Oncology Drug Development
Advantages and challenges of using stratified clinical studies

Simon J Hollingsworth
The 18th Anti-Tumour Drug Development Forum

21 February
Japan
Stratified Medicine In The Clinic
Targeted therapeutics are improving survival…

Example: NSCLC is an evolving landscape

Where we’re going
Stratified Medicine Requires Portfolio Approach
AZ/MedImmune are uniquely placed...

**Lung – adenocarcinoma**

- **Selumetinib (AZD6244)**
- **AZD5363**
- **AZD9291**
- **Iressa (AZD9291)**
- **Medi-4736**

**KRAS**

**EGFR**

**Unknown**

**MAP2K1**

**NRAS**

**ROS1**

**fusions**

**PIK3CA**

**AKT1**

**BRAF**

**ALK**

**fusions**

**Lung – squamous**

- **Caprelsa (vandetanib)**
- **AZD5363**
- **AZD8186**
- **AZD2014**
- **AZD4547**

**FGFR 2/3 mutation**

**FGFR1 amplification**

**FGFR translocations**

**Volitinib**

**Met expression**

**Met amplification**

**PDL-1 expression**

**PDL-1 amplification**

**Unknown**

**Alexander Drilon, Natasha Rekhtman, Marc Ladanyi, Paul Paik**

*Lancet Oncol* 2012; 13: e418–26
Reality Of Drug Development
Current trial paradigm isn’t working…?

Screening approaches don’t work – for patients, physicians or Pharma

- Low frequency events are difficult to find
- Diagnostic sample quality/quantity compromises multiple analyses
- Poor patient and physician experience with cycles of repeat diagnostics
- Current regulatory requirements to validate companion diagnostics

We need…

- Innovative trial designs suited for development of highly targeted molecules
- Diagnostic standards and methods standardisation
- Regulators to engage with new types of (different) datasets
- Improved patient access (NGS-based companion diagnostic)
Reality Of Drug Development
Delivering stratified medicine requires innovation...

Reality of conventional screening

1. Ph.1 expansion – molecular subgroup
2. 2% prevalence IHC / DNA ($1,125)
3. 15% test fail 75% patient conversion = patient recruited

<table>
<thead>
<tr>
<th>AZ Sponsored Study</th>
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<tbody>
<tr>
<td>Screening / patient recruited (assay, processing, logistics, reporting)</td>
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<tr>
<td>Patients screened / recruited</td>
</tr>
<tr>
<td>For 20 patient study</td>
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<tr>
<td>1,560 patients screened</td>
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<tr>
<td>Operational delivery</td>
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<tr>
<td>Physician’s experience</td>
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<tr>
<td>Patient experience</td>
</tr>
<tr>
<td>Up – potential trial</td>
</tr>
<tr>
<td>Down – not eligible</td>
</tr>
<tr>
<td>Repeat biopsies</td>
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<tr>
<td>Limited drug options</td>
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Stratified Medicine In Drug Development

Basket studies offer a practical solution…

Choosing the patient for the trial

“Baskets” – choose the trial for the patient

“basket” – portfolio, multidrug, umbrella, etc…
Basket Studies By Tumour Type And Region

Global level of innovation...

- Lung
- Solids
- Lymphoma
- Cholangiocarcinoma
- Endometrial

- Lung
- Breast
- Colorectal
- Solids (epithelial)
- Sarcoma
- Ovarian
- Pancreatic

- Lung
- Gastric

Lung Master Protocol
NCI MATCH
NCI MPACT
SAFIR
MATRIX, SMP2
AURORA – BIG WIN Consortium
SPECTA-Lung
VIKTORY
SCRUM-Japan
Basket Studies In Lung Cancer Are being done at a National level…

MATRIX National Lung Cancer Trial – Cancer Research UK

Lung Master Protocol – Friends of Cancer Research USA

'Master protocol' aims to revamp cancer trials (2013). Pilot project will bring drug companies together to test targeted lung-cancer therapies.
The key things we have learnt…
Basket Studies – Success Requires Innovation in clinical diagnostics…

Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing

Clinically actionable alterations in patient samples

Unprecedented detail
Basket Studies – Success Requires Innovation in clinical diagnostics…

Detail and accuracy are essential –

- What mutations, specifically
- What regions of the gene
- What evidence supports they are clinically actionable
- What about mutations with little or no evidence

**Tier 1** – clinically actionable (prospective selection)
**Tier 2** – research interest (retrospective analysis)
**Tier 3** – do not use

We want to select patients with PIK3CA mutations

- Do they select the same patients
- How can we cross-validate

Which next-generation-sequencing (NGS) platform
Basket Studies – Success Requires Innovation in clinical trial design...

