Management of EGFR-mutant NSCLC

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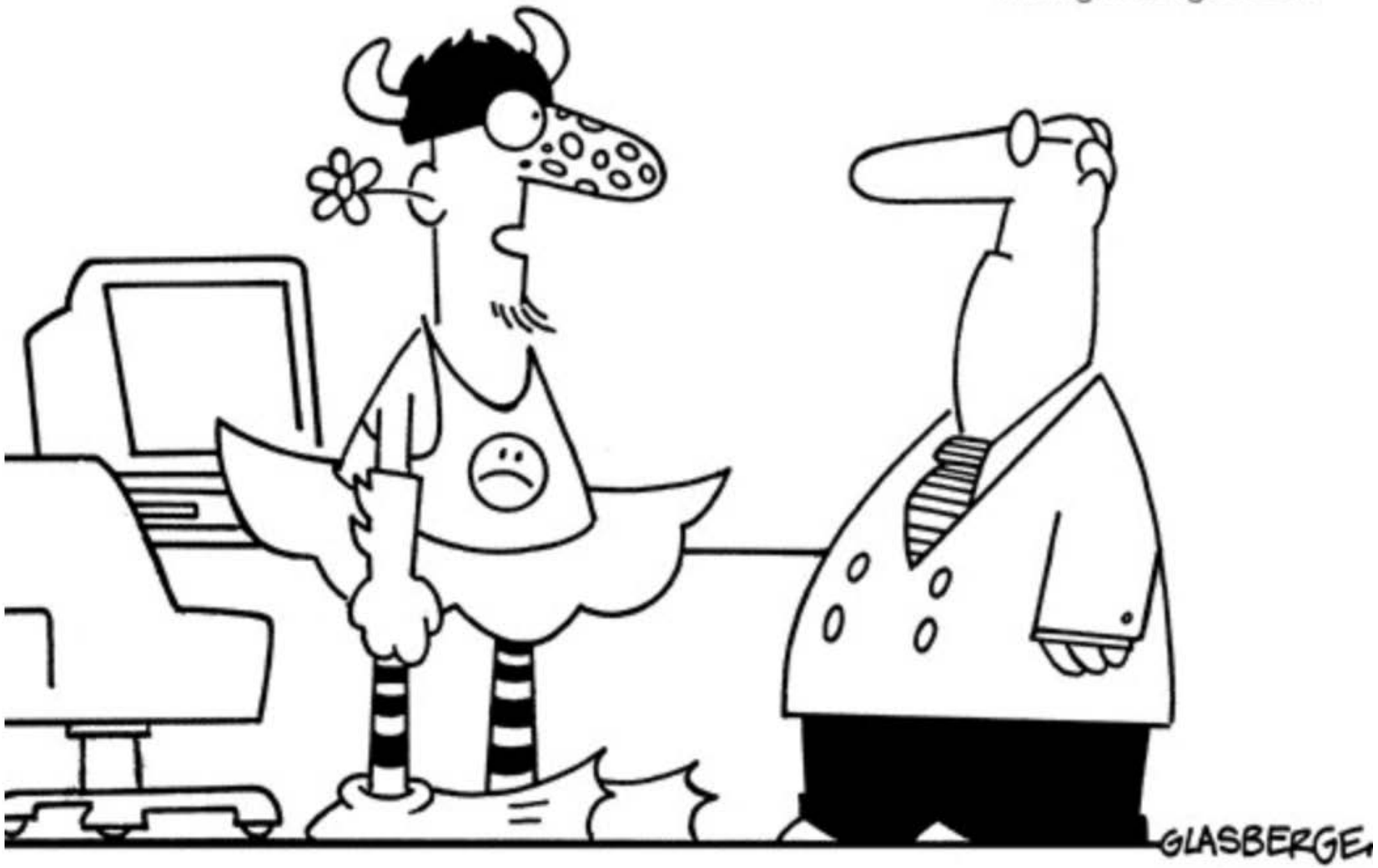
Disclosures

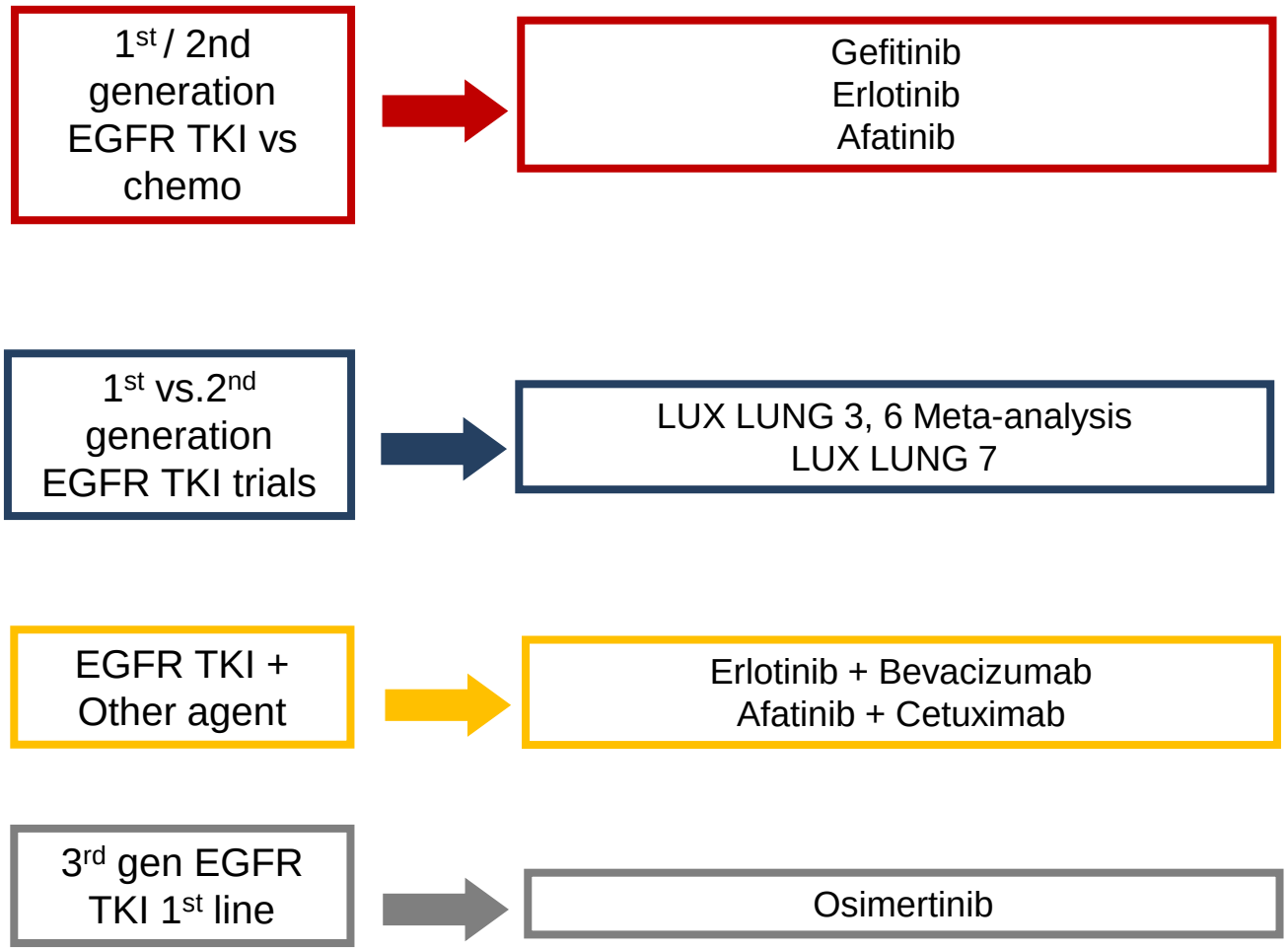
Research Funding: Merck, Novartis, AstraZeneca, Millenium

Consulting: AbbVie, MedTronic, Ariad, Celgene, Clovis

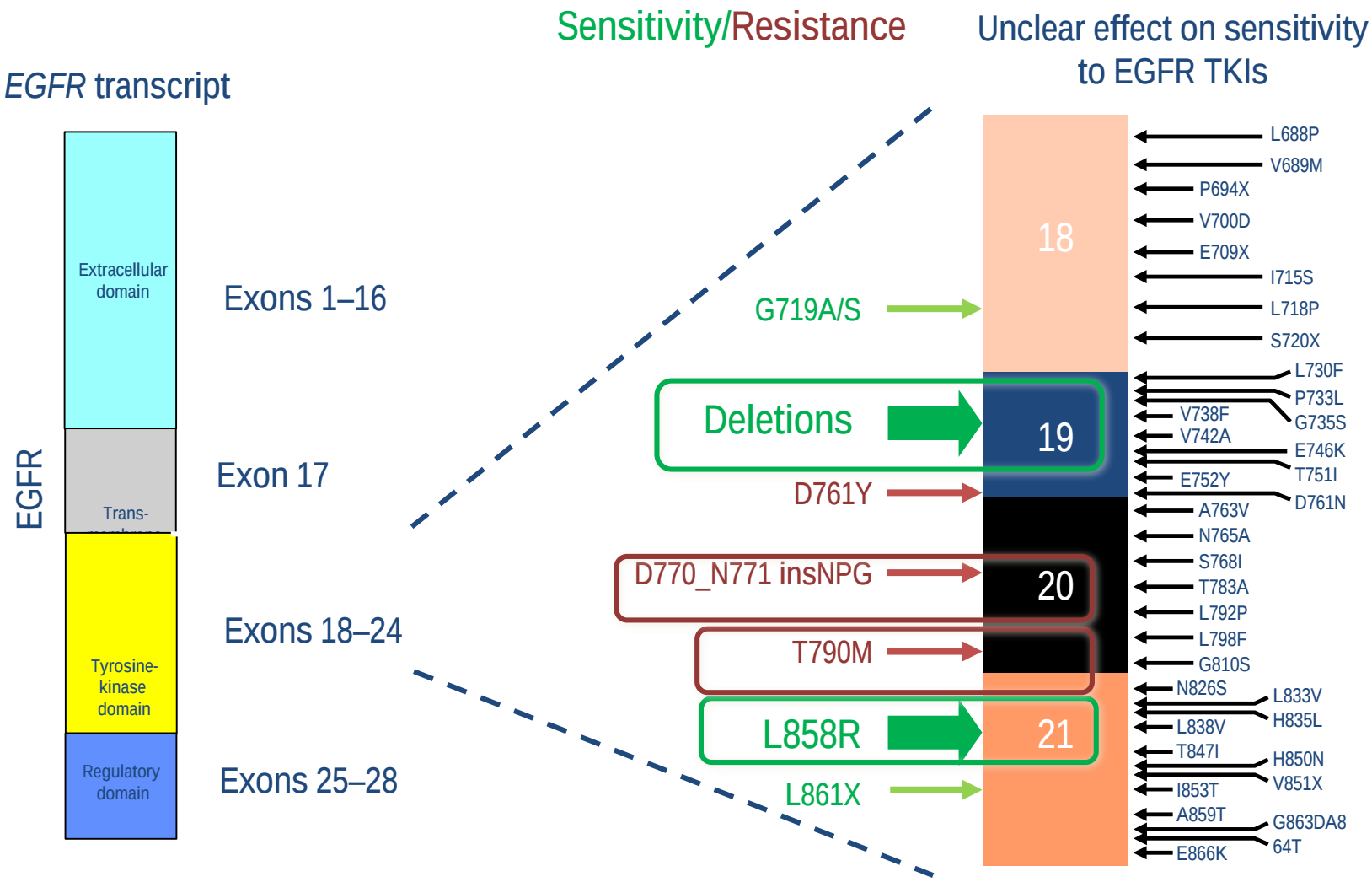


"I *am* dressed for success! Of course, my idea of success may not be exactly the same as yours."

Outline: *EGFR* Mutant NSCLC- 1st line



Varying Sensitivity of EGFR Mutation Subtypes to EGFR TKI Therapy



Adapted from Riely GJ, et al. Clin Cancer Res. 2006

IPASS: Gefitinib vs Chemotherapy in East Asian Patients with Advanced Lung Adenocarcinoma

Eligibility
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIB / IV disease

Gefitinib

Paclitaxel-Carboplatin

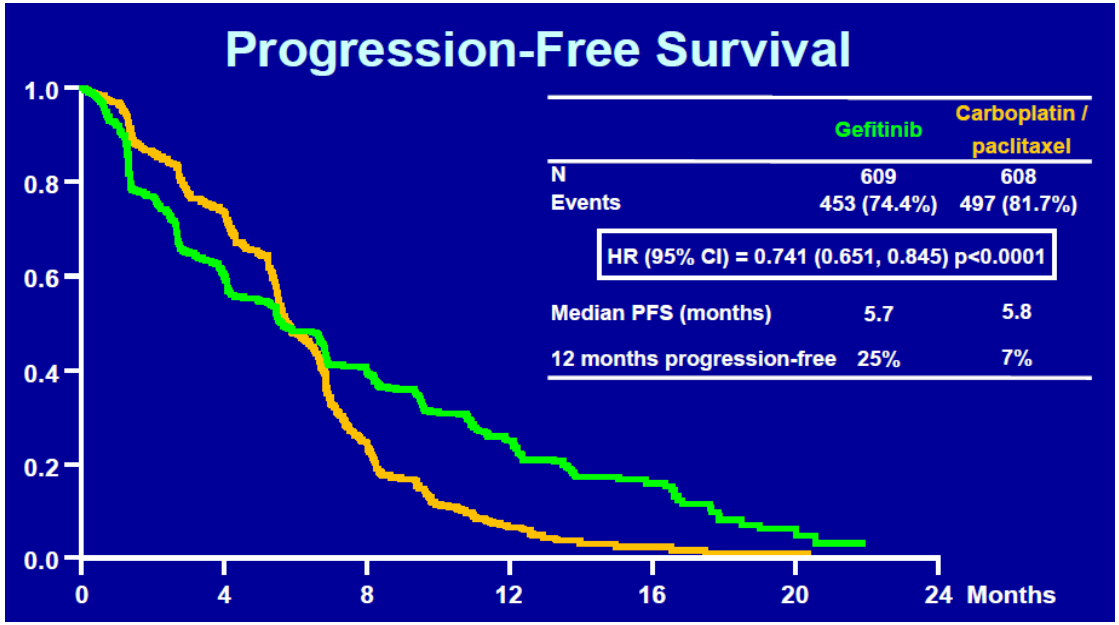
Endpoints

Primary
- Progression-free survival

Secondary
- Objective response rate
- Overall survival
- Quality of life/Toxicity

