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HTA-Perspektiven

Sind Onkologika anders zu bewerten als andere Arzneimittel ?

IQWiG-Herbsttagung
23. November 2012

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1. Hintergrund
2. Methode: Horizon Scanning neuer Onkologika in Österreich
3. Ergebnisse: HTA/Frühbewertung neuer Onkologika in Ö und in EU-Kooperation (EUnetHTA)
4. Diskussion: Zusammenfassung der „Herausforderungen“

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Kapitel 1

Hintergrund

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Märkte in Bewegung

Industrie – unter Druck

Wenig Innovationen, auslaufende Patente,

Protektion der Märkte, Re-Allokation der Marketing Ressourcen

Gesundheitssysteme unter Druck

Finanzierungsprobleme: Demographie, strukturelle Probleme (zu viele Spitäler), teure Technologien, Management/Kontrolle der Nachfrage

Entwicklung von Strategien (auf beiden Seiten)

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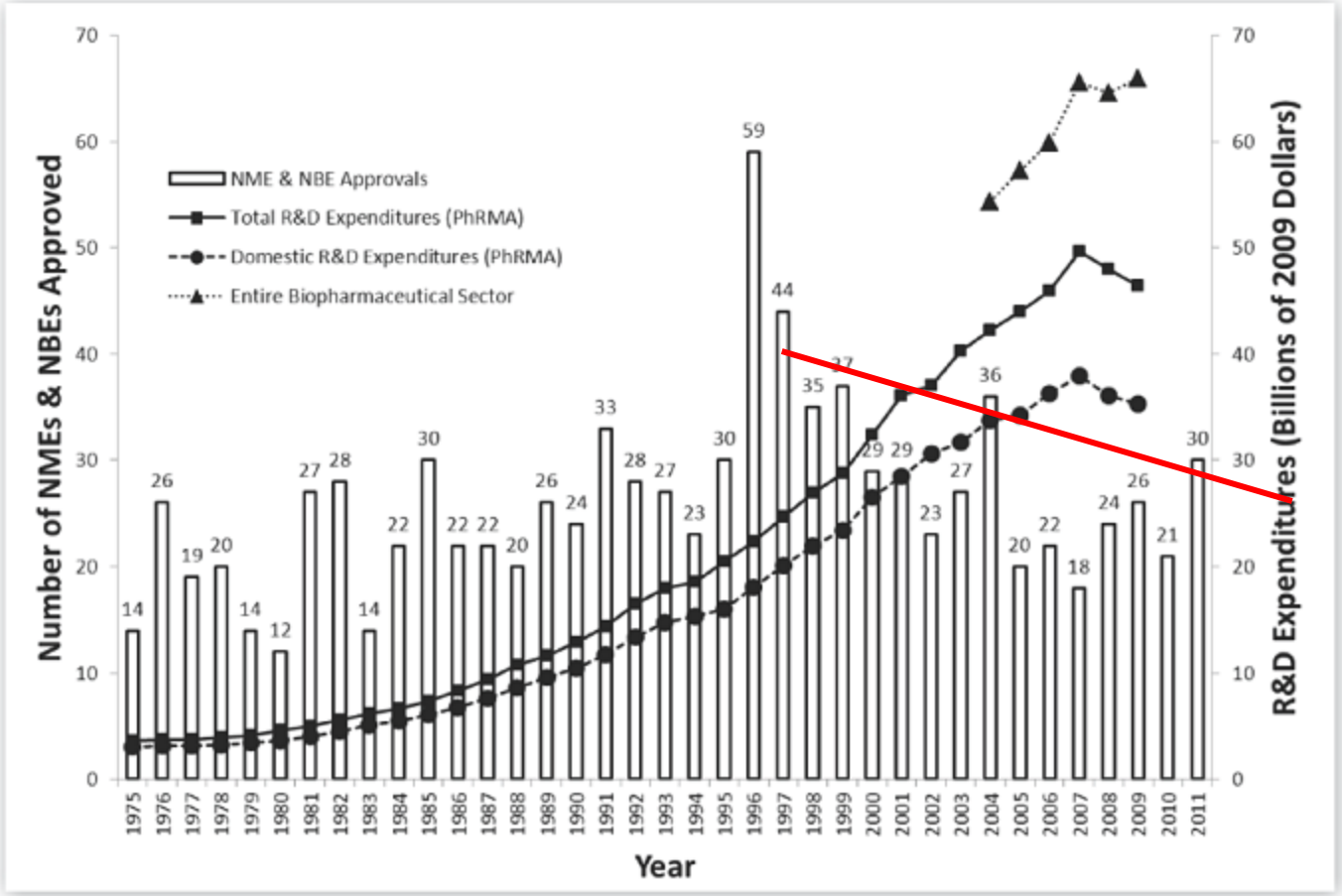
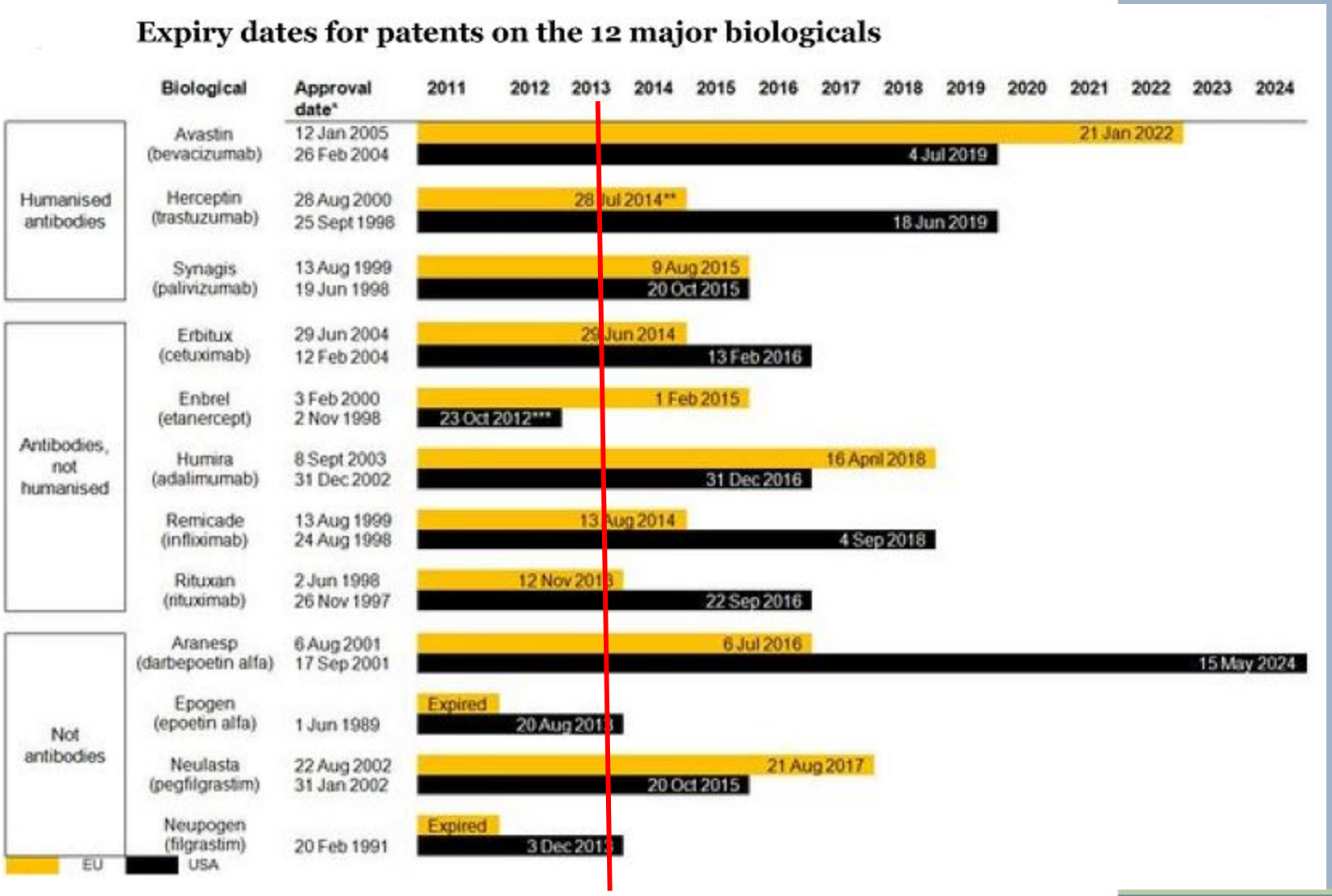
Annual NME/NBE Approvals versus R&D Expenditures in 2009 Dollars.
(b) Estimates of Cost to Companies per New Molecular Entity in 2009 Dollars.



Quelle: US-Advisors on Science and Technology.
http://www.actsi.org/news/2012/Documents/PCAST.pdf



Quelle: http://www.gabionline.net/Biosimilars/Research/US-54-billion-worth-of-biosimilar-patents-expiring-before-2020

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Wenig Innovationen:

"50% of applications at EMA are declined

of the EMA approved: further 20% are declined by regulators/ reimbursers

only 30% demonstrate therapeutic innovation (added value)

about 5-8 products/innovations p.a."

