

Welche wissenschaftlichen Erkenntnisse benötigen wir für eine Nutzen- und Kosten-Nutzen-Bewertung medikamentöser Therapien in der Hämatologie/Onkologie?

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Ethik in der Onkologie
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Leitthema

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Teure Innovationen in der Onkologie – für alle?
 Überlegungen zu Voraussetzungen für eine rationale Pharmakotherapie und ethische Herausforderungen

Medikamentöse Tumorthherapie: Status quo

- demographische Entwicklung
- großer Bedarf an echten Innovationen/Therapieverbesserung
- (enorme) Fortschritte in der molekularbiologischen Forschung
- > 400 neue Arzneimittel (ca. 180 Firmen) in klinischer Prüfung
- Zulassungsgeschwindigkeit neuer Arzneimittel ▲
- große Zahl an neu zugelassenen, sehr teuren Arzneimitteln
- TOP 200 Arzneimittel (2005): 11/18 aus der Häm/Onk (Blockbuster)
- Evidenzlücken für Einsatz der neuen Arzneimittel in der Onkologie (zum Zeitpunkt der Zulassung)
- fundierte wissenschaftliche Erkenntnisse aus klinischen Studien
- Definition des medizinischen Standards häufig nicht möglich

„Bedeutung von Spezialpräparaten nimmt weiter zu“*

Year	Specialty (billions USD)	Primary care (billions USD)	Specialty %	Primary care %	Annual growth rate
2001	577	39%	67%	23%	
2002	503	40%	60%	23%	
2003	514	42%	58%	26%	
2004	583	44%	56%	26%	
2005	526	45%	55%	26%	
2006	5243	45%	55%	26%	

* Gudixen M et al.: Nature Rev Drug Discovery 2008; 7:5637

„With each advance in treatment, the magnitude of the increase in the cost of treatment exceeded the magnitude of improvement in efficacy.“

The NEW ENGLAND JOURNAL of MEDICINE
 INTERACTIVE GRAPHIC
 Graphics updated February 5, 2009

Brand drug name

1985-1989: ca. 500 US \$
 2005-2009: ca. 7.000 US \$

Wachstumsmarkt Onkologie = 20-25%/a.
 2008: 48 Mrd. US \$
 2013: 75 Mrd. US \$

Limits on Medicare's Ability To Control Rising Spending On Cancer Drugs
 *Bach PB: 2009; 360:626-633

z.B. Onkologie, Transplantationsmedizin, AIDS, Rheumatologie

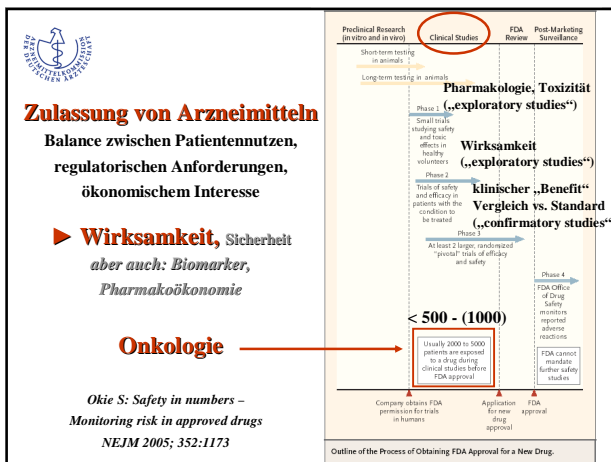
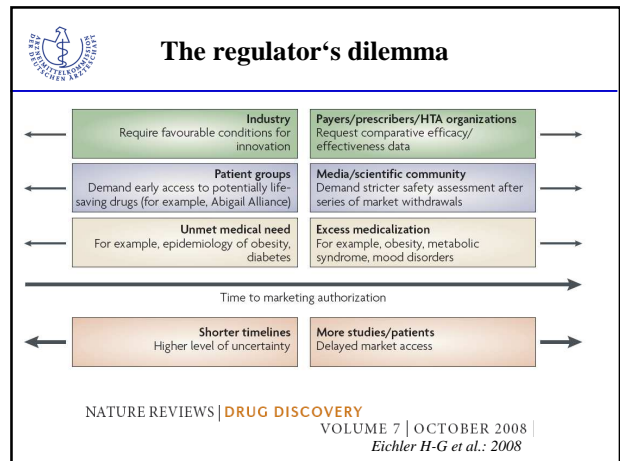
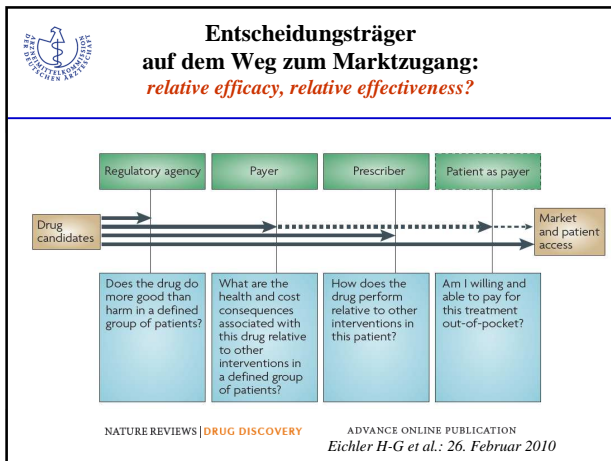
GRV-Arzneimittelindex **Wido**

