# Challenges of Collaboration between Academia and Industry

## *Early Drug Development of Targeted Therapies in NSCLC*

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# Financial disclosure

- **I have no financial disclosure to decline for this presentation**

## What is the issue?

**An academic trial** is designed to evaluate (Phase I/II) and compare (Phase III) a drug, a drug combination or a therapeutic modality with existing standard treatments in order to improve the survival of a predefined population

**An industry-driven study** is mainly focused on the activity of a drug or a drug combination on a predefined disease in order to get a registration or promote its experimental drug

An **academic-driven** study will mainly evaluate the overall effect of a treatment on patients life (OS) while an industry-driven study will focus on the activity of a drug on the disease (PFS)

# General introduction and background

**How has the field of drug use, manufacture and development evolved over the decades?**

**To understand the current landscape of all aspects of medicine regulation we need to know how the story has developed**

**To understand how to build a registration-driven study, we need to know the rules**

**To be the patients' defenders, we need to evaluate the impact of a protocol constraints for the patients**

**This is not essentially 'new' but has really come into its own in the past few decades**

# Regulatory mission of FDA

## To protect and promote public health

**Quality, safety and efficacy**

**Protection for users of medicines**

**Adequate and appropriate information for patients and physicians**

# Drivers for regulation in the 20th century

**Food and Drug Act 1906 in the US, driven fundamentally by concerns in food industry**

**Harrisson Act in 1914 (narcotics)**

**Elixir sulfanilamide (treatment of streptococcal infections) 1937**

**Thalidomide 1961**

**This followed on from a public health mission that began in 1862**

# And in EU ?

**EEC Directive 65/65/EEC – law, regulation and administrative action relating to medicinal products**

**Harmonization took 10 years to develop**

**Two directives in 1975 (75/318/EEC and 75/319/EEC)**

**87/22/EEC – introduced a centralized procedure and paved the way for Council Regulation (EEC/2309/93 EMEA) and re-established CHMP to formulate opinion for the agency**

EEC = European Economic Community Clinical Trial Directive; EMA = European MedicinesAgency; CHMP = Committee for Medicinal Products for Human Use.

# Harmonization

**The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is unique in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration**

**ICH = International Conference of Harmonization.**

# Licensing approval scenarios

## Regular approval on completion of Phase III clinical studies

Full data package with sufficient data to demonstrate

- Safety and efficacy
- Clinical benefit (OS, PFS)

## Accelerated approval

Intended to make promising products for life-threatening diseases available on the basis of preliminary evidence prior to formal demonstration of patient benefit

Approval based on a surrogate endpoint

Considered provisional approval with a written commitment to complete clinical studies

# EMA versus FDA: One dossier for each new chemical entity

- EMA
  - One complete dossier = 100,000 pages for a clinical trail report of 87,000 pages = summaries, summary of product characteristics, ERA and references (1200)
  - 241 volumes
  - 203 DVDs
  - Paper: 2173 volumes
- FDA
  - **One complete dossier = 500,000 pages**
- Six copies (approximately 3 tons of paper)

# Considerations for oncology drug approval: Basic principles

**Does it work?**

**Is it safe?**

- **Robust scientific evidence required**
- **Views of FDA and EMA may be different**
- **Longer survival**
- **Improved QoL**
- **Safety – safer than alternatives**
- **Benefit must outweigh risk**

PRO=patient reported outcomes.

# Clinical trial endpoint selection in last two decades

## Strict legal requirements to demonstrate benefit

- Randomized controlled trials (how many are necessary?)
- Primary endpoint: Valid and reliable measure that provides the most clinically relevant and convincing evidence
- Wrong design or lack of efficacy are the most important reasons for rejection

## The commonly used endpoints are based on

- Survival OS then PFS
- Tumor response
- Symptom assessment
- Toxicity

OS = overall survival; PFS = progression-free survival.

