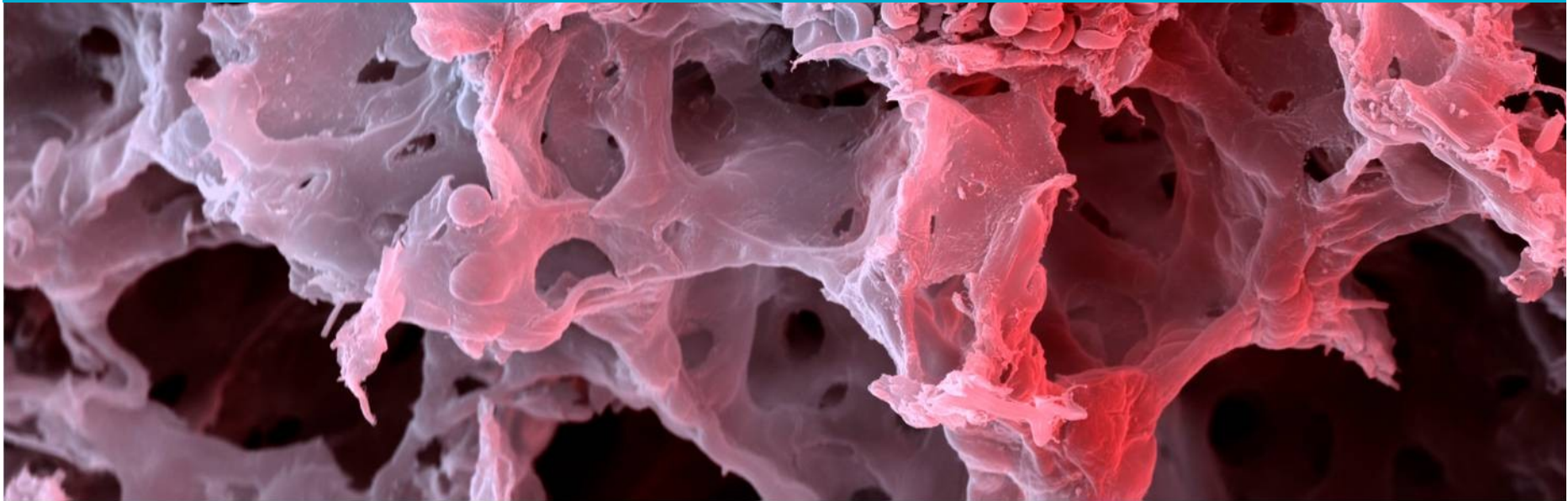


Oncology Drug Development

Advantages and challenges of using stratified clinical studies

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

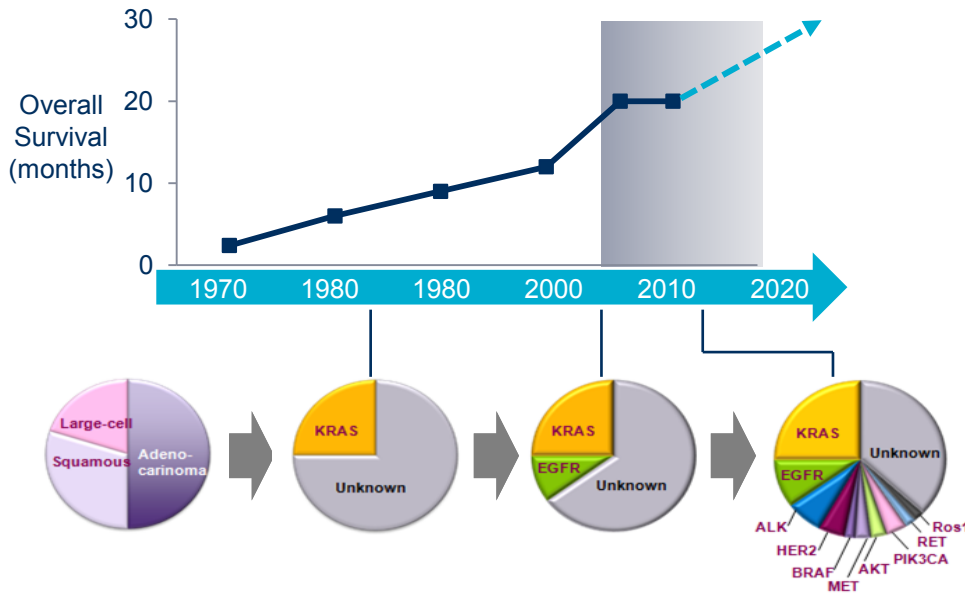
21 February
Japan



Stratified Medicine In The Clinic

Targeted therapeutics are improving survival...

