

# Poster Discussion: Basic Science, Biomarkers, New Diagnostics and Translational Research

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# Disclosures

Honoraria for advisory board work or speaker bureau activities from Pfizer, Roche, AZD, Boehringer, BMS, MSD

# 483PD

The declaration of new lesions as a major factor of local-central discrepancy during a RECIST phase II trial

Beaumont H, Evans T, Hong S, Chadjaa M, Monoston Z

# Problem Statement

In clinical trials, discrepancy of response assessment is an issue between Local site investigators and Blinded Independent Central Review

The nature of these discrepancies has been analyzed in different trials settings



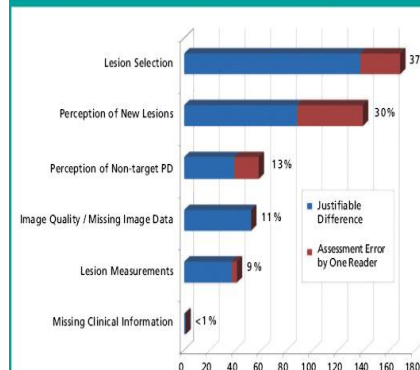
1. Incorrect use of RECIST in selection of target lesions
2. Discrepancies in tumor measurements
  - 2.1 RECIST criteria incorrectly or insufficiently applied
  - 2.2 Discrepancies in measuring tumor size
3. Discrepancies describing new or disappeared lesions

## Factors influencing site/central discordance

Workflow differences  
 Limited amount of non-radiographic clinical information  
 Treatment bias  
 Lesion selection for evaluation  
 Missing data and conventions for handling missing data  
 Inter- reader and intra-reader variability  
 Date conventions  
 Variability in protocol training  
 Understanding of and application of response criteria  
 Failure to compare all prior studies  
 Perception of new lesions  
 Subjective assessment of non-target disease  
 Tumour type  
 Drug efficacy  
 Precision of the response criteria  
 Complexity of the response assessment

R. Fort et al. Lessons learned from independent central review (2009) European Journal of Cancer 268-274

## Causes of Discordance: Percentages



Source: Kristin Borradaile et al.

**Figure 1.** The causes of discordance and classification of justifiable versus interpretive error.

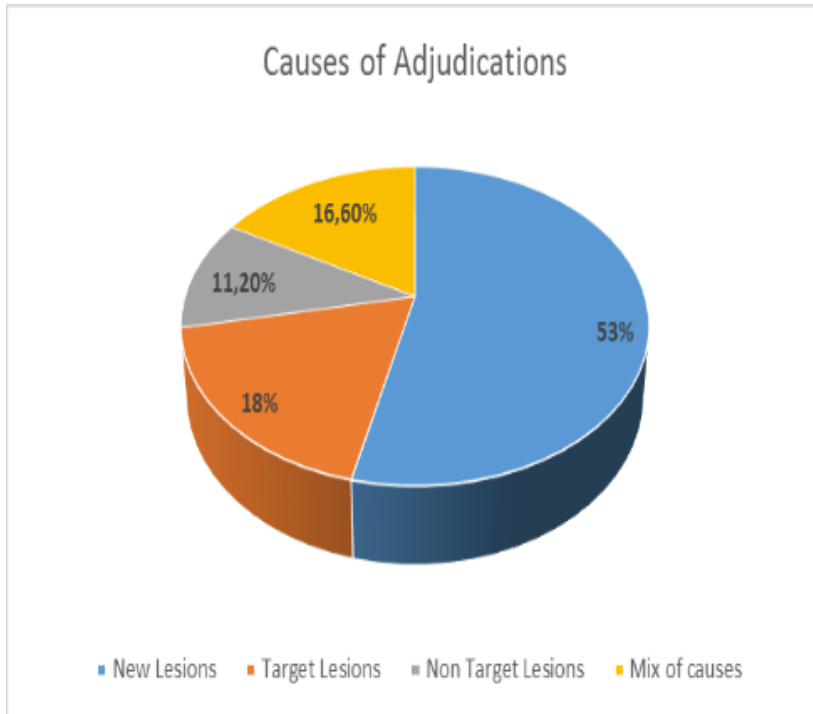
K. Borradaile et al. Lessons learned from independent central review (2009) ASCO

K. Skougard et al. Observer variability in a phase II trial assessing consistency in RECIST application (2012) Acta Oncologica, 51:6, 774-780

We analyzed a RECIST 1.1 phase II clinical trial with Local Investigator (LI)/ Blinded Independent Central Review (CR) of Small Cell Lung Cancer patients to rank major causes of discrepancies and to suggest improvements

# Results

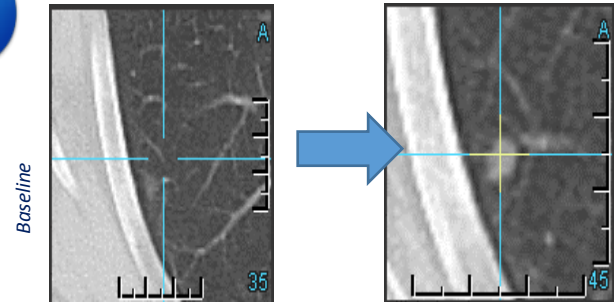
Discordance rate was 37% (by patient)



The major cause of discordance was the detection of new lesions

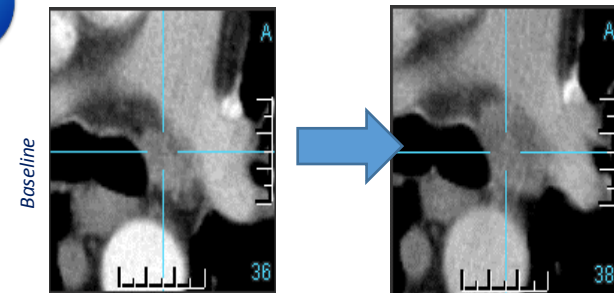
1. Because different sensitivities of LI/CR at detecting new lung lesions
2. Because Unclear definition of criteria defining new lymph node lesions

1

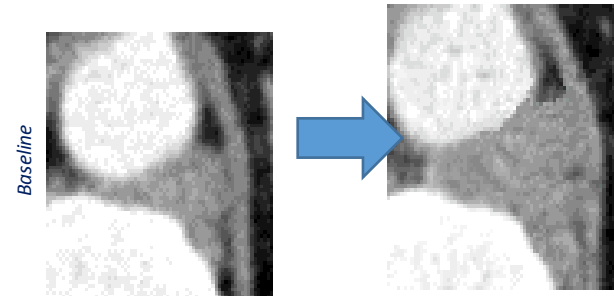


New pulmonary lesion not reported by LI

2



FU 1:  
New lymph node not reported by LI



FU 2:  
New lymph node not reported by CR

Discrepant lymph node evaluations had Shortest Axial Diameter (SAD) near 15mm or near 10mm at initial time point or a had a difference of SAD between time points smaller than 5mm

# How to reduce reader discordance?

Investigator vs. central reader discrepancies on declaring new lymph node lesions can be categorized as having two main reasons:

1. Unclear criteria: Unclear definition of threshold for stating pathological new lymph nodes. Unclear growth between consecutive time points that define progression of a pre-existing lymph node.
2. Reader's sensitivity: Local investigators declared more new nodal lesions.

To reduce discordance, it is suggested to improve/clarify the definition of new lymph node (with appropriate training)

1. Shortest Axial Diameter (SAD) greater than 15mm and smaller at previous time point.
2. SAD measurement of new nodal lesion shall be performed when lesion first appearing. SAD measurement shall be performed at previous time point if the nodal lesion was visible.
3. SAD measurement can be performed manually, however, an automatic volume-derived SAD assessment is preferred.
4. Detection of a new nodal lesion should be confirmed by another progressive factor

Whenever possible, enable a computer-aided detection system dedicated to new lung lesions (trained with adequate dataset)

# RECIST 1.1 Guidelines: Contents

1. Contents
2. Basic Paradigm
3. Image Acquisition
4. Measurable Lesions
5. Non-Measurable Lesions
6. Special Lesion Types
7. Target Lesions
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16. Missing Assessments and Non-evaluable Designation
17. Recurrence of Lesions
18. Evaluation of Overall Time Point Response for Patients with Measurable Disease at Baseline
19. Evaluation of Overall Time Point Response for Patients without Measurable Disease at Baseline
20. Confirmation
21. Modifications and Variants

# RECIST 1.1: Basic Paradigm

Assess at baseline

- Look for measurable lesions
- Select target and non-target lesions
- Measure target lesions
- Add up to get tumour burden

Treat patient

Follow-up evaluation

- Measure target lesions
- Assess non-target lesions and look for new lesions
- Calculate time point response



# RECIST 1.1: Image Acquisition

## CT

- Slice thickness  $\leq 5\text{mm}$  if possible, contiguous
- IV and oral contrast used (3-phase liver if appropriate)
- Field of view adjusted to body habitus (include the whole body, out to the skin)

## MRI

- Axial T1 and T2, axial T1 post contrast
- $\leq 5\text{mm}$  contiguous slices if possible
- Use the same machine for all time points

## PET/CT

- Not required, but may be useful for assessment of new lesions on future time points
- CT portion of PET/CT is usually of lower quality, and should not be used instead of dedicated diagnostic CT. If the CT is of high quality, with oral and IV contrast, use with caution. Additional information from PET may bias CT assessment.
- Use the same machine for all time points

Calipers – Hard to use reproducibly

- Include ruler in photograph for skin lesions

Chest x-ray (CXR) – Use CT instead (if possible)

