



Lilly Jahressymposium 2009
„Onkologie, quo vadis –
Krebsbekämpfung durch Gesetze?“

Wege aus der Klemme: Bausteine und Lösungen
Medizinische Nutzenbewertung
Status Quo, 6 Impulse \Rightarrow Resümee

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Robert-Rössle-Klinik im HELIOS Klinikum Berlin-Buch
Klinik für Hämatologie, Onkologie und Tumorimmunologie

Nutzen \neq „Benefit“ (1)

- „confirmatory trials: ... **to establish the benefit-risk profile of the experimental medicinal product, including supportive measures, in a well characterised target population of relevance for the clinical practice**“
- **Nutzenbegriff** (Bewertung \Rightarrow medizinische Profession, s. SGB V) *nach Hart D & Francke, 2007*
 - ✓ Nutzen ist das Ergebnis einer bewertenden **Abwägung** zwischen **positiven** (effectiveness) und **negativen** (Risiken, Sicherheit) **Effekten unter Alltagsbedingungen** im Hinblick auf die Indikation
 - ✓ Nutzenbewertung erfolgt **vergleichend gegen den geltenden Standard** einer guten Behandlung
 - ✓ Nutzenbewertung erfolgt auf der Basis sich **wandelnder Erkenntnisse** in **einem auf Dauer angelegten** iterativen **Prozess**



Nutzenbewertung von Arzneimitteln (AM): *Grundlagen*

- **medizinische Fachliteratur (Originalpublikationen, RCT)**
- Meta-Analysen
- Systematische Übersichtsarbeiten (SÜ) nach stringenten Kriterien (z.B. Cochrane Collaboration)
- Health Technology Assessment (HTA) \Rightarrow NICE, IQWiG
- Leitlinien (Fachgesellschaften/AWMF)
- Therapieempfehlungen (z.B. AkdÄ)
- Bewertung neuer AM bzw. neuer Therapiestrategien in unabhängigen Arzneimittelbulletins (ISDB)



Medikamentöse Tumorthherapie: *Status quo* (2)

- Science 2006: „*Celebrating a Glass Half-Full*“
- großer Bedarf an echten Innovationen/Therapieverbesserung
- große Zahl (> 400) an neuen Arzneimitteln von ca. 180 Firmen in der Onkologie in Phasen der klinischen Prüfung
- Markt für einzelne Arzneimittel ▼, Wettbewerb ▲
- Zulassungsgeschwindigkeit neuer Arzneimittel ▲
- supportive Arzneimittel (2001: \$ 7,6 Mrd., **2005: \$ 14,3 Mrd.**)
- „spezifische“ Wirkstoffe - **TOP 200**
(2001: N=14, \$ 10,5 Mrd., **2005: N=18, \$ 23,5 Mrd.**)
- sehr rascher „*market uptake*“ von Imatinib, Rituximab, Trastuzumab, Bevacizumab(► Blockbuster)



Neue Wirkstoffe in der Onkologie*: *Zulassung in den USA vs. andere Wirkstoffe*

Table 2. Regulatory Characteristics of New Therapeutic Oncology and Other Drugs Approved in the United States, 1990-2005

Characteristic	%	
	Oncology Drugs	Other Drugs
FDA priority rating*	70.9	40.2
Orphan drug designation	48.5	18.5
Expedited access†	47.1	13.4

*Therapeutic new molecular entities approved by FDA's Center for Drug Evaluation and Research (CDER).

†Drugs that were developed under at least one of the following three FDA regulatory mechanisms: subpart E, accelerated approval, fast track.

