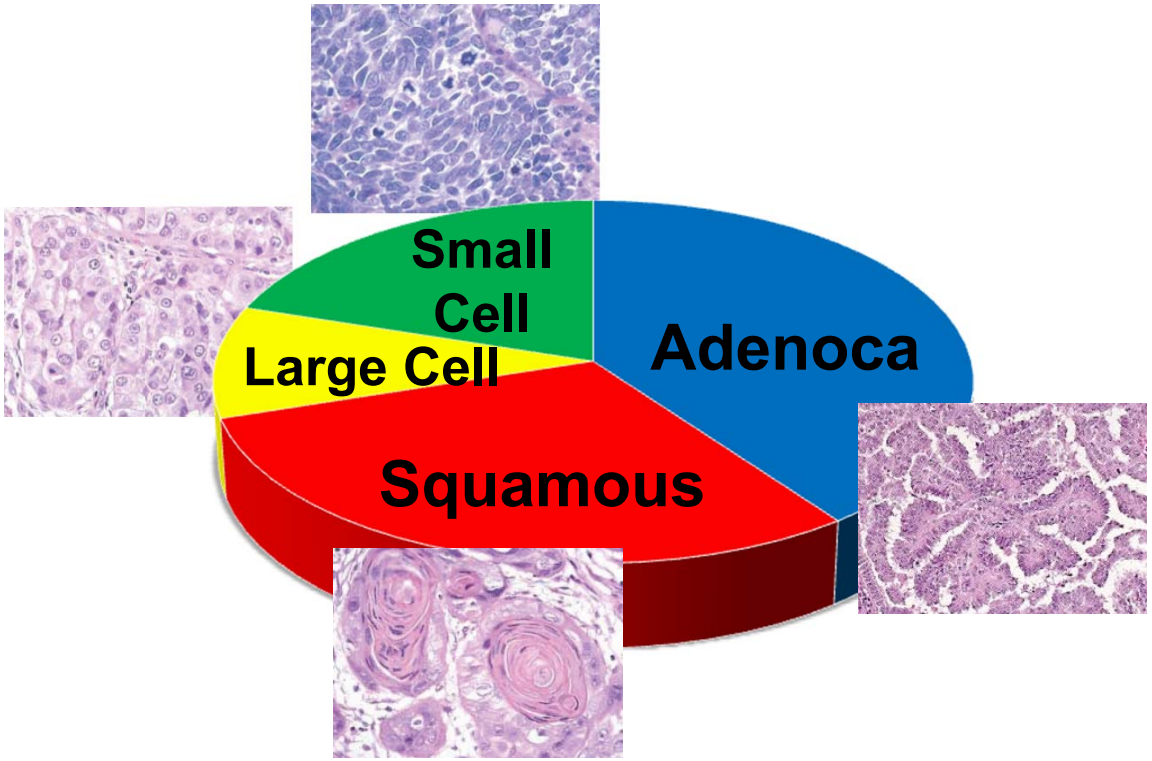
Molecular Basis of Lung Cancer Therapy

Dr. Bababk Salimi thoracic oncologist

Comprehensive Thoracic Oncology Program

Traditional View of Lung Cancer



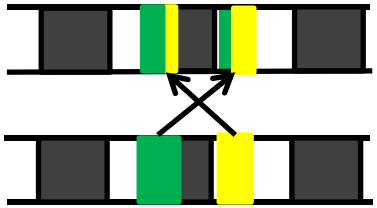
Presentation

- EGFR mutations
  - RADIANT adjuvant results in EGFR mutations
  - Uncommon EGFR mutations
  - Resistance in EGFR mutations (+) patients
- ALK gene rearrangements
  - Resistance in ALK gene rearrangement (+) patients
- BRAF mutations
- Other mutations, fusions and amplifications

Genomic alterations in cancer

Structural variants

- Translocations
- Fusions
- Inversion

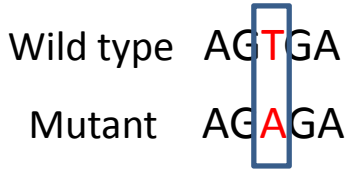


Copy number alterations

- Amplifications
- Deletions
- LOH

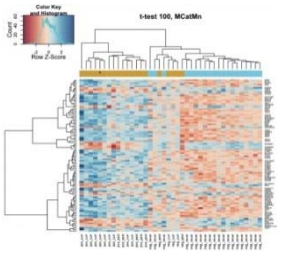
Point mutations & indels

- Missense
- Nonsense
- Splice site
- Frameshift



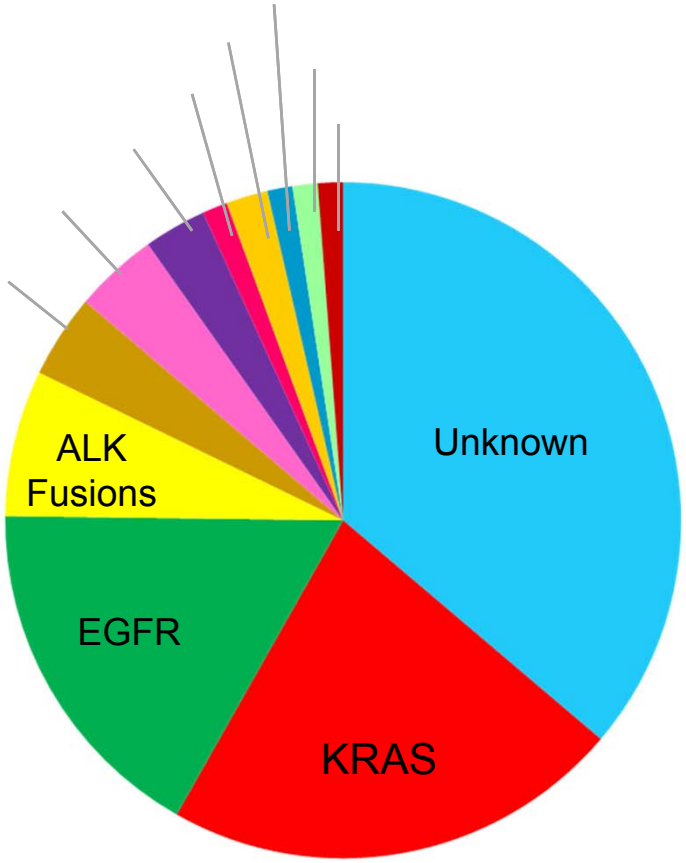
Gene expression

- Outlier expression
- Isoform usage
- Pathways & signatures

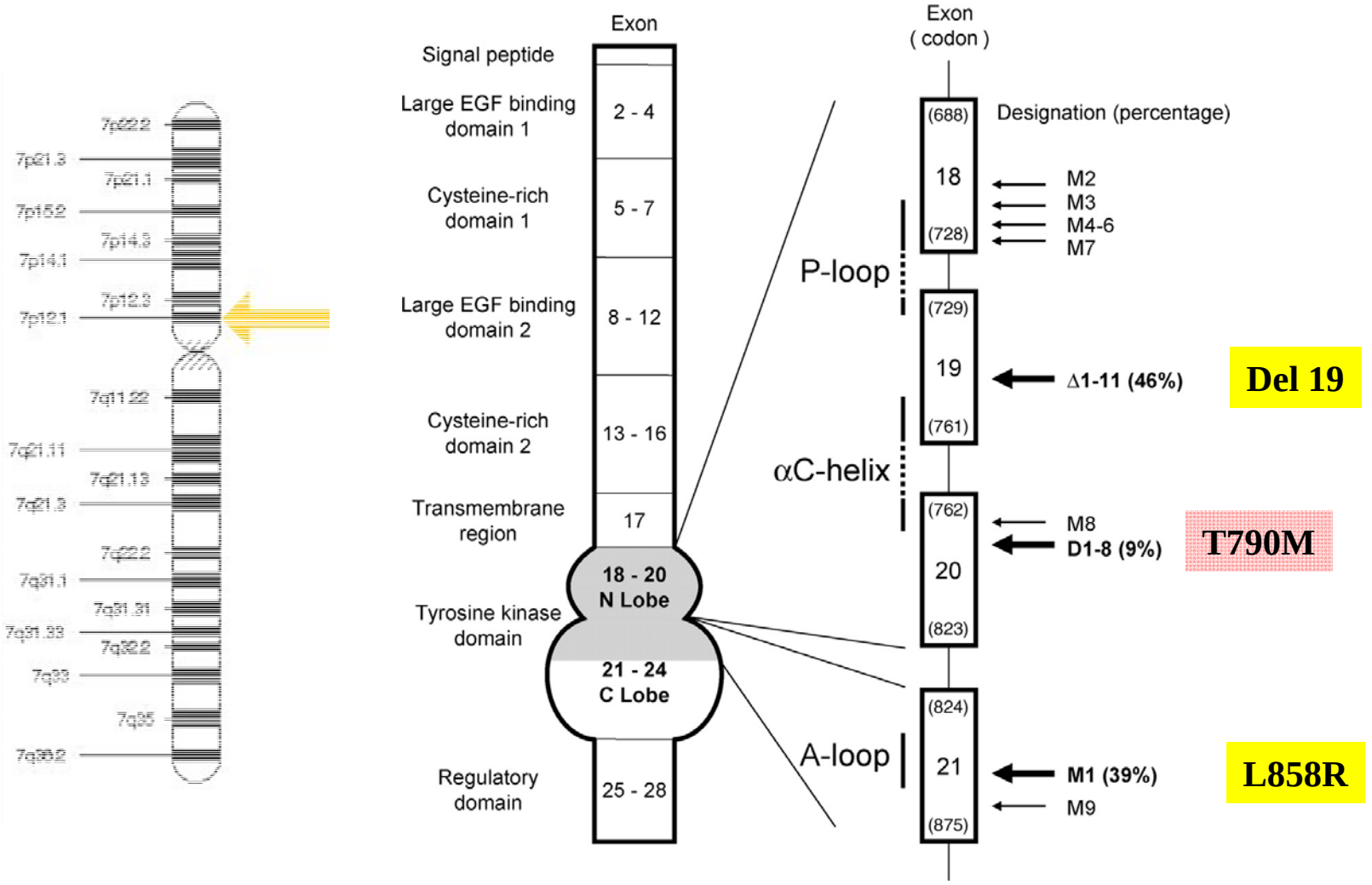


Adapted from: Roychowdhury et al. Sci Transl Med; 20122

Molecular Subsets
Adenocarcinoma Lung Cancer



Locations and Types of the 134 EGFR Gene Mutations Detected in Lung Cancers

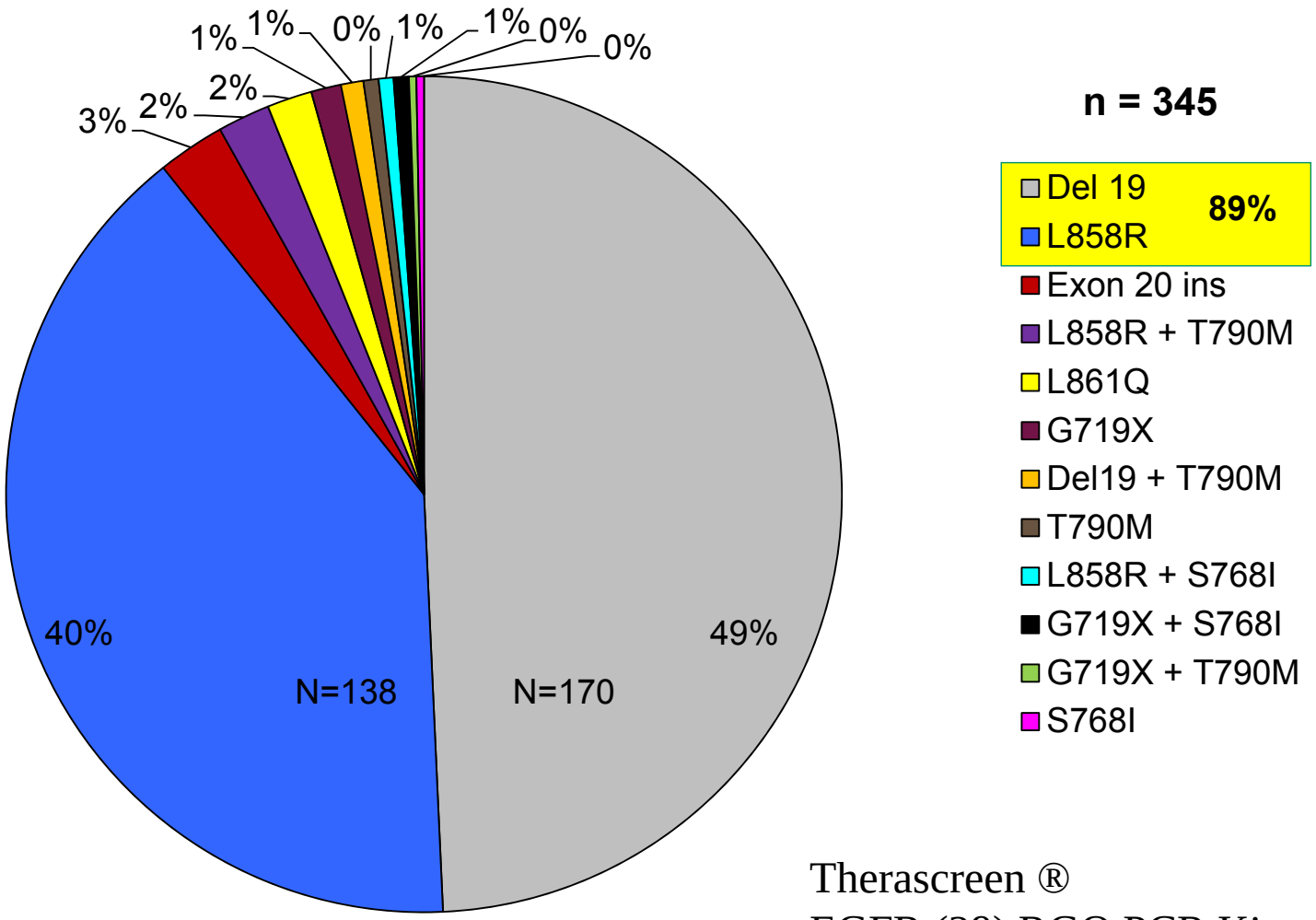


Shigematsu H et al. JNCI J Natl Cancer Inst 2005;97:339-346

Journal of the National Cancer Institute, Vol. 97, No. 5, © Oxford University Press 2005, all rights reserved.

