EUROPEAN LUNG CANCER
CONFERENCE 2016

Targeting EGFR and ALK driven tumours

Invited Discussant for posters 59PD and 60PD
Rafael Rosell

Catalan Institute of Oncology, Badalona,
Barcelona, Spain

Thursday, 04/14/2016, 02:45 - 04:00 PM, Room W

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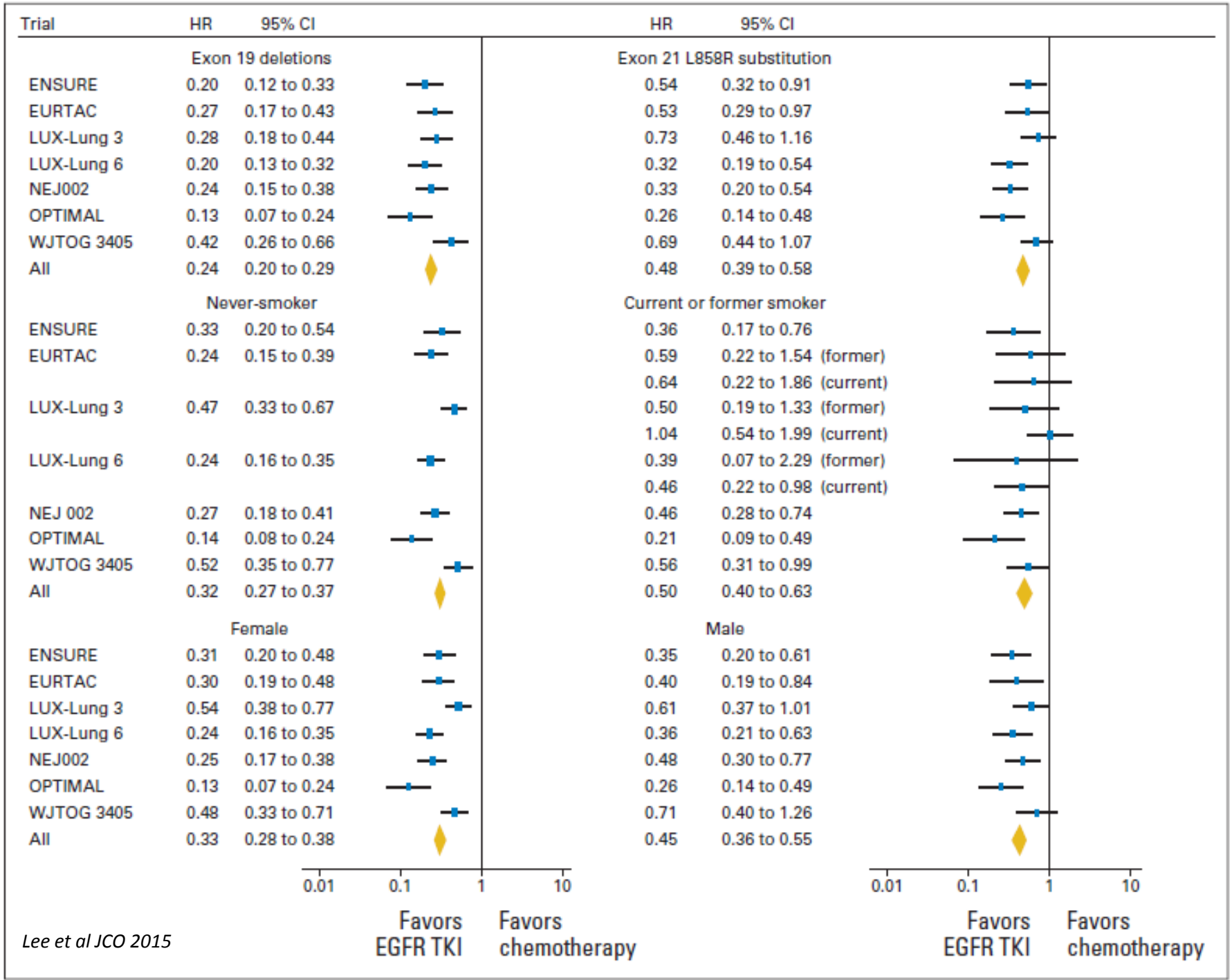
Association of *EGFR* mutation subtypes with clinical and demographic characteristics of patients with aNSCLC: IGNITE and ASSESS pooled analysis

Baohui Han,[1] Marianne Ratcliffe,[2] Vincent Haddad,[3] Helen Brown,[2] Sergei Tjulandin,[4] Koichi Hagiwara,[5] Martin Reck,[6] and Nicola Normanno[7]

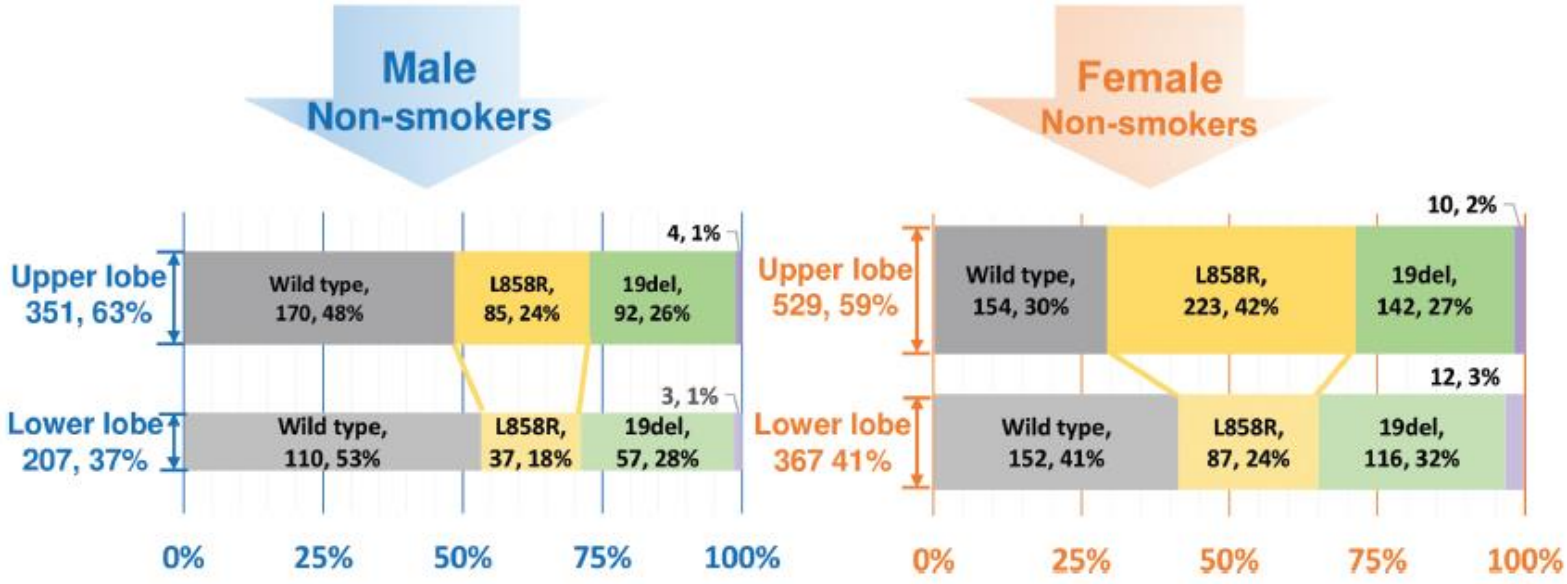
[1]Department of Respiratory Medicine, Shanghai Chest Hospital, Jiao Tong University, Shanghai, China; [2]Personalised Healthcare and Biomarkers, AstraZeneca, Macclesfield, UK; [3]AstraZeneca, Royston, UK; [4]Department of Clinical Pharmacology and Chemotherapy, Russian Cancer Research Centre, Moscow, Russia; [5]Comprehensive Medicine 1, Saitama Medical Center, Jichi Medical University, Saitama-ken, Japan; [6]Department of Thoracic Oncology, LungenClinic Grosshansdorf GmbH, Airway Research Center North (ARCN), Member of the German Centre for Lung Research (DZL), Grosshansdorf, Germany; [7]Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori "Fondazione Pascale", IRCCS, Naples, Italy

