SYDDANSK UNIVERSITET

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The Pharmacoeconomic Perspective

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From televised debate between the two candidates for premierminister on the topic of high prices on hospital dispensed drugs

”Jeg kan ikke se for mig en situation, hvor vi skal prioritere. Borgerne forventer verdensklasse, når de møder det danske sundhedsvæsen”

Statsministerkandidat, TV2 – June 5th 2015
ved debat om ‘dyr’ medicin

I can’t imagine a situation where we must prioritize. Citizens expect world class when they meet the Danish health care system

When we in Denmark introduce new (cancer) drugs price/costs must not be considered

For instance September 9th: The council on introduction of new hospital dispensed medicines, KRIS, recommende six cancer drugs

… comments on two drugs: bevacizumab (Avastin) and nivolumab (nivolumab BMS):

- **'in the council we emphasized that for patients treated with Avastin we observed a survival gain of 3.7 months compared to chemotherapy.**

- **As concerns Nivolumab BMS … a considerable better effect compared to existing treatment was observed. Patients' median survival was *3.2 months longer,* og 1-year survival proportion was doubled.**

- **The side effects of both drugs were manageable.'**

Council chairman Steen Werner Hansen

A challenging cancer report (2011)

The Lancet Oncology Commission

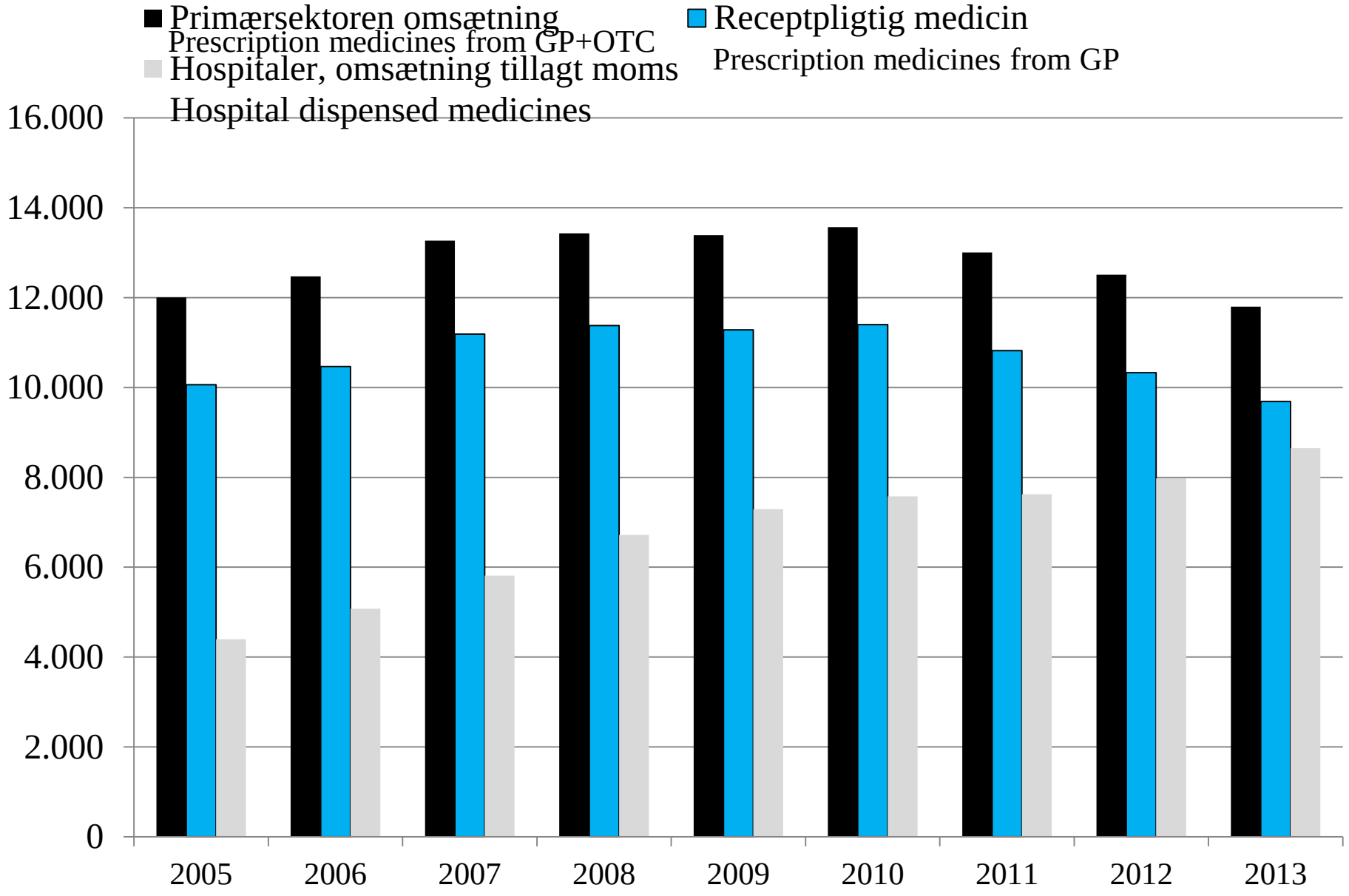
Delivering affordable cancer care in high-income countries