Ultrasound – Not reproducible

# RECIST 1.1: Measurable Lesions

## Measurable Lesions

- Tumour  $\geq 10$  mm in longest diameter (LD) on an axial image on CT or MRI with  $\leq 5$  mm reconstruction interval
  - If slice thickness  $> 5$  mm, LD must be at least 2 times the thickness
- Tumour  $\geq 20$  mm LD by chest x-ray (if clearly defined & surrounded by aerated lung); CT is preferred (even without contrast)
- Tumour  $\geq 10$  mm LD on clinical evaluation (photo) with electronic calipers; skin photos should include ruler
  - Lesions which cannot be accurately measured with calipers should be recorded as non-measurable
- Lymph nodes  $\geq 15$  mm in short axis on CT (CT slice thickness no more than 5 mm)
- Ultrasound cannot be used to measure lesions

# RECIST 1.1: Non-Measurable Lesions

All other definite tumour lesions

- Masses <10 mm
- Lymph nodes 10-14 mm in short axis
- Leptomeningeal disease
- Ascites, pleural or pericardial effusion
- Inflammatory breast disease
- Lymphangitic involvement of skin or lung
- Abdominal masses or organomegaly identified by physical exam which cannot be measured by reproducible imaging techniques

Benign findings are NEVER included. Also, do not include equivocal (“cannot exclude”) findings



# RECIST 1.1: Special Lesion Types

## Bone Lesions

- NMBS, PET scans & plain films can be used to confirm the presence or disappearance of bone lesions, but NOT for measurement
- Bone lesions with identifiable soft tissue components seen on CT or MR can be measurable if the soft tissue component meets the definition above
- Blastic bone lesions are unmeasurable

## Cystic Lesions

- Simple cysts are not included as lesions
- Cystic metastases may be selected, but prefer to use non-cystic lesions as “target”
- Clarify with sponsor as to their acceptability before study start

# RECIST 1.1: Target Lesions

- Choose up to 5 lesions
  - Up to 2 per organ
- Add up longest diameters (LD) of non-nodal lesions (axial plane)
- Add short axis diameters of nodes
- This is the “sum of the longest diameters” (SLD)



# RECIST 1.1: Baseline Documentation

Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

## Target Lesions

- A maximum of five (5) target lesions in total (up to two (2) per organ)
- Select largest reproducibly measurable lesions
- If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be ...

## Non-Target Lesions

- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”)

## RECIST 1.1: Lesions with Prior Local Treatment

- Lesions in previously irradiated areas (or areas treated with local therapy) should not be selected as target lesions, unless there has been demonstrated progression in the lesion
- Conditions in which these lesions would be considered target lesions should be defined in study protocols



# RECIST 1.1: Evaluating Response at Each Time Point

- Measure previously chosen target lesions even if they are no longer the largest
- Evaluate all previously identified non-target lesions
- Look for new definite cancer lesions





# RECIST 1.1: Target Lesion Evaluation Guidelines

- Measure LD (axial plane) for each target lesion
- Measure short axis for target lymph nodes
- Add these measurements to get the SLD
- If too small to measure, a default value of 5 mm is assigned.
- If the lesion disappears completely, the measurement is recorded as 0 mm.
- Splitting or coalescent lesions
  - If a target lesion fragments into multiple smaller lesions, the LDs of all fragmented portions are added to the sum
  - If target lesions coalesce, the LD of the resulting coalescent lesion is added to the sum

# RECIST 1.1: Target Lesion Evaluation

RESPONSE	DEFINITION
Complete Response (CR)	Disappearance of all extra nodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis.
Partial Response (PR)	At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	<p>SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest)</p> <p>The SLD must also demonstrate an absolute increase of at least 5mm.</p> <p>(Two lesions increasing from 2 mm to 3 mm, for example, does not qualify)</p>

# RECIST 1.1: Non-Target Lesion Evaluation

RESPONSE	DEFINITION
Complete Response (CR)	<p>Disappearance of all extra nodal non-target lesions</p> <p>All lymph nodes must be non-pathological in size (&lt;10 mm short axis).</p> <p>Normalization of tumour marker level</p>
Non CR/Non PD	<p>Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits</p>
Progressive Disease (PD)	<p>Unequivocal progression of existing non-target lesions. (Subjective judgement by experienced reader)</p>

# RECIST 1.1: New Lesions

- Should be unequivocal and not attributable to differences in scanning technique or findings which may not be a tumour
  - Does not have to meet criteria to be “measurable”
- If a new lesion is equivocal, continue to next time point. If confirmed then,
- PD is assessed at the date when the lesion was first seen.
- Lesions identified in anatomic locations not scanned at baseline are considered new
- New lesions on US should be confirmed on CT/MRI



# RECIST 1.1: FDG-PET

New lesions can be assessed using FDG-PET

- A 'positive' FDG-PET scan lesion means one with uptake greater than twice that of the surrounding tissue on the attenuation corrected image
- (-) PET at baseline and (+) PET at follow-up:
  - Progressive Disease (PD) based on a new lesion
- No PET at baseline and (+) PET at follow-up: PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of PD is the date of the initial PET scan.
- No PET at baseline and (+) PET at follow-up corresponding to a pre-existing lesion on CT that is not progressing is not PD

# RECIST 1.1: Missing Assessments

- If all lesions cannot be evaluated due to missing data or poor image quality the patient is not evaluable (NE) at that time point
- If only a subset of lesions can be evaluated at an assessment, the visit is also considered NE, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response
  - E.g. PD based on other findings

# RECIST 1.1: Recurrence of Lesions

- For a patient with Stable Disease (SD)/Partial Response (PR), a lesion which disappears and then reappears will continue to be measured and added to the sum
  - Response will depend on the status of the other lesions
- For a patient with Complete Response (CR), reappearance of a lesion would be considered Progressive Disease (PD)



# RECIST 1.1: Evaluation of Overall Time Point Response for Patients with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Not Evaluable



## RECIST 1.1: Evaluation of Overall Time Point Response for Patients without Measurable Disease at Baseline

Non-Target Lesions	New Lesions	Overall
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal Progression	Yes or No	PD
Any	Yes	PD