Source: EMA-representative: Stockholm, Dez 2009

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Strategie 1: Protektion des Marktes

European Commission: Pharma Sector Inquiry (DG Competition): 28. Nov 2008

„Originator companies use „tool-box“ for blocking and delaying generic companies or other competitors“ – patenting strategies, oversized clinical studies.“

Source:
http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/preliminary_report.pdf

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Strategie 2: Re-Allokation der Marketing-Ressourcen

- From direct-marketing (massive cutback of pharma-salesmen/women)
- to patient-/ consumer-lobbies &
- to awareness-lobbies (Cancer-United)

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Strategie 3: Orphan Drugs

The era of 'niche-busters' is within your reach

As patent expiry, dry pipelines and strict approval guidelines continue to slow drug discovery growth, Orphan Drugs provide the industry with attractive opportunities to reduce the impact of revenue loss whilst offering up significant new commercial opportunities.

- The global prescription drug market was worth a staggering $800bn+ in 2010
- Orphan drugs will account for approx. 30% of all new marketing applications to the EMEA going forward of 2010
- With over 6000 indications available for target, the market remains enormous

Two months ago, the World Orphan Drug Congress commissioned a Survey to analyse the challenges and opportunities in this industry. The results have now been put together and are available to download follow the link below

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Strategien der Gesundheitspolitik (Admin, Planung, Refundierung)

1. Pragmatische Klinische Studien
2. REA/Relative effectiveness, CER/comparative effectiveness
3. Medien & Patienten/Konsumenten: „Health Literacy“, Partizipative Entscheidungsfindung/SDM
4. HTA, Frühbewertung: Horizon Scanning/ Early Warning
5. CED/ Coverage with Evidence Development

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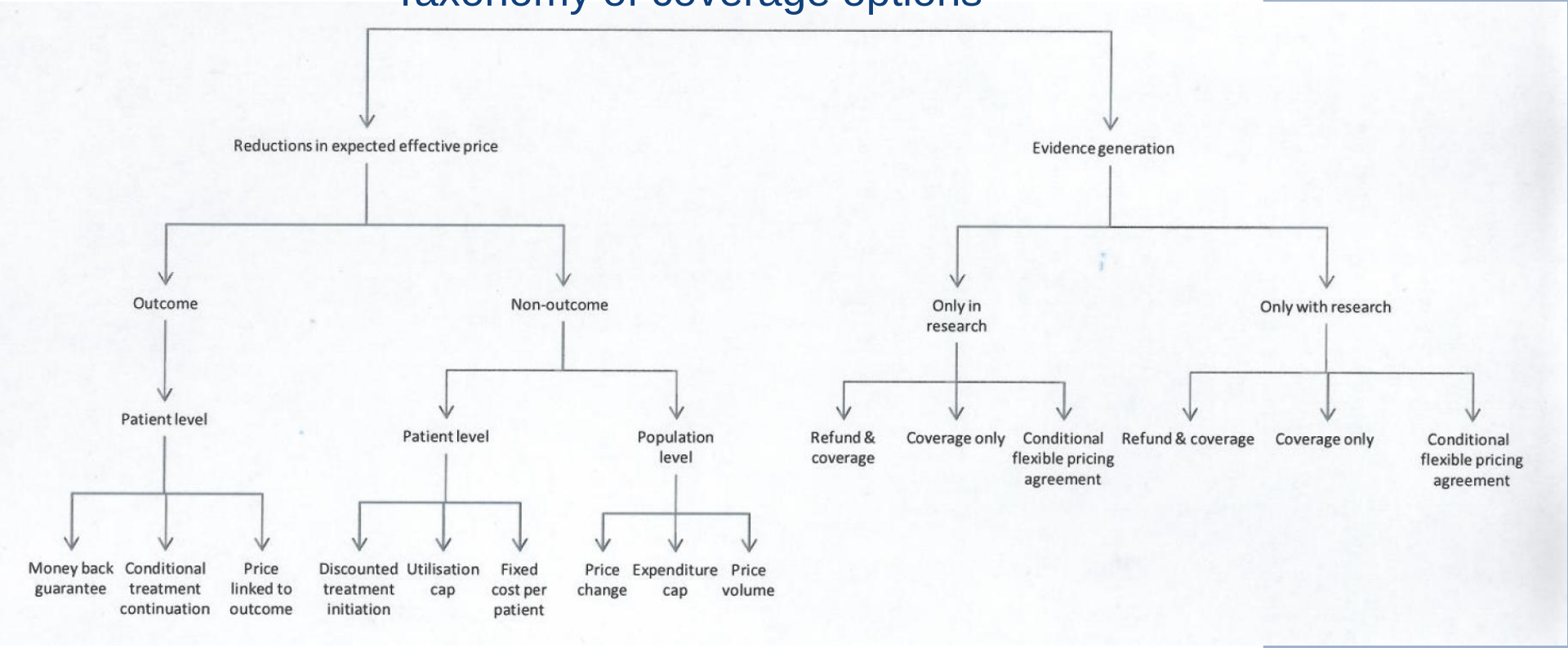
Gesundheitspolitische Optionen:
Ergebnis-basierte Refundierungsinstrumente

Taxonomy of coverage options



Source: Walker, S et al: Coverage with evidence development, only in research, risk sharing or patient access schemes? A framework for coverage decisions. 2012 CHE Research Paper 77

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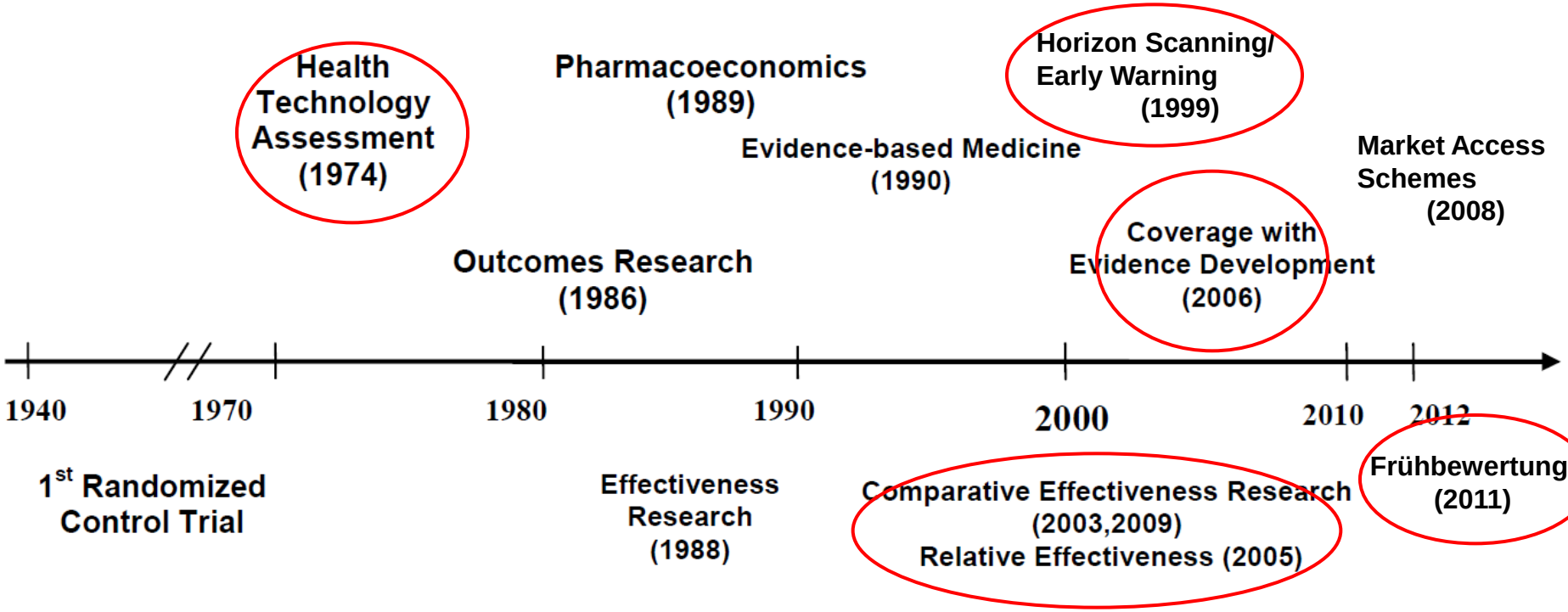
ZEITREISE – lernende Systeme: Methoden - WEITER - Entwicklung



Adaptiert nach C. Goodman, Stockholm, Dez 2009

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Kapitel 2

Methode: HSO/ Horizon Scanning neuer Onkologika in Österreich

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"Frühbewertung"