Previous meta-analyses show significant PFS prolongation in patients with exon 19 deletions, never smokers and women. *(Lee et al JCO 2015)*

Different pulmonary lobar locations depend on the type of EGFR mutations. L858R mutation are more common in women, never smokers and upper lobes. *(Tseng et al Carcinogenesis 2016)*



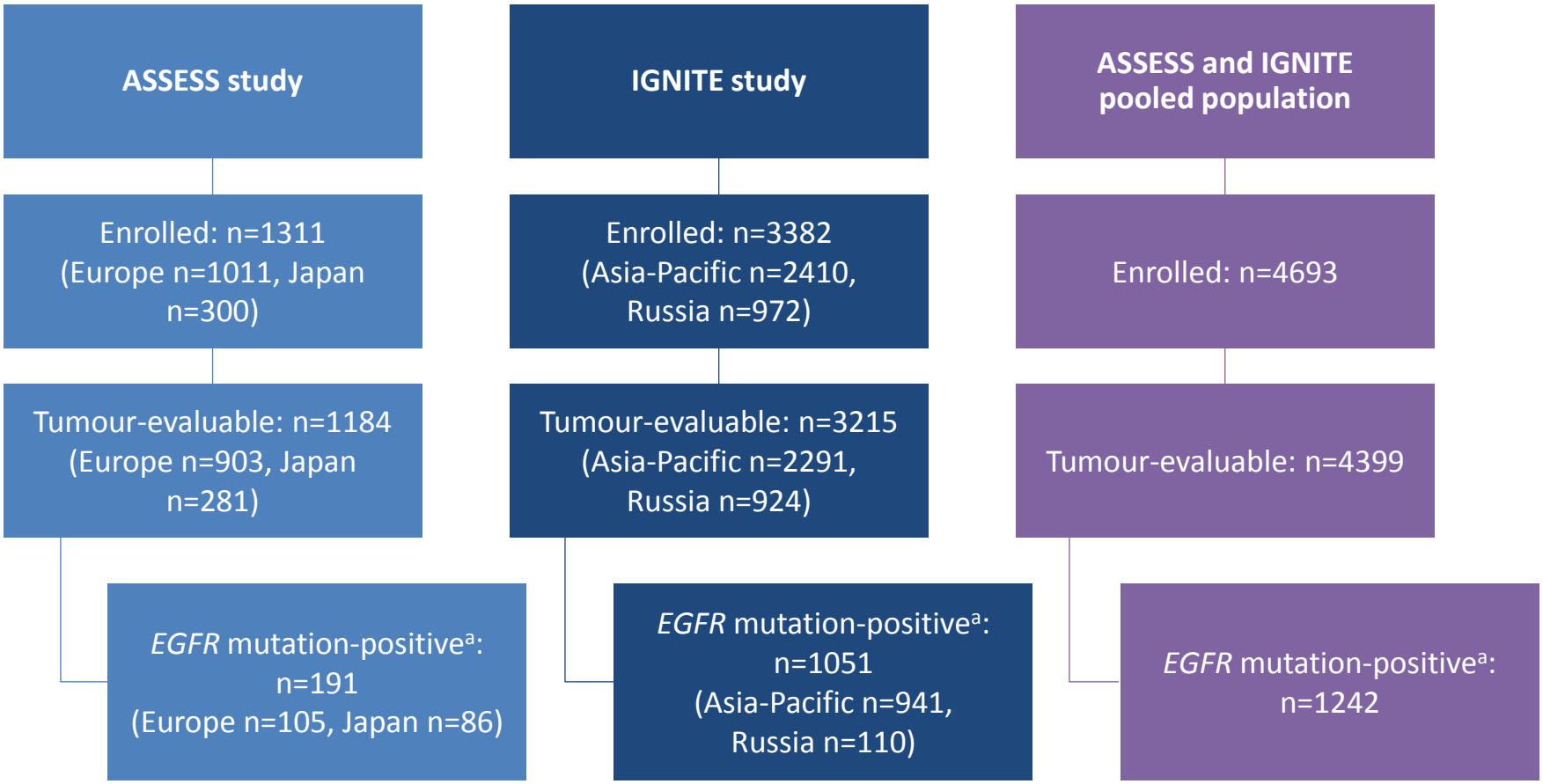
Lee et al JCO 2015



Tseng et al Carcinogenesis 2016

Effect (*EGFR* mutation-positive patients / tumour-evaluable patients)		OR	OR 95% CI
Histology	ADC (1069/3156) vs non-ADC (101/1184)	3.919	3.082, 4.984
Current disease stage	IIIA (47/374) vs IV (1106/3456)	0.564	0.396, 0.805
	IIIB (89/562) vs IV (1106/3456)	0.619	0.471, 0.813
Ethnicity	Asian (1015/2539) vs Caucasian (217/1823)	4.176	3.489, 4.998
Gender	Female (687/1484) vs male (555/2915)	1.603	1.311, 1.960
Smoking status	Never-smoker (818/1597) vs ever-smoker (424/2802)	2.854	2.336, 3.485