Richard Sullivan, Jeffrey Peppercorn, Karol Sikora, John Zalcberg, Neal J Meropol, Eitan Amir, David Khayat, Peter Boyle, Philippe Autier, Ian F Tannock, Tito Fojo, Jim Siderov, Steve Williamson, Silvia Camporesi, J Gordon McVie, Arnie D Purushotham, Peter Naredi, Alexander Eggermont, Murray F Brennan, Michael L Steinberg, Mark De Ridder, Susan A McCloskey, Dirk Verellen, Terence Roberts, Guy Storme, Rodney J Hicks, Peter J Ell, Bradford R Hirsch, David P Carbone, Kevin A Schulman, Paul Catchpole, David Taylor, Jan Geissler, Nancy G Brinker, David Meltzer, David Kerr, Matti Aapro

The burden of cancer is growing, and the disease is becoming a major economic expenditure for all developed *Lancet Oncol* 2011; 12: 933–80

"A radical shift in cancer policy is also required. Political toleration of unfairness in access to affordable cancer treatment is unacceptable. The cancer profession and industry should take responsibility and not accept a substandard evidence base and *an ethos of very small benefit at whatever cost*; rather, we need delivery of fair prices and real value from new technologies."

Danish expenditures on pharmaceuticals



Pharmaceutical expenditures make up 16% of to health expenditures

Expenditures for cancer drugs have increased by 47% 2010 – 2015 (without increasing number of cancer cases)

Total expenditures for hospital dispensed drugs increased by **28 %** 2010 til 2014, equivalent to app. 1.5 mia. billion DKK.

Development in cancer drug expenditures.

Figur 1. Udviklingen i omsætning af kræftlægemidler i mio. kr.

	2010	2011	2012	2013	2014	2015*
L01- Cytostatika	1.173	1.177	1.313	1.394	1.550	-
L02 - Hormonterapi	222	179	127	223	291	-
L03 – Immunstimulerende midler	84	89	84	78	78	-
L04 - Immunsuppressiva	36	42	69	78	72	-
Total	**1.515**	**1.486**	**1.594**	**1.773**	**1.991**	**2.236**

* Estimat: samme procentstigning som fra 2013 til 2014

Kilde: AMGROS (SygehusApotekets IndkøbsPris: leverandørens tilbudspris med tillæg af AMGROS avance, svarende til regionernes udgifter til sygehusmedicin)

If the percentage increase over the past two years continues in 2015, expenditures in 2015 will increase by app. 239 mill. DKK (12% increase compared to 2014)

