# 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.

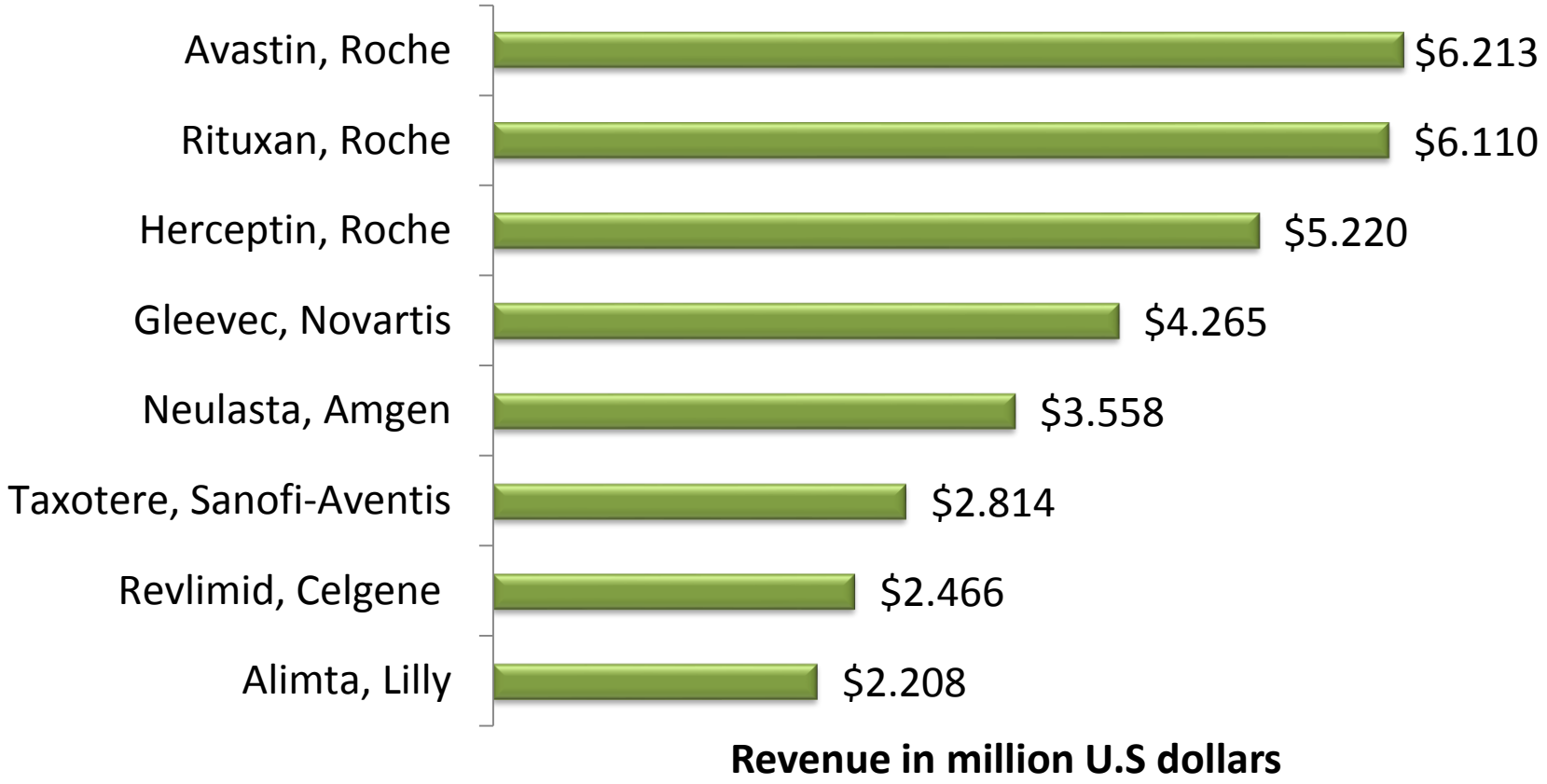
# Disclosures (2)