Example: NSCLC is an evolving landscape



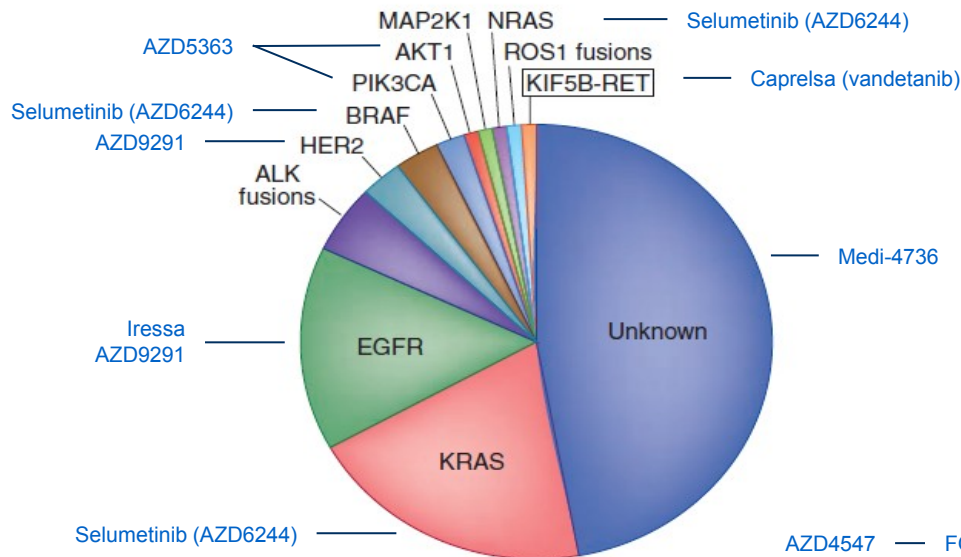
Where we're going



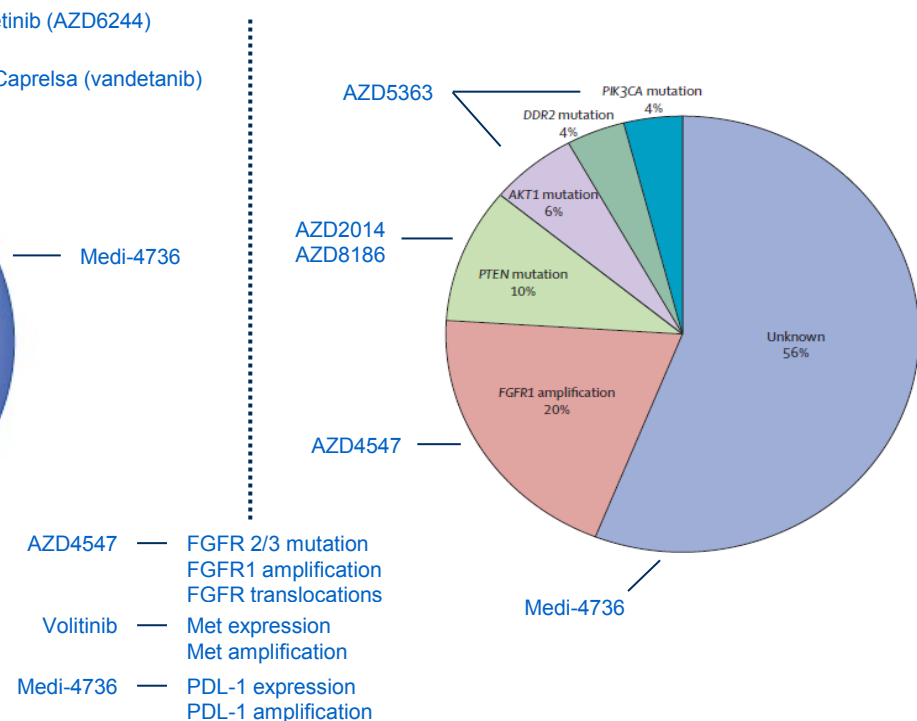
Stratified Medicine Requires Portfolio Approach

AZ/MedImmune are uniquely placed...

