



Biomarkers in Oncology Drug Development

Molecular & Cellular Proteomics
Implementation of Guidelines for Clinical Proteomics
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Overview

- Biomarkers
- Why and what biomarkers for drug development ?
- Selected Considerations
 - Study Design, Evaluable Samples, Ethics
- Summary

Definitions

- **Clinical endpoint**
 - how a patient feels, functions or survives
- **Surrogate endpoint**
 - a biomarker which can definitively substitute for a clinical benefit endpoint in measurements of drug efficacy
- **Biomarker**
 - a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
- **A Useful Biomarker**
 - Informs risk/benefit ratio when there is a decision to be made
 - Does so in a better/faster/earlier /cheaper way than existing approaches
 - Generally applicable: sample and technology must be available/accessible
 - Has known identity(ies)

Omics is the answer..... What was the Question ?

Patient

- What is my lifetime risk of cancer ?
- Have I got cancer ?
- What type of cancer have I got and therefore what is my prognosis ?
- What treatment is best for me ?
- Is my treatment working ?
- Will my cancer come back ?




Pharma

- What are the decisions in cancer drug development ?
- When are these decisions made ?
- What are the existing approaches ?
- What are the available samples ?
- Who do we need to convince ?

Biomarkers in Oncology Drug Development

- **Early Trials: Molecular Efficacy**
 - Pharmacological audit trail
 - Dose & schedule to test the hypothesis
- **Late Trials and Beyond: Personalised Medicine**
 - Further classification of patients in addition to tumour type by defining a new sub-set of patients on the basis of a molecular test
 - Benefit/risk ratio is significantly higher (for a particular dose of) our drug (compared to competition) in a particular sub-set of patients as defined by the test.
- **Late Trials: Registrable endpoint (accepted surrogate)**
- **(Biomarker Development)**

Early Trials – Molecular Efficacy

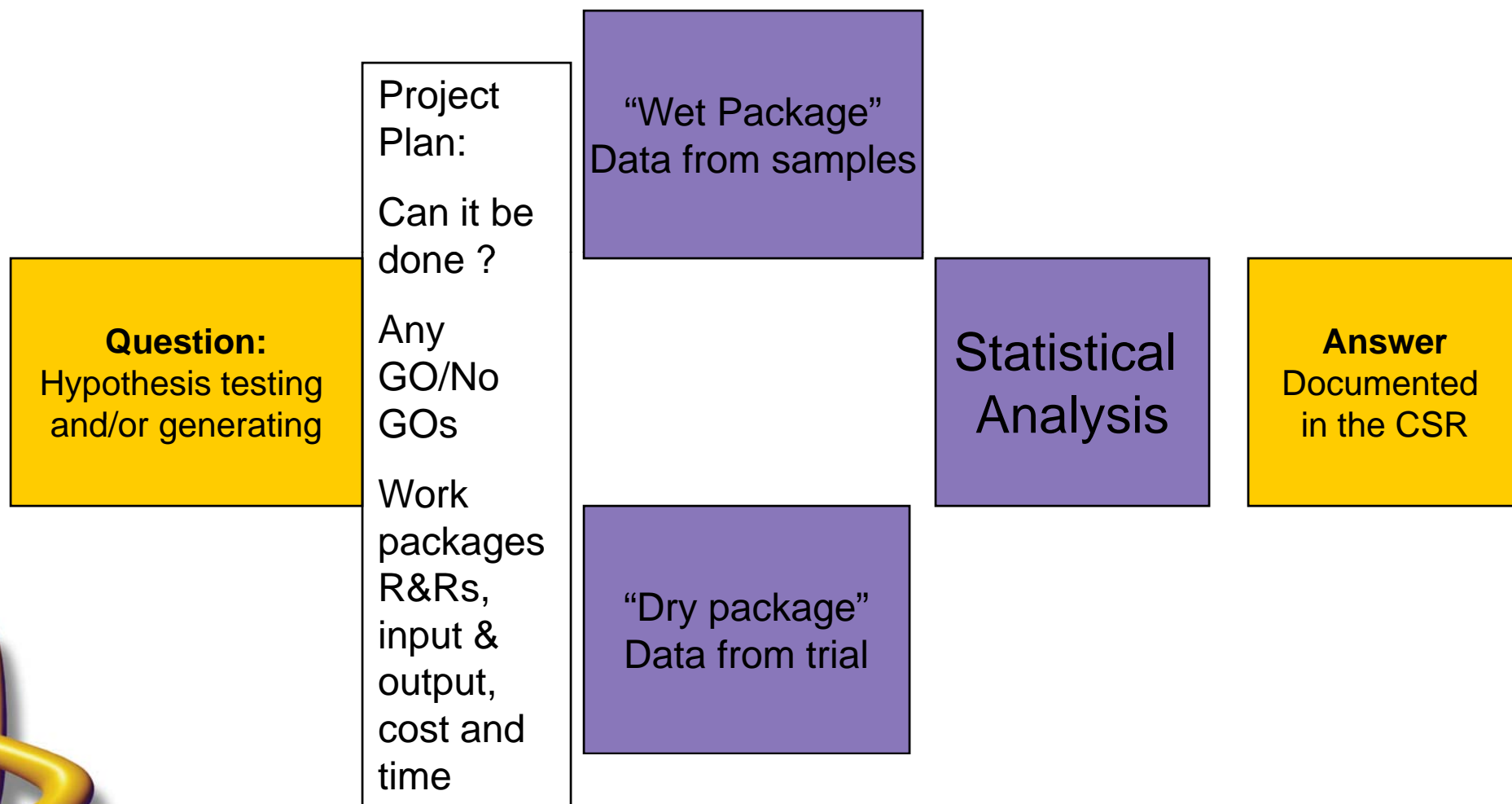
Question	Result
Does it hit the target in man ? 	<u>Proof of mechanism (PoM)</u> e.g. enzyme inhibition, receptor blockade
Does it have an effect on the disease phenom 	<u>Proof of Principle (PoP)</u> e.g. Increased cell death markers
Does this result in a beneficial clinical effect? 	<u>Proof of Concept (PoC)</u> e.g. Tumour size reduction,