Complex designs need flexible protocols –

**MATRIX**
National Lung Cancer Trial

Starting line-up...

**Adenocarcinoma**
- PI3K/AKT deregulation
- AKT1 mutation
- FGFR mutation
- LKB1 mutation
- TSC1/2 mutation
- CDK4 amplification
- CCND1 amplification
- KRAS mutation
- MET amplification
- ROS1 gene fusions
- EGFRm+ & T790M+
- NF1 mutation
- NRAS mutation
- No actionable change

- A3 → A6 → B1 → C1 → C2 → D2 → D3 → D4 → E1 → E2 → F1 → G2 → G3 → H1

- AZD5363 → AZD4547 → AZD2014 → Palbociclib → Crizotinib → AZD9291 → Selumetinib + Docetaxel → MEDI4376

**Squamous cell carcinoma**
- PI3K/AKT deregulation
- AKT1 mutation
- FGFR mutation
- LKB1 mutation
- TSC1/2 mutation
- CDK4 amplification
- CCND1 amplification
- MET amplification
- ROS1 gene fusions
- EGFRm+ & T790M+
- NF1 mutation
- NRAS mutation
- No actionable change

- A1 → A2 → A4 → A5 → A6 → B2 → C1 → C2 → D1 → D2 → D3 → E1 → E2 → F1 → G1 → G3 → H1

- AZD5363 → AZD4547 → AZD2014 → Palbociclib → Crizotinib → AZD9291 → Selumetinib + Docetaxel → MEDI4376
Basket Studies – Success Requires Innovation in clinical trial design…

Differing flexibility – differing needs...

**Single protocol**
Requires amendment

Screening protocol
Core inc-/exclusion criteria
Core trial design
  - Supplement 1
  - Supplement 2
  - Supplement 3
  - Supplement 4
  - Supplement 5

**Individual, flexible**
Regulatory friendly

Screening protocol
Protocol 1
Protocol 2
Protocol 3
Protocol 4
Protocol 5

**Modular, flexible**
Requires amendment

Screening protocol
Core inc-/exclusion criteria
Core trial design
  - Sub-protocol 1
  - Sub-protocol 2
  - Sub-protocol 3
  - Sub-protocol 4
  - Sub-protocol 5
Basket Studies – Success Requires New models for implementation…

MATRIX National Lung Cancer Trial – Cancer Research UK

ECMC Network
- UK-wide National network
- +28 feeder hospitals in “hub-and-spoke” model

LC-SCRUM-Japan – National screening programme

National programmes – Centralised Pharmacy is needed for cost-effective drug delivery

147 Institutes in 46 Prefectures participating (as of November 2013)
## Basket Studies – Success Requires

Innovation across trial design and implementation...

<table>
<thead>
<tr>
<th>Diagnostic System</th>
<th>Protocol</th>
<th>Operational Delivery</th>
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<tbody>
<tr>
<td>• Platform</td>
<td>• Single or aligned protocol</td>
<td>• Hub-and-spoke models</td>
</tr>
<tr>
<td>• Screening/selection algorithm</td>
<td>• Aligned and efficient review – centralised Regulatory/Ethics</td>
<td>• Must accommodate – diverse groups and geographical areas</td>
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<tr>
<td>• Broad patient profiling</td>
<td>• Flexible</td>
<td>• Centralised Pharmacy – to enable cost-effective delivery of multiple drugs to multiple sites</td>
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<tr>
<td>• Sample efficient</td>
<td>• Modular</td>
<td>• Highly collaborative working – across many different groups</td>
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<tr>
<td>• Robust data generation</td>
<td>• Rolling – open ended</td>
<td>• Good partners</td>
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<tr>
<td>• Cost-effective</td>
<td>• Adaptable to emerging science</td>
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<tr>
<td>• Transferable, widely deployable</td>
<td>• Allows different datasets</td>
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<tr>
<td>• Works to agreed standards</td>
<td>• Allows regulatory interactions</td>
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<tr>
<td>• Viable development route</td>
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<tr>
<td>• Support regulatory interactions</td>
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<tr>
<td>• Support for markets</td>
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**Broad and robust tumour profiling for patient selection**

**Flexible protocol with central review**

**Centralised Pharmacy and collaborative working**
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