Lung – adenocarcinoma



– squamous



William Pao & Katherine E Hutchinson
NATURE MEDICINE VOLUME 18 | NUMBER 3 | MARCH 2012

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

Screening / patient recruited
(assay, processing, logistics, reporting)

Patients screened / recruited

For 20 patient study

Operational delivery

Physician's experience

Patient experience

AZ Sponsored Study

\$88,235

78 (77 discarded)

\$1.8 million

1,560 patients screened

very complex

Limited options –
keep screening if tumour
material allows

Cycle of Disappointment
Up – potential trial
Down – not eligible
Repeat biopsies
Limited drug options

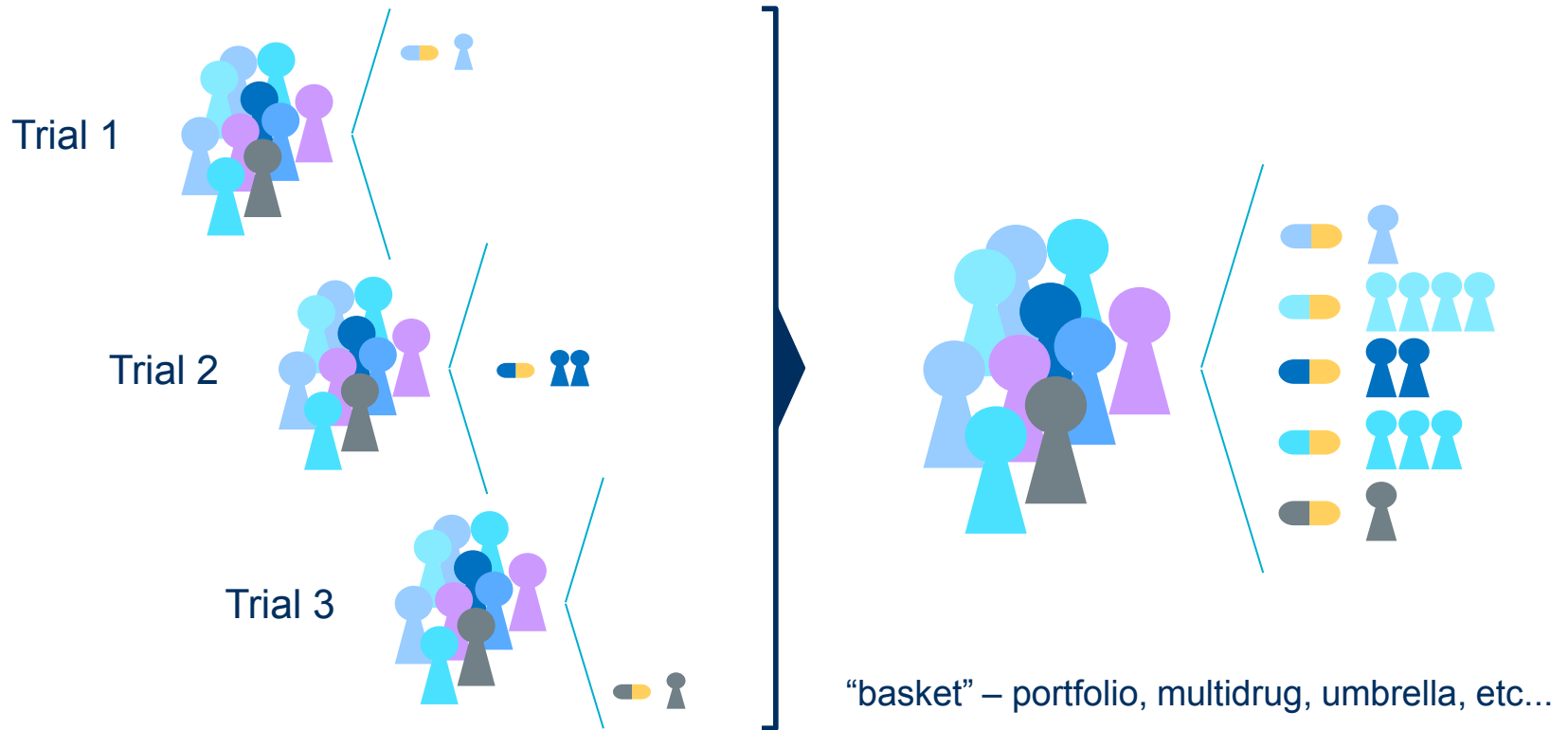


Stratified Medicine In Drug Development

Basket studies offer a practical solution...