* *DiMasi JA & Grabowski HG: JCO 2007; 25:209-216*



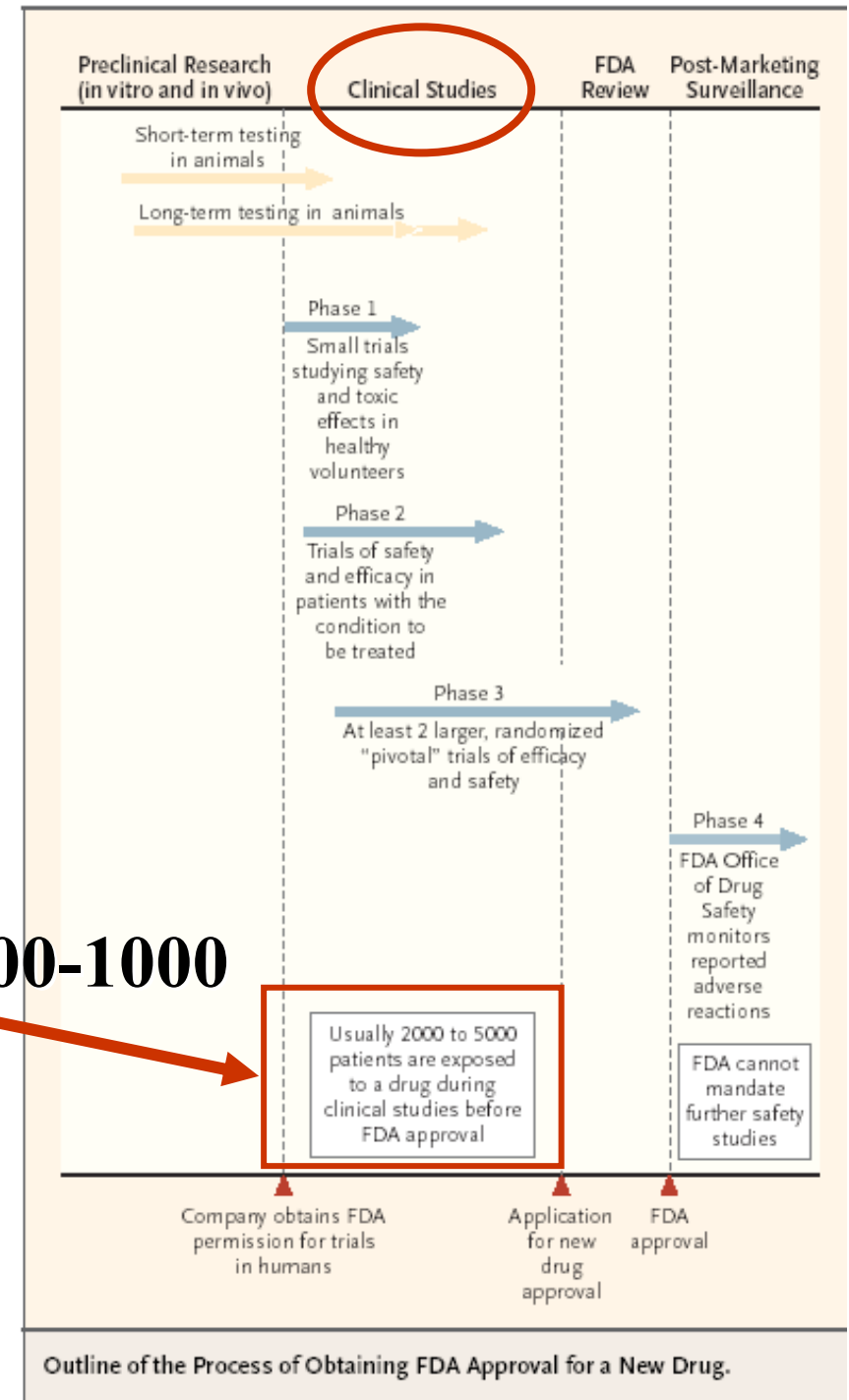
Zulassung von Arzneimitteln

Balance zwischen Pat.nutzen,
regulatorischen Anforderungen,
ökonomischem Interesse

► **Wirksamkeit, Sicherheit**

Onkologie < 500-1000

*Okie S: Safety in numbers –
Monitoring risk in approved drugs
NEJM 2005; 352:1173*





Relevante primäre Endpunkte? (3)

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

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

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



(Zusatz-)Nutzen bewiesen? (4) **(bei Zulassung für hämatologische Neoplasien; EMA, 11 NCE, 1995-2006)***

- Grundlage der Bewertung EPAR (zentralisiertes Verfahren)
- 11 Wirkstoffe (für 17 Indikationen)
(u.a. 4 Biopharmazeutika, 3 moAk, 2 „small molecules“)
- 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)**
- **„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*



Stopping a trial early in oncology: for patients or for industry?