JNCI

EGFR Gene Mutations in Adenocarcinoma Lung Cancer



Therascreen ®
EGFR (29) RGQ PCR Kit

EURTAC Study Design

- Stage IIIB/IV NSCLC
- *EGFR* exon 19 deletion or exon 21 L858R mutation (DNA sequencing/Genescan and Taqman)
- Chemonaive
- ECOG PS 0–2
- Measurable or evaluable disease

R

Erlotinib 150 mg/day → PD

Stratification
- Mutation type
- ECOG PS (0 vs 1 vs 2)

Platinum-based doublet chemotherapy q3wks x 4 cycles* → PD

Primary endpoint
- Progression-free survival (PFS)

US FDA approval May 14, 2013

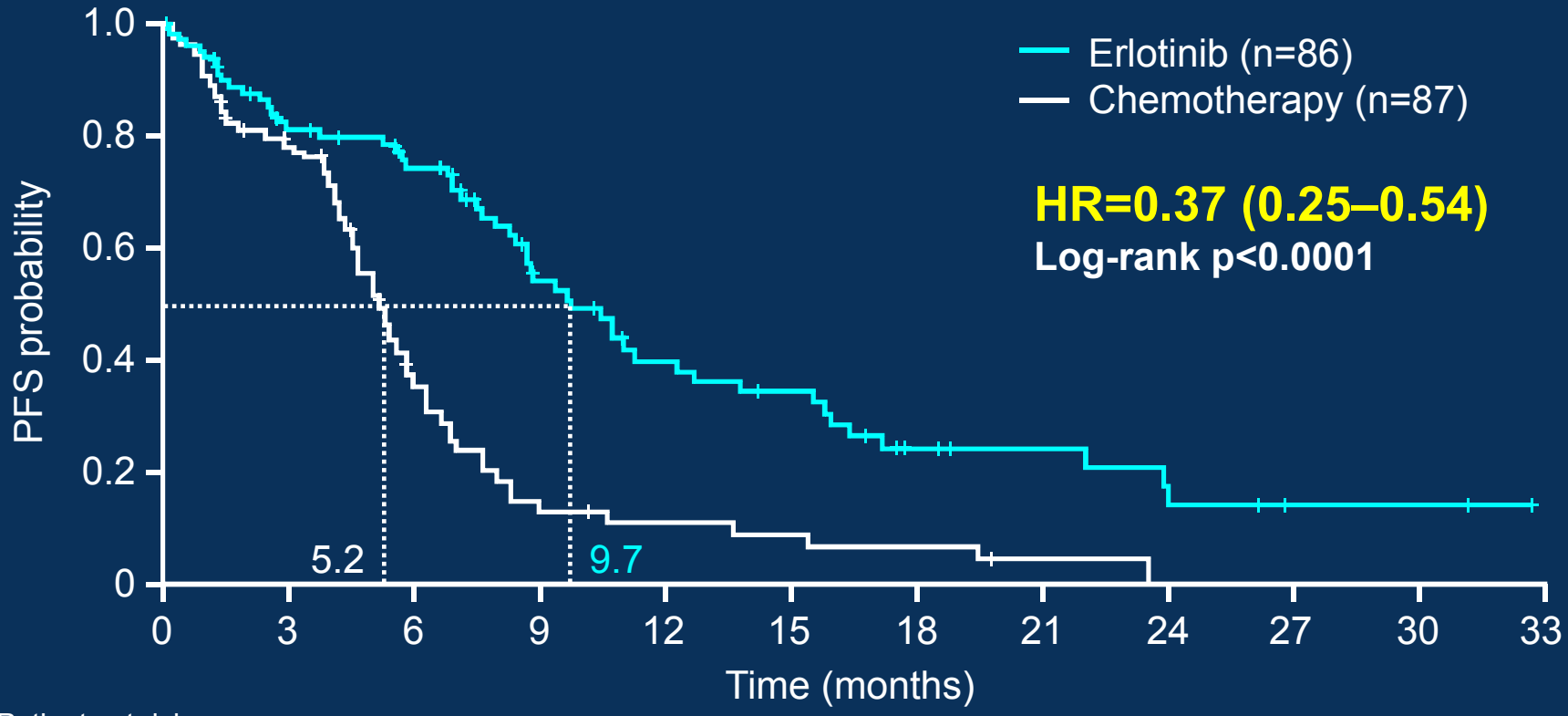
Cobas® EGFR Mutation Test
41 mutations in Exons 18, 19, 20 and 21

Secondary endpoints
- Objective response rate
- Overall survival (OS)
- Location of progression
- Safety
- *EGFR* mutation analysis in serum
- Quality of life

ECOG = Eastern Cooperative Oncology Group; PS = performance status; PD = progressive disease

*Cisplatin 75mg/m^2 d1 / docetaxel 75mg/m^2 d1; cisplatin 75mg/m^2 d1 / gemcitabine 1250mg/m^2 d1,8; carboplatin AUC6 d1 / docetaxel 75mg/m^2 d1; carboplatin AUC5 d1 / gemcitabine 1000mg/m^2 d1,8

Primary endpoint: PFS in ITT population (updated analysis 26 Jan 2011)



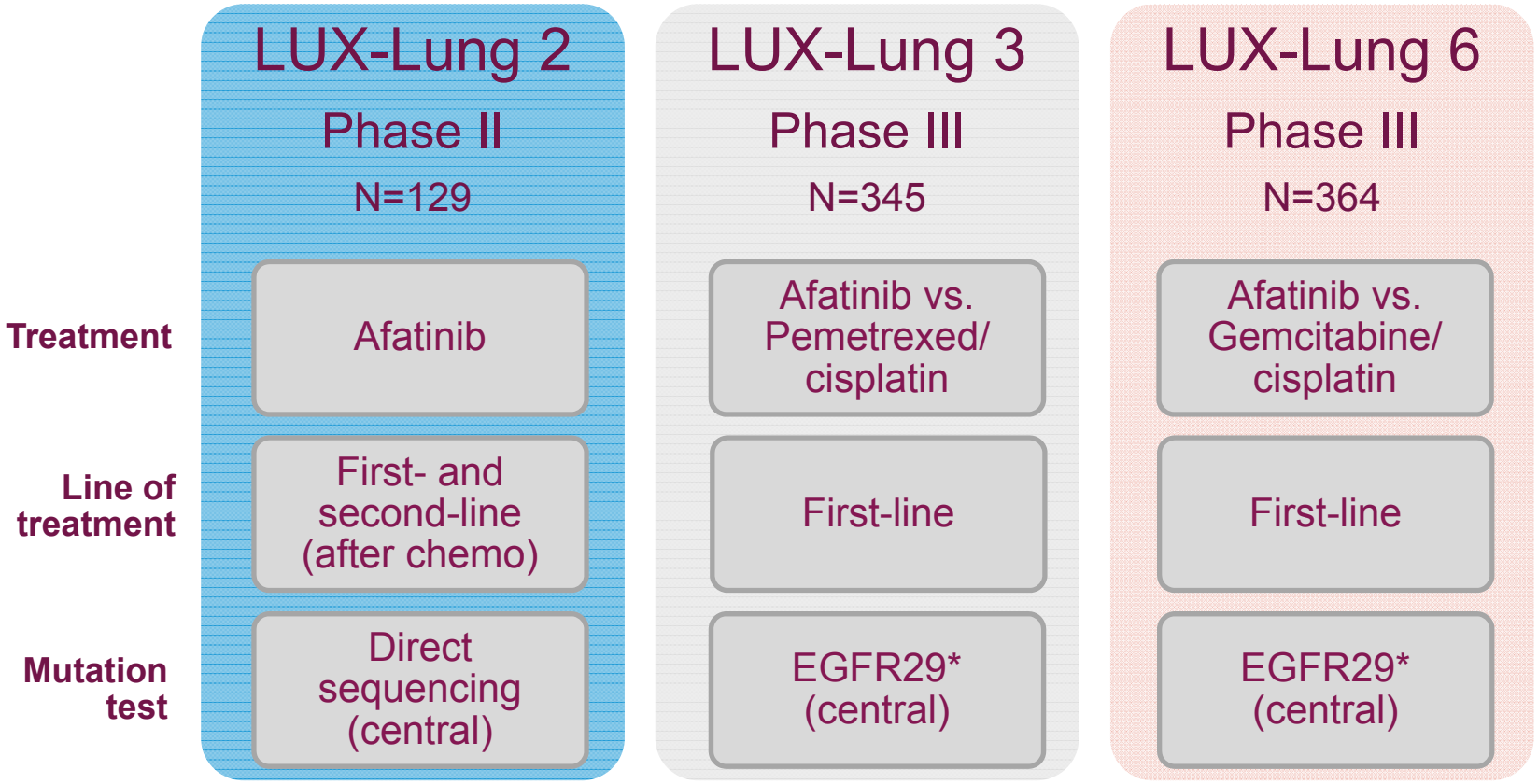
Patients at risk

Erlotinib	86	63	54	32	21	17	9	7	4	2	2	0
Chemo	87	49	20	8	5	4	3	1	0	0	0	0

Data cut-off: 26 Jan 2011

US FDA approval May 14, 2013

LUX-Lung clinical trials and eligibility

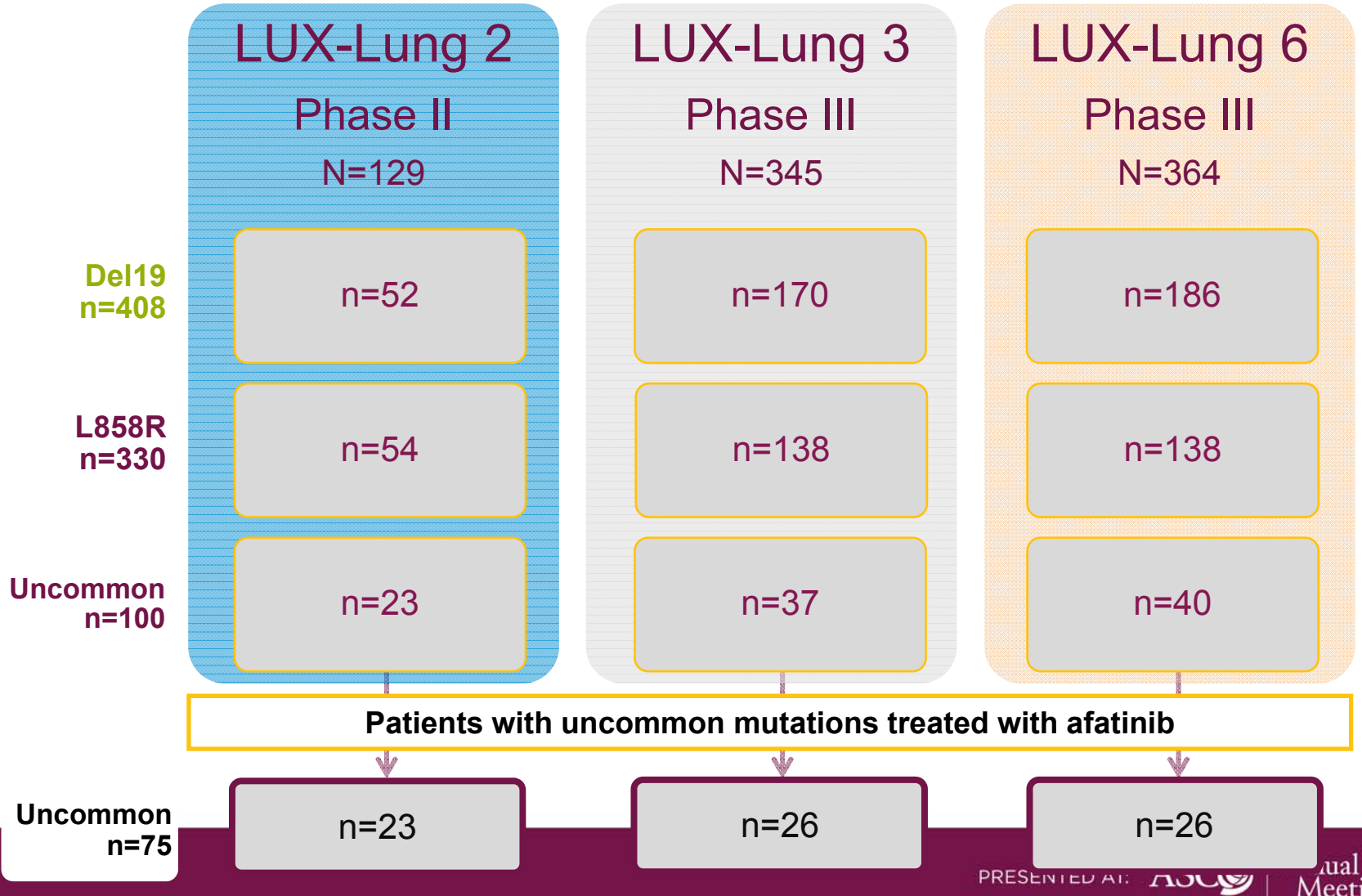


*EGFR mutations detected by TheraScreen EGFR29 test:

– Common: 19 deletions in exon 19 and L858R in exon 21

– Uncommon: 3 insertions in exon 20, L861Q, T790M, G719S, G719A and G719C, S768I

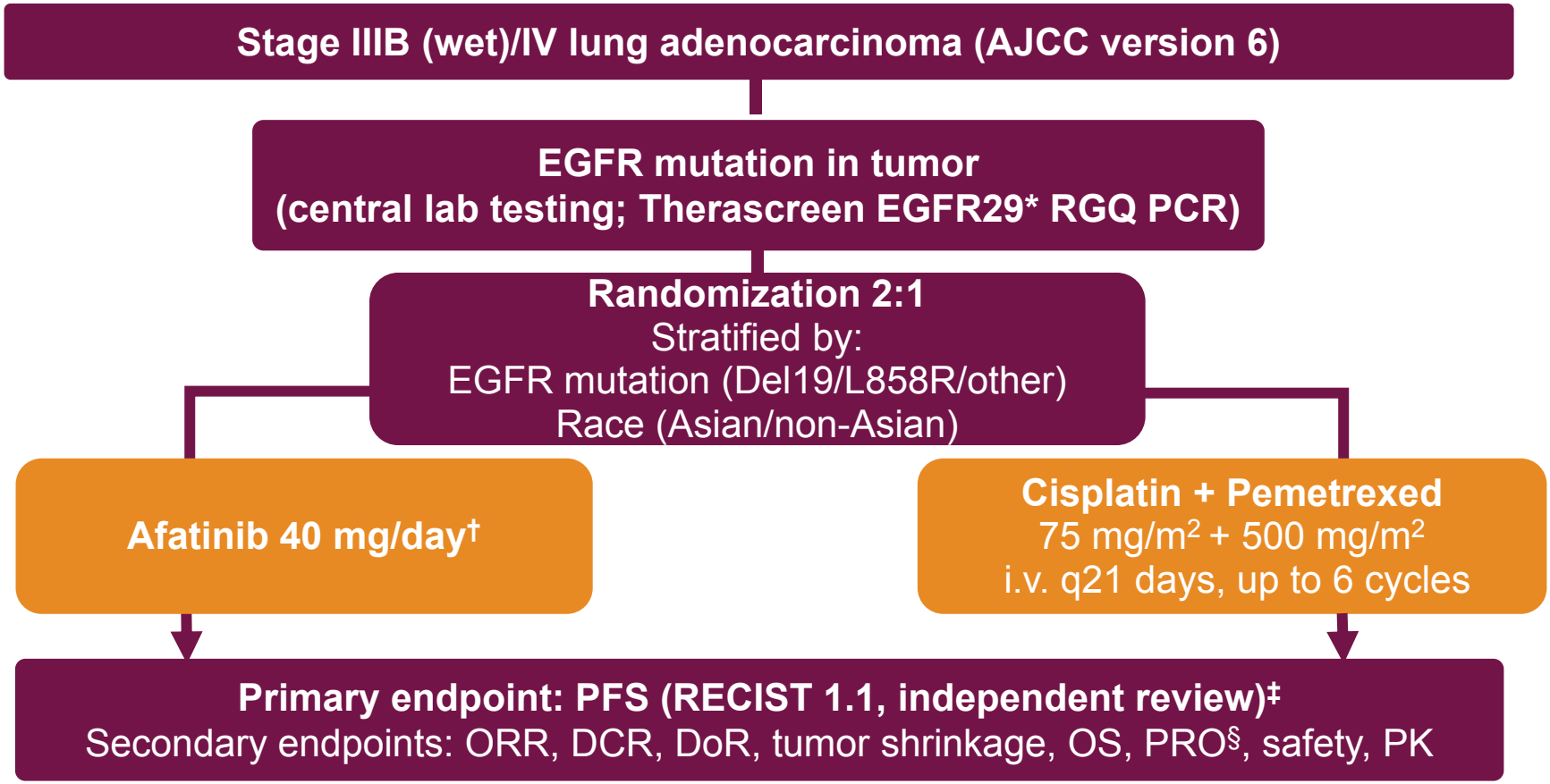
EGFR mutation-positive patients in LUX-Lung trials



Subgroups of patients with uncommon mutations

Categories	*De novo* T790M	Exon 20 insertions	Other (exon 18, 19, 20, 21)
n=	14	23	38
Mutations (n)	T790M alone (3) T790M+Del19 (3) T790M+L858R (6) T790M+G719X (1) T790M+L858R+G719X (1)	n/a	L861Q alone (12) G719X alone (8) G719X+S768I (5) G719X+L861Q (3) E709G or V+L858R (2) S768I+L858R (2) S768I alone (1) L861P alone (1) P848L alone (1) R776H+L858R (1) L861Q+Del19 (1) K739_1744dup6 (1)

Study design



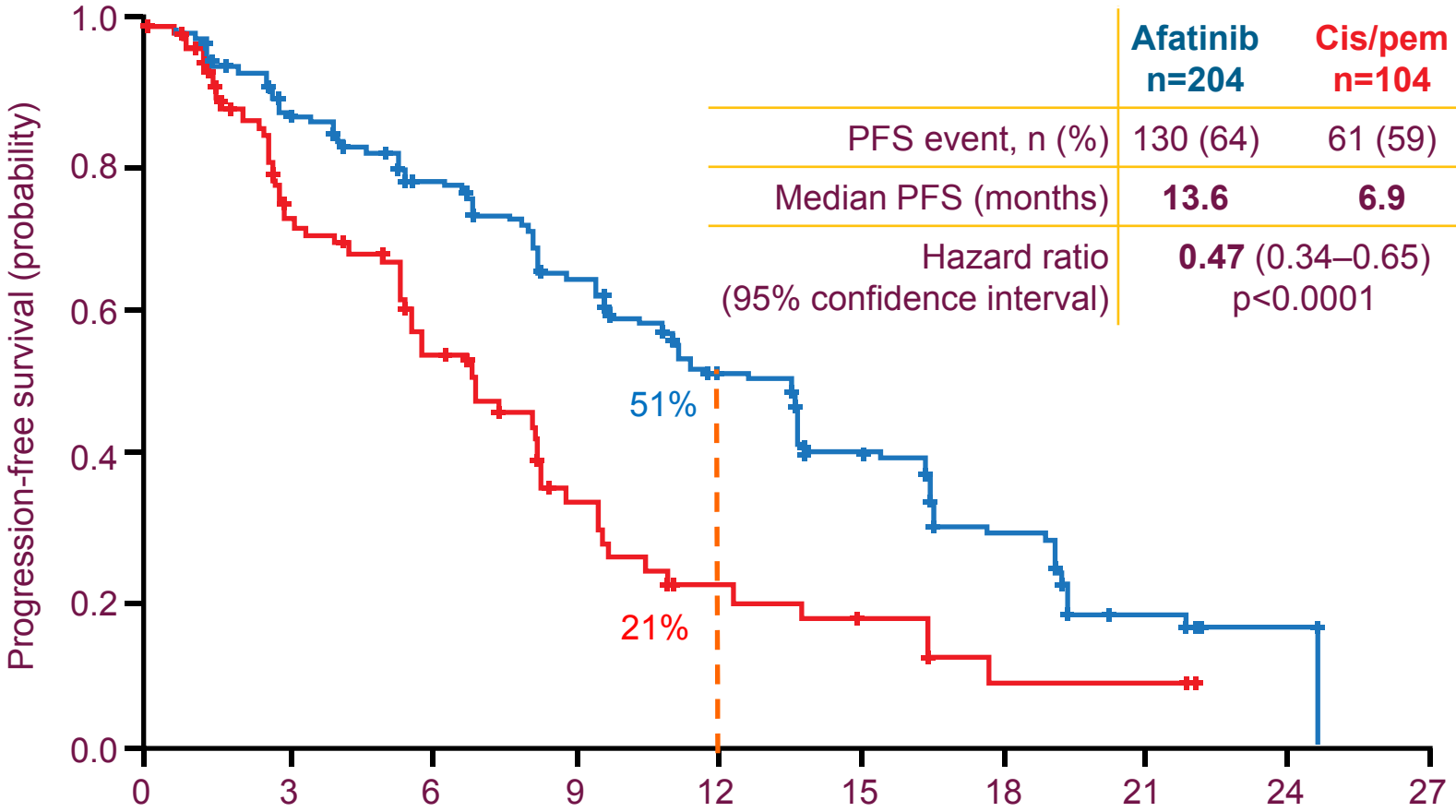
*EGFR29:19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.
†Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10 mg decrements in case of related G3 or prolonged G2 AE.
‡Tumor assessments: q6 weeks until Week 48 and q12 weeks thereafter until progression/start of new therapy.
§Patient-reported outcomes: Q-5D, EORTC QLQ-C30 and QLQ-LC13 at randomization and q3 weeks until progression or new anti-cancer therapy.

US FDA approval July 12, 2013

Yang JC, et al. PRESENTED AT: ASCO Annual '12 Meeting

PFS: Common mutations (Del19/L858R)

Independent review – patients with Del19/L858R (n=308)



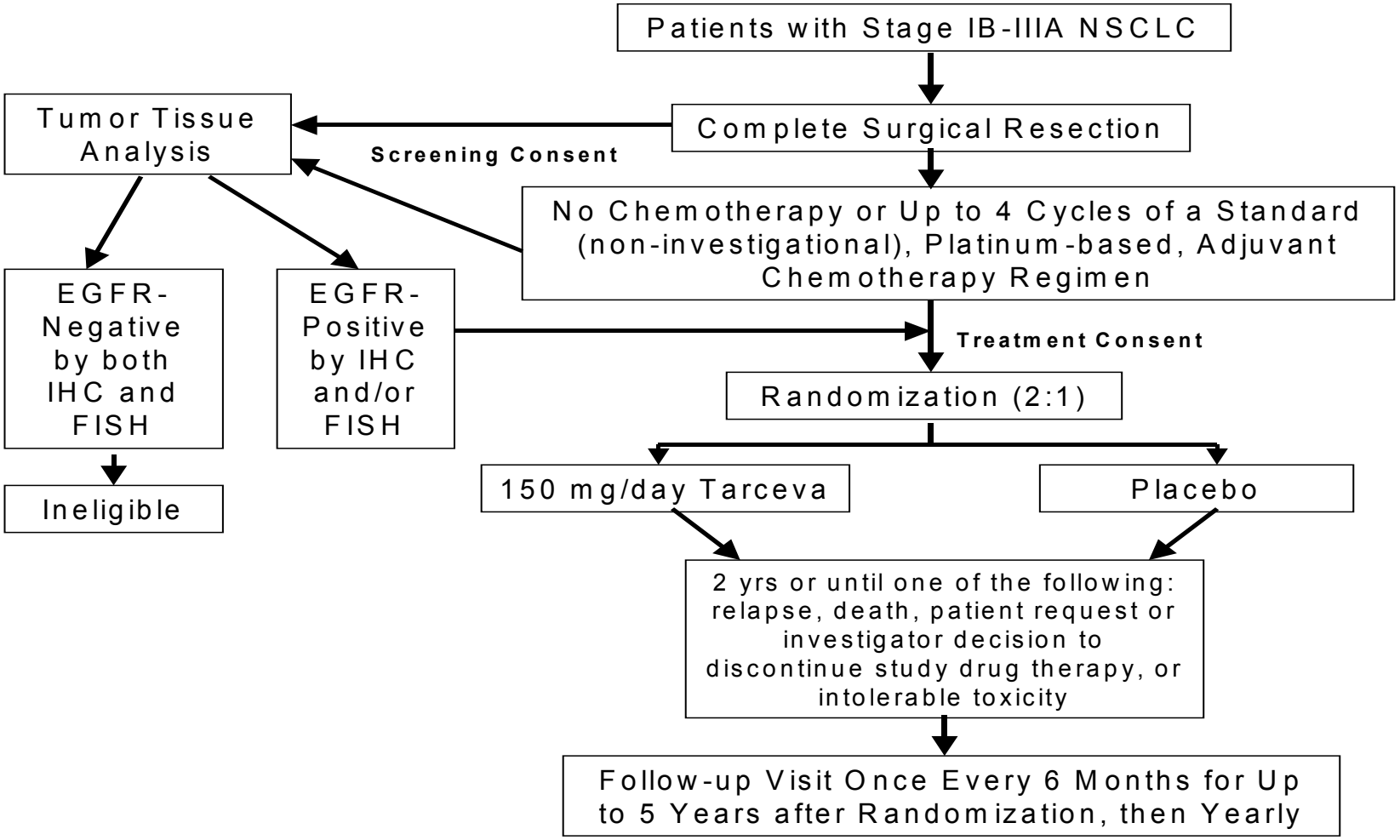
	Afatinib n=204	Cis/pem n=104
PFS event, n (%)	130 (64)	61 (59)
Median PFS (months)	**13.6**	**6.9**
Hazard ratio (95% confidence interval)	**0.47** (0.34–0.65) p<0.0001	

