Precision Medicine – Interactions between Academia and Pharma

AstraZeneca
What science can do

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DISCLOSURE

- I am a full time employee of AstraZeneca PLC and own stock in AZ

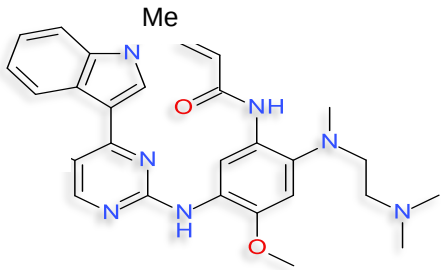
Overview

- Successes, and challenges with the implementation of precision medicine
  - EGFR – osimertinib (AZD9291)
  - FGFR - AZD4547
  - AKT – AZD5363
- Academic-Pharma precision medicines trials - design and practice implications
- Collaborative NGS tool development
- Example of collaboration to understand mechanisms of resistance to osimertinib

MedImmune

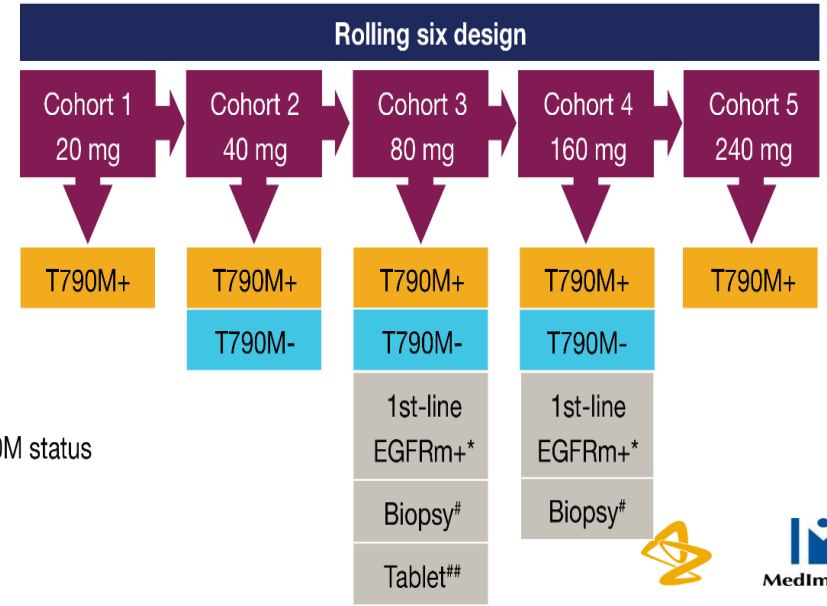
Phase I clinical plan for osimertinib

- Dose escalation limited to EGFRm patients who had failed one or more EGFR TKI therapies
- Expansion cohorts (T790M +/-) triggered by >1 clinical response in an escalation cohort
- Multiple expansion cohorts could be run in parallel
- First line cohorts triggered when sufficient second line patient safety data available



Escalation
Not preselected
by T790M status

Expansion
Enrolment by local
testing followed by
central laboratory
confirmation
(cobas® EGFR Mutation Test) of T790M status
or by central laboratory testing alone



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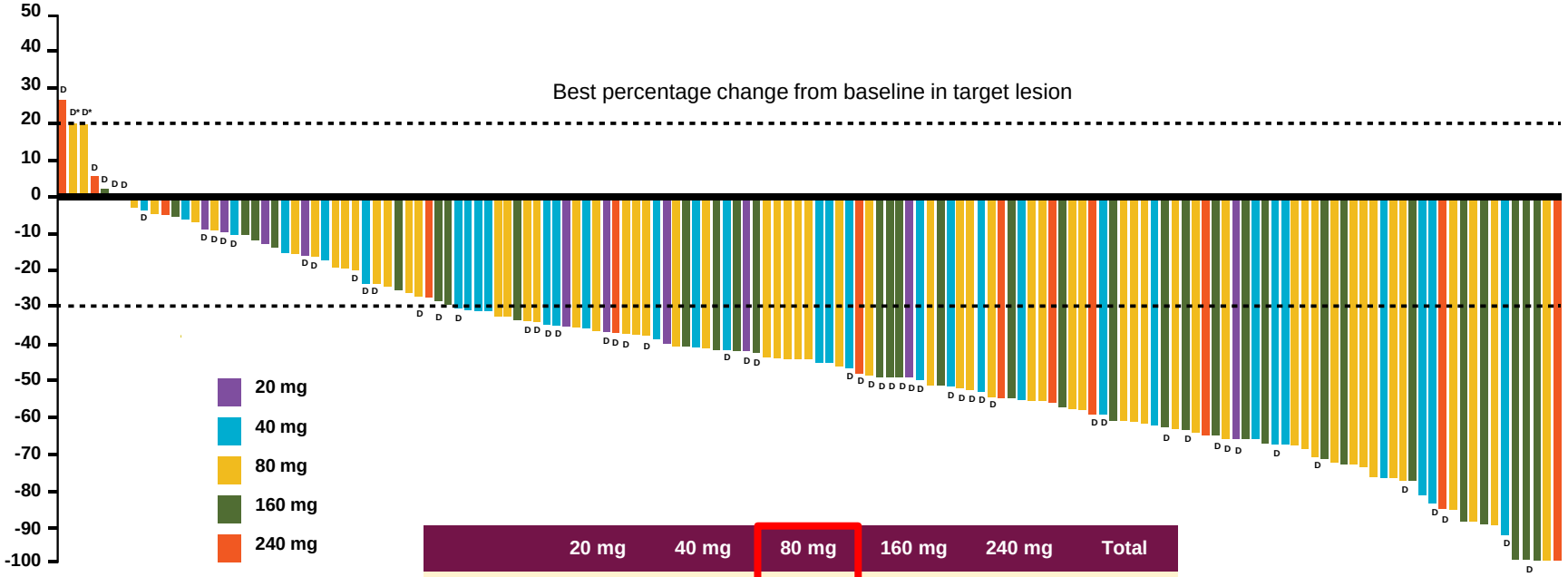
ORR in second-lineT790M +ve cohorts (central test)



	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

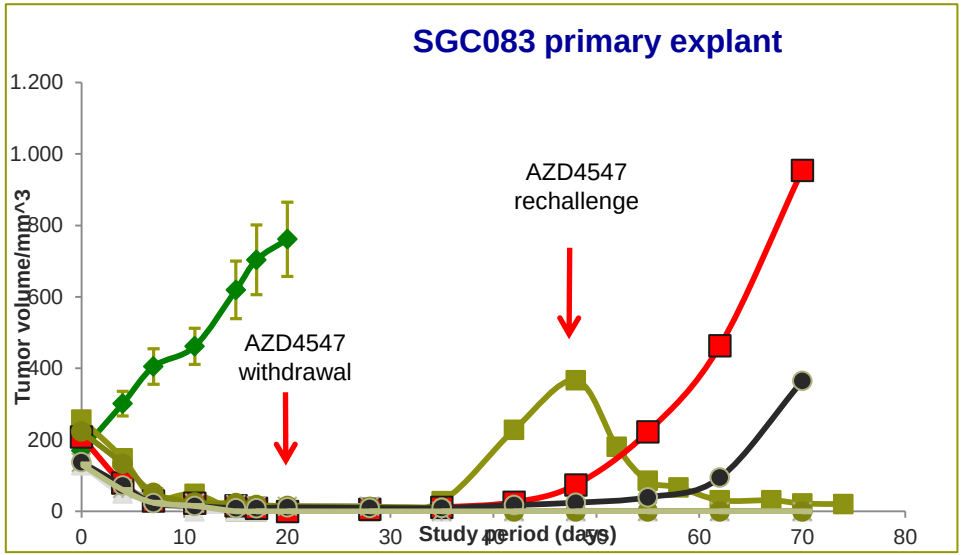
*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments
Nine patients (seven in the 160 mg cohort) currently have a best overall response of not evaluable, as they have not yet had a 6-week follow-up RECIST assessment
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014
CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

