EGFR Management and Resistance

Pasi A. Jänne, M.D.,Ph.D.
Lowe Center for Thoracic Oncology
Dana Farber Cancer Institute

HARVARD MEDICAL SCHOOL

Disclosure Information

Pasi A. Jänne, MD, PhD

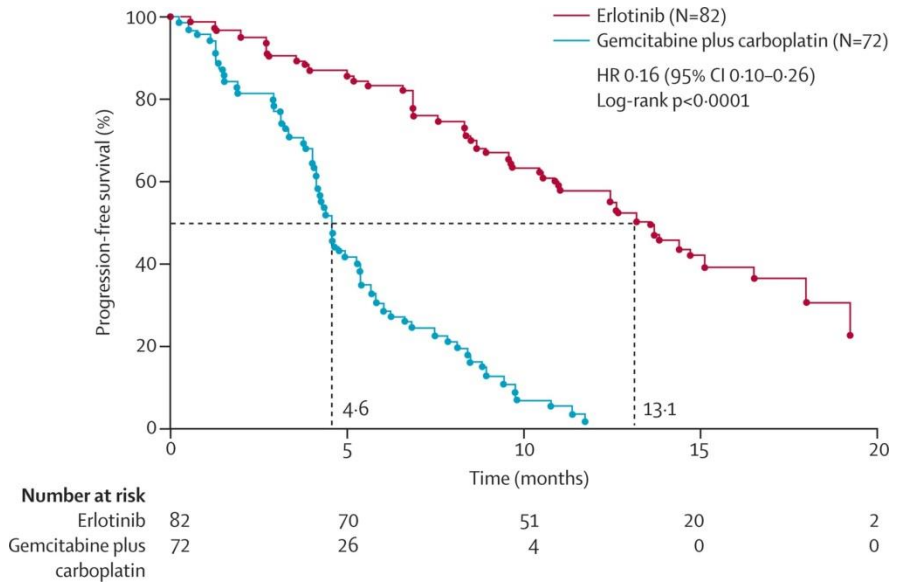
Consultant for: Astra Zeneca, Boehringer Ingelheim, Pfizer, Genentech, Roche, Sanofi-Aventis, Clovis Oncology, Chugai Pharmaceuticals, Merrimack Pharmaceuticals

Research Support: Astellas, AstraZeneca

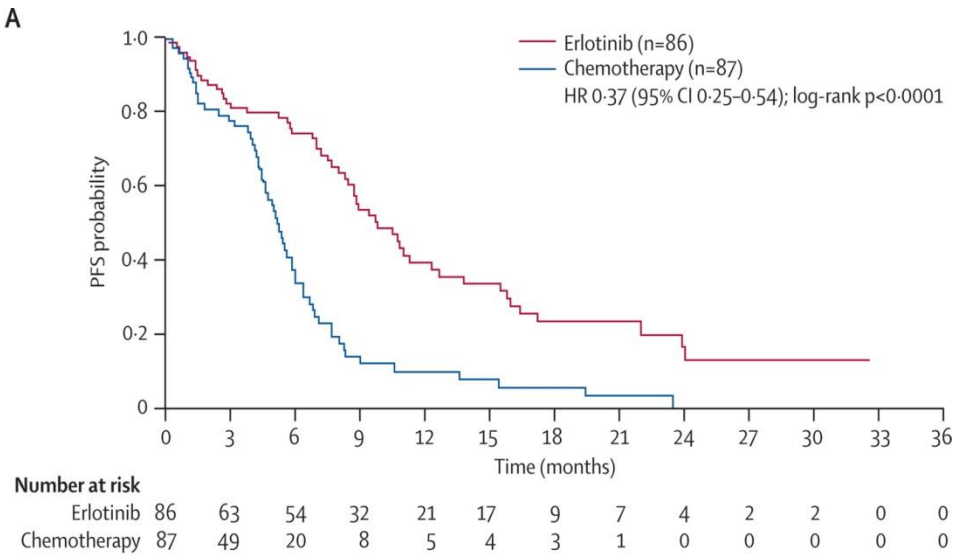
Stockholder in: Gatekeeper Pharmaceuticals

Other: LabCorp – post-marketing royalties from DFCI owned intellectual property on EGFR mutations

Erlotinib vs. Chemotherapy in EGFR mutant NSCLC



China



European Union

Zhou et al. Lancet Oncol 2011; Rosell et al. Lancet Oncol 2012

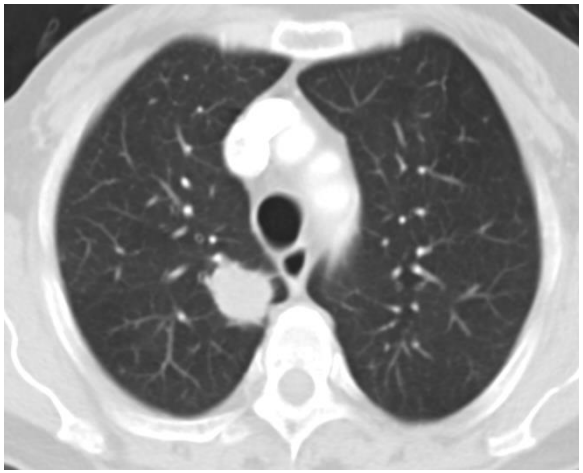
EGFR-TKI as standard 1st-line therapy for patients with *EGFR* mutations

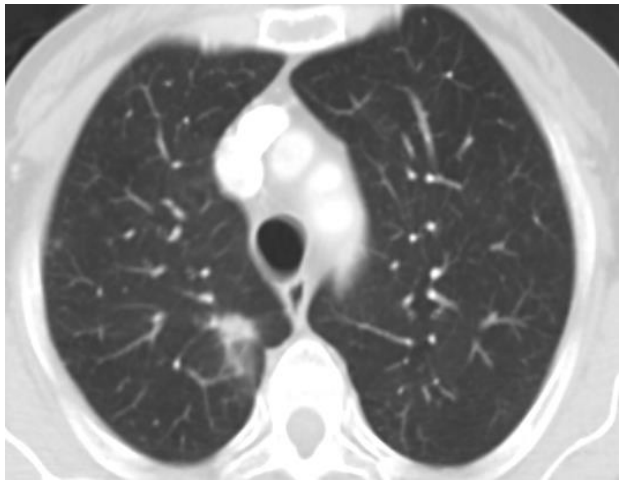
Study	Drugs	N (*EGFR* mutation)	RR	Median PFS (months)
IPASS	**Gefitinib** vs carboplatin/paclitaxel	261	**71.2%** vs 47.3%	**9.5** vs 6.3
WJTOG 3405	**Gefitinib** vs cisplatin/docetaxel	172	**62.1%** vs 32.2%	**9.2** vs 6.3
NEJGSG002	**Gefitinib** vs carboplatin/paclitaxel	224	**73.7%** vs 30.7%	**10.8** vs 5.4
EURTAC	**Erlotinib** vs cisplatin/docetaxel	173	**58.1%** vs 14.9%	**9.7** vs 5.2
OPTIMAL	**Erlotinib** vs gemcitabine/carboplatin	154	**83.0%** vs 36.0%	**13.7** vs 4.6
LUX-Lung 3	**Afatinib** vs cisplatin/pemetrexed	345	**56.0%** vs 23.0%	**11.1** vs 6.9
LUX-Lung 6	**Afatinib** vs gemcitabine/cisplatin	364	**66.9%** vs 23.0%	**11.0** vs 5.6

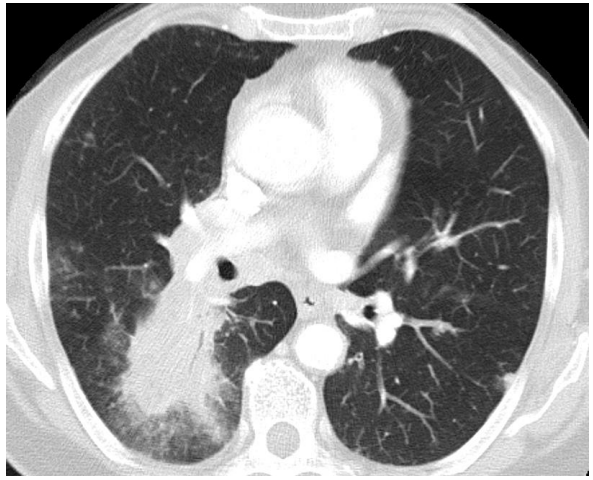
Gefitinib EU Summary of Product Characteristics;
Mitsudomi et al. Lancet Oncol 2010;11:121–1128; Maemondo et al. N Engl J Med 2010;362:2380–2388;
Rosell et al. Lancet Oncol 2012;13:239–246; Zhou et al. J Clin Oncol 2012;30: Abs 7520;
Sequist et al. J Clin Oncol 2013;31:3327–3334; Wu et al. Lancet Oncol 2014;15:213–222

Acquired Resistance to Erlotinib

Erlotinib





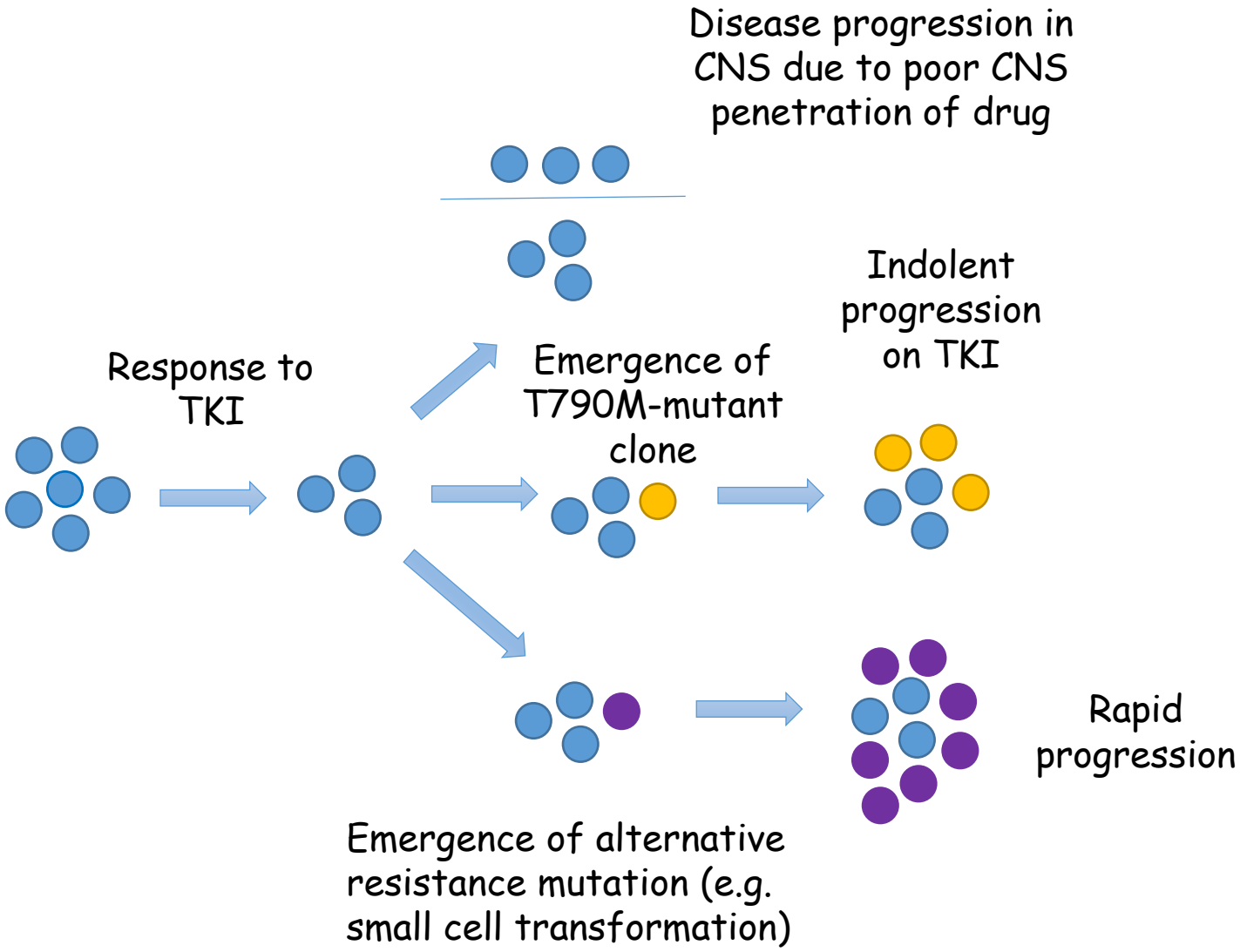


Diagnosis

EGFR Exon 19 del

3 months

20 months

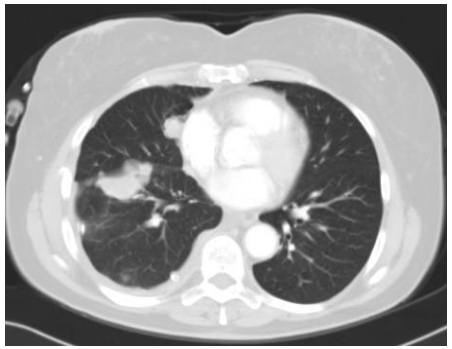


Sacher, Jänne & Oxnard Cancer 2014

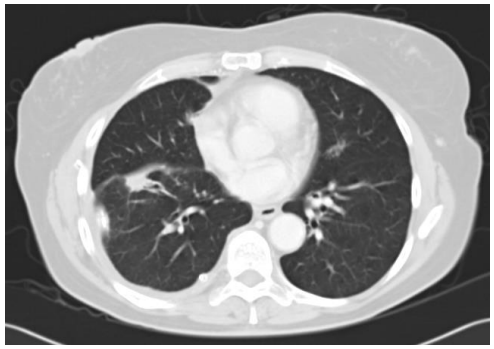
Approach to the management of *EGFR* mutant NSCLC with progression on first-line EGFR TKI