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

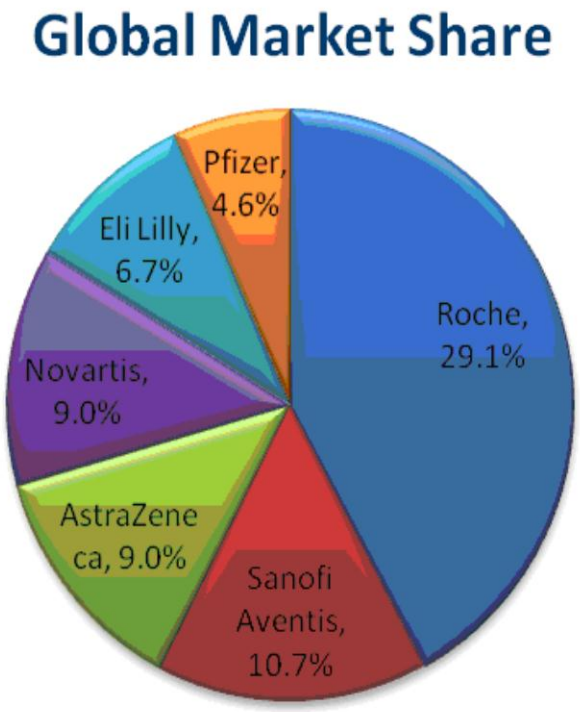
# Top ten best-selling drugs in 2010

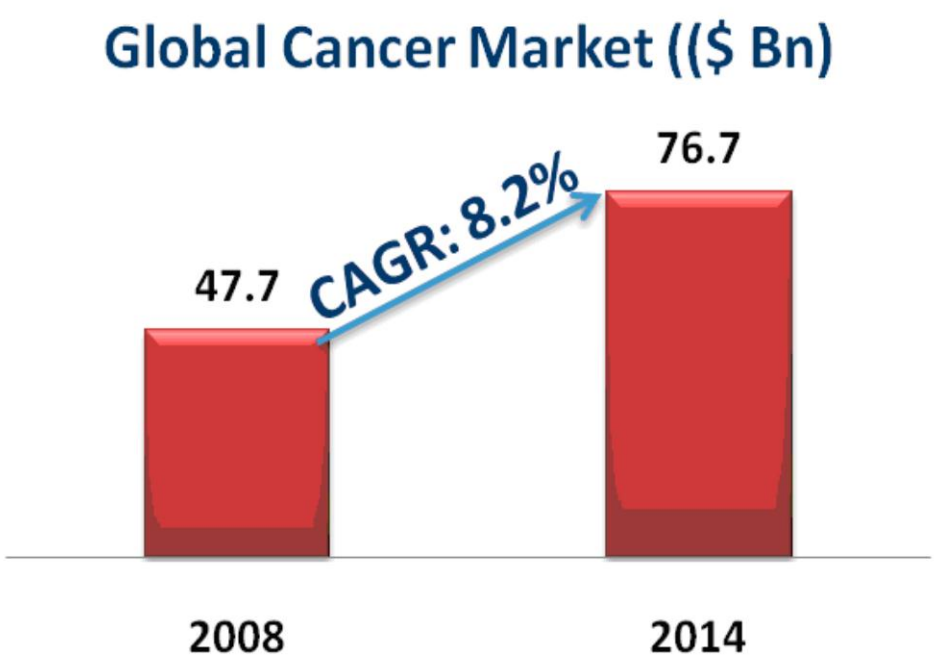
| Trade name | Pharmaceutical company | Therapeutic field | Global Turnover ($ bln) |
|---|---|---|---|
| Lipitor | Pfizer | Cholesterol | 11.7 |
| Plavix | Sanofi/Bristol | Anticlotting | 9.6 |
| Advair | GlaxoSmithKline | Asthma/COPD | 9.0 |
| Remicade | Merck/J&J | Arthritis | 7.4 |
| Enbrel | Pfizer/Amgen | 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