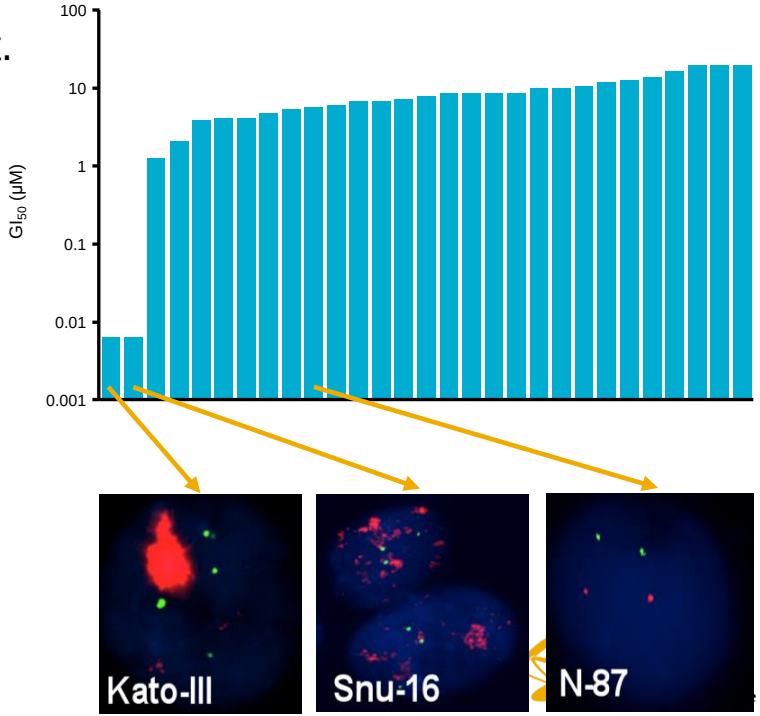
Presented by Pasi A Jänne at the 2015 European Lung Cancer Conference. Ann Oncol 2015; 26(Suppl 1): i60, LBA3.

MedImmune

FGFR2 amplification in gastric cancer

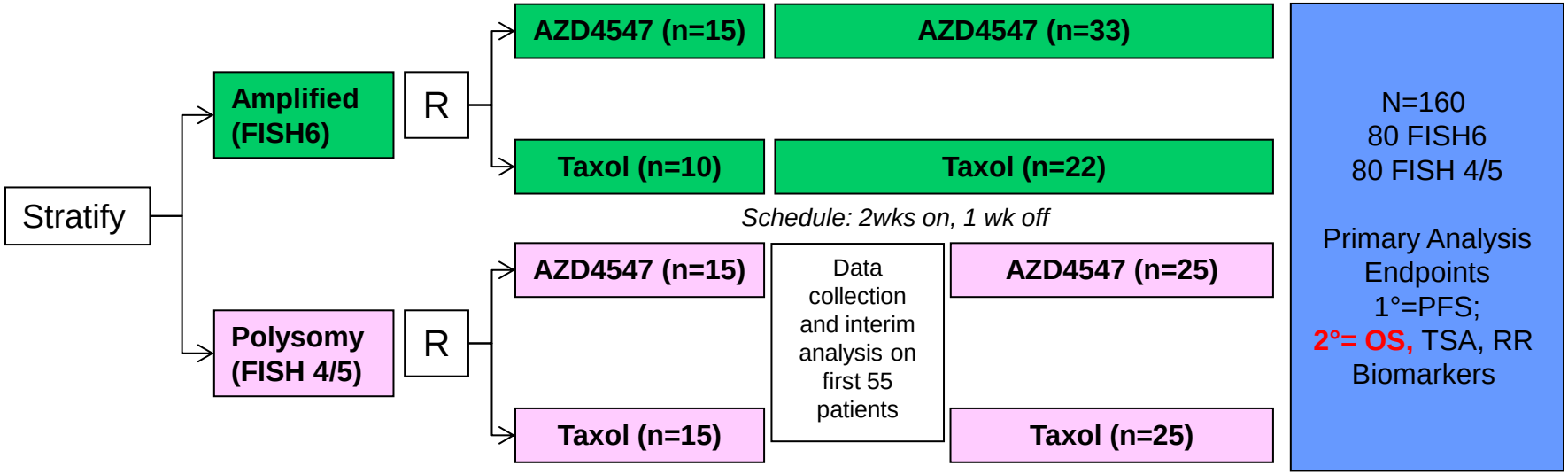
- *FGFR2* amplification in 5%-7% gastric cancer associated with increased FGFR2 expression
- Gastric cell lines with FGFR amplification are sensitive to AZD4547
- Tumour regression observed in an *FGFR2* amplified gastric explant model and amplified SNU16 xenograft.
- Additive effects in combination with cytotoxics





SHINE Study included amplified and polysomy patients

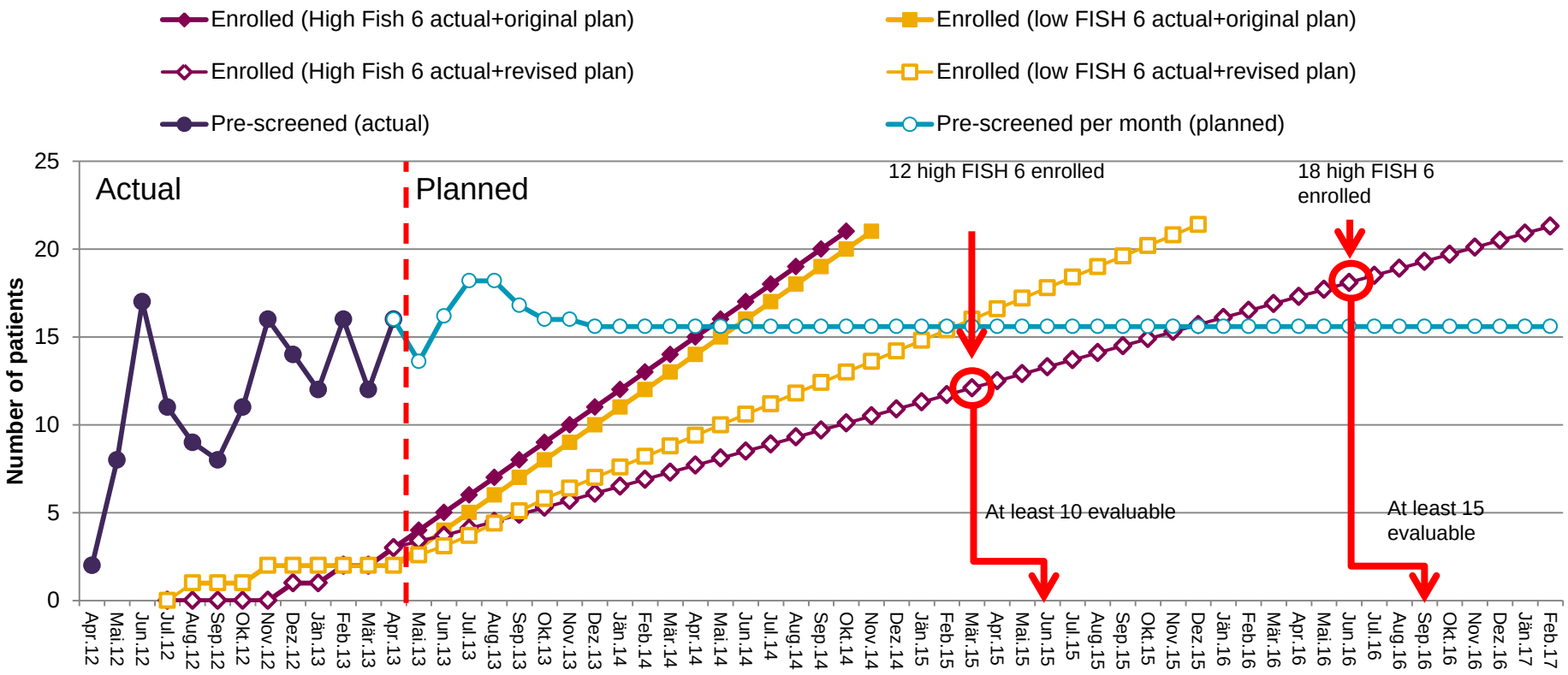
Open-label randomised monotherapy study – FGFR2 polysomy (FISH4/5) & amplified (FISH6) advanced adeno gastric cancer relapsed/refractory after one 1st line combination chemo. (including rapid progression after peri-surgical chemo) \