(horizon scanning, early awareness & alert systems, early warning systems

Ziel: Entscheidungsträger **FRÜHZEITIG** mit Informationen zu neuen onkologischen Arzneimittel, für die wesentliche Auswirkungen auf das Gesundheitssystem erwartet werden können, zu versorgen, um

1. *evidenzbasierte Entscheidungen über den Einsatz von Krebsmedikamenten zu erleichtern*
2. *bessere Einschätzung der Budgetimplikationen zu ermöglichen*

Neue Onkologika: OS/ Überleben

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Produktname	Arzneistoff	Indikation/Erkrankung	OS
Afinitor®	Everolimus	Nierenzellkarzinom	0
Afinitor®	Everolimus	Pankreas	0
Yondelis®	Trabectedin	Weichteilsarkom	0
Hycamtin®	Topotecan	Lungenkrebs	0
MabThera®	Rituximab	diffuses großzelliges B-Zell Lymphom	
MabThera®	Rituximab	chronische lymphoblastische Leukämie/CLL	
Sutent®	Sunitinib	Pankreaskarzinom	
Glivec®	Imatinib	chronische myeloische Leukämie/ CML	
MabCampath®	Alemtuzumab	diffuses großzelliges B-Zell Lymphom	
Sprycel®	Dasatinib	chronische myeloische Leukämie/CML	
Tasigna®	Nilotinib	chronische myeloische Leukämie	
Zevalin®	Ibritumomab tiuxetan	follikuläre NHL vom B-Zell-Typ	0
MabThera®	Rituximab	follikuläres Lymphom	
Tarceva®	Erlotinib	Bauchspeicheldrüsenkrebs	+ 12 Tage
Teysuno®	Tegafur/Gimeracil/Oteracil	Magenkrebs	+ 21 Tage
Xeloda®	Capecitabin	Darmkrebs	27 Tage
Xeloda®	Capecitabin	Magenkrebs	+ 36 Tage
Avastin®	Bevacizumab	Brustkrebs	+ 51 Tage
Erbitux®	Cetuximab	Darmkrebs	+ 51 Tage
Sutent®	Sunitinib	gastrointestinale Stromatumoren/ GIST	+ 1,8 Monate
Avastin®	Bevacizumab	Nierenkrebs	+ 60 Tage
Vectibix®	Panitumumab	Darmkrebs	+ 60 Tage
Avastin®	Bevacizumab	Lungenkrebs	+ 60 Tage
Tarceva®	Erlotinib	Lungenkrebs	+ 60 Tage
Hycamtin®	Topotecan	Eierstockkrebs	+ 2,2 Monate
Jevtana®	Cabazitaxel	Prostatakrebs	+ 2,4 Monate
Votrient®	Pazopanib	Nierenzellkarzinom	+ 2,4 Monate
Tyverb®	Lapatinib	Brustkrebs	+ 2,4 Monate
Halaven®	Eribulin	Brustkrebs	+ 2,5 Monate
Torisel®	Temsirolimus	Mantle Zelllymphom/MCL	+ 2,5 Monate
Javlor®	Vinflunine	Urothelkarzinom	+ 2,6 Monate
Pixuvri®	Pixantrone dimaleate	NHL vom B-Zell-Typ vom B-Zell-Typ	+ 2,6 Monate
Erbitux®	Cetuximab	Kopf-und Halskrebs (2st line)	+2,7 Monate
Alimta®	Pemetrexed	Lungenkrebs	+ 2,8 Monate
Alimta®	Pemetrexed	Brustfellkrebs	+ 2,8 Monate
Nexavar®	Sorafenib	Leberzellkarzinom	+ 2,8 Monate
Hycamtin®	Topotecan	Gebärmutterhalskrebs	+ 2,9 Monate
Irissa®	Gefitinib	Lungenkrebs	+ 2,9 Monate
Afinitor®	Everolimus	Nierenzellkarzinom	+ 3,0 Monate
Hycamtin®	Topotecan	Lungenkrebs	+ 3,0 Monate
Xeloda®	Capecitabin	Brustkrebs	+ 3,0 Monate
Yondelis®	Trabectedin	Ovarialkarzinom	+ 3,3 Monate
Nexavar®	Sorafenib	Nierenzellkarzinom	+ 3,4 Monate
Irissa®	Gefitinib	nicht kleinzelliger Lungenkrebs (1st line)	+ 3,5 Monate
Torisel®	Temsirolimus	Nierenzellkarzinom	+ 3,6 Monate
Zelboraf®	Vemurafenib	Melanom mit BRAF V600-Mutation	+ 3,6 Monate
Yervoy®	Ipilimumab	Melanom	+ 4,0 Monate
Herceptin®	Trastuzumab	Magenkrebs	+ 4,2 Monate
Zytiga®	Abiraterone acetate	Prostatakrebs	+ 4,6 Monate
Avastin®	Bevacizumab	Darmkrebs	+ 4,7 Monate
Sutent®	Sunitinib	Nierenzellkarzinom	+ 4,5 Monate
Afinitor®	Everolimus	Bauchspeicheldrüsenkrebs	+ 6,4 Monate
Herceptin®	Trastuzumab	Brustkrebs	+ 7,0 Monate
Vidaza®	Azacitidine	Myelodysplastisches Syndrom	+ 9,5 Monate
Velcade®	Bortezomib	Multiples Myelom/MML	+ 13,3 Monate
Erbitux®	Cetuximab	Kopf-und Halskrebs	+ 19,7 Monate

ca 23% kein Überlebensvorteil

ca 50%
Tage bis 3 Monate

Ca 25% mehr als 3 Monate

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Comparator Report on Patient Access to Cancer Drugs in Europe

February 15, 2009

Nils Wilking MD PhD, Karolinska Institutet, Stockholm, Sweden
Bengt Jönsson, Professor, Stockholm School of Economics, Stockholm, Sweden
Daniel Högberg, i3 Innovus, Stockholm, Sweden
Nahila Justo, i3 Innovus, Stockholm, Sweden

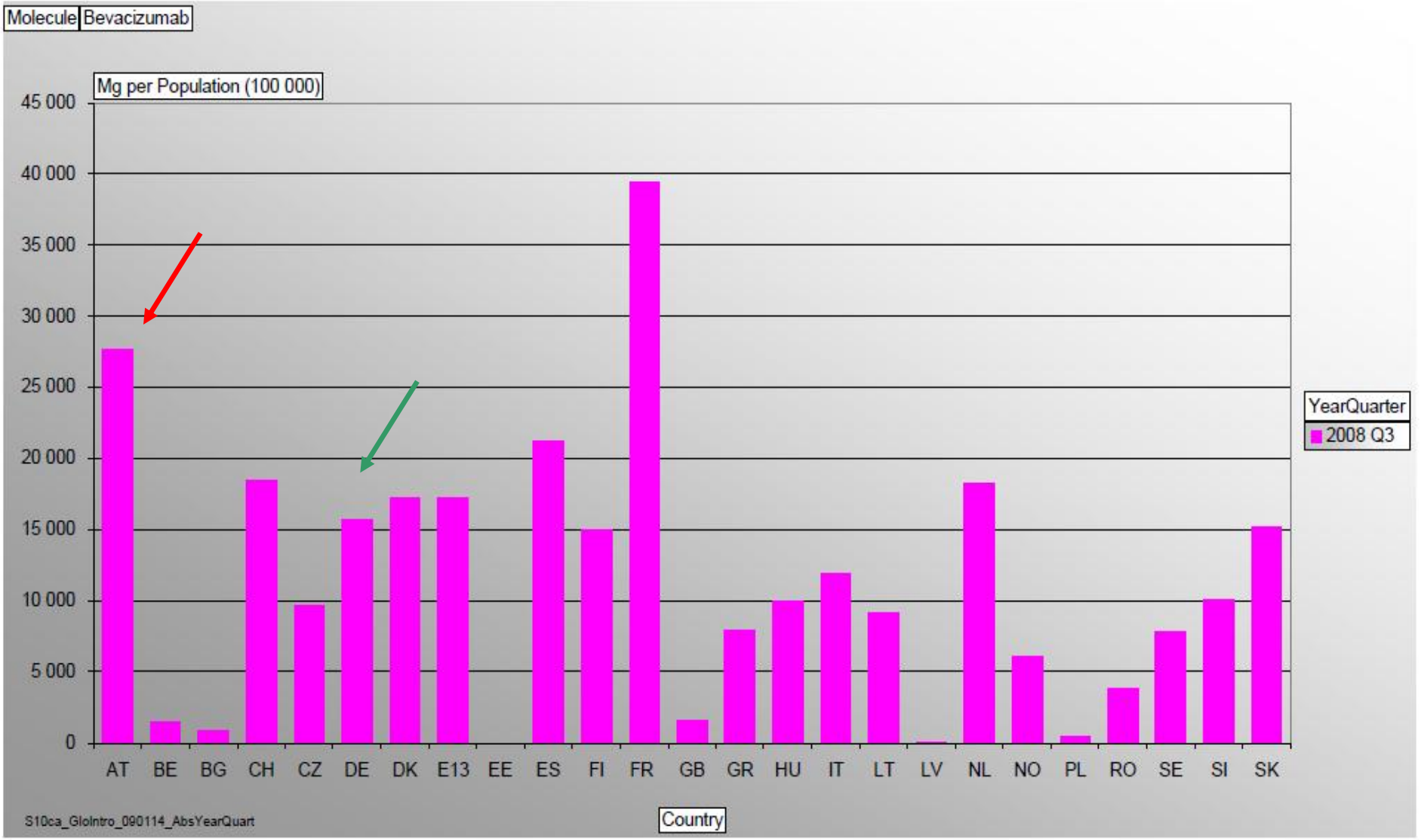

Figure 3-27. Usage of bevacizumab in 2007, expressed as sales in mg/100,000 inhabitants in E13 as well as 24 European countries. Please note that bevacizumab is also indicated for breast-, lung- and renal cell cancer.