Number at risk										
Afatinib	204	169	143	115	75	49	30	10	3	0
Cis/Pem	104	62	35	17	9	6	2	2	0	0

US FDA approval July 12, 2013

Yang JC, et al. PRESENTED AT: ASCO Annual '12 Meeting

RADIANT Study Schematic



RADIANT Study Results

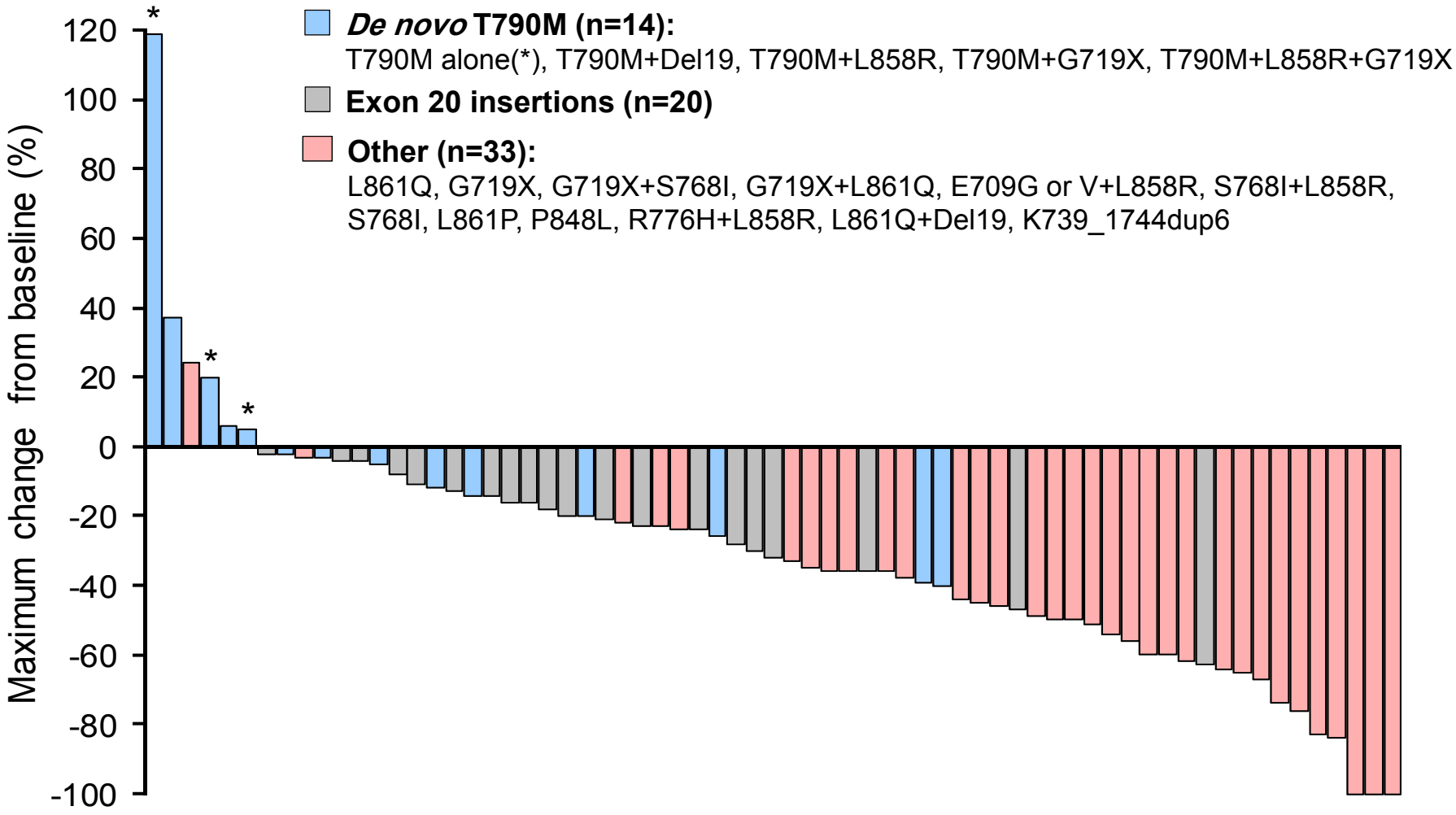
	Median (m)			
	E (N=623)	P (N=350)	HR (95% CI)	P value
DFS	50.5	48.2	0.90 (0.741-1.104)	0.3235
OS	NR	NR	1.13 (0.881-1.448)	0.3350

***EGFR* M+ subset**

	Median (m)			
	E (N=102)	P (N=59)	HR (95% CI)	P value
DFS	46.4	28.5	0.61 (0.384-0.981)	0.0391*
OS	NR	NR	1.09 (0.545-2.161)	0.8153

Hierarchical testing rendered all secondary endpoints non-significant.

Tumour shrinkage in patients with uncommon mutations

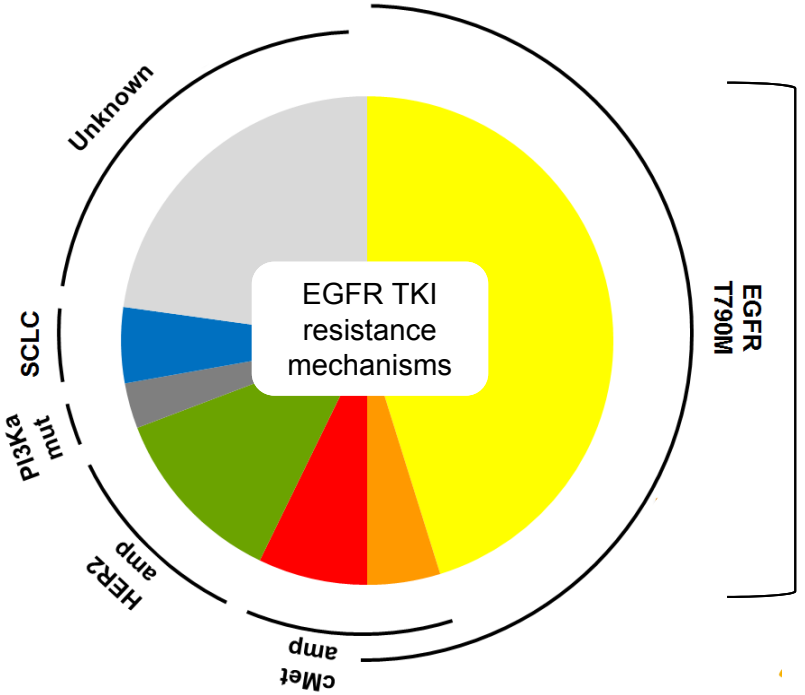


†8 patients were not included due to insufficient data

T790M+ EGFR- TKI failures 2nd/3rd line NSCLC

An area of high unmet medical need

There are no current proven treatment options for these patients.
Chemotherapy or EGFR-TKIs are used, but their benefit isn't proven



AZD9291 or CO1686

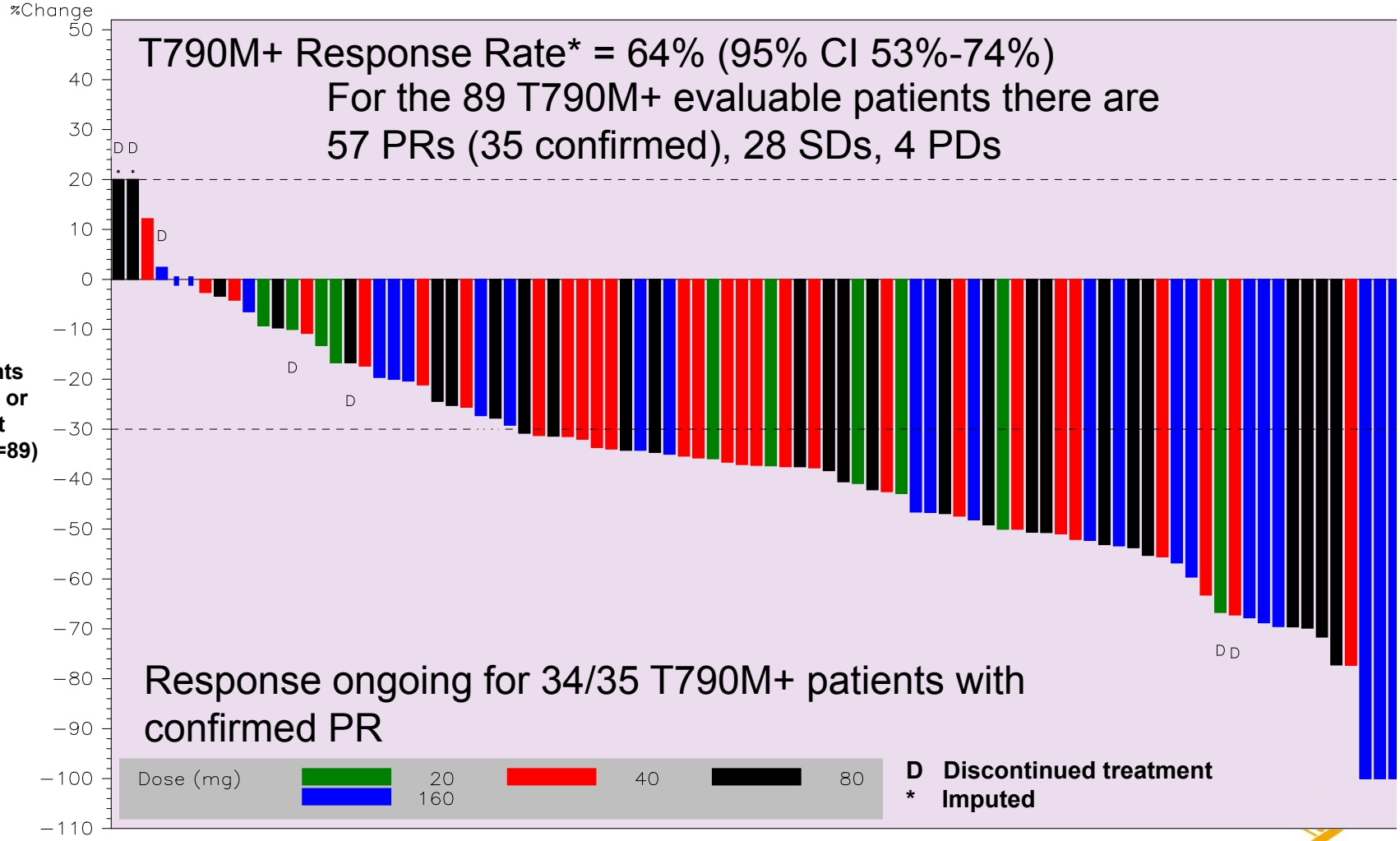
[1]

"Patients with EGFR-mutant lung adenocarcinoma develop acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) after a median of 10-16 months. In half of these cases, a second EGFR mutation, T790M, underlies acquired resistance" Oxnard, et al. *Clin Cancer Res Dec 6, 2010*