Percentage growth in regional health expenditures
Fixed 2014 prices

	% growth						
	2007 - 2008	2008 - 2009	2009 - 2010	2010 - 2011	2011 - 2012	2012 - 2013	2013 - 2014
Hospital, incl. hospital disp. drugs	4,0	7,1	0,6	-2,8	0,3	2,3	0,7
GPs	4,6	4,1	-0,1	0,9	-1,8	-2,3	-2,2
Office based specialists	7,5	6,3	4,1	-1,3	-3,0	-0,7	2,8
Prescription medicines	-4,5	-5,8	0,5	-10,0	-9,4	-9,8	1,0
Tandlægebehandling	3,0	1,9	-0,2	-0,6	-1,4	-12,3	-0,6
Fysiurgisk behandling	-2,0	-13,0	1,6	7,2	1,8	2,3	2,8
Kiropraktor	3,9	5,0	-1,6	1,8	-5,1	0,3	1,8
Fodterapeuter	31,5	-3,8	-2,7	-0,9	-18,2	10,0	6,4
Psykologbehandling	31,2	27,2	7,4	4,9	8,9	0,2	-2,7
TOTALt	**3,4**	**5,5**	**0,7**	**-2,9**	**-0,6**	**0,9**	**0,6**
							Kilde: Statistikbanken tabel REGR31 og Prisberegner

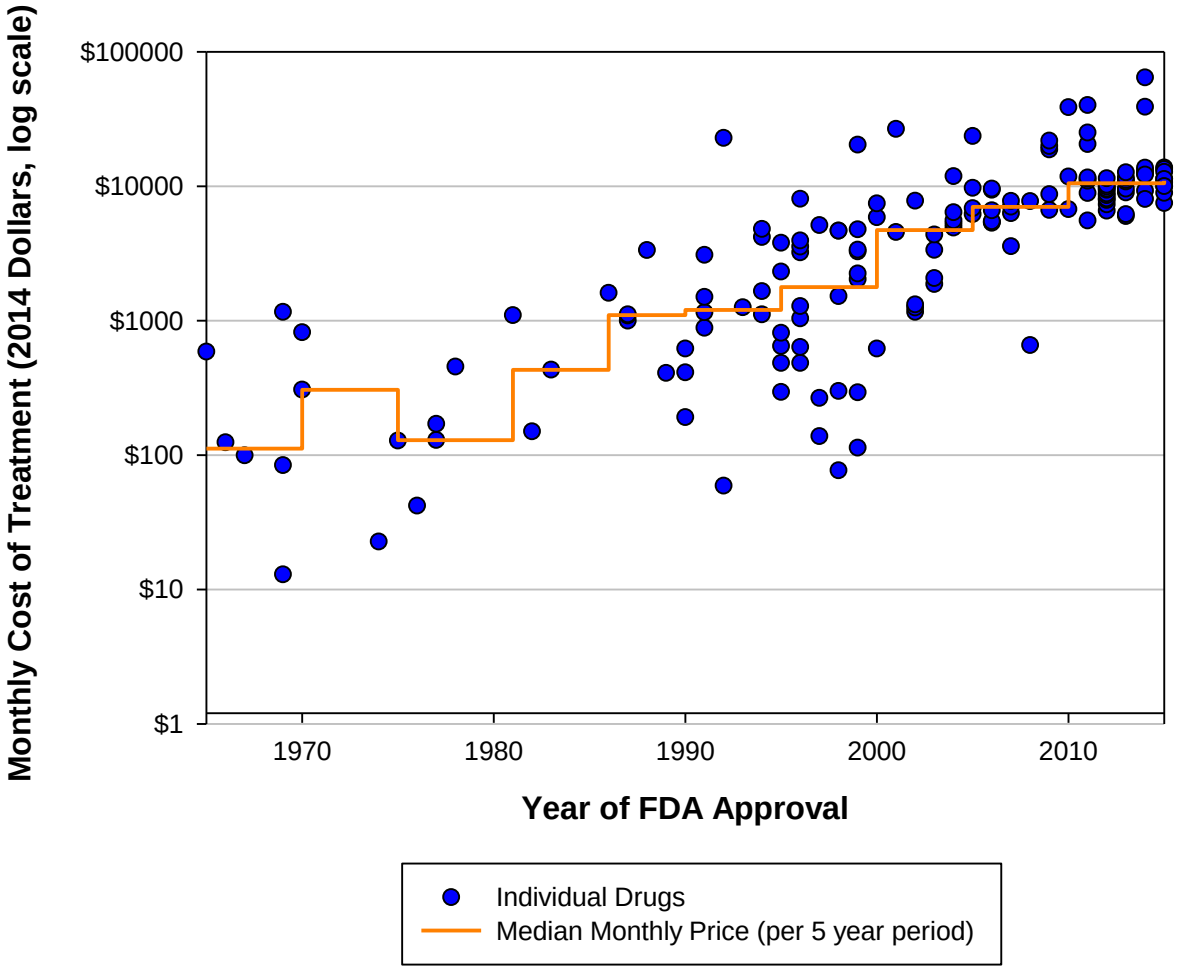
Low percentage growth in total health expenditures and high growth rates in expenditures for hospital dispensed drugs create dilemmas …

Expenditures for treatment with cancer drugs has gradually increased.