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Not Evaluable

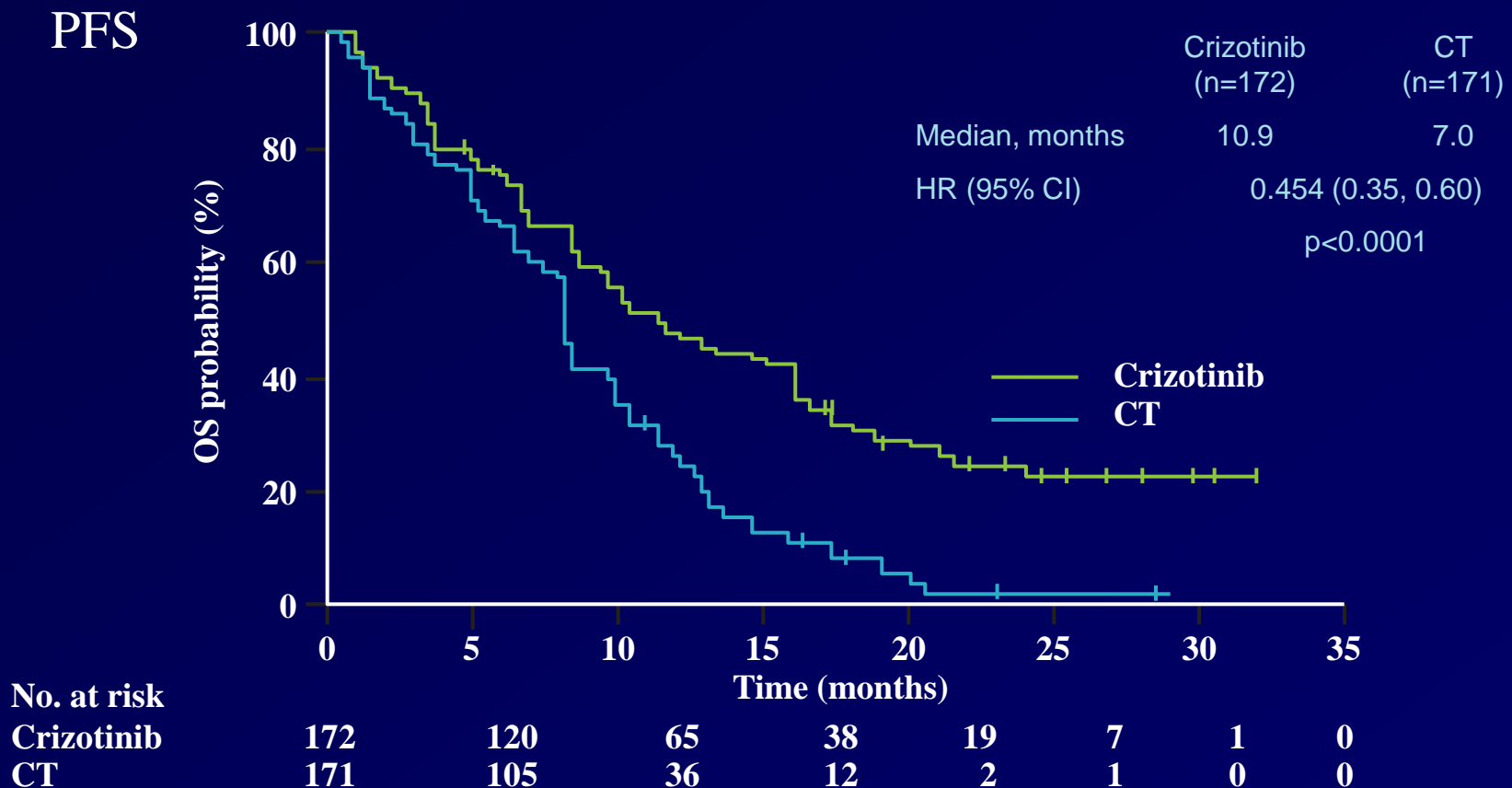
# An Overview of RECIST 1.1

RESPONSE	RECIST 1.1	Modifications to RECIST
Stable Disease (SD)	<ul style="list-style-type: none"> <li>Neither 30% decrease compared to baseline nor 20% increase compared to nadir</li> </ul>	<ul style="list-style-type: none"> <li>No change</li> <li>Confirmation not required</li> </ul>
Complete Response (CR)	<ul style="list-style-type: none"> <li>Disappearance of all target and non-target lesions</li> <li>Nodes must regress to &lt;10mm short axis</li> <li>No new lesions</li> <li>Confirmation required</li> </ul>	<ul style="list-style-type: none"> <li>No change</li> <li>Confirmation required</li> </ul>
Partial Response (PR)	<ul style="list-style-type: none"> <li>≥30% decrease compared to baseline</li> <li>Confirmation required</li> </ul>	<ul style="list-style-type: none"> <li>No change</li> <li>Confirmation required</li> </ul>
Progressive Disease (PD)	<ul style="list-style-type: none"> <li>≥20% +5mm absolute increase compared to nadir</li> <li>Appearance of new lesions</li> <li>Unequivocal progression of non target disease</li> </ul>	<ul style="list-style-type: none"> <li>Continue treatment if stable until next imaging time point</li> <li>If progression is confirmed but there is a decrease in tumour burden compared to the prior time point, consult sponsor</li> </ul>

# First-line crizotinib versus pemetrexed-cisplatin or pemetrexed-carboplatin in patients (pts) with advanced *ALK*-positive NSCLC: results of a phase III study (PROFILE 1014)

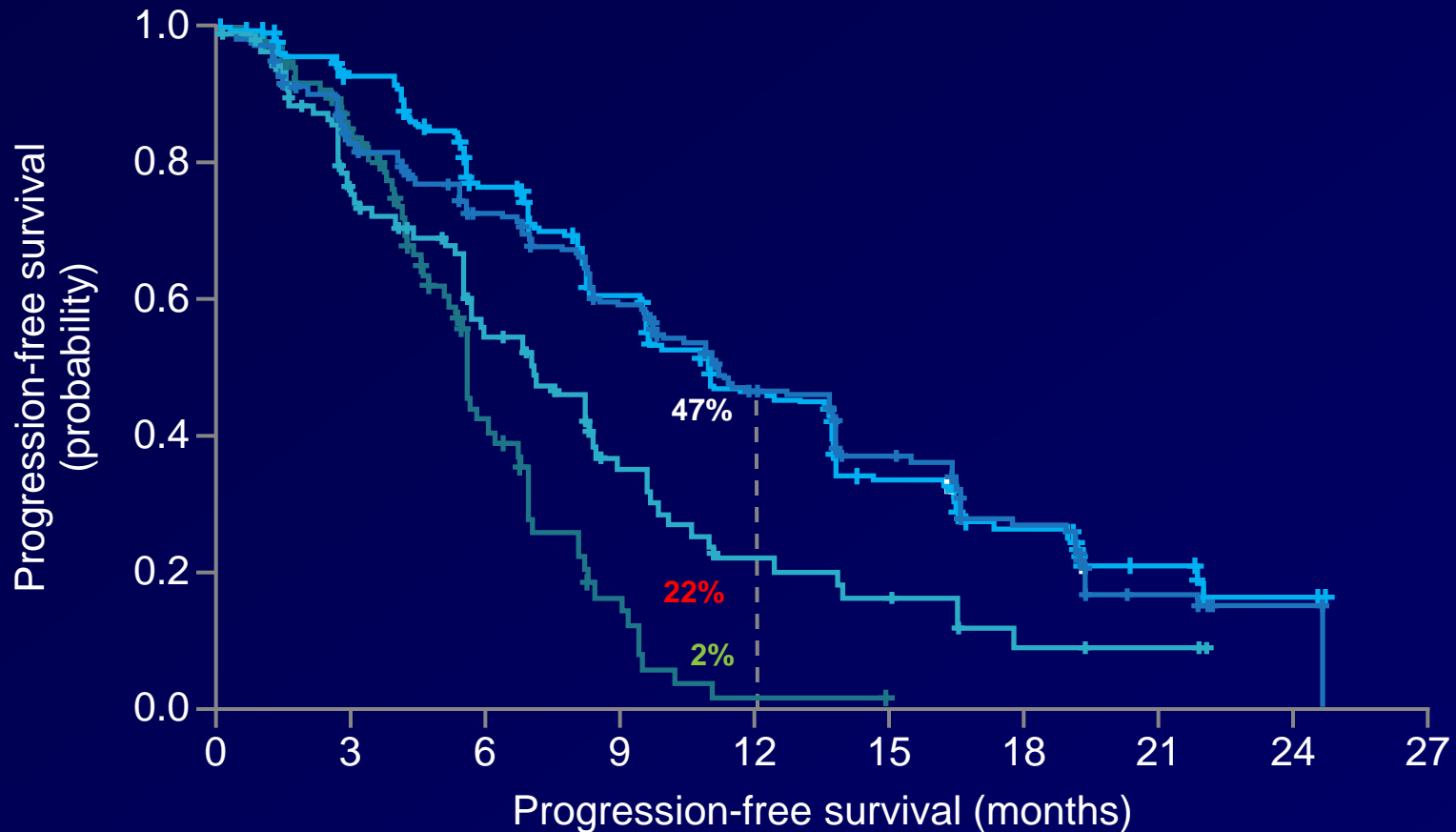
- Key results

- Addition of crizotinib significantly improved PFS but not OS compared with CT alone



# Primary endpoint: PFS LL3 and LL6 superimposed Independent review

All randomized patients

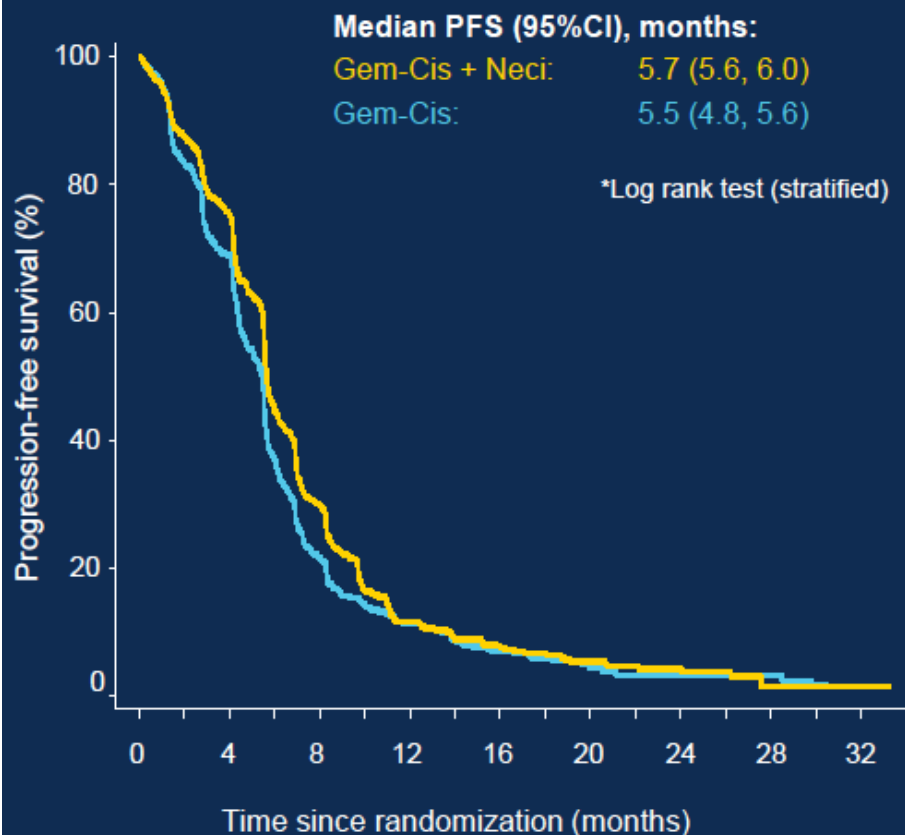


Number at risk

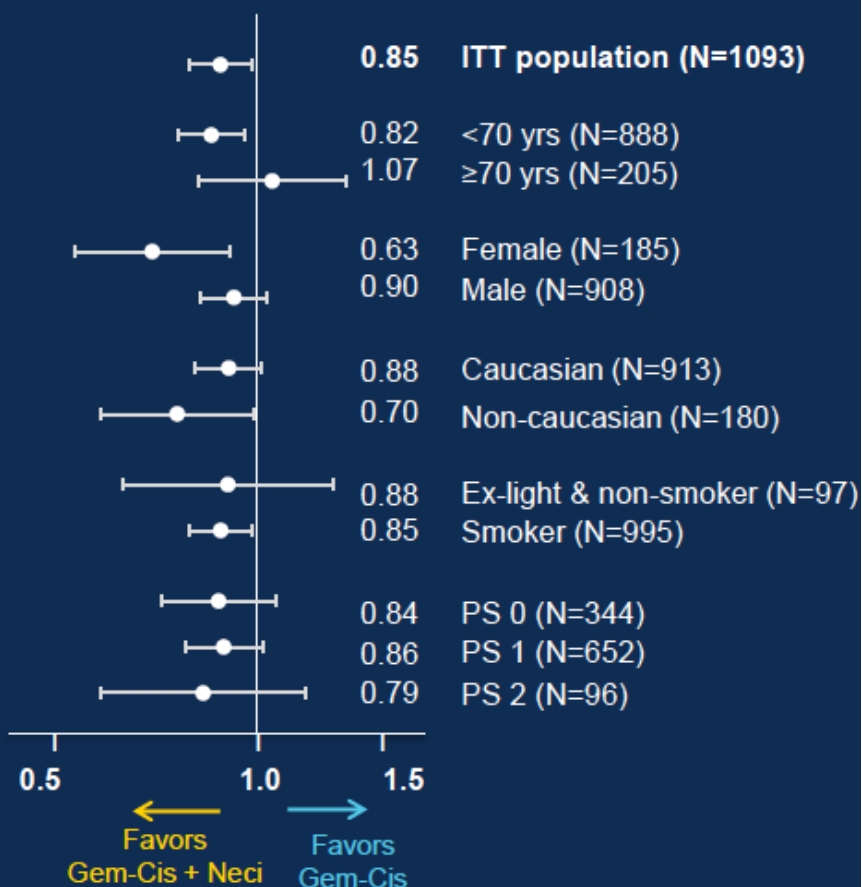
Afatinib	230	180	151	120	77	50	31	10	3	0
Cis/Pem	115	72	41	21	11	7	3	2	0	0
Afatinib	242	208	166	126	89	60	35	12	4	0
Cis/Gem	122	70	25	8	1	0	0	0	0	0

