EMEA/EFPIA Workshop on Biomarkers Oncology

London
December 2006
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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
- Optimised benefit/risk

"bio-markers"

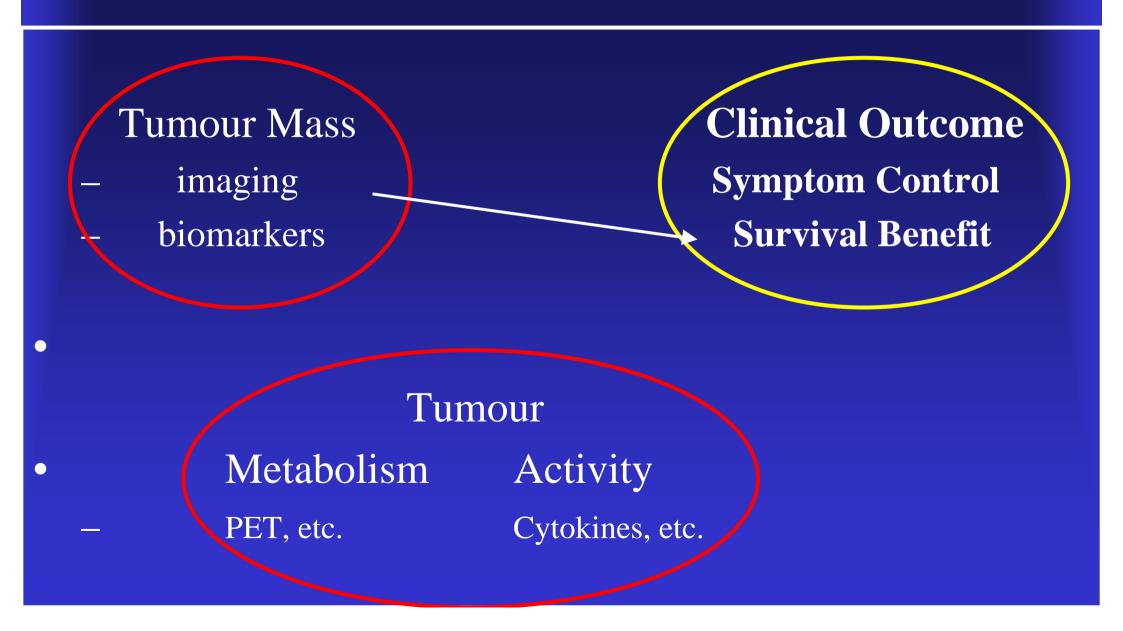
Biomarkers and Confirmatory Studies

- 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



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