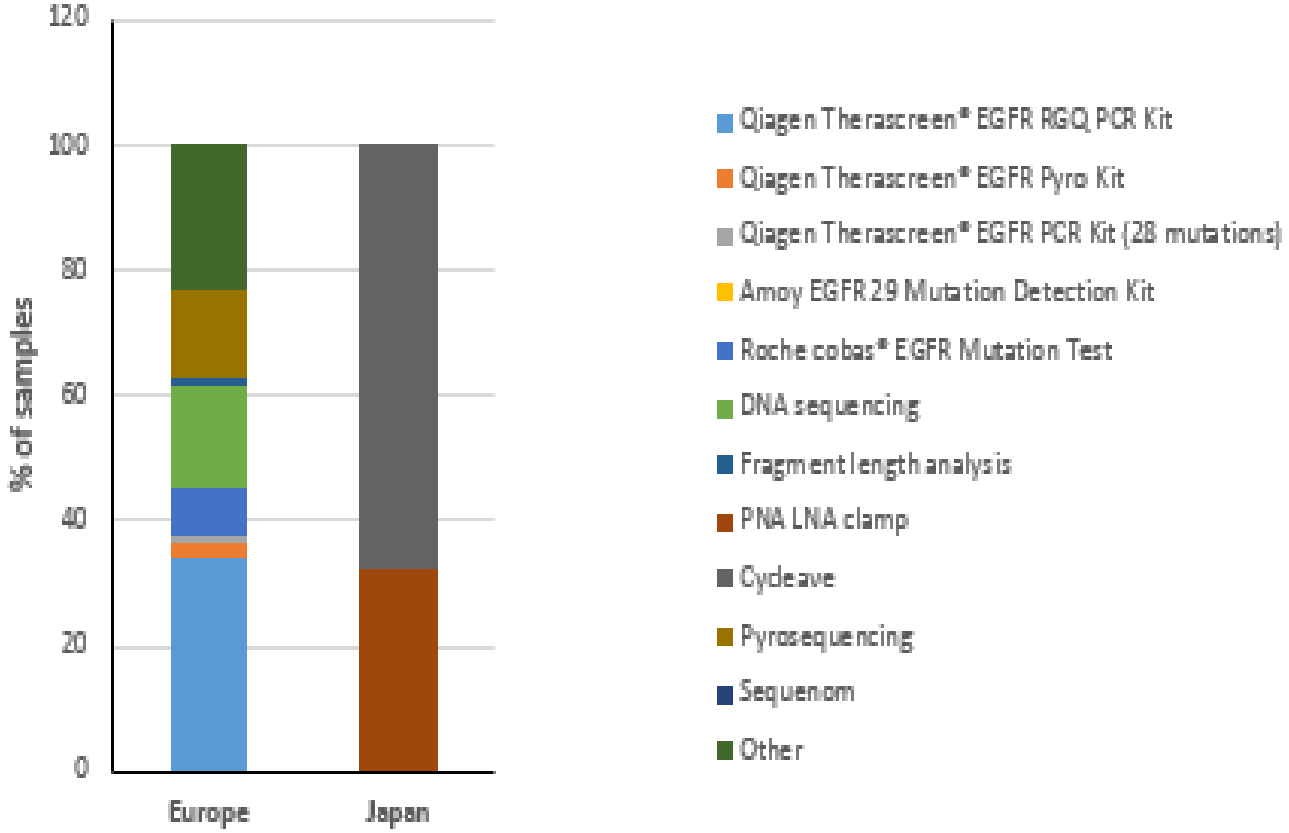
Poster 59PD, Han et al (Nicola Normanno)



EGFR mutation rate, 16% (191/1184)
Europe, 12% (105/903)
Japan, 31% (86/281)
(Reck et al ELCC 2015)

42% (952/2249)
Asia-Pacific, 49% (862/1749)
Russia, 18% (90/500)
(Han et al ELCC 2015)

Poster 59PD, Han et al (Nicola Normanno)



(Reck et al ELCC 2015)

EGFR mutation testing was carried out in various sites with different methods.

ASSESS: EGFR mutational analysis was performed in 43 academic, hospital and commercial laboratories

IGNITE: EGFR mutational analysis was performed in 9 participating countries, also in academic, hospital and commercial laboratories

(Courtesy of Nicola Normanno)

- **EGFR mutations were more frequent in Stage IV**. The odds of having an *EGFR* positive tumour were reduced by 44% for Stage IIIA versus Stage IV (38% for Stage IIIB vs Stage IV)

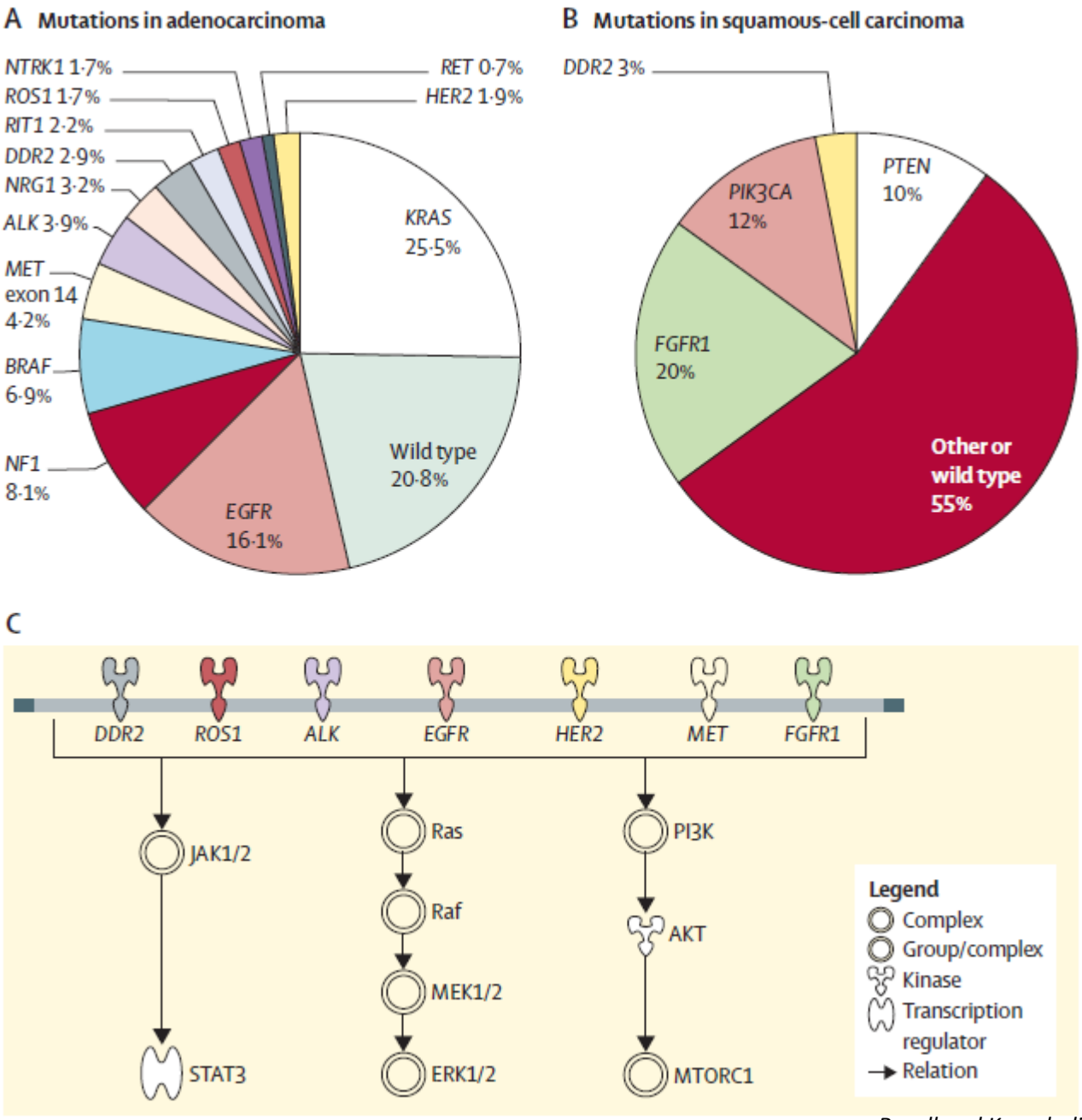
- **Rare *EGFR* mutations (G719X, L861Q/P and exon 20 insertions) were more common in smokers** than never-smokers compared with L858R mutations / exon 19 deletions

- **Exon 20 insertions only detected in adenocarcinoma**

- **Caucasians, aged <65 years, or those with adenocarcinoma, more likely to harbor exon 19 deletions**

Poster 59PD, Han et al (Nicola Normanno)

ASSESS and IGNITE studies have paved the way for standard genotyping assessment In lung adenocarcinoma.