Sacher, Jänne & Oxnard

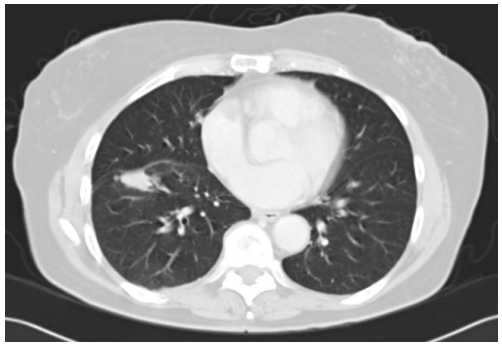
Radiographic progression does not always result in clinical or symptomatic progression



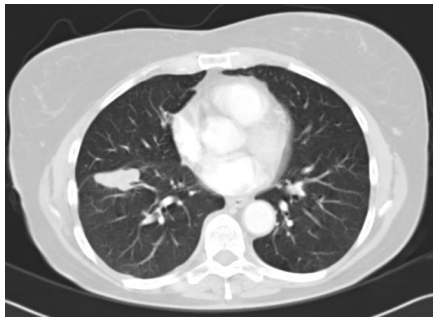
Baseline: Start erlotinib



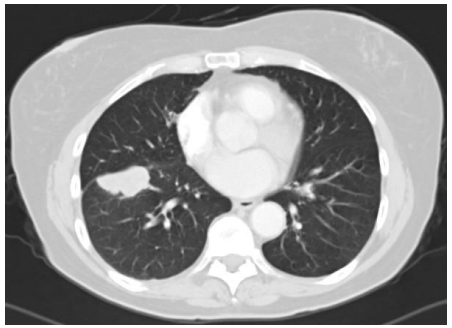
3m: Response



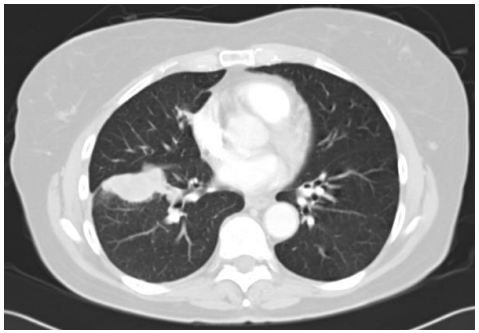
14m: PD



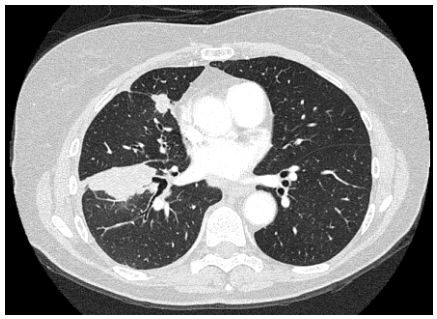
18m



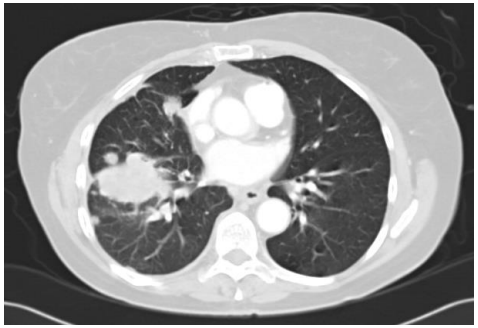
24m



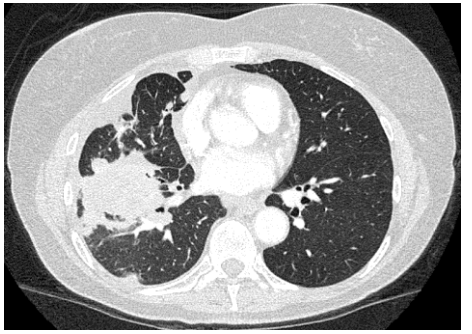
30m: Re-biopsy



35m

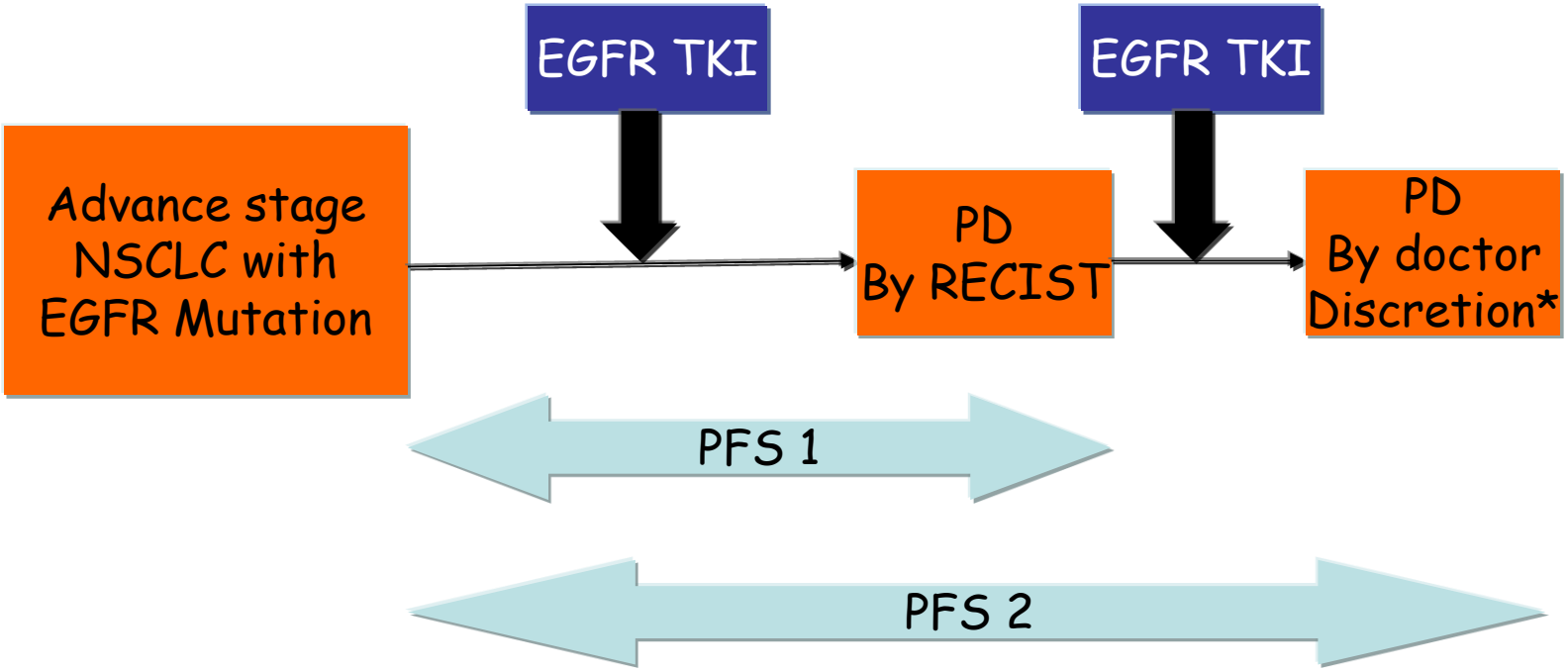


37m: Offered trial



39m: First dyspnea

ASPIRATION: To optimize treatment duration

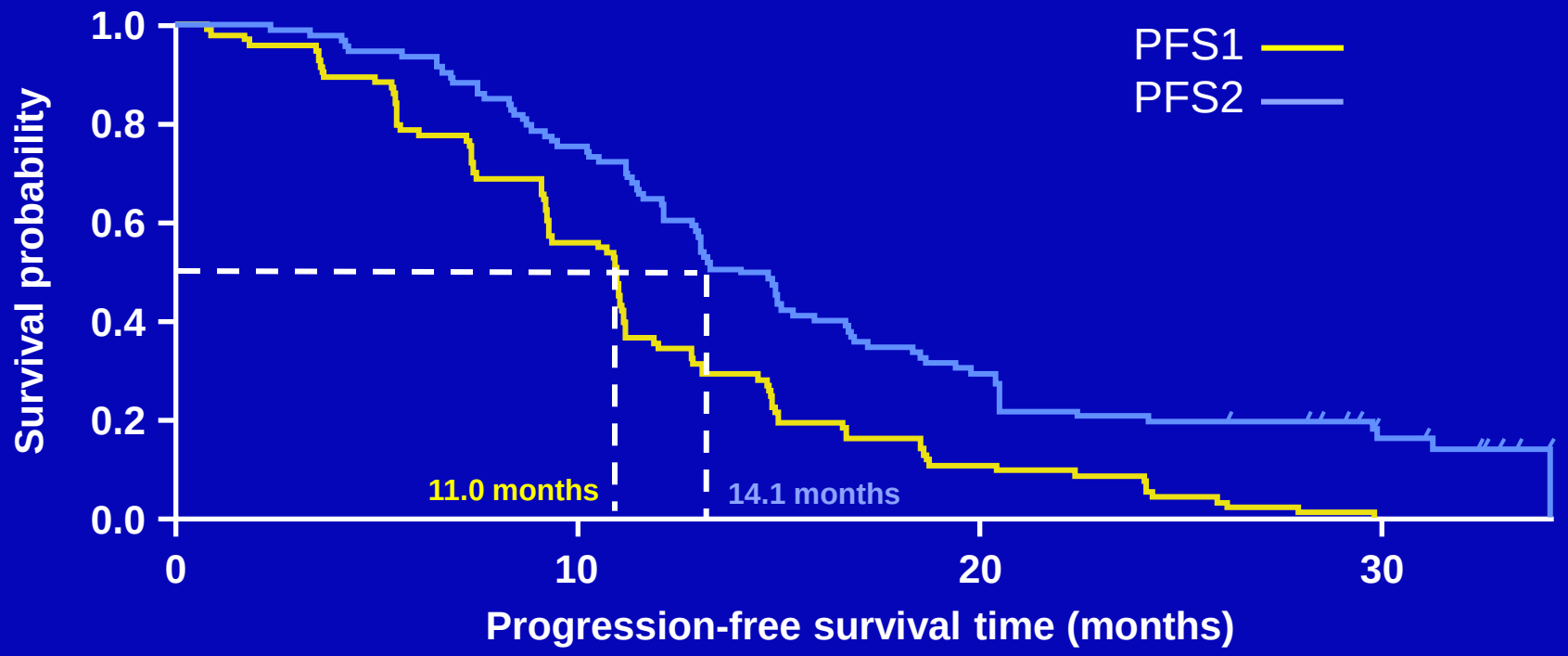


*Doctor's Discretion: Symptomatic progression, multiple progression Threat to major organ…etc

