THE CHALLENGES OF CLINICAL RESEARCH: RISK OF EXTINCTION?

A DRUG COMPANY PERSPECTIVE

Alain HERRERA, MD

Oncology Consultant

Disclosures (1)

Between 1985 and 2008, as an employee, I worked for the following companies :

- Roger Bellon (Rhône Poulenc) where I started the clinical development of oxaliplatin and irinotecan,
- Pierre Fabre where I launched vinorelbine in NSCLC and mBC,
- Chiron where I developed and launched in EU interleukin 2,
- Sanofi where I launched oxaliplatin in EU and US and then docetaxel in Prostate, Gastric and H&N.

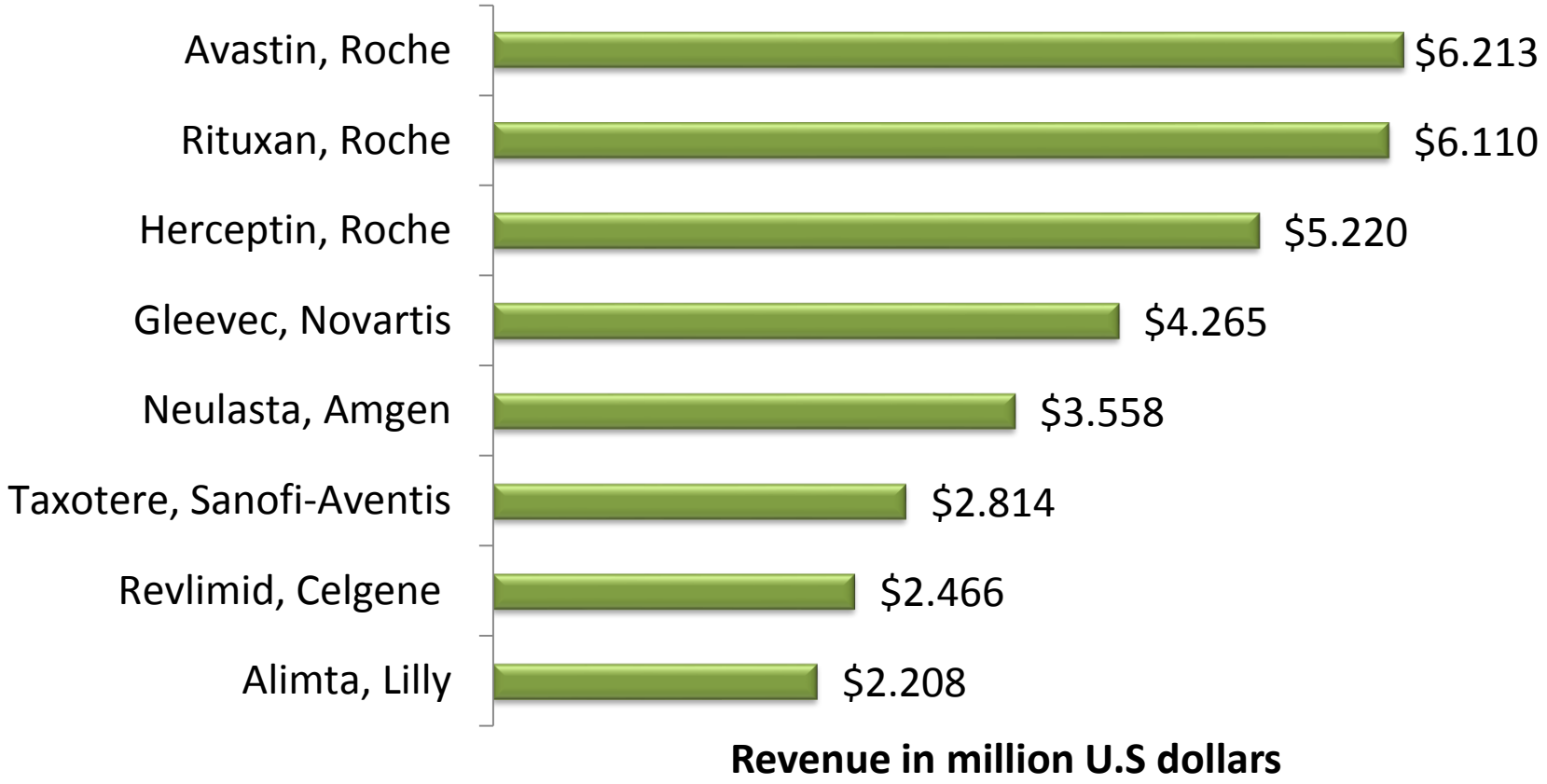
Disclosures (2)

Since 2009, as an independent consultant:

- I had collaboration with more than 50 companies,
- I am currently providing support to more than a dozen of pharmaceutical firms.