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Ann Oncol, April 9, 2008; advance access

1997-2007

Characteristics	No. (%)
Type of stop	
Crossover to treatment group	3 (12)
Stop enrolment	12 (48)
Disclosure of results	5 (20)
Stopped for economical consideration	1 (4)
Crossover to treatment group + stop enrolment	3 (12)
Stop enrolment + disclosure of results	1 (4)
DSMC	
Present	19 (76)
Absent	6 (24)
Discrepancy in end point used (planned versus interim)	
Same	22 (88)
Different	1 (4)
Not available	2 (8)
Study purposes	
Registration trial	12 (48)
Non-registration trial	13 (52)
Date of publication	
2005–2007	14 (56)
1997–2004	11 (44)

- **↑ vorzeitig beendete RCTs**
(Wirksamkeit überschätzt)
- **~ 3300 pts./events ↓**
anstatt 8000 pts./events
- **78% der RCTs (letzte 3 Jahre)**
⇒ Zulassung



Aussage zur Sicherheit nicht möglich (5)*

„It is simply not possible to identify all the side-effects of drugs before they are monitored. The difficulty is not a failure of the drug-development process or of the drug-approval process; it is the expected consequence of the biological diversity of humans and the fact that low-frequency adverse effects are unlikely to be detected in the few hundred or thousand patients studied in trials before a drug is approved.“*

** Wood AJJ, Stein CM, Woosley R: N Engl J Med 1998; 339:1851-4*



Medizinische Nutzenbewertung bei Zulassung nicht möglich*

Limitation

No systematic provisions for obtaining important data to guide clinical practice

Premarketing trials are powered inadequately to determine safety of widely used drugs

Safety of long-term therapy is unknown

No systematic surveillance is conducted after marketing to detect rare adverse effects

Special populations are underrepresented in premarketing studies

Off-label use is not studied

Relative efficacy is unknown

Surrogate end points are the only outcomes studied

Conflicts of interest

Failure to effectively communicate data to practitioners and patients

Drug and Example of Resulting Problem

Coxibs: increased risk of serious cardiovascular disease confirmed 5 years after introduction and after use by millions of patients

HRT: prolonged use increases risk of breast cancer

Terfenadine: causes torsades de pointes when used with other drugs that inhibit its metabolism

ACE inhibitors: risk of angioedema increased for blacks

Fenfluramine–phentermine: this off-label combination found to cause primary pulmonary hypertension and damage to cardiac valves after use by 6 million patients

Coxib vs. NSAID plus proton-pump inhibitor: no adequately powered studies of the relative gastrointestinal safety of these two therapies have been conducted