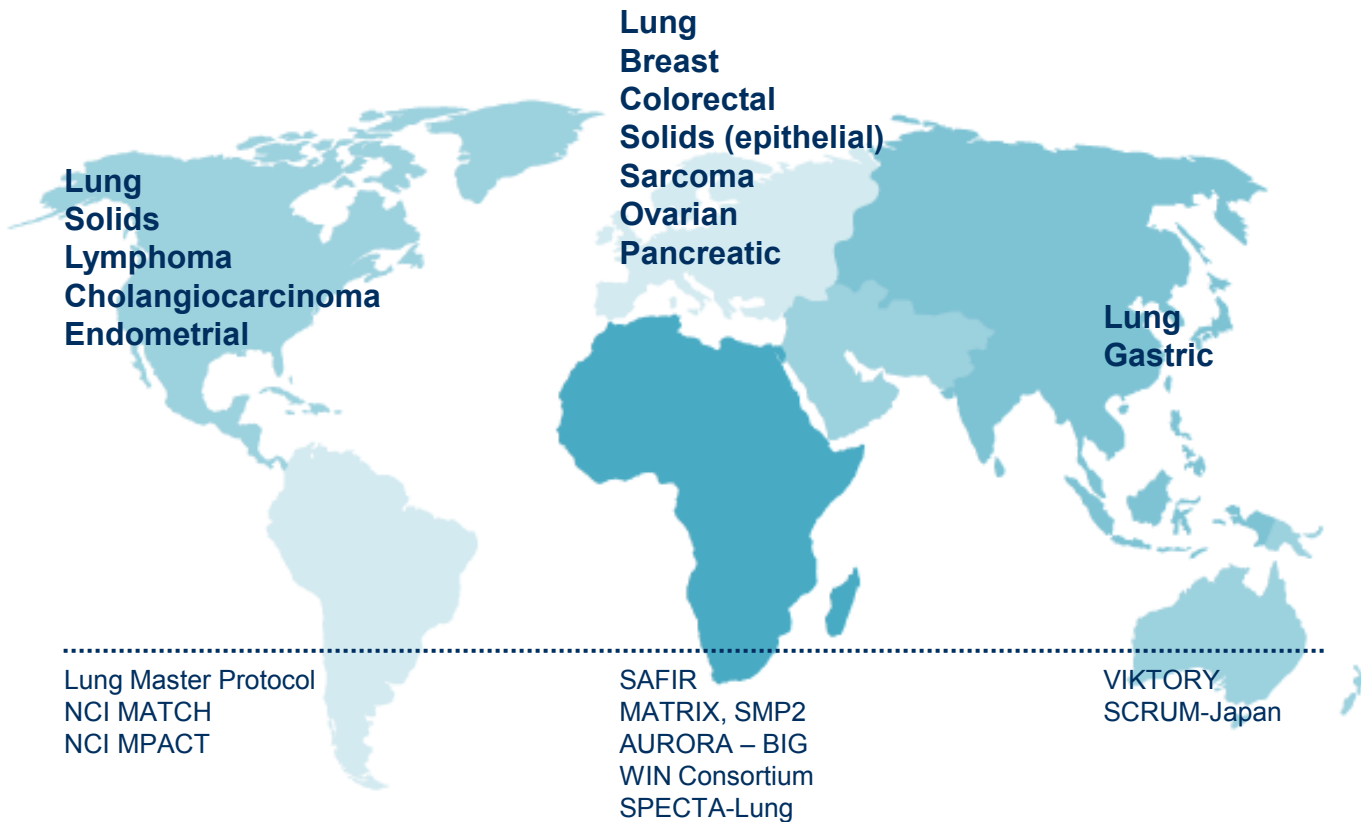
Choosing the patient for the trial

“Baskets” – choose the trial for the patient



Basket Studies By Tumour Type And Region

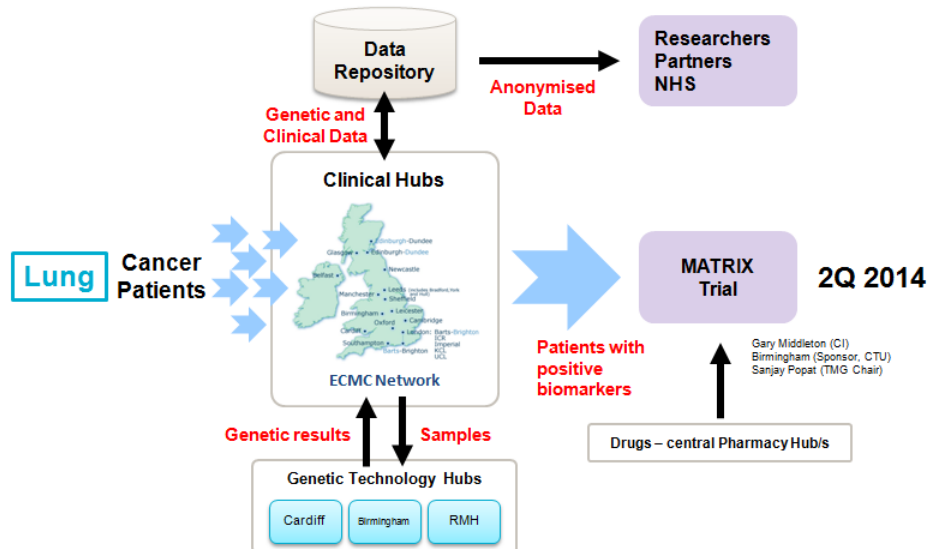
Global level of innovation...



Basket Studies In Lung Cancer

