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The Effect of Crossover in Oncology Clinical Trials on Evidence Levels in Early Benefit Assessment in Germany

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ABSTRACT

Background: In oncology clinical trials, crossover is used frequently but may lead to uncertainties regarding treatment effects. **Objective:** To investigate the handling of evidence from crossover trials by the European Medicines Agency (EMA) and the German Federal Joint Committee (G-BA). **Methods:** For oncology medicines with early benefit assessments before January 2015, presence of crossover, clinical data, EMA requests for additional data, and G-BA benefit ratings/evidence levels were analyzed from manufacturers' dossiers, G-BA appraisals, European Public Assessment Reports, and original publications. **Results:** Eleven of 21 benefit assessments included crossover trials. Significant intergroup differences ($P < 0.05$) in overall survival (OS) were noted in 7 of 11 trials with and 7 of 10 without crossover. For 6 of 11 medicines with crossover, these were demonstrated before crossover. Treatment effects generally worsened with increasing proportions of crossover. The EMA requested additional data more frequently if crossover was performed, particularly if no OS data were available before crossover. The G-BA granted a considerable benefit to 73% of medicines with crossover and 40% of those without. Evidence levels were intermediate for 50% and 75%, respectively. None of the medicines received the highest evidence level. **Conclusions:** In G-BA appraisals, oncology medicines with crossover received better additional benefit ratings, but were assigned lower evidence levels, than those without. The five medicines with crossover after progression were assigned lower evidence levels than the six medicines with crossover after demonstration of superior OS, indicating that the way in which crossover is implemented may be one factor influencing the assignment of evidence levels by the G-BA.

Keywords: AMNOG, crossover design, early benefit assessment, evidence level, health technology assessment, oncology.

Introduction

In oncology clinical trials, "crossover" usually describes trial designs that allow patients from the control group to switch to the intervention arm and receive the investigational product after a predefined study event, for example, either after disease progression or after demonstration of clinical superiority of the investigational medicine [1]. Such designs are used frequently to maximize the number of patients who have access to the investigational drug in the study [2,3]. Moreover, they facilitate recruitment by increasing the trial's attractiveness to candidate patients [2,3] because patients may be more willing to enroll in a trial in which they are guaranteed to receive a given experimental treatment at some point. This is particularly true when early-phase data suggest a substantial treatment effect of the investigational agent. However, implementing crossover in a trial will reduce the treatment differences between the randomized arms for long-term trial end points, such as overall survival (OS) [1,2,4] and thus can influence a study's ability to answer a clinical question [5]. Results from a simulation study indicate that a crossover rate of more than 50% dramatically decreases the probability of detecting differences in OS by up to 90% [6].

Favorable effects on OS are still considered the most persuasive outcomes of a clinical trial in oncology [4]. The European Medicines Agency (EMA) recommends that crossover after disease progression should generally be avoided and be used only if there is confidence that the objectives of the trial can be met and adequate conclusions can be drawn [4,7].

Given the challenges in determining OS, particularly in the presence of crossover, additional efficacy end points, such as progression-free survival (PFS), are frequently used in clinical trials in oncology. There is an ongoing debate whether PFS is a useful surrogate for OS in oncology [8,9]. Although PFS may be accepted as a primary end point in oncology trials by regulatory agencies in certain settings and under certain conditions [7],

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reliable and unbiased OS estimates are still likely to be required for health technology assessments [10].

In Germany, an early benefit assessment against the appropriate comparator therapy has been mandatory for new medicines since January 2011 [11–13]. The German Federal Joint Committee (*Gemeinsamer Bundesausschuss* [G-BA]) as the decision body and the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* [IQWiG]) as the scientific assessment body are charged with evaluating a medicine's additional benefit. This evaluation is based on a dossier submitted by the manufacturer and is conducted according to the principles of evidence-based medicine [11,14,15]. In addition to the extent of additional benefit versus the appropriate comparator therapy—major, considerable, minor, not quantifiable, or no additional benefit (or less benefit) [13,14]—the quality of the evidence base is evaluated. The evidence level is rated as proof (A), indication (B), or hint (C) on the basis of the number and characteristics of the submitted studies, the certainty of the results, and the consistency of the observed treatment effects [15]. The highest evidence level (A) requires a statistically significant effect in a meta-analysis or at least two independent randomized controlled trials showing statistically significant treatment effects in the same direction. Lower evidence levels are assigned when the presented evidence is based on only one randomized controlled trial or is considered to have a higher potential for bias [15]. Both the extent of additional benefit and the evidence level, together with other parameters, are considered by the National Association of Statutory Health Insurance Funds (*Spitzenverband Bund der Krankenkassen*) during the subsequent price negotiations with the manufacturer [16].