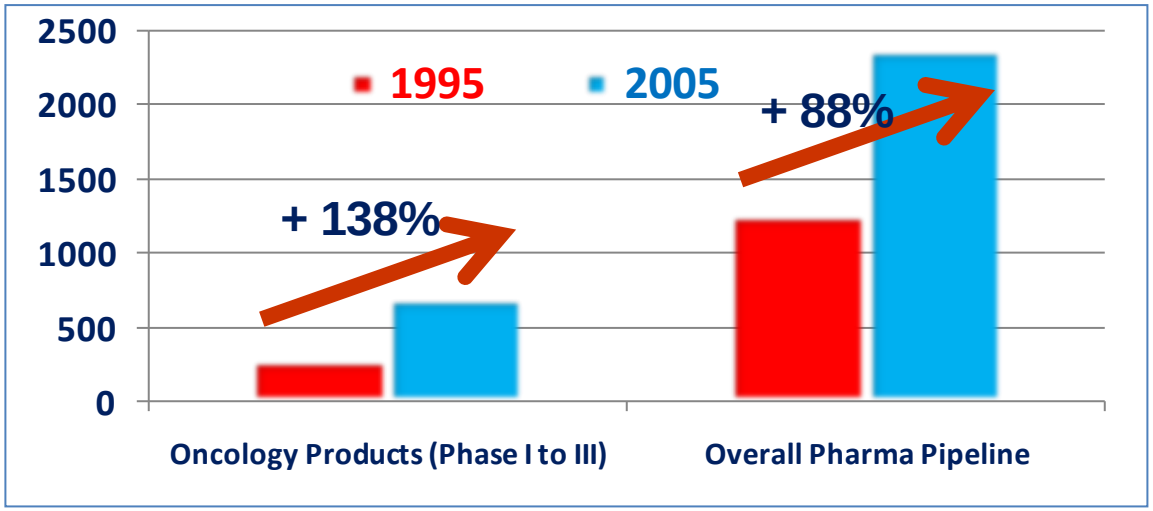



Source: Business insights

# 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

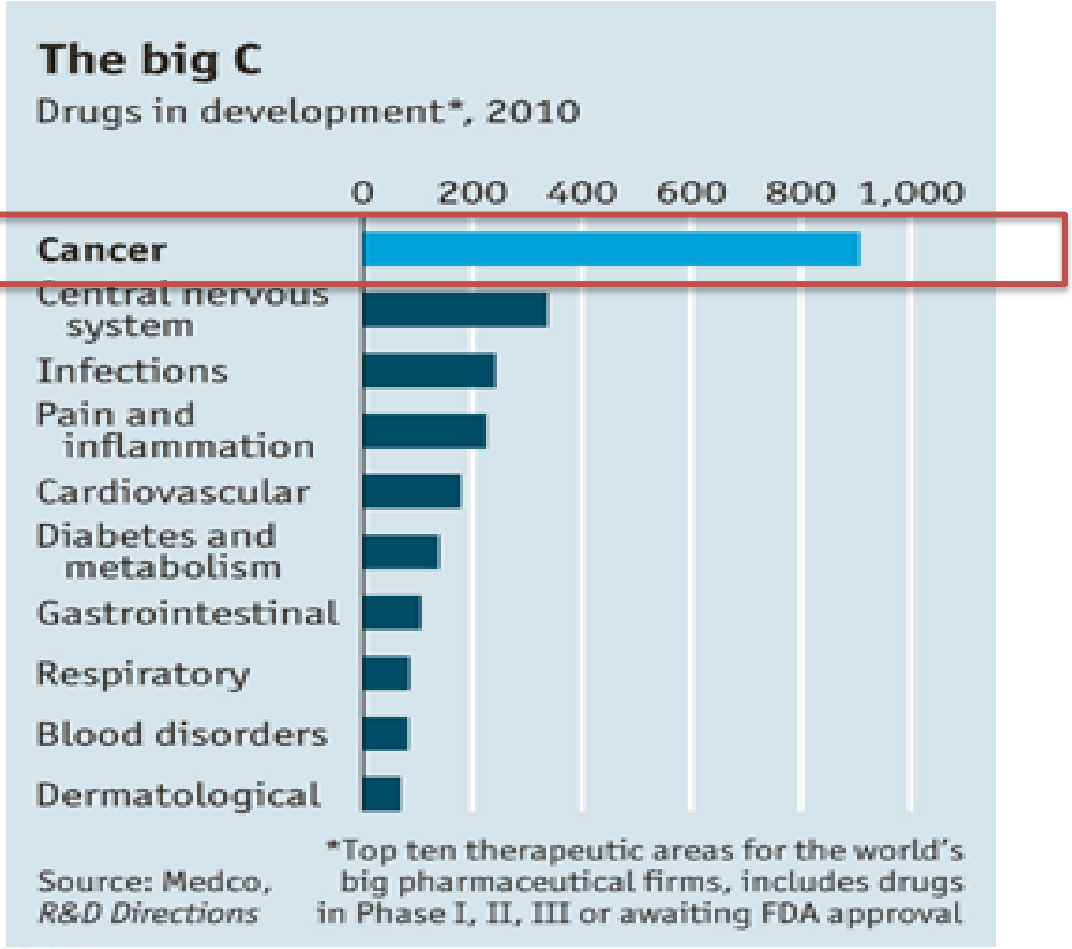



- This increase was approximately 1.5x higher than the overall pharmaceutical pipeline growth which rose by 88% from 1,268 to 2,375 drug candidates

