# Considerable added benefit of ipilimumab in advanced melanoma

November 9 2012

The humanized antibody ipilimumab (trade name Yervoy) has been approved since August 2011 for the treatment of adult patients with advanced melanoma (black skin cancer) who have already been treated. The term "advanced" means that the melanoma can no longer be removed by an operation or that metastases have formed. The German Institute for Quality and Efficiency in Health Care (IQWiG) has examined the added benefit of the drug pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG). According to the findings, the drug offers major advantages with respect to overall survival, but is accompanied by major potential harm in the form of side effects. The overall conclusion is that ipilimumab offers considerable added benefit.

## "Best supportive care" as appropriate comparator therapy

As specified by the Federal Joint Committee (G-BA), ipilimumab was to be compared with so-called "best supportive care". This means the best possible supportive therapy, optimized for the individual patient, which guarantees alleviation of the symptoms and improvement in the quality of life.

The only study relevant to this benefit assessment compared ipilimumab in combination with "best supportive care" with "best supportive care" alone. This study was informative (randomized controlled trial, RCT)

and included three parallel study arms. Patients in arm 1 were treated with ipilimumab. Patients in arm 2 were treated with ipilimumab and an experimental tumour vaccine (gp100), which has been examined in studies since 1996, but which has not yet been submitted for approval. The patients in the comparator arm (arm 3) were given a placebo and the tumour vaccine. All patients in the study were also given "best supportive care".

In its assessment, the Institute came to the conclusion that the administration of gp 100 had no relevant influence on the effects of ipilimumab measured in this study, in comparison to "best supportive care".

## Longer survival means major added benefit

The assessments performed by IQWiG always concentrate on patient-relevant outcomes, such as survival time, symptoms and complaints and quality of life. The study provided an indication that ipilimumab can prolong life. Whereas half of the patients who had not received ipilimumab already died after 6.5 months, half of the patients who had received ipilimumab died after 10 months. This prolongation of life provides an indication of major added benefit of ipilimumab in combination with "best supportive care" in comparison to "best supportive care" alone.

Symptoms and complaints caused by the disease (morbidity) were not examined in the study. Thus, added benefit for ipilimumab for these outcomes is not proven.

There was no relevant difference between ipilimumab and placebo with respect to quality of life (general state of health, functionality, symptoms such as fatigue, nausea, pain, digestive disorders etc.). Thus there is no proof of added benefit.

## Major potential harm in the form of side effects

The overall rates of adverse events, severe adverse events (according to the general terminology criteria CTCAE grade ≥ 3) and serious adverse events were comparable in the different treatment groups. Therefore greater or lesser harm from ipilimumab is not proven for these outcomes.

Adverse events which led to discontinuation of treatment were more frequent in the ipilimumab group than in the placebo group. Nevertheless, greater harm from ipilimumab is not proven, as it cannot be excluded that the effect size is only marginal.

The evaluation of the overall rate of immune-related adverse events and study discontinuations due to events of this type provided an indication of considerable harm from ipilimumab for both outcomes. There are also indications of major harm from ipilimumab with respect to severe (≥ CTCAE grade 3) and serious immune-related events.

## Potential harm reduces the extent of added benefit

If a proof of benefit is to be deduced from a single study, this study has to fulfil special requirements. These requirements are not fulfilled for the present study. Thus, in the early benefit assessment of ipilimumab it is not possible to derive conclusions on added benefit with the highest degree of probability (proof); the data can at most provide indications of added benefit.

In summary, there are positive and negative results of the same degree of certainty (indications). On the positive side, the greatest extent - namely "major" - is attained for overall survival. On the negative side and as a result of side effects, there is an indication of greater harm, and this is

also of major extent. For this reason, the Institute downgrades the overall added benefit of ipilimumab relative to the appropriate comparator therapy "best supportive care" from major to considerable.

## 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 its assessment by IQWiG, the G-BA initiates a formal commenting procedure which can provide further information and result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

You can also find easily understandable and brief German-language information about ipilimumab on the website gesundheitsinformation.de, published by IQWiG.

The G-BA website contains both general English-language information about the procedure of benefit assessment pursuant to §35a Social Code Book V and specific German-language information on the assessment of ipilimumab.

Provided by Institute for Quality and Efficiency in Health Care

Citation: Considerable added benefit of ipilimumab in advanced melanoma (2012, November 9) retrieved 9 May 2024 from https://medicalxpress.com/news/2012-11-considerable-added-benefit-ipilimumab-advanced.html

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