The Oncology market today

The top eight best-selling cancer drugs in 2010



Worldwide; 2010

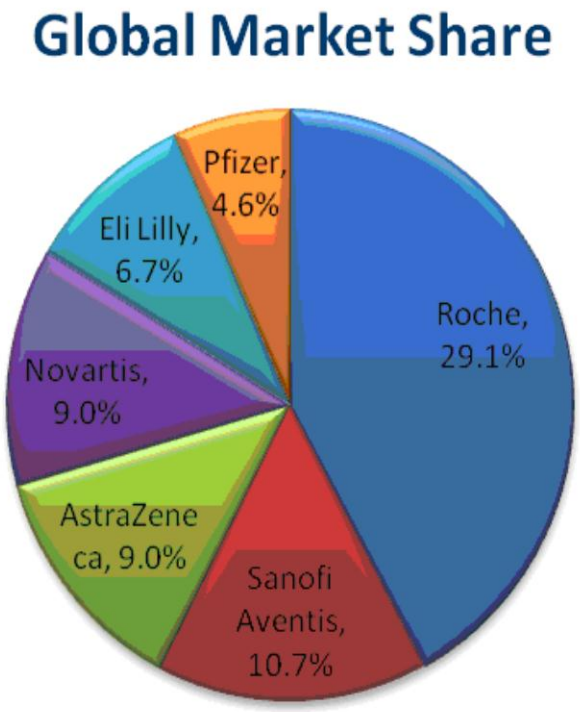
Source: PhRMA, FDA Office of Oncology Drug Products, Annual

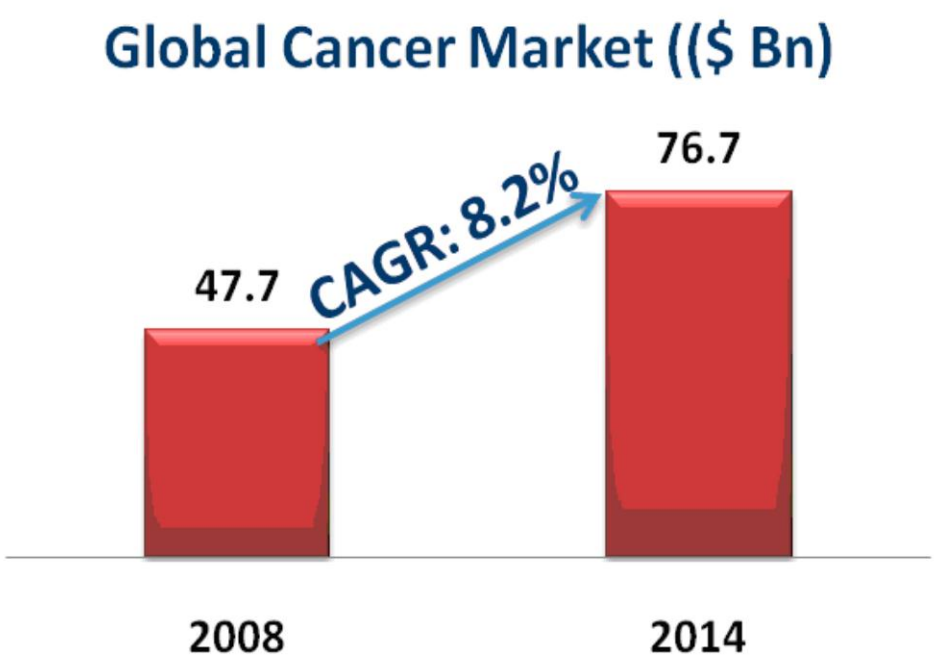
Top ten best-selling drugs in 2010

Trade name	Pharmaceutical company	Therapeutic field	Global Turnover ($ bln)
Lipitor	Pfizer	Cholesterol	11.7
Plavix	Sanofi/Bristol	Anticlotting	9.6
Advair	GlaxoSmithKline	Asthma/COPD	9.0
Remicade	Merck/J&J	Arthritis	7.4
Enbrel	Pfizer/Amgen	Arthritis	7.1
Humira	Abbott	Arthritis	6.8
Avastin	**Roche**	**Cancer**	**6.7**
Rituxan	**Roche**	**Cancer**	**6.1**
Diovan	Novartis	Hypertension	6.0
Crestor	AstraZeneca	Cholesterol	5.8