PI: K Park

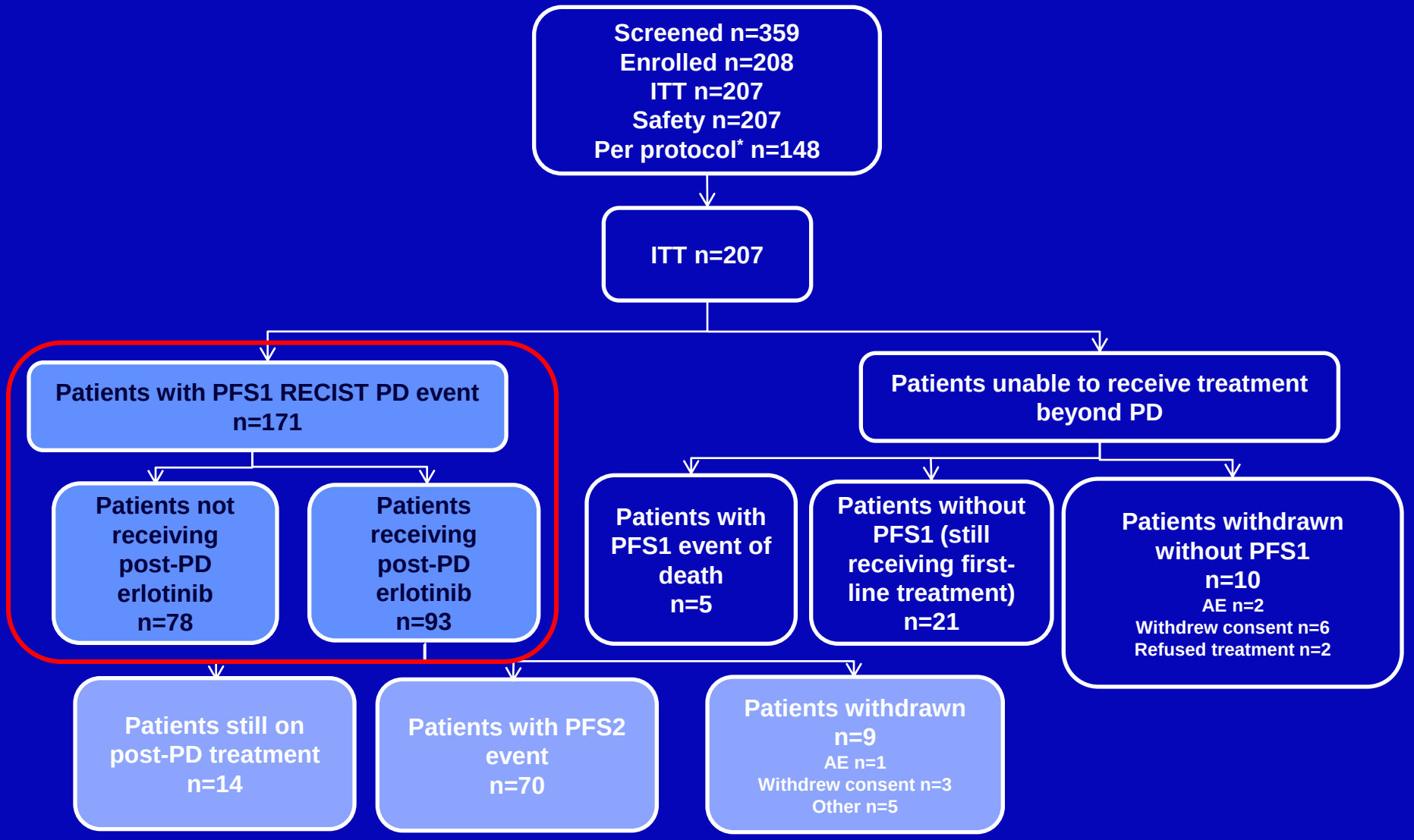
Continuation of erlotinib post-PD extended PFS

- In patients receiving post-PD erlotinib (n=93)
  - PFS1 was 11.0 months
  - the difference between PFS1 and PFS2 was an additional **3.1** months



Park et al., ESMO 2014

Patients eligible for treatment beyond PD



*Per-Protocol (PP) population is defined as those patients who have *EGFR* mutations confirmed by study designated central laboratory.

Park et al., ESMO 2014

Post-PD erlotinib versus no post-PD erlotinib

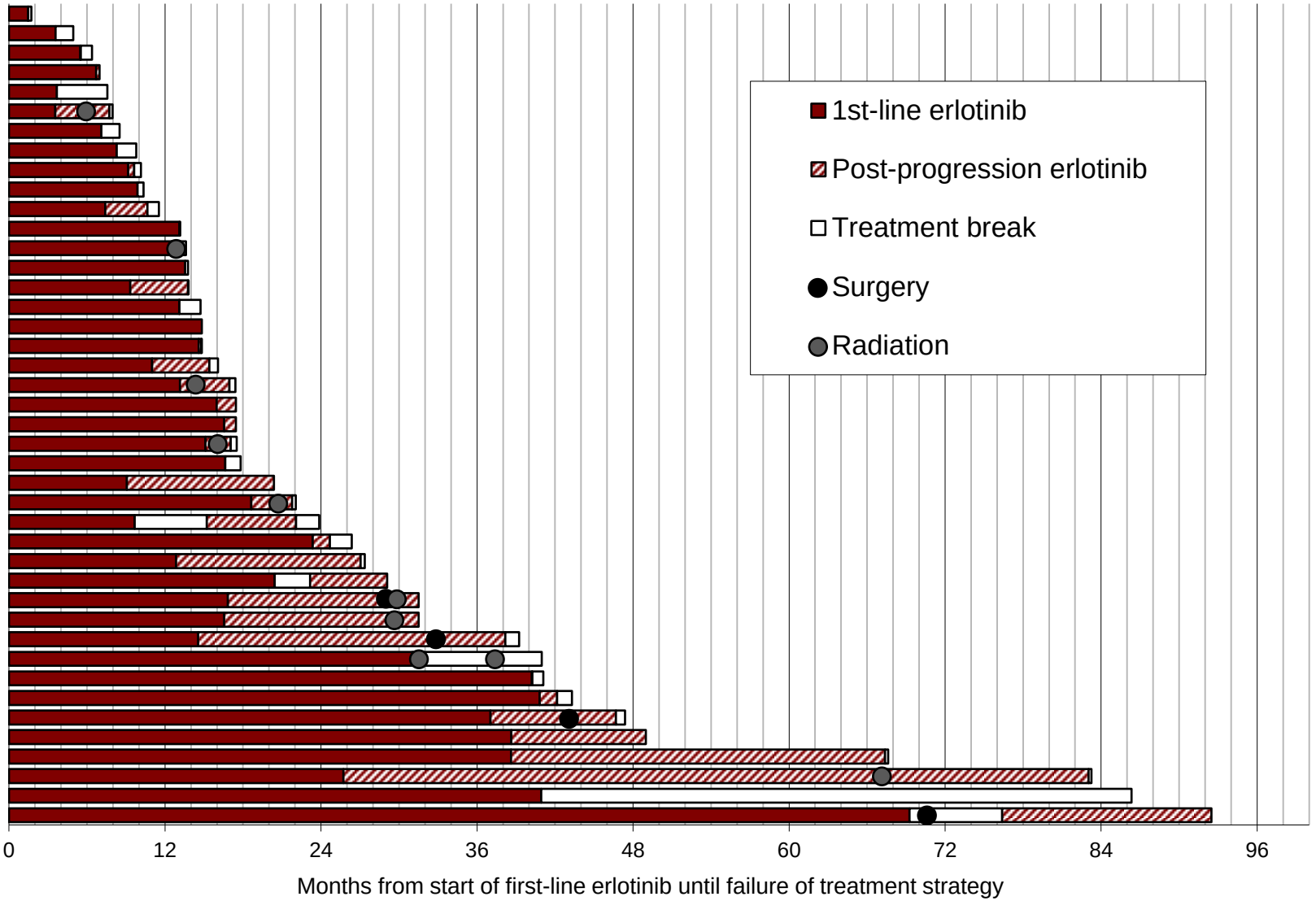
- Statistically significant differences between patients receiving post-PD erlotinib and those not receiving post-PD erlotinib were seen in the exploratory analysis for
  - recurrent disease at baseline
  - median PFS1
  - median depth of response
  - median time from BOR to PFS1
  - ECOG PS 0/1 at time of PFS1

	Post-PD E N=93	No post-PD E N=78	P value
Recurrent disease at baseline, n (%)	15 (16.1)	3 (3.8)	0.0091
Median PFS1, months	11.0 (95% CI 9.1–11.0)	7.4 (95% CI 5.6–9.2)	0.0096
Median depth of response*, %	-48.7†	-42.2‡	0.0389
Median time from baseline to BOR, days	56	59	0.8840
Median time from BOR to PFS1, days	169	113	0.0047
ECOG 0/1 at PFS1, %	95.7	78.2	0.0005
Ongoing grade ≥3 AEs at PFS1,%	19.4	19.2	0.9837

*Depth of response is the maximum % decrease from baseline for each patient in the 'sum of diameters of target lesions' prior to the date of the first occurrence of PD. †n=90, ‡n=70

Park et al., ESMO 2014

On-study erlotinib versus post-progression erlotinib in the EGFR-mutant cohort.



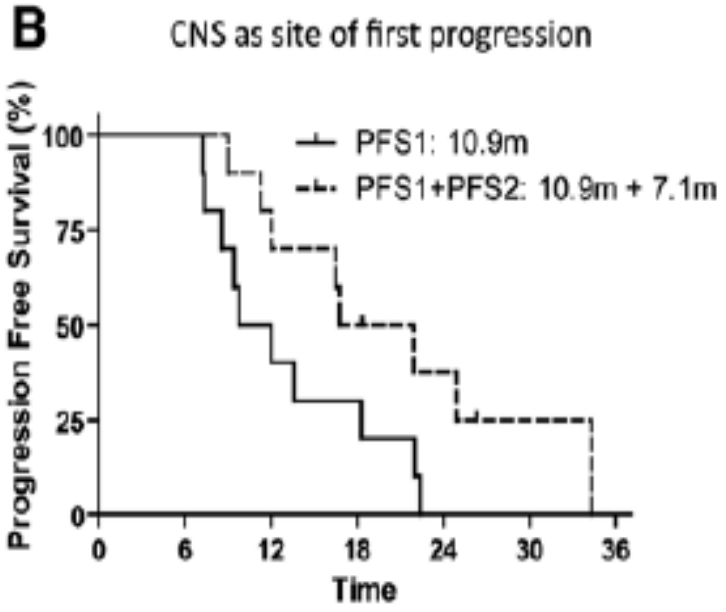
Lo et al. Cancer 2015

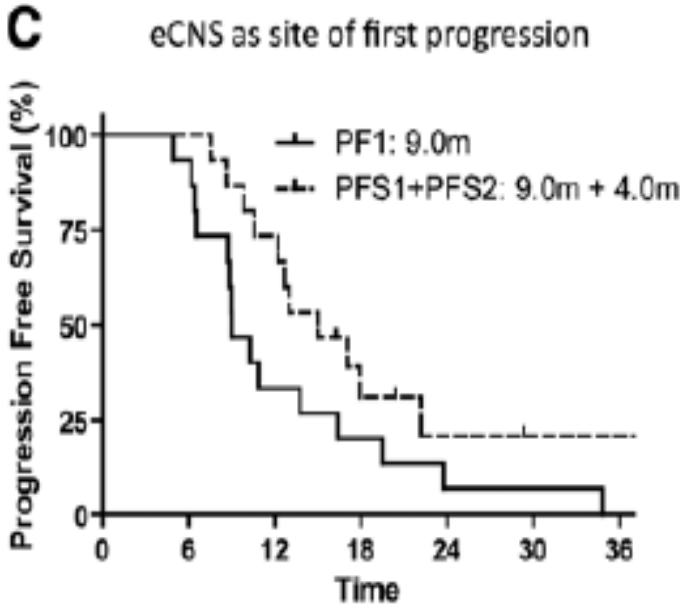
Approach to the management of *EGFR* mutant NSCLC with progression on first-line EGFR TKI

Sacher, Jänne & Oxnard

Local Therapy in Acquired Resistance

65 pts (38 ALK+, 27 EGFR mut)of whom 51 (28 ALK, 23 EGFR) progressed
25 (49%) with CNS (no LMC) or ≤4 extracranial sites of progression





