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Oncology 2011 – Innovation and Trends

European Decision Maker Forum
LSE

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Darmstadt, Germany

Disclaimer:

This presentation is based on my own personal views and by no means expressing a company view.

My thoughts should offer an alternative view in order to stimulate a dialogue.

Where Pharma is going: Emerging Markets

2010 BIOTECH CHINA

Asia Presents New Growth Opportunities

Key advantages include:
- World's Easiest Place to Do Business

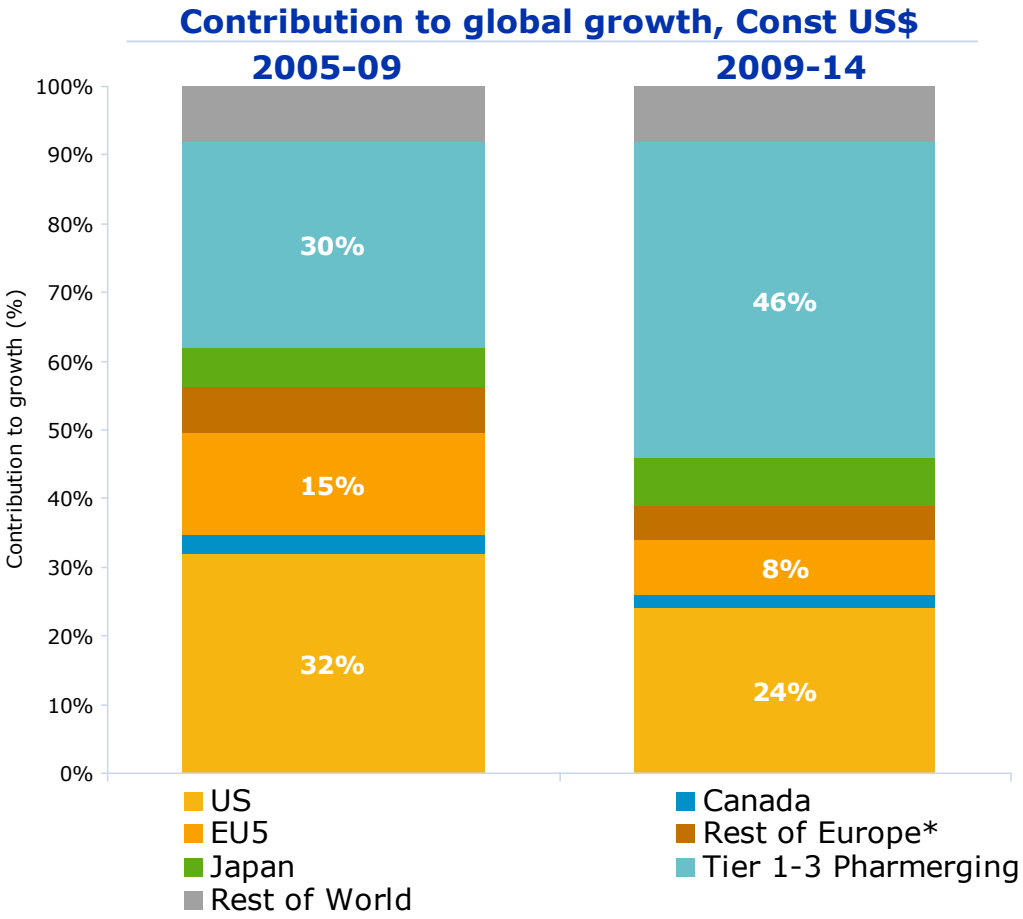
Could China Steal America's Biotech Crown?

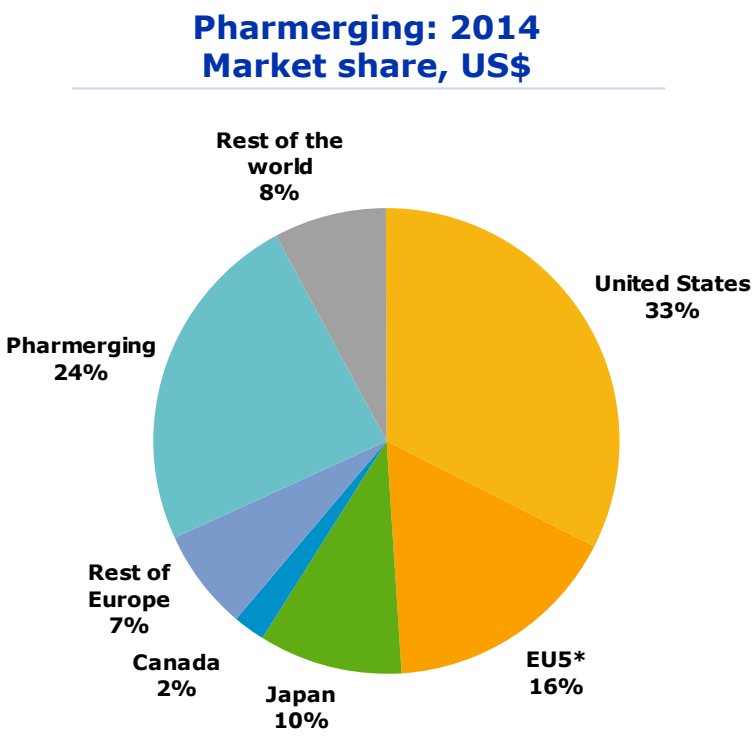
Over the coming decades, will Asia replace the United States as the center of the pharmaceutical world? One of the drug industry's central figures thinks so.