Exploratory
- EGFR mutation

*All East Asian
80% female
94% never-smokers



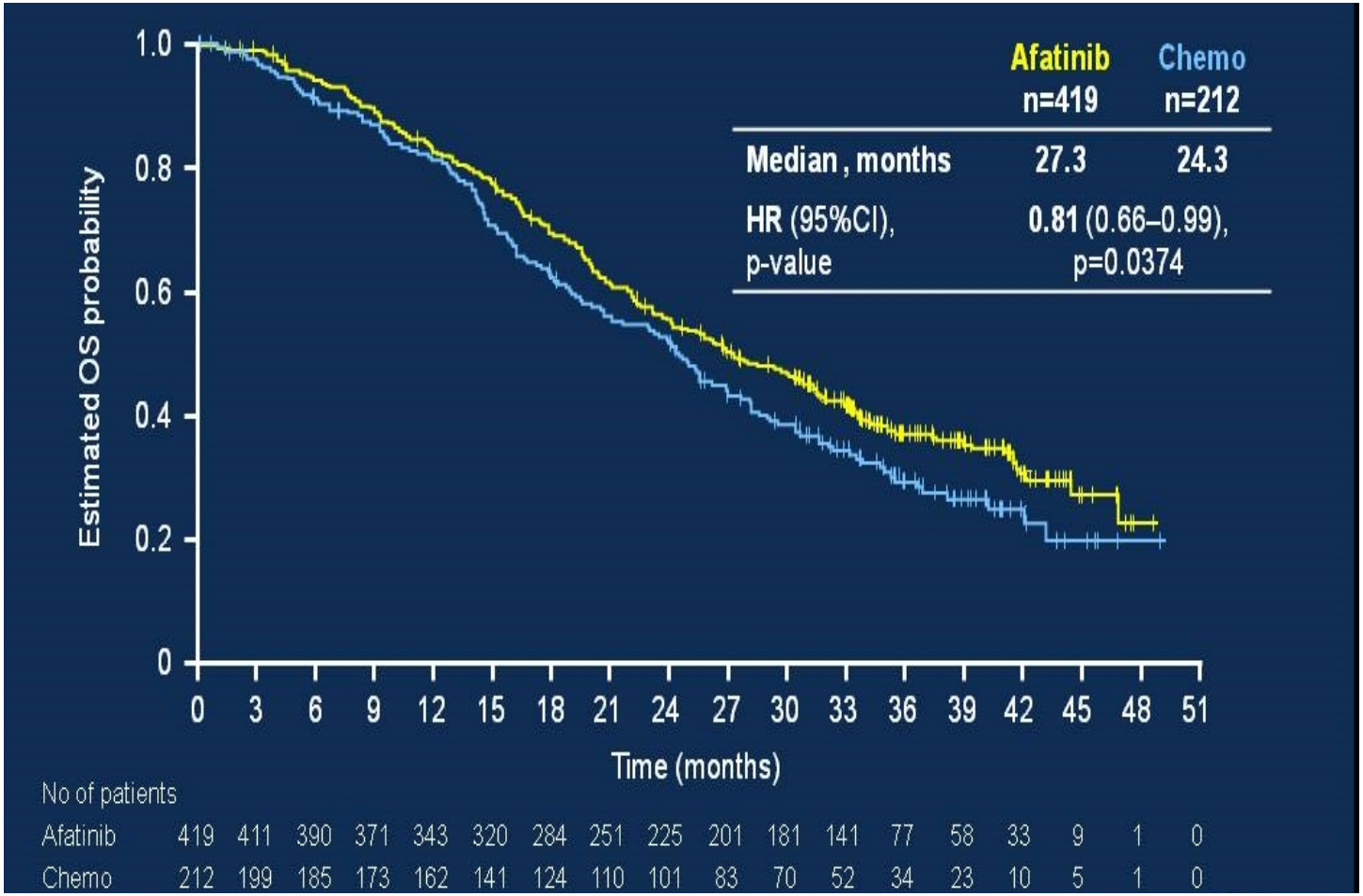
Mok et al: NEJM, 2009

EGFR TKIs vs Chemotherapy in *EGFR*-Mutated NSCLC

Study	Treatment	RR	Median PFS (mo)	Median OS
NEJ002[1] N=230	Gefitinib vs carboplatin/ paclitaxel	74 v 31%	10.8 vs 5.4 (*P* < .001)	30.5 vs 23.6 HR = 0.89
WJOTG[2,3] N=177	Gefitinib vs CDDP/ docetaxel	62 v 32%	9.2 vs 6.3 (*P* < .0001)	36 vs 39 HR = 1.25
OPTIMAL[4,5] N=165	Erlotinib vs carboplatin/ gemcitabine	83 v 36%	13.1 vs 4.6 (*P* < .0001)	30.4 vs 31.5 HR = 1.065
EURTAC[6] N=174	Erlotinib vs platinum-based chemotherapy	58 v 15%	9.7 vs 5.2 (*P* < .0001)	19.3 vs 19.5 HR = 0.93
LUX-Lung 3[7] N=345	Afatinib vs CDDP/Pem	61 v 22%	11.1 vs 6.9 (*P* < .0004)	28.2 vs 28.2 HR = 0.88
LUX-Lung-6 N=364	Afatinib vs CDDP/Gem	67 v 23%	11.0 v. 5.6 HR = 0.28	23.1 vs 23.5 HR = 0.93

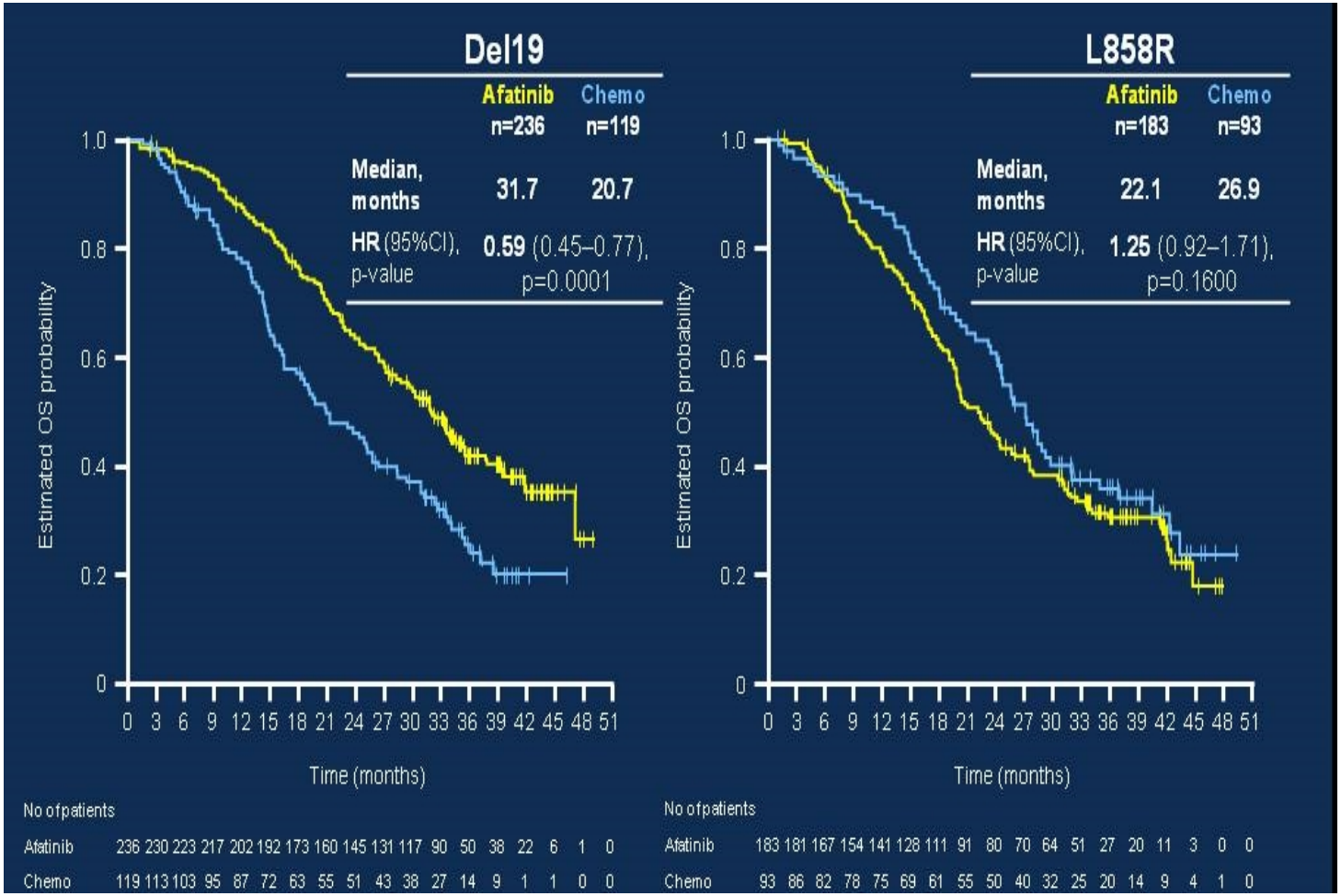
- Gefitinib, Erlotinib & Afatinib all superior to Platinum chemotherapy for RR & PFS
- No improvement in OS in these randomized trials

Combined OS with Afatinib: Common Mutations



Yang et al., ASCO 2014; Abstract 8004; Yang JC, et al. *Lancet Oncol.* 2015;16(2):141-151.

Combined OS with Afatinib by Mutation Categories



Yang et al., ASCO 2014; Abstract 8004; Yang JC, et al. *Lancet Oncol.* 2015;16(2):141-151.

LUX-Lung 7: Phase 2b trial

- Stage IIIB/IV adenocarcinoma of the lung
- *EGFR* mutation (Del19 and/or L858R) in the tumor tissue*
- No prior treatment for advanced/ metastatic disease
- ECOG PS 0/1

1:1

Afatinib 40 mg once daily†

Gefitinib 250 mg once daily

Stratified by
- Mutation type (Del19/L858R)
- Brain metastases (present/absent)

Primary endpoints:
- PFS (independent)
- TTF
- OS

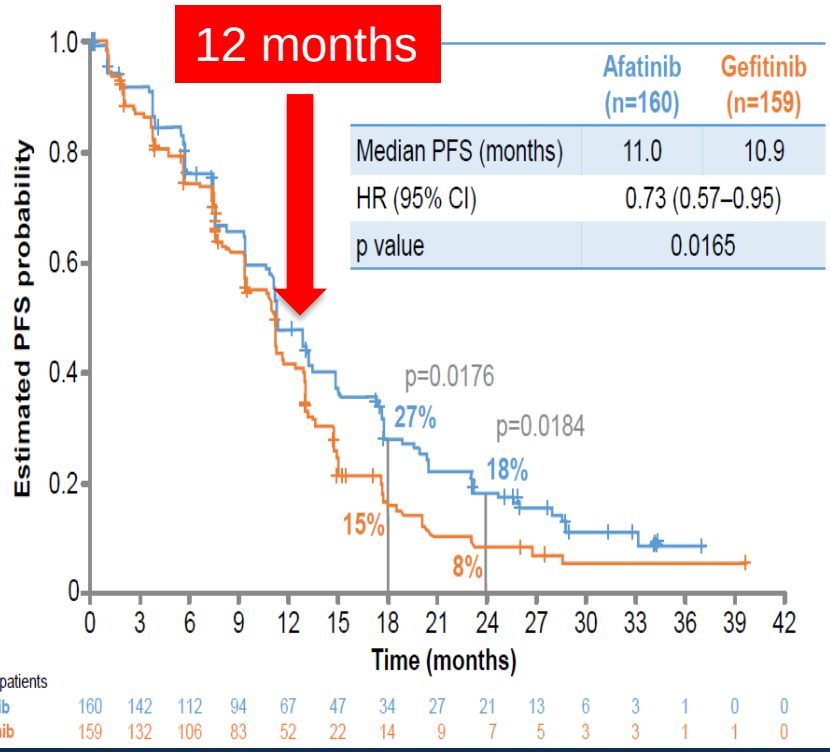
Secondary endpoints:
- ORR
- Time to response
- Duration of response
- Duration of disease control
- Tumor shrinkage
- HRQoL
- Safety

		Afatinib (n=160)	Gefitinib (n=159)
EGFR mutation, %	Del19	58	58
	L858R	42	42

open label ✓

controlled brain mets ✓

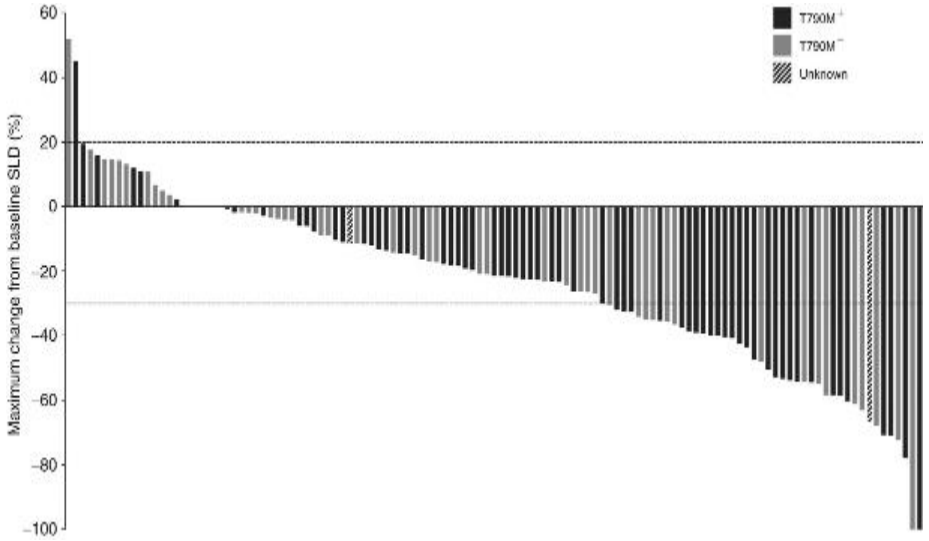
PFS by independent review



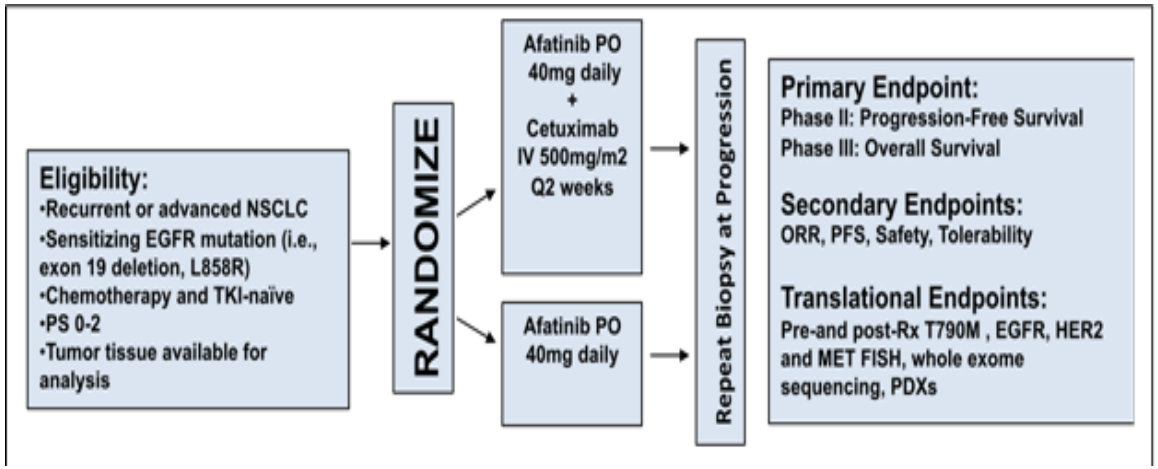
	Afatinib (n=160)	Gefitinib (n=159)
Median PFS (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	

Park Lancet Oncol (2016)

S1403: A Randomized Phase 2/3 Trial of Afatinib + Cetuximab Versus Afatinib Alone in Treatment-Naïve Pts With Advanced, EGFR Mutation + NSCLC

