BIOMARKER DRIVEN EARLY PHASE ONCOLOGY CLINICAL TRIALS; CHALLENGES IN THE REAL WORLD

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Cancer; Some Sobering Thoughts

- Getting cancer is one of our greatest fears. > 1 in 4 deaths are cancer related.
- Someone in the UK is diagnosed with cancer every 2 minutes.
- 1 in 2 people in the UK will develop cancer.
- In 2013, >350,000 new cases of cancer identified and in 2012 >150,000 died of cancer.
- A disease well controlled by surgery and radiotherapy when localised and caught early.
- A disease that **kills when metastasised** and where **new treatments are desperately needed**.
Drug Development – the Challenge

5% success rate from Ph 1 to registration - not sustainable

Total Number of Drugs in Research and Development World Wide
Shared wish list by patient, physicians, payers and industry

More effective Drugs → Fewer Failures → Faster development cycles

CHEAPER → BETTER → FASTER

Right dose/Schedule → Right patient → Monitor impact of therapy → Right commercial opportunity

IS IT TIME FOR “NO BIOMARKER NO EARLY PHASE TRIAL”?
Centre for Drug Development (CDD)

- Based in London.
- Manages preclinical development and sponsors phase I and II trials of new anticancer agents (currently~ 30 active projects).
  - agents in multiple tumor types, including on CRUK priority areas (Pancreatic, Lung, Brain, Oesophageal)
  - Small molecule therapeutics, antibodies, cell therapies, gene therapies, imaging agents.
  - Global partnerships with academia and industry
- Over 100 agents taken into early phase trials and 5 are available to patients (abiraterone, temozolomide, etoposide, pemetrexed, dexrazoxane)
So what is the focus of CDD?

• Develop novel agents where expertise and/or resources to support further development are lacking.

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<tr>
<th>COMPANY</th>
<th>DRUG</th>
<th>KEY CRUK ACTIVITIES</th>
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<tr>
<td>Immatics Biotechnologies</td>
<td>IMA950 Multipeptide vaccine</td>
<td>FIH clinical trial</td>
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<tr>
<td>GSK</td>
<td>GSK1070916A Small molecule Aurora Kinase B/C inhibitor</td>
<td>FIH clinical trial</td>
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<tr>
<td>AstraZeneca</td>
<td>AZD3965 Small molecule</td>
<td>FIH clinical trial</td>
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• ‘Sweet-spot’ around translation from preclinical to FIH
• First in class agents (>80% of portfolio) – highly desirable
• Focus on biomarkers
• >90% of assays performed in CRUK funded academic labs
So what are biomarkers?

“A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (FDA definition)

- Pharmacodynamic (PD) – PoM/PoP/PoC
  - does the compound bind to my target?
  - does the compound alter target-signalling pathway?
  - does the compound modulate tumour response?
- Predictive
- Prognostic
- Safety
- Early detection/screening biomarkers
Ideal PD strategy in early phase trials

ADME PROCESSES
Absorption
Distribution
Metabolism
Excretion

Plasma PK

Exposure in tumour

Proof of mechanism

Proof of principle

Proof of clinical Concept

Enrichment/personalised

Today’s Science, Tomorrow’s Medicine
What makes a good biomarker – (4S’s)

1. Science
   - is there a “scientifically relevant” biomarker we can use. Need to understand deep biology and test hypotheses

2. Suitability (fit-for-purpose)
   - Pre-study assessment of sensitivity, specificity, magnitude of effect and reproducibility are essential to understand the underlying “noise” of the assay. Include patient material where relevant. Analytical and technical validation

3. Study design
   - statistics ? when do we take samples and from where ? Escalation or expansion or both, Use preclinical PKPD as a guide.

4. Sample
   - how much sample do you need ? Stability ? How quickly does it need analysing ? Freeze thaw? Shipping conditions etc
Typical early phase oncology study – aims & objectives

Stopping dose likely to be estimated based on pre-clinical tox, pre-clinical biomarkers, PK, maximal administered drug

Starting dose determined by pre-clinical tox, safety, efficacy, PK, pharmacology .....holistic approach (ICH S9)

Safety, tolerability

PK, ADME parameters

PoM, PoP biomarkers (primary, secondary or tertiary end points)

