Incorporating pharmacodynamic, response and patient selection biomarkers

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Biomarkers key for:

• Strong hypothesis
• Dose/schedule selection
• Target engagement/phenotypic change (eg Ki67)
• Patient selection
• Resistance pathways

Right target

Target selection/hypothesis (unmet need)

Cell lines

Xenograft tumour models

Patient derived xenograft tumours

Right dose/schedule

Right patient
Biomarkers and target selection/validation

- Genomics
  - Mutation
    - Expression
    - Amplification
  - Deletion
- Disease linkage
  - Analysis of clinical samples corresponding to target population
- Evidence from competitor compounds
- Biomarkers to measure target engagement/inhibition in preclinical models; ideally compatible with use in clinical studies
Pharmacodynamic biomarkers confirm osimertinib activity against T790M mEGFR

Osimertinib inhibited EGFR phosphorylation in cell lines with EGFR sensitising mutations - PC-9 (exon 19del); H3255 (L858R); H1975 (L858R/T790M); PC9VanR (exon19del/T790M) – and poor activity vs wtEGFR

Pharmacodynamic confirmation of target inhibition in vivo

Pathway biomarkers inhibited in vivo - 6hr post dose in lung tumours in L858R/T790M transgenic model

Cross et al, Cancer Discov; 4(9); 1046–61. 2014
Phase 1 studies underestimate toxicity of recommended Phase II dose

45% patients treated with small molecule targeted agents required dose modifications in Phase III trials

Use preclinical PK-PD, dose and schedule modelling in conjunction with biomarkers to support dose selection

Target engagement – proof of mechanism demonstrated in AZD5363 Phase 1

Preclinical PK-PD – at tolerated dose – 100mg per kg - biomarker knockdown indicated twice daily dosing was required

Phase 1 - Biomarker knockdown in paired tumour biopsy samples – IHC analysis

Davies et al, Mol Cancer Ther 2012. 11: 873.

Elvin et al, ASCO Meeting abstracts May 2014: 2541.
Biomarkers in clinical development

- **What sample**
  - Invasive vs non-invasive - blood/urine vs tumour biopsy
  - Biomarker stability - sample logistics

- **What technology**
  - Quantifiable - assay validation and qualification
  - Samples are precious, often limited – multiplex where possible
  - IHC – linking target to pathology/histology

- **Target population data**
  - Variability of biomarker in disease – prevalence
  - Level of target inhibition – setting expectations
ctDNA avoids potential biopsy sample error

Mutational heterogeneity in primary breast cancer

Clinical response to AZD9291 according to baseline T790M status – concordance between tissue and ctDNA

Jensen et al, Clin Cancer Res, 2010; 17(4); 667–77.

ctDNA serial monitoring of treatment response

CTCs predict survival benefit in prostate cancer

- **Multiple technology platforms**
  - CellSearch FDA approved – EpCAM+ve, CD45-ve cells

- **EPIC Sciences**
  - CK/DAPI+ve, CD45-ve – all cells captured. IF analysis incorporates target specific markers

- **Genomic analysis from CTCs**
  - Provides additional avenue to address tumour heterogeneity

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de Bono et al, Clin Cancer Res 2008;14(19) 6302
CTC biomarkers - EPIC Sciences

Identifies all CTC populations with opportunity to quantify additional target related biomarkers

Source: EPIC Sciences
Right patient – disease fragmentation and targeted therapy

**Colorectal**

- Relative protein abundance (log2)
  - -2
  - -1
  - 0
  - 1
  - 2

- Proteomic subtype
  - A
  - B
  - C
  - D
  - E

- TCGA transcriptomic subtype
  - MSI
  - CIMP
  - Invasive
  - CIN

- Sadanandam et al. subtype
  - Enterocyte/Goat-like
  - TA

- Stem-like
  - Inflammatory

- De Sousa et al. subtype
  - CC51
  - CC52
  - CC53

- Methylation subtype
  - CIMP-H
  - CIMP-L

- Cluster 3

- Cluster 4

- Genomic features
  - yes
  - no
  - NA

- HNF4A Copy number
  - -2
  - 0
  - 1
  - 2

- HNF4A protein abundance (log2)
  - -2
  - 0
  - 1
  - 2

**Breast**

- Colorectal

- Lung - adenocarcinoma

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Vandetanib targeted for RET-fusion positive NSCLC

Vandetanib - an inhibitor of VEGFR2, EGFR and RET

Approved for medullary thyroid cancer - RET, VEGFR and EGFR contributing to disease progression
Activity in Phase II in differentiated thyroid cancer - RET rearrangements contribute to disease progression

RET-fusions identified in NSCLC reported in Feb 2012. Prevalence in vandetanib Phase III NSCLC tumour samples ~0.7%

Preclinical activity in LC-2 NSCLC cells – Endogenous RET fusion

FDG-PET/CT responses in patient with poorly differentiated lung adenocarcinoma harbouring a RET-KIF5B rearrangement

Matsubara et al, J Thoracic Oncol 7:1872 2012
Gautschi et al, J Thoracic Oncol 8: e43 2013
Biomarker strategy key points

• Biomarker selection to address key questions for pharmacodynamics and patient selection
• Assay validation/qualification and compatibility with clinical deployment
• Plan for success – ensure protocol anticipates potential sample use
• Sample tracking and recovery – importance of sample labelling and documentation
• Patient selection/diagnostic development needs to be in place for Phase 1 – avoid unnecessary delays