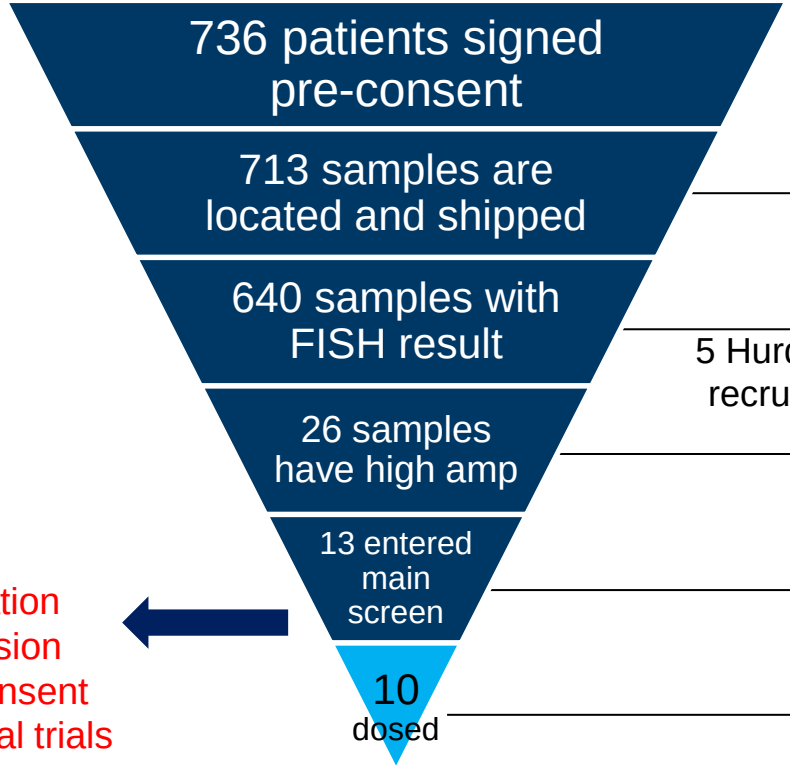
January 2012

MedImmune

Despite massive efforts, recruitment painfully slow



Screening ‘Funnel’ for FGFR studies (pan tumour)



3% **not sent**

10% attrition

5 Hurdles for recruitment

3.6% **FGFR high amp (of samples shipped)**

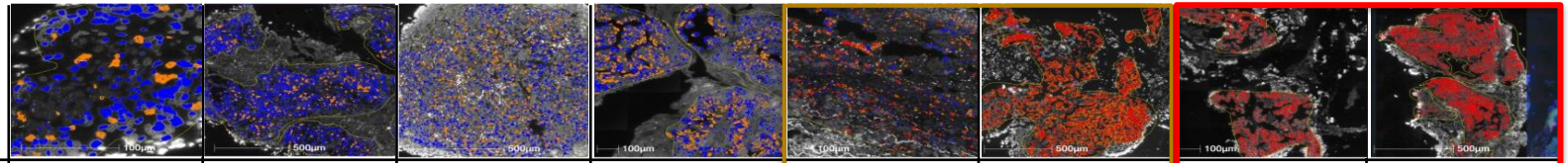
38% **drop out before main clinical screening (5 TBC)**

23% screen failure rate (clinical screening)

- Randomisation
- Clinical deterioration
- Disease progression
- Withdrawal of consent
- Competing clinical trials

>70 patients have been pre-screened for every 1 patient dosed
(includes recruitment prior stop of first line screening ~ 40% of total)

Inter-patient heterogeneity : *FGFR2* amplification does drive clinical response to AZD4547…

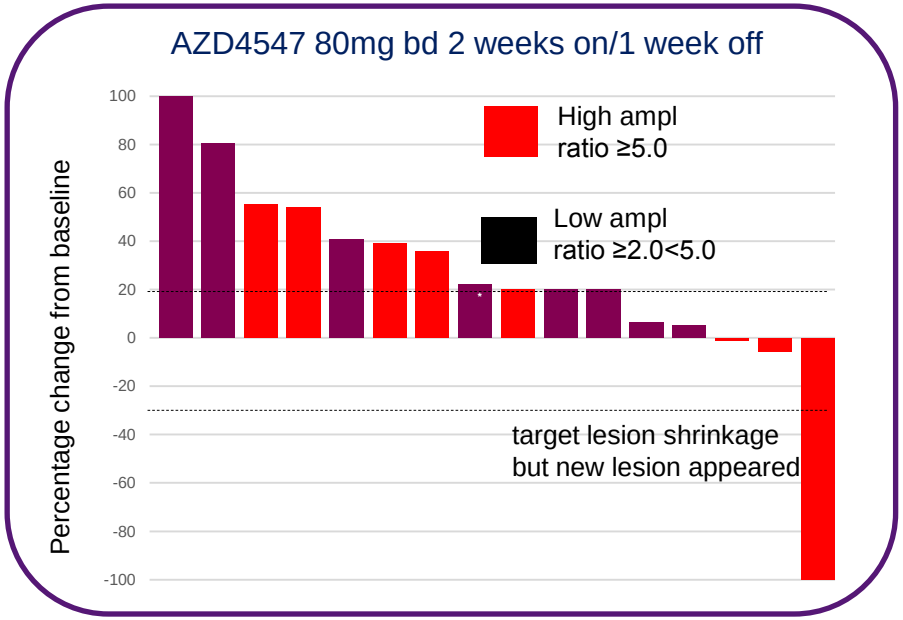
								
% amplified	**14.1**	**27**	**28**	**37**	**44**	**94**	**99**	**99**
FISH ratio (MIRAX)	**1.1**	**1.4**	**1.6**	**1.9**	**10**	**43**	**30**	**34**
FISH ratio (manual)	**1.9**	**2.0**	**3.3**	**3.9**	**12.6**	**12.0**	**25.2**	**35.3**

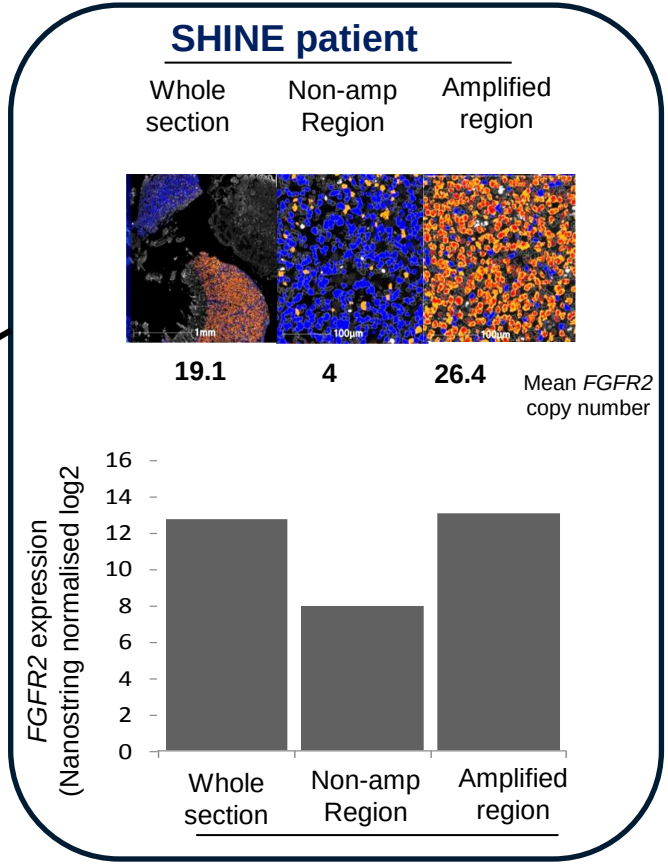
responders

Heterogeneity maps: Unamplified tumour cell Amplified tumour cell

Sections were digitally scanned using the x40 objective of a MIRAX Panoramic 250 Flash II (3D Histech)
Tumor was marked and z-stack levels examined for evidence of heterogeneity.
Correlation between screening FISH and MIRAX ratio is high (r =0.9963).