Progressive reduction of uncertainty about effects

Increasing level of confidence about outcomes

No guarantee of success

Typical Clinical Proteomics Study



Study Concept/Design Considerations

- Phenotypic correlate range, distribution and reproducibility
- Pre-work to determine biomarker evaluable sample population (ESP), variability, cut-offs and prevalence
- Powering – phenotypic frequencies and ESP
- Relative timing of biomarker sample and correlate

Complexity of implementation



Biomarker

In use

Static

Early

Discrete

Univariate

Minimally invasive

Precedented technology

Subject level

Novel

Dynamic

Adaptive

Continuous

Multivariate

Biopsy

Novel

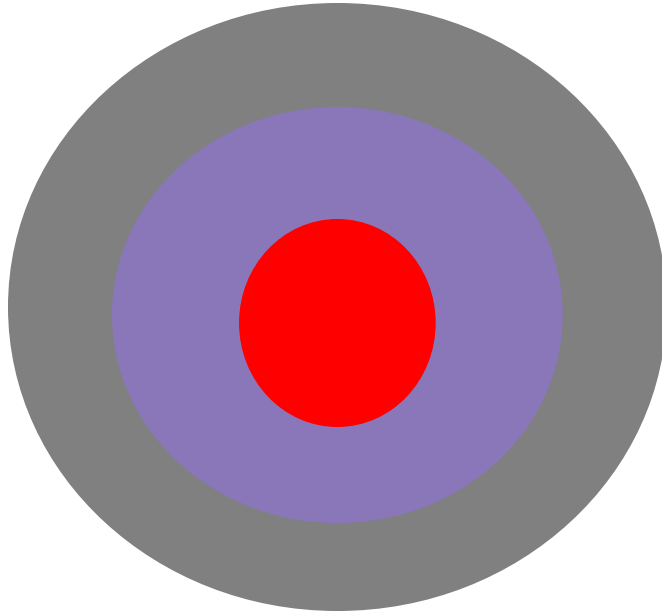
Biopsy level



Feel the Noise ?

- Where is the decision/intended use ?
 - Early Efficacy Markers ?
 - Local clinical unit ?
 - One or two centres of excellence ?
 - Diagnostic
 - 1000's of hospitals world wide
- Discover and develop biomarkers in representative patients and sample types
- Only control sample collection where it will be feasible to do so in intended use
- Generally avoid restrictive inclusion and exclusion criteria, non-robust sample collection, transport and storage requirements
- Collect and disclose data on impact of the above

Evaluable Sample Population



- Intention To Treat
- Per Protocol
- **Evaluable Sample Population**

- Do feasibility in advance
- Disclose attrition
 - Availability
 - Consent
 - Pre-qualification of samples
 - Assay fails
- Check for bias in other factors in the ESP

Business model to “qualify” a biomarker in Oncology

Identify potential biomarker(s) by LO (3y prior to clinic)