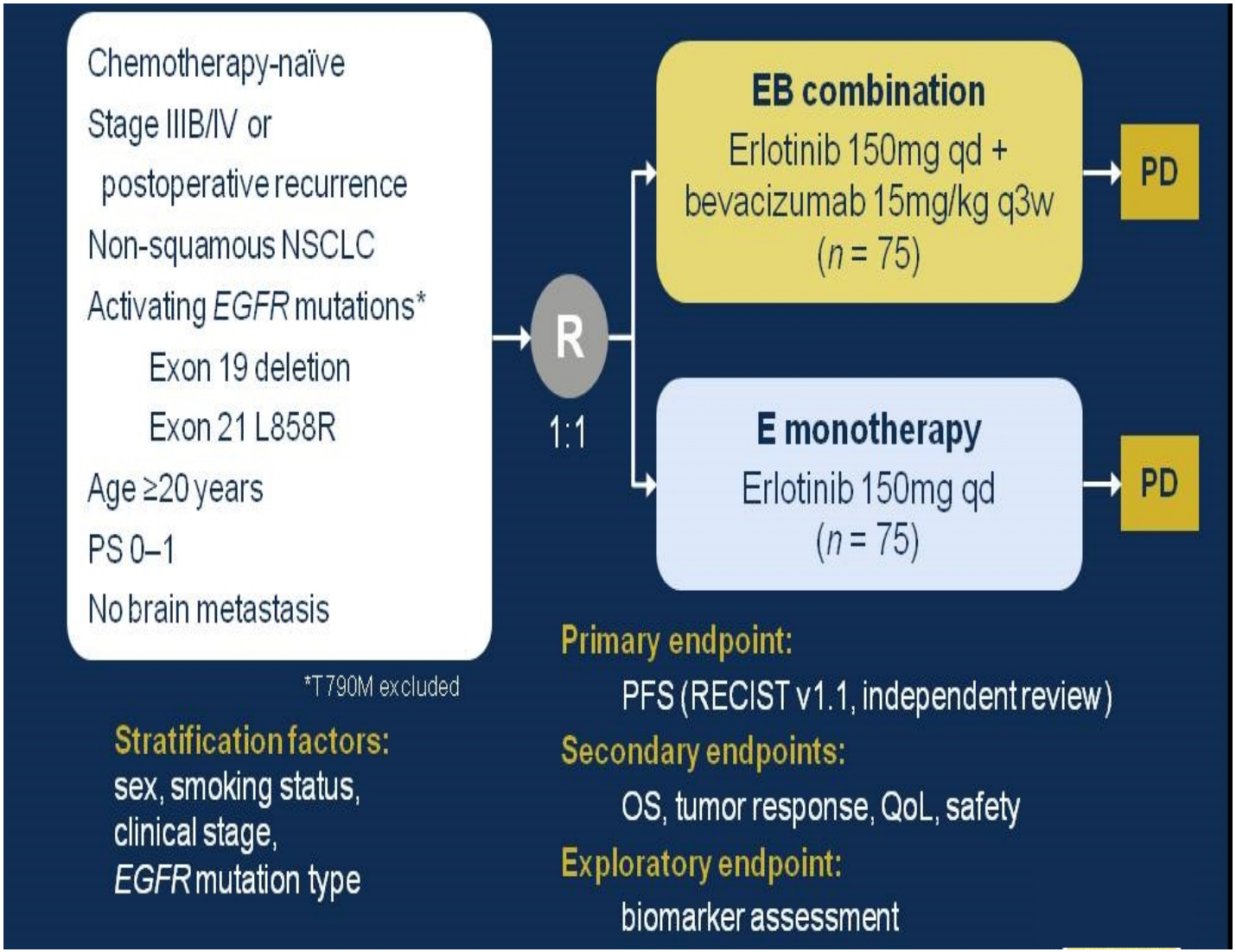


Dual Inhibition:
Afatinib + Cetuximab



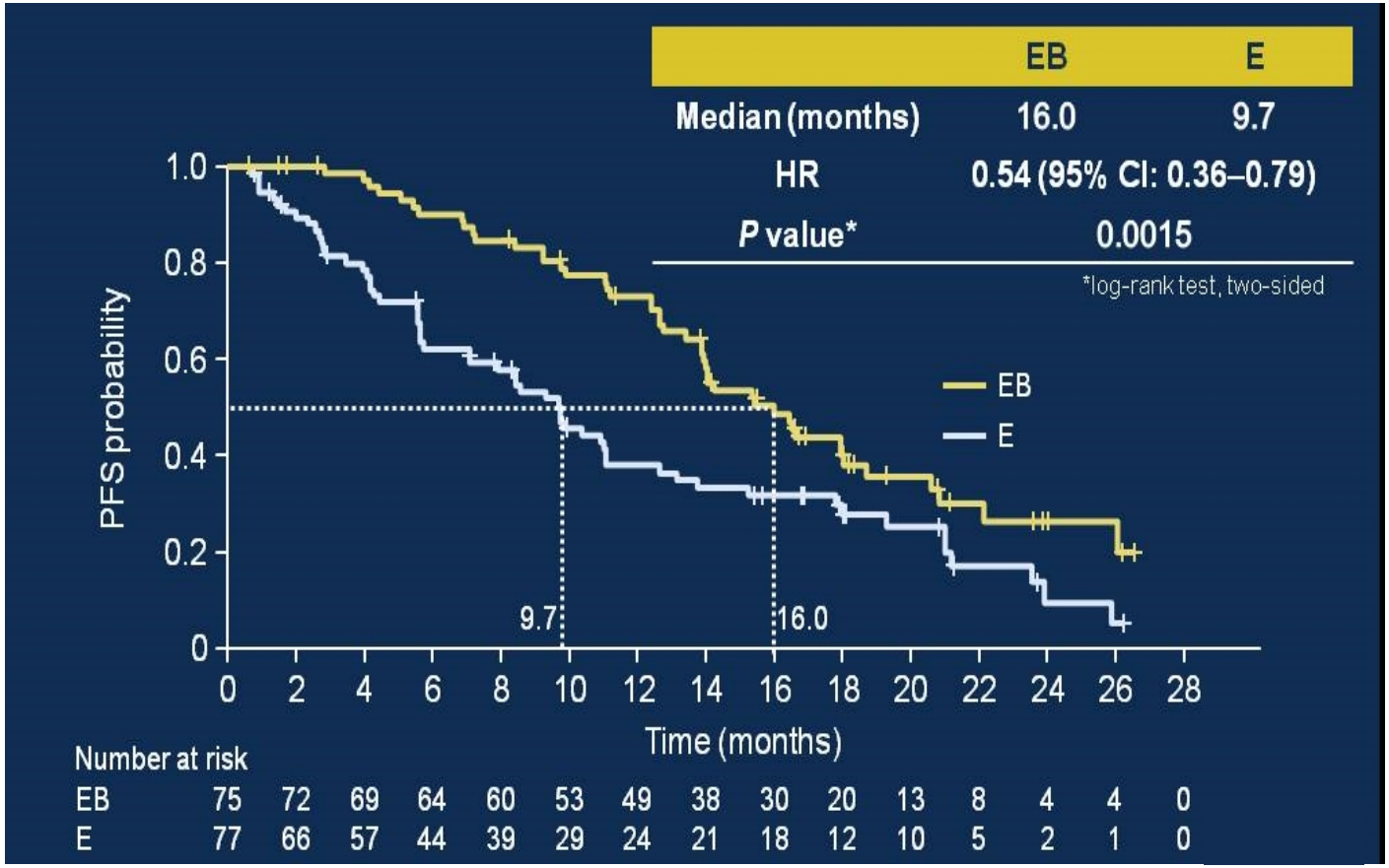
Janjigian et al., *Cancer Discov*. 2014;4:1036

Erlotinib + Bevacizumab vs Erlotinib in *EGFR* Mutated NSCLC



Kato et al., ASCO 2014; Abstract 8005; Seto T, et al. *Lancet Oncol.* 2014;15(11):1236-1244.

Erlotinib + Bevacizumab vs Erlotinib in *EGFR* Mutated NSCLC



Kato et al., ASCO 2014; Abstract 8005; Seto T, et al. *Lancet Oncol.* 2014;15(11):1236-1244.

PFS by independent review

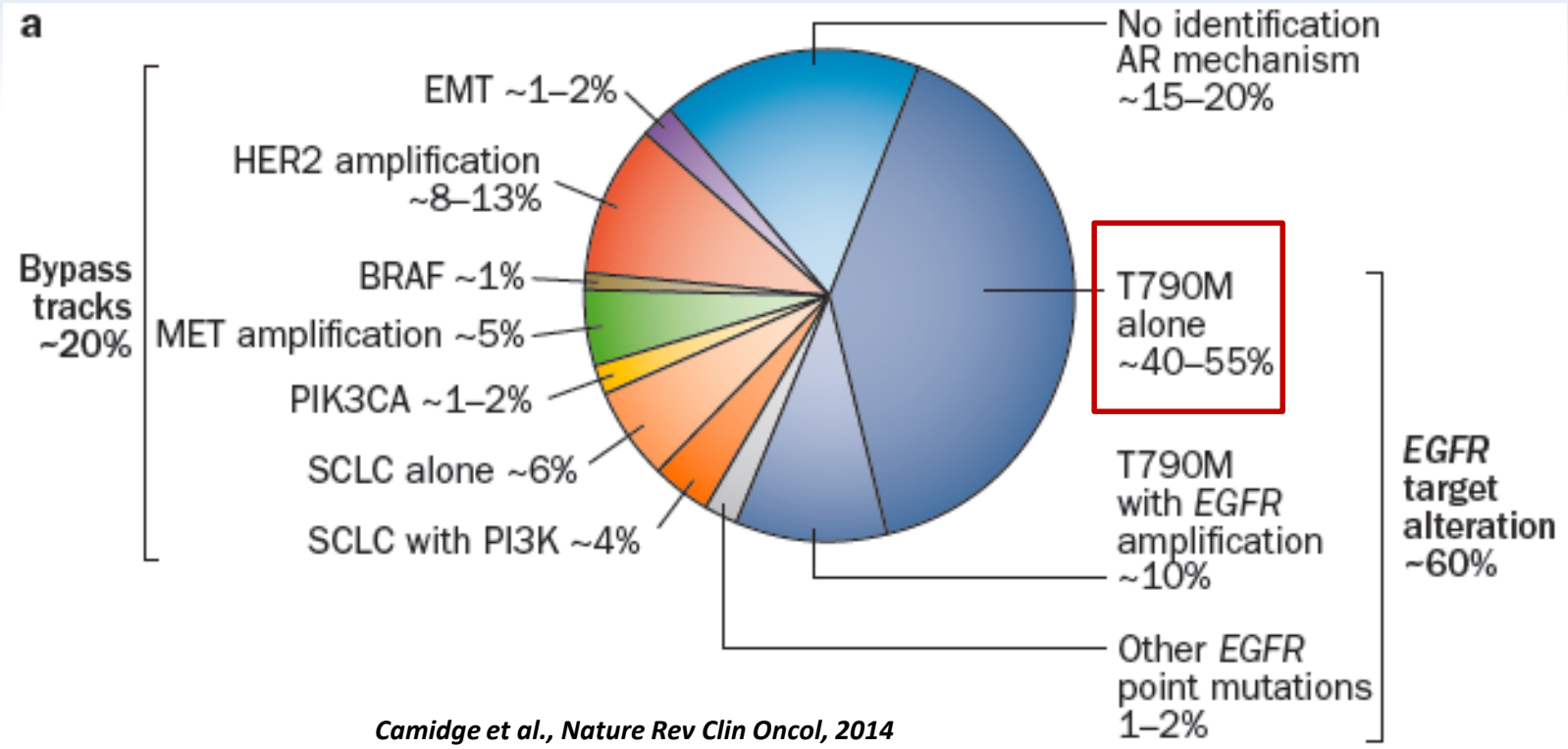
Safety Overview

	EB (n=75)	E (n=77)
Grade ≥3 AEs	68 (91%)*	41 (53%)
Serious AEs	18 (24%)	19 (25%)
Death due to AE	0 (0%)	1 (1%)**

*Higher incidence of grade ≥3 AEs in EB arm was driven by HTN events
**Drowning

Kato et al., ASCO 2014; Abstract 8005; Seto T, et al. *Lancet Oncol.* 2014;15(11):1236-1244.

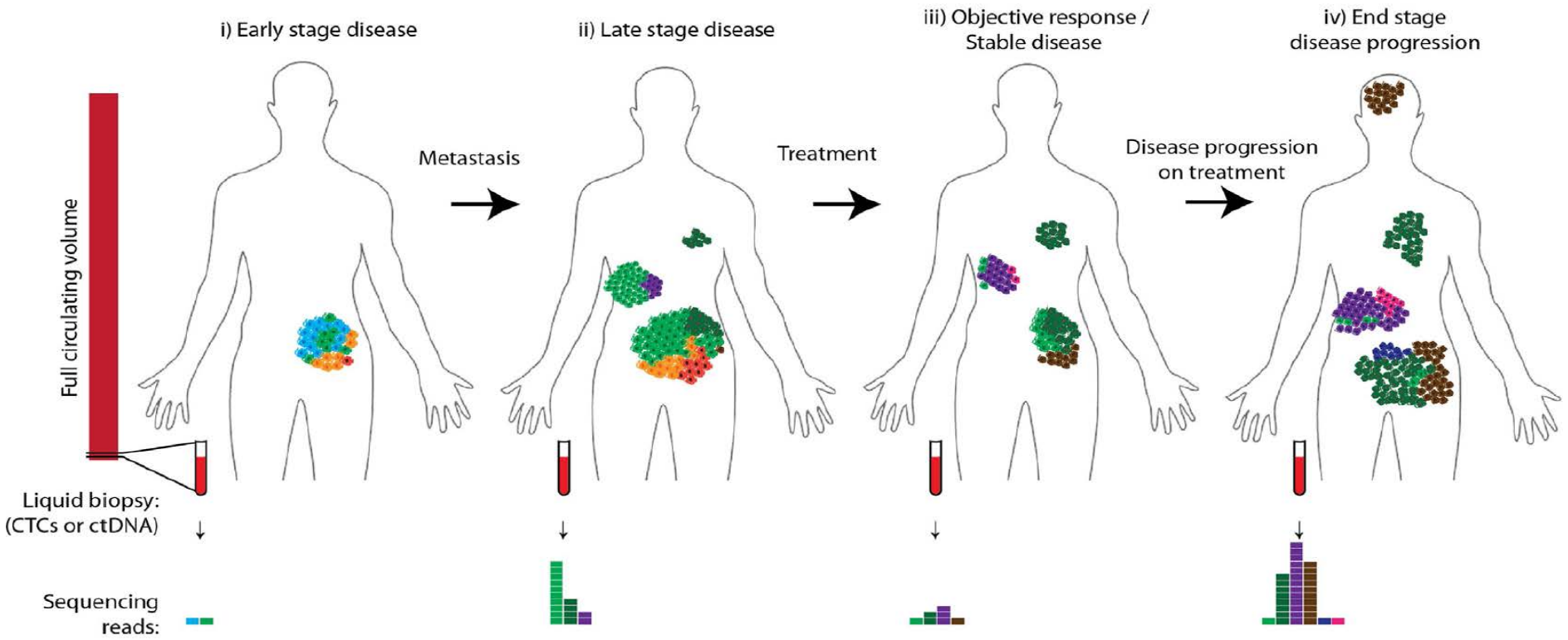
Mechanisms of Acquired Resistance to EGFR TKIs in EGFR-mutated Lung Cancers



Camidge et al., Nature Rev Clin Oncol, 2014

- **At the time of acquired resistance, T790M is found in over 50% of repeat biopsies[1]**
- **T790M may not always be the cause of clinical resistance, even when present**
- **Several bypass mechanisms of resistance, including MET or HER2 amplification, or PIK3CA or BRAF mutation, have now been identified**
- **SCLC transformation can also occur, but is uncommon-rare**

Role of "Liquid Biopsy" (Plasma cf DNA) in determining mechanisms of Acquired Resistance