(partly due to biologicals)

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval

1965-2015



Source: Peter B. Bach, MD, Memorial Sloan-Kettering Cancer Center

Why high prices?

1. Patents
   - Patents mean a de facto monopoly
     - Hence pricing based on ‘what the market will take’ (despite regulation in many countries).

2. Biosimilars are emerging as patents expire
   - Will put pressure on prices
   - Probably not to the same extent as generics

3. High prices also due to manufacturing methods (but probably a minor part of the explanation)

From: **Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs**

JAMA Oncol. Published online April 02, 2015. doi:10.1001/jamaoncol.2015.0373

Table. Last 20 Oncologic Drugs Approved Between 2009 and 2013 by the US Food and Drug Administration

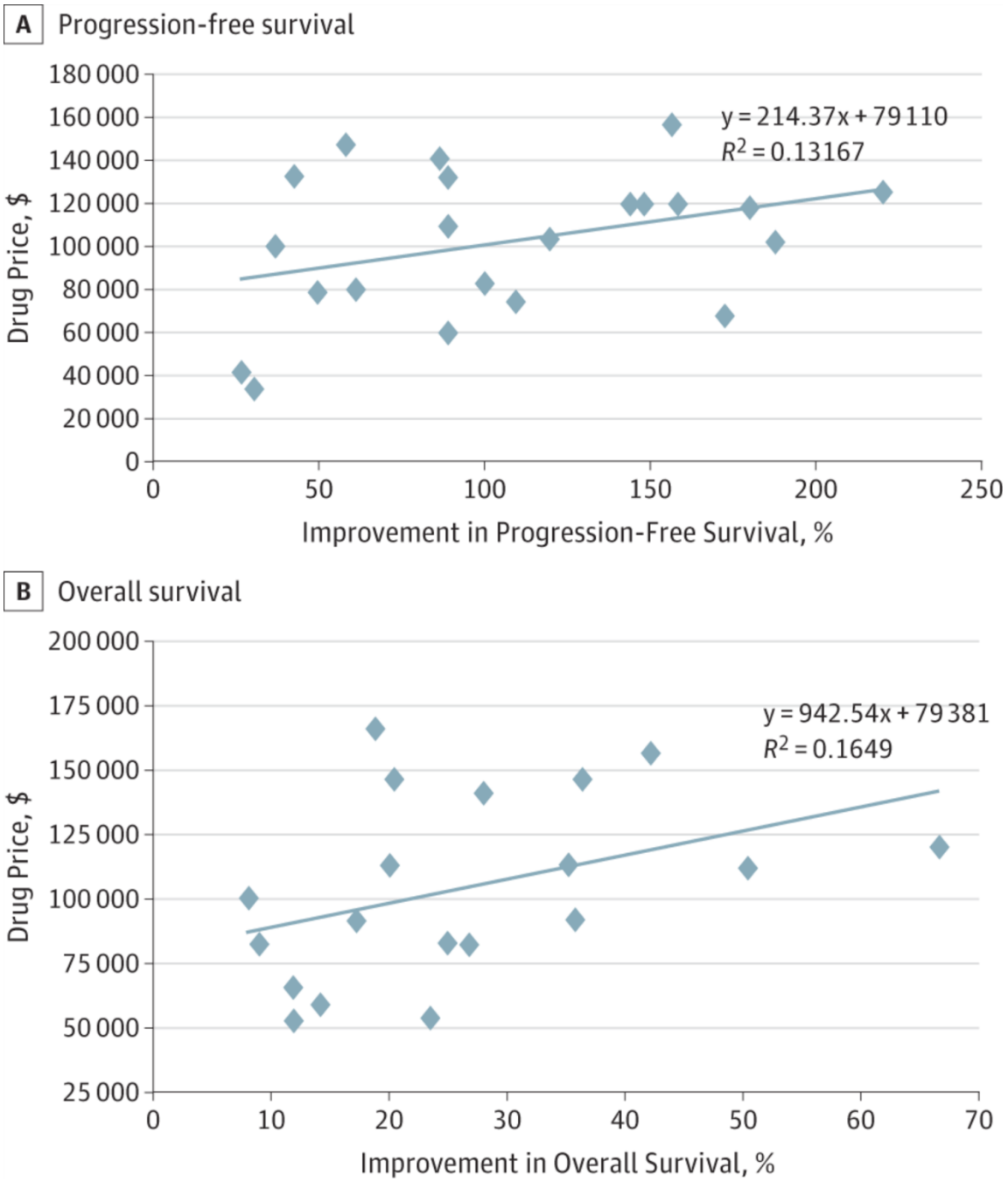
Drug and Indication	Cost per Year of Treatment, $[a]	Parent Drug	Mechanism of Action	Clinical Benefit
Sorafenib for papillary thyroid cancer	140 984	NA	First approved VEGFR and RAS tyrosine kinase inhibitor	Median PFS, 10.8 vs 5.8 mo
Crizotinib for non-small-cell lung cancer	156 544	NA	Anaplastic lymphoma kinase inhibitor	Median PFS, 7.7 vs 3.0 mo
Ibrutinib for follicular lymphoma	157 440	NA	Bruton tyrosine kinase inhibitor	RR, 66%; median DOR, 17.5 mo
Obinutuzumab for chronic lymphocytic leukemia	74 304	Rituximab	Anti-CD20 monoclonal antibody	Median PFS, 23.0 vs 11.1 mo
Pertuzumab for breast cancer	78 252	Trastuzumab	Anti-her2 monoclonal antibody	Pathologic CR, 39.3% vs 21.5%
Nab-paclitaxel[b] for pancreatic cancer	82 231	Paclitaxel	Albumin-bound paclitaxel (microtubule inhibitor)	Median OS, 8.5 vs 6.7 mo
Afatinib for non-small-cell lung cancer	79 920	Erlotinib	EGFR tyrosine kinase inhibitor	Median PFS, 11.1 vs 6.9 mo; median OS, NS