Clinical activity AZD9291 in T790M+

- Fast Track status granted by FDA in October 2013
- Breakthrough Therapy Designation submission early February 2014

Best % change from baseline in target lesions in central testing T790M+



Population: T790M+ patients with observed or imputed target lesion data (n=89)

***Confirmed+ unconfirmed response**

T790M status is assigned by central testing of a recent tumour sample
Independent review of scans is underway as per FDA request 41/43 confirmed so far

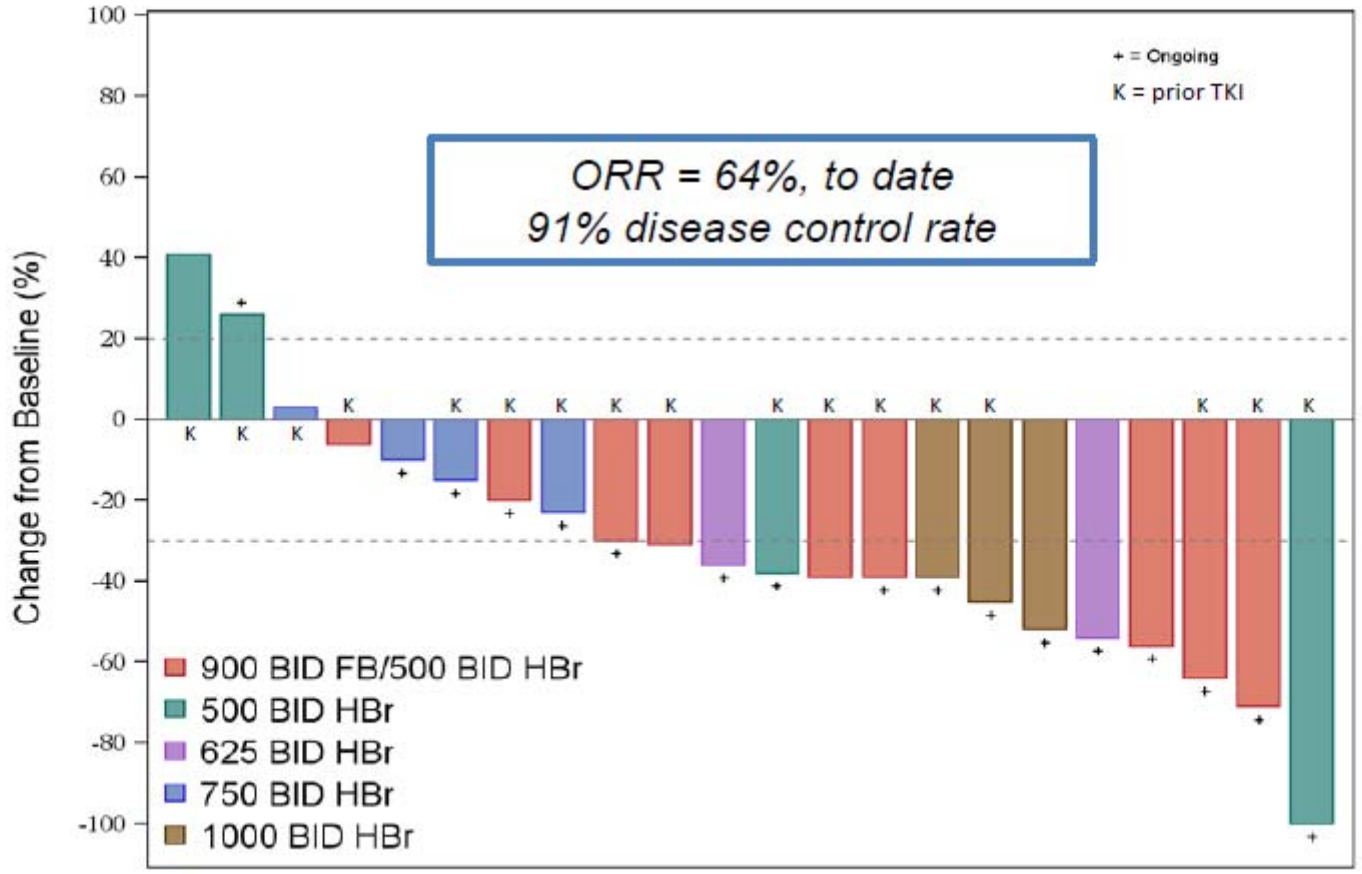
Preliminary data, data cut off 16th January 2014

elcc European Lung Cancer Conference

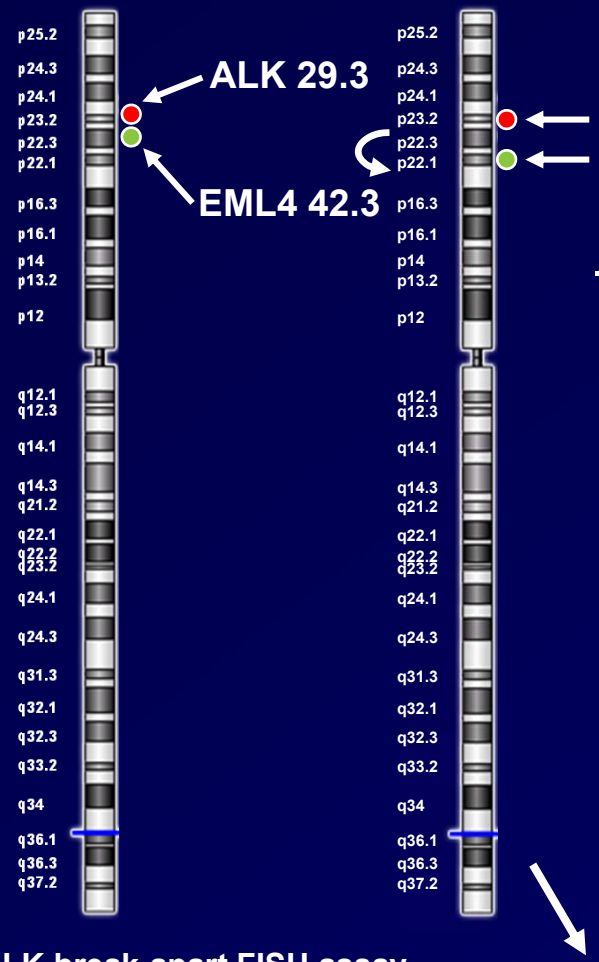
CO1686

Efficacy clear across dose levels in 22 centrally-confirmed T790M+ patients

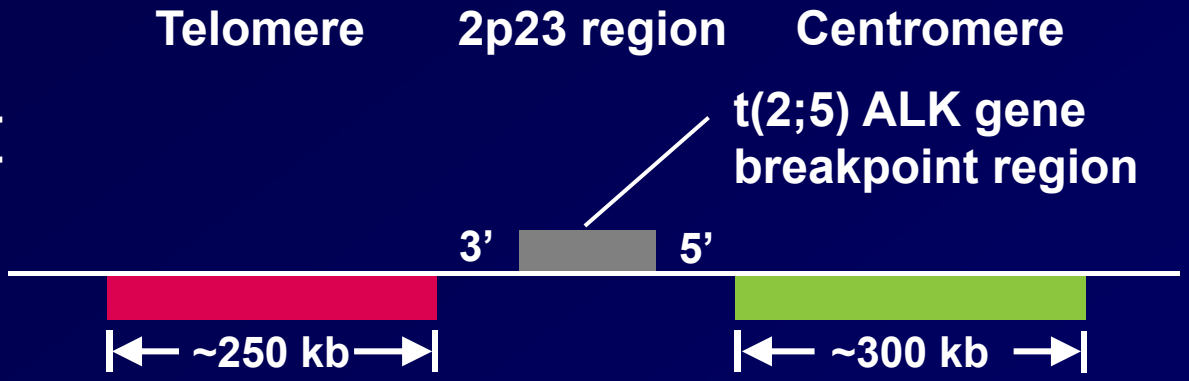
Best Response for Target Lesions
T790M Positive Patients: 900 mg BID FB and HBr by Dose



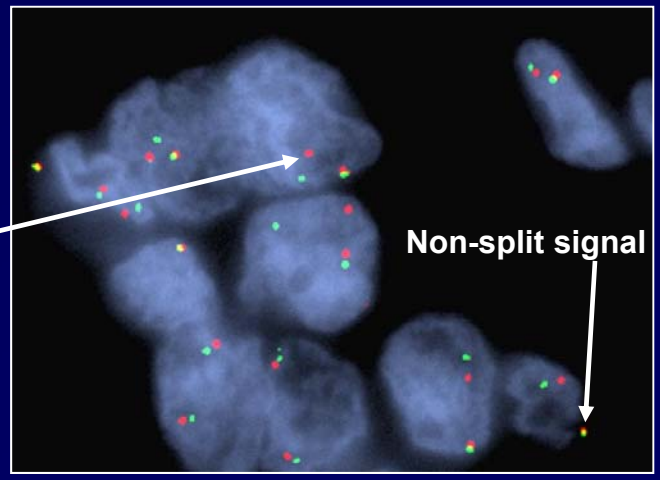
FISH Assay for *ALK* Rearrangement*



ALK break-apart FISH assay
[Courtesy John Iafrate, Massachusetts General Hospital]



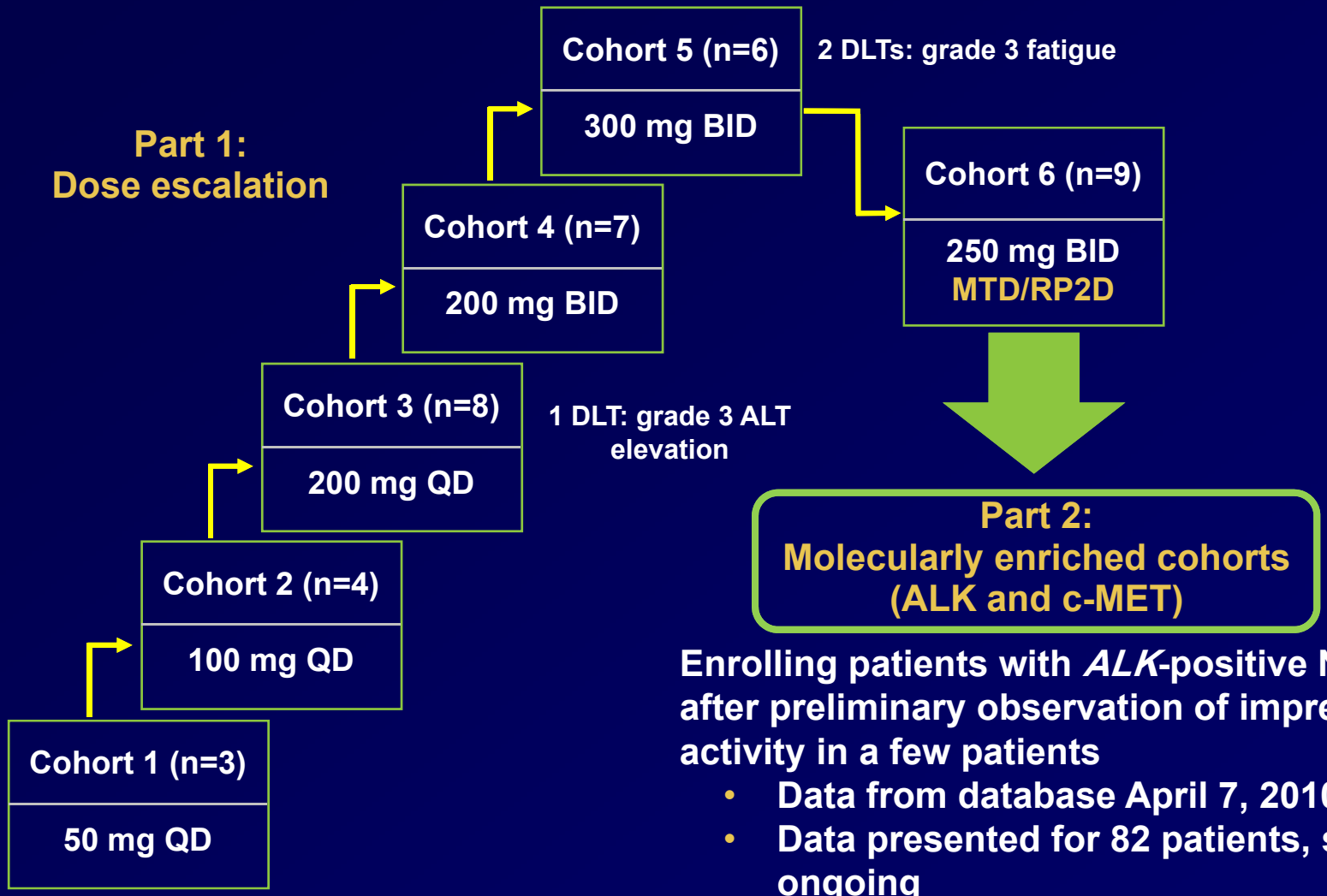
Break-apart FISH assay for *ALK*-fusion genes[1]