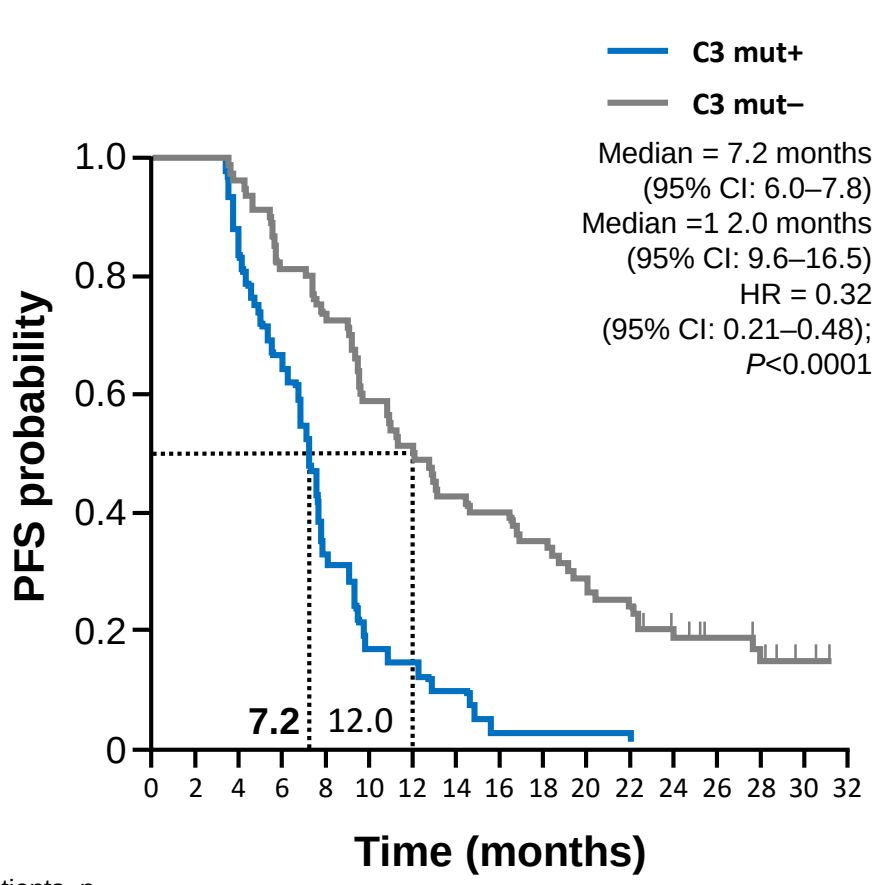


Advantages of plasma cf DNA over Tumor re-biopsy

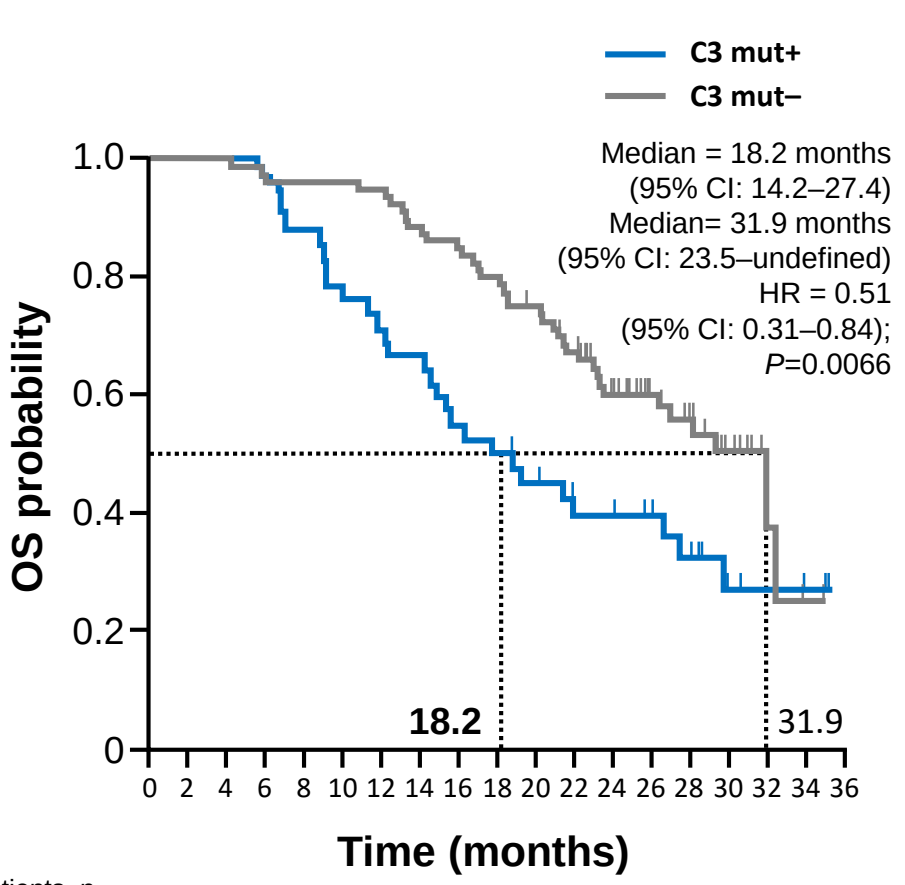
- Reflects shed tumor DNA into plasma, providing a "global perspective"
- Abrogates the issue of tumor heterogeneity
- Relatively non-invasive & can be repeated serially to monitor tumor response
- Can detect resistance mutations in plasma prior to radiographic detection

from Burrell and Swanton, Mol Oncol 2014

Association Between p*EGFR* mut+ at C3 and PFS/OS (Both Treatment Arms Combined)



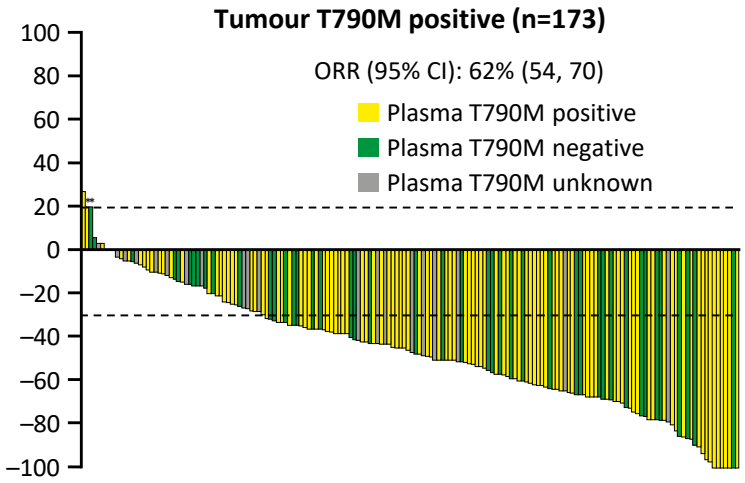
Patients, n																	
C3 mut+	42	42	35	28	14	7	6	4	1	1	1	1	0	0	0	0	0
C3 mut–	80	80	77	65	59	47	40	34	32	28	23	19	13	10	7	3	0

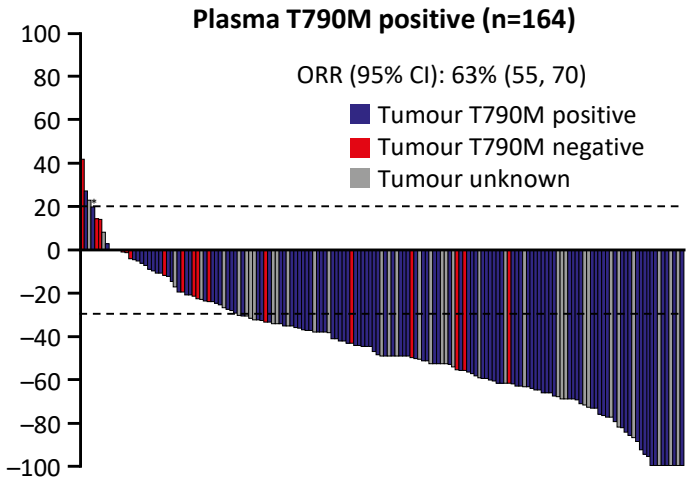


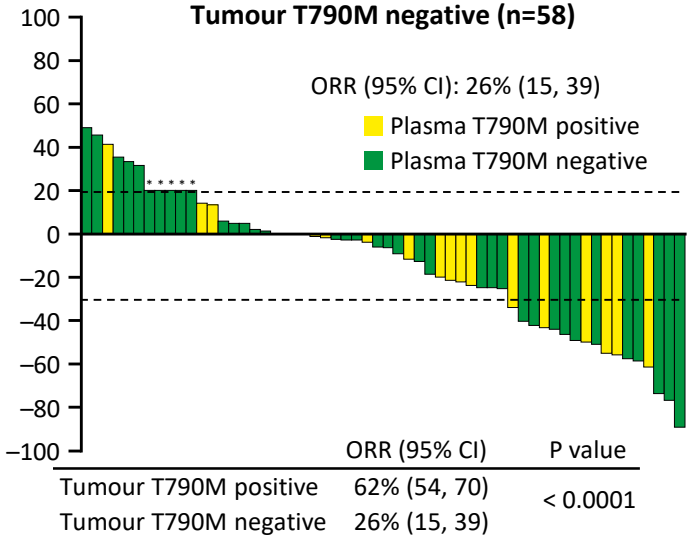
Patients, n																		
C3 mut+	42	42	42	41	37	32	30	28	23	21	18	14	14	12	9	4	3	2	0
C3 mut–	80	80	80	77	77	77	76	71	68	64	59	52	38	29	22	12	3	1	0

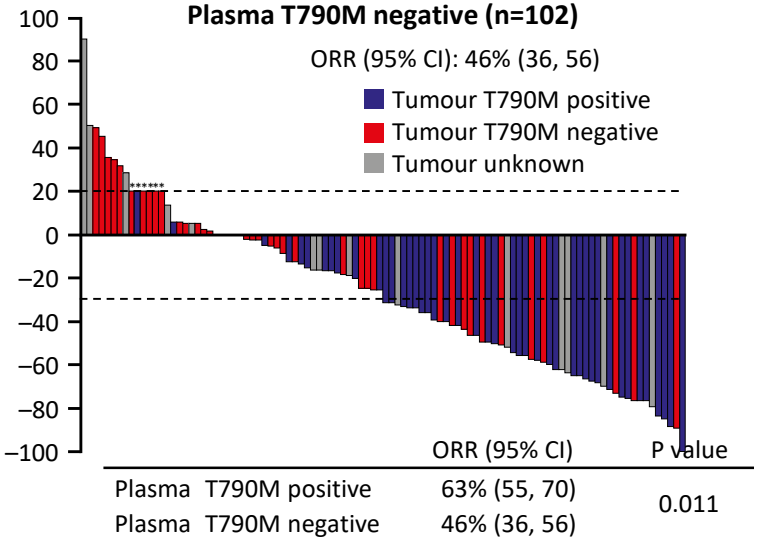
Mok et al. *Lancet Onc 2015*.

High ORR in patients with tumour or plasma positive T790M cancers treated with Osimertinib



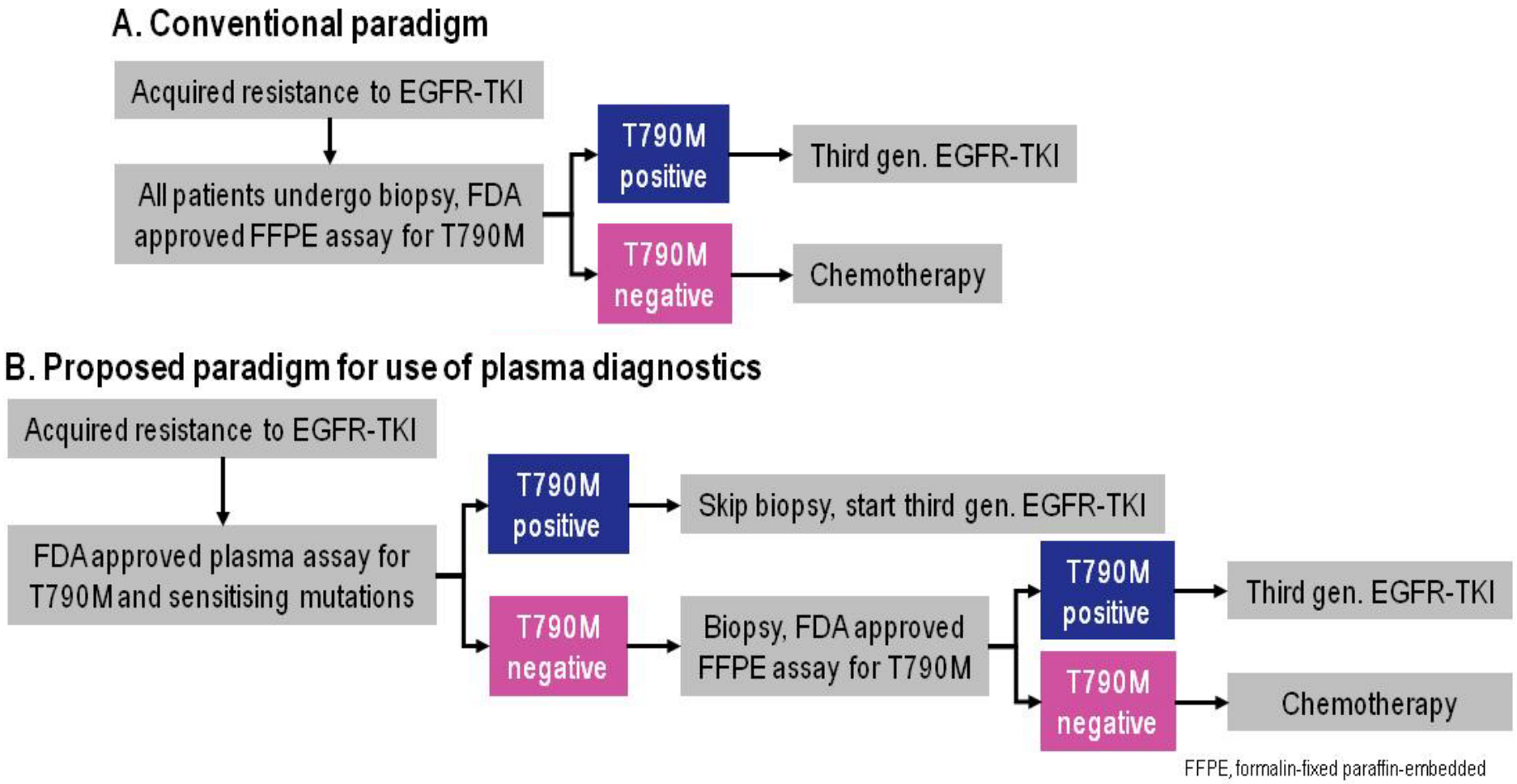






Oxnard et al. ELCC 2016

Proposed change in paradigm to integrate plasma genotyping for T790M testing



Oxnard et al. ELCC 2016

Third Generation EGFR TKIs overcome Acquired Resistance to EGFR T790M

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 30, 2015 VOL. 372 NO. 18

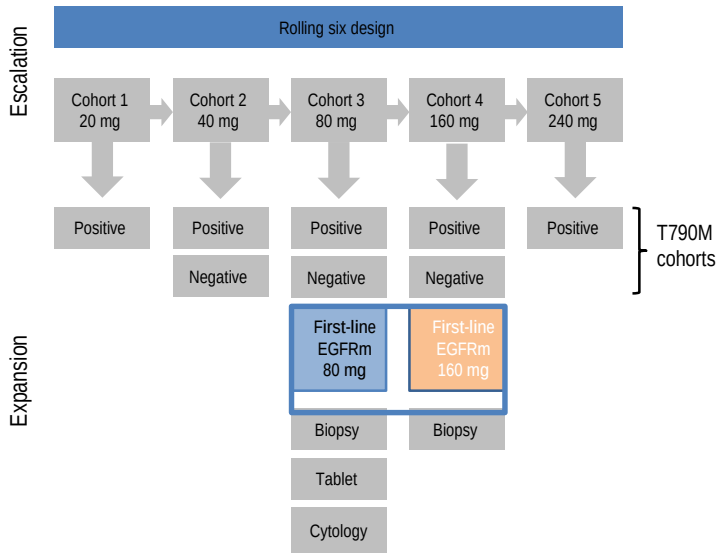
AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

Pasi A. Jänne, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., David Planchard, M.D., Ph.D., Yuichiro Ohe, M.D., Suresh S. Ramalingam, M.D., Myung-Ju Ahn, M.D., Ph.D., Sang-We Kim, M.D., Ph.D., Wu-Chou Su, M.D., Leora Horn, M.D., Daniel Haggstrom, M.D., Enriqueta Felip, M.D., Ph.D., Joo-Hang Kim, M.D., Ph.D., Paul Frewer, M.Sc., Mireille Cantarini, M.D., Kathryn H. Brown, Ph.D., Paul A. Dickinson, Ph.D., Serban Ghiorghiu, M.D., and Malcolm Ranson, M.B., Ch.B., Ph.D.