Lenalidomide for mantle-cell lymphoma	124 870	Thalidomide	Immunomodulatory drug (thalidomide analogue)	RR, 26%; median DOR, 16.6 mo
Trametinib for malignant melanoma	125 280	NA	First approved mek inhibitor	Median PFS, 4.8 vs 1.5 mo
Dabrefenib for malignant melanoma	109 440	Vemurafenib	BRAF inhibitor	Median PFS, 5.1 vs 2.7 mo; median OS, NS
Radium 223 for prostate cancer	82 800	NA	First approved radiotherapeutic drug	Median OS, 14.0 vs 11.2 mo
Erlotinib for non-small-cell lung cancer	82 827	NA	First approved EGFR tyrosine kinase inhibitor	Median PFS, 10.4 vs 5.2 mo; median OS, NS
Ado-trastuzumab emtansine for breast cancer	113 161	NA	First approved anti-her2 antibody drug conjugate	Median PFS, 9.6 vs 6.4 mo; median OS, 25.1 vs 20.9 mo
Pomalidomide for multiple myeloma	150 408	Thalidomide	Immunomodulatory drug (thalidomide analogue)	RR, 29%; median DOR, 7.4 mo
Bevacizumab for colorectal cancer	59 422	NA	First anti-VEGF monoclonal antibody	Median PFS, 5.7 vs 4 mo; median OS, 11.2 vs 9.8 mo
Ponatinib for chronic myeloid leukemia and Ph$^+$ acute lymphoblastic leukemia	137 952	Imatinib	Bcr-abl tyrosine kinase inhibitor	Major cytogenetic response, 54%; median DOR, 3.2-9.5 mo
Abiraterone for prostate cancer	92 092	Ketoconazole	Androgen biosynthesis inhibitor	Median OS, 35.3 vs 30.1 mo
Cabozantinib for medullary thyroid cancer	118 800	NA	First multikinase (including c-met and VEGF) inhibitor	Median PFS, 11.2 vs 4 mo; median OS, NS
Omacetaxine for chronic myeloid leukemia	168 366	Homoharringtonine	Protein translation inhibitor	Major cytogenetic response, 14.3%; median DOR, 12.5 mo
Nab-paclitaxel[b] for non-small-cell lung cancer	82 231	Paclitaxel	Albumin-bound paclitaxel (microtubule inhibitor)	RR, 33% vs 25%; median OS, NS
Regorafenib for colorectal cancer	141 372	Sorafenib	Multikinase inhibitor	Median PFS, 2 vs 1.7 mo; median OS, 6.4 vs 5 mo