# Progression-Free Survival (ITT)

HR (95%CI): 0.85 (0.74, 0.98); p=0.020\*



## Hazard ratio



# Clinically

- If new lesion appears or PD occurs we often make a judgement on whether or not to continue therapy
- If patient deriving clinical benefit therapy is often continued e.g. on EGFR TKI
- In some cases the progressive lesion is targeted with local therapy

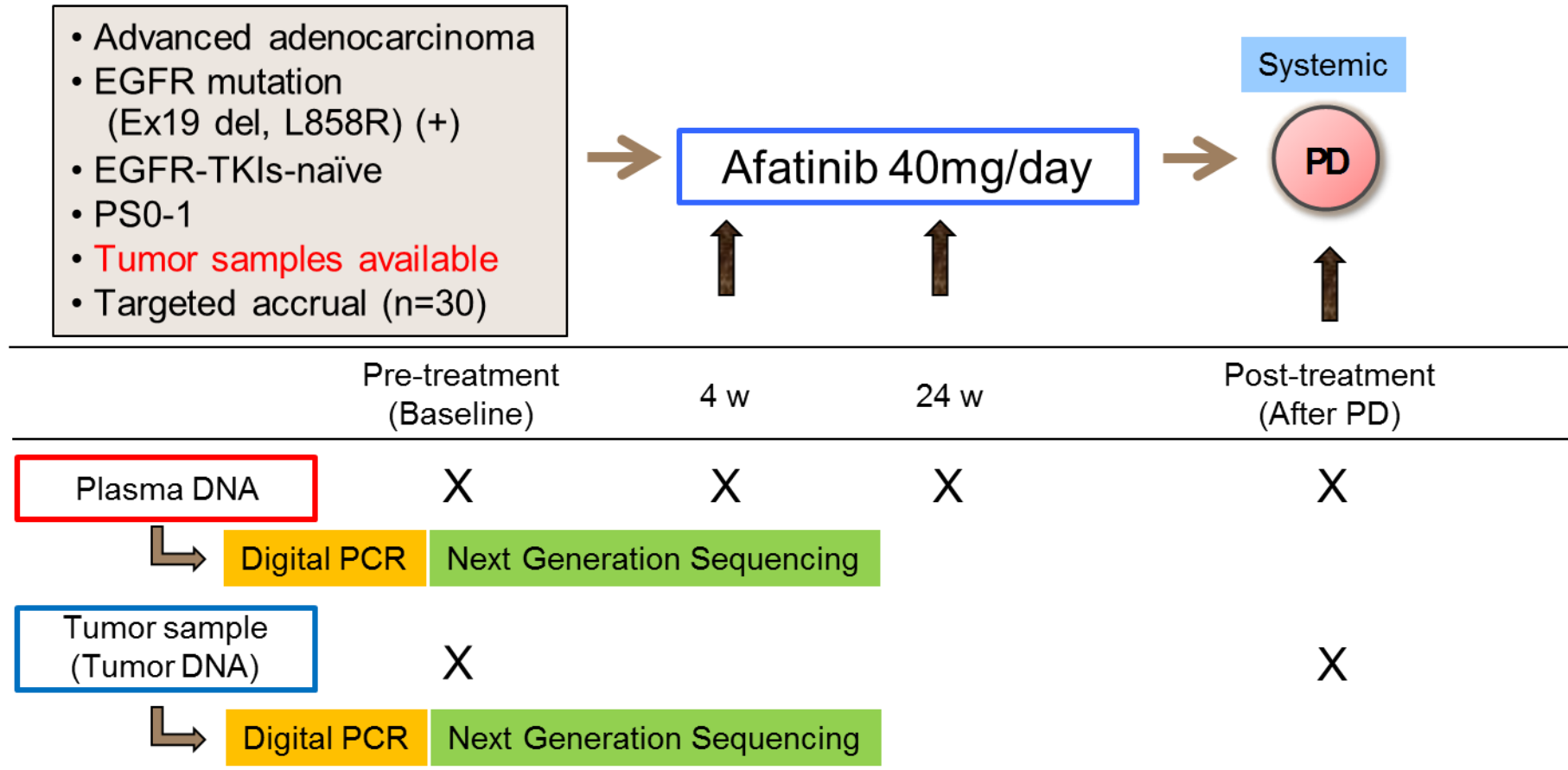


484PD

A multicenter prospective biomarker study in afatinib-treated patients with EGFR-mutation positive non-small cell lung cancer

Iwama E, Sakai K, Azuma K, Nosaki K, Harada D, Hotta K, Ohyanagi F, Kurata T, Akamatsu H, Goto K, Fukuhara T, Nakanishi Y, Nishio K, Okamoto JP.

## ~Method~



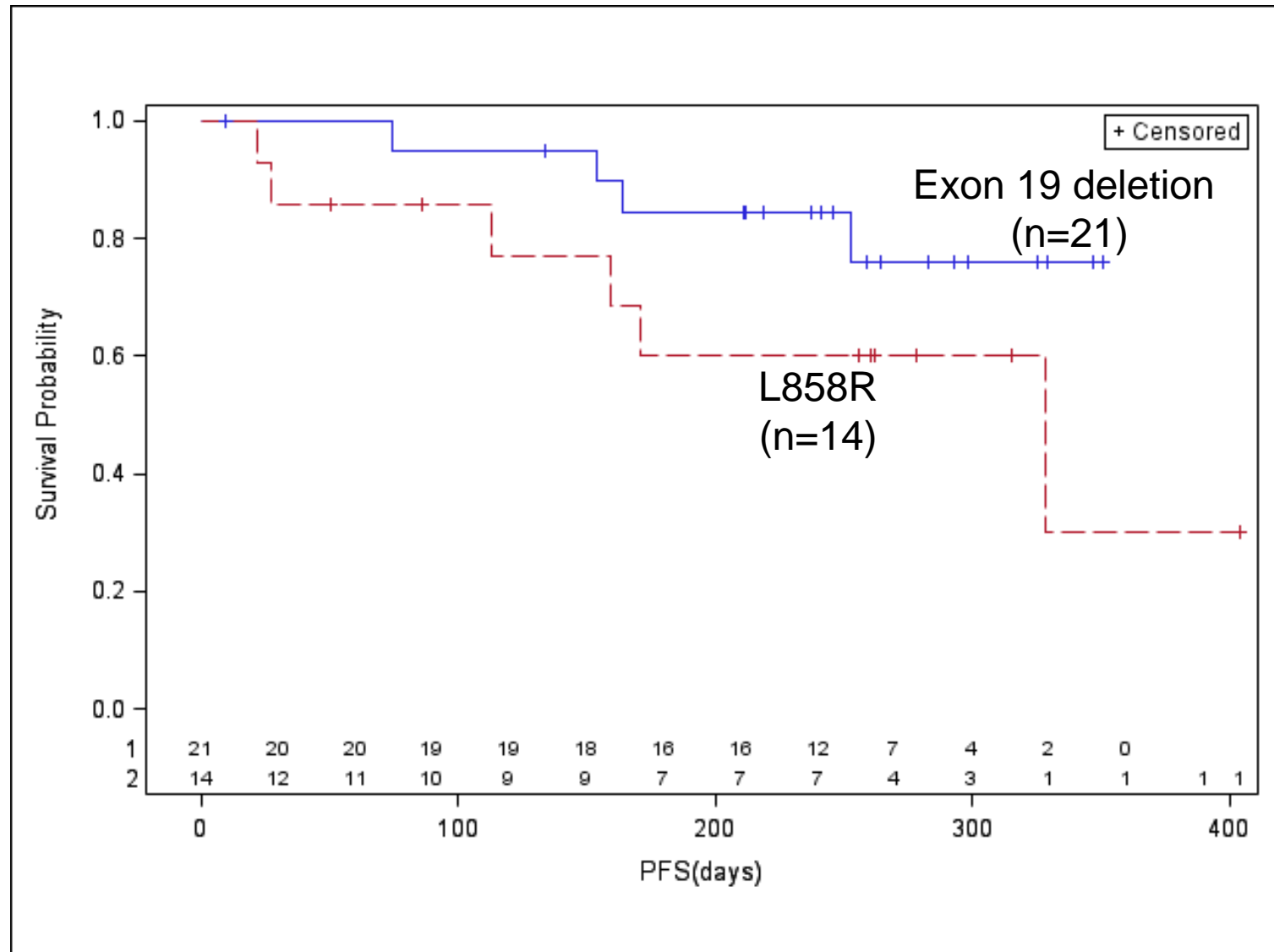
### Detection frequency of **activating mutations in plasma DNA**