Are being done at a National level...

MATRIX National Lung Cancer Trial – Cancer Research UK

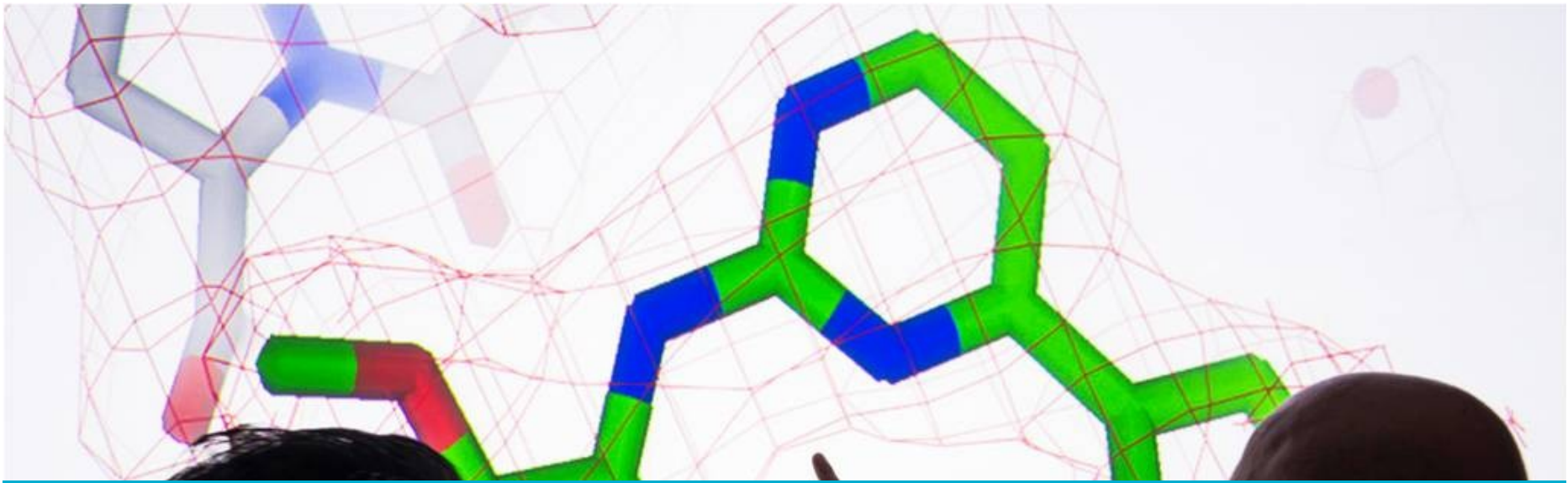


Lung Master Protocol – Friends of Cancer Research USA



nature '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...

