IQWiG in a dilemma? The oncology guidelines in contradiction to patient preferences in Germany

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Themes to be covered

- AMNOG process and the role of IQWiG
- Key findings of the IQWiGs oncology guideline
- Comparison of the IQWiG guideline recommendations with available oncology reviews
- Discussion of potential contradictions
- Introduction of a new focus: Patient preferences
- Discussion of the impact of patient preferences on the IQWiG oncology guideline and future assessments
- Conclusions
The German market access process since January 2011

- Consultation with G-BA
  - Launch – submission of dossier to G-BA*
  - Benefit assessment (e.g. by IQWiG)
  - Decision on benefit by G-BA
    - Additional benefit
      - Negotiation with national assoc. of SHI funds on reimbursed price
    - No additional benefit
      - Reference price possible
        - Reference price
        - Negotiation, but price maximum at level of comparative therapy
      - No reference price possible
        - Negotiation, but price maximum at level of comparative therapy
  - No agreement: Arbitration board

*G-BA Gemeinsamer Bundesausschuss – Federal joint committee
The additional benefit assessment drives the price negotiation

<table>
<thead>
<tr>
<th>Additional benefit*</th>
<th>Negotiation</th>
<th>Implication for Pricing</th>
<th>European prices considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>Yes</td>
<td>Adjusted premium vs. the appropriate therapy in pricing negotiation (considering the criteria in §6, see page before)</td>
<td>Yes</td>
</tr>
<tr>
<td>Significant</td>
<td>Yes</td>
<td>see above; with upside potential</td>
<td>Yes</td>
</tr>
<tr>
<td>Marginal</td>
<td>Yes</td>
<td>Reference price or at max. the price of the appropriate comparative therapy</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>No, if product can be put into a reference price group</td>
<td>Discount vs. the appropriate comparative therapy</td>
<td>No</td>
</tr>
<tr>
<td>Smaller</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Source: §5 Rules of procedure or negotiations (between Industry and SHI)
Structure of the negotiation process at the GKV-SV

Month: 1

- Two further meetings planned, between first and last meeting
- Upon agreement of parties another meeting is possible
- Last meeting max. 3 weeks prior to price publication

- First meeting within 4 weeks after GBA decision
- 5 participants per party
- 2 in addition are allowed upon agreement.

Guest of the national association of private health insurances

Private health insurance has to be informed within 5 working days after last negotiation date about rebate/reimbursement price.

Publication in official price list: Lauer Taxe

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Basket of European reference price countries for price negotiation

1. Austria
2. Belgium
3. Czech Republic
4. Denmark
5. Finland
6. France
7. Greece
8. Ireland
9. Italy
10. Portugal
11. Sweden
12. Spain
13. Slovakia
14. The Netherlands
15. UK
Oncology: Something special?

- Life-threatening disease
- Most of the times: Short survival
- Most of the times: Few and toxic treatment options
- „Death or life decision“ makes it difficult for some agencies to make unpopular negative decisions
- Study designs:
  - Use of surrogate endpoint (e.g. PFS instead of OS)
  - Cross-over
  - ...

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November 2011 IQWiG published a rapid report on the validity of surrogate endpoints in oncology.
IQWiG’s summary on surrogate endpoints

• In case of limited reliability and high correlation of the surrogate and patient-relevant endpoint:
  – At most, an indication of effects on patient-relevant endpoints.

• In case of limited reliability and medium correlation:
  – An indication of an effect on the patient-relevant endpoint can at most be inferred. Dependent on the correlation, at most a hint of an effect on the patient-relevant endpoint can be inferred.

• In case of limited reliability and low correlation:
  – Categorically no proof is available of an effect on the patient-relevant endpoint.
IQWiG’s „real life“ exercise

• The available validation studies on breast and colon cancer allow no final conclusion about the validity of tumour response parameters for overall survival in patients with these diseases.

• In most cases the correlation of the respective effects was not high enough, so that the prerequisite for proof of validity was not fulfilled.

• Additionally, in all studies reliability was classified as low.

• **Therefore, independent of the statistical results, the validity of all investigated surrogate endpoints ultimately remained unclear.**
Oncology assessments in the AMNOG process

• 17 decisions were positive in Germany (n=1 ‘significant’; n=8 ‘considerable’; n=7 ‘minor’; n=1 ‘non-quantifiable’ added benefit).

• Two products have been overall appraised negatively (TAFINLAR; TEYSUNO).

• In ten of the products for one or more subgroups the appraisal has been negative.

Data analysed using the International Prismaccess HTA database (www.prismaccess.com) - Droeschel et al. ViH 2014
No clear correlation between OS benefit and the added benefit granted by the G-BA

Data analysed using the International Prismaccess HTA database (www.prismaccess.com) - Droeschel et al. ViH 2014
The higher the PFS benefit, the higher the added benefit.