# Clinical trial endpoint selection in last two decades

**OS: Historically viewed as the most effective way, as it addresses biology of tumor and the natural history of the disease.** ***It is patient-oriented***

**PFS: Progression is associated with tumor growth, assesses tumor shrinkage and stabilization of disease.** ***It is disease-oriented***

# Future trends

- PFS is proving more challenging to employ as a regulatory endpoint
  - However, it will continue to have a future potential role in oncology drug registration if rigorous acceptance criteria and standards are met
- There will be increasing regulatory pressure to link or associate PFS benefits with other clinical trial outcomes that show direct clinical benefit (e.g. QoL benefits, disease-related symptom benefits, OS positive trends)
  - PFS may have its best future applications in symptomatic disease settings and/or where delay in disease progression correlates with delay in symptom onset
  - Benefit of delay of progression may be also measured by assessing QoL benefits pre- versus post-progression, independent of study arm

# Biomarkers

**Predictive biomarkers do not serve as primary endpoints for drug approval**

**Further research is required to establish the validity of available tests and determine which biomarkers may predict clinical benefit**

**May serve as elements of a composite endpoint in the future**

# Companion diagnostics

**More and more targeted agents are developed in a bio-selected population**

**This selection requires specific tests that may be of equivocal interpretation**

**For more and more targeted agents, a companion diagnostics may be required in order to clearly identify the selected population**

**Whether the companion diagnostics should be developed simultaneously with the agent or independently remains an open question**

# Comments about registration process and industry-driven trials

**Change is needed in the regulatory environment in the field of oncology**

**Paradigm shift from public health to more personalized medicine is required in regulatory perspective**

**Clinical community has a key role to play to effect change**

# Academic trials

**These trials are supposed to be done independently of industry (no conflict of interest)**

**They are supposed to largely contribute to national and international guidelines**

**They establish the therapeutic paradigms and the state of the art for defined populations of cancer patients**

# In an ideal World…

**Industry develops new drugs**

**Academy uses these drugs which are included in new protocols in combination with other agents and other treatment modalities simultaneously or sequentially**

**Once a drug is on the market, Academy should take the hand in order to optimize its use**

# In the real World…

**Industry develops new drugs**

**Industry designs/sponsors/controls most phase III trials**

**Industry finances most translational research programs**

**Industry establishes the dose, schedule and treatment duration**

**Why ?**

**Just because Academy does not do it !**

**The lack of financial support is almost always the good excuse. The lack of creative ideas is in fact the real problem**

# In the real World…

**What would you think if a company owning an extracorporeal circulation device was claiming that EEC is the gold standard for T4 Lung Cancer thanks to a randomized study entirely designed, led and analysed by it and make it the recommended treatment in official guidelines?**

**What would you think if Varian was establishing protontherapy as the new standard for locally advanced Lung carcinoma thanks to a randomized study entirely designed and analyzed by the company ?**

# In the real World…

**Would you agree that all your publications related to drugs and sponsored by industry (and often written by medical writers) be withdrawn from your academic biography ? What would remain for many of us…**

**Would you consider appropriate that your academic research / task include a creative improvement of the dose / schedule of drugs without any interference of industry ?**

**Who would finance this type of clinical research ?**

**…. The payer ?**

# Why is Europe a major partner for Oncology R&D?

## Strengths

- Approximately 500 million inhabitants
- Political and healthcare system is relatively homogeneous compared to rest of the world
- An established network of academic institutions and national/European cooperative groups
- Several expert centres for translational research
- Europe has consistently recruited approximately 50% of total R&D study enrolment targets
- Europe is still a growing market for oncology
- Specific rules for early access to innovative treatment (e.g. ATU in France)

## Weaknesses

- Heterogeneity of culture and language
- Unclear expectations of some national agencies
- Slow approval process for Clinical Trial Application
- Slow and complex approval process for licence application
- Far from American global headquarters
- Strong and constraining individual relationships

# In conclusion

**In the last two decades, industry has taken the hand on all drug development (and that's its job) but also on the way the drugs are used (and that's the job of academy)**

**This fact explains why the disease has supplanted the patient (PFS vs OS)**

**This fact makes more complex the management of personalized medicine that should be mostly the job of academy**