AURA Phase I dose escalation/expansion: study design

First-line cohort objective

- Safety and tolerability of osimertinib (80 mg or 160 mg qd orally) as first-line therapy
  for patients with EGFRm advanced NSCLC



Key inclusion criteria:

- Aged ≥18 (≥20 in Japan)
- Locally advanced or metastatic NSCLC
- No prior therapy for advanced disease
- Measurable disease at baseline
- Patients must have EGFR mutation positive NSCLC (local test)

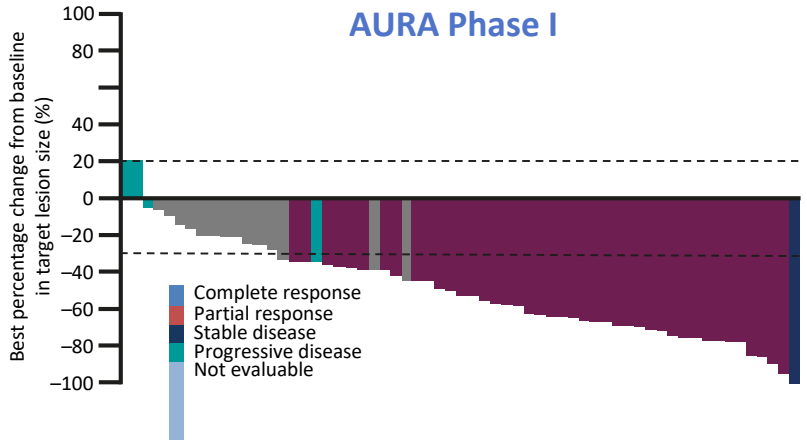
Key exclusion criteria:

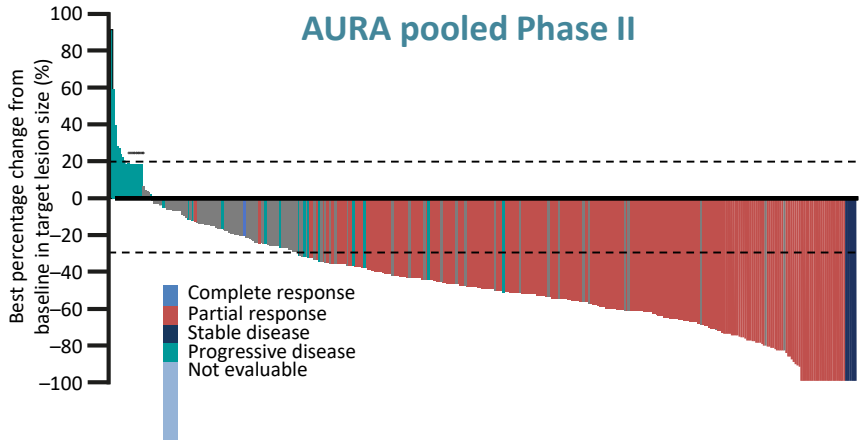
- Prior history of ILD
- Symptomatic brain metastases

- Data cut-off: 4 January 2016
- Data from cohorts in grayed out boxes are not included in the analyses reported here
- ILD, interstitial lung disease; qd, once-daily dosing

Ramalingam et al., ELCC 2016; Abstract LBA1_PR

Tumour response to Osimertinib treatment

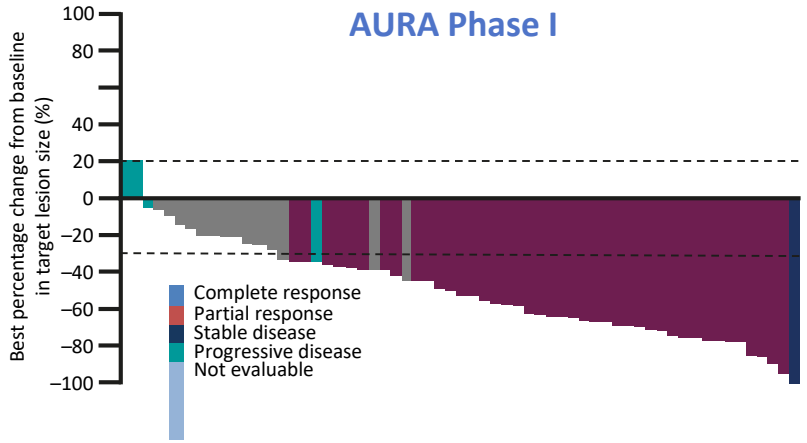


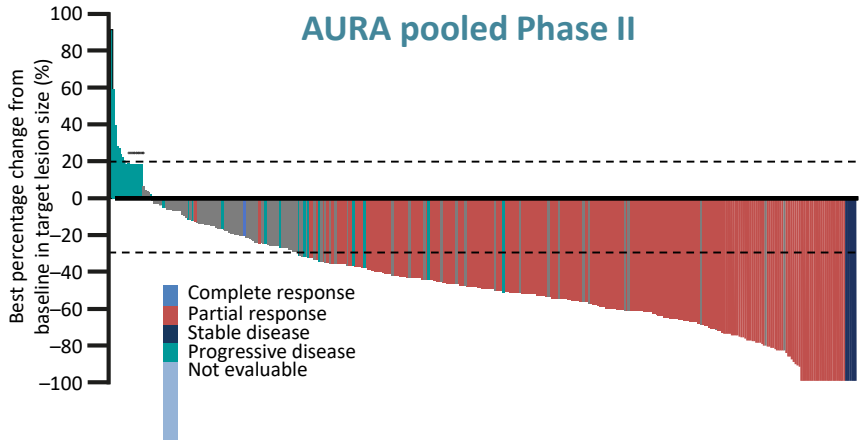


	AURA Ph I (80 mg) N=61	AURA pooled Ph II (80 mg) N=397
Confirmed ORR	71% (95% CI 57, 82)	66% (95% CI 61, 71)
Disease control rate†	93% (95% CI 84, 98)	91% (95% CI 88, 94)
Best objective response		
Complete response	1	6
Partial response	42	256
Stable disease ≥6 weeks	14	99
Progressive disease	2	25

Yang et al: ELCC 2016

Tumour response to Osimertinib treatment





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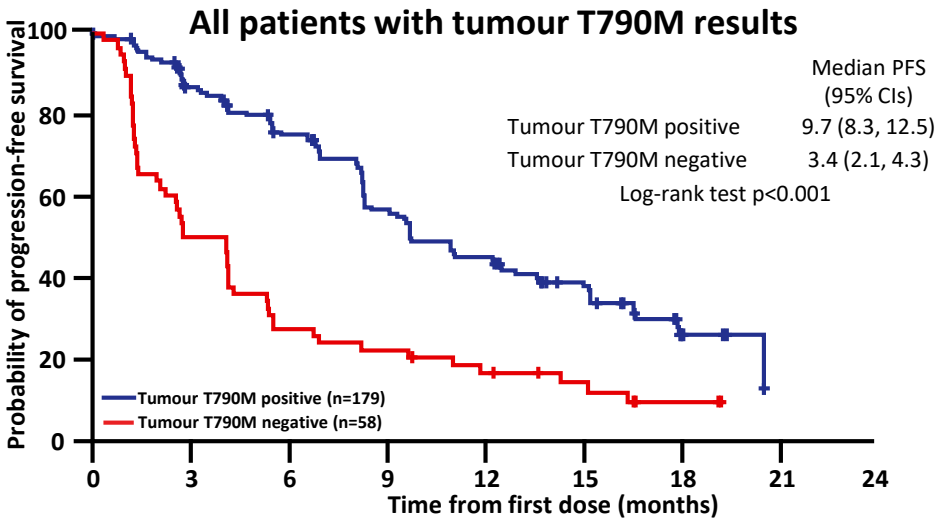
Yang et al: ELCC 2016

Osimertinib PFS is longest in those patients with T790M positive cancers

Tumour T790M positive predicts for a prolonged median PFS of 9.7 months, longer than seen in tumour T790M negative cases ($p<0.001$)

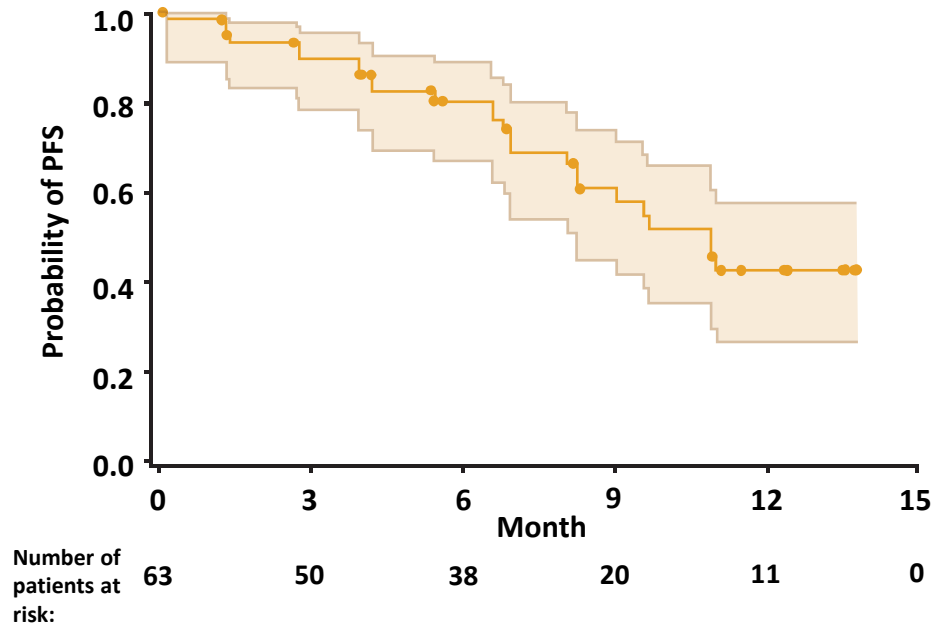


Oxnard et al. ELCC 2016

Acquired Resistance to Osimertinib emerges at about 1 year (median)

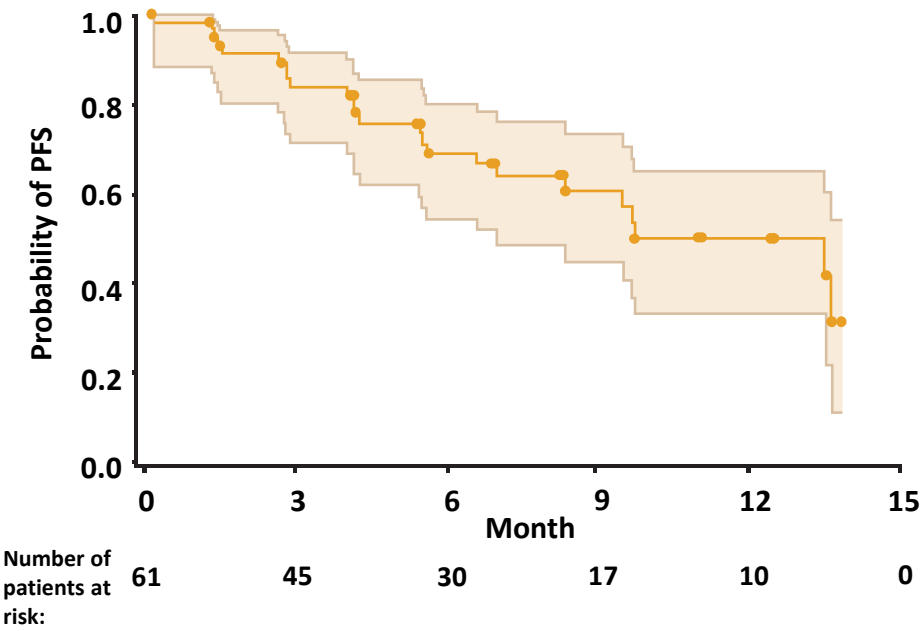
T790M Positive (Central Test) 80 mg Cohort – PFS

Investigator assessed



Median PFS, 10.9 months (95% CI: 8.3, not calculable; 40% maturity, 25/63 events)

Independent review



Median PFS, 13.5 months (95% CI: 8.3, not calculable; 38% maturity, 24/63 events)

- Despite the effectiveness of Osimertinib acquired resistance is almost universal
- However, the mechanisms of resistance are heterogeneous

AURA3 study design

Key eligibility criteria

- ≥18 years (≥20 years in Japan)
- Locally advanced or metastatic NSCLC
- Evidence of disease progression following first-line EGFR-TKI therapy
- Documented EGFRm and central confirmation of tumour *EGFR* T790M mutation from a tissue biopsy taken after disease progression on first-line EGFR-TKI treatment
- WHO performance status of 0 or 1
- No more than one prior line of treatment for advanced NSCLC
- No prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months prior to starting first EGFR-TKI treatment
- Stable* asymptomatic CNS metastases allowed

R
2:1

Osimertinib (n=279)
80 mg orally
QD

Platinum-pemetrexed (n=140)
Q3W for up to 6 cycles+ optional maintenance pemetrexed#

Endpoints

Primary:

- PFS by investigator assessment (RECISTv1.1)

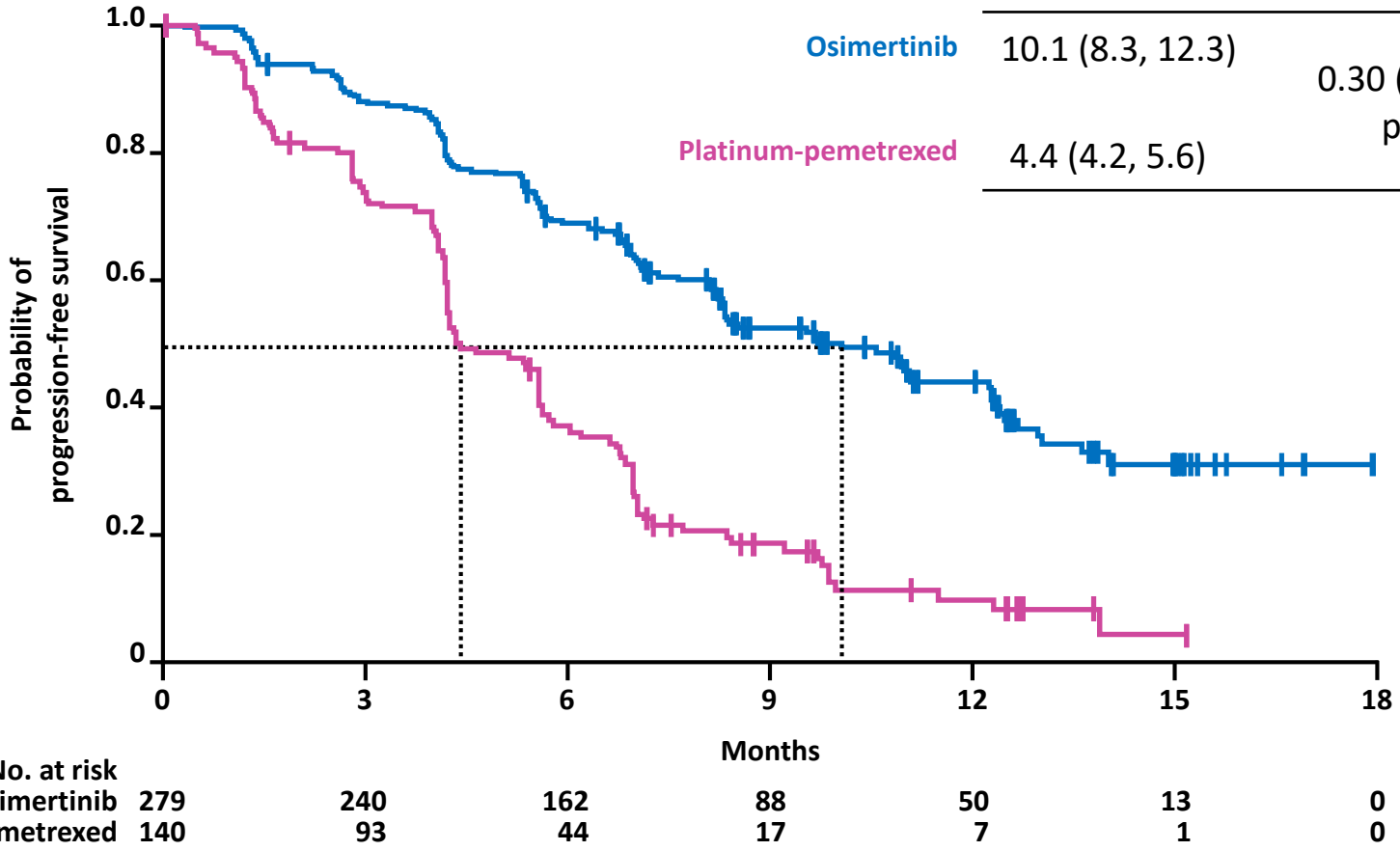
Secondary and exploratory:

- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- Tumour shrinkage
- BICR-assessed PFS
- Patient reported outcomes
- Safety and tolerability

Papadimitrakopoulou et al: ESMO 2016

AURA3 primary endpoint: PFS by investigator assessment

	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	10.1 (8.3, 12.3)	0.30 (0.23, 0.41) p<0.001
Platinum-pemetrexed	4.4 (4.2, 5.6)	



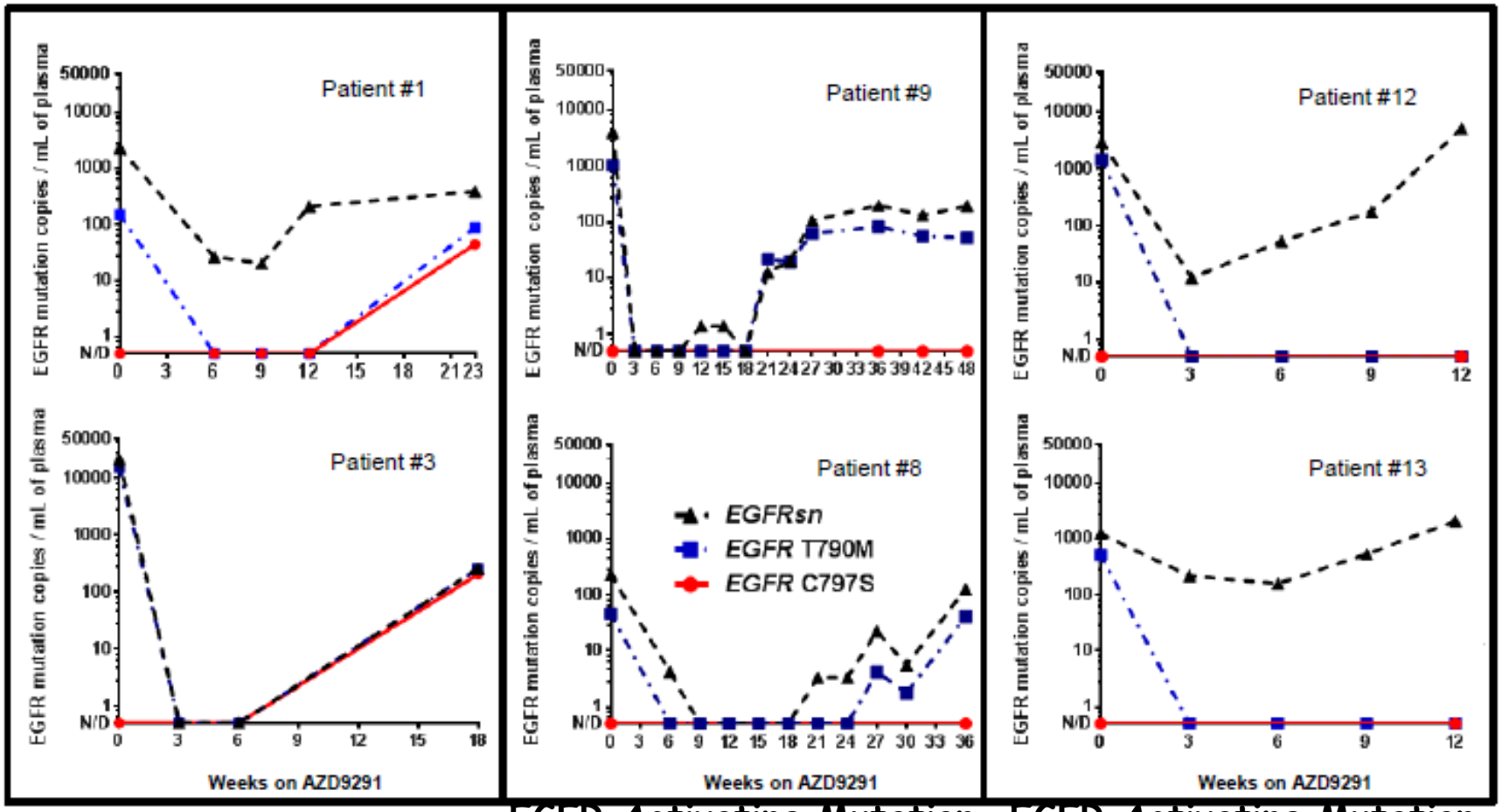
No. at risk							
Osimertinib	279	240	162	88	50	13	0
Platinum-pemetrexed	140	93	44	17	7	1	0

- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death.
Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data; CI, confidence interval

Papadimitrakopoulou et al: ESMO 2016

Mechanisms of Acquired Resistance to Osimertinib
Serial profiling of cfDNA reveals 3 molecular subtypes



EGFR Activating Mutation
+/- EGFR T790M
EGFR C797S (22% to date)

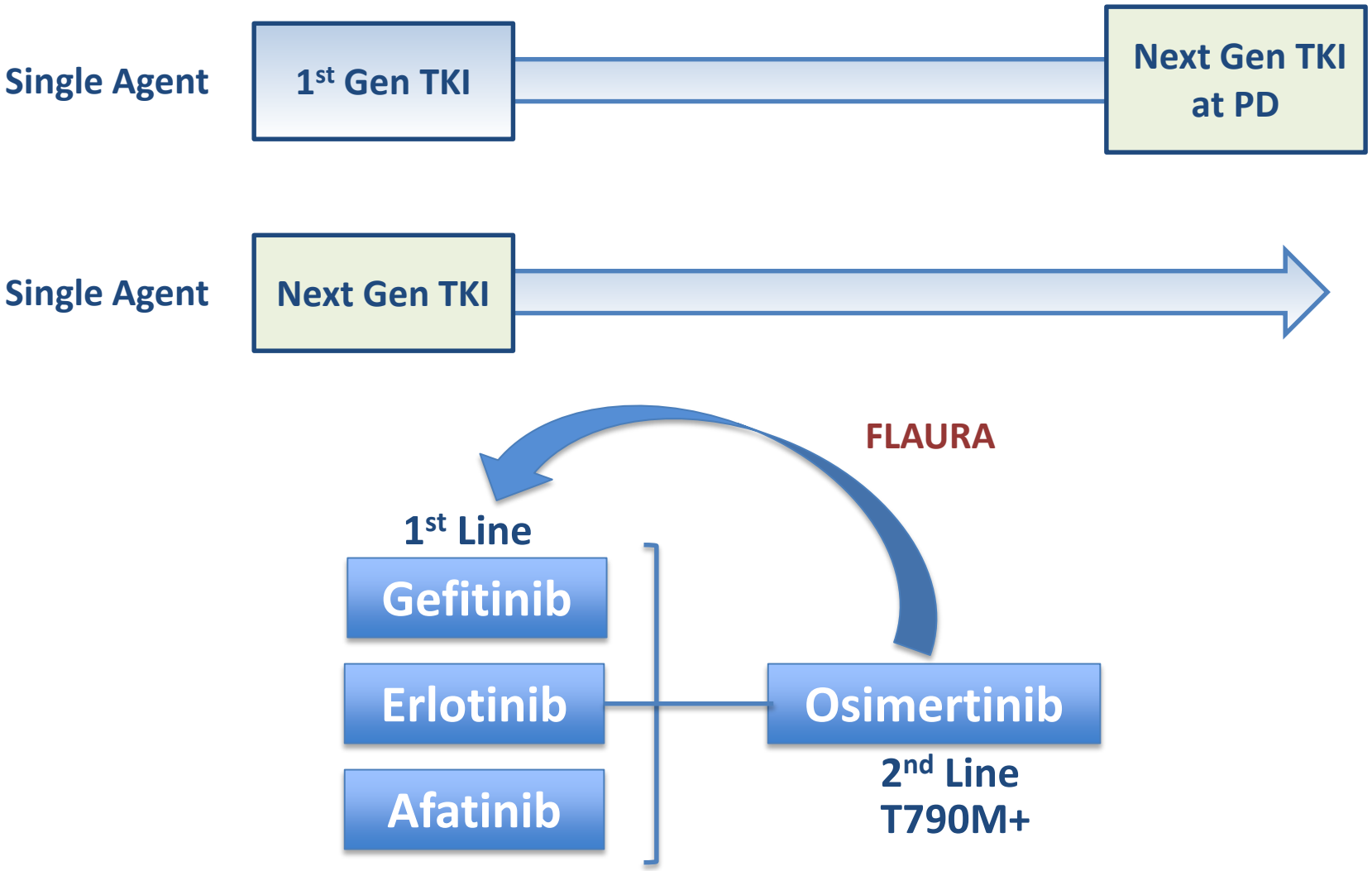
EGFR Activating Mutation
EGFR T790M still present

EGFR Activating Mutation
Loss of T790M

Other Resistance Mechanisms reported:
HER2 amplification; BRAF mutation

Thress et al, Nature Medicine, 2015

Strategies for Optimizing 1st-line Therapy for EGFR-mutated NSCLC: Is There an Optimal Sequence of EGFR Inhibitors?



Adapted from Gandara et al. JLCS 2016

Osimertinib (AZD9291) as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts

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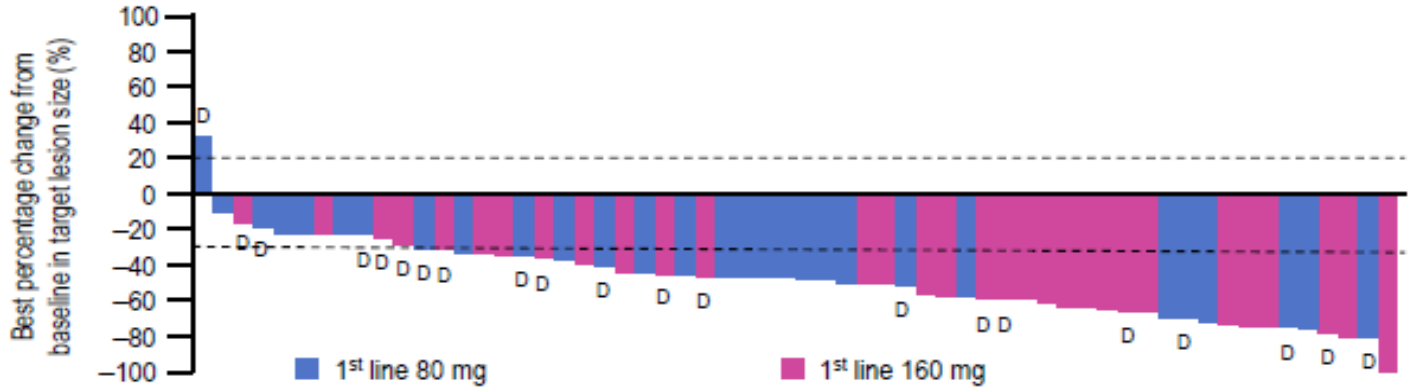
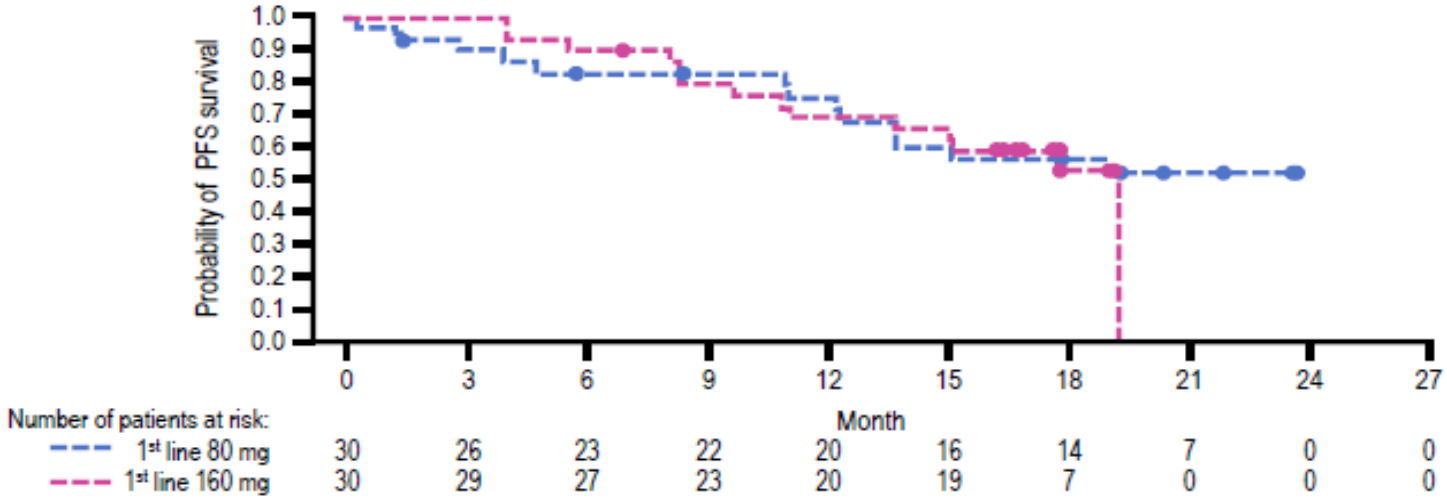
Osimertinib as 1st line therapy of EGFR-mutated NSCLC (AURA cohort): Overall Response Rate



	80 mg n=30	160 mg n=30	Total N=60
Confirmed ORR	67% (95% CI 47, 83)	87% (95% CI 69, 96)	77% (95% CI 64, 87)
Disease control rate*	93% (95% CI 78, 99)	100% (95% CI 88, 100)	98% (95% CI 89, 100)
Best objective response			
Complete response	0	2	2
Partial response	20	24	44
Stable disease ≥6 weeks	8	4	12
Progressive disease	2	0	2

Ramalingam et al., ELCC 2016; Abstract LBA1_PR

Osimertinib as 1st line therapy of EGFR-mutated NSCLC (AURA cohort): PFS



	80 mg n=30	160 mg n=30	Total N=60
Median PFS,* months (95% CI)	NC (12.3, NC)	19.3 (11.1, 19.3)	19.3 (13.7, NC)
Remaining alive and progression-free,† % (95% CI)			
12 months	75 (55, 88)	69 (49, 83)	72 (59, 82)
18 months	57 (36, 73)	53 (32, 70)	55 (41, 67)

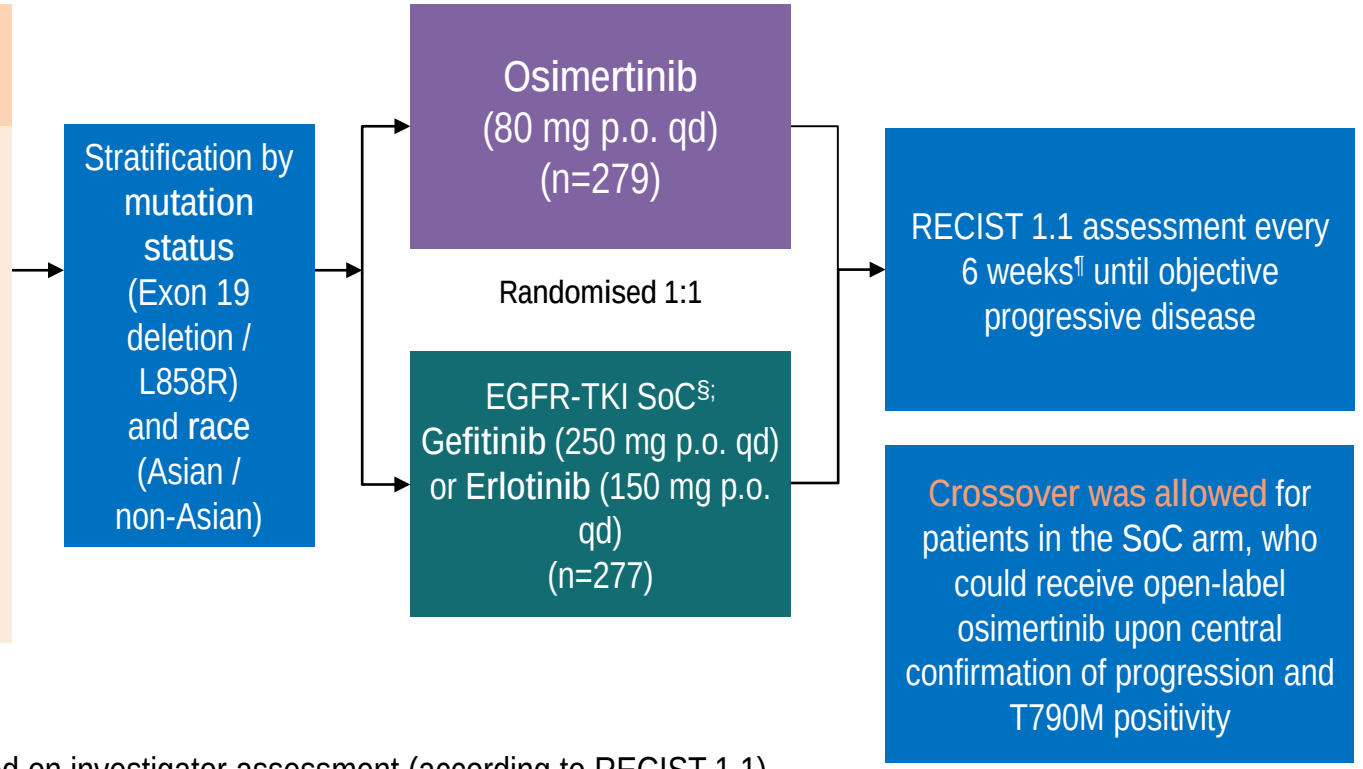
Population: safety analysis set; data cut-off: 4 January 2016
Progression events that do not occur within 14 weeks of the last evaluable assessment (or first dose) are censored
Circles on the Kaplan-Meier plot denote censored observations
*Progression-free survival is the time from date of first dosing until the date of objective disease progression or death
†Calculated using the Kaplan-Meier technique