Cerivastatin: clinical benefit unproven when launched

* Ray WA & Stein CM: NEJM 2006; 354:194-201



Studien nach Zulassung

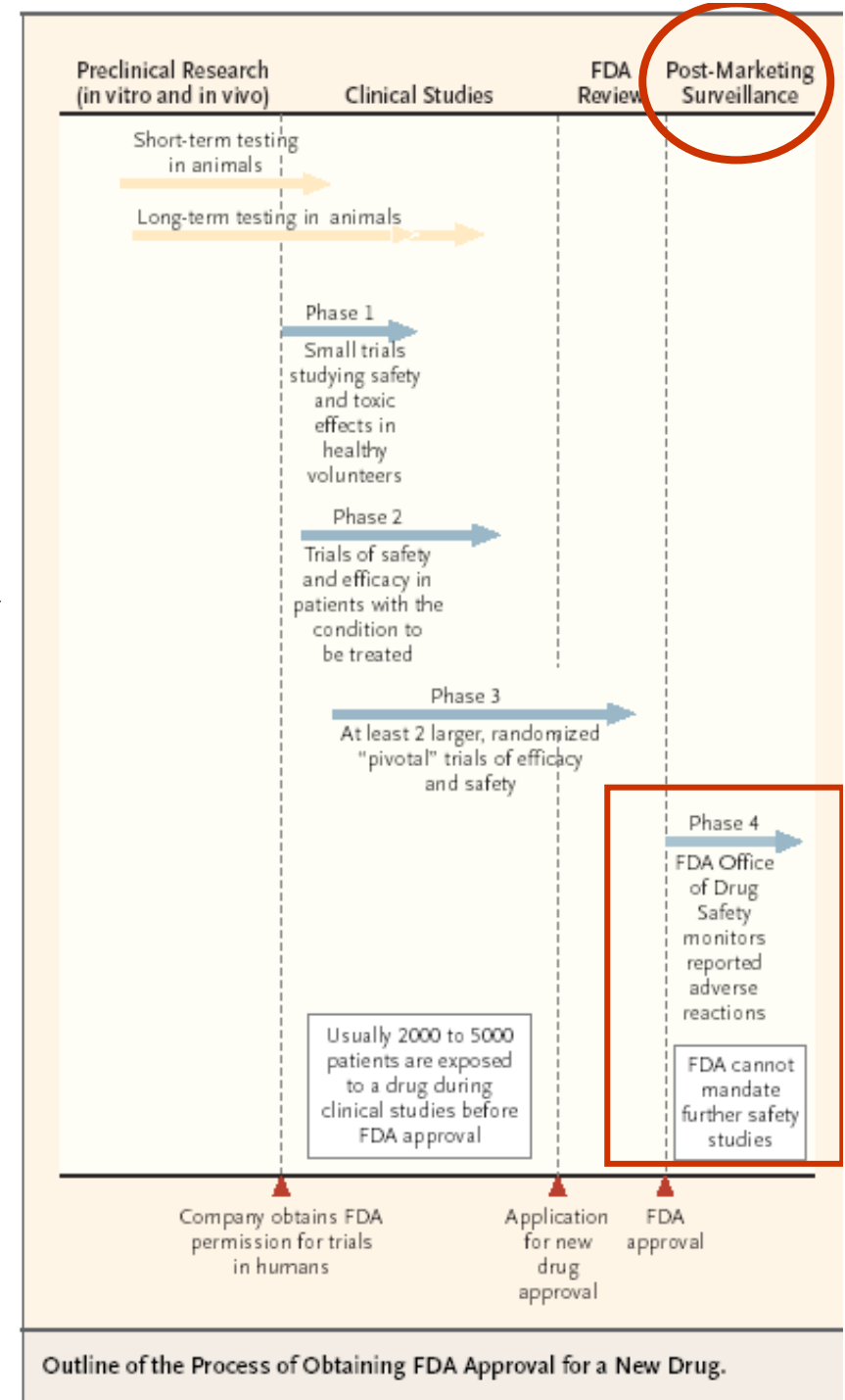
Abwägung zwischen positiven
(effectiveness) und negativen Effekten
unter Alltagsbedingungen

► Nutzen

Arzneimittelsicherheit?

Marketing?

*Okie S: Safety in numbers –
Monitoring risk in approved drugs
NEJM 2005; 352:1173*





Verbreitung neuer Wirkstoffe weltweit*

Table 3. Therapeutic Area Distribution of New Drugs for 1982-2003
Worldwide New Drug Introductions⁸

Therapeutic Area	All New Drugs	Global New Drugs	First-in-Class New Drugs	Biotech New Drugs
Central nervous system	130	57	12	1
Cardiovascular system	128	45	7	5
Systemic anti-infectives	127	62	12	6
Oncology	99	52	21	25
Alimentary tract and metabolism	86	29	13	9
Musculoskeletal system	70	28	5	7
Blood and blood-forming organs	59	24	9	15
Respiratory system	57	21	5	2
Dermatologicals	49	21	7	3
Miscellaneous	118	49	24	18
Total				

* *DiMasi JA & Grabowski HG: JCO 2007; 25:209-216*



„Provide a balanced discussion of benefits and harms“

CONSORT - Ioannidis JPA et al.: Ann Intern Med 2004

„The widespread marketing of a new drug is in fact a large experiment on a population. This is especially the case when it concerns a novel molecular entity with potentially a new set of clinical experiences. As the marketing of new drugs includes the discovery of adverse effects, the public's health would be best protected by a complementary set of techniques for the detection, verification and quantification of safety issues.“*

****Stricker BH & Psaty BM: BMJ 2004; 329:44-7***



Resümee/ Perspektiven

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



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

321 RCTs
N=171161 Pat.

Evolution of the Randomized Controlled Trial in Oncology
Over Three Decades

Christopher M. Booth, David W. Cescon, Lisa Wang, Ian F. Tannock, and Monika K. Krzyzanowska

Conclusion

RCTs in oncology have become larger and are more likely to be sponsored by industry. Authors of modern RCTs are more likely to strongly endorse novel therapies. For-profit sponsorship and statistically significant results are independently associated with endorsement of the experimental arm.

