888 (1.623)		0.643 (0.355)
Indication-related controls				
First-line	0.285** (0.182)		0.325** (0.185)	0.490* (0.179)
Orphan	33.33*** (33.16)		25.25*** (22.76)	6.782*** (3.468)
Mutation-specific assessment	0.985 (0.546)			1.067 (0.336)
Controls related to presented evidence				
Randomized controlled trials	5.329** (4.504)		3.885* (2.846)	2.548** (1.148)
Real-world evidence	10.29 (16.20)			3.698 (3.207)
Indirect treatment comparison	0.174** (0.124)		0.301** (0.175)	0.344*** (0.132)
Patient preferences	0.477 (0.325)			0.695 (0.272)
Other controls				
Year	0.968 (0.161)			0.971 (0.0899)
N	153	153	153	153
Pseudo R^2	0.446	0.251	0.404	0.445

Conclusion

For oncology-related HTAs, demonstrating evidence based on OS and QOL was found to increase the probability of a positive G-BA assessment. No further contributing factors as per evaluated endpoints could be found, with the caveat that HTA decisions could be driven by other undetected factors such as quality of evidence based on evaluated endpoints presented. So, indeed, endpoints different from OS and HrQoL are not accepted by G-BA as proof for an added benefit of an oncology therapy.

List of abbreviations

HrQoL: health-related quality of life, HTA: Health technology assessment, OR: Odds ratio, OS: Overall survival, PFS: Progression-free survival, RR: Response rate, QOL: Quality of life, TD: Treatment discontinuation, SAE: Serious adverse events

Keywords

Health Technology Assessment, G-BA, Endpoints, Logistic regression