Rosell and Karachaliou Lancet 2016

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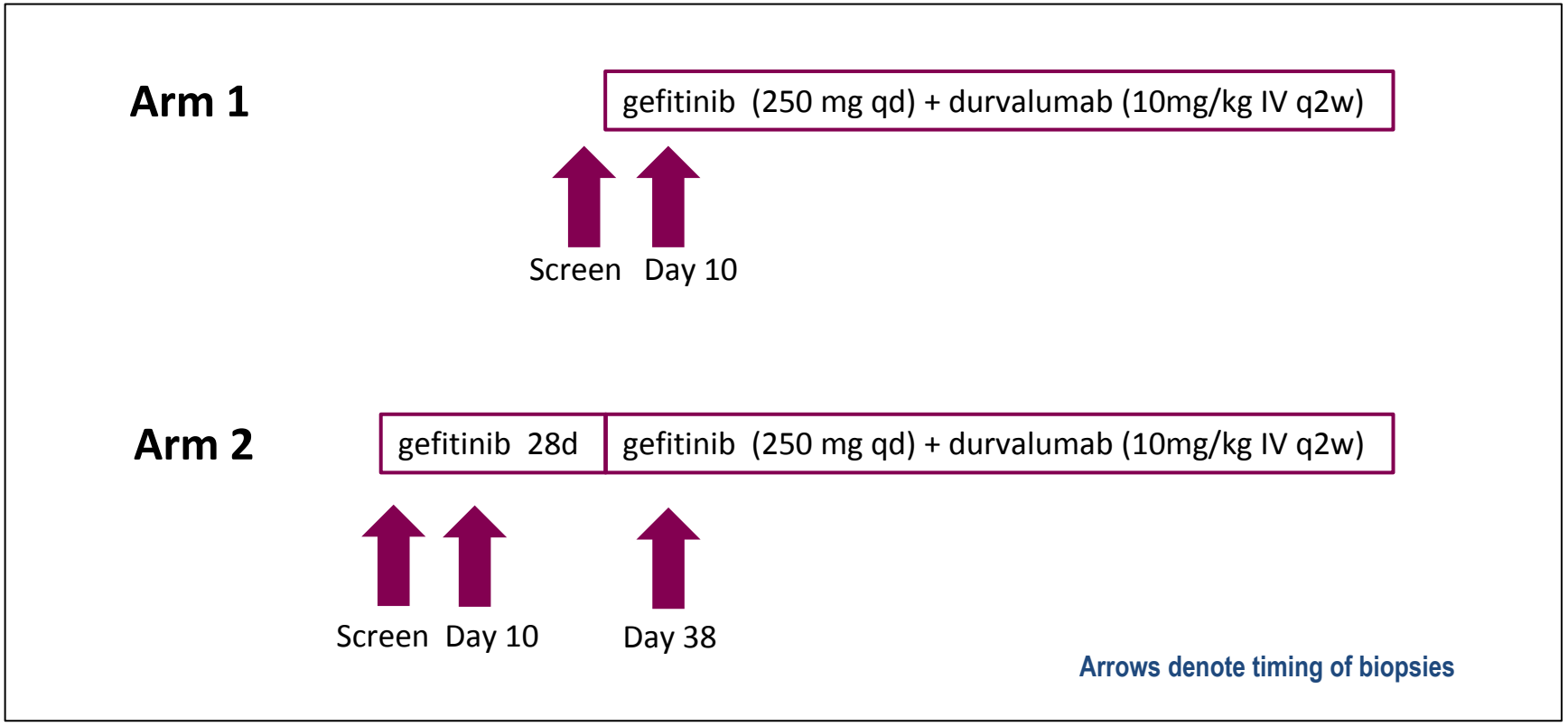
Inhibition of p*EGFR* in paired tumour biopsies from TKI treatment-naïve *EGFR* mutant NSCLC patients treated with gefitinib (*EGFR* inhibitor) or gefitinib in combination with durvalumab (anti-PD-L1)

Tammie Yeh,[1] Vivien Jacobs,[2] Helen Angell,[3] Joseph Geradts,[3] Jianmei Hou,[4] Joyson Karakunnel,[5] and J. Carl Barrett[1]

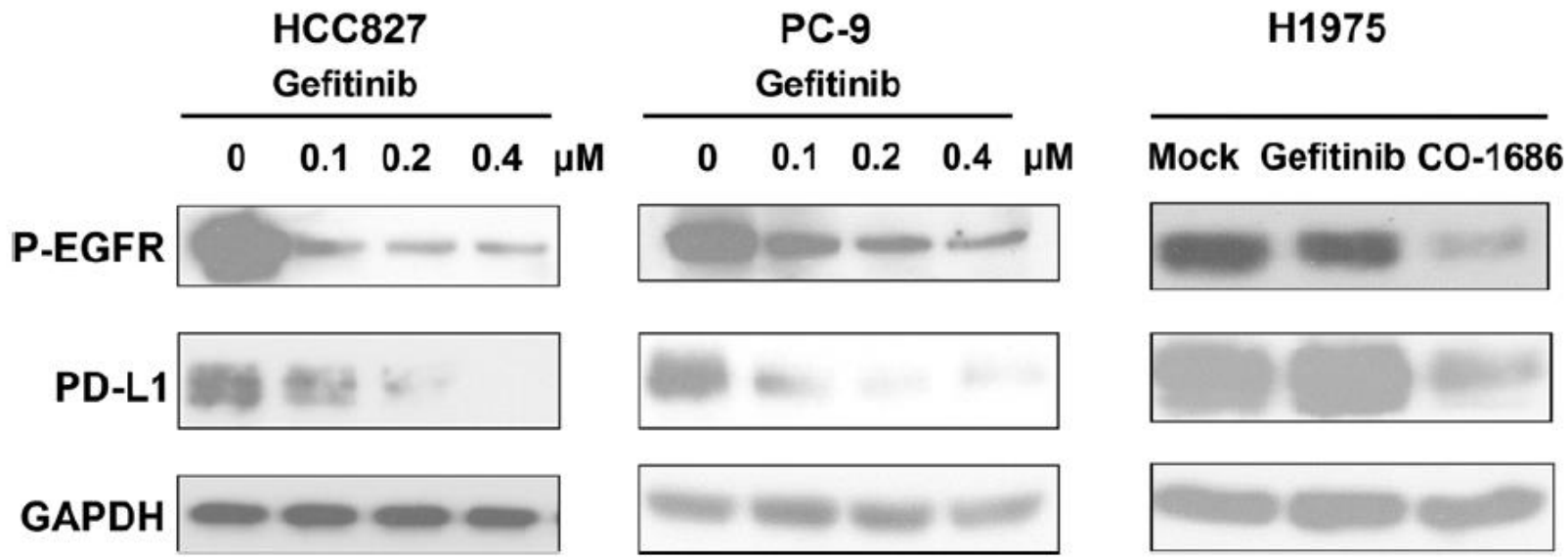
[1]AstraZeneca Oncology iMED Translational Sciences, Waltham, MA, USA; [2]AstraZeneca Oncology iMED Translational Sciences, Alderley Park, Macclesfield, UK; [3]AstraZeneca Oncology iMED Translational Sciences, Cambridge, UK; [4]AstraZeneca GMD Oncology, Shanghai, China; [5]MedImmune Oncology Clinical Development, Gaithersburg, MD, USA

Only 1 other report was examined in PD-L1 expression in post-gefitinib EGFR mutant NSCLC, including 18 specimens. *(Han et al Clinical Lung Cancer 2015)*