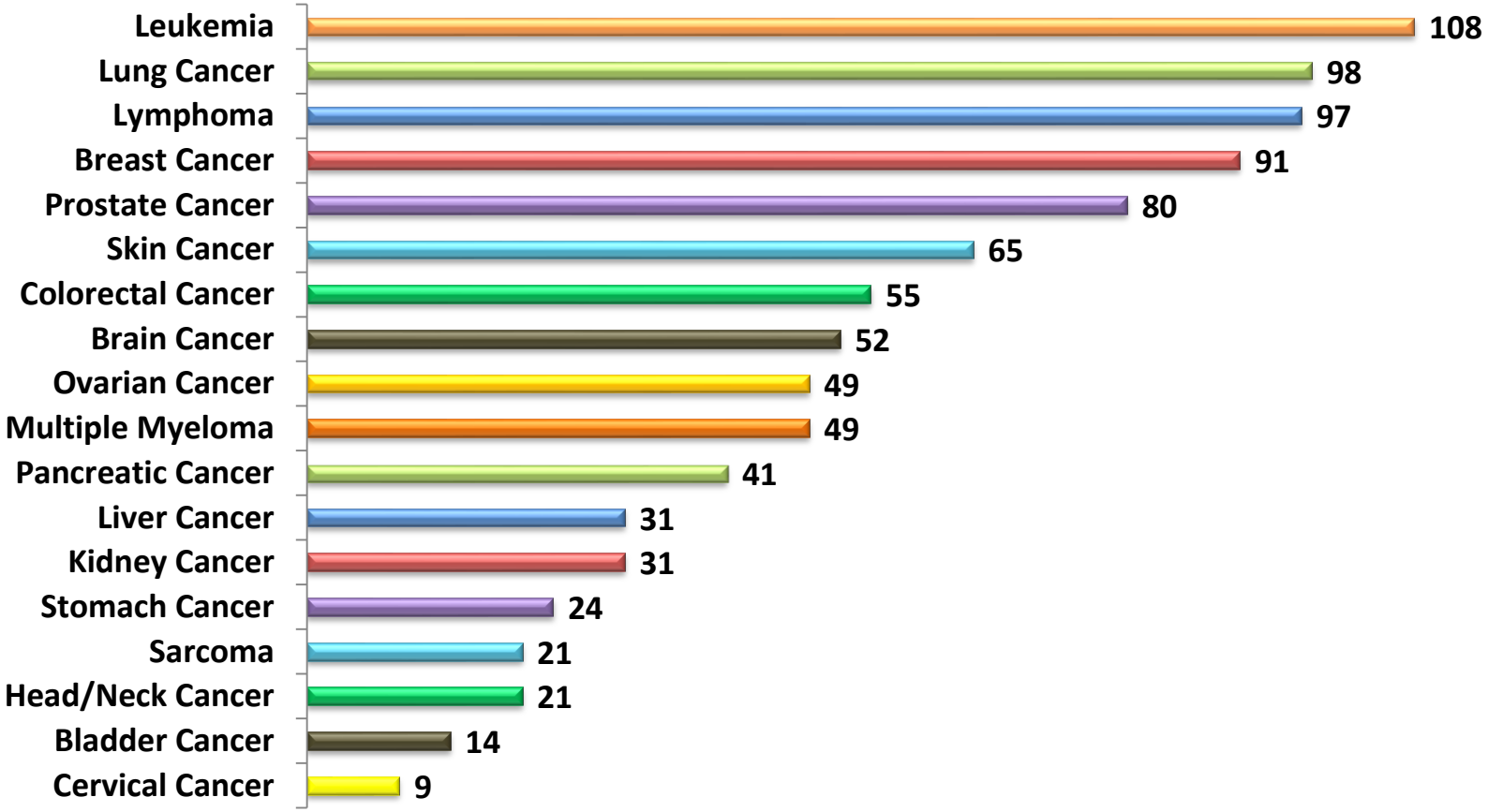


Source: Bionest partners 2006

# 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

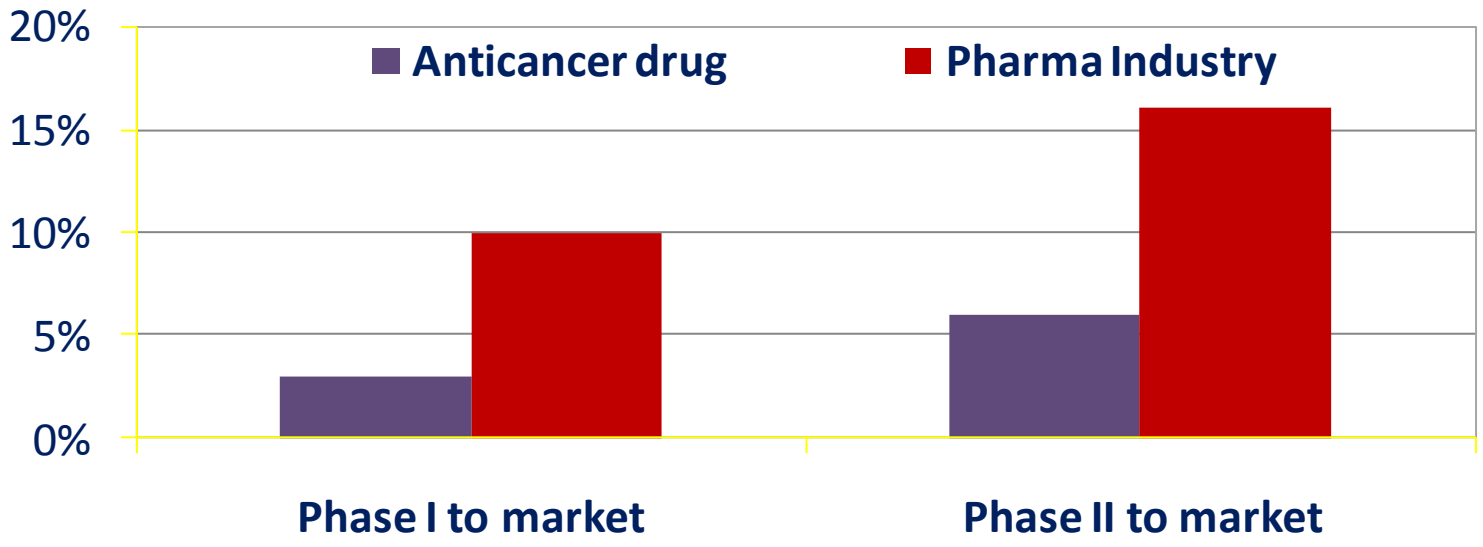
| Trade name | Pharmaceutical company | Therapeutic field | Global Turnover ($ bln) |
|---|---|---|---|
| **Avastin** | **Roche** | **Cancer** | **8.9** |
| Humira | Abbott | Arthritis | 8.5 |
| Enbrel | Pfizer/Amgen | Arthritis | 8.0 |
| Crestor | AstraZeneca | Cholesterol | 7.7 |
| Remicade | Merck/J&J | 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