Source: Thomson Reuters 2010

By 2014, total sales of the global cancer drug market will exceed $ 75 billion

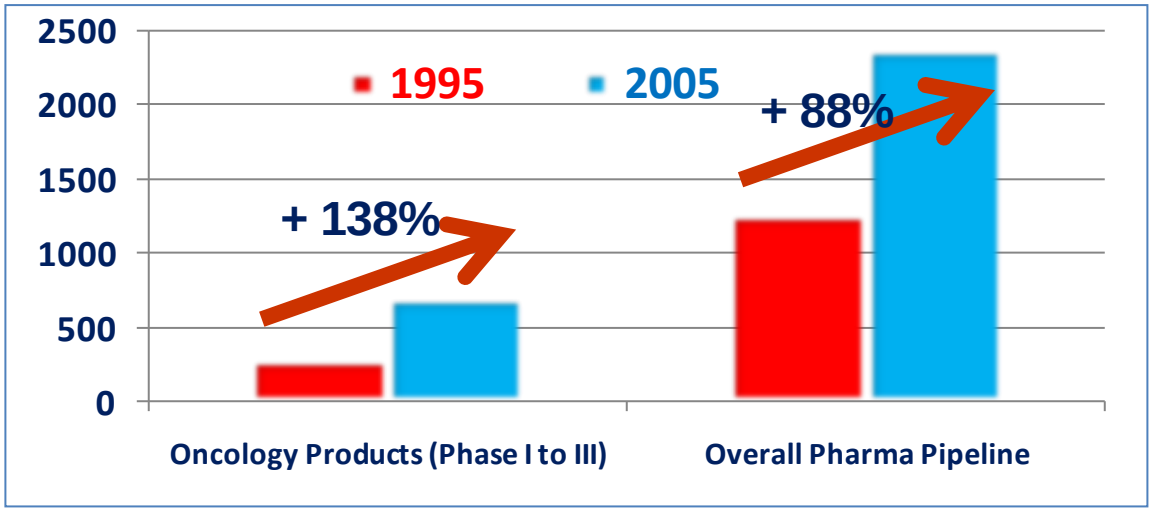




Source: Business insights

The number of anticancer drugs entering into phase 3 is increasing (1)

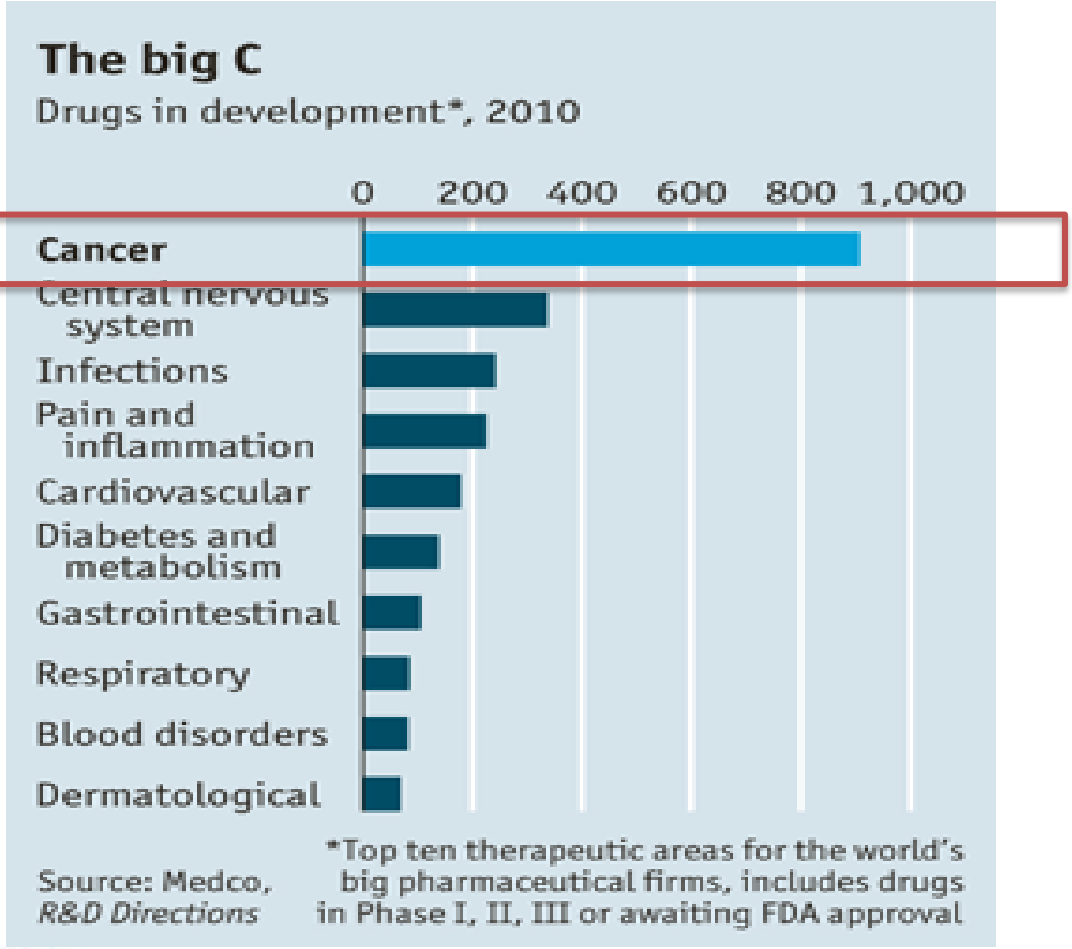
- Between 1995 and 2005, the number of Oncology products under development (phase I to III clinical trials) increased by 138% from 299 to 713