Entwicklung von Umsatz und Verordnungen bei Spezialpräparaten – vorläufiges Ergebnis 2008

Year	Verordnungen (in Mio.)	Umsatz (in Mrd. €)
1999	8,6	2,4
2000	9,1	2,8
2001	10,2	3,3
2002	11,7	3,9
2003	12,1	4,4
2004	12,0	4,1
2005	12,7	4,7
2006	13,2	5,3
2007	14,2	6,2
2008	14,9	7,0

Nur zur internen vertraulichen Nutzung

© GRV-Arzneimittelindex 2009 28. Mai 2009 38



Relative Wirksamkeit? FDA und EMA 1.1.2007-31.1.2008

Type of RE described	FDA medical review n out of 42 (%)	EPAR n out of 47 (%)
Active comparator trial of clinical efficacy in the medical review or EPAR	17 (40.5%)	24 (51.1%)
Active comparator trial of clinical efficacy in the label or SPc	13 (31.0%)	16 (34.0%)
Active comparator information on efficacy derived from an RCT with an active comparator and placebo group	2 (4.8%)	3 (6.4%)
Active comparator information on efficacy derived from an RCT with an active comparator group, but without placebo group	15 (35.7%)	21 (44.7%)
Superiority over active comparator was shown in a head-to-head RCT	1* (2.4%)	10* (21.3%)
Active comparator licensed in the relevant indication in the respective agency's jurisdiction?	15* (35.7%)	24* (51.1%)
Summary data of the active comparator trial(s) presented numerically (for example, mean, median, confidence intervals) in the medical review or EPAR	12 (28.6%)	24 (51.1%)

A new medicinal product can be said to have added therapeutic value if sound clinical data show that it offers patients better efficacy, and/or better safety and/or simpler administration, than existing alternatives

(EMA, 11 NCE, 1995-2006)*

- Grundlage der Bewertung EPAR (zentralisiertes Verfahren)
- 11 Wirkstoffe (für 17 Indikationen) für hämatologische Neoplasien**
- klinische Studien (N=25 mit 6011 Patienten)
 - Basis der Zulassung: „Single-Arm Trials“ N=9, RCTs N=8
- Endpunkte („Response“ 12/17, Gesamtüberleben 2/17)**
- randomisierte „active-control“ Studien (RaCTs) in < 50% durchgeführt**
- „added value“ (harter Endpunkt, eindeutiger klinischer Effekt, adäquate Vergleichssubstanz) **nur bei 4/11 Wirkstoffen**

*Bertele V et al.: Eur J Clin Pharmacol 2007; 63:713-9
** Van Luijn JCF et al.: Br J Clin Pharmacol 2006; 63: 159-62

Outlook

Translated from Rev Prescribe March 2009; 29 (305): 218-221

Effects of cancer drugs on survival: often poorly evaluated

- Overall survival is the gold-standard endpoint when evaluating the efficacy of cancer drugs.
- Progression-free survival is an endpoint that combines two very different components: death or objective worsening of the tumour. It is a heterogeneous endpoint and measurement of the second component is imprecise. There are few examples where a correlation has been established between progression-free survival and overall survival.
- Time to progression is an endpoint of limited interest: it only takes into account the second component of the progression-free survival composite endpoint.
- Disease-free survival is a variant of progression-free survival and is most frequently used for adjuvant treatments.

Rev Prescribe 2009; 29 (305): 218-221.

1995-2004 → **Marketing authorisations granted on a shaky basis: in Europe too**

● Only 7% of marketing authorisations for cancer drugs are based on trials where the primary objective was to evaluate survival.