Abbreviations: CR, complete response; DOR, duration of response; NA, not applicable; NS, not significant; OS, overall survival; PFS, progression-free survival; Ph$^+$, Philadelphia chromosome positive; RR, response rate;

[a] Average wholesale prices were obtained from Redbook online ([subscription required] http://www.redbook.com/redbook/online/).

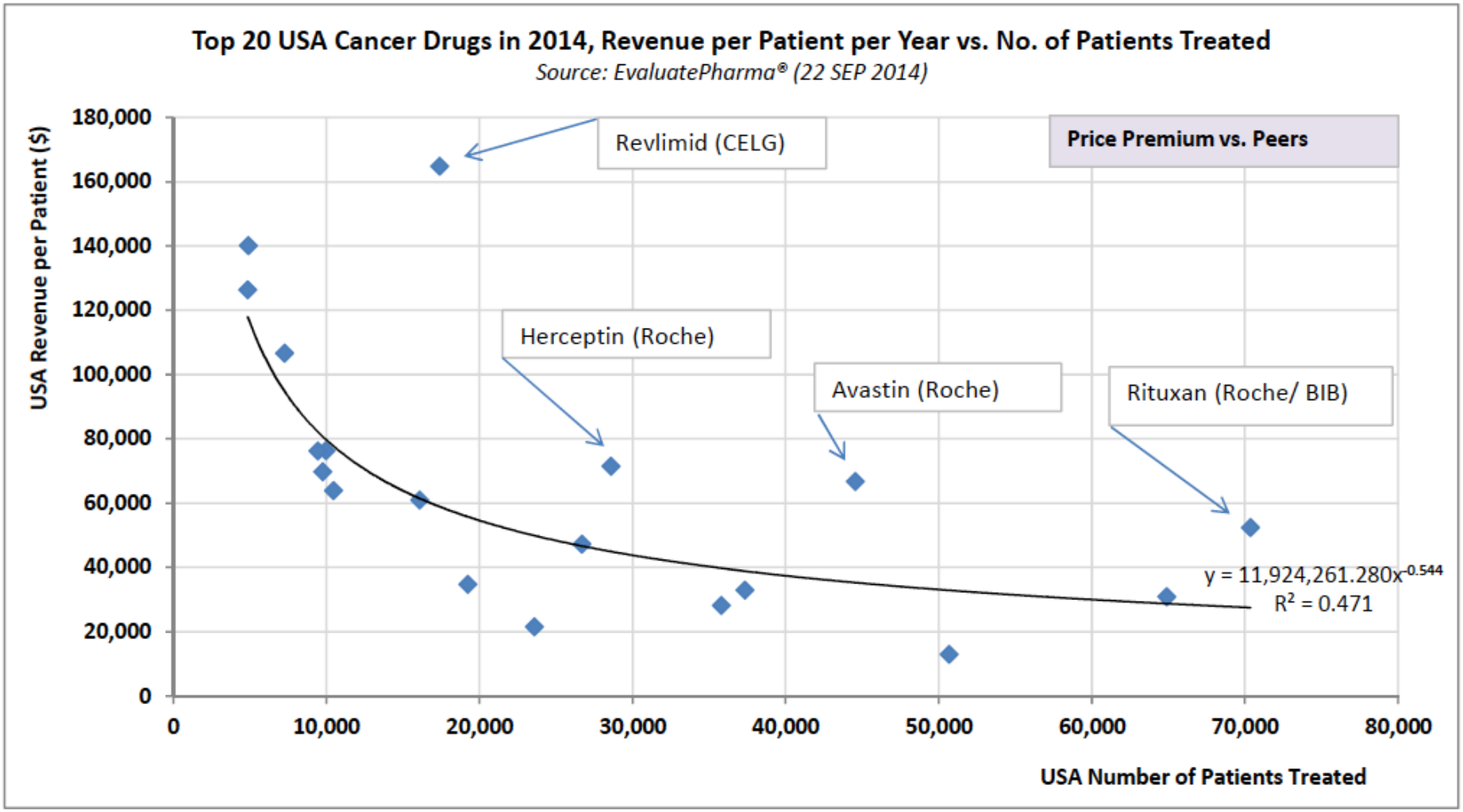
[b] This drug was approved separately for 2 indications.

