Early benefit assessment of new drugs

5-year experiences of AMNOG
(from IQWiG’s point of view)

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Deputy director
Institute for Quality and Efficiency in Health Care (IQWiG)
- IQWiG was founded as an independent scientific institute through a health care reform in 2004.

- Main task: Assessment of benefits and harms of medical interventions and production of independent, evidence-based reports.

- The legal basis of the work of IQWiG is the social code book V (SGB V).

- IQWiG is solely commissioned by the Federal Joint Committee or the Federal Ministry of Health (rather rarely), but can also cover topics on its own initiative under a general commission.
The Federal Joint Committee (G-BA) is the supreme decision-making body of the so-called self-governing system in Germany. Physicians, dentists, hospitals, sickness funds and patients are represented in the G-BA.

The G-BA issues directives and thus determines the benefit package of the statutory health insurance (GKV) covering about 70 million people. Finally, the G-BA is responsible for reimbursement decisions in the GKV.

*Act on the Reform of the Market for Medicinal Products*

- Systematic early assessment of newly approved drugs
  - Assesses and quantifies (categories) additional benefit (vs. defined [appropriate] comparator → set by G-BA [not the ministry of health])
  - Forms the basis for price negotiations (→ discount on sales price)
  - Has no formal impact on prescription
  - ‘must not contradict the statements on efficacy and safety by the drug regulation authorities’ (German Social Code Book V)
  - Exception: orphan drugs – with the fiction of ‘additional benefit by approval’ – as long as sales volume < 50 Mio. € (otherwise: full assessment)
- Assessment based on a dossier submitted by the manufacturer (at time of market access)
- No relevant role of health economics / cost-benefit-analysis
Dossier

- information on the authorised indication
- all available evidence for the assessment of additional benefit (according to international standards of evidence-based medicine)
  - all studies sponsored by the pharmaceutical company
  - all available third-party studies
  - All information to study methodology and study results (of sponsors’ studies) have to be made publicly available (no commercial-in-confidence data are acceptable)
- information on costs of the drug
- information on quality-assured use
- an incomplete dossiers means „no additional benefit“
Early benefit assessment of drugs in Germany, IQWiG’s point of view, 23.03.2016, Giens, France, SL
Questions asked by AMNOG

- Does the drug under assessment have an additional benefit compared to the appropriate therapeutic alternative (appropriate comparator [set by the G-BA])?

- What is the extent of the additional benefit?

- What is the ‘probability‘ of the additional benefit (how certain are we about this additional benefit)

- Which patient groups experience a therapeutically important additional benefit?
Added benefit according to AMNOG

- Benefit = patient-relevant Effect
  (improving health state, shortening duration of illness, increasing survival, reducing adverse events, improving quality of life)
  (only validated surrogates may be considered → e.g. SVR for hepatitis C; however, PFS by Recist criteria has not been accepted in the past)

- Added Benefit = Benefit vs. appropriate comparator
  (Selection: evidence-base, practical experience, in case of comparable alternatives selection by manufacturer)

- Approval status has to be considered! (also for appropriate comparator)
Multiple endpoints

In principle, IQWiGs' methodology requires adjustment in case of a multiplicity issue ...

In reality, however, IQWiG doesn't account for multiplicity in its assessments (up to now) ...
### ‘Probability’ (Certainty of conclusions)

<table>
<thead>
<tr>
<th>Qualitative certainty of results</th>
<th>Number of studies</th>
<th>1 (with statistically significant effect)</th>
<th>≥ 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Homogeneous</td>
<td>RCT with low risk of bias</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Indication</td>
<td>Proof</td>
<td>Proof</td>
</tr>
<tr>
<td>Moderate</td>
<td>Hint</td>
<td>Indication</td>
<td>Indication</td>
</tr>
<tr>
<td>Low</td>
<td>–</td>
<td>Hint</td>
<td>Hint</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneous</td>
<td>RCT with high risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meta-analysis statistically significant</td>
<td>Effects in the same direction(^a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clear</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Effects in the same direction refer to the consistency of the results across studies.
Extent of added benefit (acc. to directive)

- Major added benefit
- Considerable added benefit: Added benefit not quantifiable
- Minor added benefit
- Added benefit not proven
- Sustained and great improvement
- Marked improvement
- Moderate and not only marginal improvement
- Less benefit
### Extent of added benefit (acc. to directive)

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>Serious symptoms or events</th>
<th>HRQoL#</th>
<th>Non-serious symptoms or events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major added benefit</strong></td>
<td>Major increase</td>
<td>Long-term freedom or extensive avoidance</td>
<td>Major improvement</td>
<td>N.a.</td>
</tr>
<tr>
<td><strong>Considerable added benefit</strong></td>
<td>Moderate increase</td>
<td>Alleviation or relevant avoidance</td>
<td>Important improvement</td>
<td>Important avoidance</td>
</tr>
<tr>
<td><strong>Minor added benefit</strong></td>
<td><em>Any increase</em></td>
<td><em>Any reduction</em></td>
<td><em>Any improvement</em></td>
<td>Relevant avoidance</td>
</tr>
</tbody>
</table>