…but even within same patient heterogeneity is present





- **Heterogenous response - marked target lesion shrinkage but new lesion appeared**

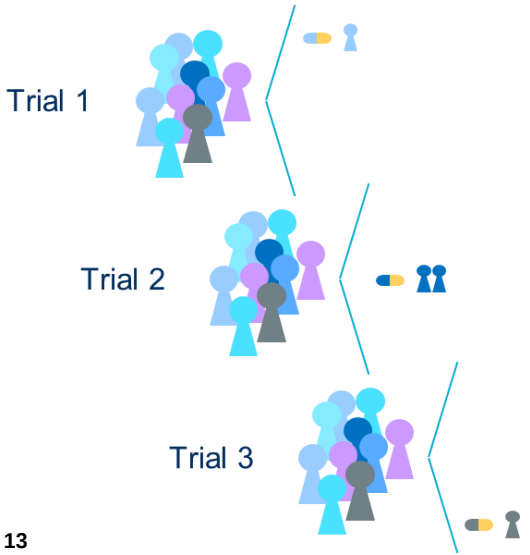
- **Heterogenous tumour – *FGFR2* amplified and non-amplified areas within tumour section**

EGFR v FGFR; the lessons for next time?

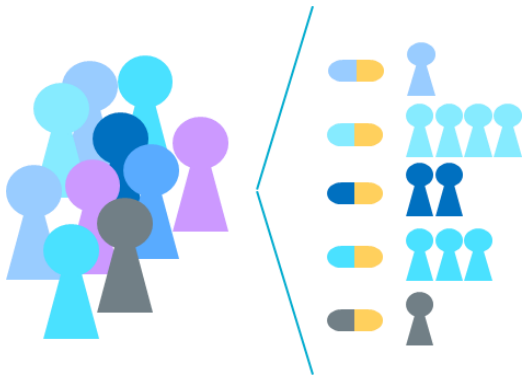
	EGFR – AZD9291	FGFR – AZD4547
Disease	EGFRm NSCLC	FGFR1 gastric cancer
Prevalence of genetic aberration	19% - Europe / US 45-50% - Korea / Japan	3-5% global
Diagnostic	Sequencing (DAKO assay)	FISH methodology
Other enrichment	Higher prevalence in female non-smokers	Unknown
Biopsy	ctDNA methods now available	Requires tumour biopsy
Tumour heterogeneity	Low, until progression	High
Breadth of utility (other tumours)	Low	High

Potential paradigm shifts in clinical trial design

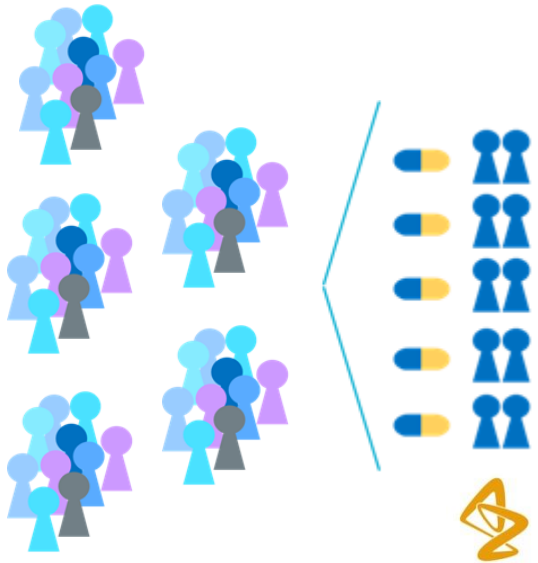
- Conventional trial design (e.g. EGFR, FGFR)
- Can be efficient (EGFR) but very high risk with novel targets (FGFR)



- Umbrella trial (multi-drug in single tumour type)
- Highly efficient if treatment arms can be balanced – e.g. Matrix



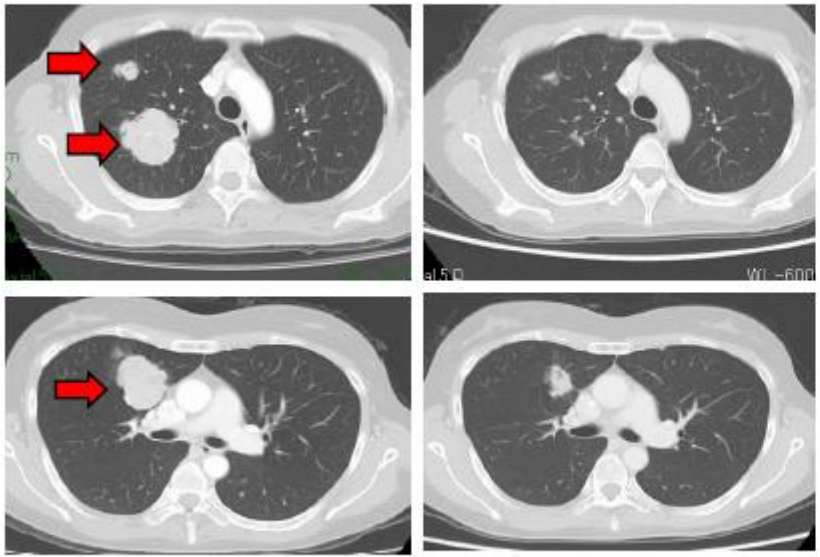
- Basket trial (single drug arm across multi-tumour setting)
- Highly efficient if suitable ‘feeder’ studies are available



AZD5363 in AKT1 mutated endometriod cancer

Case 1: Endometrioid carcinoma ovary

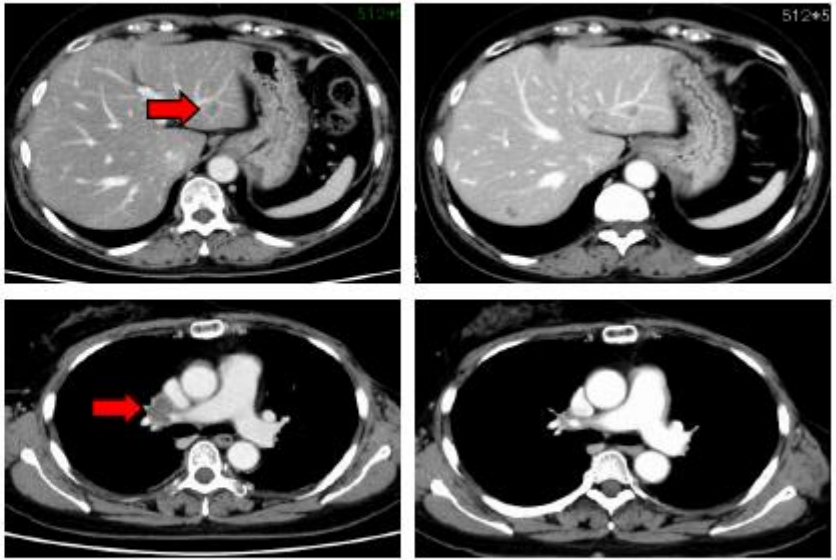
Baseline	Best Response (Day 433)



Right lung multiple metastases :
S1; from 42.3mm to 8.1mm
S2; From 43.4 mm to 22.3mm

