Role of progression free survival in the approval process and European HTA assessments

Kirchmann T, Deichmann A, Schönermark MP
SKC Beratungsgesellschaft mbH, Hannover, Germany

Objectives

Most cancers are characterized by a progressive course of disease, ultimately leading to the death of the patients. Thus, in the medical world, prevention of the disease progress, measured by progression free survival (PFS), is considered a core parameter with a clear patient relevant benefit. This is reflected in a large fraction of clinical studies in cancer in which PFS serves as the primary endpoint, and thus determines the success of the treatment. While the European Medicines Agency (EMA) considers PFS to be an important factor in assessing the efficacy of a new drug, HTA agencies such as G-BA, NICE and HAS are divided. The aim of this research is to analyze previous and current assessments of PFS by European HTA agencies and to compare them to the assessment by EMA.

Methods

- Guidelines of regulatory and HTA agencies were reviewed in terms of the acceptance and value of PFS within the approval or reimbursement assessments.
- Ribociclib and Palbociclib in the indication breast cancer as well as Olaparib and Niraparib for the treatment of ovarian cancer were selected for in-depth analysis.
- For all four active substances, published HTA documents of G-BA, HAS and NICE were reviewed for the specific role of PFS and were compared to the CHMP decisions and EPARs.

Results

Relevance of PFS in the approval decision

Europe (EMA)[1]

- Acceptable primary endpoints include cure rate, OS and PFS/DFS.
- Prolonged progression-free or disease-free survival (PFS/DFS) **as such** are in **most cases considered relevant** measures of patients benefit.
- However, the magnitude of the treatment effect should be sufficiently large to outbalance toxicity and tolerability problems.

USA (FDA)[2]

- The **role of PFS** as an endpoint to support licensing approval varies in different cancer settings.
- Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit **depends on the magnitude of the effect and the risk-benefit** of the new treatment compared to available therapies.
- **PFS can serve as an accepted surrogate** parameter for accelerated approval or regular approval.

Relevance of PFS in the reimbursement decision

Germany (G-BA)[3]

- Patient-relevant parameters to determine disease-related and treatment-related changes contain:
  1) Mortality,
  2) Morbidity (complaints and complications),
  3) Health-related quality of life.
- PFS is considered as an endpoint combining mortality and morbidity. However, in most cases morbidity is **not assessed via patient relevant symptoms**.

UK (NICE)[4]

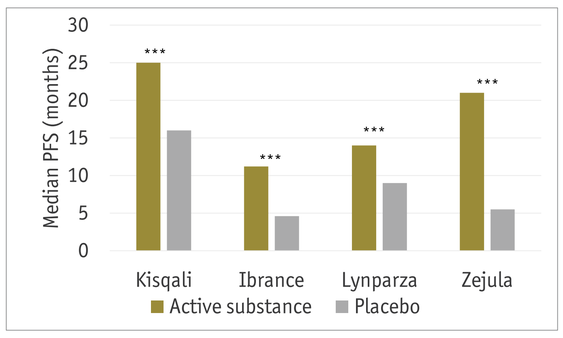
- The evaluation of effectiveness requires quantification of [...] survival, **disease progression** and health-related quality of life so that this can be used **to estimate QALYs**.
- Economic evaluations should quantify how the compared technologies affect disease progression and patients' health-related quality of life, and value those effects to reflect the preferences of the general population.

France (HAS)[5]

- [The benefit] represents the amount of absolute efficacy, preferably expressed as a reduction in the absolute risk (RRA) of a morbidity or mortality criterion (a reliable criterion that makes sense to the patient), observed and proven, resulting from studies conducted with the drug.
- This amount of effect cannot be separated from the notion of the **clinical relevance** of the observed effect.

Indication	
Ribociclib (Kisquali®) breast cancer, treatment	**Palbociclib (Ibrance®)** breast cancer, treatment
Olaparib (Lynparza®) ovarian cancer, maintenance	**Niraparib (Zejula®)** ovarian cancer, maintenance

PFS



Role of PFS in pivotal study	
Ribociclib Primary endpoint	**Palbociclib** Primary endpoint
Olaparib Primary endpoint	**Niraparib** Primary endpoint

Overall survival	
Ribociclib Median OS not reached	**Palbociclib** Median OS not reached
Olaparib Median OS not reached	**Niraparib** Median OS not reached

EMA assessment[6]

PFS was accepted as a primary outcome measure.
Considering time to progression and prolongation of PFS, the increase in median PFS over letrozole is of important clinical relevance.

PFS was accepted as a primary outcome measure. The magnitude of the effect in both pivotal studies is considered of clear clinical relevance.

Ribociclib | **Palbociclib**
Olaparib | **Niraparib**

Benefit-risk balance of olaparib as monotherapy for the [indication] is considered positive. The recommended indication of olaparib is maintenance treatment and PFS benefit is considered clinically relevant in this setting. OS data need to be presented at a later point in time.

Median PFS estimate of niraparib is uncertain, since analysis is based on immature data. It can be assumed that PFS estimate lies in the range of 14.8 and 21 months. Even in the lower range of this interval, effect is considered to be of clinical relevance.

