Enzalutamide in prostate cancer: Hints of added benefit

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Enzalutamide (trade name: Xtandi) has been approved since June 2013 for men with metastatic prostate cancer in whom the commonly used hormone blockade is no longer effective and who have already been treated with the cytostatic drug docetaxel. In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether this new drug offers an added benefit over the appropriate comparator therapy specified by the Federal Joint Committee (G-BA).

In comparison with "best supportive care", there is a hint of a major added benefit in patients whose internal organs are free of metastases of the tumour. In patients with such visceral metastases, the extent of added benefit is "considerable".

"Best supportive care" was appropriate comparator therapy

The G-BA specified "best supportive care" (BSC) as appropriate comparator therapy. BSC means a therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms (e.g. adequate pain therapy) and improve quality of life.

Adequate pain therapy questionable in approval study

Studies that tested a comparison of enzalutamide with or without BSC versus BSC alone could be considered for the benefit assessment. The approval study (AFFIRM) met these criteria. It was unclear, however, whether patients in the control group actually received adequate pain therapy throughout the entire study and whether therefore the criteria of BSC were fulfilled. Due to this increased uncertainty, at most "hints", but not "indications" could be derived from the AFFIRM results.

Survival advantage only in patients without tumours in internal organs

As the data showed, patients in the enzalutamide arm of the study survived longer than in the control group. However, there were also indications that the characteristic "presence or lack of metastases in internal organs" can influence the treatment result and is therefore a so-called "effect modifier". In separate analyses, overall survival was found to be longer only in patients without visceral metastases. Hence, there is an added benefit in mortality only for this subgroup.

Bone lesions occurred later, less pain

There were no effect modifiers regarding symptoms and late complications, i.e. the differences between the enzalutamide and the control arm apply to all patients. Bone complications like fractures occurred later in the study under enzalutamide than under BSC alone. Pain progression was also delayed, and, at the end of the study, pain intensity was lower in patients who had received enzalutamide.

Some data on side effects were not evaluable

Independent from the type of treatment, side effects occurred in almost all patients. However, most data on side effects submitted by the drug

manufacturer were not evaluable.

This is due to the fact that the treatment and observation duration of the patients differed between the two treatment arms. The longer a treatment lasts, the more likely it becomes that side effects occur. However, the manufacturer did not consider this difference adequately in the analysis of the data. Hence no conclusions can be drawn with regards to serious adverse events (SAEs) or to treatment discontinuations due to side effects.

Data were uncertain, but interpretable

Despite this uncertainty, the data could be interpreted with the result that severe adverse events occurred less frequently in men who were treated with enzalutamide. This indicates lesser harm of the new drug. Because these results might be biased, the frequency – and thus the extent of this advantage – could not be accurately assessed.

The manufacturer's dossier did not contain any evaluable data on health-related quality of life.

Overall, the evaluable data only show positive effects

Hence the overall assessment only shows advantages of enzalutamide. No disadvantages could be determined in any aspect of the treatment for which evaluable data were available. IQWiG therefore considers there to be hints of an added benefit in all patients. However, it rates their extents differently: For patients with visceral metastases, the extent is "considerable"; for patients without visceral metastases, it is "major" because of the additional survival advantage.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit assessment conducted by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and result in a change to the benefit assessment. The G-BA decides on the extent of the added benefit, thus completing the early benefit assessment.

Provided by Institute for Quality and Efficiency in Health Care

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