Earlier access tools: is speed the right priority?

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

Good decisions need good data

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Scientifically independent

- We assess the benefit or harm of medical interventions for patients.
- The contents of the assessments are not influenced by payers (health insurance funds), service providers, industry or politics.
- Neither the Institute nor its staff members receive any payments by third parties, such as industry.

Tasks

Health Technology Assessment (HTA)

- Informs reimbursement decisions
- Assessment of benefits* and harms of a new technology
- in comparison to the best available intervention so far
- Focus on patient-relevant outcomes (mortality, morbidity, and [health related] quality of life)
- Cost

(Drug) Approval

- Requirement for market entry
- Assessment of efficacy, safety, and quality of a new drug
- Comparator variable / placebo controls possible
- Positive benefit*/risk ratio
- Surrogate endpoints possible

* The term ‘benefit’ doesn’t necessarily have the same meaning for HTA and approval

Regular drug development

- Basic research, drug discovery
- Preclinical testing (is the drug safe for human testing?)
- Phase 1 (safety testing in healthy volunteers [up to 100*], pharmacokinetics, pharmacodynamics)
- Phase 2 (safety and efficacy in small patient groups [100 to 500*], dose-finding)
- Phase 3 (safety and efficacy in large patient groups [1 000 to 5 000*], benefit-risk ratio), pivotal studies
- Phase 4 (post approval)

* Figures according to PhRMA (Biopharmaceutical Research & Development:The Process Behind New Medicines. 2015. http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure.pdf)

(rather) good data

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Pivotal study	Trastuzumab emtansine	Lapatinib + capecitabine	Effect
Overall survival (median time, mo.)	30,9	23,7	HR 0,70 (p = 0,010)
HRQoL (median time to worsening, mo.)	6,6	5,5	HR 0,80 (p = 0,05)
Time to severe AEs (≥ grade 3)	ND	ND	HR 0,61 (p < 0,001)
Hand-foot syndrome (grade 3)	0%	18%	Peto-OR 0,11 (p < 0,001)

(rather) week data

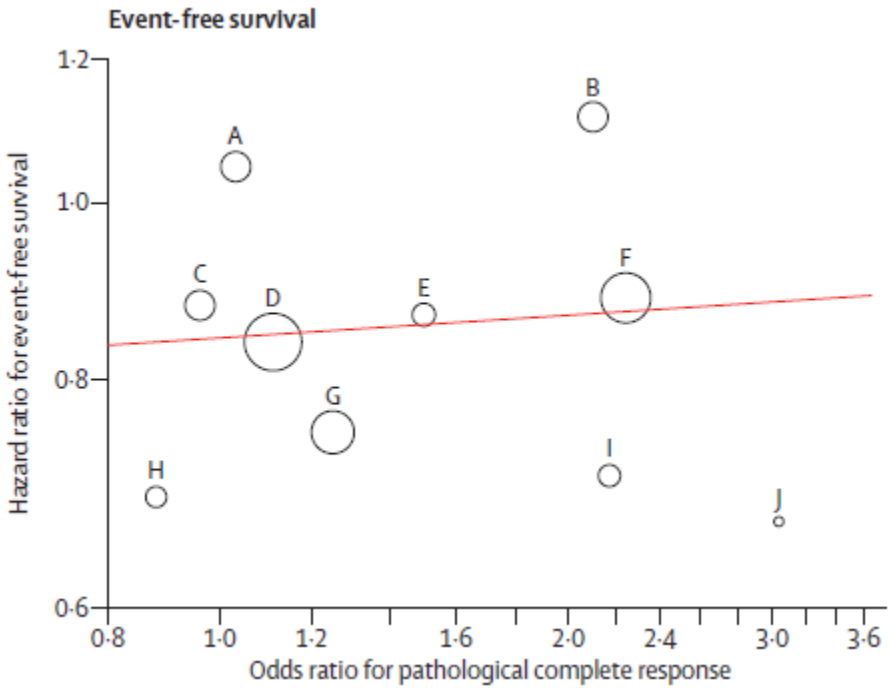
Neoadjuvant pertuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer