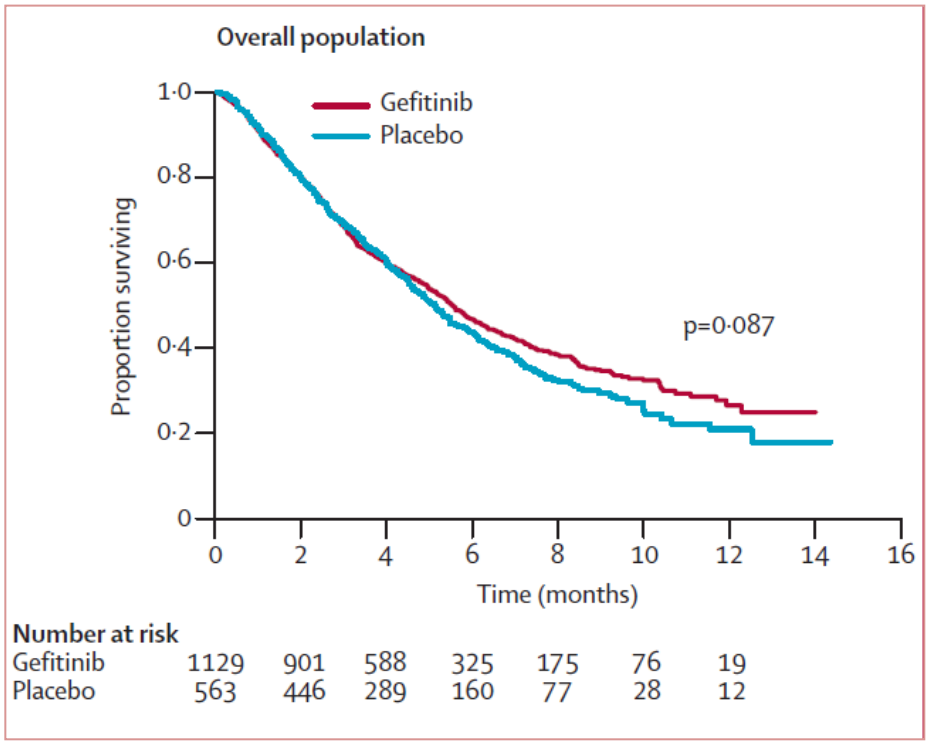


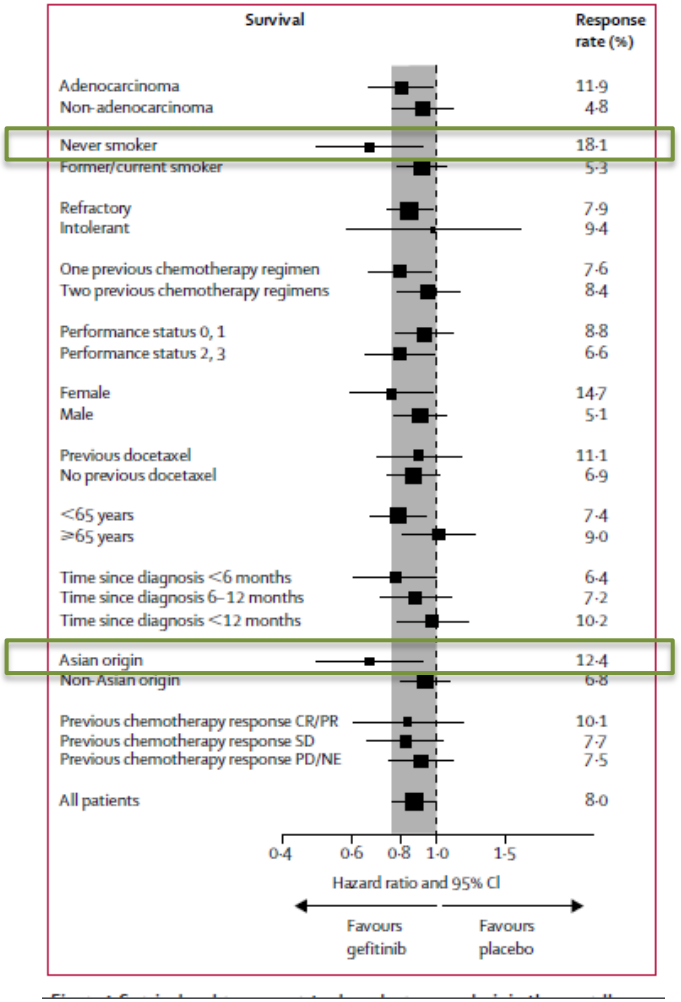

Source : Exane BNP Bionest Partners

# Why is it so risky developing anticancer drugs?

# Targeted agents = identifying the right population (1)

**Gefitinib in previously treated patients