Currently, limited experience exists regarding the view of health technology assessment agencies on crossover trial design (e.g., the impact of crossover on the perceived evidence quality) [17]. We investigated the impact of crossover trials on the evaluations by the EMA and by the G-BA. Specifically, we determined whether the G-BA considered the way crossover was used in its appraisal and whether crossover impacted the evidence levels granted.

Methods

Oncology medicines with benefit assessments completed before January 1, 2015, were evaluated [18]. Orphan drugs were excluded from the analysis because an additional benefit is granted to such drugs by law [12]. Medicines for which no dossier was submitted were excluded because the basis for their assessment was missing.

For all medicines included in the analysis, the assessed indication was recorded. Where a re-assessment of the same medicine for the same indication had been performed, only the most recent assessment was analyzed.

Trials considered in G-BA appraisals were regarded as relevant for the analyses. Manufacturers' dossiers and G-BA appraisals, both obtained from the G-BA Web site [18], European Public Assessment Reports [19], and original trial publications were used as source documents. The analyses of the selected medicines encompassed the following points:

1. Presence of crossover trials
2. Clinical data
3. EMA's assessment
4. Benefit ratings and evidence levels granted by the G-BA

Presence of Crossover Trials

For this analysis, crossover was defined as a switch from a treatment specified for one group to a treatment specified for another group or to another treatment not included in the trial protocol that could occur either after disease progression or after reaching a predefined efficacy threshold. Medicines included in this analysis were divided into medicines with and without crossover studies.

Clinical Data

For all studies included in the analysis, the comparator therapy and the primary end point were extracted from the G-BA appraisal or the manufacturer's dossier. For studies involving crossover, the manufacturer's dossier was searched for a justification of the crossover design. Data on OS, PFS, and other primary end points were evaluated. OS and PFS were chosen because they are the most commonly used primary end points in oncology trials [20]. For studies with more than one data cut, data from the cut mentioned in the G-BA appraisal or, if none was mentioned, the most recent cut, were used for evaluation. If the G-BA analyzed several patient subgroups, only data for the subgroup with the best benefit rating were considered. Statistically significant differences ($P < 0.05$) between intervention and control treatment were assessed.

For medicines with crossover studies, it was determined whether data were available before crossover and whether there were statistically significant differences ($P < 0.05$) in OS, PFS, or other primary end points between the treatment arms before crossover.

Medicines with crossover in at least one clinical trial that presented OS or PFS data from different data cuts and provided information on the proportions of crossover patients at these time points were identified to assess the development of treatment effects over time in crossover trials.

EMA's Assessment

A conditional marketing authorization may be granted by the EMA in the absence of comprehensive clinical data to ensure immediate access to the medicine also outside of clinical trials [21]. In addition, the EMA may request postauthorization measures to obtain additional data and enable a more accurate assessment of the safety or efficacy of a new medicine [22].

Requests for additional data by the EMA (conditional marketing authorizations or postauthorization measures concerning OS) as stated in the European Public Assessment Reports were identified.

Benefit Ratings and Evidence Levels Granted by the G-BA

Overall additional benefit ratings assigned to the analyzed medicines were extracted from G-BA appraisals. The additional benefit rating for mortality was analyzed separately, because mortality (i.e., OS) is the preferred benefit category in assessments of oncology medicines [20] and because OS data can be strongly influenced by crossover [2,3,7,10,17]. Whether safety data had a positive, negative, or neutral effect on the overall benefit rating was also assessed. The level of evidence granted by the G-BA in its appraisals was analyzed for medicines with positive additional benefit ratings. For medicines for which the G-BA analyzed more than one patient subgroup, only the benefit rating and evidence level for the subgroup with the highest additional benefit were taken into account.

To assess the impact of crossover on benefit assessments, a comparison of benefit ratings and evidence levels was performed for medicines with and without crossover studies.