Wilking N, Jönsson B.Comparator Report on Patient Access to Cancer Drugs in Europe Jänner 2009. Verfügbar unter: http://www.comparatorreports.se/

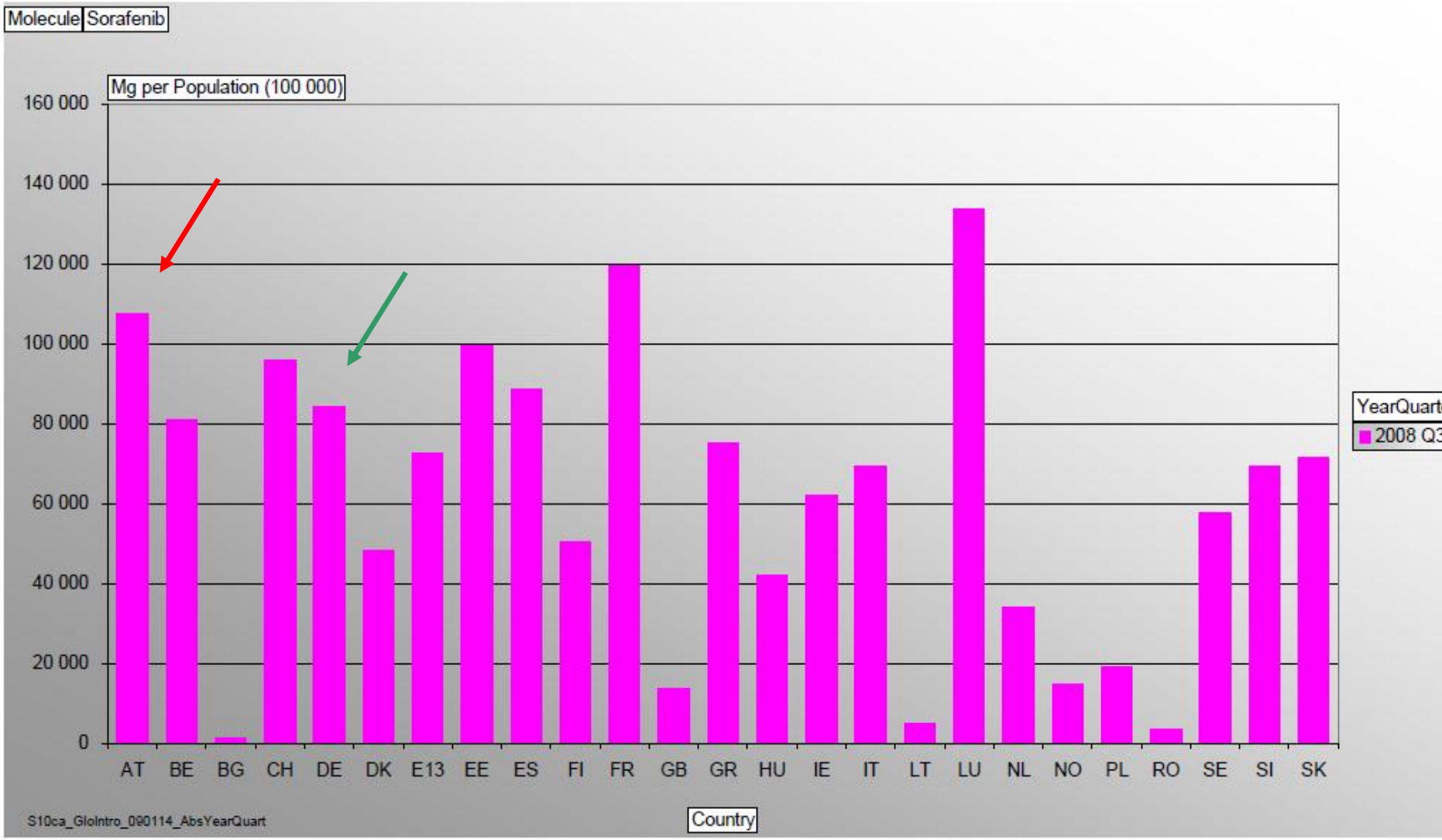

Figure 3-45. Usage of sorafenib in 2007, expressed as sales in mg/100,000 inhabitants in E13 and 24 European countries.

Wilking N, Jönsson B.Comparator Report on Patient Access to Cancer Drugs in Europe Jänner 2009. Verfügbar unter: http://www.comparatorreports.se/

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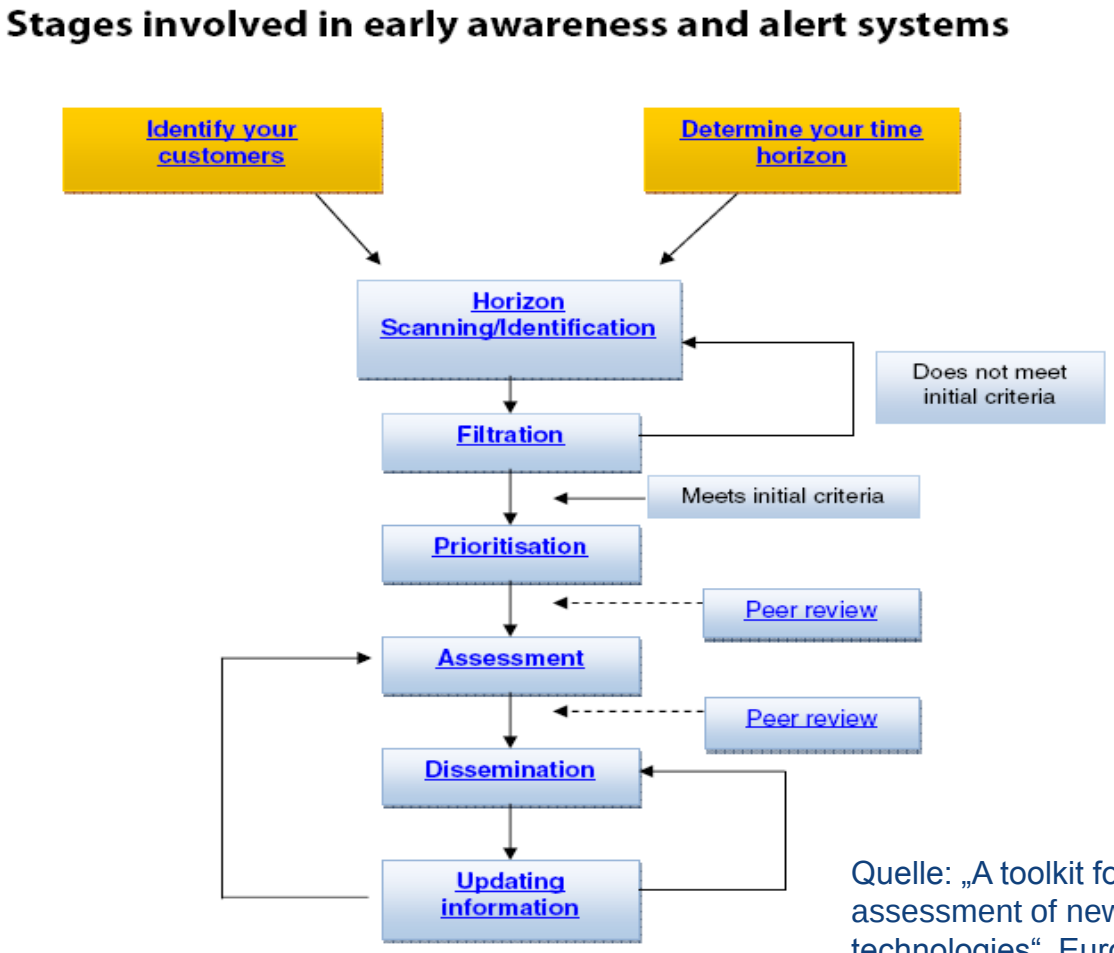
Methode



grundsätzliche Abläufe gleich (UK, Kanada, Schweden, Australien)

individuelle Anpassung an jeweiligen Kontext

Quelle: „A toolkit for the identification and assessment of new and emerging health technologies“. EuroScan homepage