A team from the Mario Negri Institute for Pharmacological Research in Italy have investigated the basis on which the European Medicines Agency (EMA) approves marketing authorisations (MAs) for new cancer drugs or new therapeutic indications for cancer drugs that are already licensed (1).

Their evaluation dealt only with solid tumours and not haematological malignancies. It was based on data available on the EMA website from January 1995 to December 2004.

MA usually granted without survival data. Marketing authorisations were granted for 14 cancer drugs in 27 different indications during the period. These MAs were granted on the basis of a total of 48 clinical trials: 12 indications (44%) were granted solely on the basis of non-comparative trials (a). 7% of MAs were granted on the basis of trials in which the primary endpoint was overall survival. 41% of MAs were granted on the basis of trials in which the primary endpoint was time to progression. 48% of MAs were granted on the basis of trials in which the primary endpoint was tumour response rate.

Overall survival was a primary or secondary endpoint in 13 of the trials. The difference in survival between groups ranged from 0 to 3.7 months (median value).

More than one comparative trial was available for only 4 indications, and overall survival was the primary endpoint for only one indication (docetaxel) as second-line therapy for advanced non-small cell lung cancer.

Stopping trials early due to "benefit" = lost information. The same team analysed comparative trials published over the last 11 years that were stopped early because a protocol-planned interim analysis showed a benefit for patients (2). Out of a total of 25 trials, only 8 had overall survival as an endpoint in both the protocol and the interim analysis. In the other cases, stopping the trial early meant that much information was lost.

In summary, just as in the United States, European marketing authorisations are rarely granted for cancer drugs on the basis of trials that evaluate survival. Yet in many cases this is the benefit that patients expect.

©Prescrire

a. One indication was granted on the basis of a therapeutic equivalence trial (trastuzumab, a new drug) (ref. 3).

b. Apolone G et al. "The years of marketing approval of anticancer drugs in Europe: regulatory trends and public awareness level in light of a balance between different pressures" *Br J Cancer* 2005; 93: 504-9.

c. Tavitia F et al. "Stopping a trial early in oncology: for patients or for industry?" *Ann Oncol* 2008; 19 (12): 1347-1353.

d. Prescrire Selection "Médicines: some pharmacovigilance differences of progress over 2007" *Prescrire* 2008; 24: 1262-70.

Primäre Endpunkte in Zulassungsstudien

(EMA, 14 Wirkstoffe, 27 Indikationen, 1995-2004)*

„A potential pitfall of this trend is that new regimens become established in clinical practice before it is determined whether they provide true benefit“

Clinical trial design (48 trials)	Type of end point (primary) (48 trials)	Difference in survival, when available (13 trials)
RCT 25	Survival 4	Range 0–3.7 months Mean 1.5 (months) Median 1.2 (months)
SAT 19	Resp. rate 30	
NC-RCT 4	TTP/PFS 14	
	No.	%
Overall survival	2	7
TTP/PFS	11	41
Response rate	13	48
Other ^d	1	4

* Apolone G et al.: *Br J Cancer* 2005; 93: 504-9

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JOURNAL OF CLINICAL ONCOLOGY COMMENTS AND CONTROVERSIES

Randomized Trials in Oncology Stopped Early for Benefit

Ryan A. Wilson, Mayo Clinic, Rochester, MN
Benjamin D. Lippman, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
Gordon H. Sargent, McMaster University, Hamilton, ON
Victor M. Montz, Mayo Clinic, Rochester, MN

↓

Clinicians must interpret RCTs stopped early for benefit with caution, especially when information about the decision to stop early is not provided and few events have occurred. Failure to do so may result in prematurely translating the findings reported in these trials into clinical practice. Our ongoing research in this matter will help identify when and to what extent results from trials stopped early for benefit are in fact too good to be true.

Adverse Event Reporting in Publications Compared With Sponsor Database for Cancer Clinical Trials

Orin Scharf and A. Dimitrios Colevas

Conclusion
Lack of consistency in and reporting of AEs are associated with NCI database and trial publication AE data discrepancy.

J Clin Oncol 24:3933-3938.