with refractory advanced NSCLC**

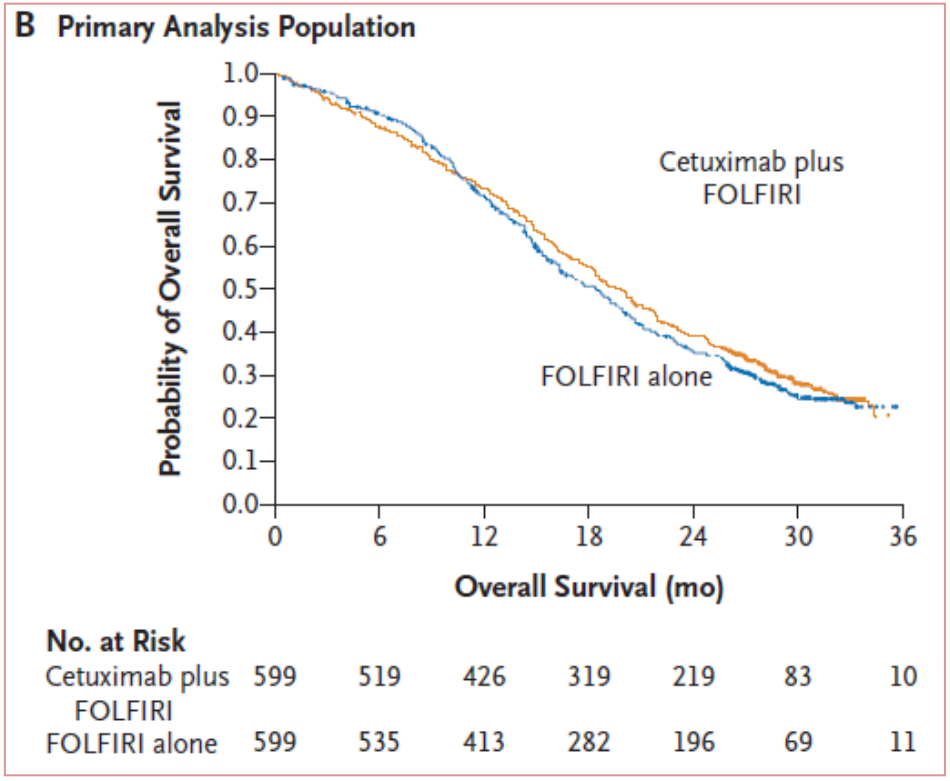


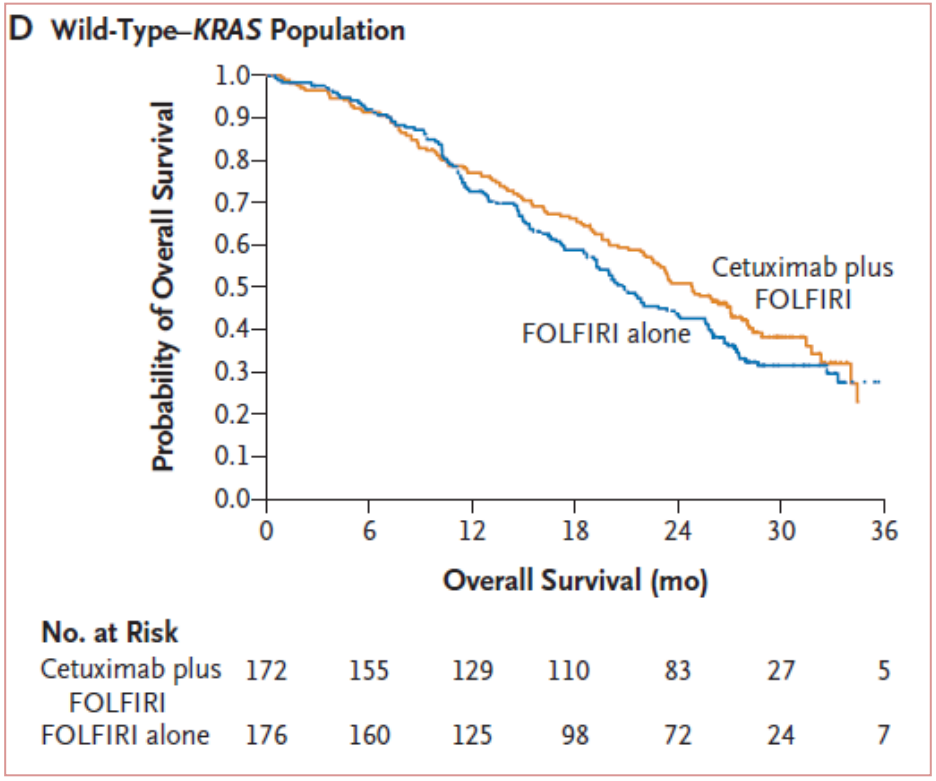




Thatcher N. et al. Lancet 2005; 366: 1527–37

# Targeted agents = identifying the right population (2)

**Cetuximab and chemotherapy in mCRC**