*Assay is positive if rearrangements can be detected in ≥15% of cells
FISH = fluorescence in situ hybridization

[1]Shaw AT et al. J Clin Oncol 2009;27:4247–4253

Crizotinib: First-in-human/Patient Trial

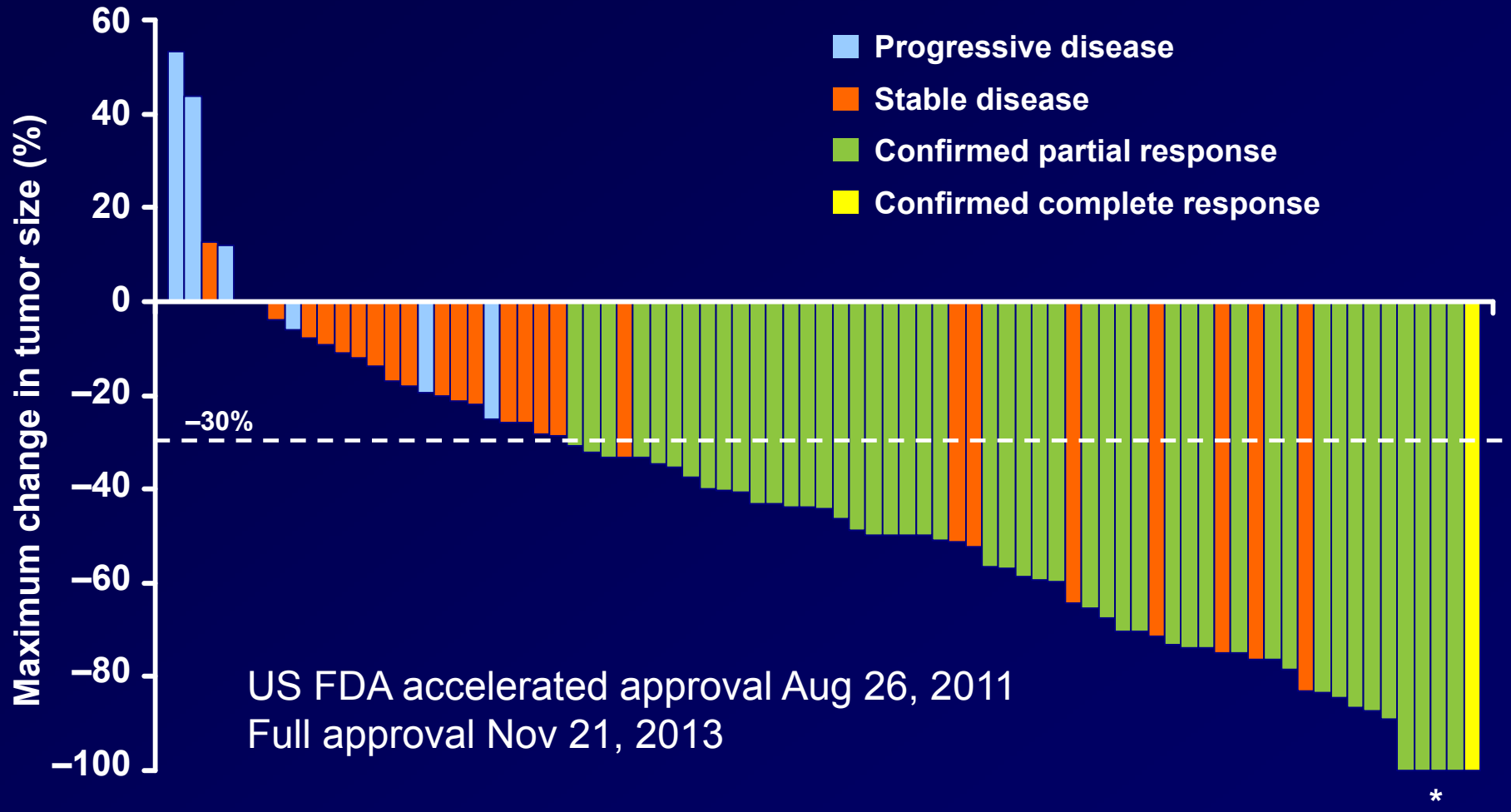


Enrolling patients with *ALK*-positive NSCLC after preliminary observation of impressive activity in a few patients

- **Data from database April 7, 2010**
- **Data presented for 82 patients, study ongoing**

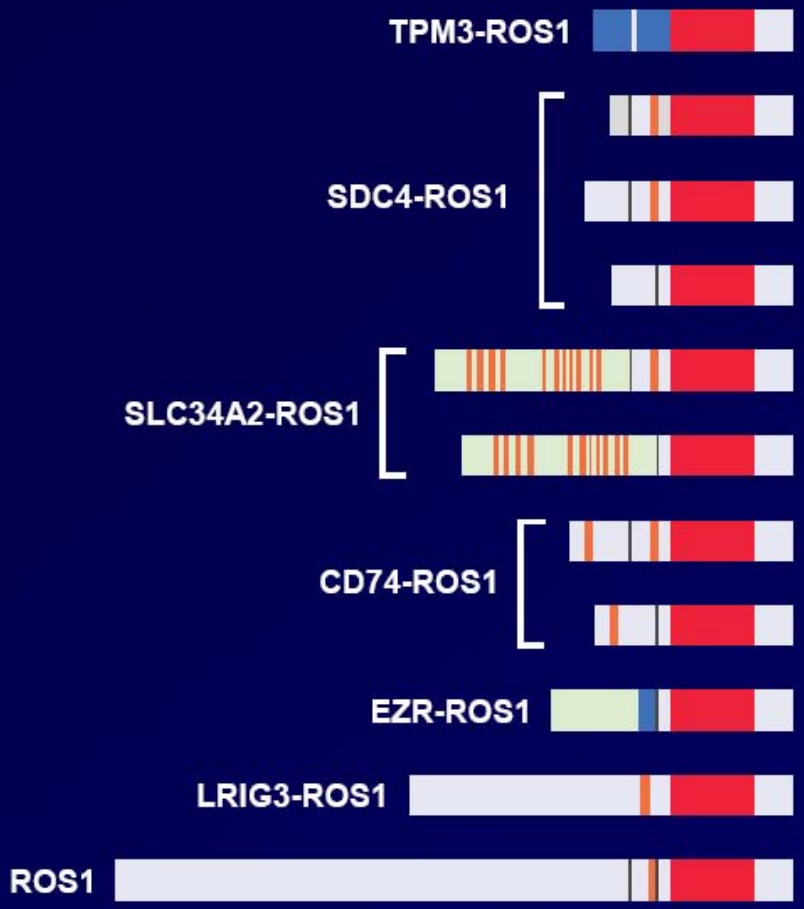
ALT = alanine aminotransferase

Tumor Responses to Crizotinib for Patients with *ALK*-positive NSCLC



*Partial response patients with 100% change have non-target disease present

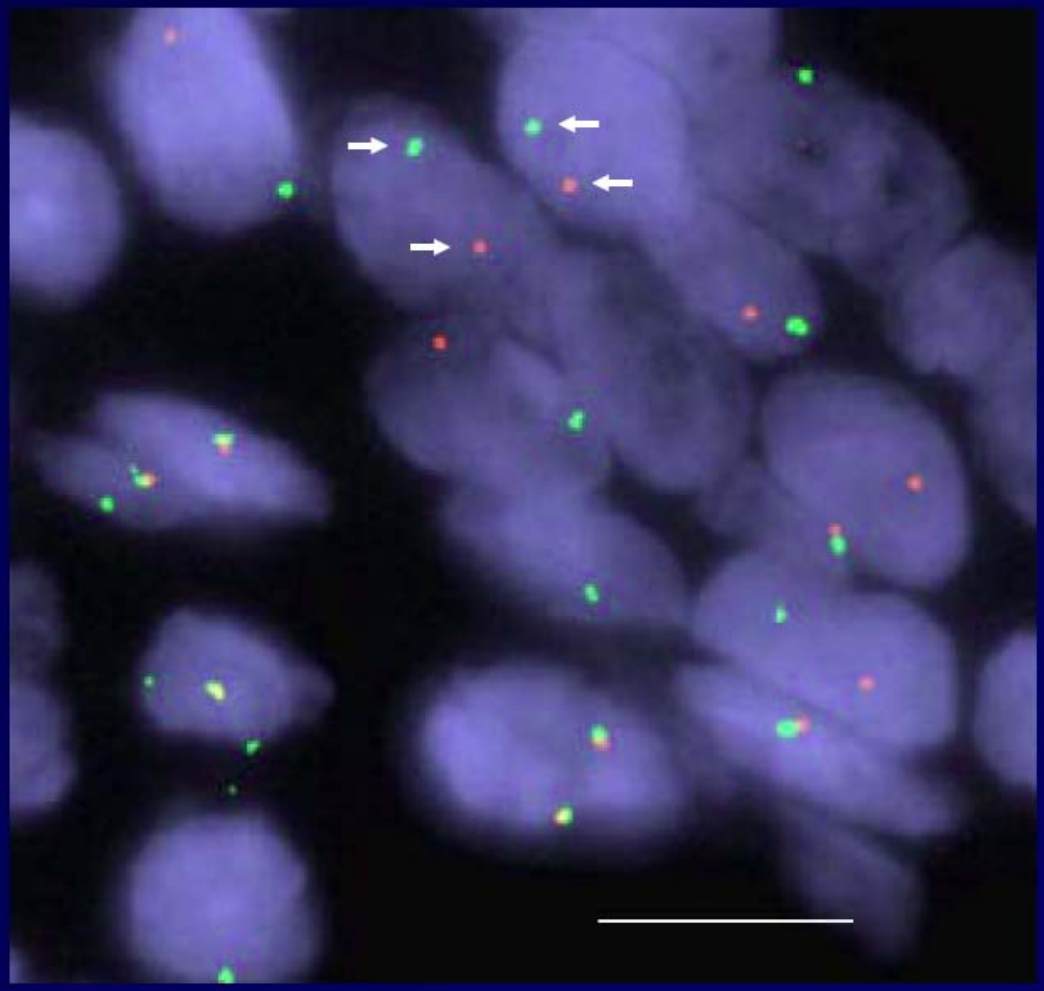
ROS1 Rearrangements in NSCLC



- Present in ~1% of NSCLC cases (also found in some GBMs and cholangiocarcinomas)
- Enriched in younger never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers

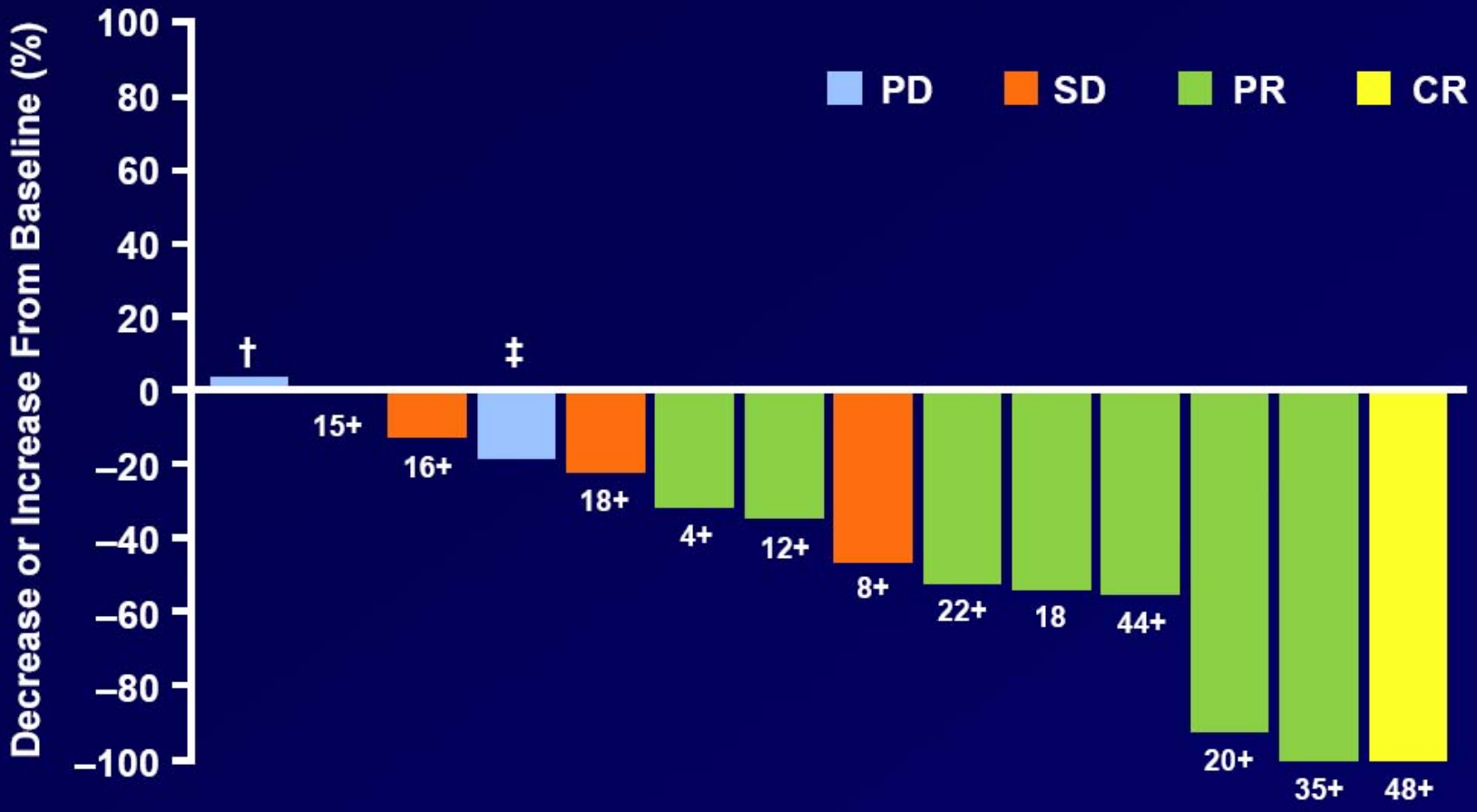
Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012