Particular value in those w/CNS as first site of PD

Weickhardt, J Thorac Oncol 2013

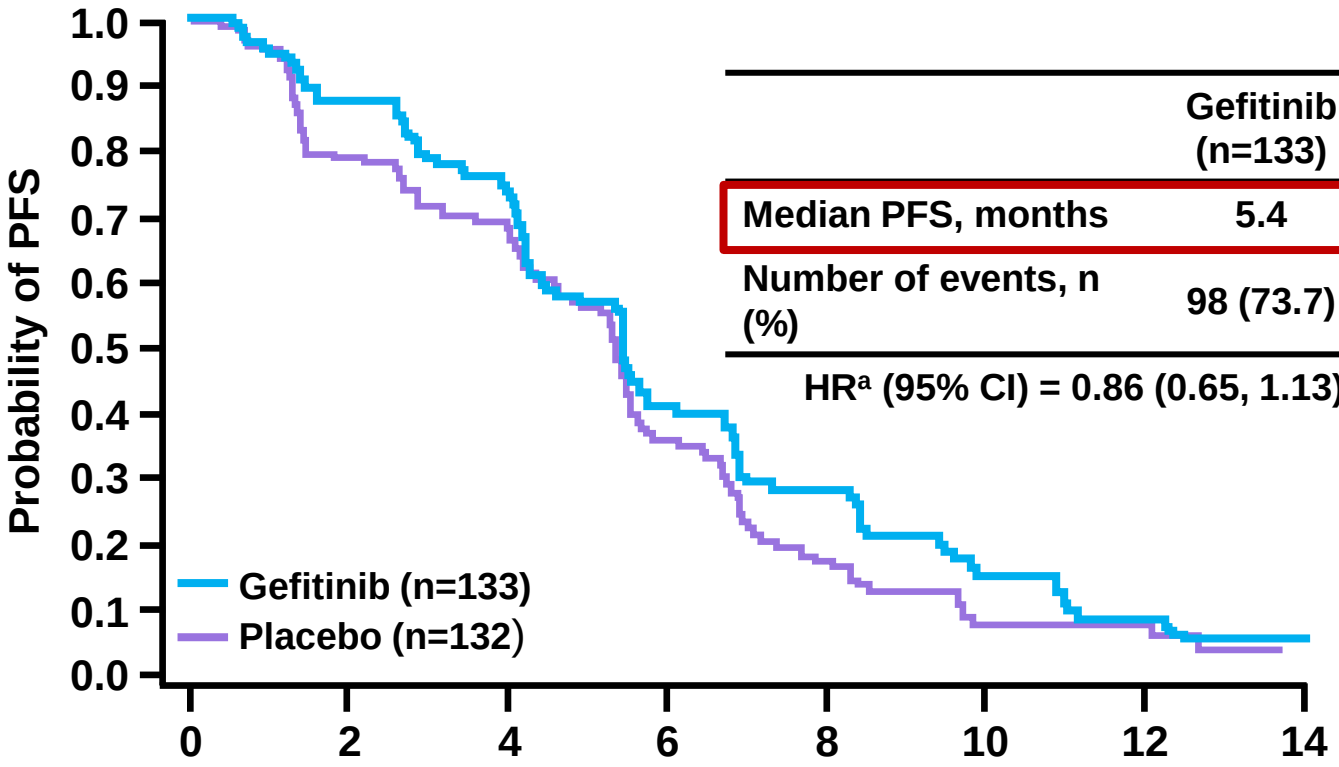
Approach to the management of *EGFR* mutant NSCLC with progression on first-line EGFR TKI

Sacher, Jänne & Oxnard

Approach to the management of *EGFR* mutant NSCLC with progression on first-line EGFR TKI

Sacher, Jänne & Oxnard

IMPRESS – continuation gefitinib vs. placebo with chemotherapy



	Gefitinib (n=133)	Placebo (n=132)
Median PFS, months	5.4	5.4
Number of events, n (%)	98 (73.7)	107 (81.1)

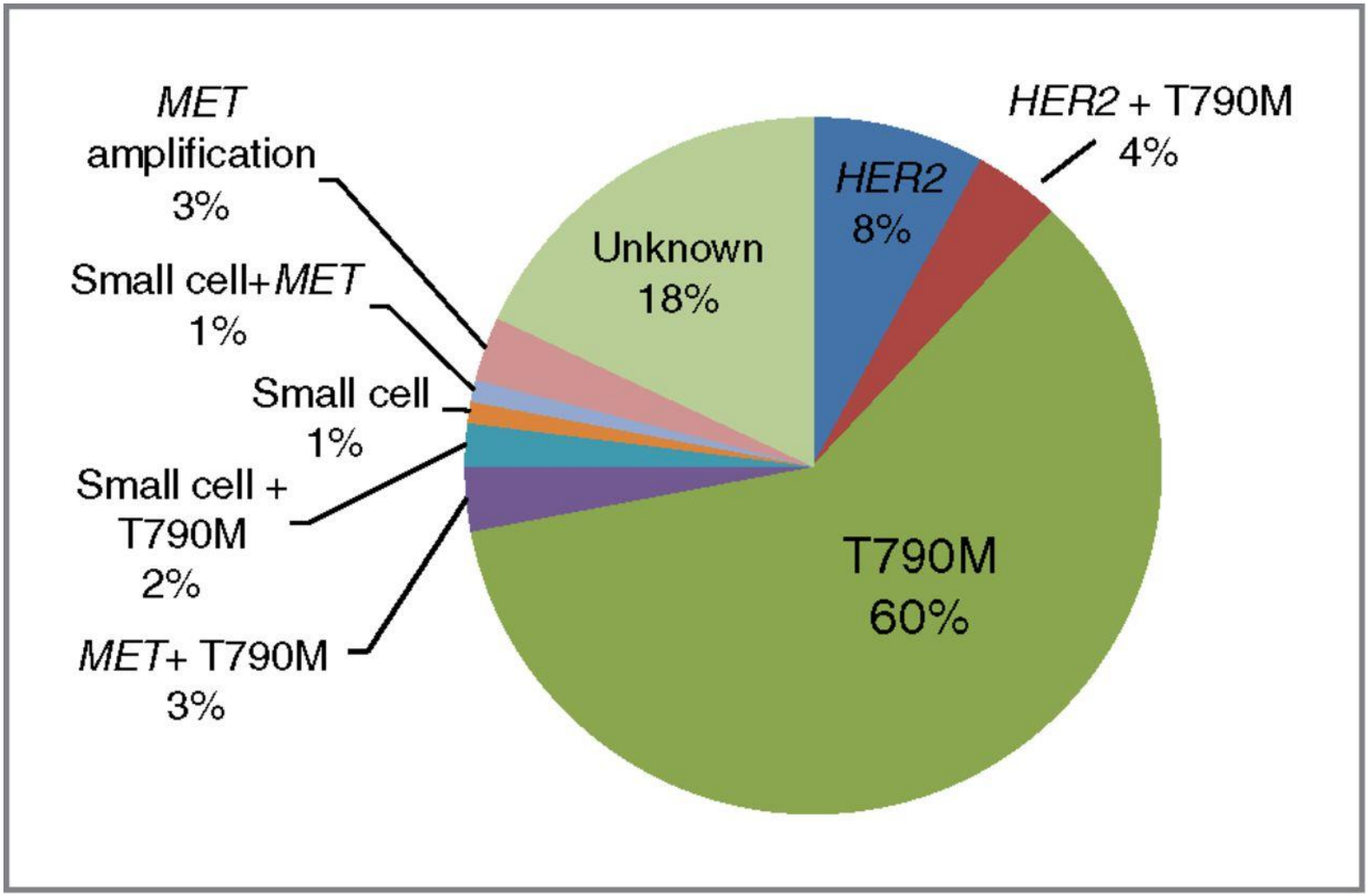
HR[a] (95% CI) = 0.86 (0.65, 1.13); p=0.273

Patients at risk:

Gefitinib	133	110	88	40	25	12	6	0
Placebo	132	100	85	39	17	5	4	0

Soria et al. Lancet Oncol 2015

The relative frequencies of the various mechanisms of acquired resistance



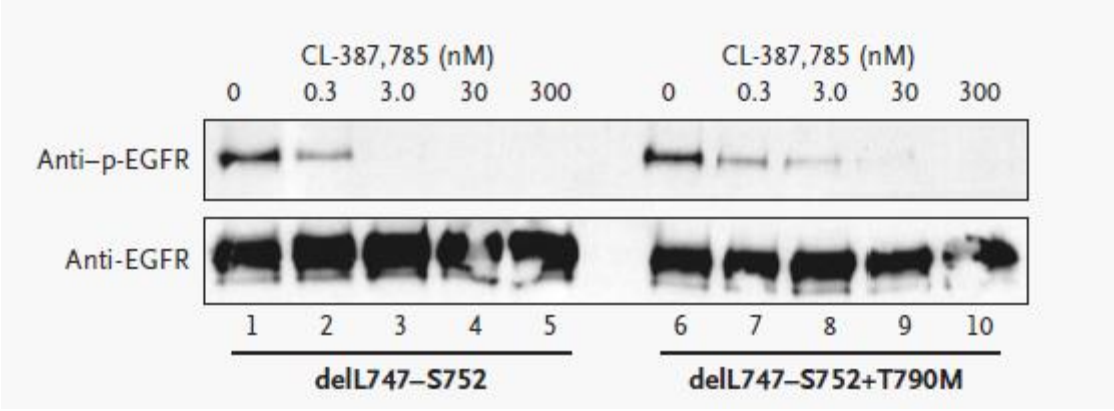
Yu H A et al. Clin Cancer Res 2013;19:2240-2247

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

EGFR Mutation and Resistance of Non–Small-Cell Lung Cancer to Gefitinib

Susumu Kobayashi, M.D., Ph.D., Titus J. Boggon, Ph.D., Tajhal Dayaram, B.A., Pasi A. Jänne, M.D., Ph.D., Olivier Kocher, M.D., Ph.D., Matthew Meyerson, M.D., Ph.D., Bruce E. Johnson, M.D., Michael J. Eck, M.D., Ph.D., Daniel G. Tenen, M.D., and Balázs Halmos, M.D.

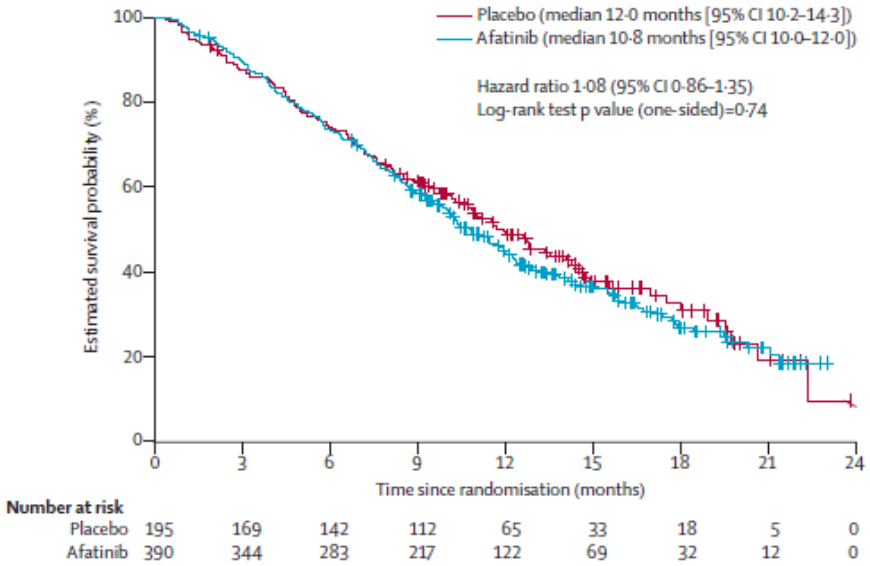


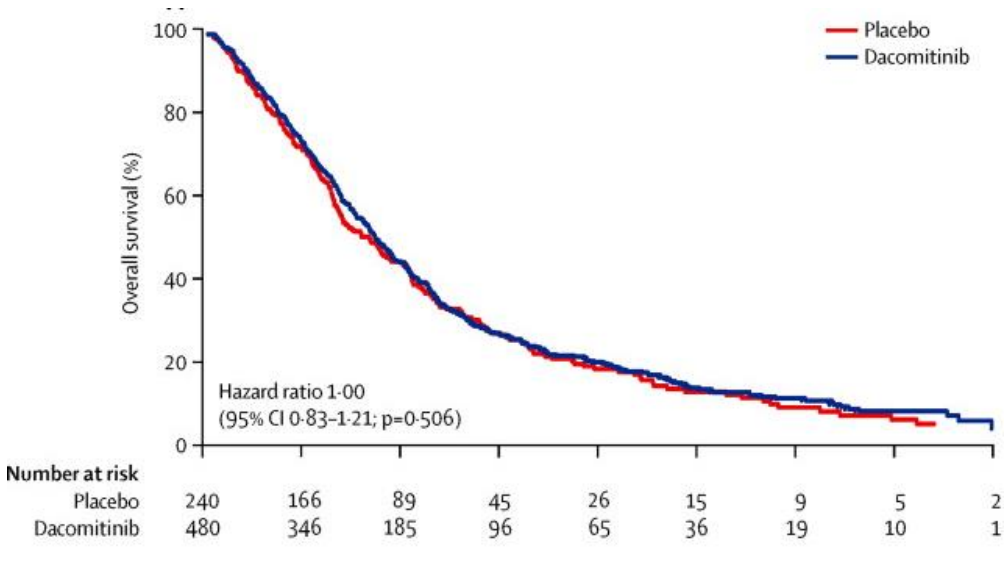
Mechanism: EGFR T790M increases ATP affinity