Matthew Herper
Forbes

The new combined 'pharmerging' market group will deliver 46% global growth 2009-2014

This = $140 billion taking share to 24% of global market





*Source: IMS Health Market Prognosis March 2010, *Germany, Spain and Greece forecasts under review; Tier 1 = China; Tier 2 = Brazil, Russia, India; Tier 3 = Venezuela, Poland, Argentina, Turkey, Mexico, Vietnam, S. Africa, Thailand, Indonesia, Romania, Egypt, Pakistan, Ukraine*

Meanwhile Pharma is restructuring out of Europe

Glaxo May Cut 4,000 Jobs, Focus on Emerging Markets, Times Says

By Alexander Kwiatkowski
Jan. 31 (Bloomberg) -- GlaxoSmithKline Plc is planning to **cut as many as 4,000 jobs**, mainly in Europe and the U.S., as the company focuses more on **emerging markets**, The Sunday Times reported, without saying where it got the information. The cuts are likely to be announced when Glaxo reports ist annual results on Feb. 4 and will be part of the company's efforts to **move away from low-growth markets** to those with greater scope to expand sales, the newspaper reported today.

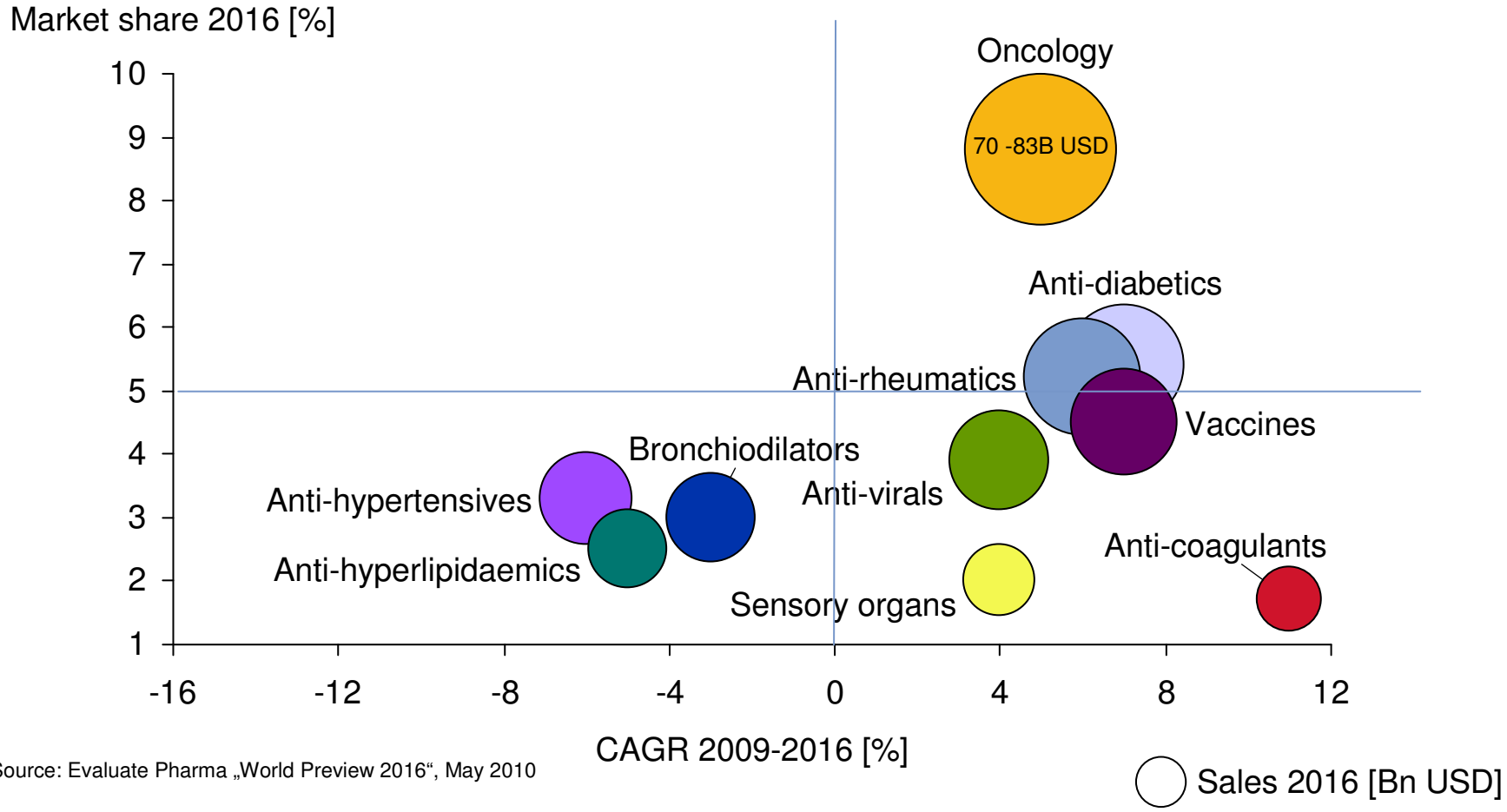
BBC, 1 February 2011 **Sandwich Pfizer research site closure a 'body blow'**

Up to **2,400 people could lose their jobs** when the research and development facility closes in the next two years. The news that drug giant Pfizer is to close its research and development site in Kent has been described as a "body blow" by local MPs. Pfizer said the majority of its 2,400 employees at the facility would be made redundant over the next two years.
It said the move was part of a **global reorganisation** of its research and development capacity.

Bayer to cut 4,500 jobs in global overhaul

It's another **big shift to emerging markets** for Big Pharma. Bayer plans to spend €1 billion on a restructuring plan that will **cut 4,500 jobs-**-but create 2,500 new ones, largely in up-and-coming countries.