Data analysed using the International Prismaccess HTA database (www.prismaccess.com) - Droeschel et al. ViH 2014
Reasons for low ratings of added benefit

- No RCT evidence
- Use of surrogate endpoint
- Wrong appropriate comparator
- No data on subgroups of interest
- Issues in the study design:
  - Quality control
  - Wrong stratification factors
  - Wrong co-medications
New IQWiG method guide: Changes?

• Major change:
  – For the overall benefit of a comparison of interventions also procedures for multi-criteria decision-making could be applied, such as...
    • Analytic hierarchy process (AHP)
    • Conjoint analysis (CA)

• So, would this change anything?

IQWiG methods 4.2 available at: https://www.iqwig.de/download/IQWiG_Methoden_Version_4-2.pdf

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What is a conjoint analysis?

• International accepted microeconomic method for determining the weights (priorities) of decision-relevant attributes (for a product/service)

• Execution:
  – Questions for decisions of two different sets of attributes (e.g. for a service)
  – Decisions by respondents being statistically analyzed to calculate the weights of attributes
How is a conjoint analysis executed?

• Example of questions:

<table>
<thead>
<tr>
<th>Factors</th>
<th>Person A</th>
<th>Person B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td>7 months</td>
<td>4 months</td>
</tr>
<tr>
<td>Pain, coughing, and shortness of breath</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Rash</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Fatigue (tiredness)</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Moderate</td>
<td>None</td>
</tr>
<tr>
<td>Fever and Infection</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Oral or Infusion</td>
<td>Oral and Infusion</td>
<td>Infusion</td>
</tr>
</tbody>
</table>

In your opinion, which person has received the better treatment?

[ ] Person A
[ ] Person B
So, what?

- Key question in the AMNOG context:
  - Is there a potential impact on decision making?
  - No real life example available
  - However, ...
    - Oncology assessments in the AMNOG context
    - Published conjoint analyses in oncology

- Research question: Would the application of conjoint analysis (have) change(d) the G-BA decisions in oncology?
Case study 1: Lung Cancer

• One AMNOG process being executed:
  – Crizotinib in ALK-positive non-small cell lung cancer (NSCLC)

  – Results:
    • Chemotherapy eligible patients: Major added benefit
    • Chemotherapy non-eligible patients: No added benefit

• One published preference study in NSCLC

Bridges JF et al. Lung Cancer 2012

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Results of the NSCLC preference study

Bridges JF et al. Lung Cancer 2012

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Impact on the decision making?

• No overall survival included in the preference analysis
  – Higher PFS = higher preference indication that OS preferred over OS?
  – No answer out of the analysis

• However, analysis would have been doable:
  • „Is there a trade-off between PFS (+ QoL) and OS in NSCLC?“
  • „Is there a difference in the subgroups G-BA defined?“
Case study 2: Colorectal cancer

- One AMNOG process being executed:
  - Aflibercept in colorectal cancer (CRC)

- G-BA decision:
  - Minor added benefit

- One published preference study in CRC
Results preference analysis CRC

• Patients received chemotherapy even...
  – if they believed that chemotherapy would not extend their life (90%)
  – that chemotherapy would not likely help with cancer related problems (89%)
  – if patients preferred treatment focusing on comfort even if it meant not living as long (90%).

• Older patients were less likely to receive combination first-line therapy.

Bridges JF et al. Lung Cancer 2012
Potential decision-making influence?

• PFS and especially QoL more important than OS

• Positive for industry: Higher acceptance of PFS as primary endpoint?

• Negative for industry: Potential new important subgroup – „patients preferring (chemo-) therapy“?
Case study 3: Prostate Cancer

- Three AMNOG processes being executed:
  - Enzalutamid: Major added benefit
  - Abiraterone (acetate): Major added benefit
  - Cabazitaxel: Minor added benefit in one subgroup

- One published preference study in prostate cancer

[www.marketaccess-pricingstrategy.de]
Clinical preference study in prostate cancer

• Clinical trial being run to understand the patient preferences between cabazitaxel and docetaxel in prostate cancer

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Patient Preference Between Cabazitaxel and Docetaxel in Metastatic Castrate-resistant Prostate Cancer (CABA-DOC)

This study is currently recruiting participants.
Verified January 2014 by Gustave Roussy, Cancer Campus, Grand Paris

Sponsor:
Gustave Roussy, Cancer Campus, Grand Paris

Collaborator:
Sanofi

Information provided by (Responsible Party):
Gustave Roussy, Cancer Campus, Grand Paris

ClinicalTrials.gov Identifier:
NCT02044354
First received: January 22, 2014
Last updated: January 24, 2014
Last verified: January 2014

https://clinicaltrials.gov/ct2/show/NCT02044354
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Conclusions

• Preference analysis might support submissions in the AMNOG context dependent also if the underlying clinical data support these findings
  – Preference for endpoints
  – Weight of clinical results for one measure?

• New submissions utilizing the preference opportunity (see cabazitaxel) are awaited
Thank you!

Please contact me in case of further questions or comments:

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