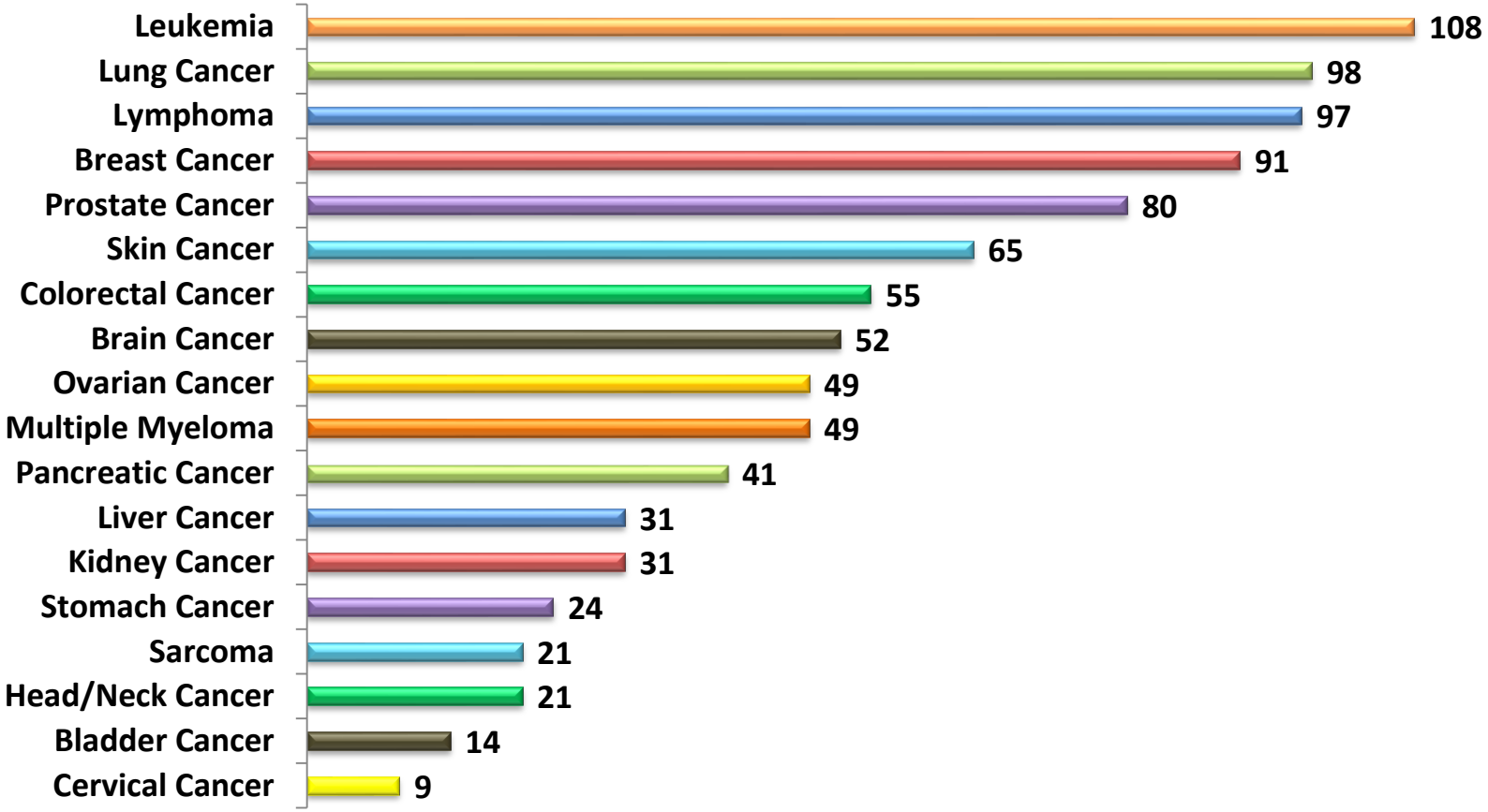
- This increase was approximately 1.5x higher than the overall pharmaceutical pipeline growth which rose by 88% from 1,268 to 2,375 drug candidates

Source: Bionest partners 2006

The number of anticancer drugs in development is increasing (2)



Number of drugs under clinical development in the different tumor types



Source: Castellani J. Medicine in development for cancer, 2011.

