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