Diagnostic "Break-Apart" FISH Assay for ROS1 Rearrangement



Bergethon et al., JCO 30(8): 863-70, 2012

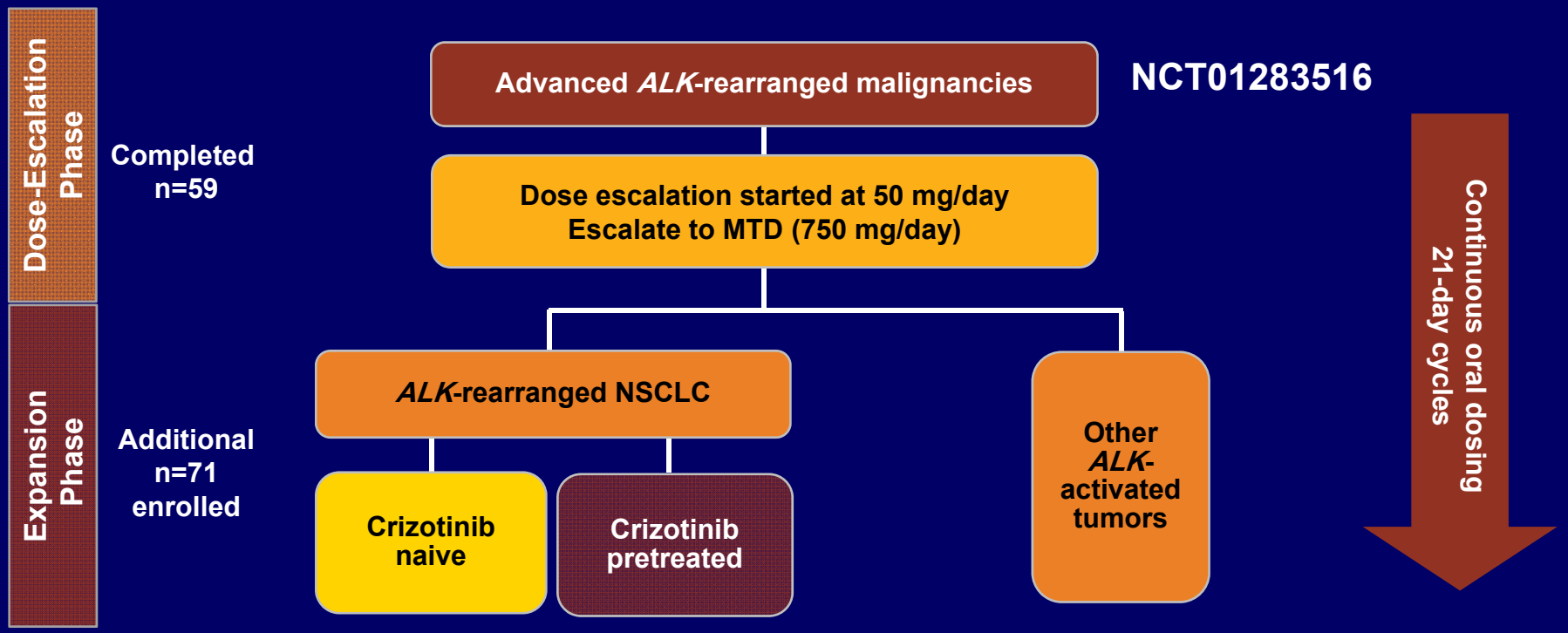
Summary of Tumor Responses in Patients with Advanced ROS1+ NSCLC (N=14*)



*Response-evaluable population. †Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression. ‡Crizotinib held for >6 wks prior to first scans which showed PD. +, Treatment ongoing. For ongoing patients, duration of response/SD is the time from first documentation of tumor response/first dose to last available on treatment scan. For discontinued patients, duration is to the time of PD or death. Duration is in weeks.

Data in the database as of April 19, 2012

Study Design – LDK378 (Ceritinib)

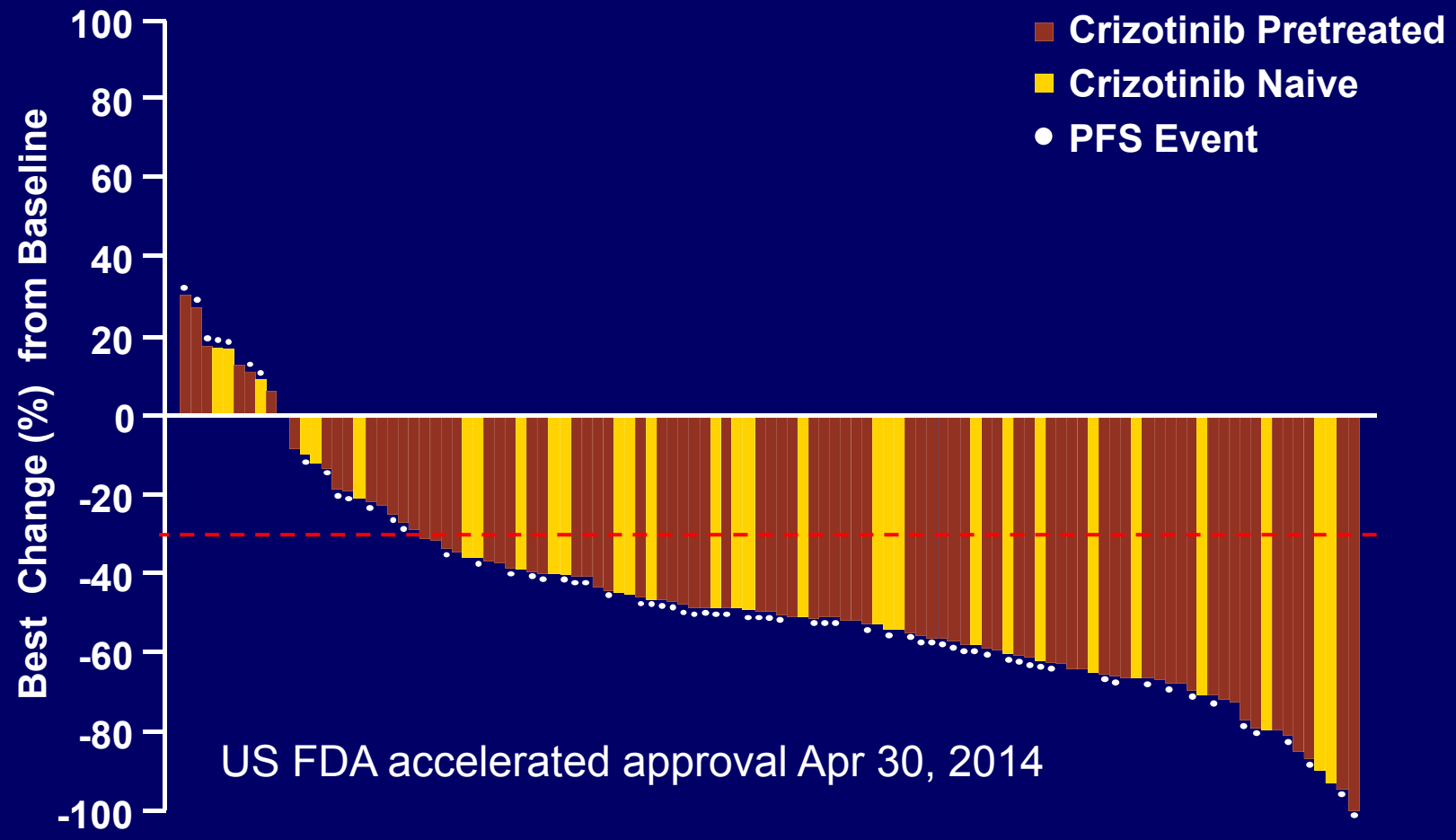


- **Primary objective:** determination of MTD
- **Secondary objectives:** characterize safety, PK, and antitumor activity

- Patients received treatment until disease progression, unacceptable toxicity, or withdrawal of consent

Shaw AT et al. *N Engl J Med*. 2014;370:1189-1197.

Best Change (%) in Tumor Response from Baseline in NSCLC Patients Treated with Ceritinib



Based on investigator assessment of response.
PFS, progression-free survival.
Shaw AT et al. *N Engl J Med*. 2014;370:1189-1197.
From *N Engl J Med*, Shaw AT, Kim DW, Mehra R, et al, Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer, Vol 370, Page 1194.
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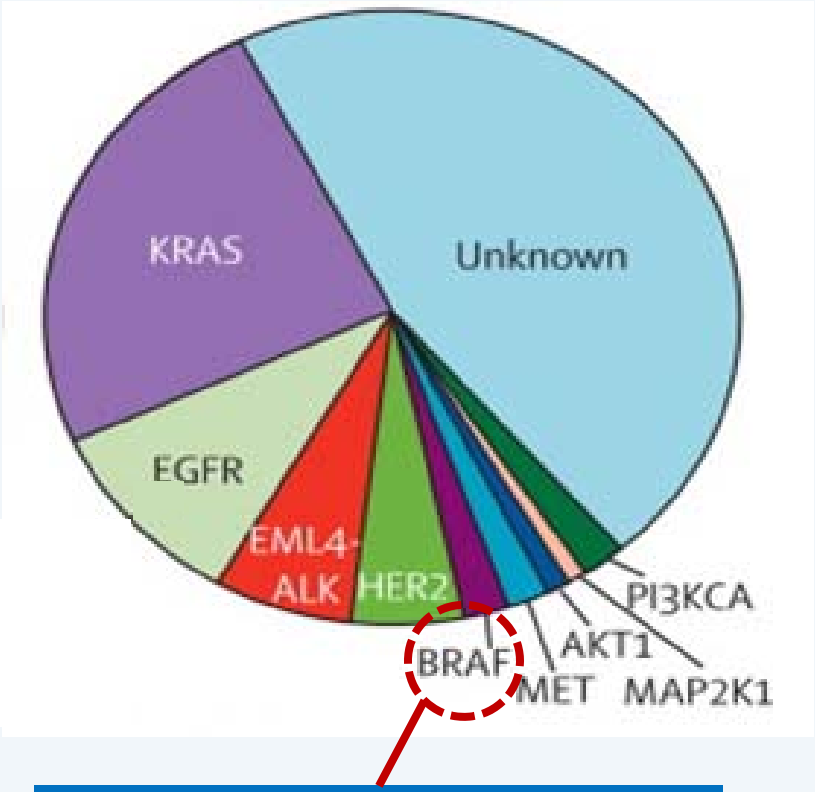
BRAF-Mutations in NSCLC