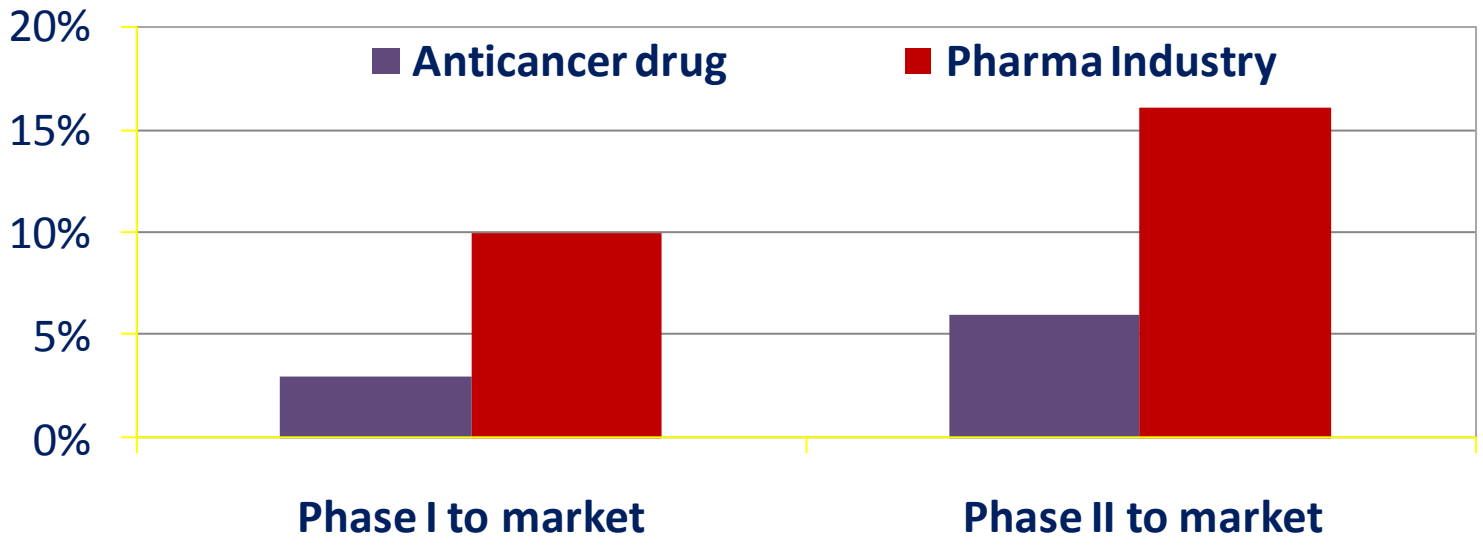
Top ten best-selling drugs in 2014

Trade name	Pharmaceutical company	Therapeutic field	Global Turnover ($ bln)
Avastin	**Roche**	**Cancer**	**8.9**
Humira	Abbott	Arthritis	8.5
Enbrel	Pfizer/Amgen	Arthritis	8.0
Crestor	AstraZeneca	Cholesterol	7.7
Remicade	Merck/J&J	Arthritis	7.6
Rituxan	**Roche**	**Cancer**	**7.4**
Lantus	Sanofi-Aventis	Diabetes	7.1
Advair	GlaxoSmithKline	Asthma/COPD	6.8
Herceptin	**Roche**	**Cancer**	**6.4**
NovoLog	Novo Nordisk	Diabetes	5.7

Source: Thomson Reuters 2010

Does the risk of clinical research extinction really exist ?

An anticancer product entering phase I has 3% chance of getting to the market versus 10% industry average and around 6% when it is entering phase II versus 16% industry average