Oncology projected to be the biggest therapeutic area of the global pharmaceutical market in 2016 with strong growth



Source: Evaluate Pharma „World Preview 2016“, May 2010

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The era of targeted therapies in oncology: a rollercoaster of hype and disappointments – innovation is not an easy, straight forward road

for illustration

1995-2000
mAB-Skepticism
"Panorex"

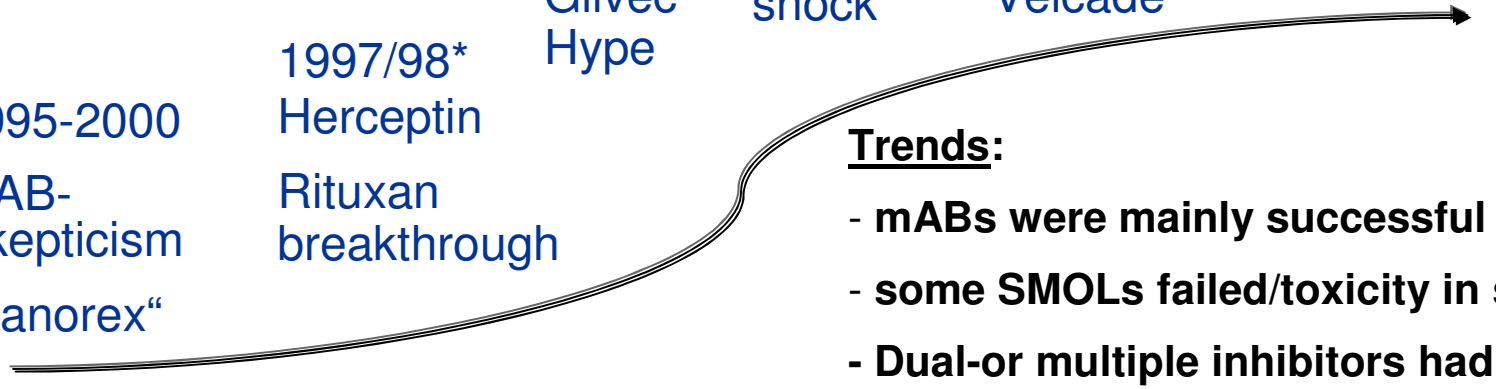
1997/98*
Herceptin
Rituxan breakthrough

2001
Glivec Hype

2001
Iressa, Tarceva shock

2003
mAB success
Avastin
Erbitux
Velcade

2005
new SMOLS success



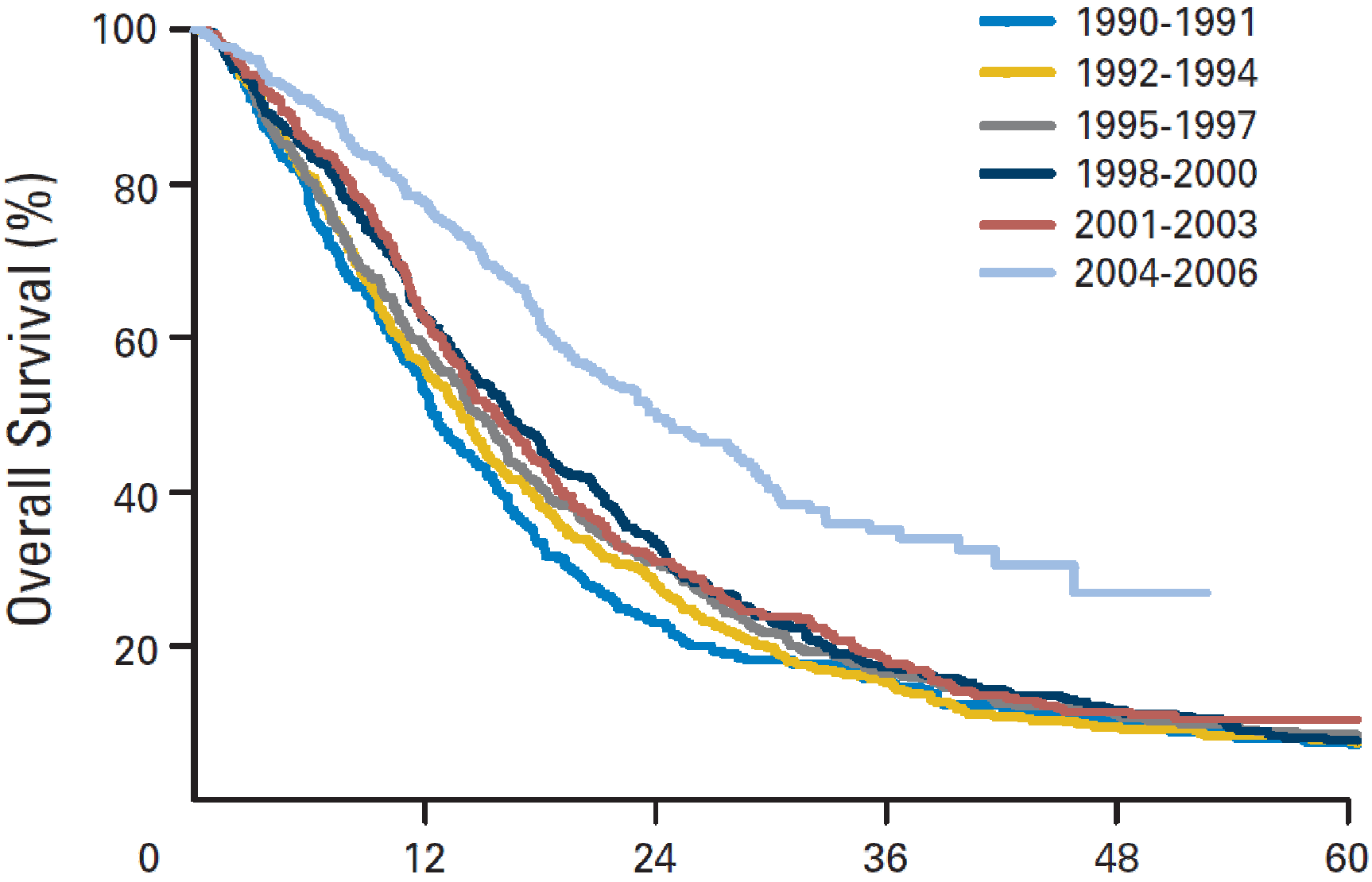
Trends:

- **mABs were mainly successful**
- **some SMOLs failed/toxicity in solid TUs**
- **Dual-or multiple inhibitors had less impact than hoped**
- **Second generations mABs coming**
- **Immuno drugs are coming**
- **Stratified approach is key!**

* FDA approval date

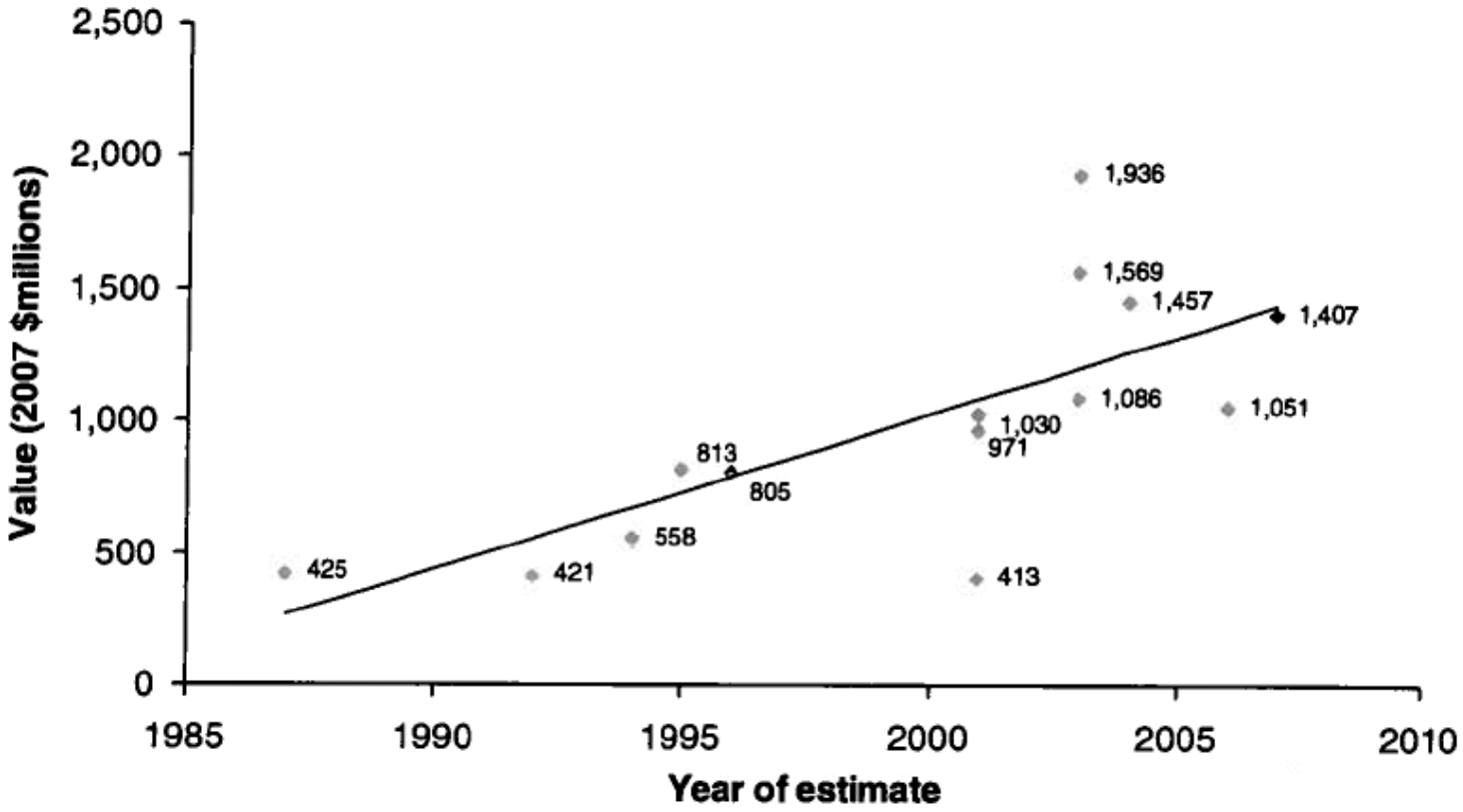
Dr. Wolfgang Wein

Survival with colorectal cancer



Kopetz et al, JCO 2009

Estimated average development costs for a new oncology product is nearing $2 billion



Source: Parexel (2008) and CRA analysis. Inflation rate from inflationdata.com (RPI-U)

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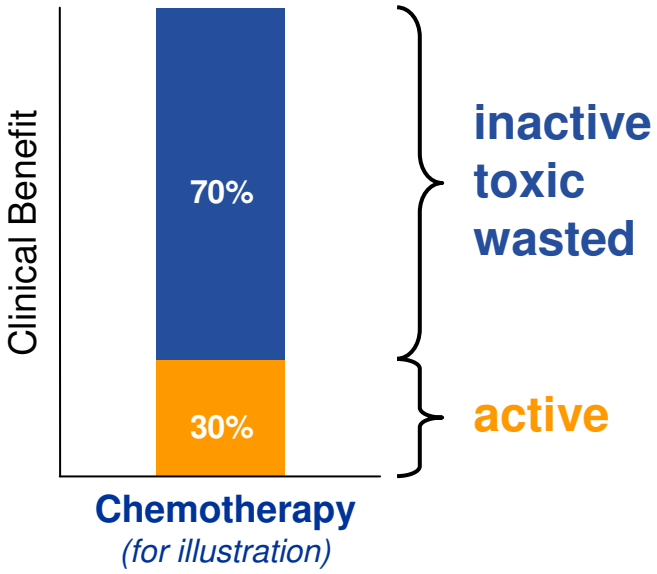
The Dream of Oncology: Identify the Patients who Benefit Most from Chemotherapy!