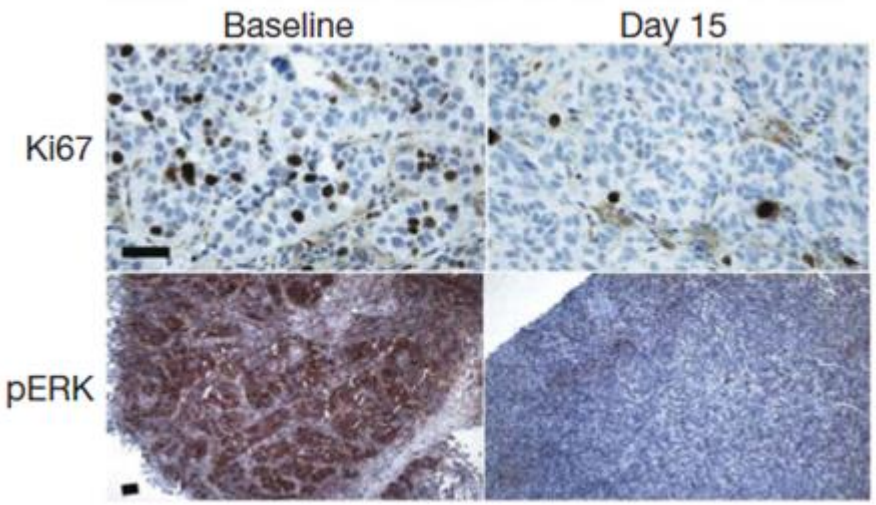


Poster 60PD, Yeh et al

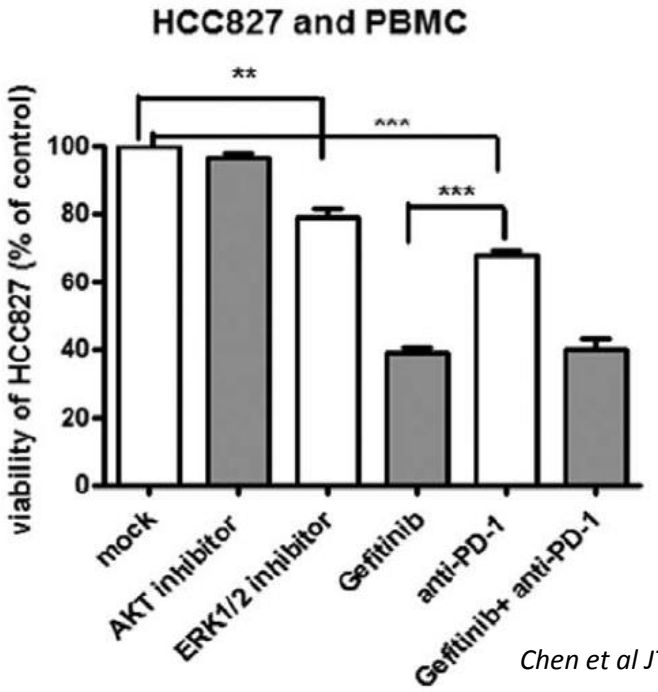
1. How can we gauge early adaptive resistance to EGFR TKIs?
2. How often does early resistance occur?
3. Are early re-biopsies really necessary?