Detail and accuracy are essential –

We want to select patients with PIK3CA mutations

- 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

Which next-generation-sequencing (NGS) platform

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



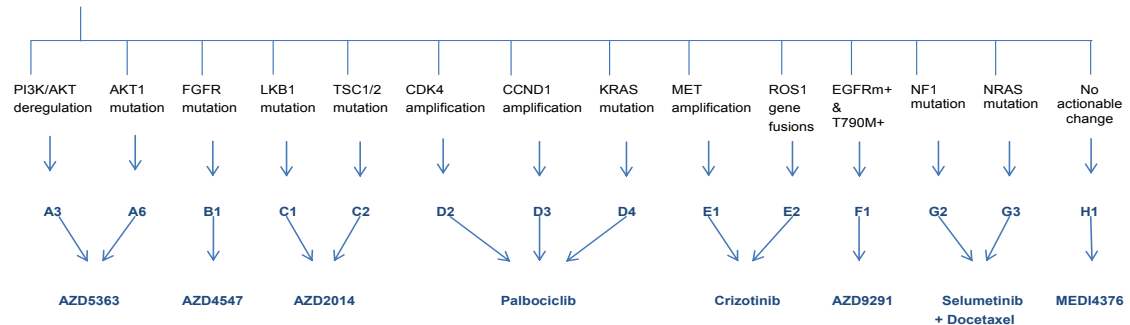
Basket Studies – Success Requires Innovation in clinical trial design...

Complex designs need flexible protocols –

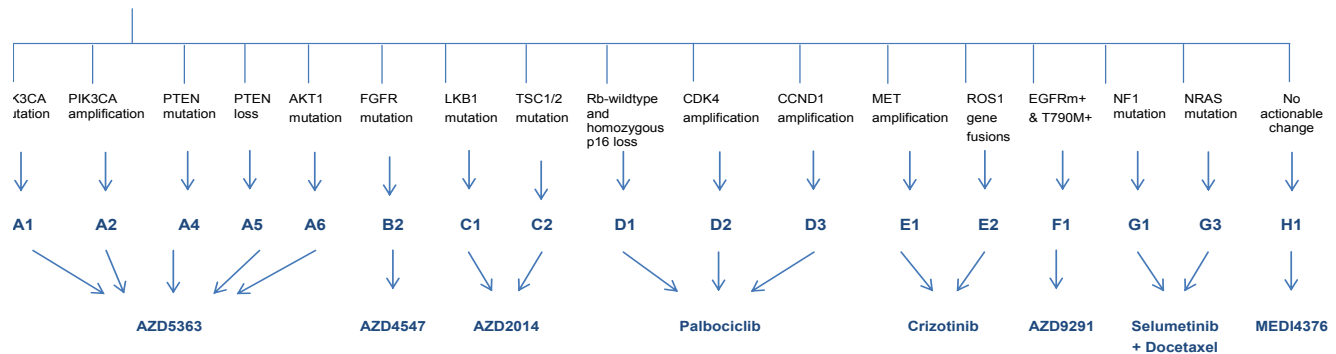
MATRIX
National Lung Cancer Trial

Starting line-up...