W. Pao, N. Girard
Lancet Oncology,
February 2011



1.5-2.5 % of NSCLC harbor BRAF V600E-mutations

A. Marchetti et al., J. Clin. Oncol. 29, 1, 2011

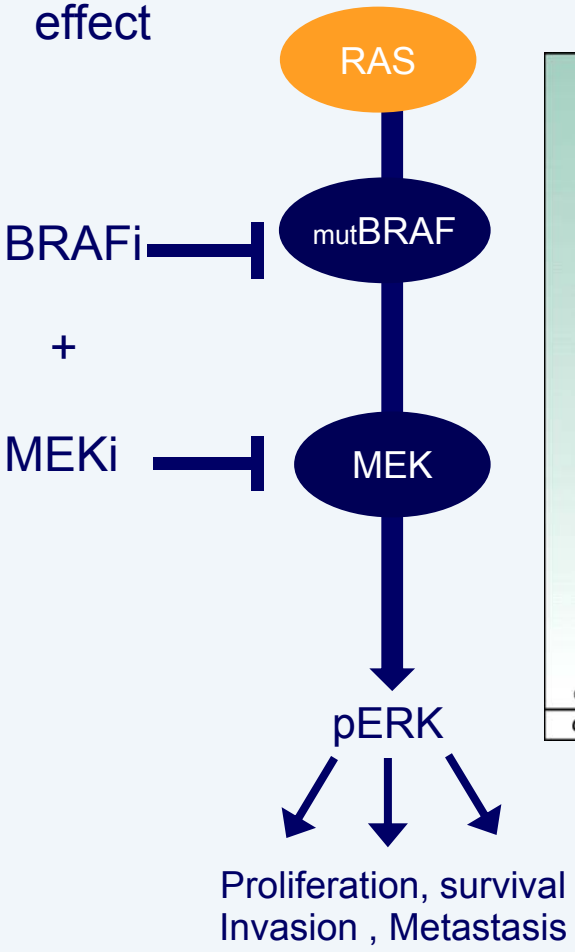
- 1,046 NSCLC samples
- Frequency of BRAF-mutations 3.5%
- BRAF-mut. in 4.9% adeno- and 0.3% SCC
- 57% $BRAF^{V600E}$-mutations
- 43 % non-activating BRAF mutations

P. Paik et al., J. Clin. Oncol. 29, 2046, 2011

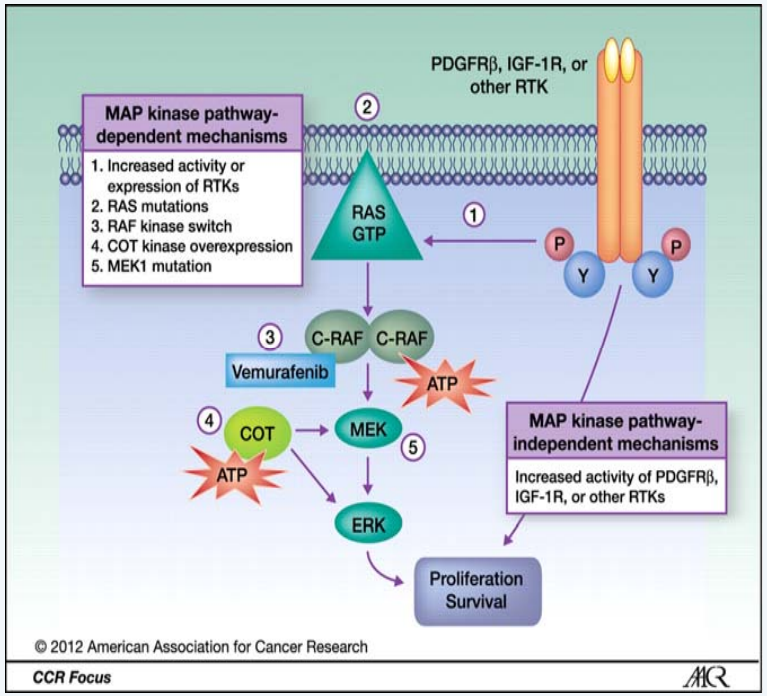
- 697 NSCLC-adeno. ca. Samples
- Frequency of BRAF-mutations 3%
- 50% $BRAF^{V600E}$-mutations
- 50% non-activating BRAF mutations

Rationale for the Combination

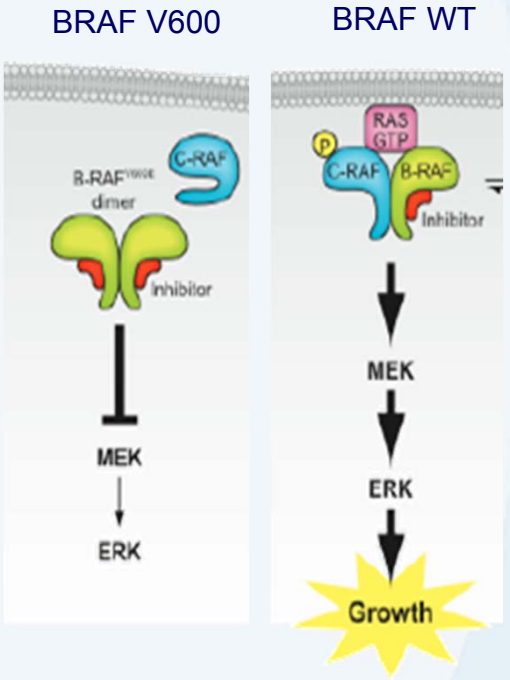
- Sustained target inhibition to observe more prolonged and durable anti-tumor effect



- Delay and potentially prevent the development of resistance

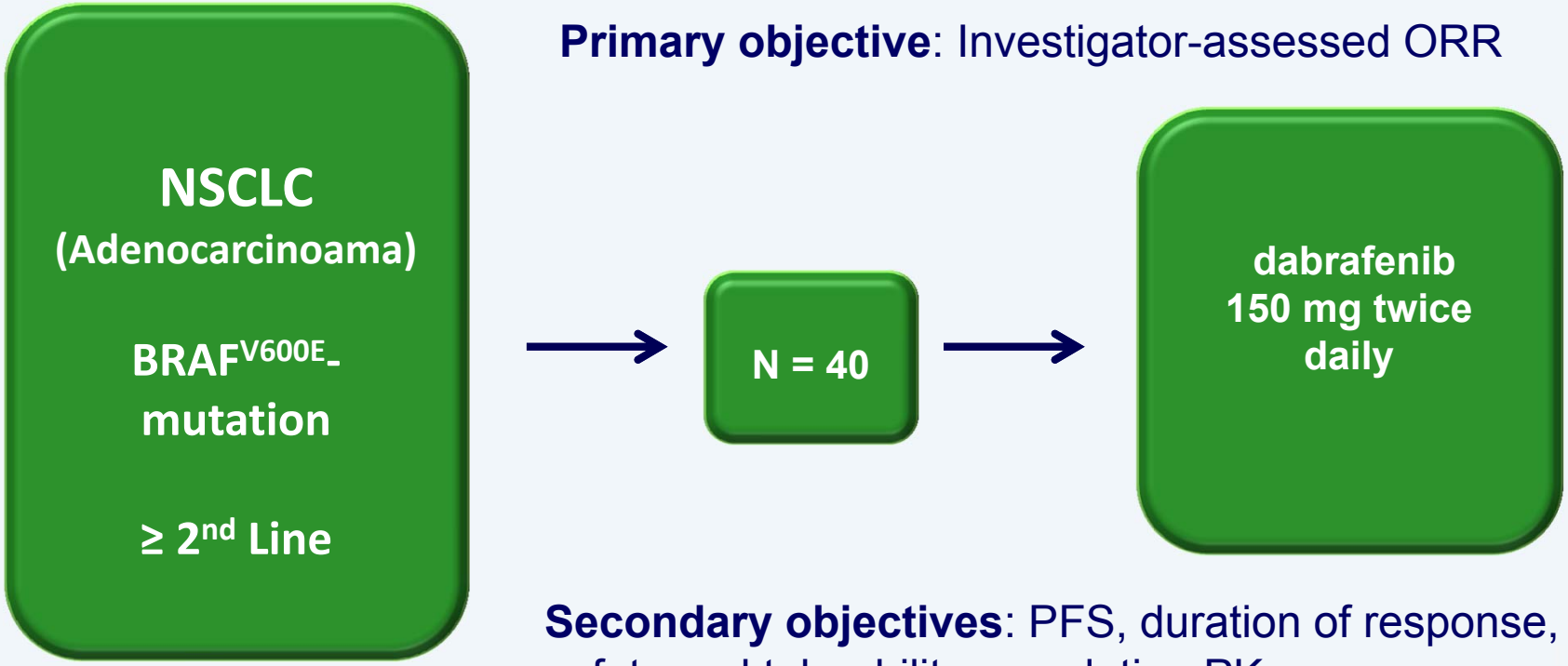


- Prevent/delay hyperproliferative lesions and secondary malignancies (Cu SCC)



BRF113928: Initial Study Design

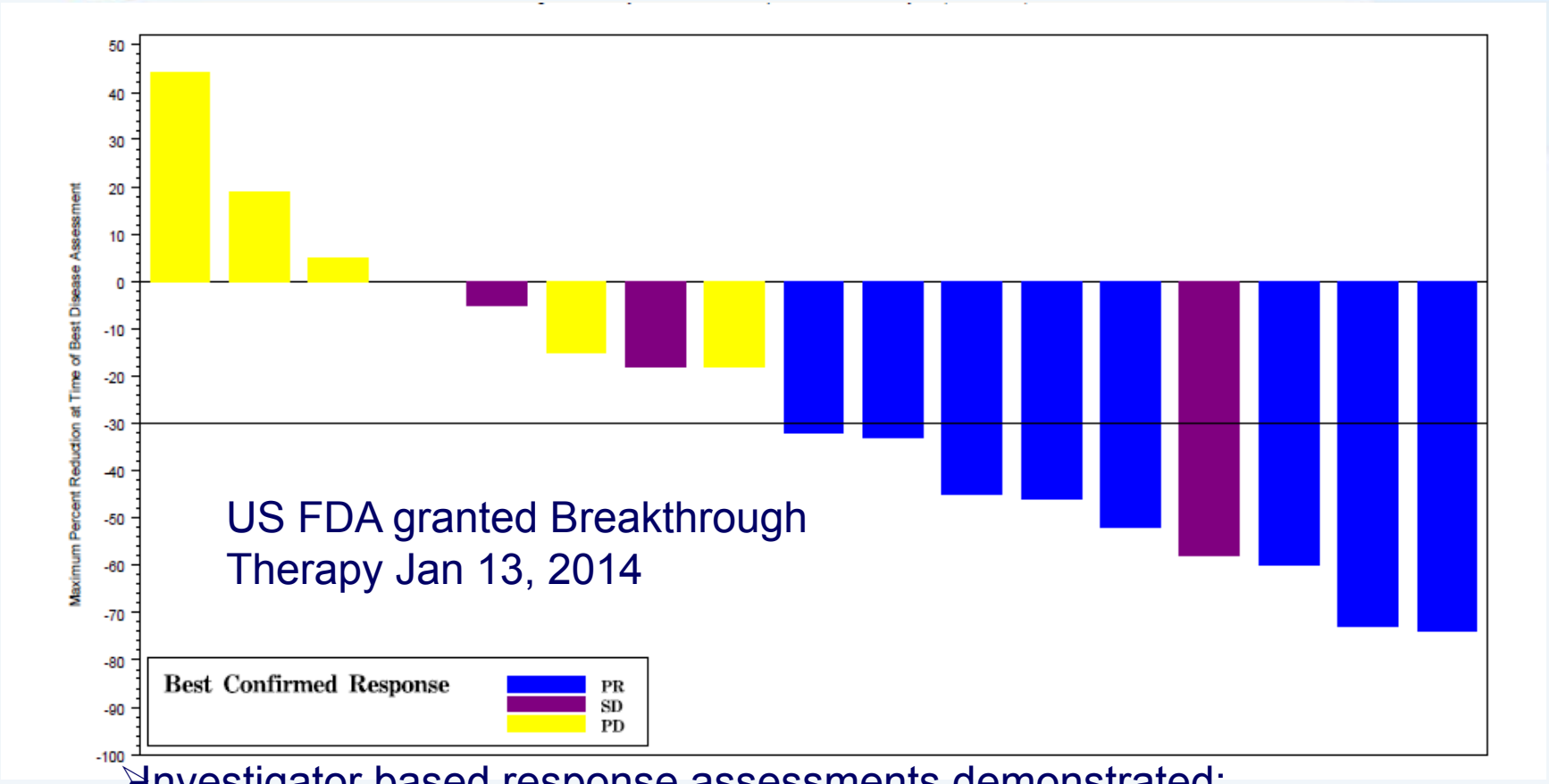
- Single arm, Phase II, open label
- Green-Dahlberg 2-stage: H(0): ORR ≤ 10% versus H(1): ORR ≥30%



Primary objective: Investigator-assessed ORR

Secondary objectives: PFS, duration of response, OS, safety and tolerability, population PK

Interim Analysis (ASCO 2013)



- Investigator based response assessments demonstrated:
  - 7PRs (5 confirmed—duration 29 and 49 weeks for 2 pts and remaining 3 patient 6+ to 24+ weeks)
  - 1 stable disease
  - 4 progressive disease

Planchard et. al. 2013 ASCO Annual Meeting Proceedings

Conclusion

- Molecular selection of patients improves therapy outcomes for patients with advanced adenocarcinoma of the lung

Future Directions

- Extent patient selection and targeted therapies to squamous cell and earlier stages of NSCLC (i.e. RADIANT)
- Next generation sequencing needed
- Molecular characterization of resistance
- Development of a structure to conduct studies in uncommon molecular selected populations (BRAF, HER2, RET, etc)
- Clinical integration of tumor genomic and proteomic testing to better direct therapy for NSCLC (Gerber)