Chen et al JTO 2015

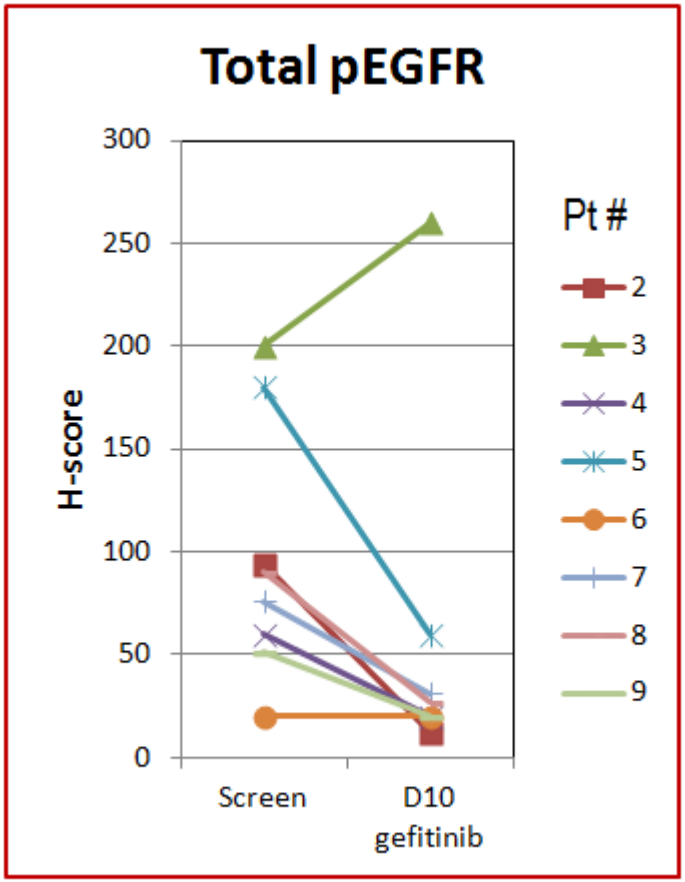


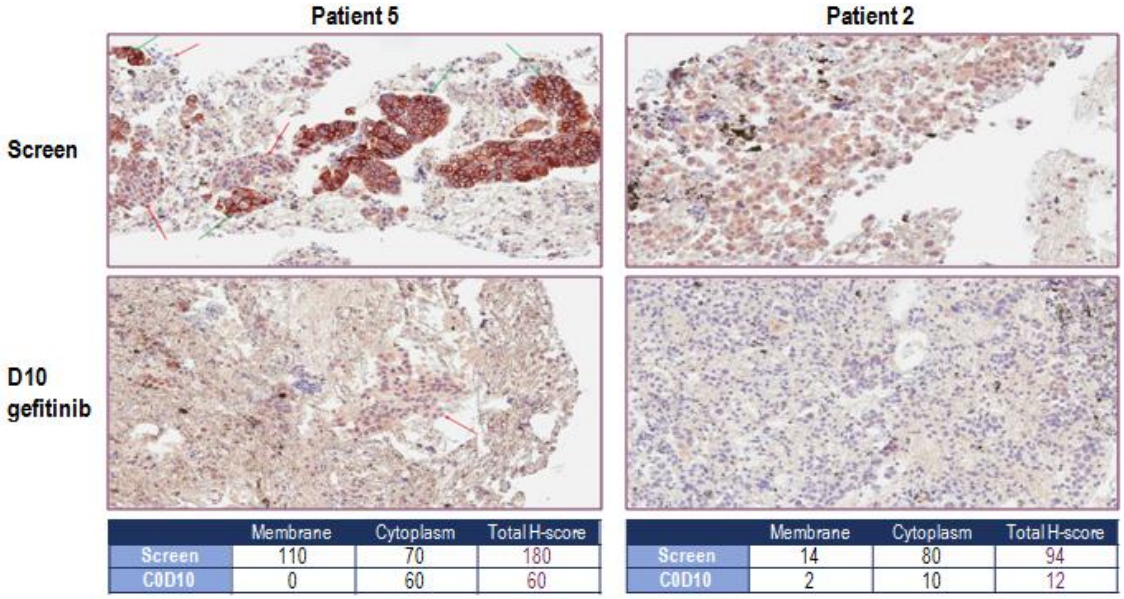
Bollag et al Nature 2010



Chen et al JTO 2015

Impact of gefitinib on p*EGFR* expression at Day 10





	Membrane	Cytoplasm	Total H-score
Screen	110	70	180
C0D10	0	60	60

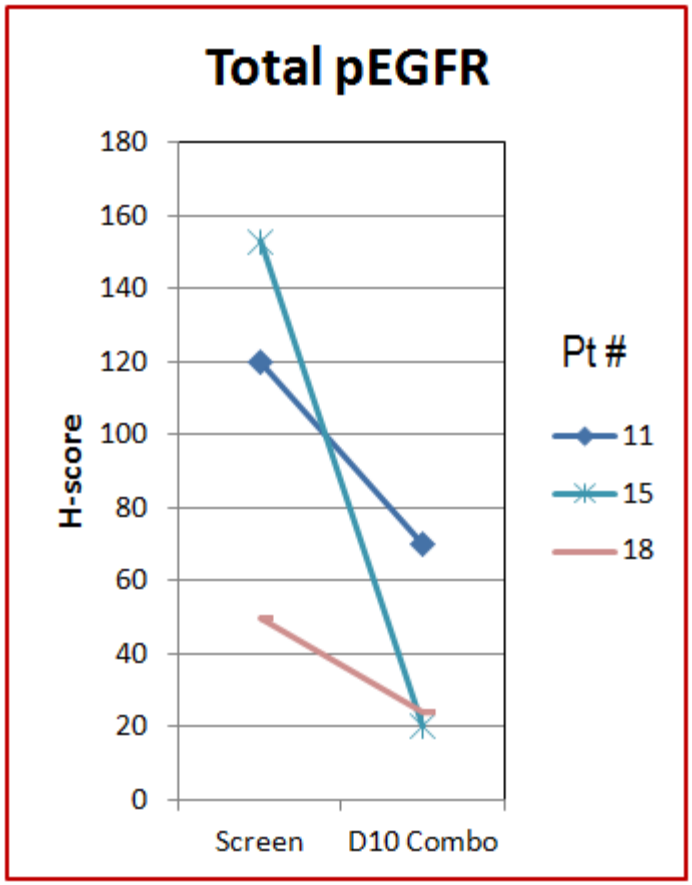
	Membrane	Cytoplasm	Total H-score
Screen	14	80	94
C0D10	2	10	12

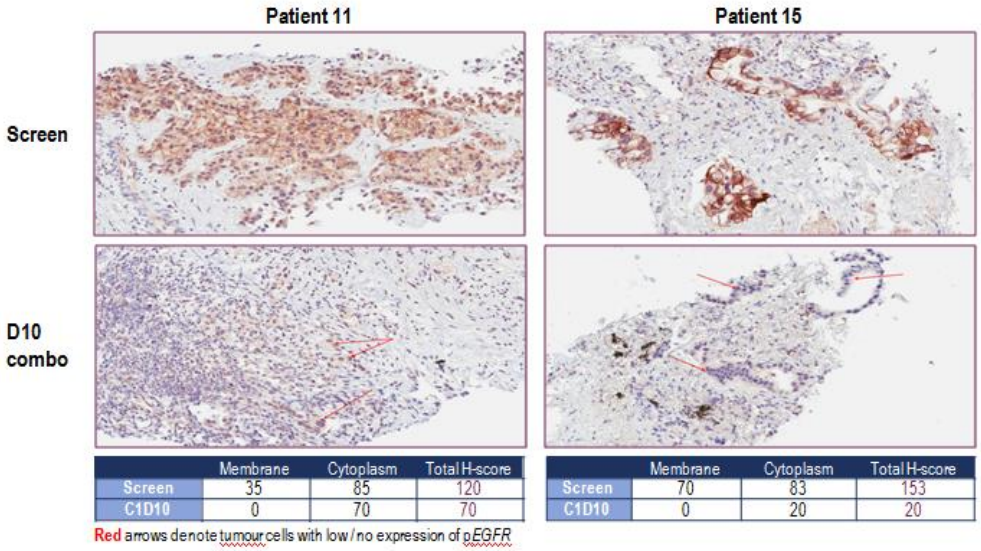
Green denotes tumour cells expressing p*EGFR*; red denotes tumour cells with low / no expression of p*EGFR*

The main goal was to demonstrate the inhibition of EGFR in clinical tumor samples.

Poster 60PD, Yeh et al

Impact of gefitinib/durvalumab on p*EGFR* expression at Day 10





	Membrane	Cytoplasm	Total H-score
Screen	35	85	120
C1D10	0	70	70

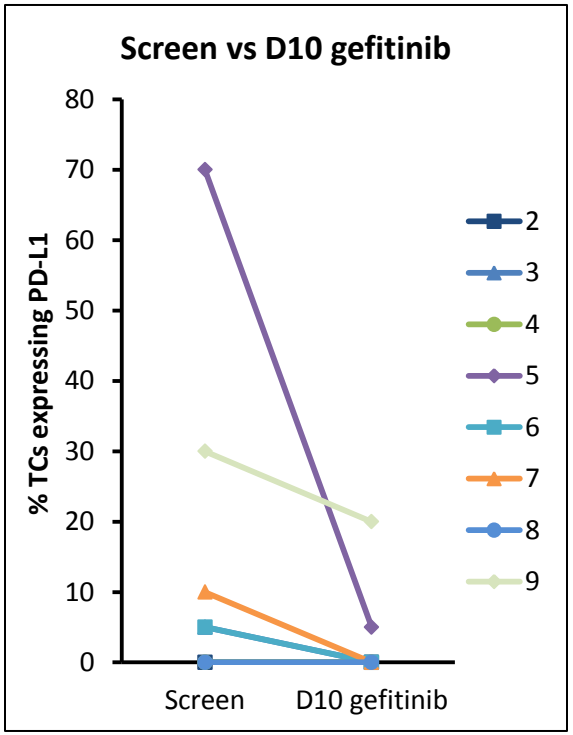
	Membrane	Cytoplasm	Total H-score
Screen	70	83	153
C1D10	0	20	20

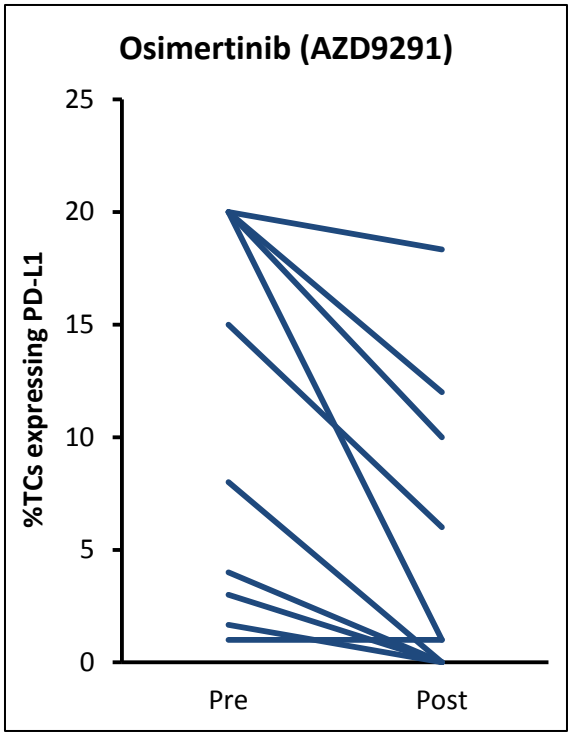
Red arrows denote tumour cells with low / no expression of p*EGFR*

