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Analysis of endpoints used in marketing authorisations versus value assessments of oncology medicines in Germany

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ABSTRACT

Background and aims: In Germany, a mandatory early benefit assessment (EBA) by the Federal Joint Committee (G-BA) is required for reimbursement of new marketing-authorised medicines. Additional benefit is based on patient-relevant endpoints in mortality, morbidity and health-related quality of life (HRQoL). We aimed to compare endpoints and related benefit categories used in marketing authorisation to those considered by G-BA in the field of oncology.
Methods: We evaluated EBAs in oncology commencing prior to 31 December 2013. Endpoints for the appropriate medicines, derived from European Medicines Agency's (EMA) Summary of Product Characteristics (SPC), manufacturers' value dossiers and G-BA decisions, were grouped into the three benefit categories.
Results: Of 23 oncology medicines evaluated, primary clinical trial endpoints were included in only 12 G-BA value decisions. Mortality endpoints were generally accepted by EMA and G-BA. However, G-BA excluded 80% of (co-)primary morbidity endpoints. Only 5 SPCs reported HRQoL instruments. G-BA accepted applied instruments in 15 medicines, but the manufacturers' analyses only in 5 medicines, of which 2 indicated an additional benefit.
Conclusions: Mortality endpoints are accepted by EMA and G-BA. EMA accepted well established and clinically relevant morbidity endpoints (e.g. progression-free survival and response rate), which were mostly excluded by G-BA from their value decisions. The applicability of methods used for benefit assessments to HRQoL differs from the mortality and morbidity categories, and requires further clarification.

1. Introduction

Access to new medicines in Germany depends on marketing authorisation from the European Medicines Agency (EMA). Since the introduction of the Act on the Reform of the Market for Medicinal Products (AMNOG) in January 2011, a demonstration of additional therapeutic benefit versus an appropriate comparator (AC) in the form of an early benefit assessment (EBA) is mandatory for all new

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medicines. The EBA is conducted as a two-step approach by the Institute for Quality and Efficiency in Health Care (IQWiG) (scientific assessment) and the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) (appraisal) [1–3]. The G-BA ultimately decides the level of additional benefit of a medicine, which in turn influences the reimbursement by statutory health insurances (SHI) [3]. Whereas a positive additional benefit supports a negotiable price premium over the AC, medicines that receive no additional benefit by the G-BA are priced no higher than the price of the comparator. Additional therapeutic benefit is based on patient-relevant endpoints grouped into three benefit categories: mortality, morbidity and health-related quality of life (HRQoL) [2–4].

The aims of the evaluation of the G-BA and the regulatory authorities clearly differ. The EMA and other regulatory agencies focus principally on efficacy and safety data derived from clinical trials to decide on whether a medicine should be licensed or not. The data are optimised to demonstrate a positive benefit–risk balance in a limited time period with high internal validity and minimal risk to patients. Clinical trials usually evaluate the clinical effect (often based on a single primary endpoint) and safety of a given medicine in a limited number of patients. Instead, the G-BA evaluates the comparative value of a new medicine versus current standard of care derived from internal criteria. However, the G-BA assesses and acts based on the same value dimensions (desirable effect [benefit and value] and harm [side effects and risks]). The marketing authorisation process is well established, and manufacturers are able to draw upon a wealth of guidance and experience in the conduct of clinical trials and acceptable clinical endpoints. In contrast to the current marketing authorisation process, current practice relating to EBAs is being guided largely by limited precedent and experience [5–7]. However, regulatory and health technology assessment (HTA) perspectives work from a comparable, given set of patient data.

Early evidence indicates that endpoints used to support marketing authorisation are not necessarily included by the G-BA in their value decision [6]. Demands on the manufacturers from the G-BA differ from those of the regulatory authorities in terms of acceptable endpoints.

In the case of oncology medicines, extensive oncology-specific guidance and experience exist relating to acceptable oncology endpoints for marketing authorisation [8–10]. In contrast, as the G-BA guidance is not specific to disease, there is no particular guidance on oncology endpoints for EBAs. In oncology, clinical efficacy is based on survival benefit and measures of disease morbidity, such as progression-free survival (PFS), disease-free survival (DFS) or overall response rate (ORR). The EMA recommends cure rate, overall survival (OS) and PFS/DFS as acceptable primary endpoints (Table 1) [8]. The EMA and FDA guidelines are generally consistent and agree that favourable effects on survival are the most persuasive outcomes of a clinical trial [8,9]. Each endpoint has its advantages and disadvantages depending on the patient population and time-frame of evaluation (Table 1).

In an attempt to further explore the interpretation of added value by the G-BA, we evaluated current value assessments in Germany for oncology medicines. We compared endpoints and related benefit categories applied in regulatory trials supporting marketing authorisation to those included in the value decisions of the G-BA.

2. Methods

We evaluated oncology medicines that received marketing authorisation and commenced EBA in Germany between 1 January 2011 (the day AMNOG was introduced) and 31 December 2013. The G-BA website was used to obtain the manufacturers' value dossiers and the G-BA value decisions [11]. We determined levels of additional benefit assigned by the G-BA according to their specified ratings [2,3]: positive (category: major [1], considerable [2], minor [3] or not quantifiable [4] additional benefit) and negative (category: no additional benefit [5]/less benefit [6]). The G-BA assesses the additional benefit for respective subgroups of patients [12]. To allow for comprehensibility, the additional benefit decisions reported in this analysis relate to the subgroup and the indication attaining the highest level of benefit. In case of a re-assessment, the more recent assessment was evaluated. The overall rating was stated.

The Summary of Product Characteristics (SPC) was used as the data source for the respective marketing authorisations and was derived from the website of the EMA. Clinical trial endpoints that supported the marketing authorisation and the benefit assessment were derived from (i) the SPCs, (ii) manufacturers' value dossiers and (iii) the G-BA value decisions (underlying document: 'Tragende Gründe' and supporting material). According to the German Social Law, the additional benefit of a new medicine has to be evaluated with respect to the three benefit categories: mortality, morbidity, and HRQoL (2–4). Any additional benefit is considered in combination with safety as a fourth benefit category. Therefore, derived endpoints from the three data sources were grouped into those three benefit categories. The subsequent analysis included three steps:

1) Endpoints covering the benefit category of mortality were identified and acceptance of those endpoints by both EMA and G-BA was compared.
2) The same approach was applied to endpoints covering the benefit category of morbidity. PFS was considered a measure of oncology-related morbidity and was therefore included in the benefit category of morbidity.
3) HRQoL endpoints and supporting standardised assessment instruments were identified. Acceptance of respective instruments by the G-BA was explored as well as methodological acceptance of the specific analysis provided by the manufacturer and the consideration of the content of the analysis as an element to support additional benefit for the medicine.

An additional comparison addressed the (co-)primary clinical trial endpoints supporting marketing authorisation as reported in the SPC. All (co-)primary endpoints of randomised controlled trials (if not available, studies with other designs were considered) were assessed and their inclusion in the G-BA value decision was determined.