Palbociclib in advanced breast cancer: Disadvantages predominate in certain patients

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Palbociclib (trade name: Ibrance) has been approved since November 2016 for the treatment of women with advanced hormone receptor-positive breast cancer who are not eligible for chemotherapy, radiotherapy or further surgery. In an early benefit assessment, the German Institute for Quality and Efficiency in Health Care (IQWiG) investigated whether this drug offers advantages for patients over the appropriate comparator therapies.

According to the findings, such an added benefit is not proven: The dossier contained no data or no suitable data on several groups of patients. Where data were available, i.e. in the first-line treatment after menopause, severe side effects were more frequent under palbociclib in combination with letrozole than under letrozole alone, which resulted in an indication of lesser benefit.

G-BA distinguished between four treatment situations

The new drug is approved for women with advanced breast cancer whose cancer cells carry receptors for hormones such as oestrogen or progesterone (HR-positive). In these patients, hormones such as oestrogen or progesterone accelerate the growth of the cancer cells. Palbociclib is used either in combination with an aromatase inhibitor or with the drug fulvestrant. Palbociclib is not approved for the treatment

of tumours carrying the human epidermal growth factor receptor 2 (HER2).

For the current assessment, the Federal Joint Committee (G-BA) distinguished between four treatment situations and specified a different appropriate comparator therapy for each of them. One criterion was whether the patients have already completed menopause, another one the line of treatment, i.e. whether and how many treatments have already been (unsuccessfully) conducted.

No relevant differences in several outcomes

The drug manufacturer presented data from two randomized controlled trials (RCTs) for one of the four treatment situations, i.e. the first-line treatment in postmenopausal women. Both RCTs tested palbociclib in combination with the drug letrozole against letrozole monotherapy.

These data showed no relevant differences between the two study arms in several outcomes. This was the case for health status (morbidity), health-related quality of life and treatment discontinuation due to side effects.

Manufacturer used results on progression-free survival

The differences were not statistically significant also in the outcome "survival" (overall survival). However, the manufacturer used results on progression-free survival (PFS), which were in favour of palbociclib. It wanted PFS to be understood as a surrogate for survival.

Since it sometimes takes years before it is shown whether new treatments actually prolong life, cancer drugs in particular are often

approved on the basis of such surrogates. It is a good sign when the tumour does not continue to grow or even shrinks under a new treatment. It is not certain, however, that patients actually survive longer.

PFS would have to be "validated" as a surrogate for survival to be able to derive an added benefit. There is validity when a change in the surrogate outcome reliably predicts a change in the same direction of a patient-relevant outcome.

Method principally suitable for validation

In its dossier, the manufacturer tried to validate PFS as a surrogate. It chose a suitable scientific method to estimate the reliability of PFS (surrogate threshold effect analysis, STE).

The study pool used by the manufacturer did not adequately represent the research question, however: On the one hand, the manufacturer used studies that compared two monotherapies. According to the approval, however, palbociclib can only be used as combination therapy. On the other, it precisely did not include studies on palbociclib in its analysis.

IQWiG therefore conducted its own analysis, which included the palbociclib studies, but not the monotherapy studies. It was shown that PFS cannot be considered to be a valid surrogate parameter for survival in this treatment situation. Hence an added benefit cannot be derived from the better results for PFS.

Disadvantage of palbociclib in severe side effects

Relevant group differences were shown in severe side effects, however: These were notably more common under the combination therapy with palbociclib, from which an indication of greater harm can be derived.

Since this disadvantage was not accompanied by advantages in other outcomes, IQWiG sees an indication of a lesser benefit of palbociclib in the overall consideration.

The dossier contained no data for the first-line treatment in women before or during menopause. Regarding the second and subsequent line of treatment before, during or after menopause, the study presented was unsuitable for the assessment because palbociclib was not tested against the appropriate comparator therapy specified. An added benefit is therefore not proven.

G-BA decides on the extent of added benefit

The dossier assessment is part of the early benefit assessment according to the Act on the Reform of the Market for Medicinal Products

More information: www.iqwig.de/en/press/amnog-at-a-glance.7723.html

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