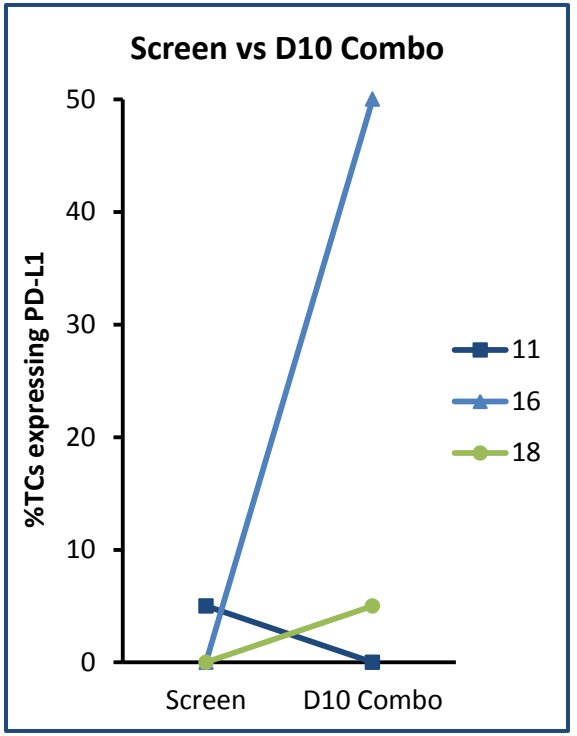
Can EGFR inhibition down-regulate PD-L1 expression, as has been shown in cell lines and animal models?

Poster 60PD, Yeh et al

IMPACT ON TUMOUR MEMBRANE PD-L1 EXPRESSION AT DAY 10







- Gefitinib treatment: all paired biopsies with baseline PD-L1 staining (5 in total) showed a decrease in PD-L1 staining (tumour membrane) after gefitinib treatment on Day 10 (left panel; patients 3 and 6 are superimposable); this is consistent with previously presented data[1] for paired tumour biopsies (post-dose taken at Day 8 / Day 15) from patients treated with osimertinib (Tagrisso™), a third-generation EGFR inhibitor (middle panel)

- Gefitinib / durvalumab treatment: only three paired biopsies were evaluable. No trend observed (right panel)

Poster 60PD, Yeh et al

- 11 sets of paired tumour biopsies (screen versus D10) were available for analysis: 3 from Arm 1 (gefitinib / durvalumab) and 8 from Arm 2 (gefitinib run-in). Seven pairs of biopsies were invaluable due to insufficient number of tumour cells in the on-treatment biopsies, consistent with the rapid decreases in tumour size observed

- Inhibition of p*EGFR* (Y1173) was observed in 9 of the 11 pairs, suggesting biological activity of gefitinib at the tumour site when dosed alone or in combination with durvalumab

- Inhibition of PD-L1 expression in tumour membrane cells by gefitinib was observed in all tumour pairs with adequate baseline expression

- Of 18 evaluable baseline tumour samples from both Arms, three were deemed PD-L1 'positive' as defined by ≥25% tumour cells with membrane expression

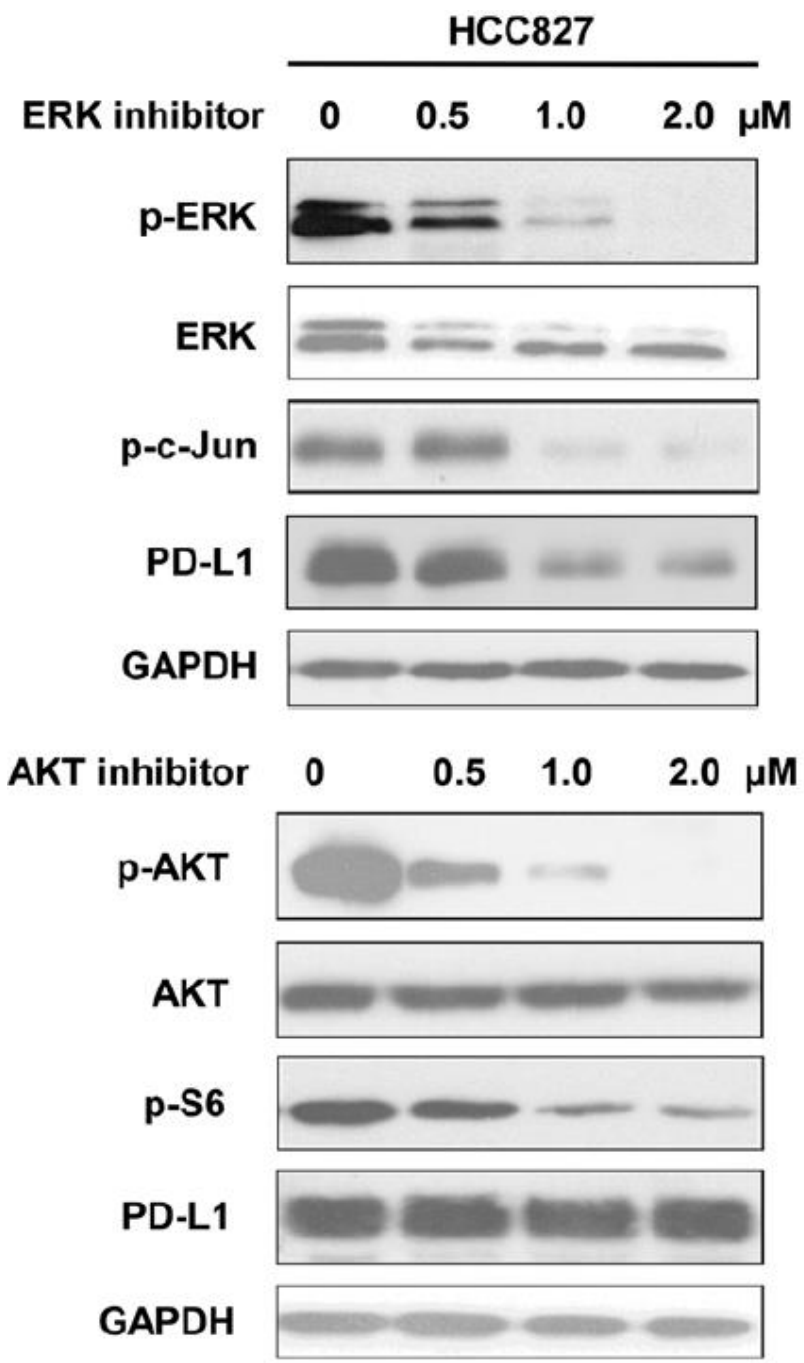
- This study highlights the challenges in evaluating biological readouts when tumours rapidly respond in parallel. The third biopsy, when available, was not informative