*before administration of afatinib*

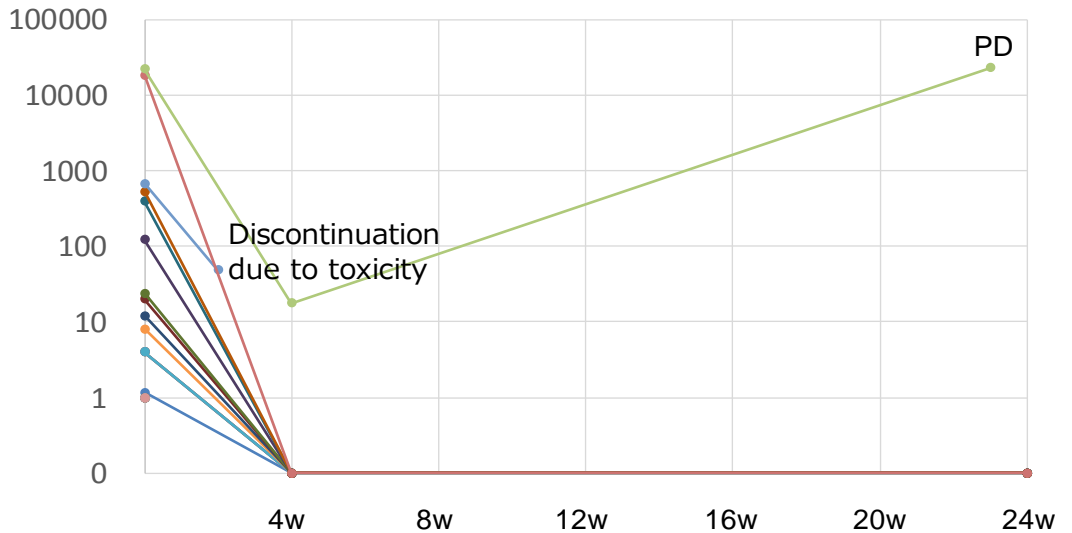
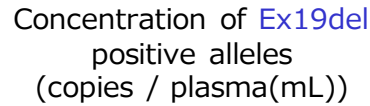
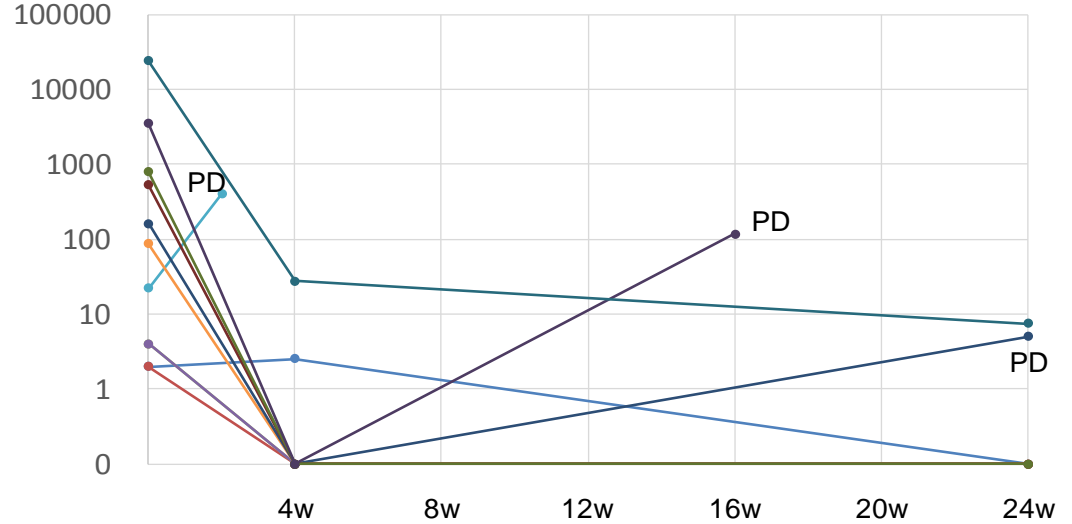
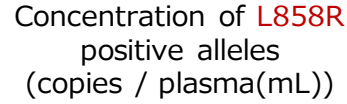
- Digital PCR (dPCR) 81.3% (26 / 32)
- Next Generation Sequencing (NGS) 75.0% (24 / 32)
- Scorpion-ARMS (ARMS) 59.4% (18 / 32)



## ~Progression Free Survival on EGFR mutation subtype~

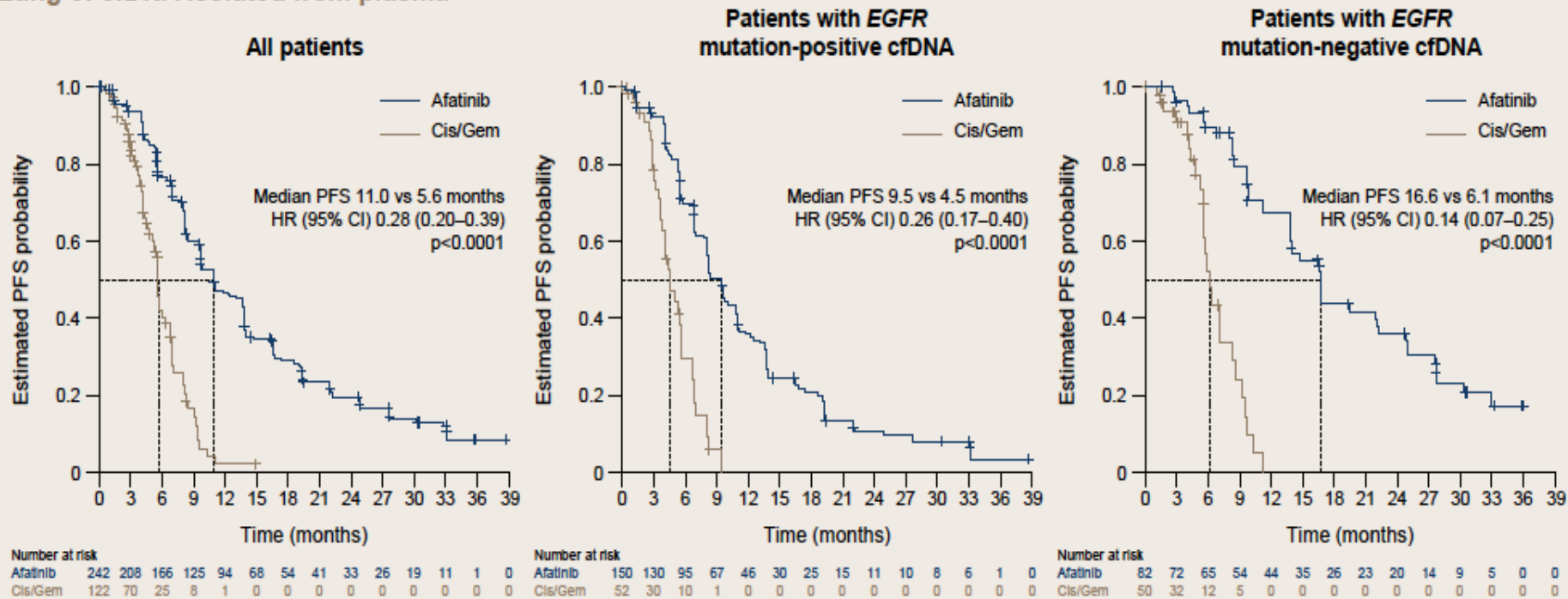


**Quantitative change of activating mutations in plasma DNA evaluated by dPCR (until 24w)**



# Outcomes for Patients with Detectable cfDNA in Plasma in the LUX-Lung 6

LUX-Lung 6: cfDNA isolated from plasma



\*PFS data at time of OS snapshot; therefore slightly different from previously published PFS snapshot data<sup>1</sup>

cfDNA; circulating cell-free tumor DNA; CI, confidence interval; Cis; cisplatin; Gem, gemcitabine; HR, hazard ratio; Pem, pemetrexed; OS, overall survival; PFS, progression-free survival

# **Tumour Molecular Profiling and Quantitative Detection of Circulating Biomarkers in Patients with NSCLC**

Elena Karampini, Wei Wang, Abdul Muhith, Hassan Farah,  
Nahid Kamal, Paul Cane, Jane Moorhead, Sabine  
Pomplun, Juliet King, Tariq Sethi, Frank McCaughan &  
James Spicer