➤ **nach Zulassung von Arzneimitteln:**

- > 50% Änderung von Fachinformation/Packungsbeilage
- ca. 20% neue Warnhinweise („black box warnings“)
- 3% - 4% Marktrücknahmen
- nur in ca. 10% (114/1191) Auflagen der Zulassungsbehörden (FDA) erfüllt

➤ **Konsequenzen?, u.a.**

- Post-Marketing Surveillance verbessern
- Risikomanagementsystem (RMP, REMS) für spezielle Arzneimittel
- Spontanerfassung verbessern

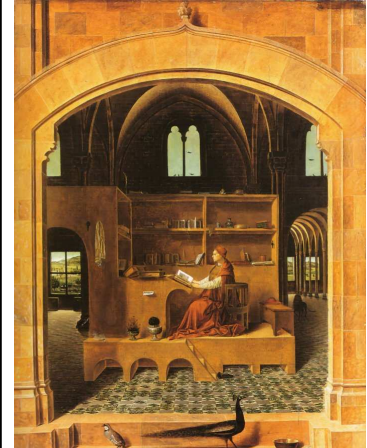
JAMA
Online article and related content current as of September 23, 2009

Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union

Thijs J. Glezen, Aukje K. Mantel-Teeuwisse, Sabine M. J. M. Straus, et al.
JAMA 2008;300(16):1887-1896 (doi:10.1001/jama.300.16.1887)

Biopharmazentika: Sicherheit betreffende regulatorische Maßnahme bei 29% innerhalb von 10 Jahren

Class of Biological	Active Substance	Drug Name	Drug Approval Date	Warning	Time to DHPC, y
Antibodies	Alemizumab	MazCampath	July 6, 2001	Cases of death related to infections	5.6
	Bevacizumab	Avastin	January 12, 2005	Tracheoesophageal fistula	2.3
	Infliximab	Remicade	August 13, 1999	Tuberculosis	1.4
Cytokines	Rituximab	Mabthera	June 2, 1998	Worsening heart failure	2.2
	Trastuzumab	Herceptin	August 28, 2000	Infections including tuberculosis; contraindications: heart failure	2.5
				Hepatosplenomegaly; lymphoma	6.8
Growth Factors				Cytokine release syndrome	0.5
				Progressive multifocal leukoencephalopathy	8.8
Enzymes	Anakinra	Kinert	March 8, 2002	Cardiotoxicity in combination with anthracyclines and need for cardiac monitoring	1.7
				Serious infections and neutropenia in combination with etanercept	0.9
Hormones	Lipiodin	Biludan	March 13, 1997	Fatal anaphylactic reactions	5.6
	Dibromin alfa	Inductos	November 9, 2002	Postoperative edema at application site	1.9
Others/Various	Insulin human (phalidon powder)	Eoubera	June 18, 2008	Implant site fluid collections	4.5
				Primary lung carcinoma	2.4
Receptors	Botulinum toxin	Neurobloc	March 14, 2001	Muscle weakness, dysphagia, aspiration	6.3
				Blood dyscrasia (pancytopenia, aplastic anemia)	0.7
				Serious infections and neutropenia in combination with kinert	3.0



Resümee Perspektiven

Antonello da Messina
(ca. 1430-1479)
Saint Jerome in His Study

Zulassungsstudien Onkologie:
Erkenntnisdefizite, Evidenzlücken

- restriktive Einschluss- und Ausschlusskriterien
- Design (Standardarm tatsächlich Standard?, häufig Vergleich neuer Wirkstoff mit alleiniger Chemotherapie, Dosierung?)
- „non-inferiority“ > „equivalence“ oder „superiority“
- Endpunkte (statistisch signifikant = klinisch relevant?)
- Zwischenanalysen, vorzeitiger Abbruch (sinnvoll?)
- Überlebenszeit, krankheitsbezogene Lebensqualität, Toxizität
- Folgebehandlung, Nachbeobachtung, Cross-Over
- Sicherheit nur bzgl. akuter Toxizität verlässlich bewertbar
- Transparenz, Publikation von Ergebnissen?

Emerging themes in design of oncology RCTs

CONSORT-Statements

A. Appropriate design of clinical trials.

„...the conduct of countless small single-arm trials is not an efficient use of patient or financial resources.“
 I. Tannock, 1983

B. Clinically relevant endpoints.

C. Reporting of trials and avoidance of bias.

Appeal for better clinical trials and improved reporting (2008)

1. Investigators (and editors) should adhere to guidelines for the design and reporting of clinical trials.
2. Oncologists should reduce their participation in phase II trials; they should be given more academic and other credit for supporting phase III trials with potential to change practice.
3. Surrogate endpoints for survival, including biomarkers in trials of targeted therapy, should only be used if they have been demonstrated to correlate with overall survival.
4. RCTs should include appropriate and validated measures of quality of life and/or symptom control.
5. RCTs should include a pharmacoeconomic analysis to evaluate the cost-benefit of new treatments.
6. Efforts should continue to reduce publication and sponsorship biases.