By testing the KRAS status, we are heading towards smart and economic, tailored treatment in 1st-line mCRC for the first time

At the same time, we offer the patient a much better outcome

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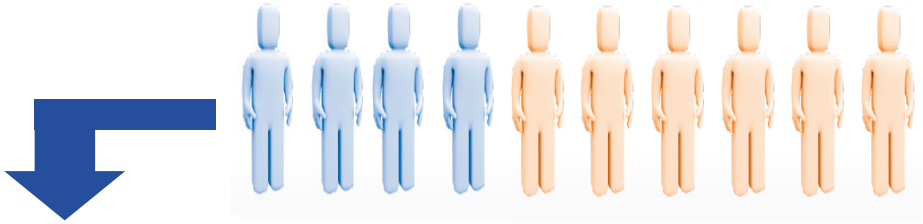
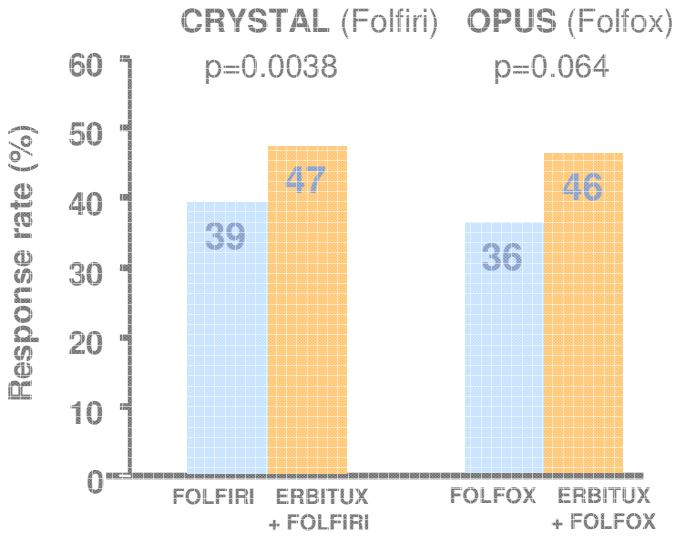
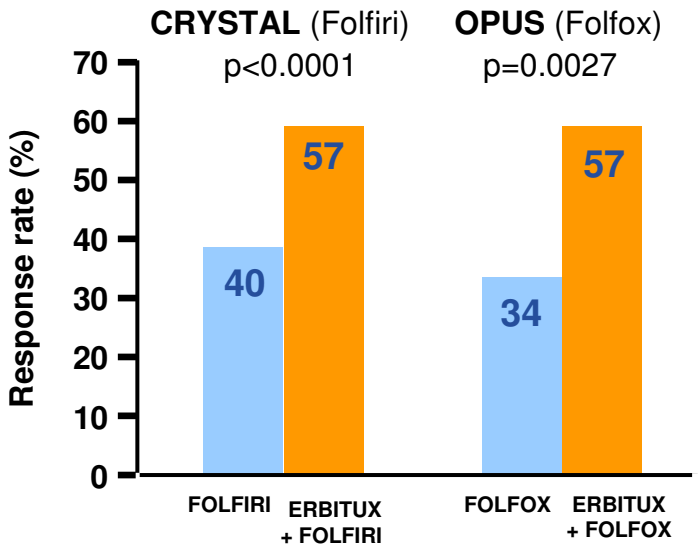
Using KRAS detection to optimize clinical outcome

Personalized treatment is a better approach than one treatment fits all



Identified 60% of patients (KRAS wt) treated with tailored therapy





Van Cutsem E, et al. N Engl J Med 2009;360:1408–1417;
Bokemeyer C, et al. J Clin Oncol 2009;27:663–671; Van Cutsem E, et al . ECCO/ESMO Congress 2009. Abstract No:6077

Biomarkers / Stratified medicine, are the key to successful and economic future of medicines

- Successful examples: Her-2, KRAS mutation testing
- Treatable population per drug will decrease - increasing segmentation and complexity
- The benefit/risk ratio in the defined population improves, the trials might become smaller, but more complex and costly (tumor sample collection, analysis, etc)
- Improved cost/benefit ratio – these drugs become more economic
- Diagnostic tests will add a new level of complexity/dependency. e.g. availability! logistics! costs! validation!
- How will biomarkers work out in combinations of 4–5 drugs? (economics; overlaps of segmentation strata per patient)

The reality: Very few efficacy-related biomarkers in current oncology drug labels for solid tumors implemented…

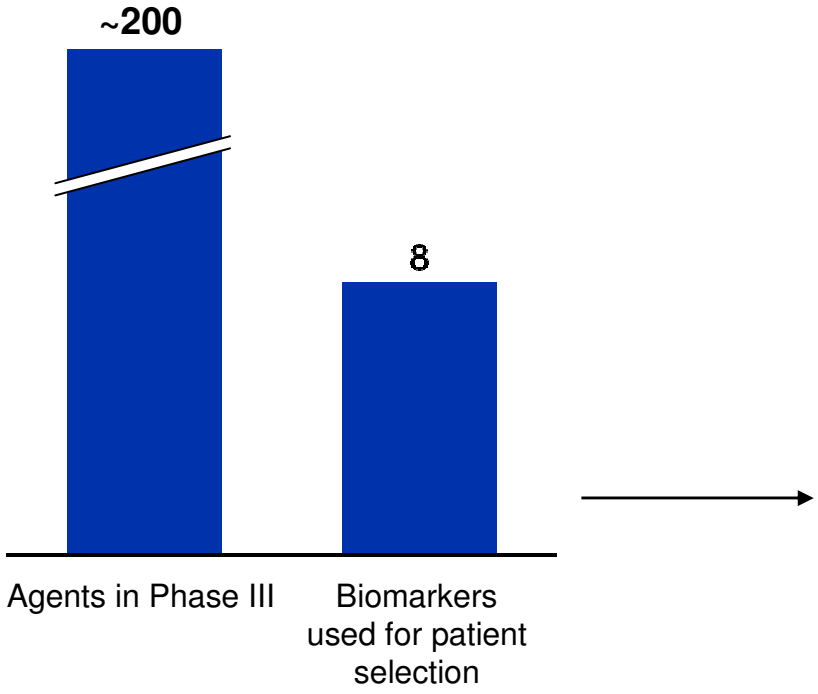
Biomarker	Drug	Indication
KRAS mutation	Cetuximab, Panitumumab	Colorectal cancer
EGFR expression	Cetuximab, Panitumumab	Colorectal cancer
EGFR mutation	Gefitinib	Lung cancer
Her2 over-expression	Trastuzumab, Lapatinib	Her2 over-expressing breast cancer

