



# Issues facing research for rare cancers in Europe

Anne Mathieu-Boué, MD, Novartis

An Industry view

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*“This presentation reflects my personal view based on my personal experience on the subject and does not necessarily reflect the views of Novartis, nor of the pharmaceutical industry within or outside of Europe.”*

# Issues facing research for rare cancers in Europe

## *Plan*

- Different situations and challenges for Companies
- From study concept to registration : real world of Clinical Trial Development :
  - Methodology concerns/Study design
  - Protocol and IC writing
  - Clinical study : Enrollment issues
- Pediatric specificity
- Challenges : Intra Pharmaceutical Companies and external
- Proposals to improve clinical development in rare cancer
- Post Marketing Authorization issues
- Conclusion

# Different situations for Companies

- What could we call «Rare Cancer» in companies' clinical research :
  - New drug developed in a rare cancer (*cf* prevalence): Orphan designation, for one indication : ATTRACTIVE
  - New indication for a marketed drug in a rare cancer
  - Subtype of frequent cancer : within the near future most of cancers will be « rare » as split by molecular profile and potential targeted treatment = personalized medicine
  - Pediatric tumors are rare cancers and raise long term safety issue
  - Clinical Studies: Pharma Sponsor or Investigator Initiative Trials

# Challenges for Companies

- Quality for MA submission : same level of requirements in rare cancers as in frequent indications
  - Same Clinical Development : not appropriate in rare cancers!
- Budget resources :
  - Rare cancers = same development costs as in frequent cancers
  - Reimbursement : discussion with HTA
  - Direct benefits: lower than for frequent cancers
- Production issues when small quantity in many countries

# From first concept to First Patient First Visit

## *Methodology concerns/ Study design*

### **Study design :**

- Prevalence of the disease : **recruitment issues** ++
- Small sample size : use “innovative” approaches as *Bayesian* and *Adaptive design* , align with FDA and EMA guidance documents (*eg* guideline on Clinical Trials in small populations...)
  - « Play the winner »
- Choice of control group, no standard of care, lack of comparators
- Appropriate choice of endpoints and hierarchy, right selection of surrogates (Biomarkers), clinical significance
- Stopping rules
- Scientific advice, protocol assistance (see EU regulation for orphan drugs)

# From first concept to First Patient First Visit

## *Protocol and Informed Consent (IC) writing*

Eligibility criteria to be enlarged (focus on pragmatic approach/«word-life» experience) to increase recruitment

Early input from patients expert - to be a partner of Patient Organizations (POs)

Informed Consent: use a more « patient friendly » wording : easy to understand and to provide relevant information

## Pathology Diagnosis :

- Check sample collection/common issues but more difficult when rare
- Under diagnosis (no data) – need **highly specialized physicians/pathologists** (rarity of expertise)
- External expert pathology review required for registration trial

# Clinical study : enrollment issues

## *need for network*

- Feasibility, selection of centers to enlarge recruitment

→ Information of patients to get support from POs

→ use appropriate tools (media, web sites *etc*)

→ To open sites in as many countries as possible : cost++

→ Practical issues : Patient referred to study sites « reference centers »:

favor information, insurance, transport reimbursement, translations; accompanying person, housing facilities if needed

→ To make it as easy as possible to cross borders to participate in a trial

- Quality control challenges when limited N of patients in a study site , cost

# Pediatrics specificity

- Regulatory aspect: Pediatric Investigation Plan required (regulation under revision)
- Clinical trial : additional issues
  - Appropriate Formulation, prepare specific treatment units
  - Dose finding according to age/ Pharmacokinetic specificities
  - Investigational centers with specific capabilities
  - Network/Reference centers
  - Family involvement in Informed Consent, different consent forms according to the age
  - Specific Family housing concerns :practical issues and cost ++
- Long term safety uncertainty



# Internal Pharma Company Challenges

- Small countries: only very few patients eligible → difficult to have a specific focused team
- Specific issues: to create and maintain enthusiasm/ pressure for a slow recruitment/long duration study compared to other key priority trials → **Maintain the study exciting**
- To inform and train our Pharma people on rare cancers and related constraints
- To **convince internal governance bodies**: especially to adapt study design and enlarge eligibility criteria...to be able to enroll patients
- To inform/advertise study within countries, use appropriate tools (web sites *etc*) and get help/input from POs and HA
- To have stable teams and recognition/acknowledgment of specific/unique capabilities, impact on career development
- **To obtain buy-in from upper management**

# Proposals to improve clinical development in rare cancer

- Why not « incentive » to set up more clinical trials - so far scientific advice is free of charge in EU ? Any experience in protocol assistance? Ask other Pharma?
- To modify registration requirements to get more appropriate files
- To reinforce links with Academic Groups, POs, pathologists
- Patient information : to «decrease » legal, bureaucratic, attitudinal barriers to establish mutual, beneficial relations with POs
- To create/reinforce specialized Clinical Trial Team for rare Cancers
- To expand access to Phase I

# Other challenges

- Avoid competition with academic trials? Try to concentrate efforts on same studies and support Investigators Initiative Studies
- To link with existing registries
- Data base sharing – no competitive collaboration
  - How feed the database
  - Basket protocols
- Tissue bank issues
- How to transfer to clinical practice

# Post-Marketing Authorization issues

- Reimbursement issues, discussion with HTAs, lack of appropriate criteria, same requirements as for frequent cancers,
- Commercial challenges
- Need for specific teams
- Post marketing surveillance and Risk Management plans
- Production issues and cost :
  - Small quantities in many countries
  - Available stock
  - Expiry date
  - Labelling

# Conclusion

- **Cost issues**
- Provide patients and oncologists with information about ongoing trials and trial results
- Involve experts patients in the design of CT before key decisions
- Expand access to innovative clinical trials in countries where access is more challenging
- Improve and adapt Clinical Research to rare Cancers
- To create more specialized expertise at both levels regulators and payors to increase interaction with Pharma
- Be Open and Transparent