aus:
 Booth CM et al.
 JCO 2008; 26:6-8

Resümee/Impulse

- Anstieg der Kosten für neue Arzneimittel in der Onkologie rascher als wissenschaftlich nachgewiesene Wirksamkeit bzw. Nutzen (d.h. relative efficacy, relative effectiveness)
- signifikant # klinisch relevant, neuer Wirkstoff # Innovation
- verstärkt benötigt: unabhängige (wissenschaftsinitiierte) versorgungsrelevante Studien nach Zulassung
- nach Zulassung rasch Evidenz für neue Wirkstoffe verbessern (Grundlage für Leitlinien, Allokation bei begrenzten Ressourcen)
- **conditional approval, - reimbursement, coverage with evidence development**, (cost sharing, payment for results, § 73d SGB V)
- öffentliche Gelder für unabhängige Studien (siehe NHS, NIH)

„We anticipate that some of the future developments outlined here will initially be driven by high profile, high-price areas such as **cancer and orphan drugs**.“

Current paradigm

MA

Regulators | Payers

- Quality, safety, efficacy (first 3 hurdles)
- Benefit-risk profile
- Emphasis on RCT, most often placebo-controlled
- Relative efficacy/effectiveness
- Cost versus health benefit.
- Budget impact (4th hurdle)
- Active-controlled RCT
- Observational studies
- Cost-effectiveness/utility analyses
- Budget impact analysis

Future paradigm?

MA

Regulators | Payers

- Dedicated relative efficacy/effectiveness assessment?
- Quality, safety, efficacy
- Benefit-risk profile
- Relative efficacy/effectiveness
- Cost versus health benefit.
- Budget impact
- Emphasis on RCT, most often active- and placebo-controlled
- Cost-effectiveness/utility analyses
- Budget impact analysis
- Active-controlled RCT
- Adaptive Phase III-IV trials
- Observational studies
- Meta-analysis

Assessors | Assessment focus | Studies/data

NATURE REVIEWS | DRUG DISCOVERY | Eichler H-G et al.: 26. Februar 2010

„...but not every incremental, statistically significant, but clinically unimportant result needs to be transformed instantaneously into the standard of clinical care“.

How Much Is Life Worth: Cetuximab, Non-Small Cell Lung Cancer, and the \$440 Billion Question

Tito Fojo, Christine Grady | JNCI | Commentary | Vol. 101, Issue 15 | August 5, 2009

Lebensverlängerung um ein Jahr von 550.000 US-Amerikanern
440 Mrd. US \$ ≈ 100fache des NCI Budget

Drug (brand name)	Regimen	Dose†	Amount needed‡, #	Cost per milligram or cost per tablet	Total cost‡	Increase in OS‡
Cetuximab (Eribix)	Loading: 400 mg/m ² ; maintain: 250 mg/m ² /wk	Loading: 600 mg; maintain: 375 mg	6975 mg	\$11.52/mg	\$80352	1.2 mo (1)
Bevacizumab (Avastin)	10 mg/kg every 14 d	600 mg every 14 d	13200 mg	\$6.88/mg	\$90816	1.5 mo (13)
Erlotinib (Tarceva)	150 mg daily	150 mg/d; 1 tablet per day	112 tablets	\$140.64 per tablet	\$15752	10 d (14)
Sorafenib (Nexavar)	400 mg twice a day	800 mg/d; 4 tablets per day	692 tablets	\$49.67 per tablet	\$34373	2.7 mo (15)

How Much Is Life Worth: Cetuximab, Non-Small Cell Lung Cancer, and the \$440 Billion Question

Tito Fojo, Christine Grady | Vol. 101, Issue 15 | August 5, 2009

Ultimately, however, what counts as a benefit in cancer treatment and how much cost should factor into deliberations are not ethical problems that can be relegated to others. No segment of society is better qualified to address these issues than the oncology community. It is time to confront these issues, lest others confront them for us. Oncologists must offer clear guidance both in the conduct of research and in prescribing chemotherapies. To begin the discussion in the profession, we suggest the following standards:

The current situation cannot continue. We cannot ignore the cumulative costs of the tests and treatments we recommend and prescribe. As the agents of change, professional societies, including their academic and practicing oncologist members, must lead the way. The time to start is now.



**Vielen Dank
für
Ihre Aufmerksamkeit**