1. Scanning

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	E-Mail notification	once/ week	once/ month	once/ 6- 12 months
FDA oncology drug updates	X			
EMA Newsletter RSS-Feeds	X	X	X	
JCO, Blood, The Lancet, NEJM	X	X		
The Lancet Oncology, Annals of Oncology	X		X	
ASCO, ASH, ESMO annual meeting				X
EuroScan		X		

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2. Identification
Data extraction

PrioDate	drug name (brand name)	Company/ Developer	Short Drug description (substance categorie, mode of action)	Patient indications (detailed information on line of treatment, cancer stage etc)	Cancer Incindence in Austria (Source: Statistik Austria, 2006; new cases per year, absolute numbers, all stages) cancer / incidence	stage of development (phase III and later stages)	completed phase III trial with available data (Yes/No - duration of phase III) clinicaltrials.gov (ID)	Is the technology already approved for other indications (incl. Orphan drug designation) by the EMA?	Is the technology already approved for other indikations (incl. Orphan drug designation) by the FDA?	costs in € (if available) NA = not available Source: ami-info (AVP) or AID (hospital)
	Bexarotene (Targretin)	Cephalon	inhibition of Retinoid-X-Rezeptors, synthetic retinoid, orally	Targretin Capsules/Cisplatin/Vinorelbine Versus Cisplatin/Vinorelbine in Chemotherapy-Naive Patients With Advanced or Metastatic Non-Small Cell Lung Cancer	Lung cancer, all forms 3903	Phase III	YES - NCT00050973 completed 2004	Targretin capsules are indicated for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) patients refractory to at least one systemic treatment since March 2001.	for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy - since 2004	Targretin 75mg Weichkapseln 100 St.: € 1,432.8
	Bexarotene (Targretin)	Cephalon	inhibition of Retinoid-X-Rezeptors, synthetic retinoid, orally	Comparing Targretin Capsules/Carboplatin/Paclitaxel Versus Carboplatin/Paclitaxel in Chemotherapy-Naïve Patients With Advanced or Metastatic Non-Small Cell Lung Cancer	Lung cancer, all forms 3903	Phase III	Yes - NCT00050960 completed 03/2005	Targretin capsules are indicated for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) patients refractory to at least one systemic treatment since March 2001.	for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy - since 2004	Targretin 75mg Weichkapseln 100 St.: € 1,432.8
	Bortezomib (Velcade)	Janssen-Cilag	a first-in-class proteasome inhibitor	VELCADE With Rituximab or Rituximab Alone in Subjects With Relapsed or Refractory, Rituximab Naive or Sensitive Follicular B-Cell Non-Hodgkin's Lymphoma	Non-Hodgkin Lymphoma 991	Phase III	NO - NCT00312845 until 08/2010	VELCADE in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant since July 2008. VELCADE is indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation since March 2005.	Multiple Myeloma and for Mantle Cell Lymphoma since 2003 and 2008	Velcade 1mg vial: € 421.35 Velcade 3.5mg vial: € 1,243.2

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3. Filtration

- Phase III results available OR application submitted to FDA/EMA
- 2 researchers

	A	B	L	M	N	O	P	Q	R	S	T
1	PrioDate	drug name (brand name)	Date of 1st announcement	Source(s) - Lit.No.	Entry in EuroScan database	ASCO Abstract/ presentation	ASH Abstract	Pubmed - publications / Journal	COMMENTS	WEB-LINKs	Evidenzupdate
26		Brentuximab vedotin, SGN-35	14.10.10	Medscape Pharmacist (426)	NHSC 01/2011 NHSC 01/2011	NO	NO	NO	lt. Firmenhomepage orphan drug designation **May 2011: FDA is reviewing brentuximab and will make separate decisions on the two applications (Hodgkin's disease and a type of lymphoma) by Aug. 30 (Lit 475)**	http://www.medscape.com/viewarticle/729509?src=mpnews&spon=7&uac=107625MK	09.05.2011
27		Calcitriol, DN 101, Asentar	NA	NA	no	No (only phase II)	no	Cancer. 2008 Jan 15;112(2):326-30	**April 2011: Phase III Study of Calcitriol in Castration-Resistant Prostate Cancer Disappoints (Lit 473)**	no weblink available	27.04.2011
28	Okt.09	Canfosfamide, TLK286 (Telcyta)	05.11.2008, 31.05.2009	drugs information (81), drugs.com (355)	NO	2007 ASCO Meeting Abstract Nr LBA5528 und LBA5529, 2009 ASCO annual meeting Abstr #5552	NO	Eur J Cancer. 2009 Sep;45(13):2324-32	experts commented that more studies are needed. New evidence available - not many alternatives available		01.09.2009

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4. Prioritization

- Quarterly
- 6 experts
  (4 Oncologists,
  2 Pharmacists)
- 6 criteria

Drug XY	
Choose Category	Highly relevant – assessment Relevant – monitor Not relevant – drop off
Are there already other treatment regimen(s) available for this specific indication or is this drug a completely new therapy?	Treatment available New therapy
Will the new drug replace a current drug regimen or is it an add-on therapy for this indication?	Add-on Replacement New therapy
Is there potential for a significant health benefit to the patient group (high clinical impact)?	Major Minor
Is there potential for a significant impact on drug budgets if the technology diffuses widely (because of expected moderate to high unit costs and/or because of high patient numbers)?	Major Minor
Is there potential for inappropriate use (off-label) of the technology?	Major Minor
Expert's Comment(s)	

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5. Assessment

- Drugs rated „highly relevant“ by majority of experts
- English
- ~14 p
- Literature search: EMBASE, OVID, CRD Database, Cochrane Library, free text search, manufacturer
- No grading of quality of evidence

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Entscheidungsunterstützung : Hierarchie von Nutzen – PatientInnen-Relevanz

- Cure
- Prolongation of survival
- Relief/ prevention of symptoms/ complications of disease
- Improved quality of life
- Reduction of syptomatic toxicity compared with standard therapy
- Prolongation of disease-free survival

Martin et al. (2001): Priority-setting decisions for new cancer drugs.

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Early Assessment of Onco-Drugs: (since Oct 2009)

Azacitidine (Vidaza®) for the treatment of myelodysplastic syndromes	**Bendamustin** (Ribomustin®/Treanda®/ Levact®) for indolent non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and multiple myeloma
Cetuximab (Erbitux®) in EGFR-expressing Non-Small Cell Lung Cancer	**Panitumumab** (Vectibix ®) for the first-line treatment of metastatic colorectal cancer
Everolimus (Afinitor®) for advanced/metastatic kidney cancer	**Trastuzumab**(Herceptin®) in addition to standard chemotherapy as first-line therapy for advanced gastric cancer
Rituximab (Rituxan® / MabThera®) for the first- and second-line treatment of chronic lymphocytic leukaemia	**Pazopanib**(Votrient®) for the treatment of locally advanced and/or metastatic renal cell carcinoma
Ibritumomab tiuxetan (Zevalin®) as consolidation therapy after first remission in patients with follicular lymphoma	**Ipilimumab** for pre-treated patients with advanced/metastatic melanoma
Gefitinib (Iressa®) for the first-line treatment of non-small cell lung cancer	**Nilotinib** (Tasigna®) for the 1st-line treatment of Philadelphia chromosome positive chronic myeloid leukemia in the chronic phase
Trabectedin (Yondelis®) for second-line recurrent platinum-sensitive ovarian cancer	Second-line chemotherapy with **Cabazitaxel** (Jevtana®) for the treatment of castration-resistant metastatic prostate cancer
Plerixafor (Mozobil®) for autologous stem cell transplantation in patients with lymphoma and multiple myeloma	**Dasatinib** (Sprycel®) for the 1st-line treatment of Philadelphia-chromosome positive chronic myeloid leukemia in the chronic phase
Lapatinib ditosylate (Tyverb/Tykerb®) as first-line therapy for the treatment of advanced/metastatic breast cancer	

Ca 10-12 p.a.
now 35 assessments

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Abiraterone acetate (Zytiga™) as 2nd-line therapy for the treatment of metastatic castration resistant prostate cancer after docetaxel therapy
Eribulin (Halaven®) as third- or late- line mono-therapy for advanced/metastatic breast cancer
Bevacizumab in combination with chemotherapy regimens for previously treated HER2-negative metastatic breast cancer
Brentuximab vedotin for the treatment of Hodgkin Lymphoma and systemic anaplastic large cell lymphoma
Everolimus (Afinitor®) for the treatment of unresectable or metastatic neuroendocrine tumours of pancreatic origin
Romidepsin for the 2nd- or further line therapy in peripheral T-cell lymphoma
Pertuzumab (Omnitarg/Perjeta®) for the first-line therapy of metastatic HER2 positive breast cancer
Bortezomib (Velcade®) as consolidation or maintenance therapy after autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma
Ipilimumab (Yervoy®) for the first-line therapy of advanced/metastatic cutaneous melanoma
Erlotinib (Tarceva®) for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations

S-1 (TeysunoTM) as first-line therapy for patients with advanced non-small cell lung cancer
Panitumumab (Vectibix®) as 1st-line combination therapy for the treatment of WT KRAS metastatic colorectal cancer - 1st Update 2011
Gefitinib (Iressa®) for the 1st-line treatment of non-small cell lung cancer – 1st Update 2011
Rituximab (Rituxan®/MabThera®)for the first- and second-line treatment of chronic lymphocytic leukaemia - 1st Update 2011
Lenalidomide (Revlimid®) for the treatment of low /intermediate-1 risk myelodysplastic syndrome with chromosome 5q deletion
Axitinib (AG013736, Inlyta®) for the second-line treatment of metastatic renal cell carcinoma (mRCC)
Everolimus (Afinitor® or Votubia®) in combination with exemestane in postmenopausal women with oestrogen receptor positive, HER2-negative locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole
Vemurafenib for patients with BRAF V600E mutation positive advanced/metastatic melanoma

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Frühbewertungsdokumente

http://hta.lbg.ac.at/de/content.php?iMenuID=96

oder auch direkt am LBI-HTA - Dokumentenserver (alle Berichte)

http://eprints.hta.lbg.ac.at

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EUnetHTA JA 1/ POP-Database planned and ongoing projects

Everolimus for the treatment of breast cancer	NICE	Reg.Veneto	CVZ	LBI-HTA
Vemurafenib for the treatment of melanoma	Reg.Veneto	CVZ	NCPE	NICE
Abiraterone acetate for the treatment of castration-resistant prostate cancer	NETSCC	NICE	NOKC	
Bendamustine	NICE	AHTAPol	NCPE	
Bevacizumab for metastatic breast cancer	NICE	CVZ	NETSCC	
Bortezomib for the treatment of multiple myeloma	NICE	LBI-HTA	AHTAPol	
Eribulin for the treatment of metastatic breast cancer	NETSCC	CVZ	NCPE	
Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small-cell lung cancer	NETSCC	AHTAPol	NICE	
Lenalidomide in Multiple myeloma (newly diagnosed/first line)	NICE	Reg.Veneto	LBI-HTA	
Nilotinib in 1st line CML therapy	AHTAPol	MoH CZ	NETSCC	
Pertuzumab for breast cancer (HER2 positive, metastatic)	NICE	Reg.Veneto	LBI-HTA	
Trabectedin (Yondelis) for the treatment of ovarian cancer	CVZ	AHTAPol	CAHIAQ	

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9 Collabs on onco drugs (among 5 agencies)

1. LBI-HTA + AHTAPol: **Dasatinib (Sprycel®) for the 1st-line treatment of Philadelphia-chromosome positive chronic myeloid leukaemia in the chronic phase; April 2011**
2. LBI-HTA + HTA Centre Bremen: **Second-line chemotherapy with Cabazitaxel (Jevtana®) for the treatment of castration-resistant metastatic prostate cancer; May 2011**
3. LBI-HTA + AHTAPol + UVEF (Reg. Veneto): **Eribulin (Halaven®) as third- or late-line monotherapy for advanced/metastatic breast cancer, July 2011**
4. LBI-HTA + HTA Centre Bremen**: Abiraterone acetate (Zytiga™) as 2nd-line therapy for the treatment of metastatic castration-resistant prostate cancer after docetaxel therapy; December 2011**
5. LBI-HTA + ULSS20: **Vemurafenib for patients with BRAF V600E mutation positive advanced/metastatic melanoma; January 2012**
6. LBI-HTA + ULSS20: **Axitinib (AG 013736, Inlyta ®) for the 2nd-line treatment of metastatic renal cell carcinoma; February 2012**
7. LBI-HTA + UVEF (Reg. Veneto) + AHTAPol: **Lenalidomide (Revlimid®) for the treatment of low /intermediate-1 risk myelodysplastic syndrome with chromosome 5q deletion; May 2012**
8. LBI-HTA + ULSS20: **Ipilimumab for the first line therapy of advanced/metastatic melanoma; July 2012**
9. LBI-HTA + ULSS20 **Lenalidomide (Revlimid®) for the first-line therapy of transplant-ineligible patients with multiple myeloma**

Umfeldanalyse
(weltweit, engl./deutsch)

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Drug	Indication	FDA approval date	EMA approval date	Early assessment reports of other HTA institutes
Gefitinib	1st-line NSCLC	05/2003	06/2009	NHSC 01/2003 (before EMA approval) CADTH 02/2004 (before EMA approval) NICE 07/2009 (1 month after EMA approval) NETSCC 11/2009 (5 months after EMA approval) HAS 11/2009 (5 months after EMA approval) **LBI-HTA 12/2009 (6 months after EMA approval)** NCPE 11/2010 (17 months after EMA approval) Ontario Ministry of Health 12/2010 MSAC 12/2010 BCBS 03/2011 CADTH 04/2011
Everolimus	Advanced/metastatic kidney cancer	03/2009	08/2009	NHSC 04/2008 (before EMA approval) **LBI-HTA 09/2009 (1 month after EMA approval)** AKDAE 11/2009 (3 months after EMA approval) HAS 01/2010 (5 months after EMA approval) NETSCC 03/2010 (7 months after EMA approval) NICE 04/2011 (19 months after EMA approval)
Lapatinib	1st-line advanced/metastatic breast cancer	01/2010	06/2010	NHSC 07/2005 (before EMA approval) HAS 07/2007 (before EMA approval) NCPE 01/2008 (before EMA approval) NOKC 06/2008 (before EMA approval) NHSC 01/2010 (before approval) **LBI-HTA 05/2010 (around EMA approval)** AKDAE 12/2010 (7 months after EMA approval) CVZ 06/2011 (13 months after EMA approval) SMC 01/2012 (20 months after EMA approval)

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EUnetHTA JA 2

Alle 3 Monate eine gemeinsame Frühbewertung

Gemeinsames Format, gemeinsame Frühbewertung

Zukunft: von Früh- bis Spätbewertung selbes Format

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HTA-Consensus: Therapie Evaluation

- Realistischer Komparator
- Patienten-relevante Endpunkte ODER validierte Surrogat-Endpunkte
- Nebenwirkungen (adverse events) als Endpunkte – visibility
- Lebensqualität

EUnetHTA REA-Handbuch, http://www.eunethta.eu/..... methodology-guidelines-for-Relative-Effectiveness-Assessment-of-Pharmaceuticals/

IQWIG 2011: Aussagekraft von Surrogatendpunkten in der Onkologie.

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Kapitel 4

Diskussion: Zusammenfassung der Herausforderungen (= Probleme)

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1. Nicht-repräsentative Population
2. Studiendesigns (cross over, Komparatoren)
3. Validität von Surrogaten
4. Bedeutsame AE/Abbruch wegen AE
5. Evidenzbasis - Orphan drugs
6. Biomarker/ Stratifizierte Medizin
7. Validität der Companion Diagnostics

Suggestivkraft der Bilder

Repräsentative Alterskohorte

soziale Schicht ?

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Beispiele: Nicht-repräsentative Population

Gefitinib (Iressa®) bei NSCLC**: kein Unterschied bei OS**, **Verbesserung des PFS + 3,2 Monate und Lebensqualität**

Studiendesign: hochselektierte, nicht-repräsentative Population: Frauen, unterdurchschnittlich jung, Nicht-Raucherinnen, Asiatinnen

!! (was PFS assessed by centralized reviewers/blinded ?)

Trastuzumab (Herceptin®) bei fortgeschrittenem Magen-Ca**, OS: + 4 Monate, PFS + 1,2 Monate, Lebensqualität (AE): gleich bis geringer**

Studiendesign: nicht-repräsentative Studienpopulation; Pts. mit gastrointestinalen Blutungen, mit Malabsorptionssyndrom aus der Studienpopulation ausgeschlossen, also nicht-operierte Pts

!! RCT stopped early (Effekt-Überschätzung möglich), Post-Hoc Subgrupenanalyse: n=20

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Beispiele: Komparatoren

Ipilimumab (Yervoy ®), bei fortgeschrittenem, *vorbehandeltem* Melanom, **OS +3,7 (Ipi vs vaccine),** BORR 11 (6-17%), 97 % AE (Grade 1-4), **45% (Grade 3+4)**

Studiendesign: Vergleich Ipilimumab mono vs vaccine (experimentell) vs. Ipilimumab+vaccine, Kein Vergleich mit einer realistischen Alternative (kein Konsens, aber Chirugie, Chemo, Radio-, Immuno….)

Komparator: experimenteller K. hat ebenfalls schlechtes Risiko-Profil…..safety might look better with Ipi.