* = Amendment to directive by IQWiG

# The condition is the use of a validated instrument and a validated response criterion. Values count for non-response.
<table>
<thead>
<tr>
<th>Added Benefit</th>
<th>Overall Survival</th>
<th>Serious Symptoms or Events</th>
<th>HRQoL</th>
<th>Non-serious Symptoms or Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major added benefit</td>
<td>Major increase</td>
<td>Long-term freedom or extensive avoidance</td>
<td>Major improvement</td>
<td>N.a.</td>
</tr>
<tr>
<td>RR0 ≤ 0,50</td>
<td>RR0 ≤ 0,17</td>
<td>RR0 ≤ 0,17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Considerable added benefit</td>
<td>Moderate increase</td>
<td>Alleviation or relevant avoidance</td>
<td>Important improvement</td>
<td>Important avoidance</td>
</tr>
<tr>
<td>RR0 ≤ 0,83</td>
<td>RR0 ≤ 0,67</td>
<td>RR0 ≤ 0,67</td>
<td></td>
<td>RR0 ≤ 0,33</td>
</tr>
<tr>
<td>Minor added benefit</td>
<td>Any increase</td>
<td>Any reduction</td>
<td>Any improvement</td>
<td>Relevant avoidance</td>
</tr>
<tr>
<td>RR0 &lt; 1,00</td>
<td>RR0 &lt; 1,00</td>
<td>RR0 &lt; 1,00</td>
<td></td>
<td>RR0 ≤ 0,67</td>
</tr>
</tbody>
</table>

RR0 = Observed relative risk
What we can expect to see …

Suppose 2 reasonably powered studies with assumed (‘true’) effect RR (and conventional null-hypothesis $H_0$: $RR \geq 1$ vs. $H_1$: $RR < 1$)

Select threshold $RR_S$ so that power for a test $H_0$: $RR \geq RR_S$ vs. $H_1$: $RR < RR_S$ (pooled estimate) is the same as for the 2 single studies (with conventional null-hypothesis)

## What we have to test (shifted hypotheses)

<table>
<thead>
<tr>
<th>Major added benefit</th>
<th>Overall survival</th>
<th>Serious symptoms or events</th>
<th>HRQoL</th>
<th>Non-serious symptoms or events</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR &lt; 0,85</td>
<td>Major increase</td>
<td>Long-term freedom or extensive avoidance</td>
<td>Major improvement</td>
<td>N.a.</td>
</tr>
<tr>
<td>Considerable added benefit</td>
<td>Moderate increase</td>
<td>Alleviation or relevant avoidance</td>
<td>Important improvement</td>
<td>Important avoidance</td>
</tr>
<tr>
<td>RR &lt; 0,95</td>
<td>RR &lt; 0,90</td>
<td>RR &lt; 0,90</td>
<td>RR &lt; 0,80</td>
<td></td>
</tr>
<tr>
<td>Minor added benefit</td>
<td>Any increase</td>
<td>Any reduction</td>
<td>Any improvement</td>
<td>Relevant avoidance</td>
</tr>
<tr>
<td>RR &lt; 1,00</td>
<td>RR &lt; 1,00</td>
<td>RR &lt; 1,00</td>
<td>RR &lt; 0,90</td>
<td></td>
</tr>
</tbody>
</table>

*RR = Relative risk*  

*# Risk must be at least 5% for at least one of the two groups compared*

### What does this mean?

<table>
<thead>
<tr>
<th>Major added benefit</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR &lt; 0,85</td>
<td>Major increase</td>
</tr>
</tbody>
</table>

If the upper limit of a 95% confidence interval for the effect estimate excludes 0,85

→ **major increase in overall survival (major added benefit)**

‘Added benefit’ of AMNOG

Completeness of information of results with regard to patient-relevant endpoints

Köhler M. et al. Information on new drugs at market entry. BMJ 2015; 350; h796
‘Added benefit’ of AMNOG

Completeness of information of results with regard to relevant subpopulations/-groups

Köhler M. et al. Information on new drugs at market entry. BMJ 2015; 350; h796
Results (IQWiG, extent)

In each case best categorization of added benefit within one assessment

Status: 15/02/2016  129 assessments
Results (IQWiG, extent)

**Oncology**

- **24%** major
- **24%** considerable
- **16%** minor
- **5%** not quantifiable
- **3%** less benefit
- **27%** added benefit not proven

**Others**

- **65%**
- **12%**
- **10%**
- **9%**

**About 30% of assessments**

Advanced disease in nearly all cases

In each case best categorization of added benefit within one assessment

Status: 15/02/2016
Major added benefit?

Observed reduction in mortality (hazard ratio) always < 50% (HR > 0.5)

Example (HR: 0.59 [0.44; 0.79])

Difference in median survival time
Difference in 1-year survival rate

from: A15-32
Results (IQWiG, PRO)

Information with regard to patient reported outcomes (PRO, symptom scales or HRQoL)

Main reasons:
- Approval status not adequately considered
- Inappropriate comparator
- Unqualified indirect comparison

In each case best categorization of added benefit within one assessment

Status: 15/02/2016
Results (IQWiG, PRO)

Information with regard to PRO, in case of relevant studies

In each case best categorization of added benefit within one assessment

Status: 15/02/2016
Information with regard to PRO, in case of relevant studies

In each case best categorization of added benefit within one assessment

Status: 15/02/2016
Results (IQWiG, HRQoL)

Information with regard to HRQoL, in case of relevant studies

In each case best categorization of added benefit within one assessment

Status: 15/02/2016
In oncology in general only one (pivotal, relevant) study available with about median 600 (suitable) patients.
### Agreement: Assessment (IQWiG) vs. decision (G-BA)

<table>
<thead>
<tr>
<th>IQWiG</th>
<th>G-BA</th>
<th>Not proven</th>
<th>Not quantif.</th>
<th>Minor</th>
<th>Considerable</th>
<th>Major</th>
<th>Sum (IQWiG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not proven</td>
<td>61</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>Not quantif.</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Minor</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Considerable</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Major</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Sum (G-BA)</td>
<td>61</td>
<td>5</td>
<td>25</td>
<td>34</td>
<td>2</td>
<td>0</td>
<td>127</td>
</tr>
</tbody>
</table>

In each case best categorization of added benefit within one assessment.
Thank you for your attention!

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