Source: Merck Serono Biomarker Strategy Team within R&D

Situational analysis 2011

Stratified medicine: Only a small % of agents use a biomarker as an inclusion criteria for the phase III trial

Cancer drugs currently in Phase III development



- Only 4-5% of phase III clinical trials use a biomarker to include/exclude patients. This implies that it is still very difficult to identify and clinically validate a biomarker prospectively.

Patient Inclusion Biomarkers

- PF-02341066 (Pfizer): ALK fusion gene
- Cilengitide (EMD Serono): MGMT methylated
- Letrozole (NCI): BRCA1 or 2
- PLX4032 (Roche/Plexxikon); V600E BRAF mutation
- GSK1572932A (GSK): MAGE A3 gene expression
- Tarceva (Genentech), Iressa (AZ), BIBW 2992 Afatinib (BI):
- EGFR exon19 deletions or exon 21 L858R mutation by the DNA direct PCR sequencing
- Others?

Source: Easton Associate, clinicaltrials.gov, EMD Serono project

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When is a biomarker truly validated?!

Example for illustration

Academia finds new biomarker 2006	more small papers; one other biomarker proposed 2007,	Inclusion into phase III as retrospective endpoint 2008

New biomarker in 2009 -
Is it real?
Predictive?
Prognostic?

Phase III pivotal trial starts in 2005 – reportable in 2008

Start new confirmatory trial?!

Commercial forecast changes dramatically!

Issues:

- A 4-5 year time lag for new findings to be prospectively studied in phase III
- Retrospective analyses are seen as problematic from a statistical / regulatory perspective!
- Some findings from small series turn out to be wrong
- "Wrong" biomarkers once used, are not allowed out of label
- Some markers turn out to be prognostic rather than predictive!

But….

- Very few biomarker guided drugs are on the market in reality
- Currently, there is to no commercial reward or incentive, despite a clearly improved economic profile!
- The market potential is reduced (in our example by 40% of the market)
- No benefits have been offered by any health care system
- Mandatory price cuts or rebates were enforced (e.g. 10% in Germany, 7.5% in Spain, 27.5% in Greece etc) for all drugs irrespective of economic profile
- Conclusion: everybody likes to recommend and talk about biomarkers, but nobody rewards or offers incentives to the pioneers detecting, developing and implementing them!

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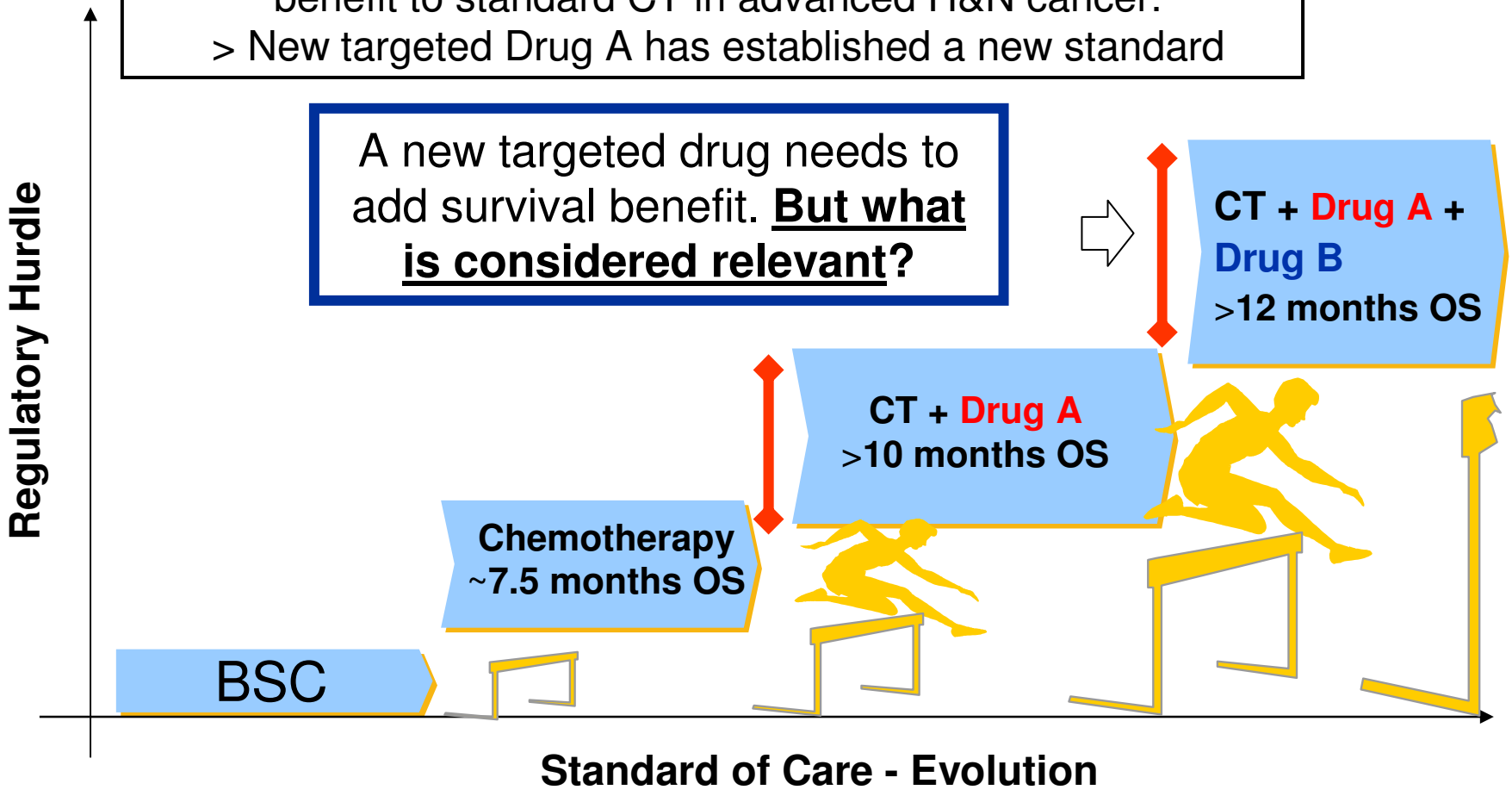
New drugs added to standard regimen: regulatory and clinical hurdles are raised with each new established standard