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Beispiele: Cross over

Everolimus (Afinitor®) bei RCC, **Verbesserung des PFS +2,1 Monate**, **keine Verlängerung OS** und Lebensqualität

Studiendesign: Cross over

Rituximab (Rituxan®/MabThera®) bei CLL, **Verlängerung des PFS um 7-10 Monate** im Vergleich zu konventioneller Chemotherapie, jedoch **verbesserte OS (Monate ?),** signifikant gehäufte Nebenwirkungen

Studiendesign: Cross over

Unreife Daten -> Zahllose weitere (Vemurafenib)!!

PFS als Schnellzug

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Beispiele: Surrogat-Endpunkte ohne Effekte auf PRO

example Avastin® and Sutent®

Breast cancer	Avastin® + Chemotherapy	PFS - 13,3 months
	only Chemotherapy	PFS - 6,7 months
	no effect on OS proved	
Renal cancer	Avastin® and Interferon alfa	PFS -10,2 months
	Interferon alfa and Placebo	PFS - 5,4 Monate
	no effect on OS proved	
Renal cancer	Sutent® andInterferon alfa	PFS - 47,3 Weeks
	Interferon alfa as Standardtherapy	PFS - 22,0 Weeks
	no effect on OS proved	

Quelle: Wild/ Piso (Ed): Zahlenspiele in der Medizin, Orac 2010

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Beispiel: PFS ohne Validierung

Ipilimumab:

„in two trials using ipilimumab for melanoma OS benefit without PFS benefit"

Everolimus (Afinitor) für neuroendokrine Pankreastumore:

OS kein Unterschied, PFS + 6,4 Monate im Vgl zu Placebo

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Beispiele: Bedeutsame AE/ Abbruch wegen AE

Risiko auf sekundäre Tumore:

- Lenalidomide bei MM: myeloplastisches syndrom; CLL/Chronische lymphatische Leukämie
- Vemurafenib – Squamöse Zellkarzinome

- Ipilimumab: 45% (Grad 3-4)
- Cabazitaxel: Studienabbruch 18% wegen AE vs mitoxantrone 8%, 5% der Todesfälle Caba wegen AE

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35% aller Orphan Drugs sind Onkologika…….Salami-Technik

	Trade Name	Substance name	Prevalence / Indication	prevalence per 10,000 population	absolute number of pts affected EU wide
1	Afinitor	everolimus	Renal cell carcionoma	4,2	193.000
2	Arzerra	ofatumumab	Chronic lymphocytic leukemia	3,5	176.000
3	Atriance	nelarabine	Acute lymphoblastic Leukemia	1,1	51.000
4	Ceplene	histamine dihydrochloride	Acute myeloid leukemia	0,7	32.000
5	Evoltra	clofarabine	Acute lymphoblastic Leukemia	0,4	15.000
6	Gliolan	5-aminolevulinic acid hydrochloride	Gliomas	1,0	37.000
7 - 1	Glivec	imatinib	Malignant gastrointestinal stromal tumours	0,1	2.250
7 - 2			Acute lymphoblastic leukaemia	0,5	23.000
7 - 3			Chronic myeloid leukaemia	0,9	34.000
7 - 4			Myelodysplastic / myeloproliferative diseases	1,6	74.000
7 - 5			Dermatofibrosarcoma protuberans	1,0	46.000
7 - 6			Chronic eosinophilic leukaemia and the hypereosinophilic syndrome	1,0	46.000
8	Litak	cladribine	Indolent non-Hodgkin's lymphoma	2,4 to 3, 65	90.000 to 138.000
9	Lysodren	mitotane	Adrenocortical carcinoma	0,11	4.000
10	Mepact	mifamurtide	Osteosarcoma	0,5	19.000
11	Mozobil	plerixafor	Mobilize progenitor cells prior to stem cell transplantation	less than 1	46.000
12 -1	Nexavar	sorafenib	Renal Cell Carcinoma	3	116.000
12 - 2			Hepatocellular Carcinoma	1	46.000
13	Revlimid	lenalidomide	Multiple Myeloma	1,3	50.000
14 -1	Sprycel	dasatinib	Acute lymphoblastic leukaemia	0,7	33.000
14-2			Chronic myeloid leukaemia	0,9	41.000
15	Tasigna	nilotinib	Chronic myeloid leukaemia	1	46.000
16	Thalidomide Celgene	thalidomide	Multiple Myeloma	1,2	45.000
17 - 1	Torisel	temsirolimus	Renal cell carcinoma	3,5	16.1000
17 - 2			Mantle-Cell Lymphoma	0,4	18.000
18	Trisenox	arsenic trioxide	Acute promyelocytic leukaemia	0,8	30.000
19 - 1	Vidaza	azacitidine	Myelodysplastic Syndromes	1,1 - to 3	41.000 – 113.000
19 - 2			Acute myeloid leukaemia	<2	<100.000
20- 1	Yondelis	trabectedin	Ovarian Neoplasms	2,4	92.000
20- 2			Soft tissue sarcoma	0,6	23.000

Quelle: Wild C. et al. Orphan drugs in Oncology. In: Pharmaceutical Policy and Law/ monography on HTA and Rare Diseases Therapies, 13 (2011) 1-11.

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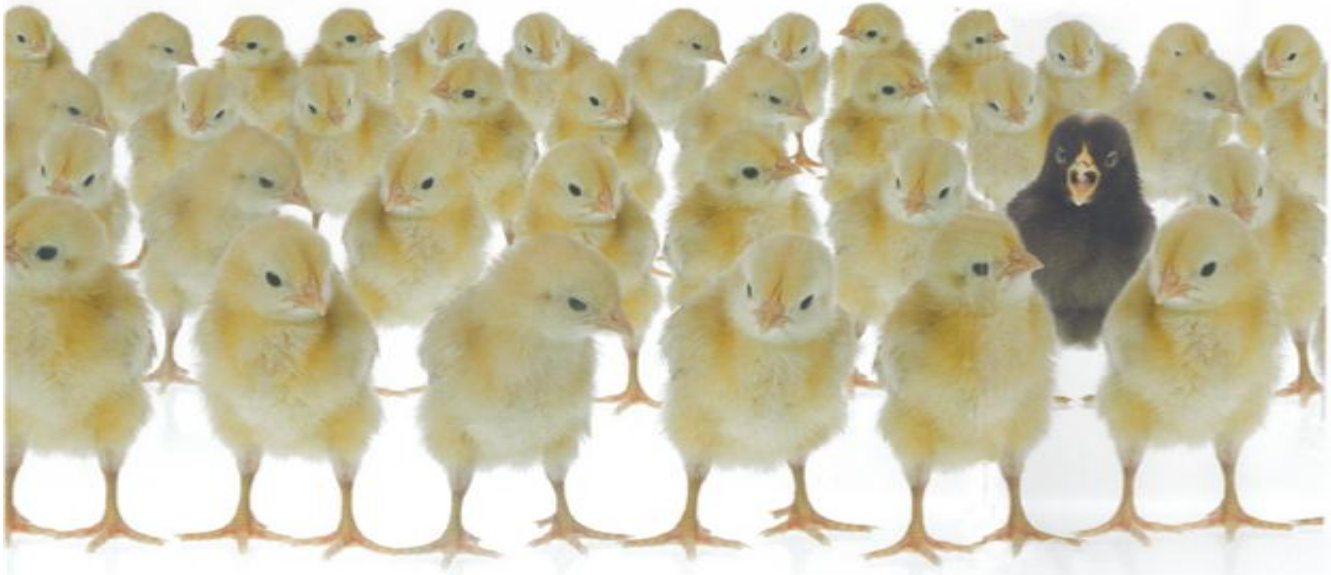
Ein tragischer Lotto-Sechser

Seltene Krankheiten sind schwer zu diagnostizieren und oft auch zu therapieren: nationale Aktionspläne sollen nun die Lage der Betroffenen verbessern.