A. Assay development in human tumour and/or non-tumour tissue
(Feasibility Study)

Lock preferred method

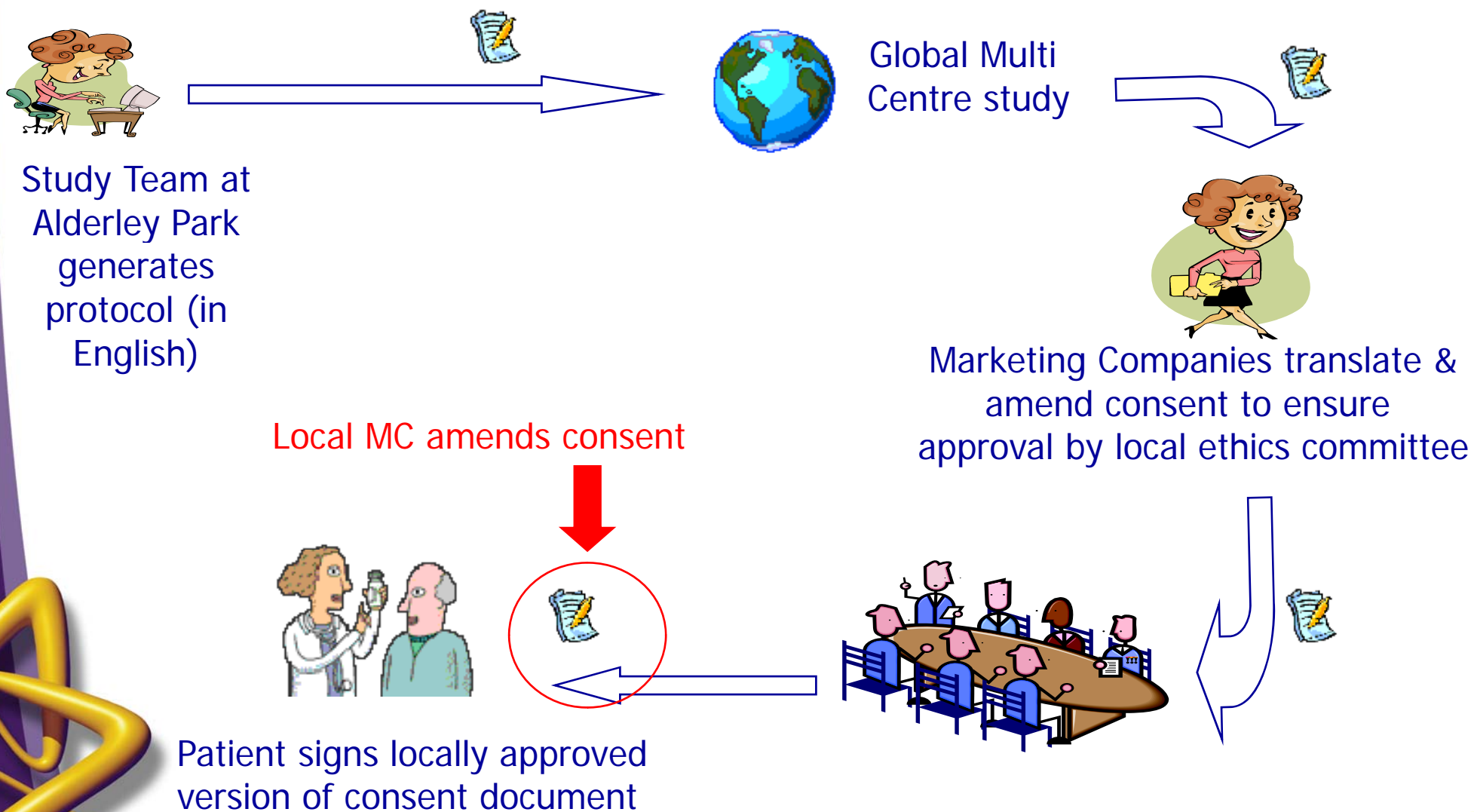
C. Preclinical sensitivity testing
with Candidate Drug
(Positive control/PK-PD)

B. Variability in intended
tumour and/or non-tumour tissue
(Reproducibility Study)

D. Clinical sensitivity / positive control study in man

Biomarker with clinical utility
(by FTIM)

Informed Consent In a Large Multinational Trial: a legal contract between AZ and the patient.



Informed Consent Issues

- Where we like to be
 - Mandatory samples for hypothesis testing
- Where we often are
 - Optional samples for an exploratory objective
- Process for obtaining and tracking samples & consent
 - Text modules for optional consent & levels of consent
 - Fully inform patients
 - Allow opt in/out at territory, centre & patient
 - Comply with local legal requirements
 - Do not impede progress towards primary study objectives

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