Adenocarcinoma

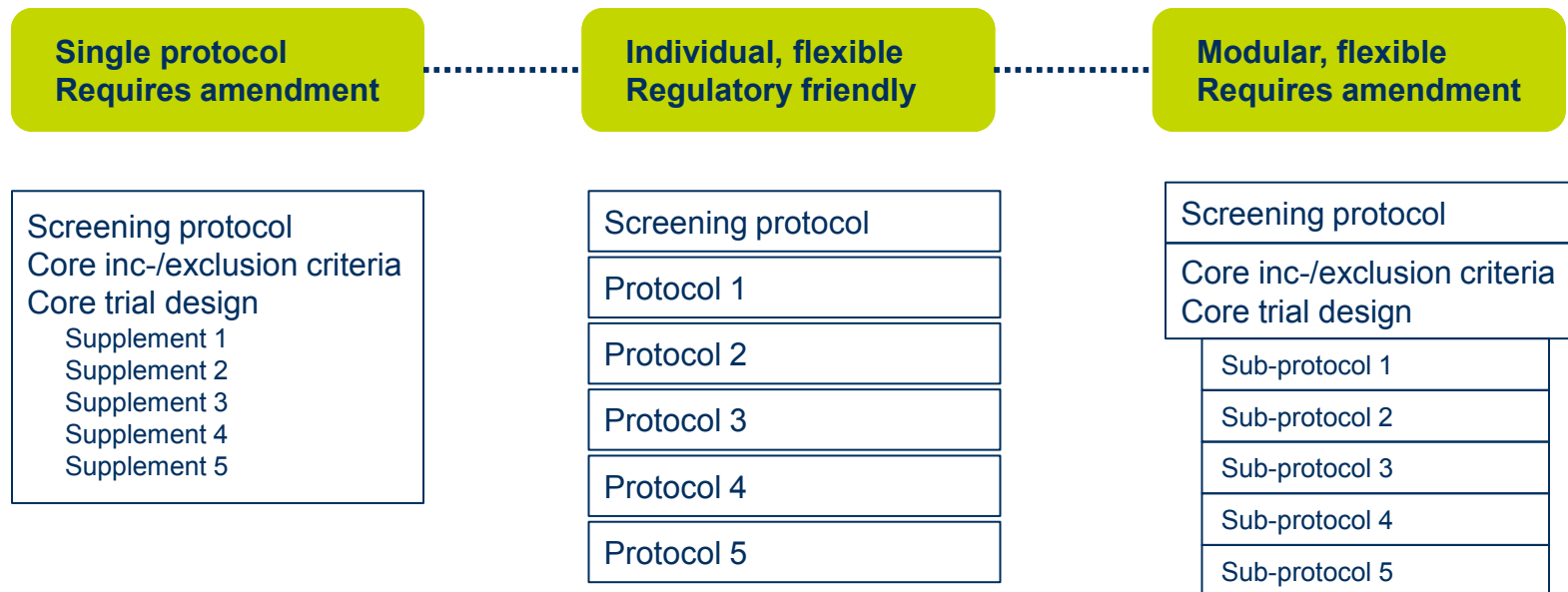


Squamous cell carcinoma



Basket Studies – Success Requires Innovation in clinical trial design...

Differing flexibility – differing needs...



Basket Studies – Success Requires New models for implementation...

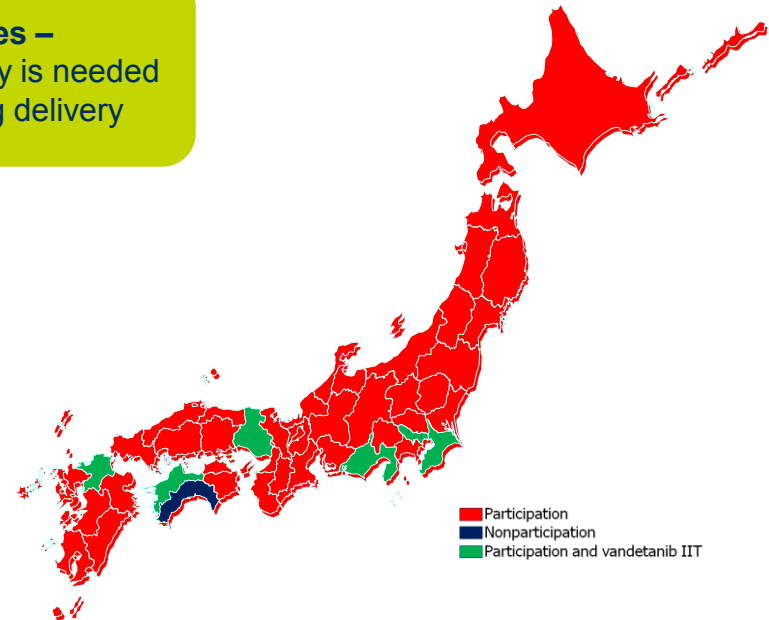
MATRIX National Lung Cancer Trial – Cancer Research UK



ECMC Network

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

LC-SCRUM-Japan – National screening programme



147 Institutes in 46 Prefectures participating
(as of November 2013)

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



Basket Studies – Success Requires

Innovation across trial design and implementation...

1 Diagnostic System

- Platform
- Screening/selection algorithm
- Broad patient profiling
- Sample efficient
- Robust data generation
- Cost-effective
- Transferable, widely deployable
- Works to agreed standards
- Viable development route
- Support regulatory interactions
- Support for markets

Broad and robust
tumour profiling for
patient selection

2 Protocol

- Single or aligned protocol
- Aligned and efficient review – centralised Regulatory/Ethics
- Flexible
- Modular
- Rolling – open ended
- Adaptable to emerging science
- Allows different datasets
- Allows regulatory interactions

Flexible protocol
with central review

3 Operational Delivery

- Hub-and-spoke models
- Must accommodate – diverse groups and geographical areas
- Centralised Pharmacy – to enable cost-effective delivery of multiple drugs to multiple sites
- Highly collaborative working – across many different groups
- Good partners

Centralised
Pharmacy and
collaborative working



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