25 chemotherapy drugs have failed to add survival benefit to standard CT in advanced H&N cancer.
> New targeted Drug A has established a new standard

A new targeted drug needs to add survival benefit. **But what is considered relevant?**



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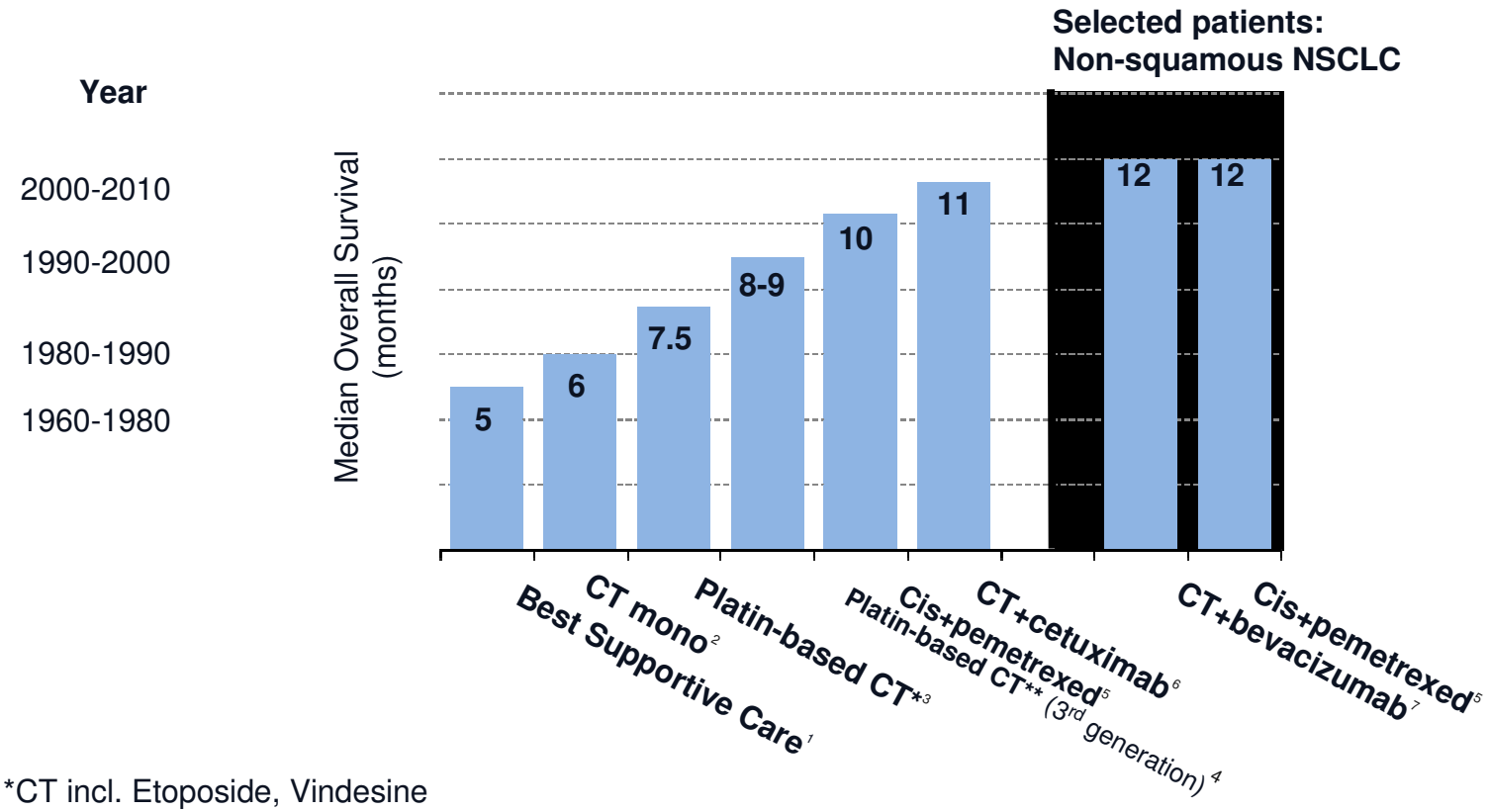
1st line therapy in NSCLC: Incremental advances over the past 50 years



*CT incl. Etoposide, Vindesine
**Gemcitabine, Vinorelbine, Docetaxel, Paclitaxel

1.) Roszkowski K et al LC 2000; 27: 145–57; 12.) Cullen M et al JCO 1999; Cormier Y et al, 1982 Cancer; Ganz PA et al 1989 Cancer; Woods RL et al 1990 BJM; 2.) Rapp E et al 1988 JCO, Cellerino R et al JCO 1991, Cartei G et al JNCI 1993; 3.) NSCLC Collaborative Group. BMJ 1995; Souquet et al Lung cancer 1995, Souquet et al Lancet 1993; 4.) Schiller J.H et al, 2002 NEJM, Ardozzoni A et al JNCI 2007; 5.) Scagliotti GV et al, JCO 2008 ; 6.) Pirker R. et al Lancet 2009 ; 7.) Sandler A et al, NEJM 2006