(few) additional months - rarely > 12 month


A
Progression-free survival
180 000
160 000
140 000
120 000
100 000
80 000
60 000
40 000
20 000
0
Drug Price, $
y = 214.37x + 79 110
R2 = 0.13167
0
50
100
150
200
250
Improvement in Progression-Free Survival, %
B
Overall survival
200 000
175 000
150 000
125 000
100 000
75 000
50 000
25 000
Drug Price, $
y = 942.54x + 79 381
R2 = 0.1649
0
10
20
30
40
50
60
70
Improvement in Overall Survival, %

"Our results suggest that *the price of cancer drugs is independent of novelty*. Additionally, we found little difference in price among drugs approved based on time-to-event end points and drugs approved on the basis of RR. Our results suggest that current pricing models are not rational but simply reflect what the market will bear."

Source: Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs



Note: In theory the products with the highest sales should represent the best patient outcome, cost out of healthcare and improved patient economic activity relative to the competition, for the indications sales are achieved in.
Within the USA market the price can rise or fall (off-invoice discounting) post approval, which in a free market system is to be expected. A price rise should signify an enhanced understanding of the drug profile vs. the competition, but may also be the company taking advantage of the risk of switching patients or entrenched prescribing habits.

Kilde: EvaluatePharma:Budget-busters: The shift to high-priced innovator drugs in the USA, spetember 2014

Top 10 USA Cancer Drugs by Sales: USA Revenue per Patient per Year vs. No. of Patients Treated 2014

	Product	Company	Sales ($m) 2014	No. of Patients	Revenue Per Patient	Patient Compliance	Off-Invoice Discount
1	Rituxan	Roche	3,707	70,347	52,459		
2	Avastin	Roche	2,928	44,552	66,828		
3	Revlimid	Celgene	2,107	17,380	164,859		
4	Herceptin	Roche	2,060	28,587	71,513		
5	Gleevec	Novartis	2,023	64,884	31,006	40%	-23%
6	Stelara	Johnson & Johnson	1,269	37,327	32,997	78%	
7	Alimta	Eli Lilly	1,251	26,674	47,300		
8	Zytiga	Johnson & Johnson	992	35,801	28,212	44%	-20%
9	Velcade	Takeda	983	16,097	61,053		
10	Afinitor	Novartis	779	7,253	106,675		-15%
	Average Top 10		1,810	34,890	66,290		
	Average Top 20		1,236	24,587	64,266		

Kilde: EvaluatePharma:Budget-busters: The shift to high-priced innovator drugs in the USA, spetember 2014

How should we decide on the introduction of new drugs?

1. As stated by the premierminister candidates: If documented positive clinical effects, we pay any price?

2. Critical evaluation of the size of the clinical effect, side effects etc. followed by price negotiatons (the German IQWiG-model)?

3. Look at added clinical effec and added adtitional costs: cost-effectiveness
   - like virtually the rest of the world

IQWiG in 2014 evaluated 36 drugs …
and 21 was labeled: ‘kein zusatsnutzen’ (no additional value)
- After ‘labeling’ follows price negotiations to be setteled within 1 year

Quelle: G-BA: Erstellung und Einreichung eines Dossiers zur Nutzenbewertung gemäß § 35a SGB V, Seite 4
g-ba.de/downloads/17-98-3518/2013-04-18_Anl2_1_Erstellung-Einreichung-Dossier.pdf (Zugriff: 27.4.2015)

Cost-effectiveness threhold & common misundertandings

(incremental cost-effectiveness ratio)

$$\text{ICER} = \frac{C_{\text{eksisteren de}}}{E_{\text{eksisteren de}}} - \frac{C_{ny}}{E_{ny}} \quad < \textbf{???} \quad \text{(cost per QALY)}$$

NEJ: No – is not equivalent to put a price on life!