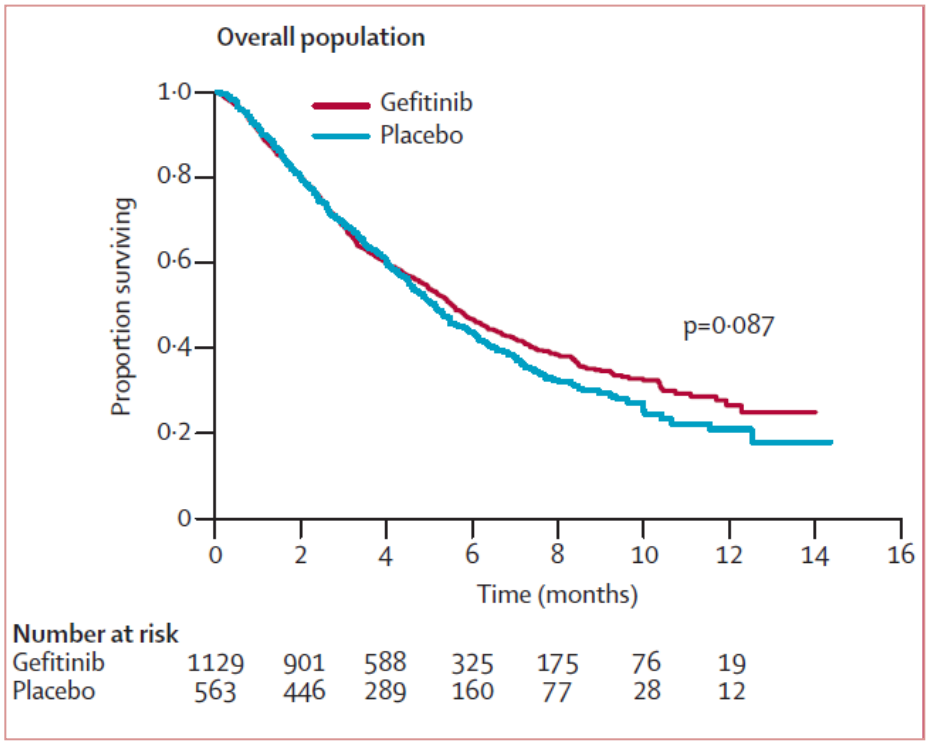


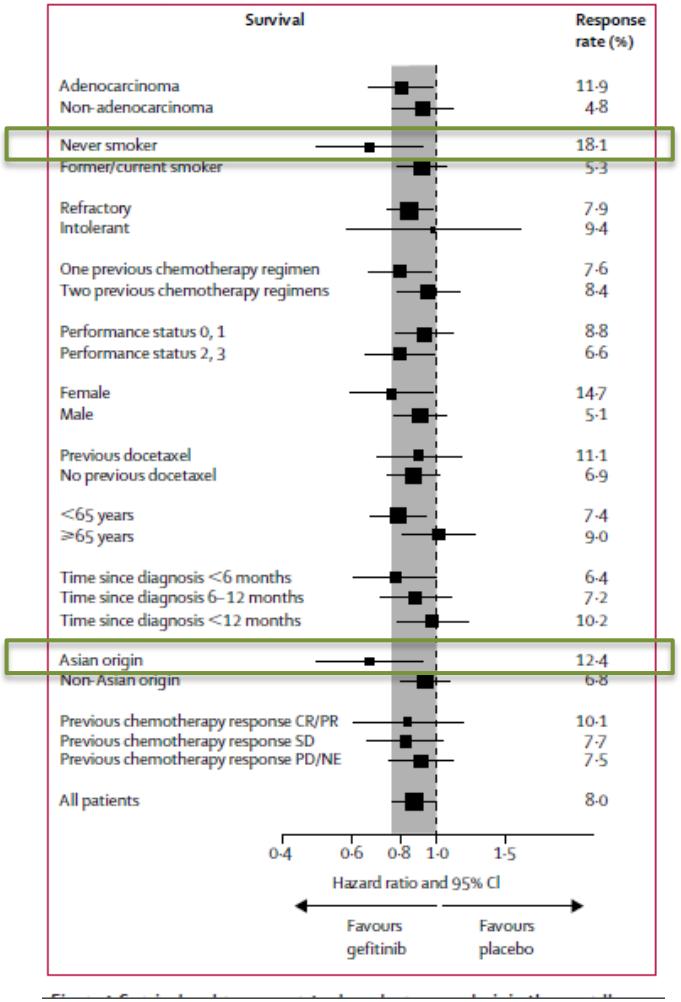
Source : Exane BNP Bionest Partners

Why is it so risky developing anticancer drugs?

Targeted agents = identifying the right population (1)