PKPD relationship

MTD, BED to determine RP2D

early measurement of drug activity/impact on disease on an ongoing basis

Patients
Trial designs in oncology

3+3 design

Expansion arm ~10-15 patients at the RD

1-3 subjects

1-3 subjects

3 subjects

6 subjects

8 subjects

10-15 subjects

Surrogate PD response detected

Surrogate PD response confirmed

Surrogate PD response plateau

BED reached/expansion in tumour

Today’s Science, Tomorrow’s Medicine
Case study 1; Challenges with a PoM PD assay for a FIC agent

Compound X is a FIC small molecule transporter inhibitor that prevents excess lactic acid being transported from tumour, that results in acidosis and cell death

• Pre-clinically lactate accumulation in PBMC (LCMSMS) was shown to be a robust PoM assay
• Similar responses observed in healthy volunteer blood at therapeutically relevant concentrations in-vitro
• Assay was selected as a primary end point for the trial
• Dose escalation underway, 5th cohort being dosed, drug administered to >25 patients, pharmacological saturation achieved based on PK

Result – no conclusive PoM response
Case study 2; How to select patients most likely to respond to an experimental therapy

Compound Y is a FIC antibody targeting a cell surface antigen that is over-expressed in ovarian and other solid tumours. Study will only select patients showing a 3+ staining thus most likely to respond

• Target antigen has been extensively studied and a range of antibodies exist for IHC evaluation. Literature reports >50% of patients showing positive staining

• One antibody was chosen during assay development and validation based on ability to demonstrate differential staining intensity in a range of tumour samples/positive/negative controls/independent pathology review etc

• Key assay for the trial as patients not expressing target unlikely to benefit from drug

• Currently only 12% success rate – implication on timelines, costs, novelty, logistics
Case study 3; Requirements for validation, the what, how and why?

Compound Z is a cancer vaccine (1 dose, 4 vaccinations) targeting two antigens in solid tumours. The aim of the study is to demonstrate immune responses

- primary end point assay – ELIspot
- secondary end point – ex vivo PBMC assays, genome analysis in PBMC
- research end points – T cell markers, effector mechanisms, cultured ELIspot, MDSCs, tumour IHC

Trial complete following 22 patients. ELIspot responses in very few patients and present only at one time point.

- No clear correlation between ELIspot and genome status or any other research end point.

- What have we learnt from the trial – the vaccine is safe!
Challenge 1

How do you go about discovering and validating pharmacodynamic biomarkers for first in class agents with suitable confidence to be tested in the clinic? (case study 1)

• Novel biology that is evolving with time

• Biomarker will be tested for the first time in the clinic, so no previous knowledge

• What degree of validation do you really need to do, can do or pragmatically worth doing?
Challenge 2

How do you define patient selection/enrichment criteria for an early phase trial during dose expansion (case study 2)

• how do you define cut-offs for eligibility

• what can you do pre-clinically to define acceptance criteria for patient selection assays

• what other factors would contribute to seeing a difference between validation work and trial samples? What can be done to minimise this effect?

• how do you validate tumour based PD biomarker assays in the absence of tumour material
Challenge 3

Is there a consensus on the extent of validation that would be required for primary vs secondary vs research based assays? (case study 3)

• Should there be a difference or should all assays be validated to same degree? What does fit-for purpose mean to you?

• Are there any guidelines or regulatory requirements for biomarker assays validation for primary/secondary or research assays that you can recommend?

• How do you define acceptance criteria that would give you confidence to detect a signal above noise in a heterogeneous patient group consisting of 3-6 patients per dose?
Limitations in the real world

• Biomarkers are never “black and white”, mostly shades of grey!
• Little evidence to correlate PD effect with clinical outcome.
• How do you correlate expression levels of target with response. What % of cells need to be positive, to what degree of positivity?
• To what degree, how long, in what tissue do you need to see PD
• Tumour PD markers not dynamic. Correlation between tumour and blood borne markers – not there yet.
• Resistance and degrees of tumour heterogeneity
• Challenges at sites with sample handling, processing, shipment and storage
• Degree of variation in analytical assay validation – what does “fit for purpose” mean to you?
Summary

• Biomarkers are key to the success of early phase oncology trials and help minimise phase II attrition

• Keep a balanced and pragmatic view of the agent/trial. Biomarkers are a key component of future drug development but not the only one!

• Be clear on which assay you need to address a specific question, the expectation of the assay and how it will help with trial design, success criteria, future investment.

• Think quality vs quantity, cost to know, value added and accept that there will be limitations with each assay

• It is challenging to discover, develop and have a robust validated clinical assay, particularly for FIC agents.
Thank You & Questions?

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