Studiengröße ▲
multizentrisch, international
kleine Unterschiede werden signifikant
Toxizität, Lebensqualität, Symptomkontrolle ??



Emerging themes in design of oncology RCTs

A. Appropriate design of clinical trials.

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.

Design of oncology RCTs

B. Clinically relevant endpoints.

C. Reporting of trials and avoidance of bias.



Medizinische Nutzenbewertung: **„echte“ nächste Gesundheitsreform (6)**

- **Beseitigung der Defizite bei Zulassungsstudien**
- **unabhängige wissenschaftliche Studien nach Marktzulassung zur Wirksamkeit und Sicherheit unter Alltagsbedingungen**
 - Beschaffung praxisrelevanter wissenschaftlicher Erkenntnisse (Phase-IV-Studien: Nutzen?; nicht-interventionelle Prüfungen: u.a. Pharmakovigilanz, Lebensqualität etc., Register)
- **Beachtung der Charta zur ärztlichen Berufsethik** (z.B. gerechte Verteilung begrenzter Ressourcen, Nutzung wissenschaftlicher Erkenntnisse, angemessenes Verhalten bei Interessenkonflikten)
- **unabhängige Informationen für Ärzte und Patienten**



*Löffler M &
Brosteanu O:
Onkologie 2008*

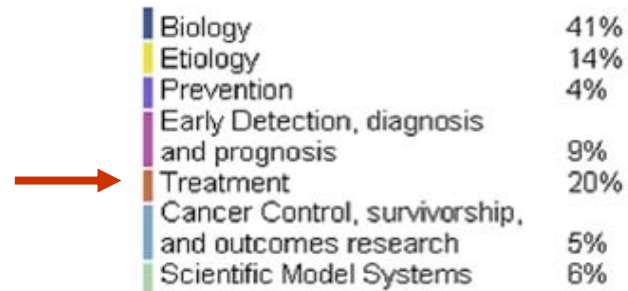
Merkmale	Zulassungsstudien	versorgungsnahe Studien
verantwortlich	pharmazeutische Hersteller	Studiengruppen, klinische Institutionen
Ziel	Zulassung	Kenntnislücken schließen, Therapieoptimierung
Arzneimittel	nicht zugelassen	zugelassen
Einschlusskriterien	stark selektiert	wenig selektiert
studienbezogenes Qualitätsmanagement	ressourcenaufwendig	ressourcenschonend und problemorientiert
Fallpauschalen	sehr hoch	niedrig
Finanzierung	Industrie	öffentliche Förderer, GKV
Resümee	Zulassung ja/nein Nutzen-Risiko?	Verbesserung der Qualität der Behandlung



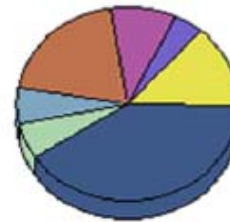
Public Funding of Cancer Research in the EU

Eckhouse S & Sullivan R: PLoS 2006; 3:e267

Percentage of Direct Cancer Research Spend by CSO Category



European Union (62 Organisations Reporting)

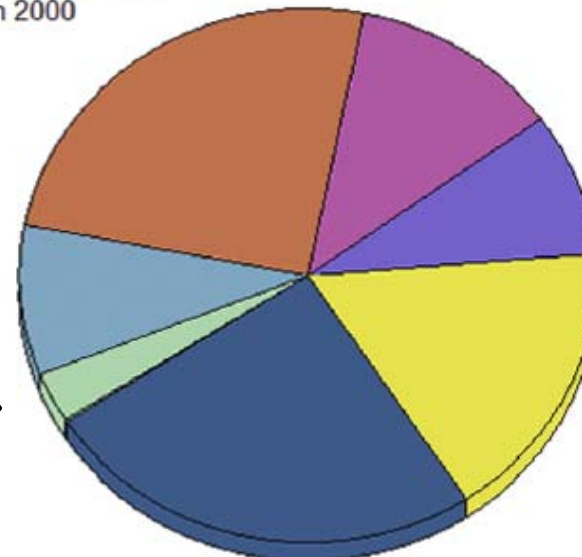


€ 2,56/Kopf

National Cancer Institute (USA) Extramural Cancer Research Portfolio Funded in Fiscal Year 2000



