EMEA/EFPIA Workshop on Biomarkers Oncology

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Use of Biomarkers

Exploratory Studies - Aims (NfG)

- Disease, patient, compound, dose identification
  - target expression
  - prerequisites for activity/resistance
  - pharmacodynamic activity
  - pharmacodynamic interaction

  “bio-markers”
- Optimised benefit/risk

Biomarkers and Confirmatory Studies

- Formal validation of biomarker as surrogate endpoint
  - Prognostic endpoint *vs.* validated surrogate endpoint
- Changes in the surrogate endpoints (SE) explain changes in the "true endpoint"
  - Validation has to be based on randomised, controlled trials showing a difference in the true endpoint
- Formal validation rarely doable
  - Formally trustworthy only for the same class of compounds

"Accepted SE:s"
In Practice

- "Accepted SE"
  - Face validity
  - Stood the test of time: critical thinking and experimentation
  - Acceptance in the scientific community at large
  - Regulatory consistency
- Oncology: PFS used this way (NfG)

Anti-Tumour Activity Measures

Tumour Mass
- imaging
- biomarkers

Clinical Outcome
Symptom Control
Survival Benefit

Tumour

- Metabolism
  - PET, etc.
- Activity
  - Cytokines, etc.

Biomarkers as Alternative Measure of Tumour Mass

- NfG diagnostics - Truth Standard
  - Imaging (small - large tumour burden) correlation with Biomarker level (serum markers)
  - Probably disease specific
  - Off and on treatment
    - Unbiased in relation to different classes of compounds?

Biomarkers as Alternative Measure of Tumour Growth

- NfG diagnostics - Truth Standard
  - Imaging: growth stabilisation, progression
    - correlation with
  - Biomarker: stabilisation, progression (PET, serum markers, etc)
  - Probably disease specific
  - Unbiased in relation to different classes of compounds?

Biomarker as Primary Endpoint

- When PFS is acceptable (NfG)
  - When validated as proper measure of tumour mass or stabilisation and growth
  - When unbiased in relation to class of compounds
- Value – easier to follow
- Confirmation of progression by imaging?

Biomarkers and Tumour-related Symptoms

- When symptom control acceptable endpoint (NfG)
  - Correlation between symptom level and biomarker (e.g. cytokines) on/off therapy
  - Value: symptom control studies are hard to design and conduct, especially time to symptom progression studies
- Maybe useful as supportive evidence

Early Biomarkers Predictive of Negative Clinical Outcome

Prediction of Resistance

(e.g. effects on metabolic activity)

- Predictive of progression within x weeks (based on ph. II data)
  - When PFS superiority is sufficient
  - As treatment strategy in OS studies
- To reduce duration of inefficient therapy
- Improve benefit – risk
- How to do in the control arm?
  - PFS studies
  - OS studies

Early Biomarkers Predictive of Positive Clinical Outcome

- When proof of survival benefit is needed (NfG)
  - Not doable as validation not possible
- When PFS superiority sufficient (NfG)
  - Would probably need proper validation to act as a surrogate
  - In theory possible
- Are relaxed conditions foreseeable?
  - New "indications" same target expression, mechanisms of resistance understood, …. ?
  - When it is possible to argue convincingly for response rate instead of PFS

Effects on Biomarkers as Confirmatory Evidence of Clinical Benefit

- Yes – as alternative measure of already accepted surrogate endpoint such as PFS
- Yes – early predictors of progression
- Rarely - as conceptually new surrogate endpoint