But ratherMEN

Could the same money have created higher health gains elsewhere in the health care system?
(alternative costs/opportunity costs/displacement)

NICE threshold values

1. <£20.000 per QALY bliver i de fleste tilfælde godkendt, da interventionen er ”omkostnings-effektiv”.

2. £20.000-£30.000 per QALY godkendes i tilfælde, hvor der er stor sikkerhed omkring udfaldet eller effekten af behandlingen.

3. >£30.000 per QALY afvises. Dog kan behandlingen godkendes under særlige omstændigheder. Der er fx en særlig kategori med ”end-of-life” præparater m. en højere tærskelværdi.

Den første kategori er en anbefaling der følger EMAs indikation.
I kategori 2 er grænsen flydende. Der er fire grunde til ikke at have en absolut tærskelværdi (Rawlins & Culyer, 2004):

- at tærskelværdien ikke er en værdi baseret på videnskabelig fakta
- situationer hvor NICE vil vælge at ignorere en fastsat tærskelværdi (f.eks. end-of-life)
- Ved at sætte en fastsat tærskelværdi, vil man indikere at effektivitet vejer tungere end for eksempel etiske aspekter
- En fastsat tærskelværdi vil ikke skabe incitament til konkurrence fra i industriens side.

“Given the fixed budget of the NHS, the appropriate threshold is that of the opportunity cost of programmes displaced by new, more costly technologies”

Kilde: 2004 Guide to the Methods of Technology Appraisal

”There is no empirical basis for assigning a particular value (or values) to the cut-off between cost effectiveness and cost ineffectivenes. The consensus amonst the Institute’s economic advisors…”

Kilde: NICE, Social value judgement, guidelines, 2005

“The threshold therefore represents the additional cost that has to be imposed on the system to forgo 1 quality-adjusted life-year (QALY) of health through displacement. There are no empirical estimates of the cost-effectiveness threshold used by the National Institute for Health and Care Excellence”.

Kilde: Claxton et al. 2015

NICE om Kadycla:

Our job is to recommend whether it should transfer into the NHS budget. We are very aware of the importance that people place on life-extending cancer drugs and a decision **not to recommend a cancer treatment** for routine NHS funding is never taken lightly. We apply as much flexibility as we can in approving new treatments, but the reality is that given its price and what it offers to patients**, it will displace more health benefit which the NHS could achieve in other ways, than it will offer to patients with breast cancer**." Andrew Dillon, adm. direktør NICE

"Although Roche proposed a discount to the full list price of Kadcyla, it made little difference to its value for money, leaving it well above the top of our specially extended range of cost effectiveness for cancer drugs" (NICEs hjemmeside).

A thought provoking addition to price negotaions is found the the following BBC-article the nest day: "Officials at Roche told me that they were willing to come down on price "significantly", but that there was a limit to this considering other European countries, including Sweden, Switzerland, **Denmark** and Austria had agreed to pay the full price. (BBC 08.08.2014, KMP's bold letters)"

Another source says that the firm's list price should be reduced by 60% to bring the ICER below the NICE threshold

Recent NICE decision

The National Institute for Health and Care Excellence's, NICE appraisal committee gave a thumbs-down to Cyramza (ramucirumab) for use alone or in combination with another cancer drug, paclitaxel.

The drug's cost rings in at about £42,000 per QALY, NICE, said in an appraisal document, well and above the watchdog's usual price recommendations

But it's not just the price tag that has NICE concerned. It's the cost in light of Cyramza's survival data. In one trial, patients who took Cyramza and paclitaxel survived just 2.27 months longer on average than those in the control arm. In another study, Cyramza beat out placebo by adding 1.4 months to patients' lives.

NICE said in its appraisal document. NICE is taking public comments for Cyramza until Oct. 6 and will hold a second appraisal committee meeting on Oct. 20, the cost gatekeeper said

Kilde: Fierce Pharma 15.09.2015