Poster 60PD, Yeh et al

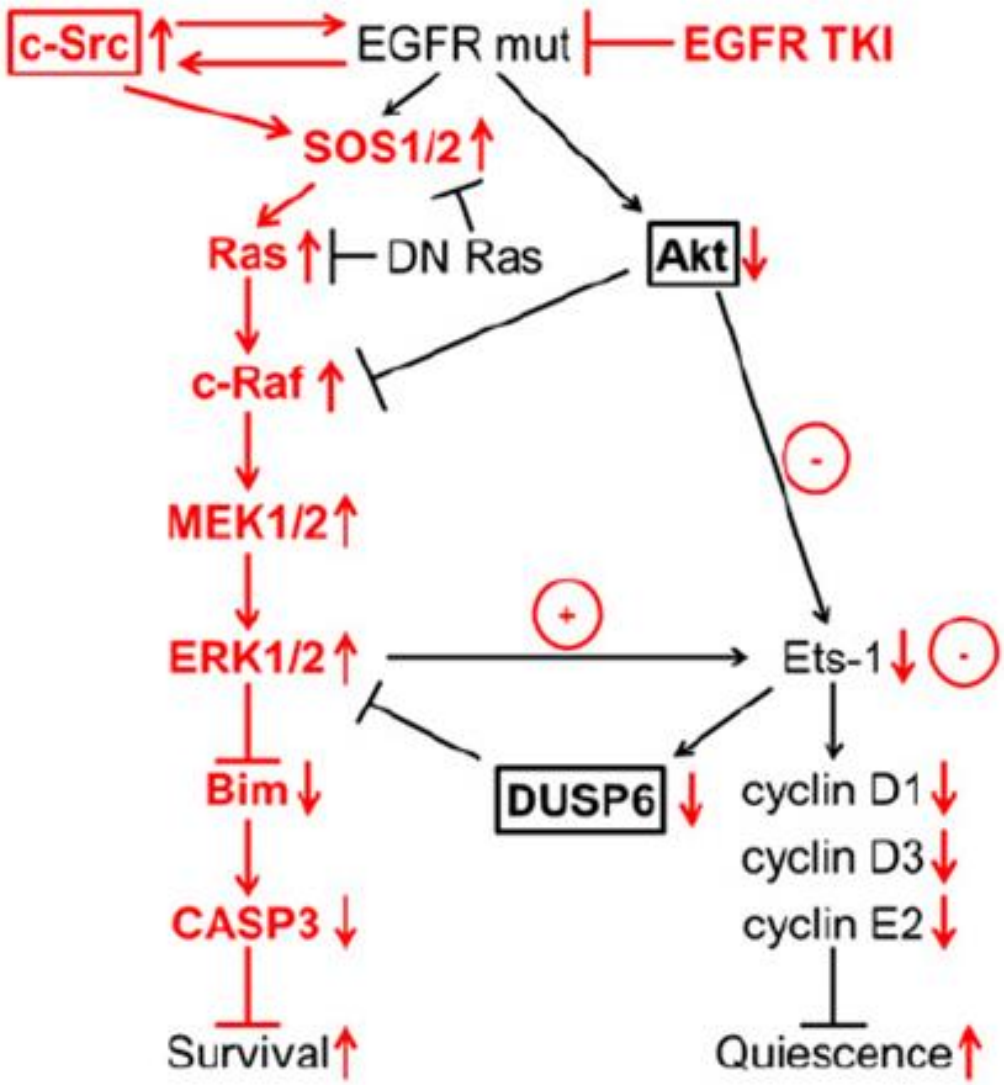
Why early re-biopsies in lung cancer?

An in depth look at re-wiring signaling pathways following single EGFR TKIs :

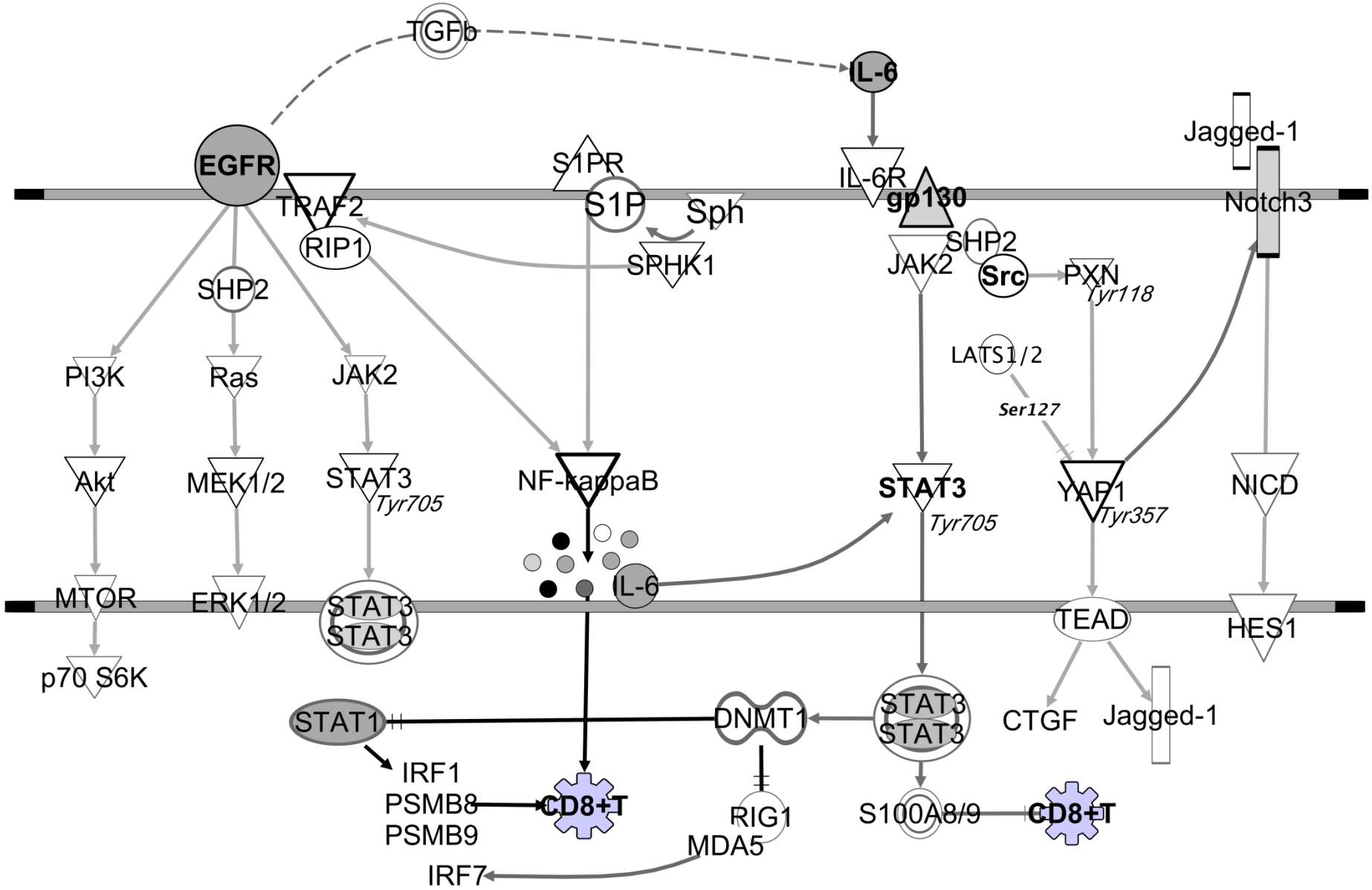
- Explanations and solutions can be found in EGFR mutant cell lines
- Biomarkers can accompany mutational analysis



Chen et al JTO 2015



Phuchareon et al, PNAS, 2015



Our working model (Rosell, Karachaliou, Chaib et al)

An in depth look at trends in lung cancer

- Benefit of monoclonal antibodies against PD-1 and PD-L1 is determined by baseline CD8+ T cell infiltration in the tumor microenvironment.
- The up-regulation of signal transduction and activation of transcription 3 (STAT3) occurs soon after EGFR TKI.
- STAT3 leads to the activation of DNMT1, dampening T cells in the tumor microenvironment.
- Liquid biopsy for cancer immunotherapy: PD-1 expression on circulating CD8+ T cells could serve as a biomarker.
- Circulating RTK levels (sheddase substrates), such as AXL, MET and others, predict resistance to MAPKi