Ramalingam et al., ELCC 2016; Abstract LBA1_PR

FLAURA: Osimertinib vs Gefitinib/Erlotinib in EGFR-mutated NSCLC

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
- **≥18 years***
- WHO performance status 0 / 1
- Exon 19 deletion / L858R (enrolment by local[#] or central[‡] EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

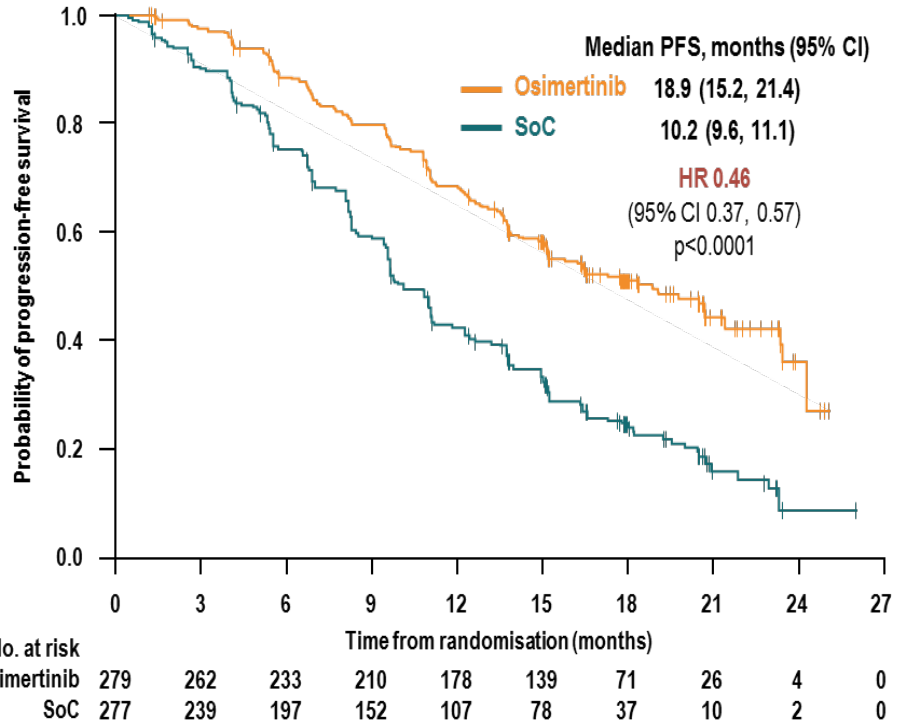


Endpoints
- Primary endpoint: PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- Secondary endpoints: objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

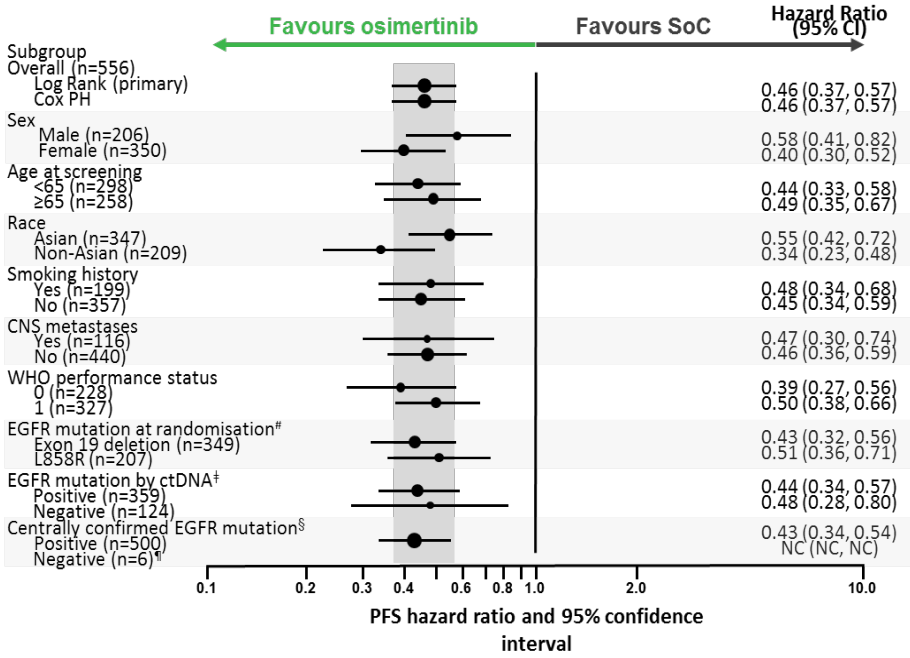
FLAURA data cut-off: 12 June 2017; NCT02296125
*≥20 years in Japan; [#]With central laboratory assessment performed for sensitivity; [‡]cobas EGFR Mutation Test (Roche Molecular Systems); [§]Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; [¶]Every 12 weeks after 18 months
CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; qd, once daily; SoC, standard-of-care;
TKI, tyrosine kinase inhibitor; WHO, World Health Organization

Ramalingam S, et al. ESMO 2017. Abstract LBA2_PR

FLAURA: Primary End Point of PFS by Investigator



PFS in patients with brain mets (n=116) HR=0.47
PFS in patients without brain mets (n=440)
HR=0.46



Ramalingam et al. ESMO 2017. Abstract LBA2

FLAURA : Objective Response Rate & Interim OS

	Osimertinib (n=279)	SoC (n=277)
ORR (95% CI)	80% (75, 85)	76% (70, 81)
Odds ratio# (95% CI)	1.28 (0.85, 1.93); p=0.2335	
Complete response, n (%)	7 (3)	4 (1)
Partial response, n (%)	216 (77)	206 (74)
Stable disease ≥6 weeks	47 (17)	46 (17)
Progression, n (%)	3 (1)	14 (5)
Not evaluable, n (%)	6 (2)	7 (3)
Remaining in response§, (95% CI)		
At 12 months	64% (58, 71)	37% (31, 44)
At 18 months	49% (41, 56)	19% (13, 26)

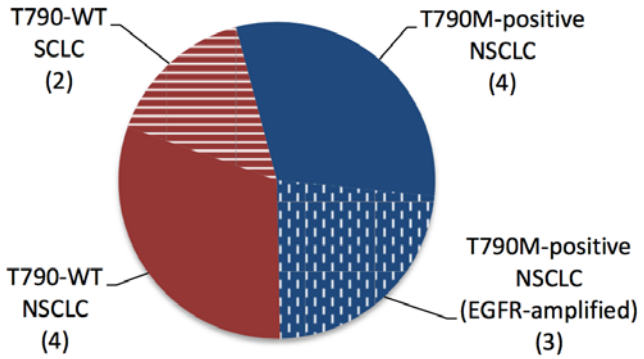
Interim OS results: favor Osimertinib vs SoC, HR 0.63 (95% CI: 0.45, 0.88), p=0.0068 (NS)

Note: A p-value of <0.0015 was required for statistical significance at 25% maturity

Take Home Messages:

- **Based on FLAURA, Osimertinib is " a new Standard of Care" in the 1st line therapy of EGFR-mutated NSCLC**
- **Superior activity of Osimertinib against brain metastases and prevention of new CNS lesions**
- **Fewer side effects with Osimertinib**

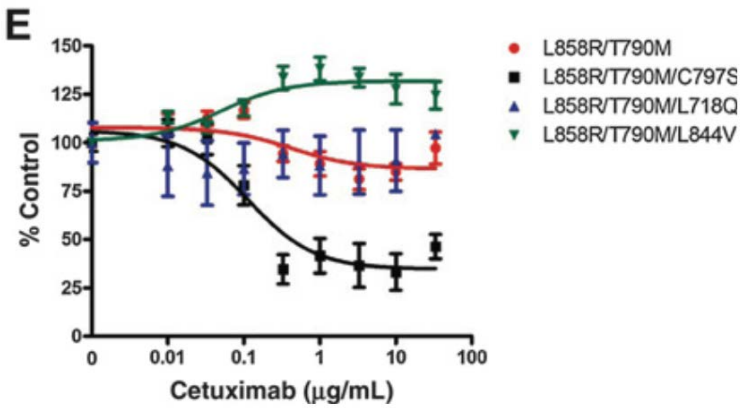
Dual EGFR-Blockade with Osimertinib and Necitumumab to Overcome Acquired Resistance to 3rd Generation EGFR-TKI



A. EGFR-amplification as a resistance mechanism To Rociletinib

Z Piotrowska et al. Cancer Discovery 2015.

L. Sequist et al. JAMA Oncol. 2015



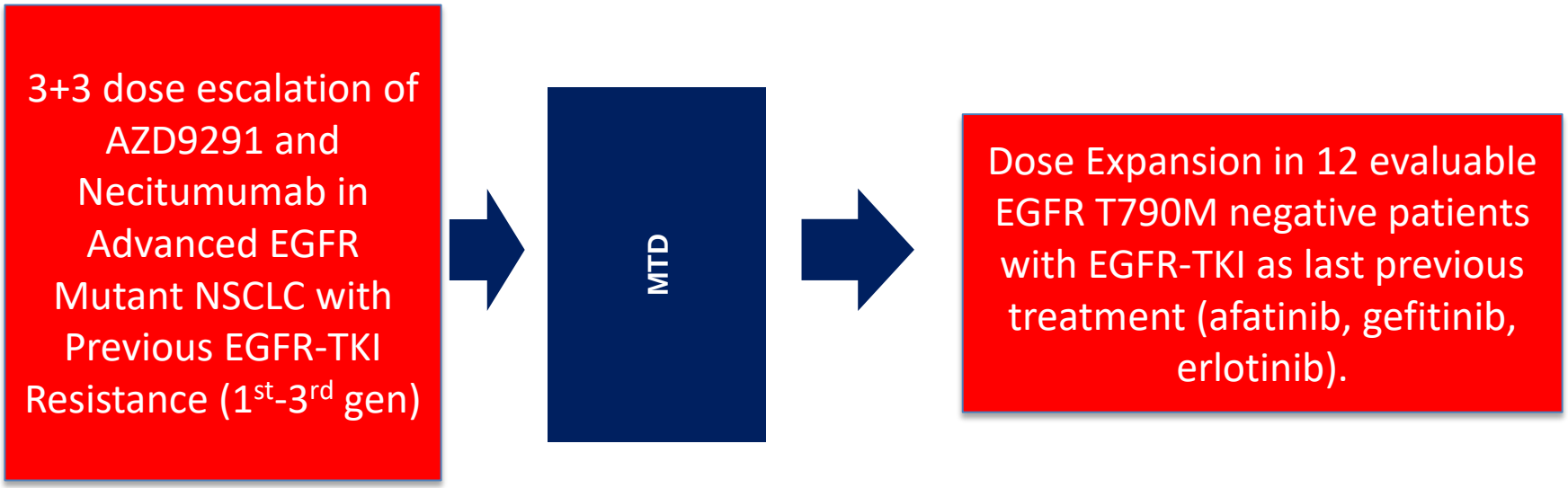
B. Activity of EGFR-Monoclonal Antibody in EGFR-L858R/C797S/T790M Model

D. Ercan et al. CCR. 2015.

Targeting a New Spectrum of Resistance Mechanisms

Combo Drug	Mechanism	PI
Bevacizumab	Anti-VEGF	H. Yu (MSKCC)
Bevacizumab (brain mets)	Anti-VEGF	S. Goldberg (Yale)
Dasatinib	SRC inhibitor (synergy Cripto-1 overexpressing tumors)	G. Giaccone (Georgetown)
Gefitinib	EGFR-TKI (C797S)	A. Redig (DFCI)
Ramucirumab or Necitumumab	Anti-VEGFR2/EGFR-moAb (T790M+ve)	Lilly
Necitumumab / Gefitinib	EGFR-moAb / C797S	JW Riess (UC Davis)
Navitoclax (T790M+ve)	Anti-Bcl2/Bcl-xL (pre-clinical synergy T790M+)	G. Oxnard (DFCI)
Savolitinib	MET	G. Oxnard (DFCI)

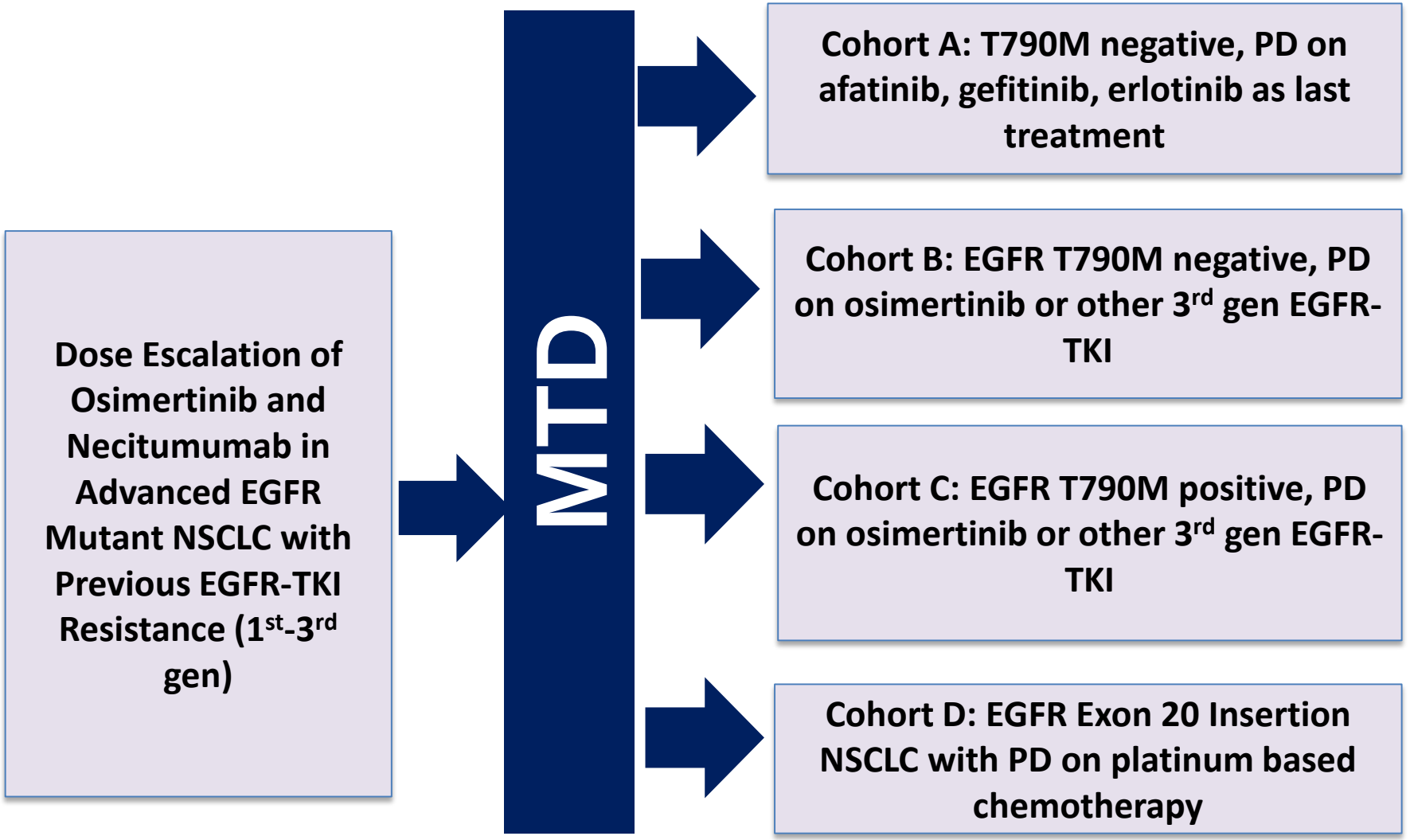
A Phase I Trial of AZD9291 and Necitumumab in EGFR Mutant NSCLC with Previous EGFR-TKI Resistance