Gefitinib in previously treated patients with refractory advanced NSCLC

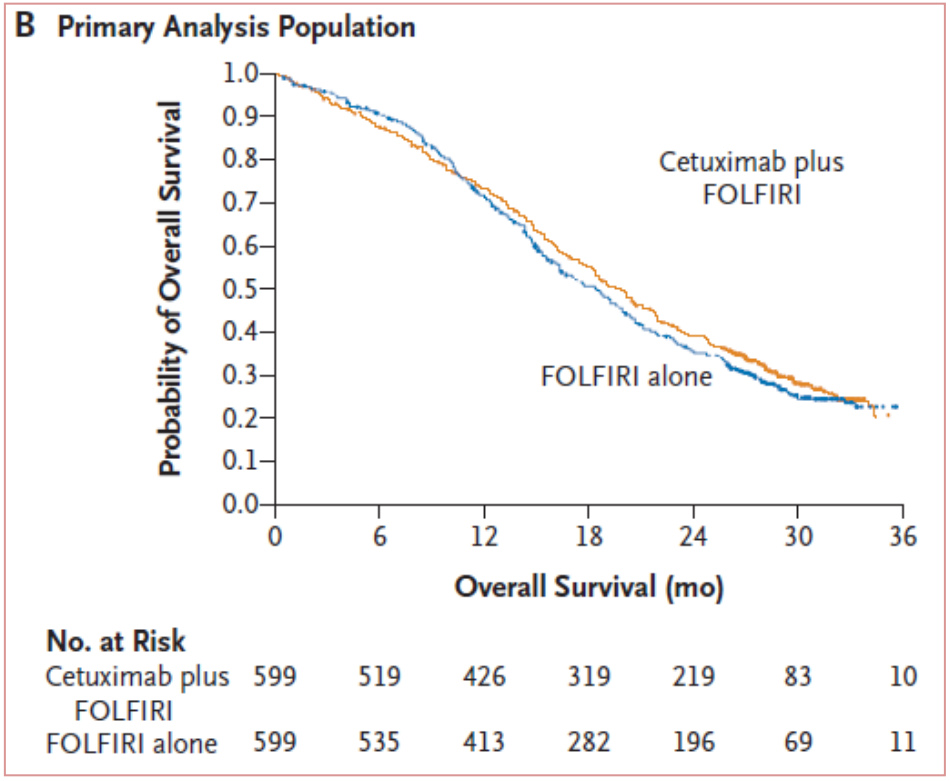


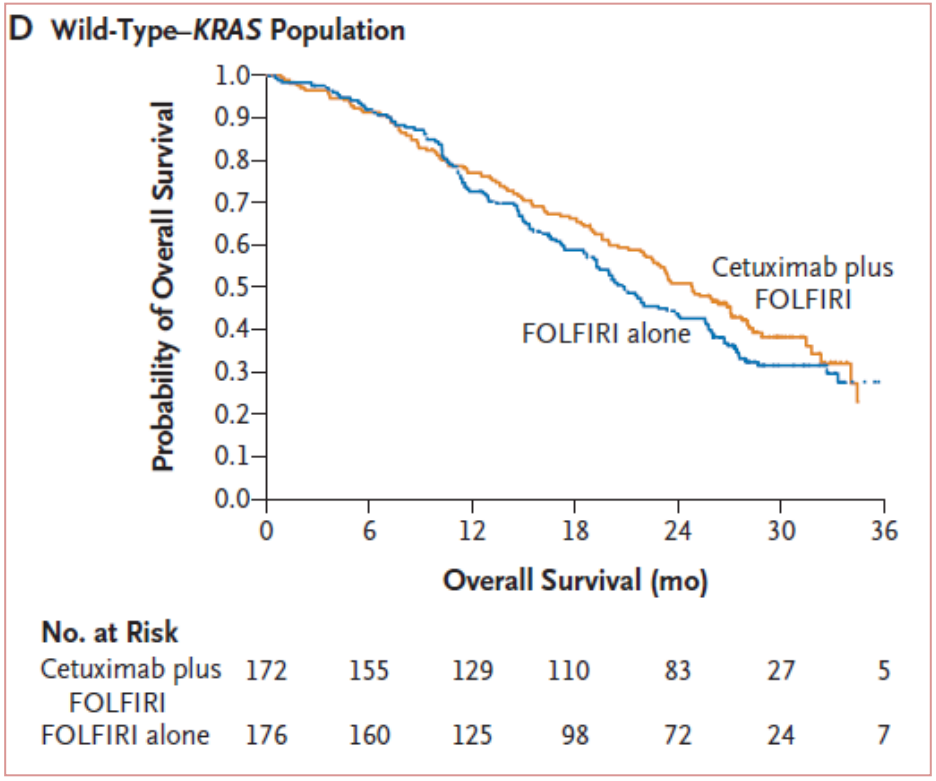


Thatcher N. et al. Lancet 2005; 366: 1527–37

Targeted agents = identifying the right population (2)

Cetuximab and chemotherapy in mCRC





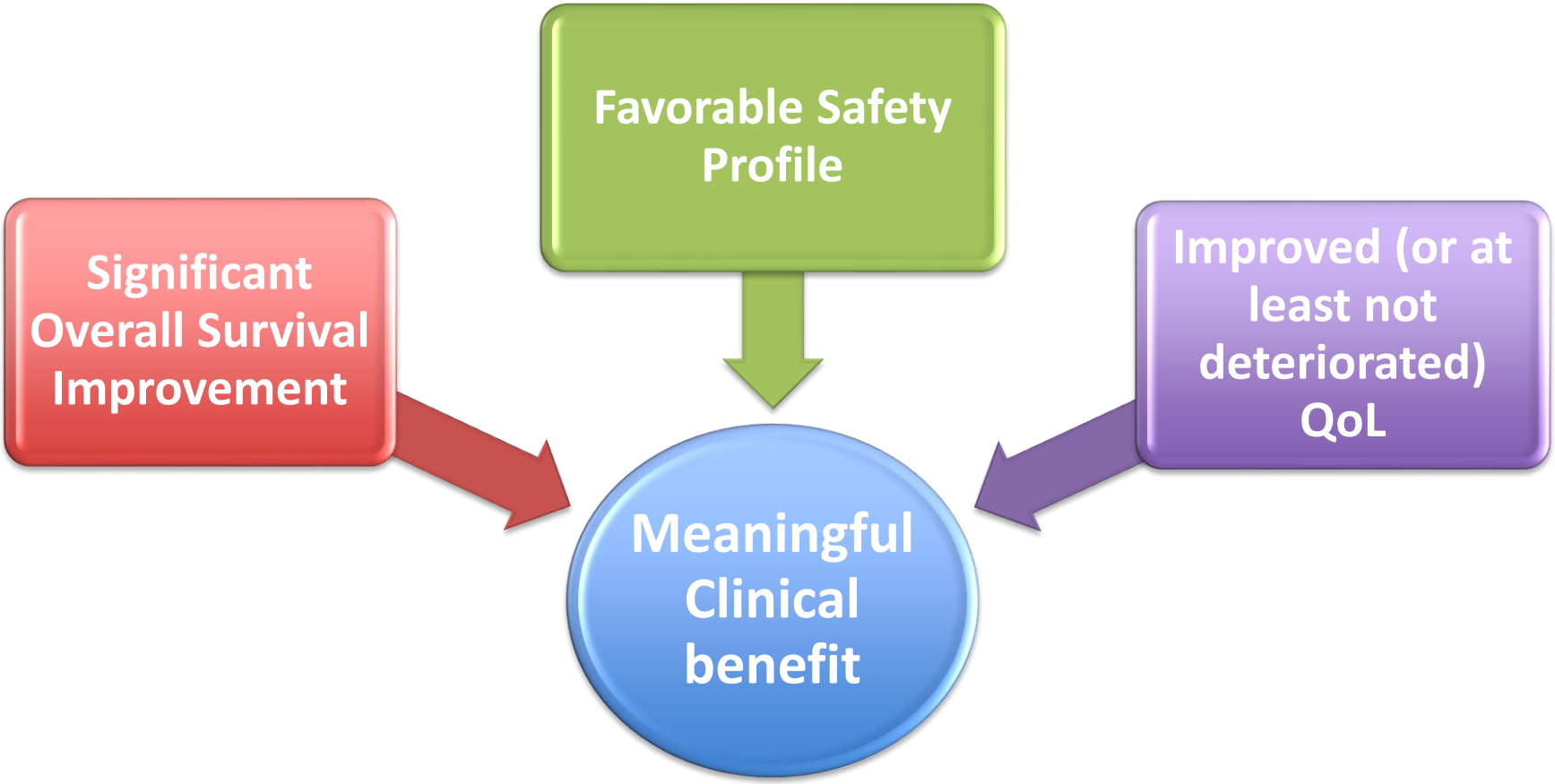
E. Van Cutsem et al. N Engl J Med 2009;360:1408-17