USA (NCI) Extramural Spend in 2000



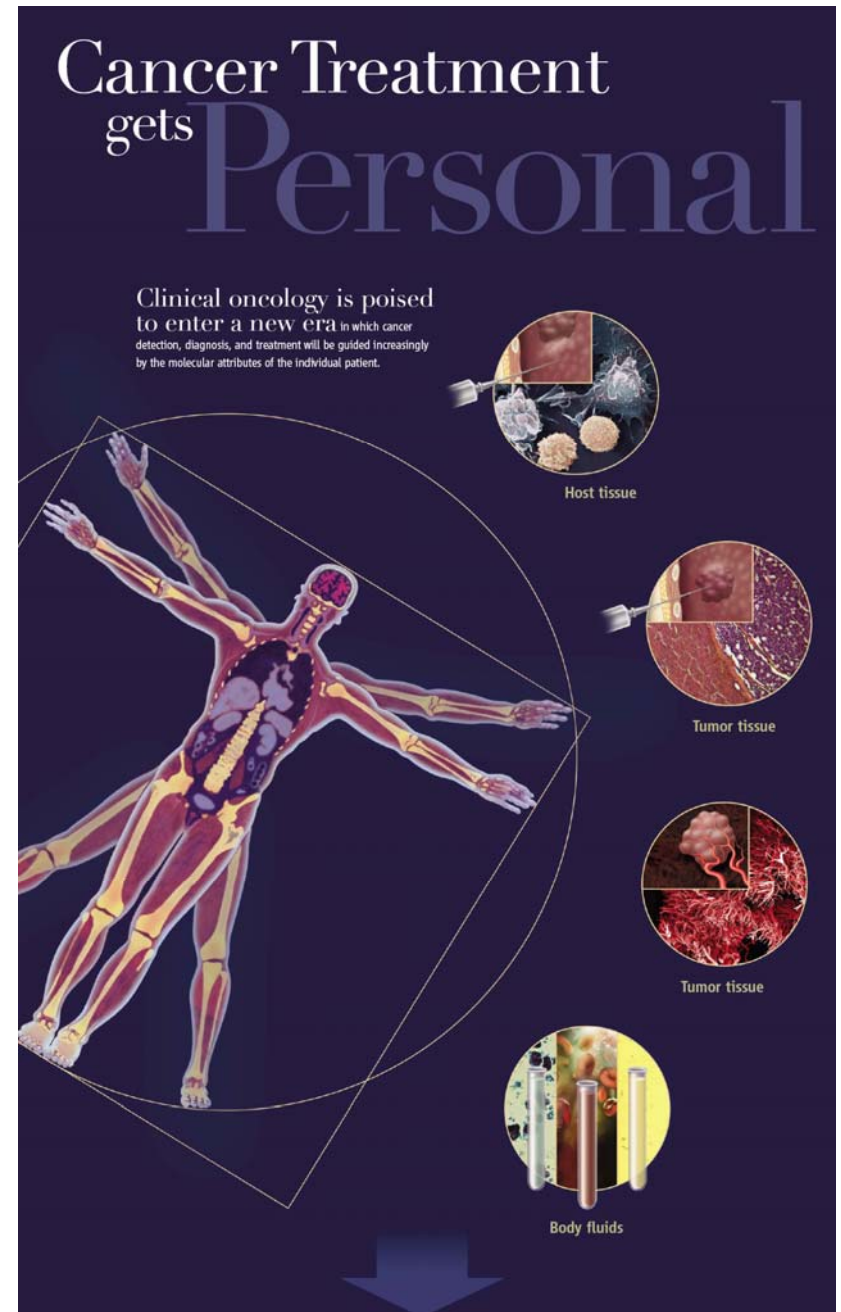
€ 17,63/Kopf



Changes in the „culture“ of oncology

„A description of cancer in molecular terms seems increasingly likely to improve the ways in which human cancers are detected, classified, and treated. Transformation of oncology is possible in the future, but concomitant changes in the culture and politics of research are essential“

H. Varmus, 2006





**Vielen Dank
für
Ihre Aufmerksamkeit**