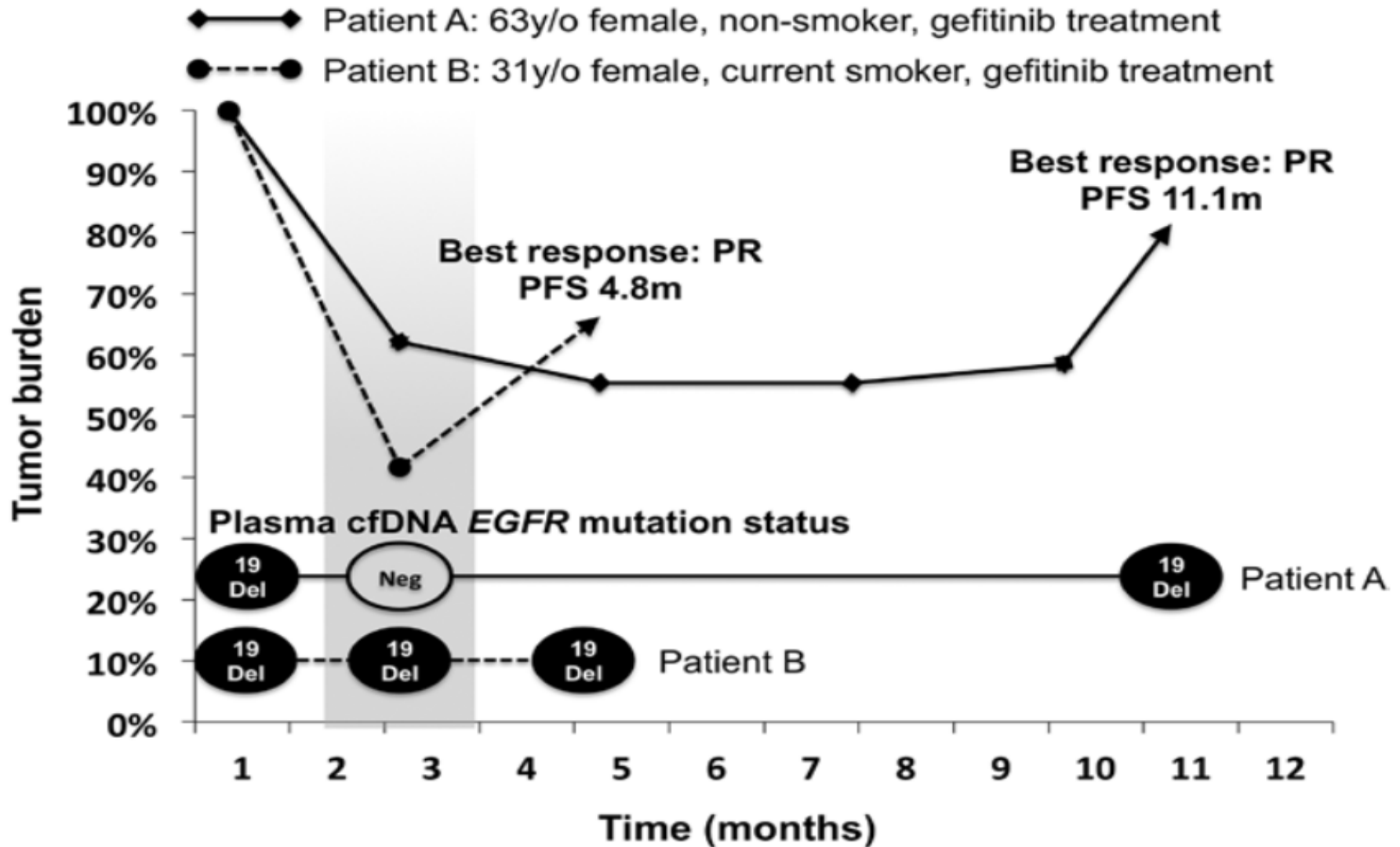
**King's College London at Guy's Hospital, UK**

# ctDNA analysis

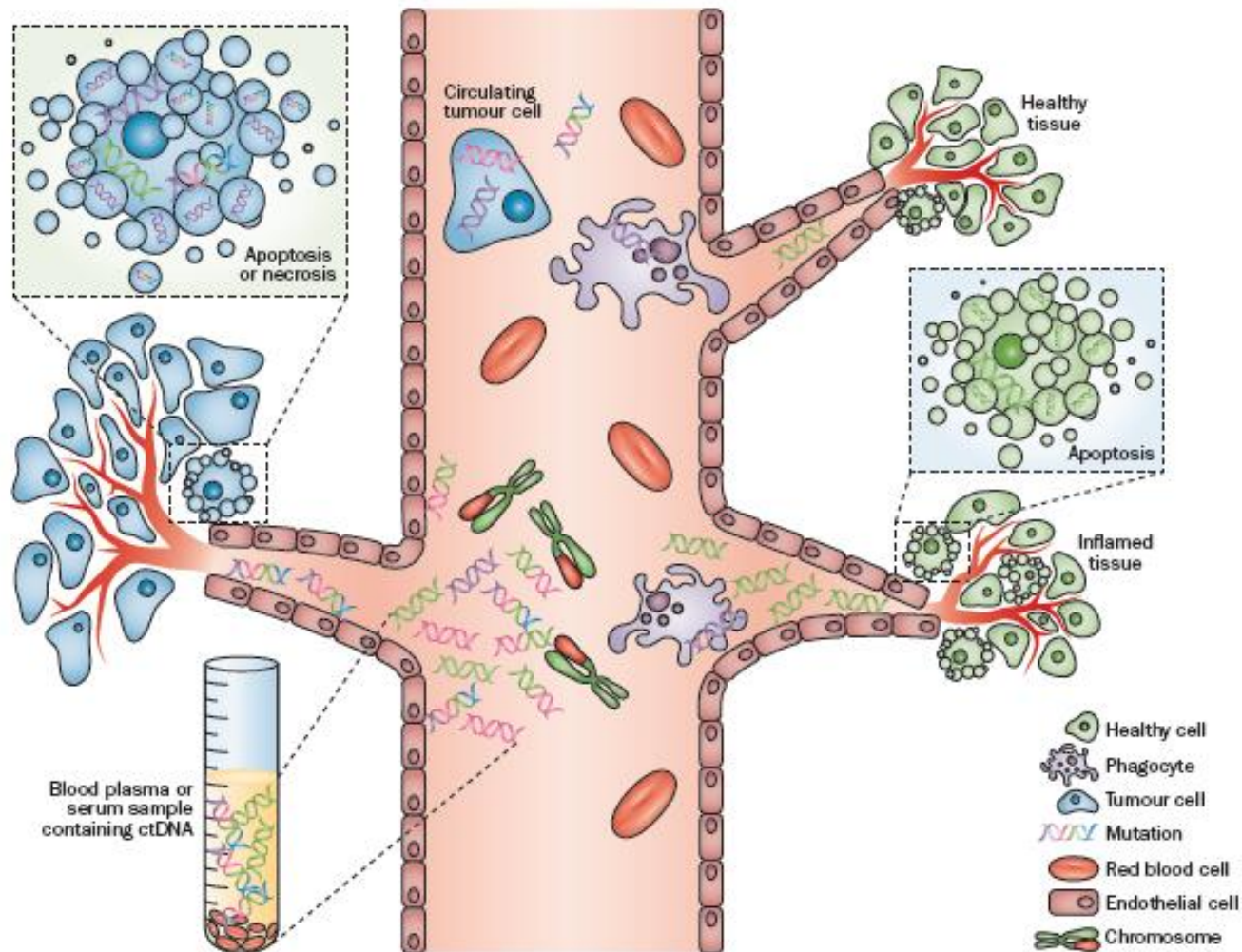
- 1/20 probe validation ongoing
- 1/20 no mutation to assay
- 16/20 patients (80%)  $\geq 1$  mutation in pretreatment plasma
  - - MAF range 0.03 – 66%
- For lower MAF, higher plasma requirements (2mls vs 0.5mls)

Probe Used	Plasma volume used	ddPCR		MAF (%)
		Number of mutants detected	Number of wildtypes detected	
EGFR Ex19 Del	0.5 ml	124	1550	8
TP53 G154V	0.5 ml	3	261	1.1
PIK3CA H1047R	0.5 ml	10	181	5.2
KRAS G12C	0.5 ml	37	611	6
KRAS G12V	0.5 ml	3	293	1
EGFR Ex19 Del	0.5 ml	78	844	8.5
TP53 R273L	0.5 ml	62	3356	1.8
TP53 K132E	0.5 ml	1	139	0.7
TP53 C141Y	0.5 ml	2071	1079	66
TP53 K152S	2 ml	2	5925	0.03
TP53 R273C	2 ml	3	8469	0.03
TP53 E258*	0.5 ml	6	2612	0.23
BRAF V600E	0.5 ml	9	1021	0.9
KRAS G12C	0.5 ml	7	185	4
KRAS G12V	0.5 ml	1	86	1.2
KRAS G12C	0.5 ml	1	428	0.2