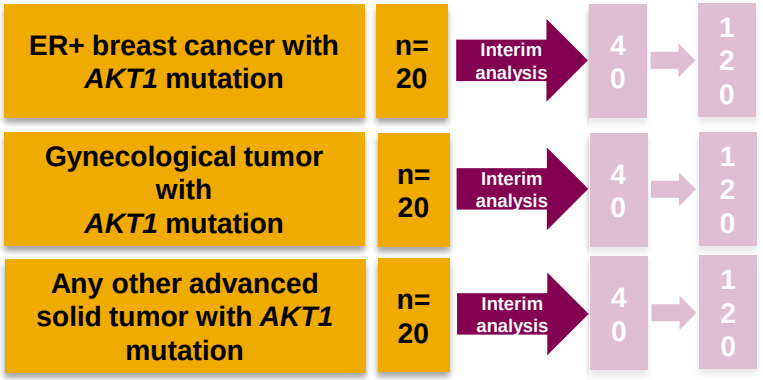
Case 2: ER+, HER2- breast cancer

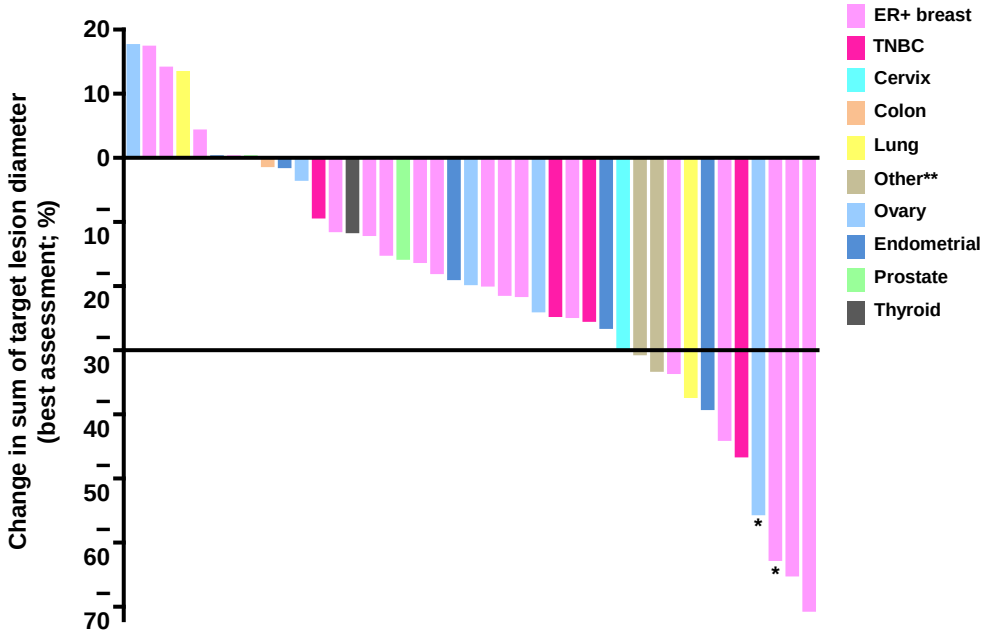
Baseline	Best Response (Day 205)



Mediastinal lymph node and liver metastases:
S3; from 19.5mm to 4.8mm
S4; From 17.2 mm to 14.8mm

Basket trial with AZD5363 in AKT1 mutation positive tumours- (Hyman et al)

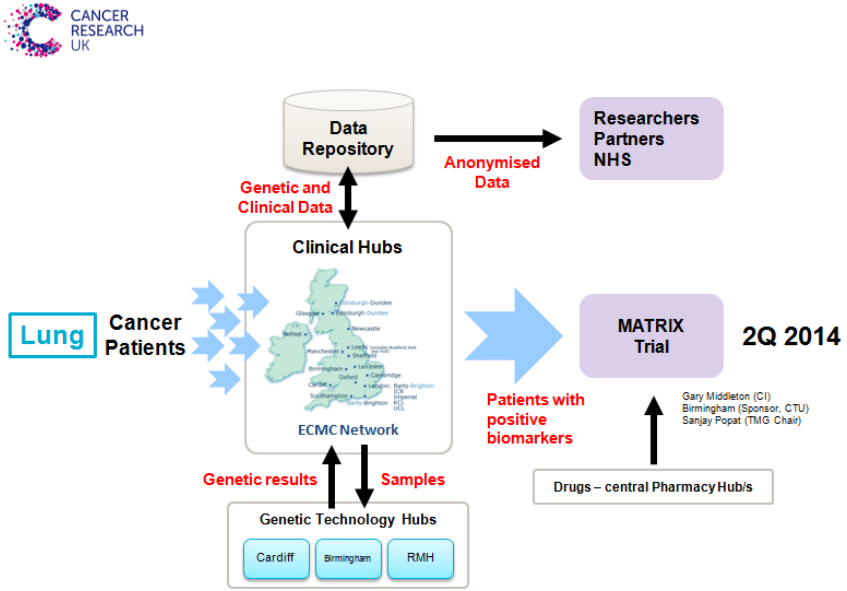




EORTC/NCI/AACR November 2015 – Hyman et al, AZD5363 a catalytic pan-AKT inhibitor in AKT1 mutation positive patients

Experience with MATRIX National Lung Trial – CRUK…

MATRIX National Lung Cancer Trial –
Cancer Research UK



Advantages –

- Systematic and parallel testing of multiple hypotheses, and rapid signal searching
- Cost effective
- Patient-centric approach
- Flexible to drop-in/take-out drugs/markers
- Opportunity to exploit small molecule inhibitors and large molecule immune system modulators – more options available for patients, from multiple Pharma

Challenges –

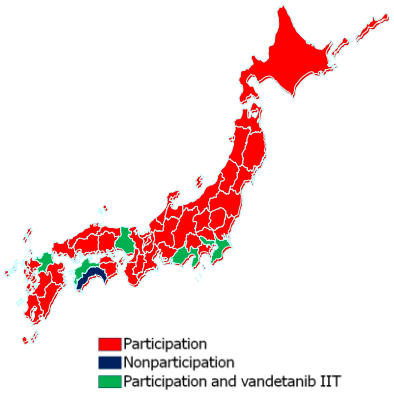
- Operationally complex
- UK only – but Nationwide programme
- Requires extensive technology evaluation

New models for implementation are building…

MATRIX National Lung Cancer Trial –
Cancer Research UK

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

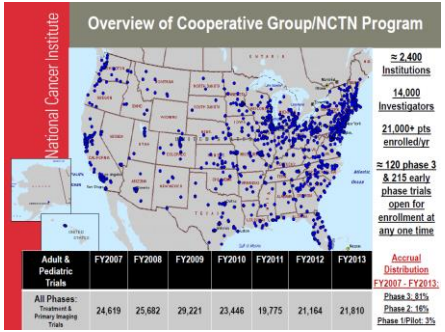
LC-SCRUM-Japan –
National screening programme



147 Institutes in 46 Prefectures
(as of November 2013)

Breast International Group –
EU screening programme

NCI MATCH –
US screening programme



Critical roles for Precision Medicine Trials across multiple academic centres (eg Cancer Core Europe)

- Possible to run clinical trials in small patient sub-sets but requires multiple conditions to be met to maximise recruitment of eligible patients

- Diagnostic methodology must be standardised -
  - Agreement on assay formats, protocols, cut-offs etc.
  - Laboratory training and monitoring
  - Tumour sampling protocols
  - Management of issues around tumour heterogeneity

- Non value-adding activities must be eliminated -
  - Convergence of documentation and processes
  - Seamless electronic data handling
  - Ability to integrate patients identified from parallel screening programmes

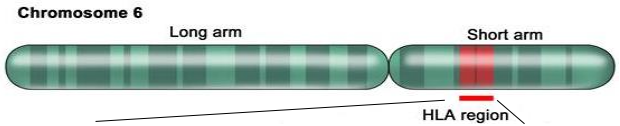
Working with Harvard to Develop Capabilities for NGS Analytics

Miika Ahdesmaki, Oliver Hofmann, Brad Chapman, Rory Kirchner, Zhongwu Lai, Danielle Greenawalt, Jonathan Dry, Justin Johnson

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Cancer genomes are complex and heterogeneous. New computational methods improve our ability to detect genomic changes relevant to treatment success. Collaborating with the Harvard Chan School of Public Health, we tested and validated approaches for assessing **immune system complexity**, **tumor heterogeneity**, and **structural rearrangements**:

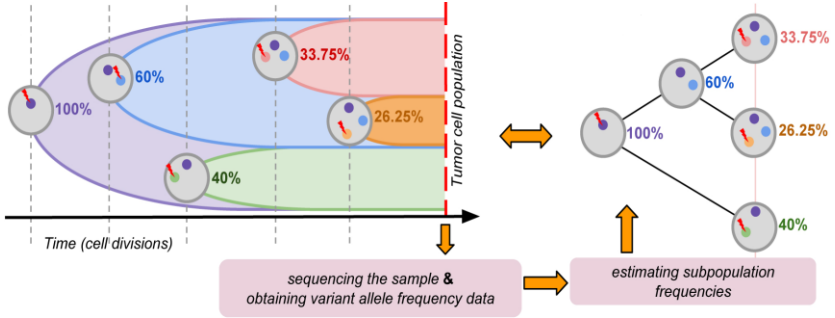
Immuno Oncology: **Validated HLA typing** from NGS data, enabling ongoing work in correlating HLA type with mutational load, PD-1 expression, and patient response.