Potential Solution: Covalent EGFR inhibitor

N Engl J Med. 2005 Feb 24;352(8):786-92; Yun et al. PNAS 2008

Afatinib & Dacomitinib in patients previously treated with EGFR Inhibitors





LUX Ling 1 – Afatinib vs Placebo

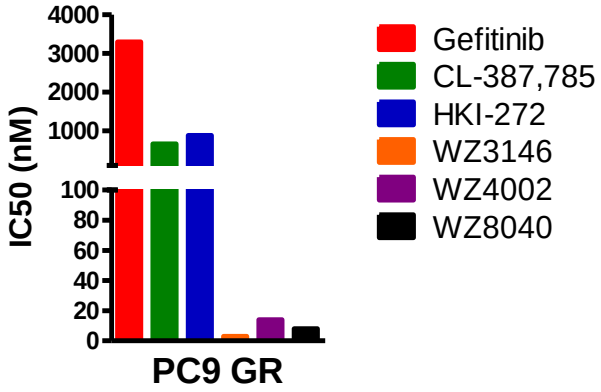
PFS: 3.3 vs. 1.1 months
RR < 10%

BR.26 – Dacomitinib vs Placebo

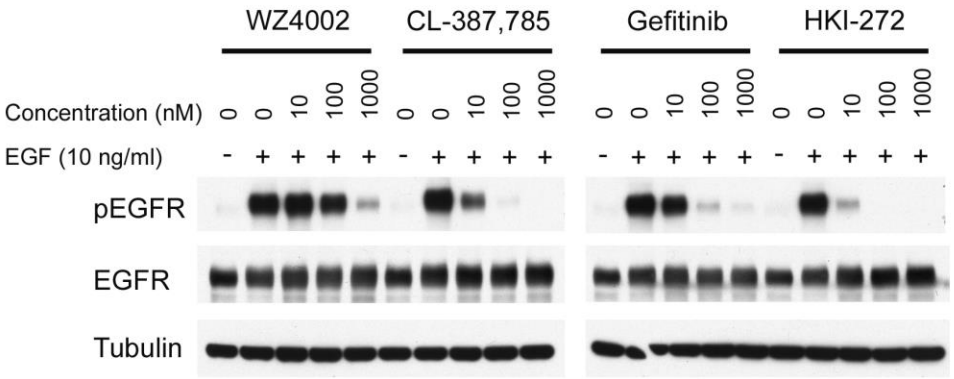
PFS: 2.7 vs. 1.4 months
RR < 10%

Miller et al. Lancet Oncol 2013; Ellis et al. Lancet Oncol 2014

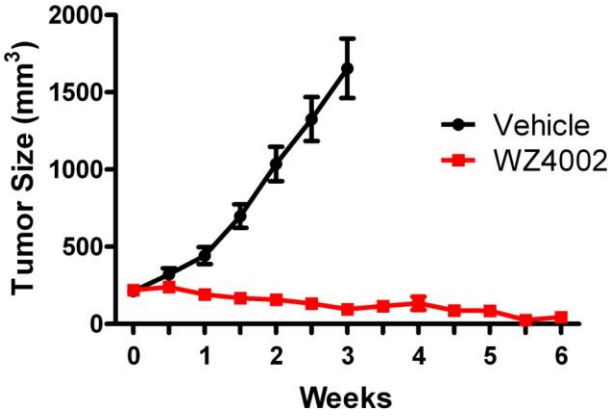
Properties of Mutant Selective EGFR Inhibitors



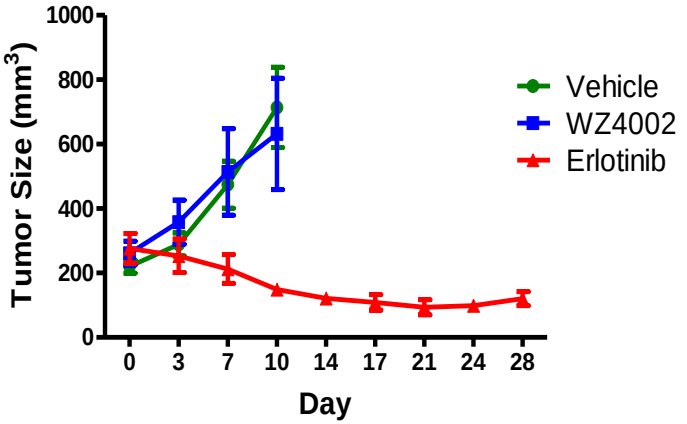
Increased potency in T790M bearing models compared to current clinical agents



Less effective against WT EGFR



PC9 GR (EGFR Del19/T790M)

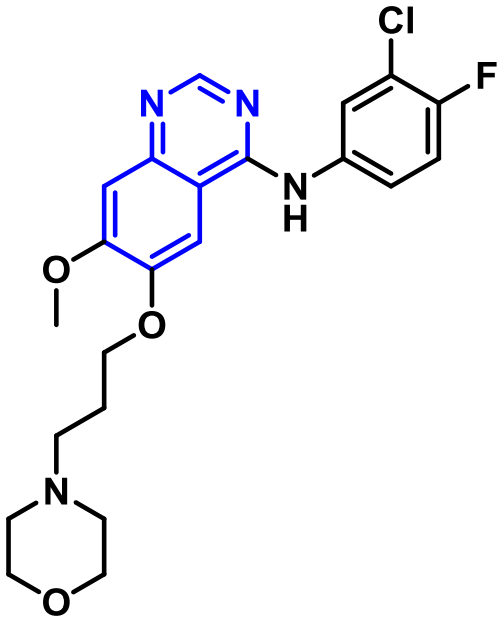


A431 (EGFR WT; amplified)

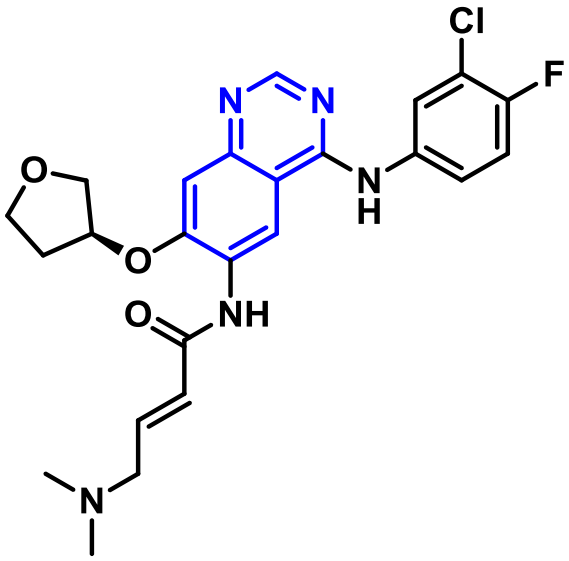
Zhou et al. Nature 2009

Potent and Mutant Selective in vivo

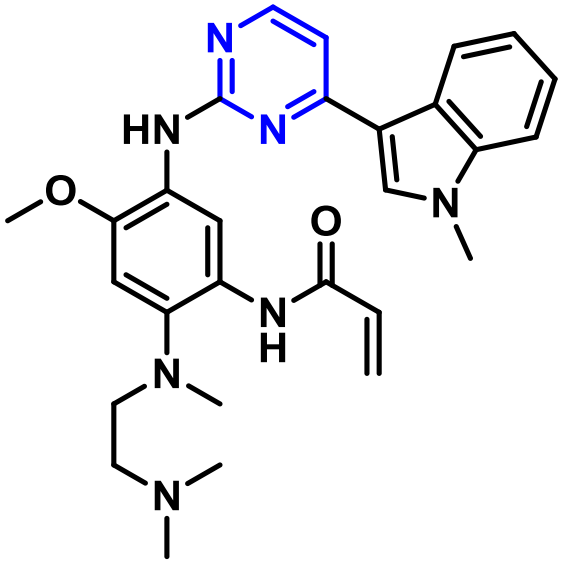
Activity Profiles of EGFR Inhibitors



Gefitinib



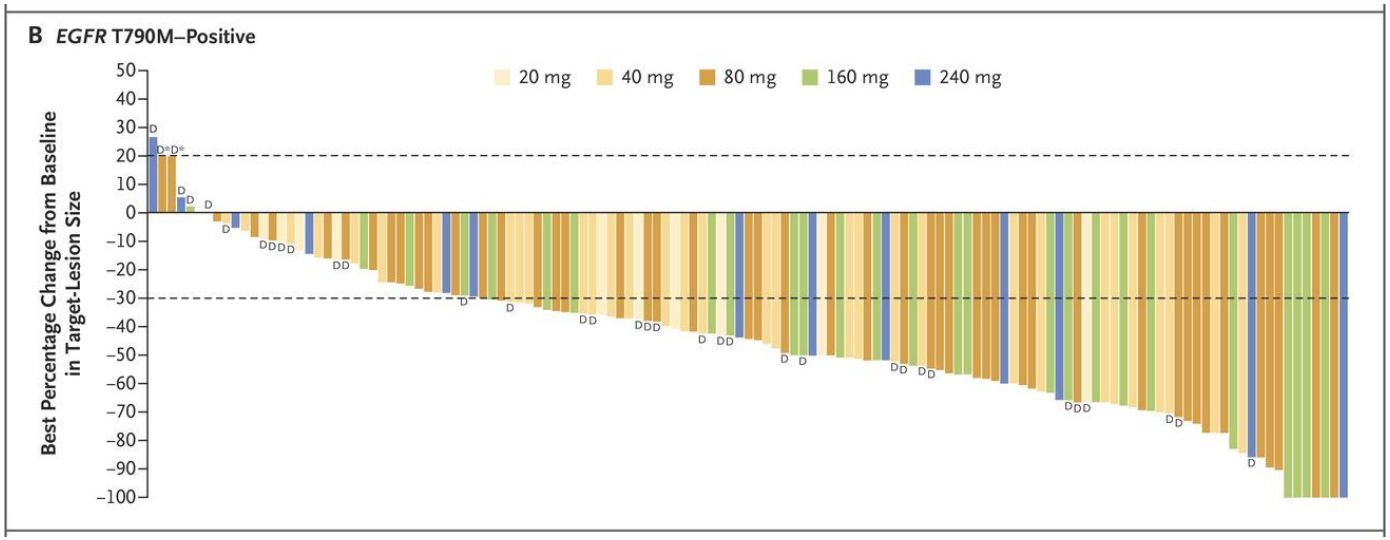
Afatinib



AZD9291

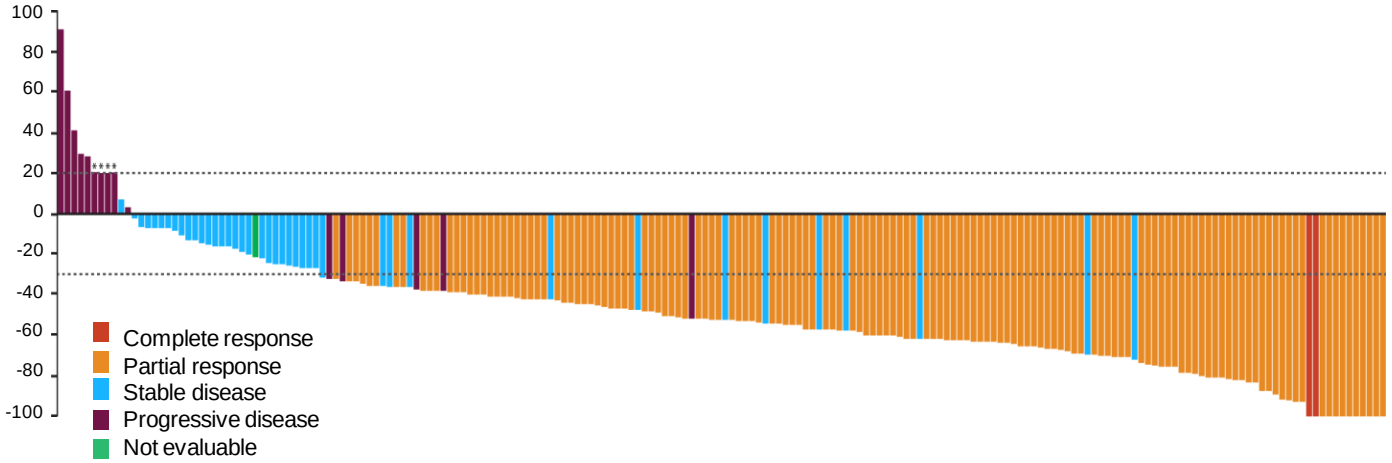
	Gefitinib	Afatinib	AZD9291
Wild Type EGFR	+++	++++	+
EGFR exon 19/L858R	+++	++++	++++
EGFR T790M	-	+	++++