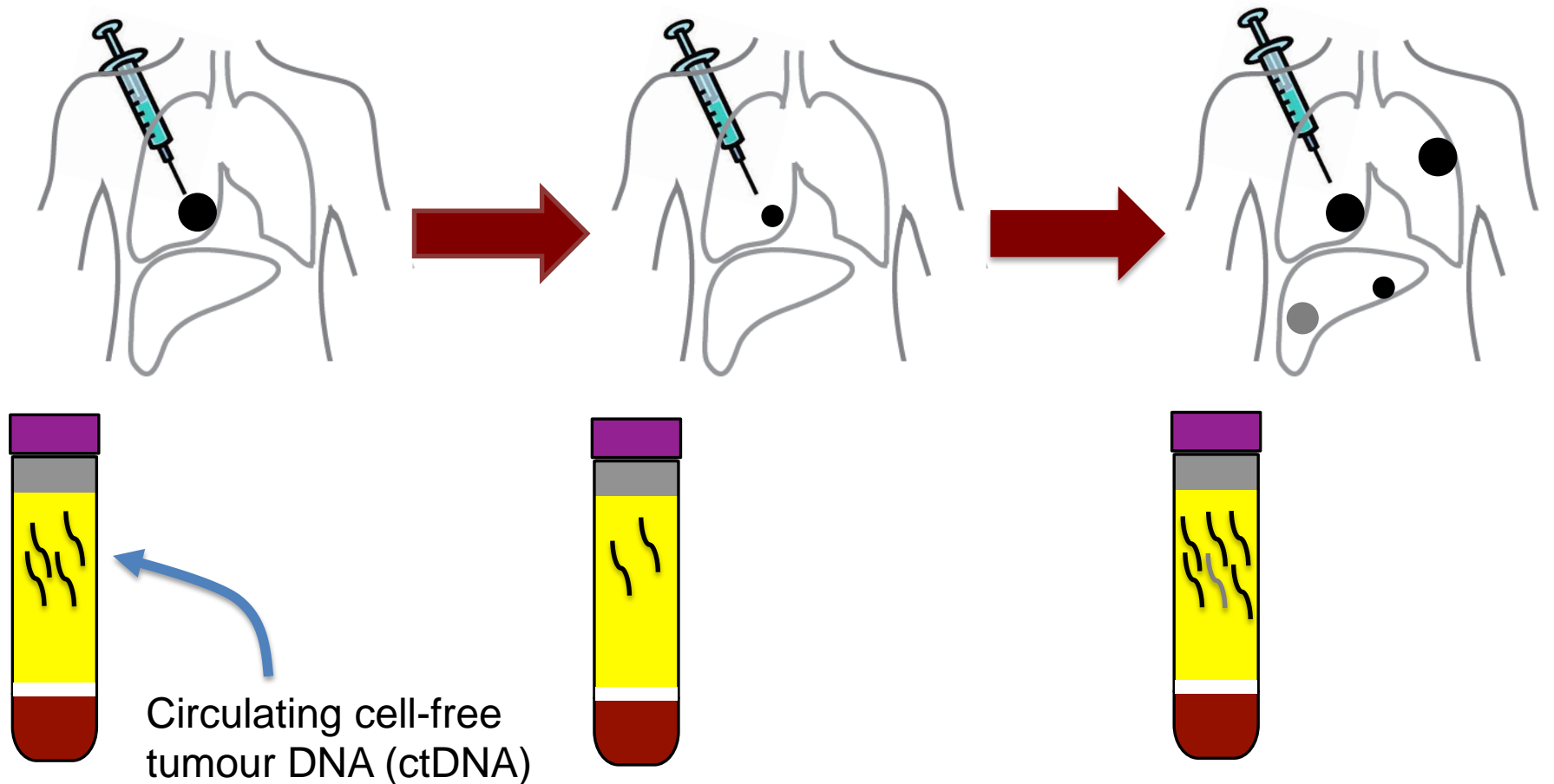
# Monitoring of Tumor Response to EGFR-TKI by ctDNA



# Circulating Biomarkers

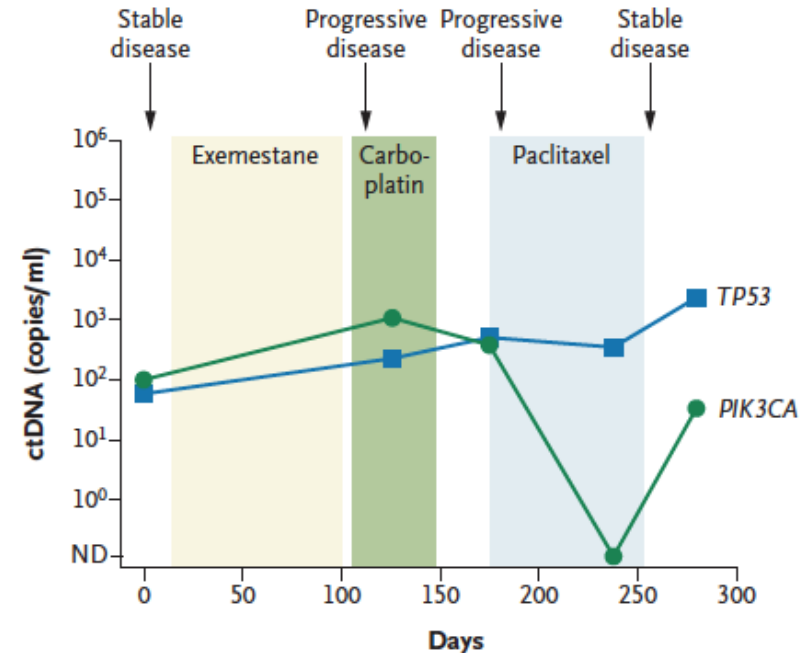
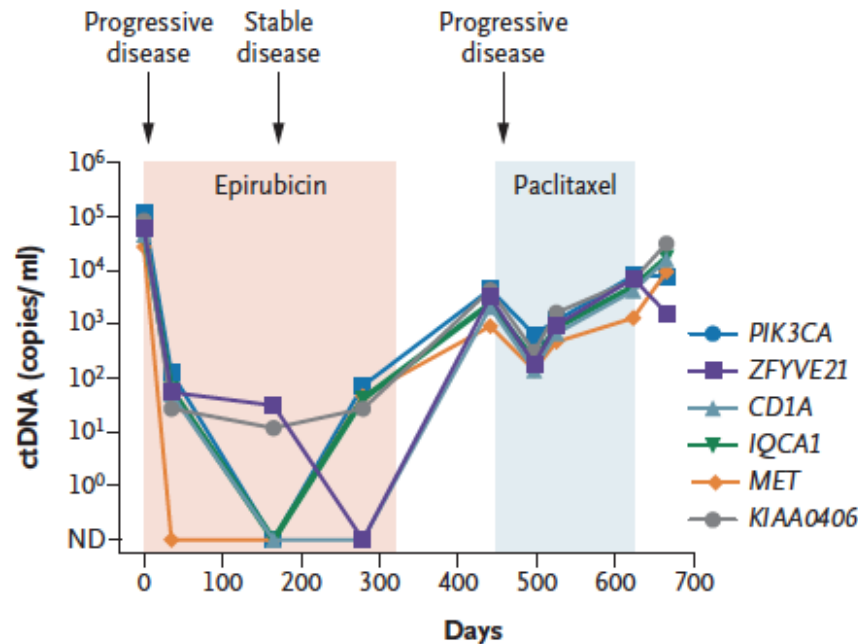


# ctDNA as a “Liquid Biopsy”



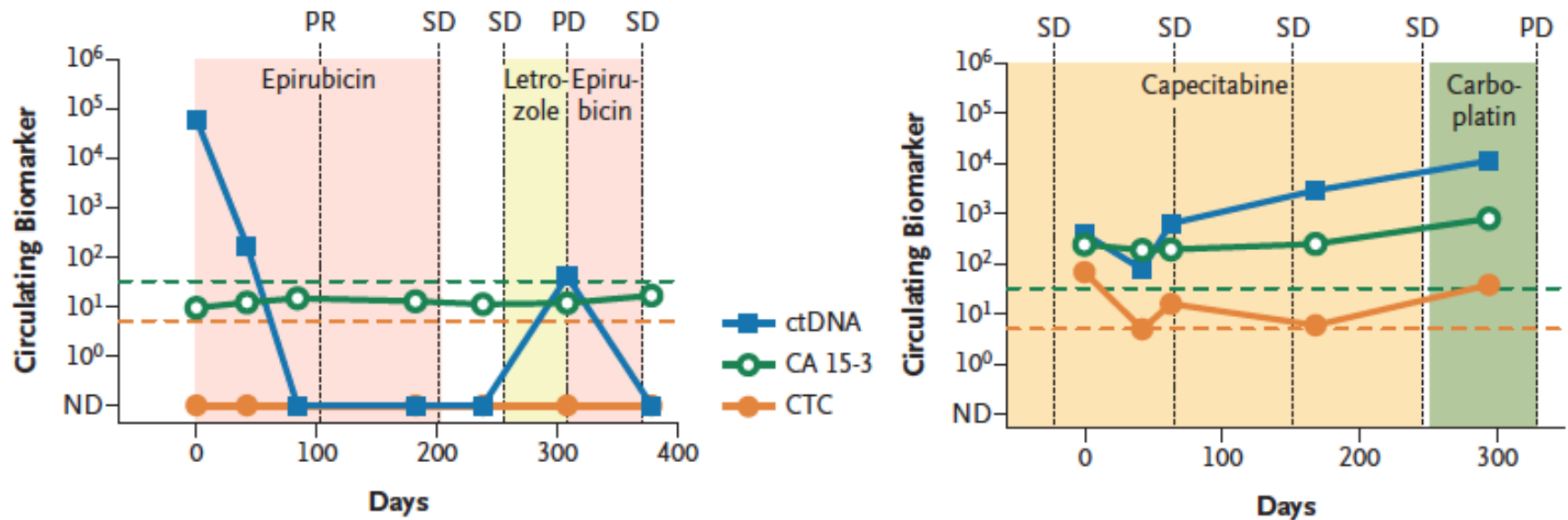


# Monitoring tumour dynamics



- Multiple mutations often show similar dynamic changes when tracked simultaneously
- Evidence of clonal heterogeneity: different clones show diverging patterns over the course of treatment

# Monitoring tumour dynamics



- ctDNA levels accurately reflect changes in tumour burden
- Rising ctDNA levels often predate progressive disease on imaging
- Average lead time in ctDNA changes prior to changes on imaging was 5 months

# 485PD

## Genetic variation in immune genes and prognosis of locoregionally advanced nasopharyngeal carcinoma

Huai Liu<sup>1,2,3</sup>, Yan-xian Li<sup>3</sup>, Yue-feng Wen<sup>4</sup>, Mei-yin Zhang<sup>3</sup>, Qiu-yan Chen<sup>3</sup>, Ying Luo<sup>1,2</sup>, Hui Wang<sup>1,2</sup>, Hui-yun Wang<sup>3</sup>, Hai-qiang Mai<sup>3,\*</sup>

<sup>1</sup>Hunan Cancer Hospital, Changsha, <sup>2</sup>The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, P.R. China

<sup>3</sup>Sun Yat-sen University Cancer Center, Guangzhou, <sup>4</sup>Affiliated Tumor Hospital of Guangzhou Medical College, Guangzhou, P.R. China

# Materials and Methods

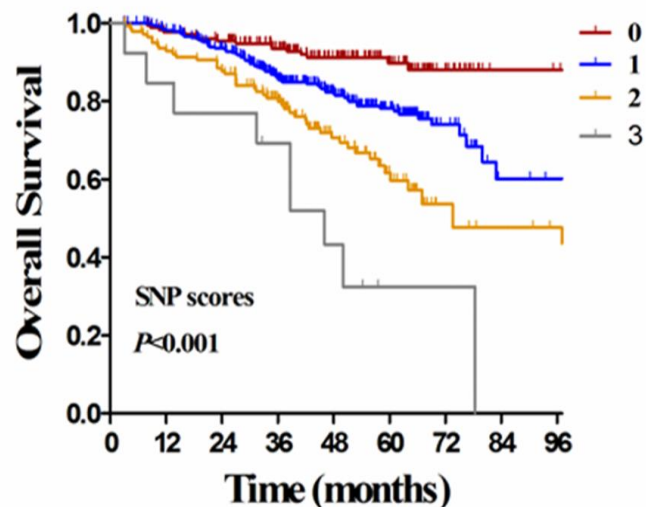
- This study used the training and validation method. The training cohort included 312 LANPC, and the validation cohort prospectively recruited 420 LANPC.
- Forty-three immune genes and 107 potential functional SNPs were selected using the candidate gene approach.
- Genotypes were detected by SNP microarray in the training cohort, and by PCR-LDR technique in the validation cohort.