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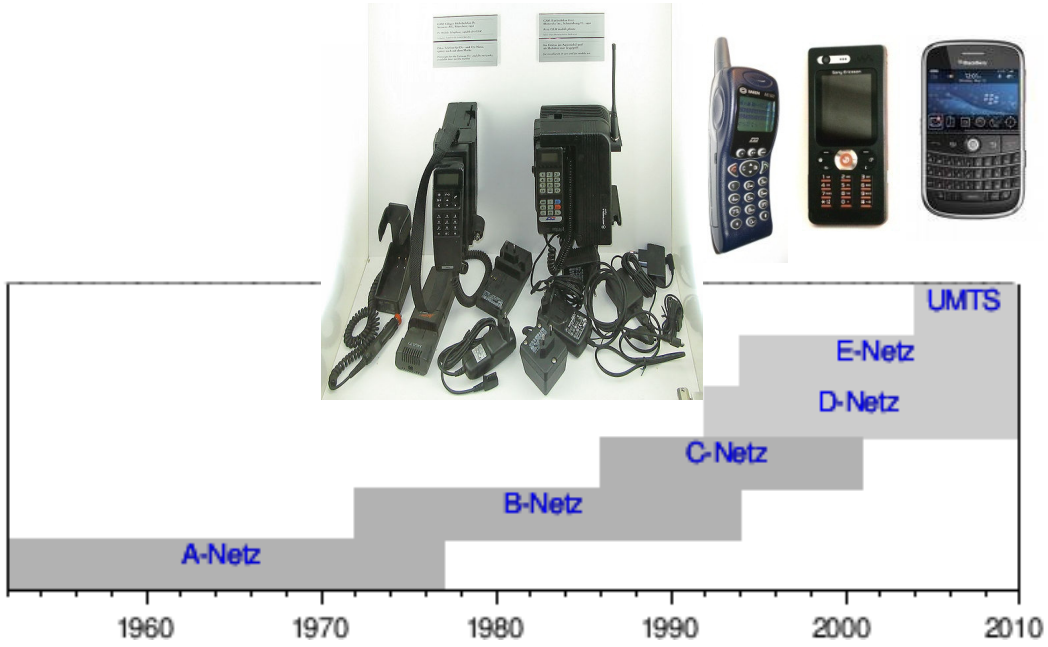
What means progress in oncology? Incremental vs. Quantum leap

Example: development of mobile telecommunication



Chemotherapy	Targeted agents

Incremental benefits could be commercialised laying the basis for quantum leaps!

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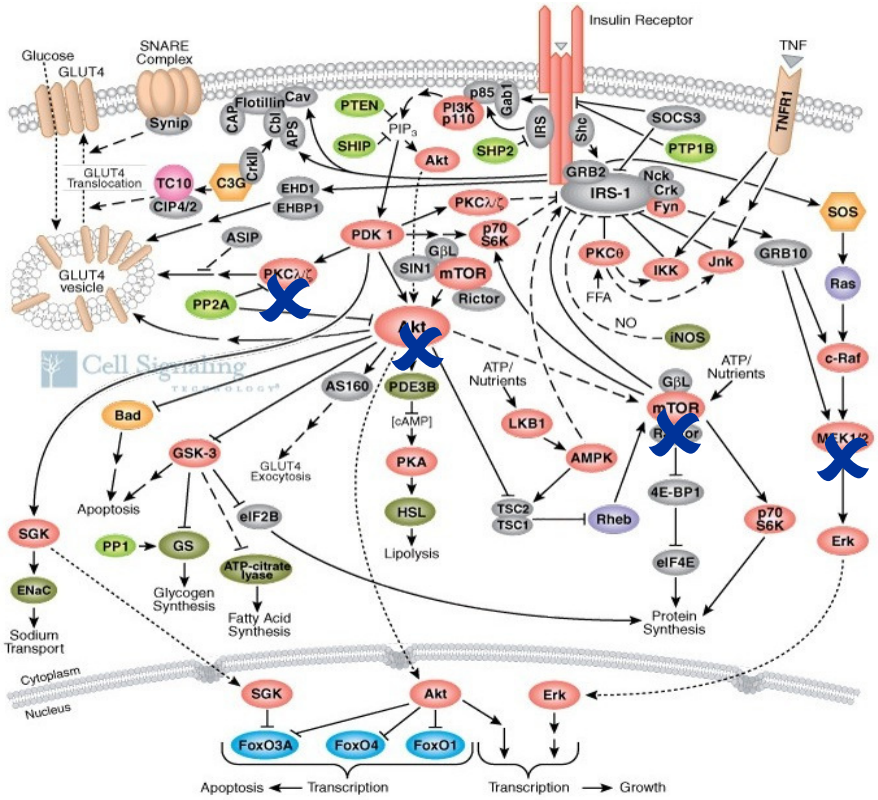
How can we block several pathways, if each drug´s activity is too marginal to get approval?



Possible strategies:

- Combine standard chemo with new pathway drug
- Combine standard chemo with several new pathway drugs
- Combine several new pathway drugs together without chemo (Novel-Novel)
- Combine new pathway drugs plus an environment drug and/or immuno drug and/or other technologies like payloads, toxins, RT
- Dual inhibitors have struggled

Europe seems to be increasing the risk… and decreasing the benefits…

- Very large, highly regulated trials including biomarker sampling and analysis needed – driving cost, where is the limit?
- "Benefit/risk ratio" – what is an approvable improvement? Are we too optimistic, losing touch with reality?
- Why are personalized medicines not receiving incentives in the market?
- Restricted labels becoming more common, how small can a label become to recoup investment?
- Lowering the entry bar for biosimilars might further impact the innovative pharma industry in Europe and support the exodus to the Emerging Markets

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Thank you for your attention!