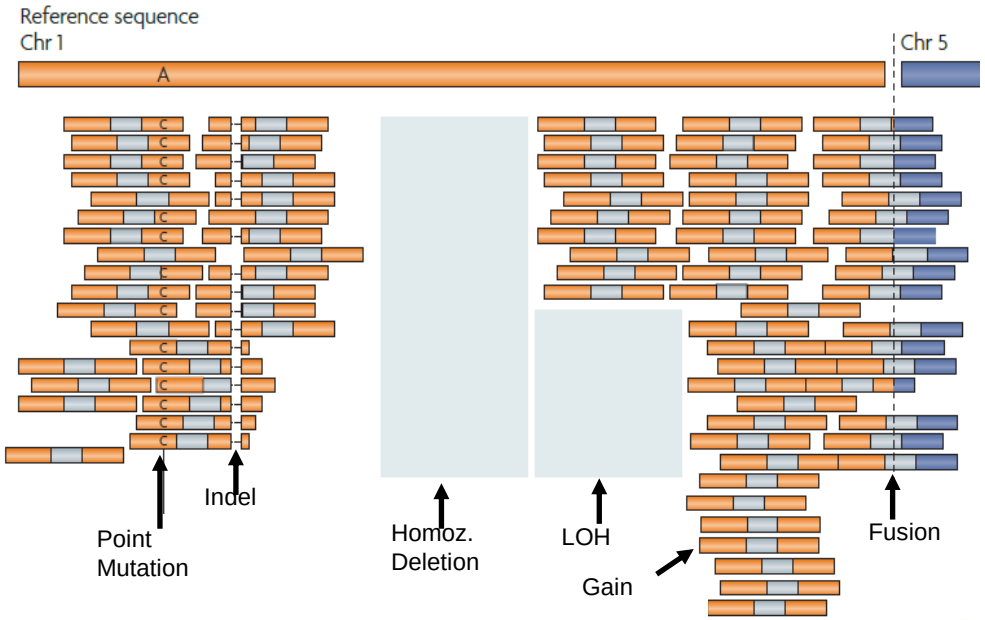
	Standard Method	AZ Method
HLA-A Genotype	**Wrong**	Correct
HLA-B Genotype	Correct	Correct
HLA-C Genotype	Correct	Correct

Consistently find ~1/3 of known HLA types are missed with the standard algorithms

Heterogeneity: To identify minority genomic changes driving drug resistance, we improved low frequency variant detection with VarDict and used the variant allele frequency to determine subclonal composition.



Large structural variation events are key tumor drivers, but difficult to detect. We improved speed, sensitivity and precision of detection of mutations including structural variants for downstream validation.



VarDict: a NGS computer algorithm

Zhongwu Lai, Jonathan Dry, Aleksandra Markovets, Miika Ahdesmaki, Brad Chapman, Justin Johnson

Features

- Handles ultra-deep sequencing with high computational efficiency
- Enables interpretation of tumor genetic evolution from ctDNA.
- VarDict is the only available NGS variant caller able to remove bias introduced by all commonly used targeted sequencing platforms.

Improved productivity

- Reprocessed 22K exomes in in 25 days vs several months with standard systems.

Publication:

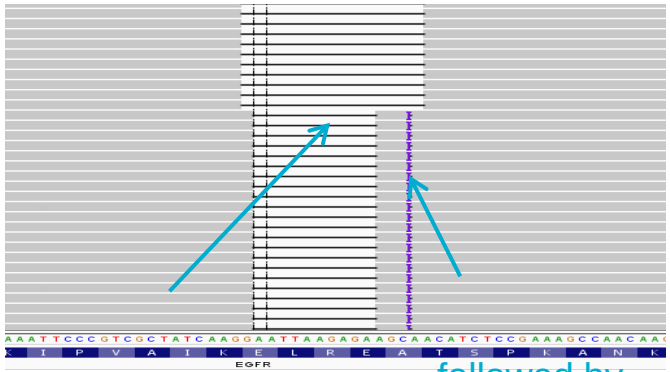
- Submitted and under review
- The Vardict algorithm was independently peer reviewed and accepted into the BCBio platform of gold-standard NGS processing
- A recent independent Genome Biology paper by Fang et al reviewing the world's best variant calling algorithms described VarDict as "the best single tool" for variant calling and "the best indel detector".
- The VarDict algorithm has been released, and applied by world leading genome centers and initiatives including Cornell, Genomics England, & MSKCC.

Technical Advancement
Ability to detect complex composite haplotypes
Ability to detect large deletions
Ability to detect copy number variation in targeted seq
Algorithm (and computational capacity) to variant call in ultra-deep sequencing
Capacity to process huge volumes of samples

EGFR activating mutations may be missed by standard NGS variant callers

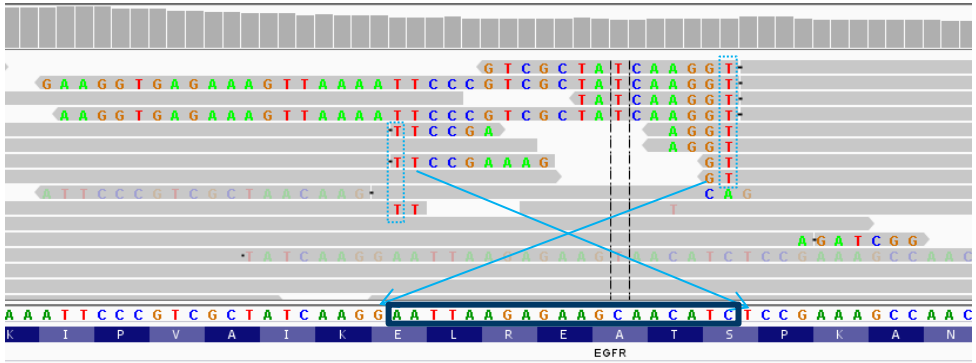
- Standard callers fail to identify complex activating mutations in EGFR; typically mis-aligned or called as frameshift deletion (20% of exon 19 deletions)
- VarDict (Zhongwu Lai, AZ) calls as in-frame deletion so clinically actionable

Trial patient B



10bp deletion followed by 1bp insertion

TCGA-05-4425-01 Lung adenocarcinoma *EGFR* exon 19

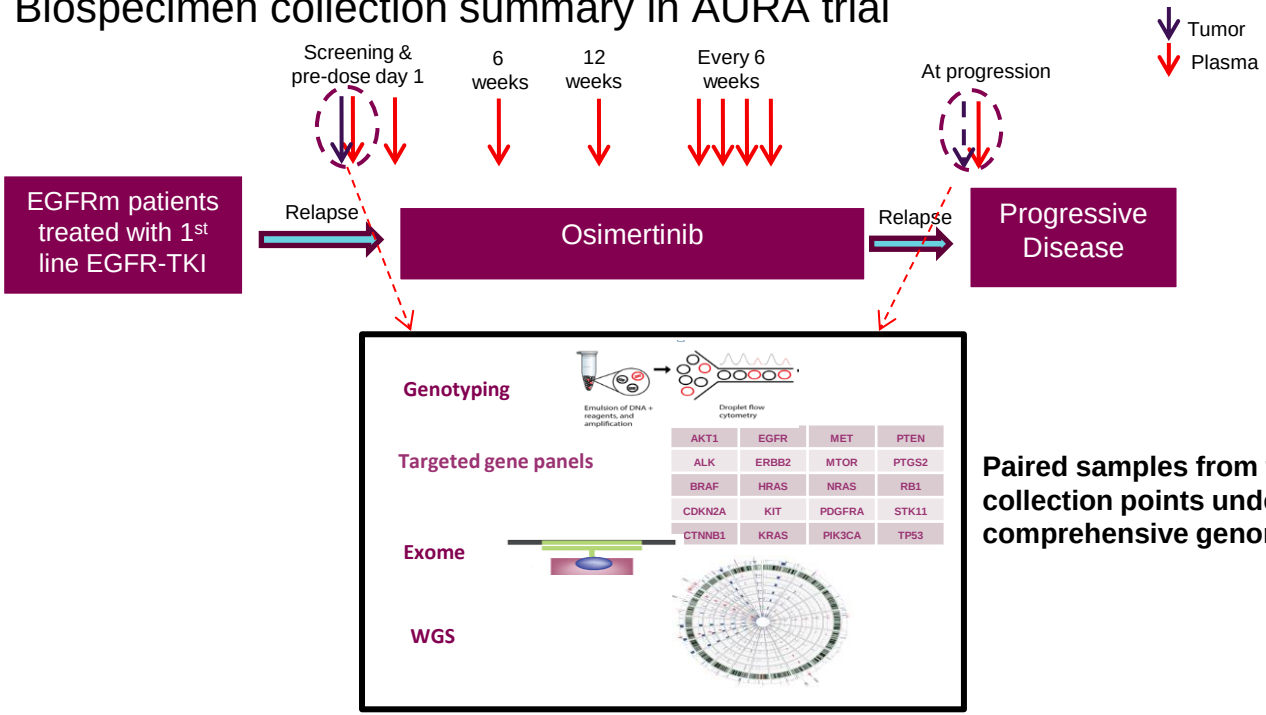


`c.2237_2255 del AATTAAGAGAAGCAACATC ins T`

- Cooperate with proximal insertions to result in activation

Collaboration to define mechanisms of resistance to osimertinib

Biospecimen collection summary in AURA trial



Paired samples from these 2 collection points undergo comprehensive genomic profiling