<b>Gene</b>	<b>SNPs</b>	<b>Model-free <i>P</i></b>
<b><i>CCR2</i></b>	<b>rs1799864</b>	<b>0.009</b>
<b><i>CD5</i></b>	<b>rs2229177</b>	<b>0.115</b>
	<b>rs2241002</b>	<b>0.133</b>
<b><i>CSF3</i></b>	<b>rs25645</b>	<b>0.134</b>
<b><i>EGF</i></b>	<b>rs11568943</b>	<b>0.052</b>
<b><i>IL10RA</i></b>	<b>rs2228054</b>	<b>0.115</b>
<b><i>IL15RA</i></b>	<b>rs2296139</b>	<b>0.097</b>
<b><i>IL16</i></b>	<b>rs1803275</b>	<b>0.146</b>
	<b>rs8031107</b>	<b>0.016</b>
	<b>rs61752774</b>	<b>0.004</b>
<b><i>IL1A</i></b>	<b>rs20540</b>	<b>0.108</b>
<b><i>IL1B</i></b>	<b>rs1143634</b>	<b>0.139</b>
<b><i>IL1RN</i></b>	<b>rs315952</b>	<b>0.129</b>
<b><i>IL3</i></b>	<b>rs40401</b>	<b>0.060</b>
<b><i>TNFRSF10A</i></b>	<b>rs2230229</b>	<b>0.092</b>
<b><i>SEMA3C</i></b>	<b>rs1058425</b>	<b>0.119</b>

# Multivariate analysis for all patients (N=732)

Variables	HR	95%CI	<i>P</i>
Age ( $\leq 45$ y vs. $>45$ y)	1.720	1.227-2.413	0.002
Gender (Male vs. Female)	0.937	0.618-1.420	0.759
Histology (WHO type II vs. III)	1.334	0.640-2.783	0.442
T classification (T1-2 vs. T3-4)	1.051	0.727-1.519	0.791
N classification (N0-1 vs. N2-3)	1.488	1.058-2.093	0.022
Radiation technique (2D-CRT vs. IMRT)	0.341	0.084-1.383	0.132
<i>IL16</i> rs8031107 (GG/AG vs. AA)	1.858	1.326-2.602	$<0.001$
<i>CCR2</i> rs1799864 (AA/AG vs. GG)	1.956	1.350-2.834	$<0.001$
<i>IL16</i> rs61752774 (CC/CT vs. TT)	2.875	1.701-4.857	$<0.001$

**a**



NO. at risk

0	174	170	164	138	96	61	27	7	6
1	381	368	342	258	174	111	36	13	11
2	142	128	121	92	57	32	9	6	4
3	13	11	10	8	4	1	1	0	0

**b**

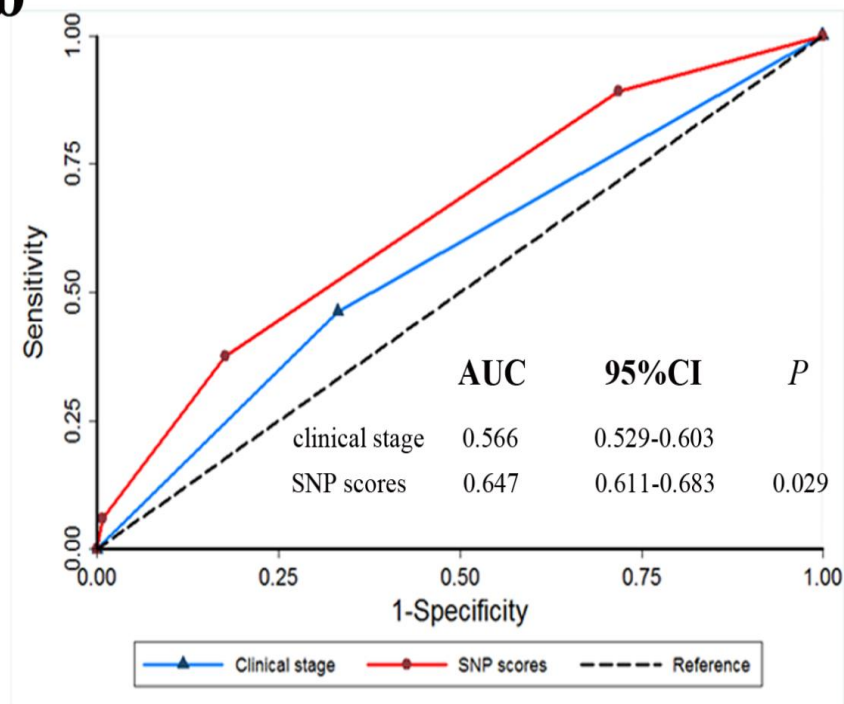


Figure1. (a) Overall survival curves in patients with different SNP score. (b) ROC curves for overall survival.

## Conclusion

Immune gene polymorphisms (*IL16* rs61752774, *IL16* rs8031107 and *CCR2* rs1799864) maybe novel prognostic factors in patients with LANPC. Our results should be validated in large patient cohort from multiple centers.

Variables	HR	95%CI	P
Age (≤45y vs. >45y)	1.707	1.217-2.393	0.002
Gender (Male vs. Female)	0.934	0.616-1.416	0.747
Histology (WHO type II vs. III)	1.348	0.722-2.818	0.427
T classification (T1-2 vs. T3-4)	1.405	0.536-1.511	0.817
N classification (N0-1 vs. N2-3)	1.482	1.054 -2.085	0.024
Radiation technique (2D-CRT vs. IMRT)	0.340	0.084-1.380	0.131
SNPs score			<0.001 <sup>#</sup>
0	Ref	NA	
1	2.295	1.336-3.940	0.003
2	4.131	2.324-7.344	<0.001
3	10.991	4.771-25.318	<0.001



# Discussion

- Interpretation of SNP results always difficult
- The multiple biomarker analysis also muddies the water in this study making interpretation of the results difficult
- In contrast to this study CCR2-64I (rs1799864) has been shown to be a protective factor in prostate cancer when compared with benign prostatic hypertrophy, although the statistically significant difference was lost after correction for multiple comparisons.
- No association was found with bladder cancer risk in a North Indian population
- A significant correlation between CCR2-V64I allelic variant and HER2 immunohistochemical positive samples has been found
- In gastric cancer genotypes with the T allele of CCL2 rs4586 have also been significantly associated with shorter OS compared with the C/C genotype in the US cohort [hazard ratio (HR) 2.43; P = 0.015] but longer OS in the Japanese cohort (HR 0.58; P = 0.021)
  - Patients with the A allele of the NFKB1 rs230510 have been found to have significantly longer overall survival (OS) compared with those with the T/T genotype in gastric cancer

# 486PD

MicroRNA-125b functions as a key arbitrator for Mucin1 expressing breast cancer stem-like cells proliferation, migration and drug resistance

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# Summary of Findings

- Emerging evidence suggests that mucin and MUC1 play important roles in tumor metastasis and drug resistance
- Muc(+) breast cancer stem cells (BCSCs) exhibit downregulation miR-125b compared to adhered and Muc(-) cell population.
- miR-125b overexpression attenuates BCSC's self renewal and proliferation potential along with Muc1, Dicer 1, Prominin1, ELF4EBP1, ALDH4A1, DDR1, KRAS and BCL2 expression, whereas knockdown of miR-125b promotes these
  - Ectopic expression of miR-125b provides a promising strategy to inhibit cancer stem cells.

# Role of miRNA-125b Controversial

- inhibit ovarian cancer cell invasion and migration, and induce apoptosis, through post-transcriptional inactivation of EIF4EBP1
- suppresses the epithelial-mesenchymal transition and cell invasion by targeting ITGA9 in melanoma
- sensitizes human hepatocellular carcinoma cells to 5-fluorouracil through inhibition of glycolysis by targeting hexokinase II

BUT

- promotes tumor metastasis in NSCLC through targeting tumor protein 53-induced nuclear protein 1
- promotes leukemia cell resistance to daunorubicin by inhibiting apoptosis
- confers resistance of ovarian cancer cells to cisplatin by targeting pro-apoptotic Bcl-2 antagonist killer 1

# Discussion

- Cancer Stemness is an important area of research for the future

Evidence suggests cancer stemness

- is associated with resistance to chemo- and radiotherapy and targeted agents such as EGFR TKIs
- Metastatic potential
- A reduced likelihood of response to immune checkpoint inhibitors
- miRNA research may provide important insights into the mechanisms involved in inducing stemness in cancer cells