G-BA assessement[7]

No sufficient evidence that PFS is a valid surrogate for OS in the indication. No proof of an association of PFS with an improvement in morbidity or HRQoL. Even if a positive effect was assumed due to a delay in the subsequent therapy [...], this would have to be compared with the pronounced side effects.

The extent to which the negative side effects on the one hand and the prolonged PFS on the other have an effect on OS cannot yet be assessed.

Ribociclib | **Palbociclib**
Olaparib | **Niraparib**

An additional benefit exists, but cannot be quantified because the scientific data basis does not permit this.

Available survival data should be regarded as immature and therefore interpreted with caution. The overall consideration of the side effects shows a clear disadvantage for the drug to be evaluated.
The extent to which the negative side effects on the one hand and the prolonged PFS on the other have an effect on OS cannot yet be assessed.

NICE assessement[8]

Ribociclib plus letrozole improves PFS, but uncertainty remains if improvement leads to a survival benefit. With the PAS discount, ribociclib is a cost-effective use of NHS resources and it can be recommended.

Palbociclib has a clear and important benefit for improving PFS, and that it is likely that this would result in some improvement in OS. [...] discount agreed in the PAS, palbociclib is a cost-effective use of NHS resources and it can be recommended.

Ribociclib | **Palbociclib**
Olaparib | **Niraparib**

ERG considered OS, rather than PFS, to be the most clinically relevant measure to assess the effect of a treatment on survival. [...] uncertainty about the survival benefit with olaparib. Only recommended in 3L.

Niraparib extends PFS compared with routine surveillance, but the final results on OS are not available yet. Because of the uncertainty in the clinical evidence, the estimates of cost effectiveness are very uncertain. Therefore niraparib cannot be recommended for routine use in the NHS.

HAS assessement[9]

Considering a gain in PFS (+9.3 months), but lack of evidence of an overall survival gain plus an increase in toxicity; [...] addition of KISQALI to letrozole does not improve the medical service provided (ASMR V) in the [indication].

Studies demonstrated a gain in PFS (+10.3 months) of palbociclib in addition to letrozole or fulvestrant. No overall survival gain has been demonstrated to date. IBRANCE provides a minor improvement (ASMR IV).

Ribociclib | **Palbociclib**
Olaparib | **Niraparib**

The actual benefit of LYNPARZA is substantial. Minor (ASMR IV) in efficacy has been demonstrated versus placebo in terms of PFS, though with no demonstrated impact on overall survival.

Niraparib provides a minor (ASMR IV) improvement in PFS compared to placebo. [...] impact of ZEJULA only on morbidity; the impact on mortality has not yet been demonstrated and no significant difference has been observed on quality of life.

Conclusion

- Analysis of EMA approvals showed that over the past years, PFS results were a major decisive factor for granting marketing approval. In contrast, European HTA agencies have a contradictory approach in their benefit assessment and reimbursement decisions. Of all drugs assessed by G-BA, in no case PFS was considered patient-relevant and thus did not contribute to the additional benefit of the drug. Other HTA agencies showed similar results, albeit in a weaker form.
- While PFS is a combined endpoint composed of endpoints of the categories mortality and morbidity, the mortality component is already collected via OS. The morbidity component is not assessed on the basis of symptoms so far, but exclusively by means of imaging procedures (according to RECIST criteria). Therefore, the availability of data on morbidity and health-related quality of life could be used to interpret PFS results.
- It is a major issue that endpoints are only collected up to disease progression and therefore only allow statements to be made up to the time of progression. However, to assess the possible impact of radiologically determined progression on quality of life and morbidity, robust analyses of data before and after the time of radiologically determined progression are required. In addition, OS is complex and difficult to interpret due to further lines of treatment that patients would have. The extent to which the prolonged PFS translates into prolonged survival could therefore not be assessed with the available data.
- In the analysis it became clear that PFS is not a major decisive factor for HTAs. NICE and HAS considered PFS in their assessments under uncertainty with regard to OS, while the G-BA does not reflect on it. Therefore, G-BA decided on no benefit for all four drugs. HAS and NICE concluded only in one case that there was no recommendation for a drug (HAS: ribociclib; NICE: niraparib).
- However, whereas in England and France HTA outcome is directly linked to the reimbursement of the respective drug, in Germany the final price is negotiated later on the basis of the HTA decision. Despite acceptance by NICE, use of two drugs was only recommended at PAS discount levels. Similarly, HAS granted only a minor benefit (ASMR IV) in three cases, on the basis of PFS, resulting in high discounts. Thus, even with no granted benefit, drug prices in Germany can be found to be higher than in England and France.

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schönermark kielhorn collegen

SKC Beratungsgesellschaft mbH, Hannover, Germany | www.skc-consulting.de
Email: kirchmann@skc-beratung.de | Fon: +49 511 64 68 14-0
PCN25 – Poster presented at ISPOR Europe 2018, 10-14 November 2018 in Barcelona, Spain