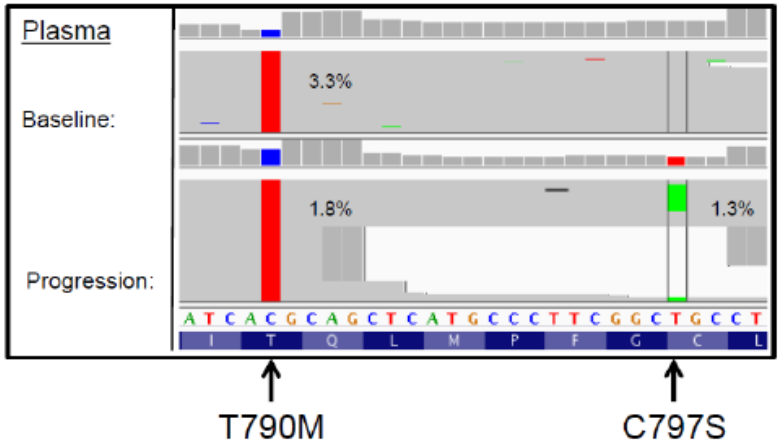
Actual sample collection rate for AURA Phase I expansion

	Tumor	Plasma
Baseline	>90%	100%
Progression	<1%	>80%

Plasma samples saved the day!

Identification of an acquired *EGFR* C797S mutation through NGS of ctDNA from an osimertinib-relapsed patient

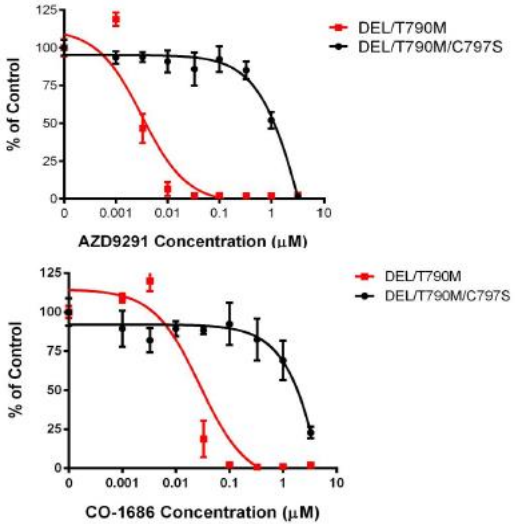
Patient initiates osimertinib and has a response after 6 weeks, followed by systemic progression after 23 weeks



NGS on plasma ctDNA reveals a new T→A mutation at time of progression (green) encoding for an *EGFR* C797S mutation.

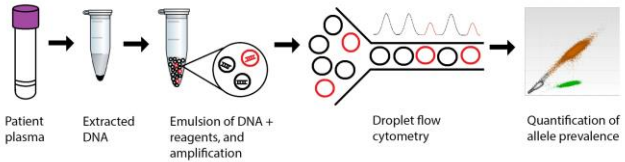
Thress et al, *Nature Medicine,* 2015

Academic collaboration with DFCI (G Oxnard, P Janne) enabled rapid progression



In vitro proof-of-principle

The C797S mutation dramatically decreases the ability of AZD9291 and CO-1686, another irreversible mutant selective TKI in clinical development, to inhibit growth in engineered Baf3 cells



Droplet digital PCR (ddPCR)

Established C797S ddPCR assay for patient plasmas enabled rapid assessment of C797S prevelance

Oxnard et al. Clin Cancer Res 2014;20:1698–1705.

EGFR C797S acquired mutation

nature medicine

Acquired *EGFR* C797S mutation mediates resistance to AZD9291 in non–small cell lung cancer harboring *EGFR* T790M

Kenneth S Thress[1], Cloud P Paweletz[2,3], Enriqueta Felip[4,5], Byoung Chul Cho[6], Daniel Stetson[1], Brian Dougherty[1], Zhongwu Lai[1], Aleksandra Markovets[1], Ana Vivancos[4], Yanan Kuang[2,3], Dalia Ercan[2], Sarah E Matthews[2], Mireille Cantarini[7], J Carl Barrett[1], Pasi A Jänne[2,3] & Geoffrey R Oxnard[2]

IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 • DENVER, COLORADO, USA

Mechanisms of acquired resistance to AZD9291 in EGFR T790M positive lung cancer

Geoffrey R. Oxnard[1], Kenneth S. Thress[2], Cloud P. Paweletz[1], Daniel Stetson[2], Brian Dougherty[2], Zhongwu Lai[2], Aleksandra Markovets[2], Enriqueta Felip[3], Ana Vivancos[3], Yanan Kuang[1], Lynette Sholl[4], Amanda J. Redig[1], Mireille Cantarini[5], J. Carl Barrett[2], Rathi N. Pillai[6], Byoung Chul Cho[7], David Planchard[8], Jean-Charles Soria[8], Pasi A. Jänne[1]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]AstraZeneca, Gatehouse Park, Waltham, MA, USA; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]Brigham and Women's Hospital, Boston, MA, USA; [5]AstraZeneca, Alderley Park, Macclesfield, UK; [6]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [7]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; [8]Gustave Roussy, Paris, France

Presented by GR Oxnard at the World Conference on Lung Cancer 2015
Journal of Thoracic Oncology 2015; 10(9, Suppl 2): S207, abstract Oral 17.07

15 patients with ctDNA following progression on AZD9291 (osimertinib)

-6 acquired C797S, 4 'lost' T790M, 5 'unknown'

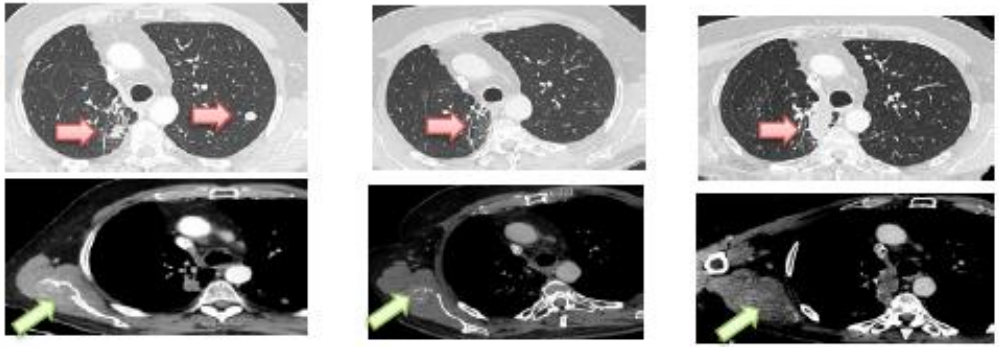
UPDATE

- **67 patients met the eligibility criteria for C797S analysis**
- **15/67 (22%) had detectable C797S on ddPCR, all with detectable T790M**
- **C797S more common with EGFR exon 19 del mutations (30%) vs. those with L858R mutations (8%, p=0.06)**

HER2 amplification in tumor re-biopsies (Planchard,et al)

- 54-year-old man
- Former smoker (20 patient-years)
- Adenocarcinoma
- Metastatic to brain, bone
- EGFR Ex19del

BASELINE IMAGING UNAVAILABLE



LUNG BIOPSY
EGFR Ex19del
T790M negative

Gefitinib

LUNG BIOPSY
EGFR Ex19del and
T790M positive
No HER2 amplification (CGH)