Targeted agents = identifying the right population (3)

% Pts with Target in the Study	Hazard Ratio For Benefit In Patients with Target		
	1.3	**1.5**	**2.0**
10	**32 000**	11 000	3 900
30	**3 600**	1 800	600
50	**1 700**	780	280
70	**900**	400	150

Dancey and Freidlin, Lancet 362:62-64, 2003

Registration = demonstration of a "meaningful clinical benefit"



« Meaningful clinical benefit »

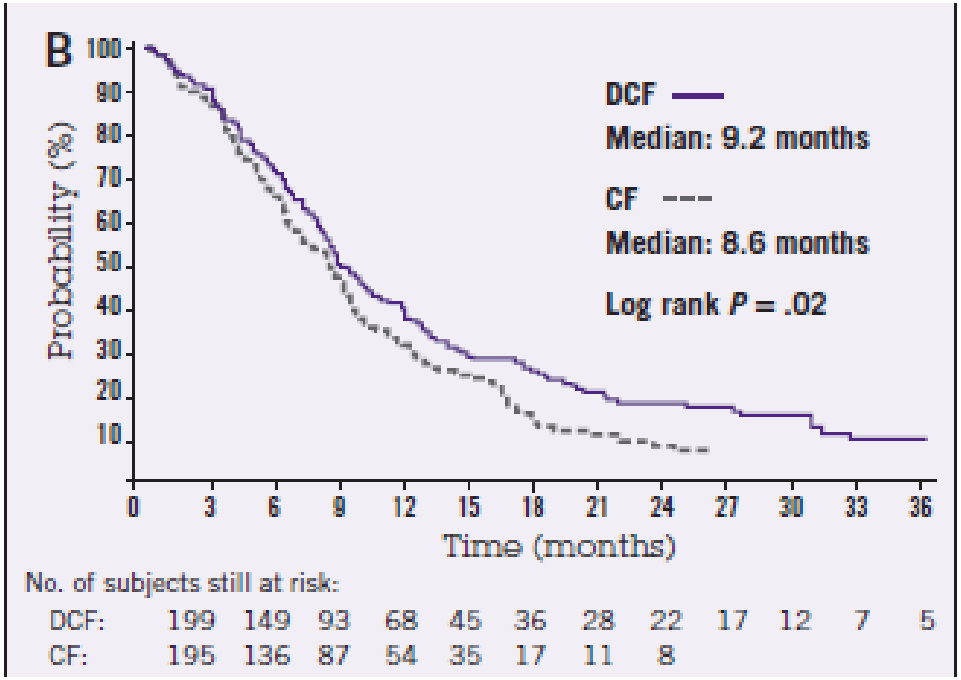
Regulatory Bodies

Physicians

Payors

Patients

The example of docetaxel in AGC



What is the most relevant benefit?

- **Median Overall Survival:**
  DCF 9.2 months vs CF 8.6 months
- **Death Risk Reduction (HR):** 1.29
- **Long Term Survivors (patients alive at 2 year):**
  DCF 18% vs CF 9%

E. Van Cutsem et al. J Clin Oncol, 24 (31): 4991-4997, 2006

How these can negatively impact clinical research?

Phase 1 are today THE crucial step in the clinical development process

- If the right population cannot be identified development will be discontinued,

- If on the opposite the right target is identified registration can be obtained very quickly with a small confirmatory trial targeting the right, even limited, population (i.e. crizotinib in NSCLC),

When the expected clinical benefit seems too low (i.e. less than 30% death risk reduction) pharmaceutical firms will hesitate embarquing in **large risky clinical trials which can allow registration but not reimbursement!**

Targeting is often linked with limited indications compared with cytotoxics:

docetaxel is approved in 12 indications covering 5 different tumor types and this was obtained through several screening and large confirmatory trials,

Can other factors also negatively impact clinical research?

- **“Big Pharma”** are more and more asking for clear clinical PoC before in-licensing new drugs while it is more and more difficult for **“Biotechs”** to find the necessary fundings for performing such trials.

- Clinical trials, primarily translational trials, are becoming more and more expensive and trials implementation is longer and longer.

- In addition, the number of eligible patients to be enrolled in clinical trials is limited and can even be more limited according to target expression.

Conclusion

- The risk exist but is limited,

- Among the measures which can be considered for improving the situation, aligning registration and reimbursement/market access is certainly of paramount importance.