Quelle: Pharmig Zeitschrift

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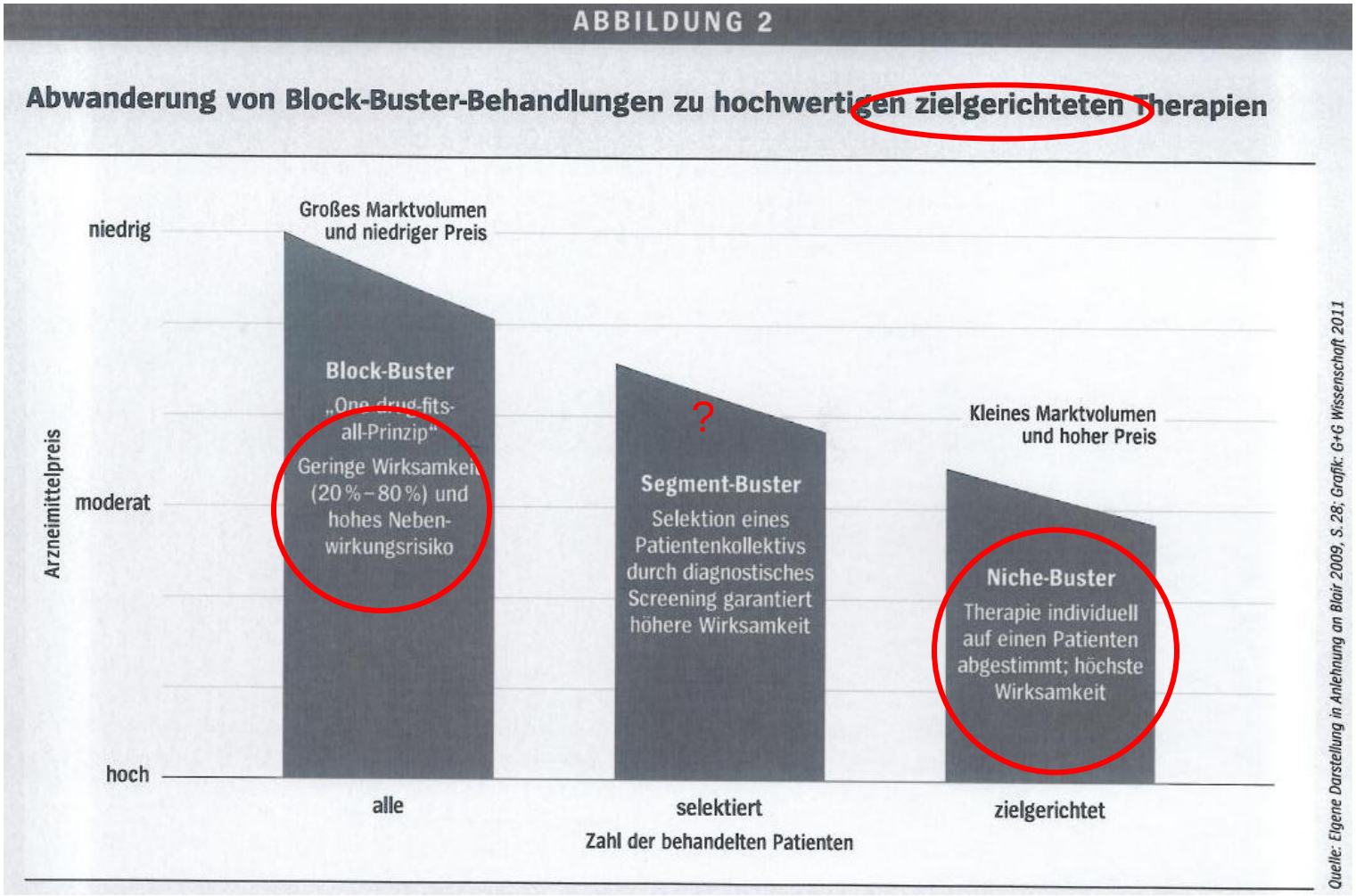
Hohe Ansprechraten/ geringes Nebenwirkungsprofil (als Versprechen)



Quelle: Greiner 2012 Wirtschaftliche Potentiale individualisierter Medizin, GGW 1(Jan).

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Biomarker-basierte neue Onkologika: zumeist post hoc……Validierung ?

Biomarker	Drug
EGFR/ KRAS	Cetuximab/ Erbitux ® Erlotinib/ Tarceva® Gefitinib/ Iressa® Panitumumab/ Vectibix®
HER2	Lapatinib/ Tyverb® Pertuzumab/ Perjeta ® Trastuzumab/ Herceptin®
Ph+	Imatinib/ Glivec® Nilotinib/ Tasigna® Dasatinib/ Sprycel®
DPD	Capecitabine/ Xeloda®
BRAF	Vemurafenib/ Zelboraf®

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Biomarker/ Stratifizierte Medizin

Trastuzumab
PFS: ARR 5,5%/ NNT 18,2
OS: ARR 1,7%/ NNT 55
QoL: ?
AE 2% Herzinsuffizienz, NNH 50

- Biomarker basierte (stratifizierte) neue Arzneimittel (Onkologika) sind nicht notwendigerweise Garant für klinische Effektivität (für alle Pts. mit „Tumor-Expression“)
- Onkologie: ausgehend von sehr niedrigem Niveau (10-20% Ansprechen)

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Validität der Companion Diagnostics

- Pathologien: Intra- und Inter- Observer und Labor- Unterschiede bei 2+ Bewertung
- klinische Signifikanz von „low-level“ Amplifikationen
- weniger HER2 positive Patientinnen als aus klinischen (Herceptin-) Studien hervorgeht (20-30% vs 15-20%)

Quelle: Korencan/ Wild 2007, Testing for HER2 Positive Breast Cancer Challenge for Improvement of Current Conditions and Practice, http://eprints.hta.lbg.ac.at/716/1/HTA-Projektbericht_008.pdf

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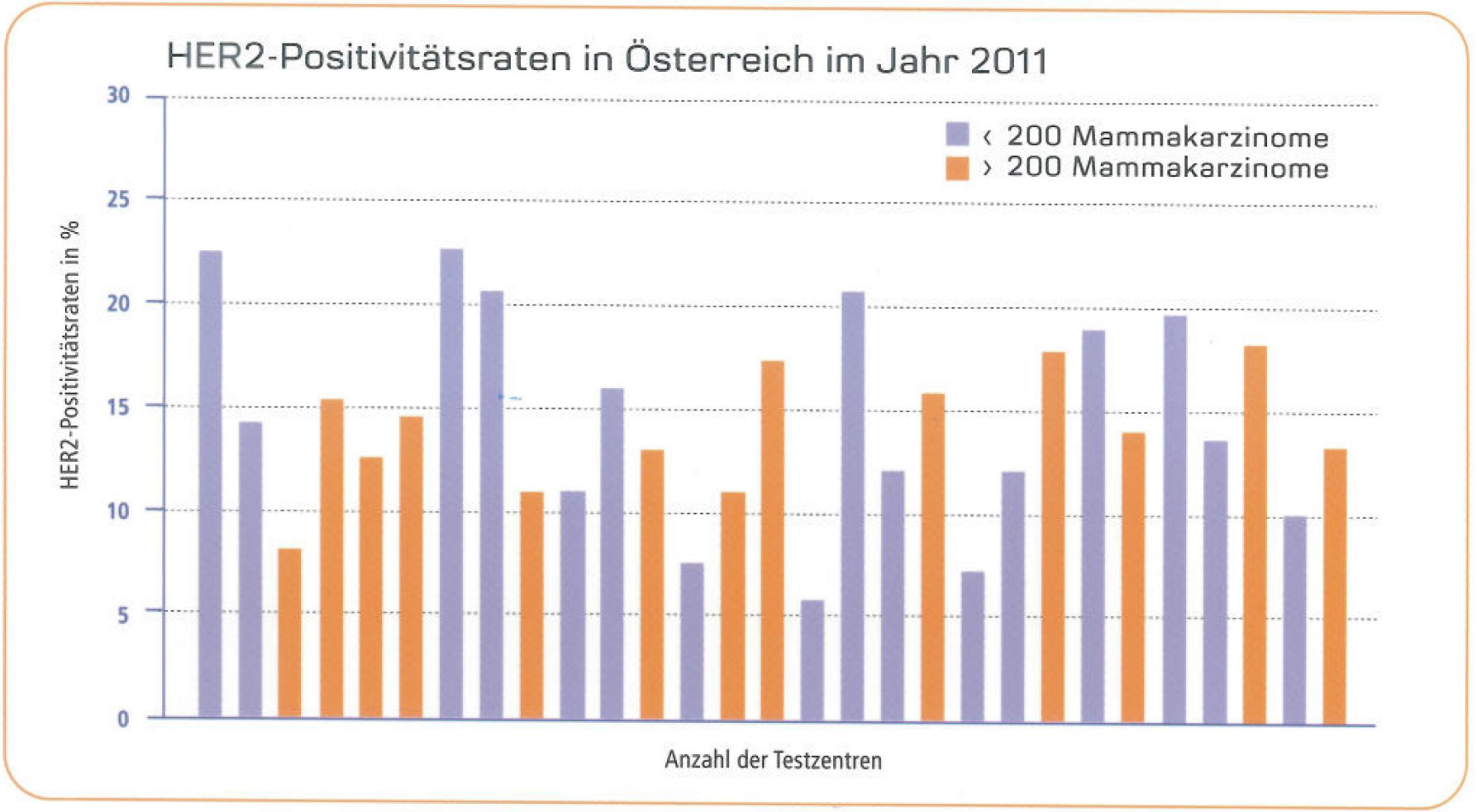
Validität der Companion Diagnostics 2: nach 12 Jahren !!!!



Quelle: Roche Datenerhebung, HER2 Positivitätsraten beim Mammakarzinom in Ö

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Conclusio

- Realität: zum Zeitpunkt der Zulassung wenig Wissen - Orphan drug-Status, Surrogat-Endpunkte + Cross over-Design
- Große öffentliche Aufmerksamkeit – systematische/strukturierte Darstellung – immer mehr kritische OnkologInnen (sozialer Mut ?)
- Nationaler Onkologiebeirat (Roadmap)
- Größeres Verständnis für brit. (NICE) Entscheidungen