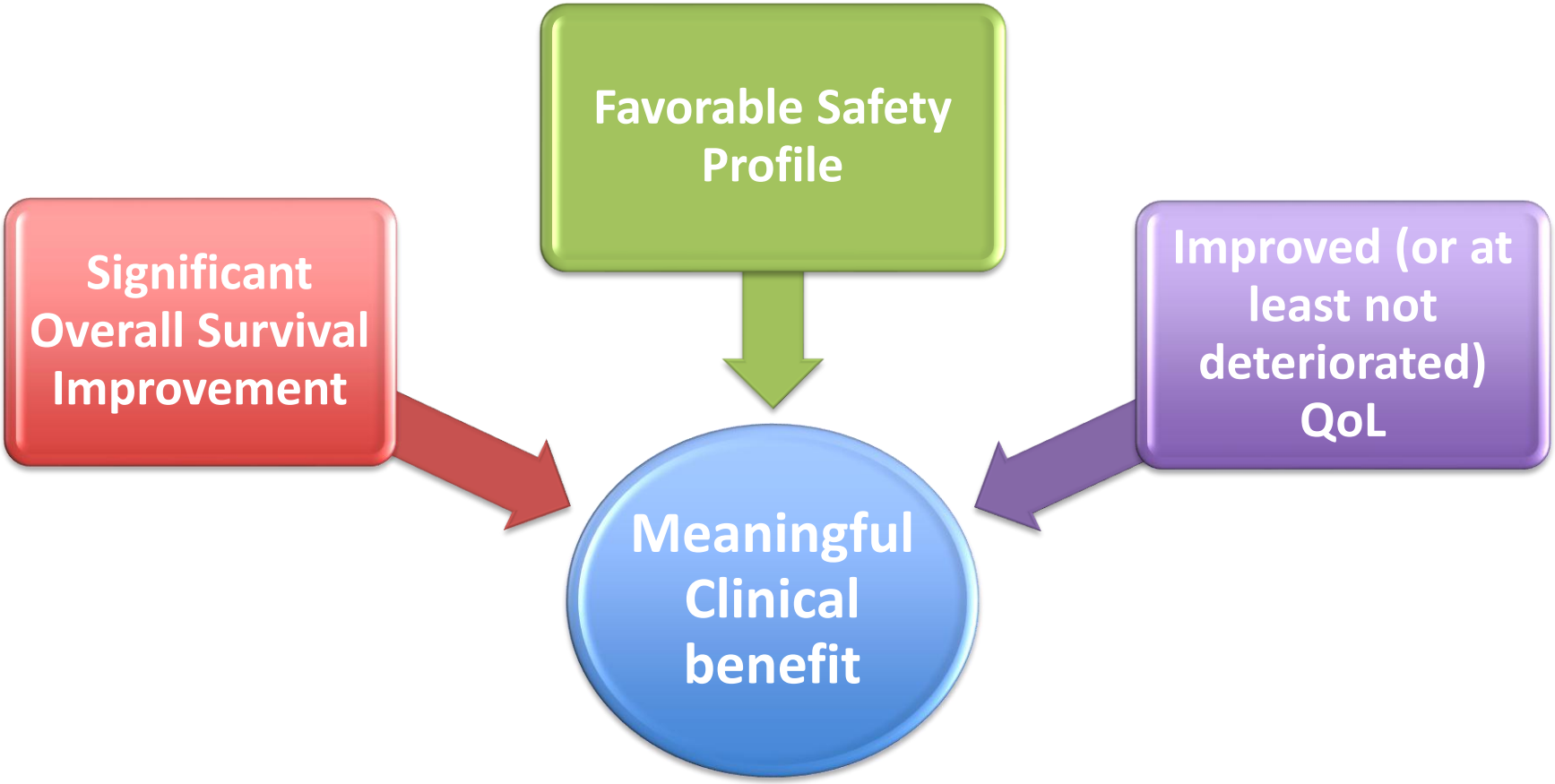

E. Van Cutsem et al. N Engl J Med 2009;360:1408-17

# 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 »

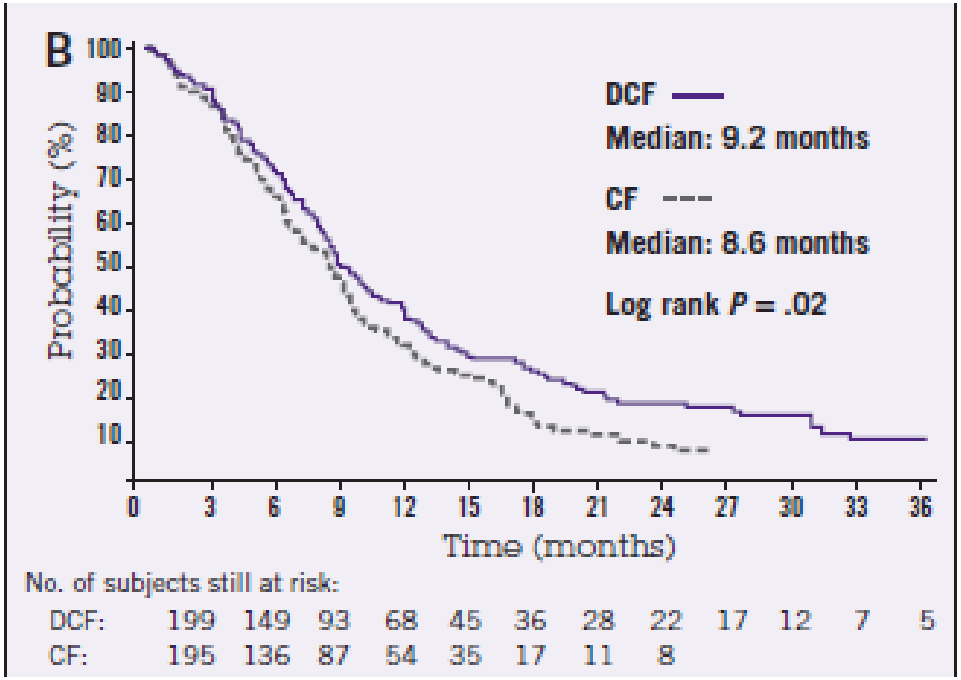
Regulatory Bodies

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.