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Rare Cancers and Drug Development

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Rare Cancers or ..

- Orphan EU: prevalence <50/100.000
- Orphan USA: affecting <200.000 in the US
- RARECARE: incidence <6/100.000
- From a drug development perspective "**small populations**"
  - defined (by me) as indications where it is complicated, if at all possible, to conduct conventional well-controlled, randomised trial with standard outcome measures (PFS, OS) with convincing results (p<<5%) also if relevantly active drug.

"Small Target Populations"

- "Small" is < "rare"
- Not only incidence; competing studies, interest for a specific compound, drug target and disease.
- "Common" might become "Rare" or even "Small", e.g.
  - ALK positive NSCLC
  - Late-line Hodgkin lymphoma
  - Children
- From a methodological/regulatory perspective same issues - truly rare histopathological entities or small study populations for other reasons.

Scientific Advice Procedures

- EMA/CHMP oncology advice procedures:
  369 (2001-2010, includes follow-up advice)

- Thereof **common** cancers (RARECARE) 103
  - simple top level classification
  - e.g. triple negative breast cancer = breast cancer

Scientific Advice Procedures

- "Small" study populations
  - 11 cases, e.g. CML with mutation T315I, Li Fraumeni, relapsed peripheral T-cell lymphoma (according to company)
  - might be some hidden target specific developments
- The majority of advices thus referred to "rare cancers" (RARECARE), but were considered suitable for "standard drug development".
- Right or wrong (biomarker guided drug development encouraged)

Scientific Advice Procedures

- The majority of advices thus referred to "rare cancers" (RARECARE), but were considered suitable for "standard drug development".
  - Right or wrong
  - Biomarker guided drug development encouraged/expected

Guidelines?

EMA/CHMP

- Guideline on Clinical Trials in Small Populations

- Evaluation of Anticancer Medicinal Products in Man
  - Draft for consultation deadline comments 31 May

Anti-cancer NfG

- Increase the target population
  - Opens for alternatives to histopathological delineation, such as related to "pivotal, molecularly well-defined target structure"
- Acceptance of "under-powered" randomised studies.
  - What is possible to accomplish within a reasonable time frame

Anti-cancer NfG

- Within patient comparison
  - Adjudicated TTP on last prior line vs. PFS on experimental therapy, superiority expected.
    - perhaps
  - in combination with under-powered randomised study

- (Single arm studies
  - outcome should be obviously beneficial when assessed by qualified persons)

Anti-cancer NfG

- Small study populations
- All evidence with respect to activity, efficacy and safety must be taken into account, including non-clinical data, effects on biomarkers (PD), PK/PD relationship, ORR, PFS etc.
- The totality, not primary, secondary, etc. endpoints.
- "Frequentist in planning, Baysian in the interpretation"

Regulations

- Conditional Approval
  - In EU rather close to "full approval"
  - Comprehensive data post-approval

- Exceptional circumstances
  - Comprehensive data **cannot** be provided