Efficacy of osimertinib (AZD9291) in EGFR inhibitor resistant EGFR T790M NSCLC



Phase I – all doses

RR: 61% (95% CI, 52-70)

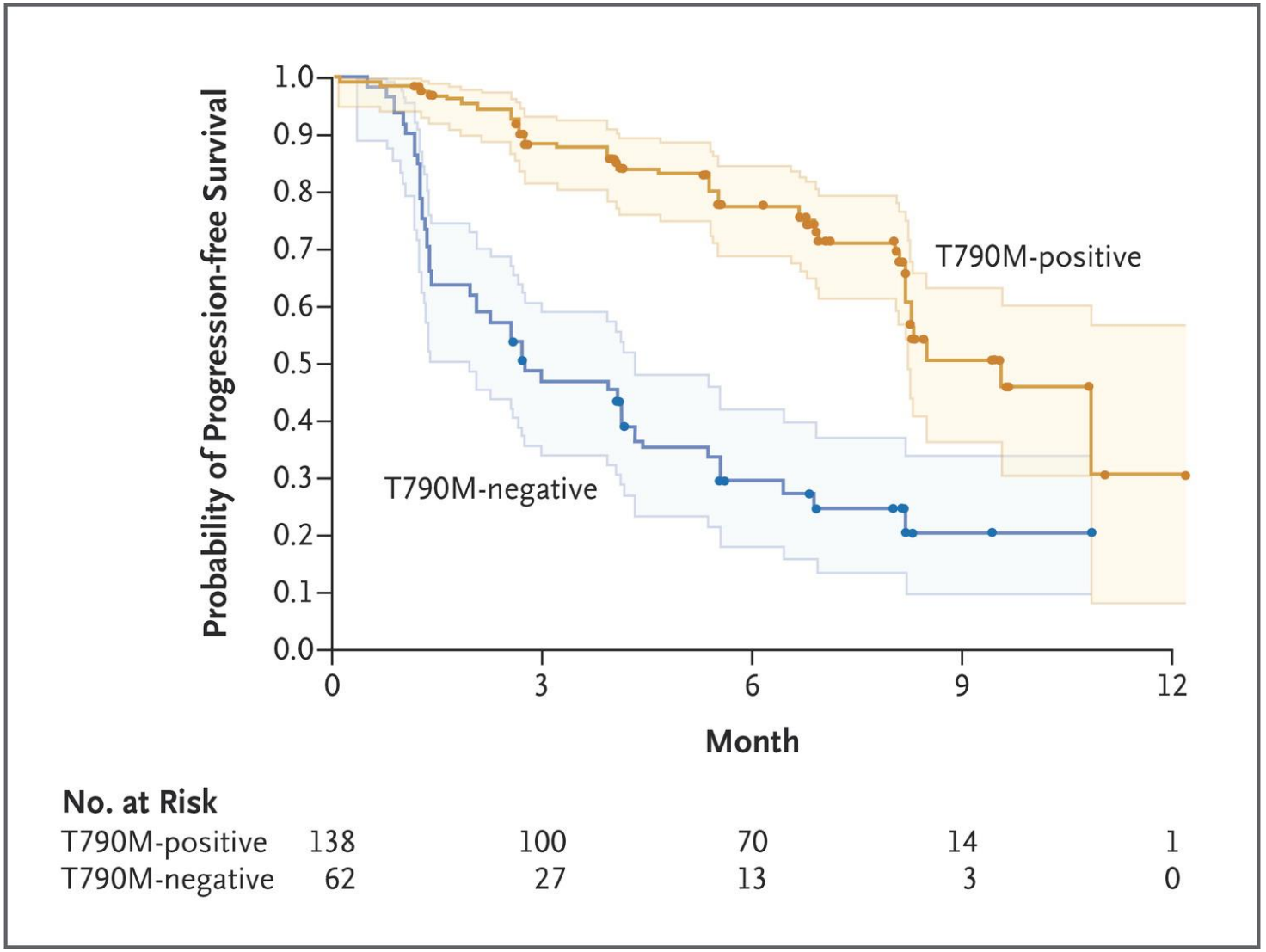


Phase II – 80 mg

RR: 71% (95% CI, 64-77)

Jänne et al. NEJM 2015; Mitsudomi et al. IASLC 2015

Efficacy of AZD9291 is greater in T790M positive patients



Jänne et al, NEJM, 2015

Efficacy and Toxicity of 3rd Generation EGFR TKIs

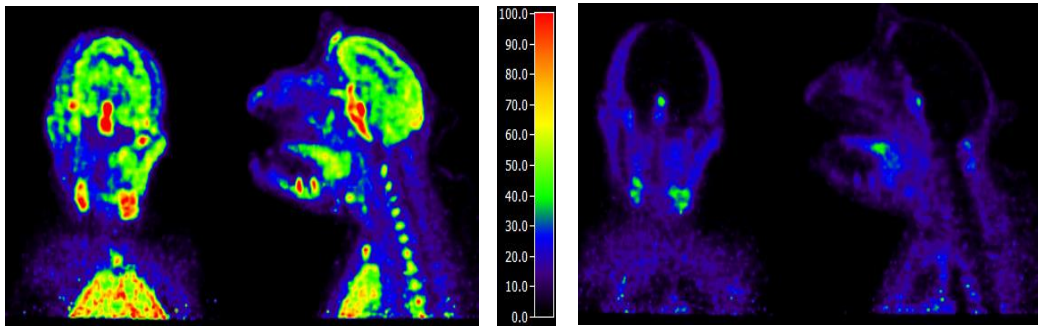
Drug	T790M RR	PFS	Toxicities
AZD9291[1,2]	61%	9.6 (13.5#)	ILD, rash
Rocelitinib[3,4]	~ 30%	?	Hyperglycemia, QTc, cataracts
HM61713[5]	55%	Too early	Palmar Plantar Erythema, rash
ASP8273[6,7]	36%-50%	Too early	Hyponatremia
EGF816[8]	60%	Too early	Rash, diarrhea

#At 80 mg dose, centrally reviewed

[1]Jänne NEJM 2015; [2]Jänne ELCC 2015; [3]Sequist NEJM 2015; [4]Sequist ASCO2015; [5]Park ASCO 2015; [6]Yu et al. ASCO 2015; [7]Goto ASCO 2015; [8]Tan ASCO 2015

Osimertinib (AZD9291) effectively penetrates the brain

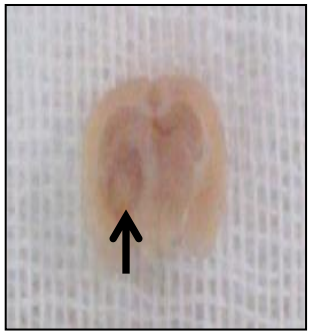
[^{11}C]AZD9291 Radioactivity (kBq / cc) [^{11}C]CO-1686

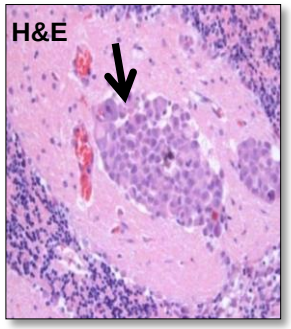


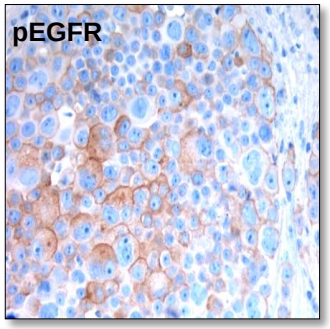
Summation images acquired 5 min up to 2 h after intravenous microdose (<3 μg) injection

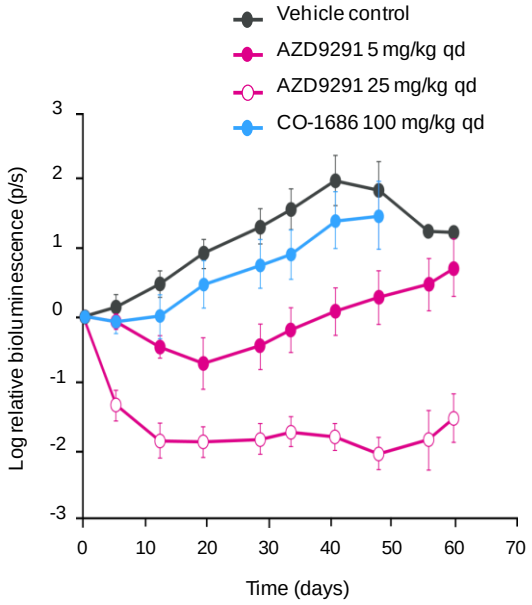
	Brain to blood ratio $AUC_{0-90\ min}$ (corrected for radioactivity in cerebral blood)
[^{11}C]AZD9291 (n=3)[1]	2.6 ± 1.4
[^{11}C]CO-1686 (n=2)[1]	0.025
[^{11}C]gefitinib (n=2)[2]	0.28