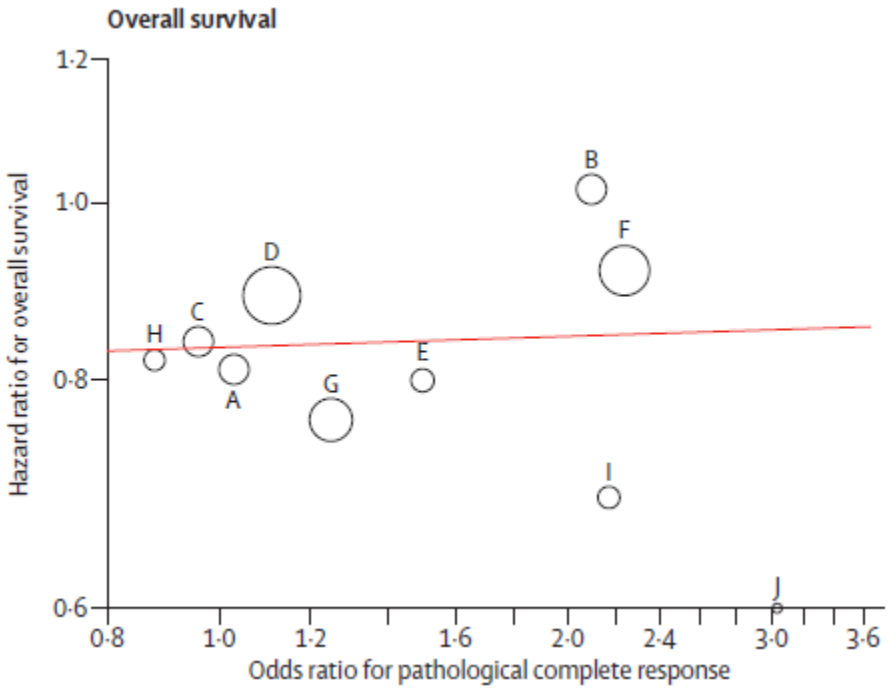
- Phase 2 study
- 214 patients (relevant for assessment)
- Surrogate endpoint (pathological complete response)
- No statistical significant difference in disease-free (or overall) survival (after 5 years [Lancet Oncol 2016; 17: 791–800])
- Statistically significant disadvantage with respect to discontinuation of study drug
- No data on health-related quality of life or other patient-reported outcomes

https://www.iqwig.de/en/projects-results/projects/drug-assessment/a15-34-pertuzumab-new-therapeutic-indication-benefit-assessment-according-to-35a-social-code-book-v-dossier-assessment.6943.html

(rather) week data

Surrogate: pathological complete response





‘Our pooled analysis could not validate pathological complete response as a surrogate endpoint for improved EFS and OS.’

Lancet 2014; 384: 164–72

Accelerated / facilitated approval

Orphan drugs

Exceptional circumstances

Conditional approval

New: Priority Medicines (PRIME)

Adaptive pathways?

Use of the Conditional Marketing Authorization Pathway for Oncology Medicines in Europe*

- New active substances approved for a first oncology indication by European Medicines Agency (EMA) in the period 2006 to 2013

Pivotal study	Regular approval (31)	Conditional approval (11)
No. of patients (median)	626	154
RCT	90%	45%
Active comparator	48%	9%
Surrogate	39%	100%

*Clin Pharmacol Ther. 2015; 98: 534-41.

Adaptive pathways

- iterative development, which either means:
  - approval in stages, beginning with a restricted patient population then expanding to wider patient populations;
  - confirming the benefit-risk balance of a product, following a conditional approval based on early data (using surrogate endpoints) considered predictive of important clinical outcomes;
- gathering evidence through real-life use to supplement clinical trial data;
- early involvement of patients and health-technology-assessment bodies in discussions on a medicine's development.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp

‘Real world evidence’

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Survival Associated With Treatment vs Observation of Localized Prostate Cancer in Elderly Men*

‘Conclusions This study suggests a survival advantage is associated with active treatment for low- and intermediate-risk prostate cancer in elderly men aged 65 to 80 years. Because observational data cannot completely adjust for potential selection bias and confounding, these results must be validated in randomized controlled trials of alternative management strategies in elderly men with localized prostate cancer.’

- **Observational data (‘real world evidence’) are inherently and severely limited by selection bias which cannot be controlled by any statistical method**

*JAMA. 2006; 296: 2683-2693

Thank you for your attention!

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