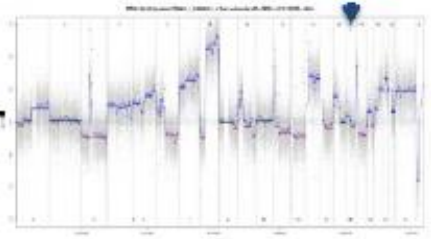
AZD9291 (80 mg)

SCAPULAR BIOPSY
EGFR Ex19del
T790M negative

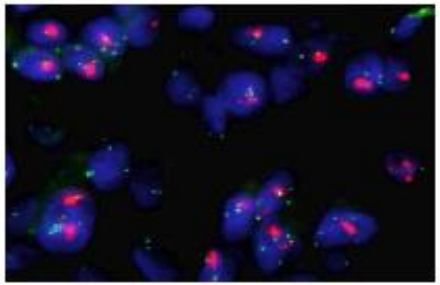
LUNG BIOPSY
EGFR Ex19del
T790M negative
C797S negative
HER2 amplification

SCAPULAR BIOPSY
EGFR Ex19del
T790M negative

HER2



HER2 amplification by CGH: log ratio x3.32



HER2/CEP17: 6.65
HER2 in red; centromere 17 in green

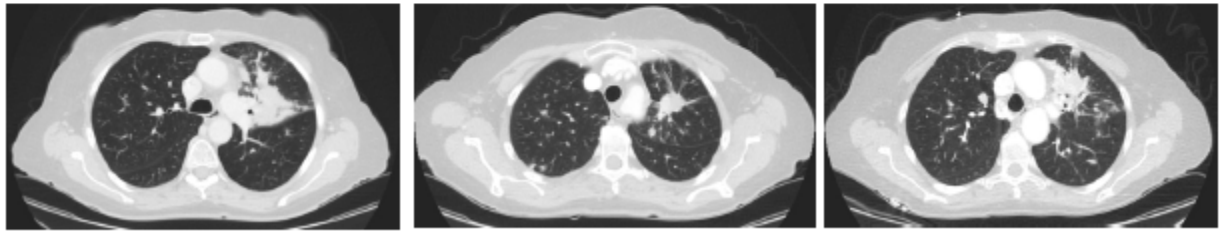
NGS: Ion Torrent Personal Genome Machine®
CGH: Agilent technology
HER2-FISH: Dako DNA probe kit

Planchard et al. Ann Oncol 2015;pii: mdv319 (Epub ahead of print)
CGH, comparative genomic hybridization; Ex19del, exon 19 del; FISH, fluorescence *in situ* hybridization

MET amplification in tumor re-biopsies (Pillai, et al)

- 69-year-old female with EGFR-mutant NSCLC metastatic to liver, adrenal, bones who had progression after first-line chemotherapy and subsequent erlotinib
- Resistance biopsy was inadequate for genotyping, but plasma genotyping positive for L858R (26%) and T790M (4%)
- Initiated AZD9291 and responded on the first scan (-40%) but progressed after 24 weeks
- Resistance biopsy undergone for targeted NGS:
  - Positive for L858R, negative for T790M, positive for MET amplification
  - MET protein overexpression also seen on IHC

Pre-AZD9291 plasma genotype:
L858R (26%)
T790M (4%)



Baseline | 4 months | 6 months

Progression tumor genotype:
L858R
T790M negative
MET amplified

Data source: R. Pillai; S. Ramalingam
IHC, immunohistochemistry; NSCLC, non-small cell lung cancer

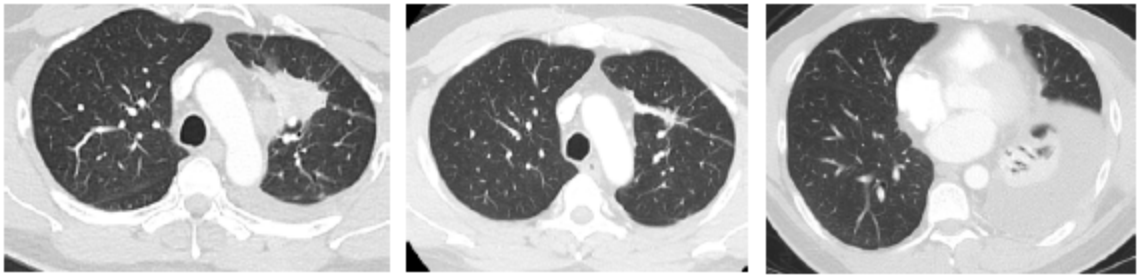
BRAF mutation in tumor re-biopsies (Janne, et al)

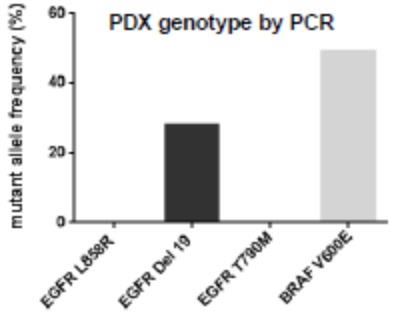
- 49-year-old male with metastatic NSCLC positive for EGFR exon 19 deletion
- Developed resistance to first-line erlotinib after 11 months, T790M positive biopsy
- Had a confirmed PR to AZD9291 but growth of lung mass, effusion after 5 months
- Targeted NGS of progression biopsy shows exon 19 deletion (8% of reads), no T790M, BRAF V600E (6% of reads)
  - A patient-derived xenograft is in development

Pre-AZD9291
Ex19del/T790M

2 months

6 months
Ex19del/BRAF V600E



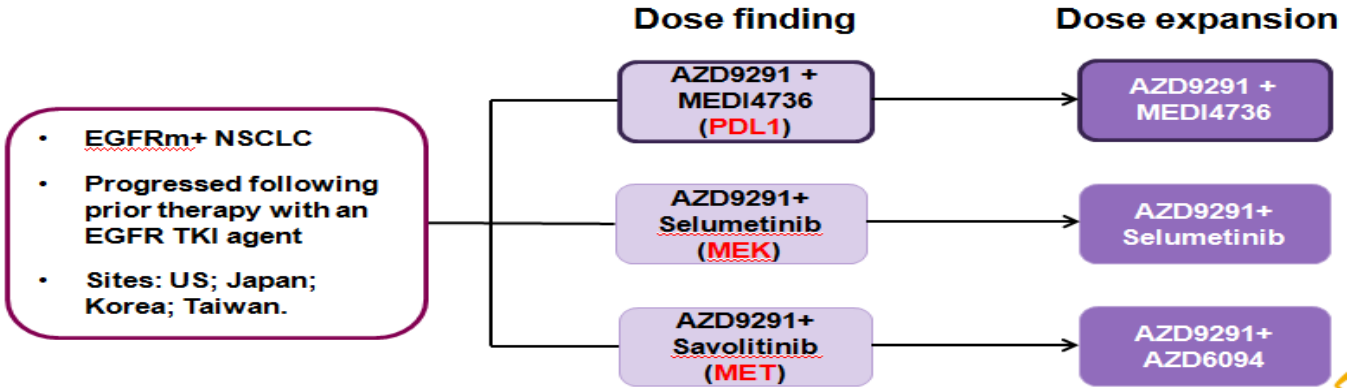


Data source: P.A. Jänne, A.J. Redig

Future Directions in EGFRm NSCLC

1. '4th Generation' inhibitors to address C797S-mediated resistance to AZD9291
   - Drug discovery efforts to develop novel compounds capable of interacting and inhibiting the C797S variant of EGFR

2. Combination treatments to delay the development of non-C797S mediated resistance
   - TATTON clinical trial (NCT02143466); G Oxnard PI (DFCI)



Oxnard, et al; Preliminary results of TATTON, a multi-arm Phase Ib trial of AZD9291 combined with MEDI4736, AZD6094 or selumetinib in EGFR-mutant lung cancer. ASCO Annual Meeting, Chicago, May 2015

Conclusions

- To make precision medicine truly applicable to the majority of cancer patients requires:
  - Collaboration
  - Standards
  - Changes in clinical trial designs
  - Comprehensive tissue and plasma collection – at diagnosis and on progression
  - Shared NGS tools to deal with more complex genetic aberrations
  - Tolerable combinations to address & prevent emergence of resistance

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