Intra carotid injection model of brain metastases using PC9 cells





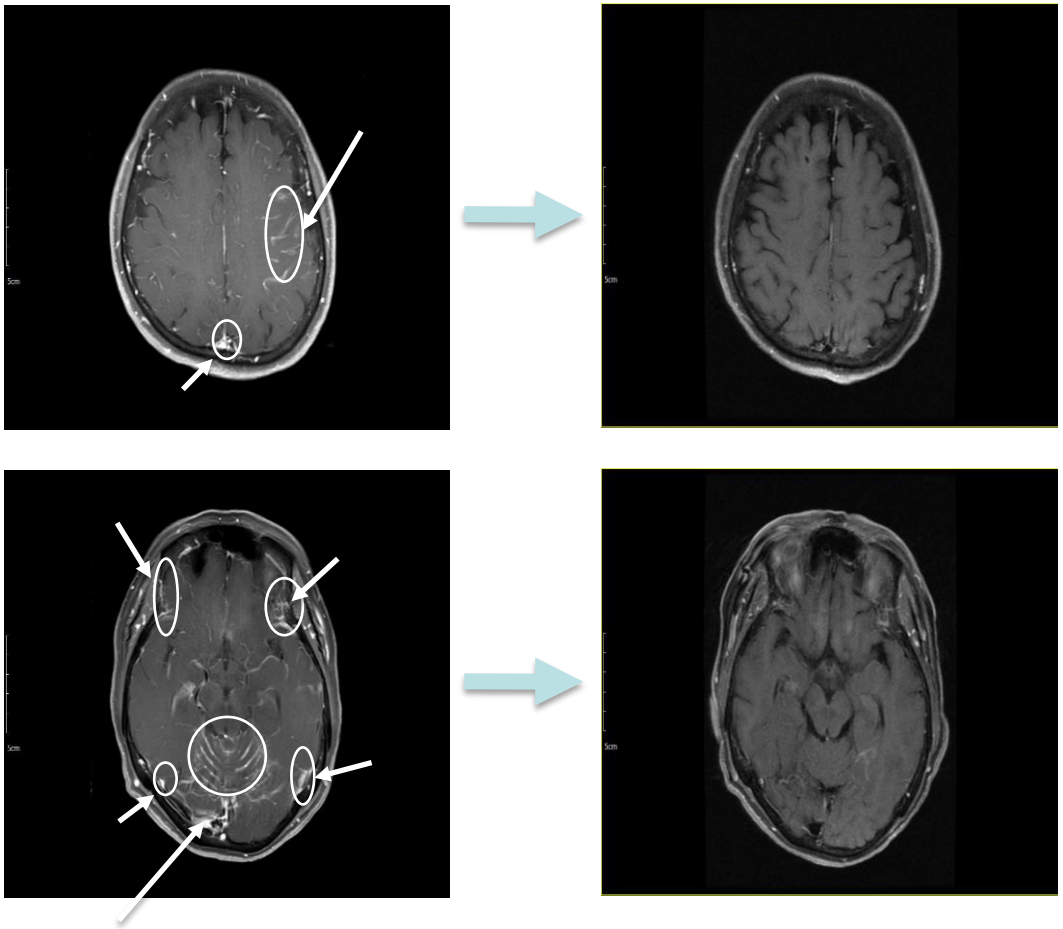


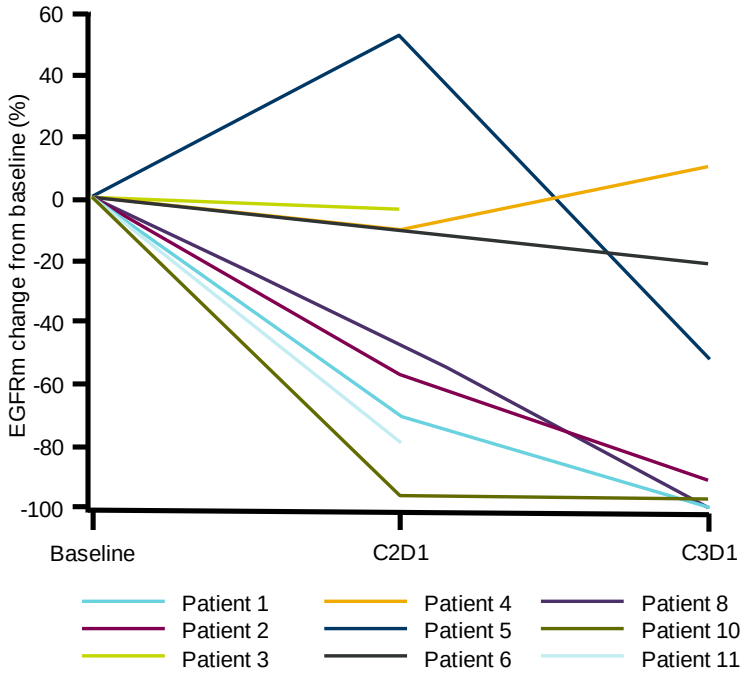


[1]Ballard et al. Presented at WCLC 2015; Mini 10.12; 2. AstraZeneca data on file; AUC, area under the curve; CNS, central nervous system; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily

Osimertinib (AZD9291) is effective clinically in patients with leptomeningeal carcinomatosis

Brain MRI – baseline **Brain MRI – 3 months**



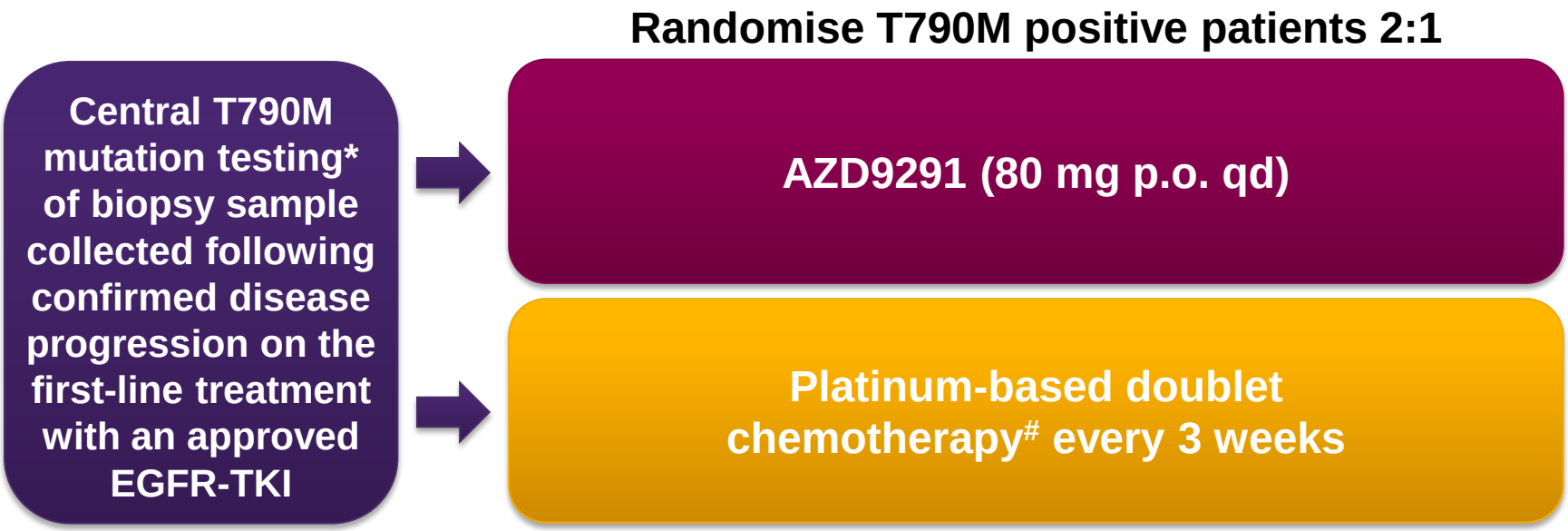


Changes in EGFR mutant copy number in CSF with drug treatment

Presented by Dae Ho Lee at the AACR-NCI-EORTC Congress, 5-9 Nov 2015; abstract PR07.

AURA3 study design

A Phase III, open-label, randomised study to assess the safety and efficacy of AZD9291 vs platinum-based doublet chemotherapy for patients with advanced or metastatic NSCLC whose disease has progressed following treatment with an EGFR-TKI and whose tumours are T790M mutation positive



*cobas® EGFR Mutation Test (Roche Molecular Systems). Tissue and plasma samples will be collected to understand: a) the utility of multiple sample types for the identification of T790M positive tumours, b) the molecular evolution of the disease

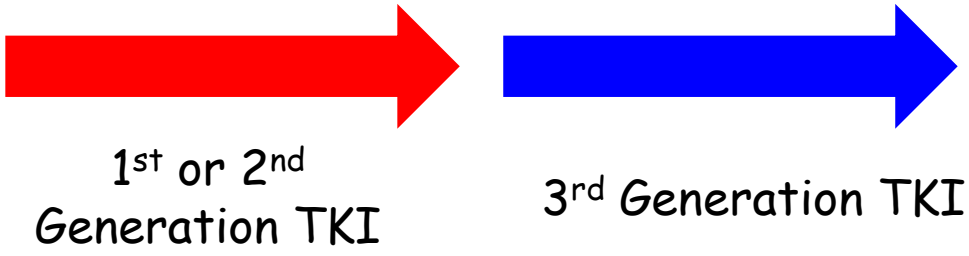
#Pemetrexed 500 mg/m^2 + carboplatin AUC5 or pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; patients may crossover from chemotherapy arm to AZD9291 when they are determined to have disease progression according to RECIST 1.1

NCT02151981, www.clinicaltrials.gov; AstraZeneca. Data on file

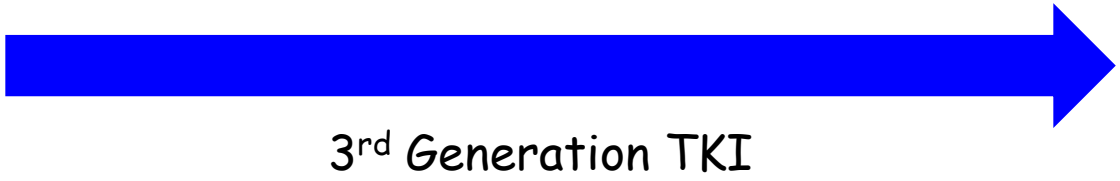
AUC5, area under the plasma concentration–time curve 5 mg/mL^{-1} per minute; EGFRm, EGFR mutation; EGFR-TKI, EGFR tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; p.o., orally; qd, once daily