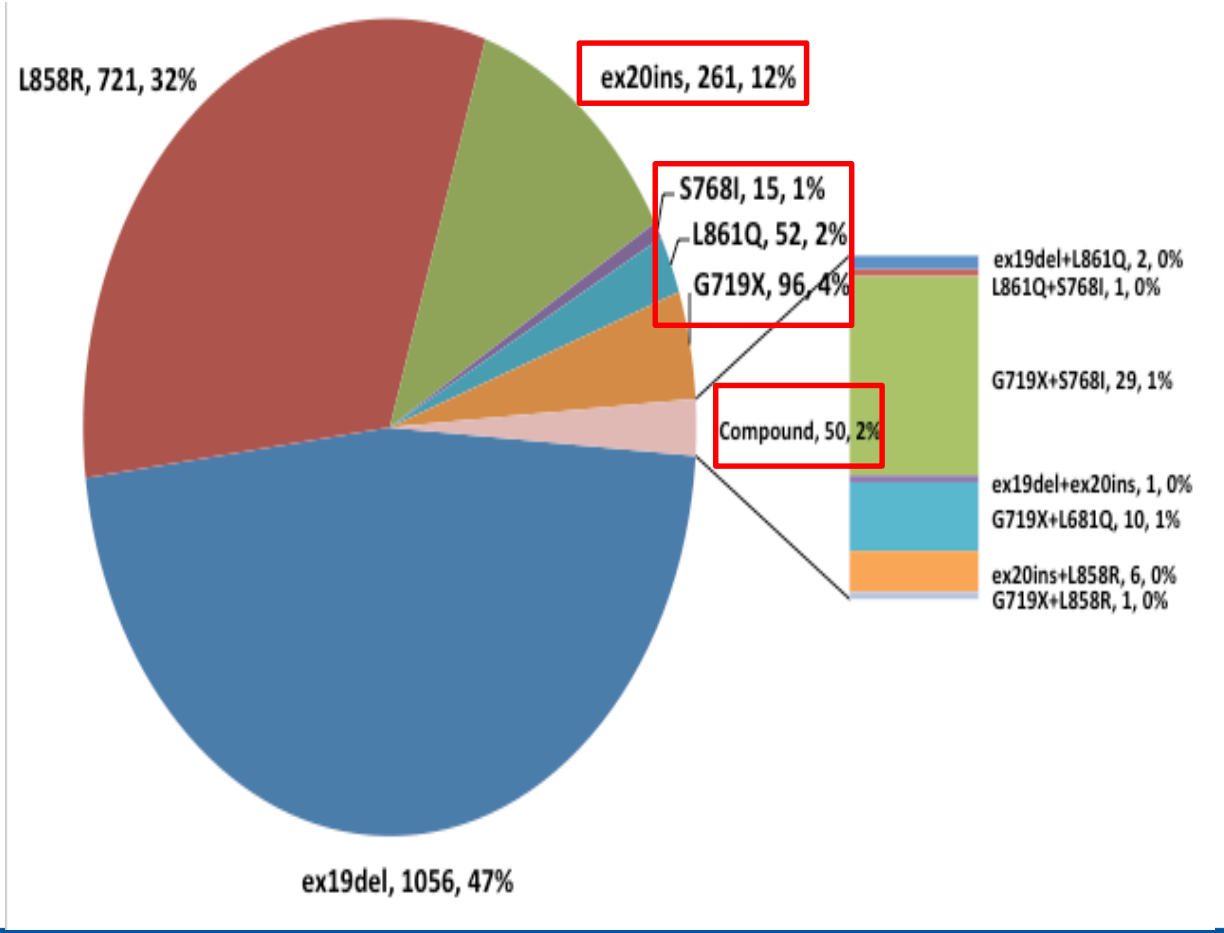
Primary Endpoint: Safety and Tolerability
Main Secondary Endpoint:
ORR is T790M negative population (3≥12 responses)

PI: JW Riess (UCD)
Co-PI David Gandara (UCD)
Statistician: Susan Groshen (USC)

Molecular Studies
Biopsy – Pre-treatment and post progression for EGFR T790M, EGFR FISH and NGS
Plasma cfDNA for EGFR-TKI resistance mechanisms
Creation of EGFR-TKI resistant PDX
Single Cell NGS for Intratumoral Heterogeneity


Dose Escalation of Osimertinib and Necitumumab in Advanced EGFR Mutant NSCLC with Previous EGFR-TKI Resistance (1st-3rd gen)
MTD
Cohort A: T790M negative, PD on afatinib, gefitinib, erlotinib as last treatment
Cohort B: EGFR T790M negative, PD on osimertinib or other 3rd gen EGFR-TKI
Cohort C: EGFR T790M positive, PD on osimertinib or other 3rd gen EGFR-TKI
Cohort D: EGFR Exon 20 Insertion NSCLC with PD on platinum based chemotherapy

Frequency and Distribution of EGFR-mutations Detected by CGP in this series

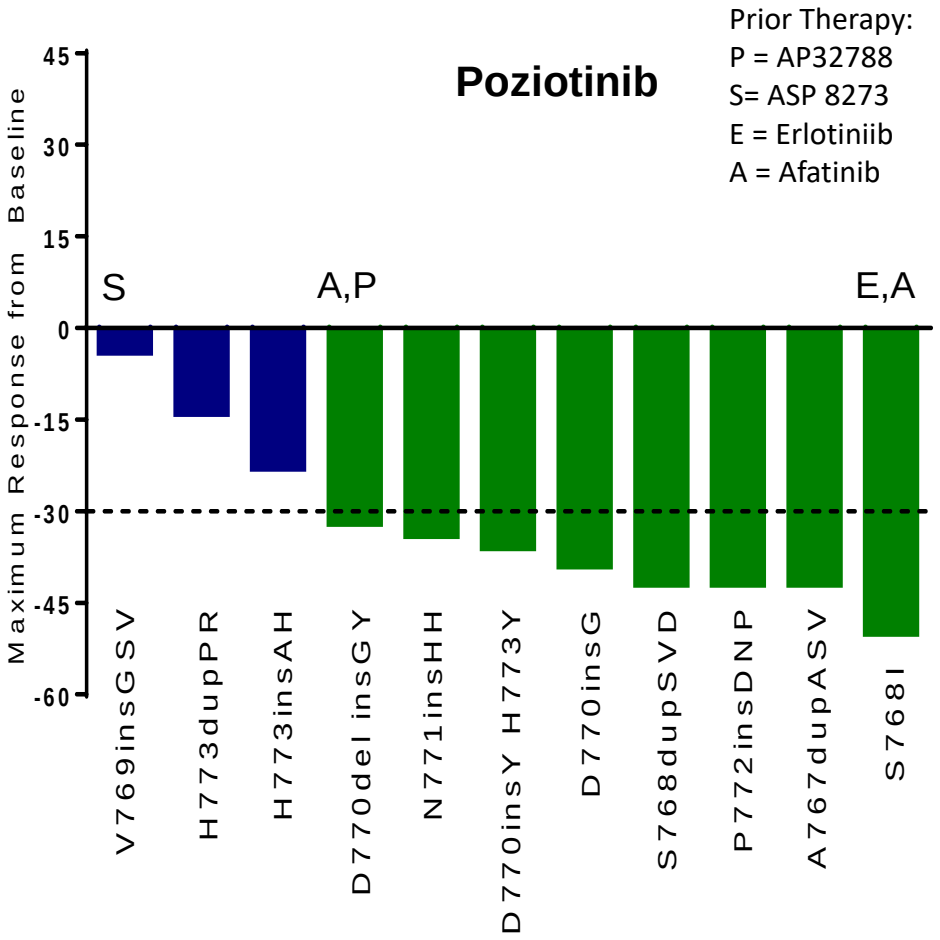


- EGFR mutations were detected in 2,251/14,483 NSCLC cases (**~15%**)
- *EGFR* Exon 20 insertions comprise **12%** of EGFR-activating mutations
- **3rd** most common group of mutations) and **1.8%** of NSCLC samples tested

Poziotinib in EGFR Exon20 Ins NSCLC induces partial responses in EGFR Exon 20 mutations

-11 EGFR exon 20 patients with baseline and follow up scans at 2 m (longest on treatment=6 months).
-**Activity**: 8/11 PR observed; 2 patients have had additional follow up scans confirming PR.
-duration of response not yet evaluable; only one patient with PD thus far.
-Evidence of CNS activity in patient with CNS metastasis and another with LMD
-additional patient treated on compassionate use IND (CIND) also had PR

-**Toxicities**: significant EGFR-related toxicities include rash, diarrhea, paronychia, mucositis consistent with those previously described.
-55% underwent dose reduction to 12mg thus far



Abstract ID 10369, Elamin et al. WCLC 2017

PD-L1 Expression in EGFR-Mutant versus KRAS-Mutant NSCLC

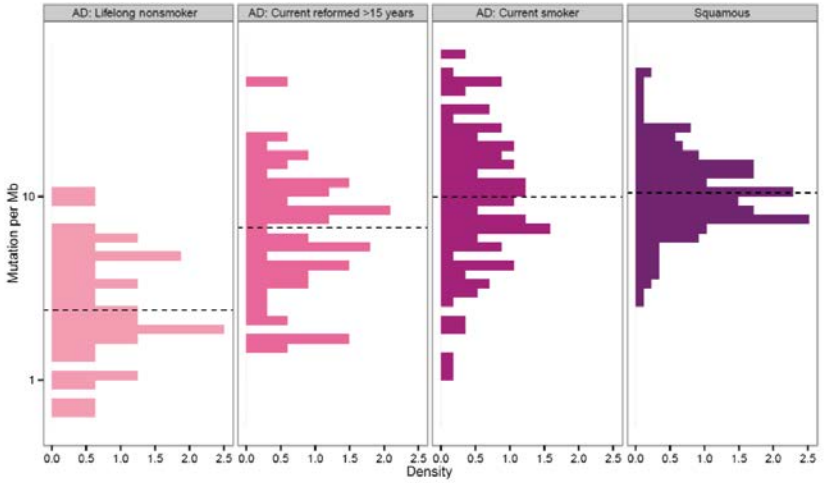
	EGFR-Mutant (N=62)	KRAS-Mutant (N=65)	P Value
PD-L1+ (≥50%)	7 (11%)	11 (17%)	0.449
CD8+ TILs[a] per mm^2			
Median	185.1	330.1	0.011
Range	(6.1-1161)	(8.5-2567)	
Concurrent PD-L1 Expression & CD8+ TILs			
PD-L1+ (≥50%) & high CD8+ TILs[b]	2/46 (4.3%)	10/56 (18%)	0.061

[a]Cytology specimens were excluded from evaluation of CD8+ TILs.

Gainor JF, et al. Clin Cancer Res 2016

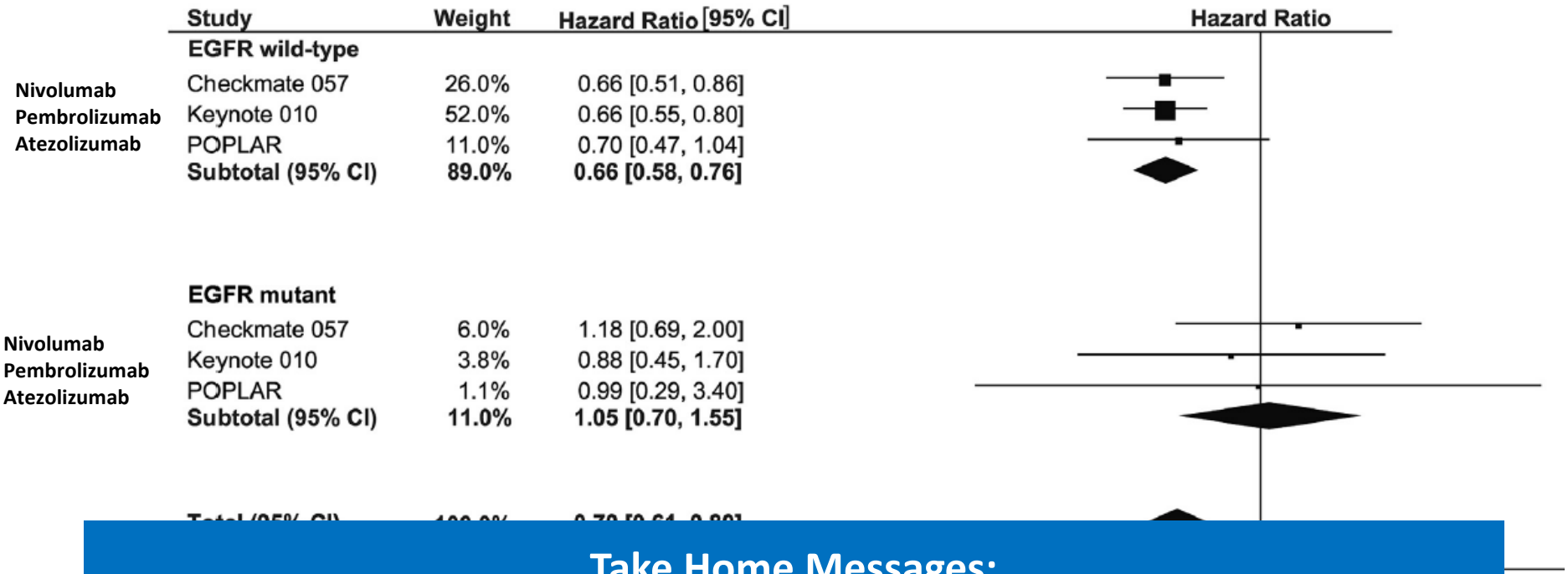
[b]High CD8+ TILs defined as ≥ median in the pretreatment control population (330 cells/mm^2)

Mutational Load: Smokers vs. Non-smokers



Rizvi N, et al. Science 2015;348(6230):124-128; Gibbons DL, et al. *Mol Cancer Res*. 2014;12(1):3-13

Clinical Experience of PD-(L)1 Inhibitors in EGFR+ NSCLC



Take Home Messages:

EGFR-mutant NSCLC less responsive to single agent PD-(L)1 blockade.

This is c/w non-smoking associated lung cancers, likely due to low PDL1 expression, mutational load, less relevant immune cells (CD8).

Look for clinical trials with for these patients (immunotherapy combos)

Lee

Take Home Points

- Osimertinib new standard 1st line treatment for metastatic EGFR-mutant NSCLC
- Likely new spectrum of resistance mutations post-1st line osimertinib (no T790M other resistance mutations (C797S)) with need for new clinical trials
- PD-(L)1 antibodies as single agents appear to be less effective in EGFR-mutant NSCLC compared to smoking related cancers.
- Newer EGFR/HER2 TKI agents such as poziotinib and AP32788 in early phase clinical development and may have activity in EGFR Exon 20 Insertion NSCLC
- Plasma cfDNA can be used to detect EGFR-activating and resistance mutations, but if negative it is not a substitute for tissue biopsy.