Current and Potential Future Treatment of EGFR mutant NSCLC

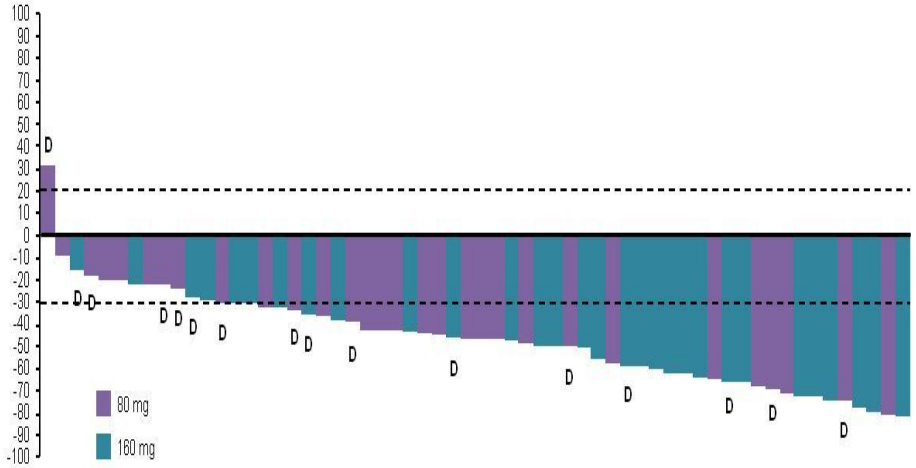
Today

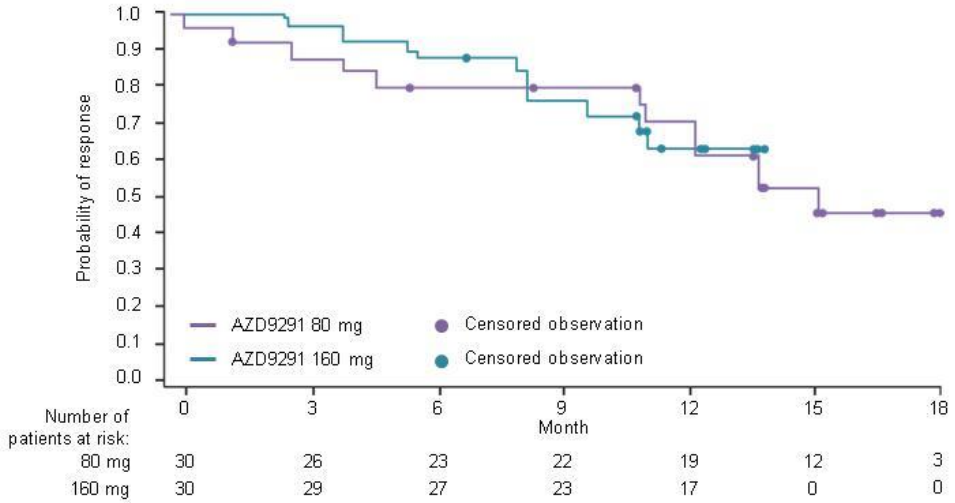


In Clinical Trials



AZD9291 in EGFR TKI naïve EGFR mutant NSCLC

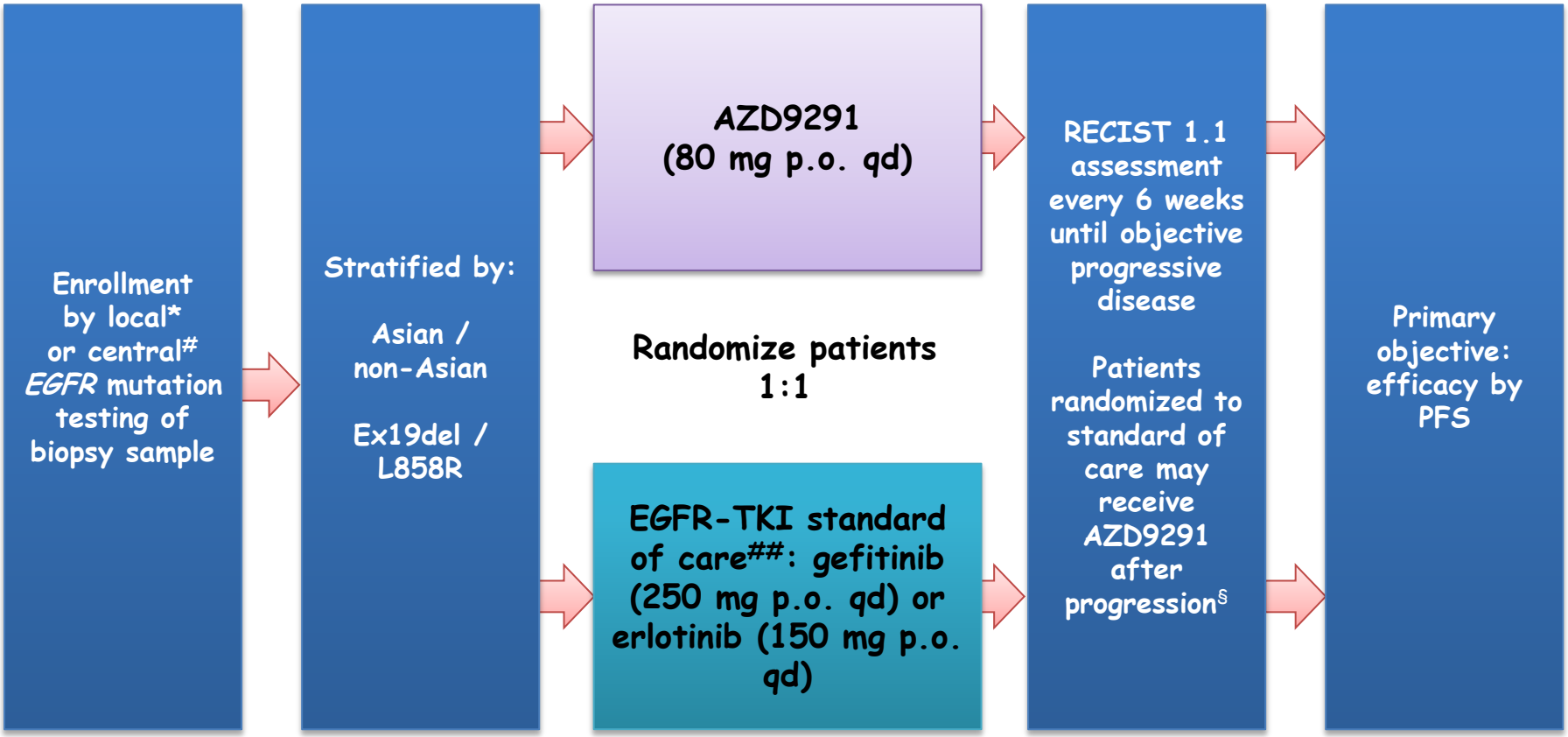




	80 mg N=30	160 mg N=30	Total N=60
Confirmed objective response rate	**67% (95% CI 47, 83)**	**83% (95% CI 65, 94)**	**75% (95% CI 62, 85)**
Disease control rate	93% (95% CI, 78, 99)	100% (95% CI 88, 100)	97% (95% CI 89, 100)
Median PFS, months (95% CI)	NC (12.3, NC) Maturity: 40%	NC (11.1, NC) Maturity: 30%	NC (13.7, NC) Maturity: 35%
Maximum PFS, months	19.2	13.8	19.2
Remaining alive and progression-free,† % (95% CI) 9 months 12 months	 83 (64, 93) 75 (55, 87)	 80 (60, 90) 69 (48, 82)	 81 (69, 89) 72 (58, 82)

Ramalingam et al. IASLC 2015

FLAURA Study Design



*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
§Patients randomized to the standard of care treatment arm may receive open-label treatment with AZD9291 on central confirmation of both objective disease progression and T790M positive tumor
OS, overall survival; PFS2, second progression-free survival (time from randomization to second progression); p.o., orally

TATTON study – ongoing

Part A – Dose escalation (all with acquired resistance to EGFR-TKI)	Part B – Dose expansion (different lines of treatment)
Dose 2 AZD9291 (qd) + durvalumab (q 2 weeks)	
Dose 2 AZD9291 (qd) + durvalumab (q 4 weeks)	EGFR-TKI naïve: AZD9291 + durvalumab
Dose 2 AZD9291 (qd) + durvalumab + tremelimumab (q 4 weeks)	
Dose 2 – continuous AZD9291 (qd) + selumetinib (bid) Asia	Acquired resistance to initial EGFR-TKI, cMET negative: AZD9291 + selumetinib
Dose 2 – continuous AZD9291 (qd) + selumetinib (bid) ROW	Acquired resistance to T790M-directed EGFR-TKI, cMET negative: AZD9291 + selumetinib
Dose 2 – intermittent: 4 days on / 3 days off AZD9291 (qd) + selumetinib (bid) ROW	
	Acquired resistance to initial EGFR-TKI, cMET positive: AZD9291 + savolitinib
Dose 2 AZD9291 (qd) + savolitinib (qd)	
	Acquired resistance to T790M-directed EGFR-TKI, cMET positive: AZD9291 + savolitinib

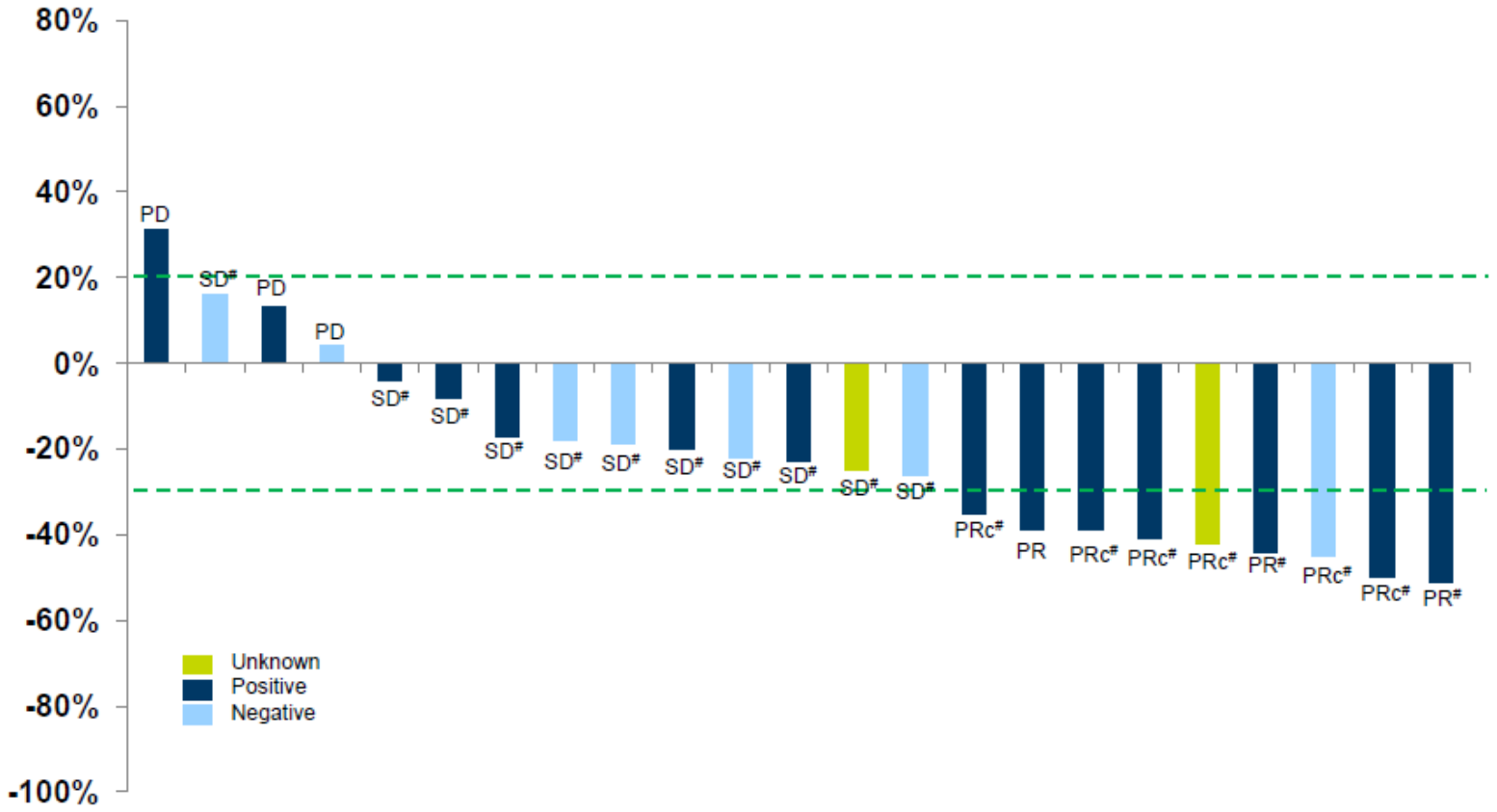
NCT02143466
Sites: USA, Japan, Korea, Taiwan
bid, twice daily, q, every; qd, once daily; ROW, rest of the world

Ongoing & planned combination studies with mutant selective EGFR inhibitors

EGFR Inhibitor	AZD9291	Rociletinib	EGF816
Combination	MEDI4736	Trametinib	INC280 (MET)
	Volitinib (MET)	Pembrolizumab	Nivolumab
	Selumetinib	Atezolizumab	
	Necitumumab	Aurora Kinase	
	Navitoclax		
	MLN0218		

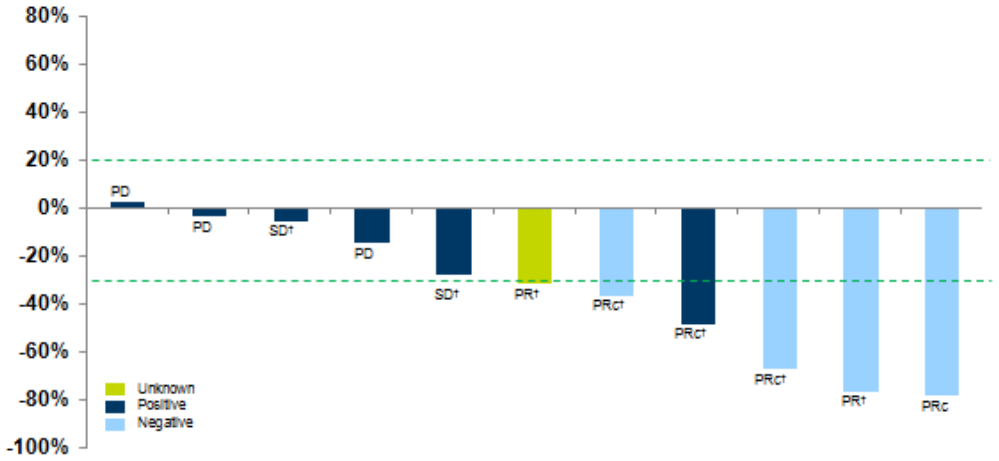
Which combination therapy should be used and when ?

Ongoing phase I trial of AZD9291 & Selumetinib in EGFR mutant lung cancer

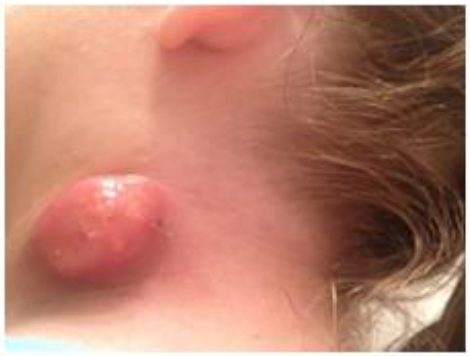


Oxnard et al. ASCO 2015

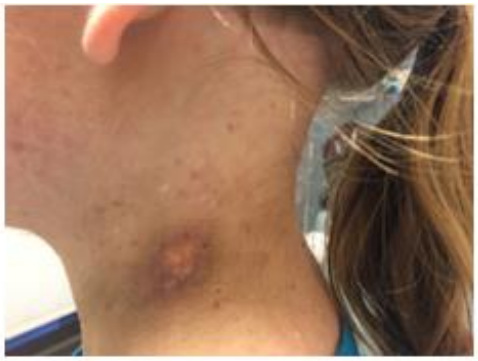
Efficacy of Osimertinib/Savolitinib in EGFR Mutant Lung Cancer



*Population: All patients dosed who had a baseline and 6-week RECIST assessment
†Patients ongoing treatment at data cut off
PD, progressive disease; PR, partial response; PRc, confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease



Pre-treatment



4 weeks

- 32-year-old female with a tumor harboring exon 19 deletion and high MET amplification responds to AZD9291/savolitinib 800 mg

Oxnard et al., *ASCO* 2015

EGFR Management and Resistance

- EGFR TKIs are the standard of care for first line EGFR mutant NSCLC
- Acquired resistance limits successful long term treatment with EGFR TKIs
- Next generation EGFR TKIs are approved or entering clinic
  - Overcome EGFR T790M
  - Better CNS penetration
- Long term success will require combination therapies