First Line Treatment of EGFR Mutant NSCLC – an evolving landscape

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Disclosure Information

Pasi A. Jänne, MD, PhD

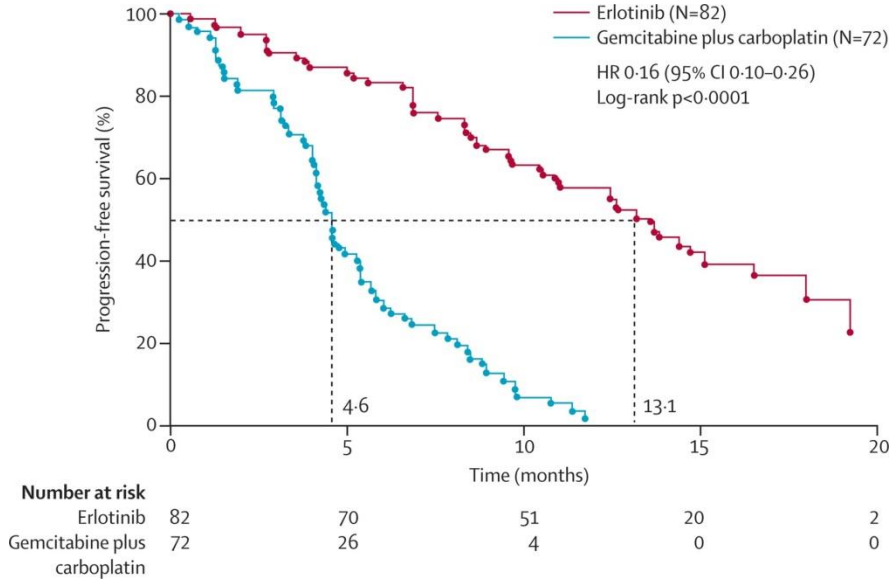
Consultant for: AstraZeneca, Boehringer Ingelheim, Pfizer, Genentech, Roche, Sanofi-Aventis, Clovis Oncology, Chugai Pharmaceuticals, Merrimack Pharmaceuticals

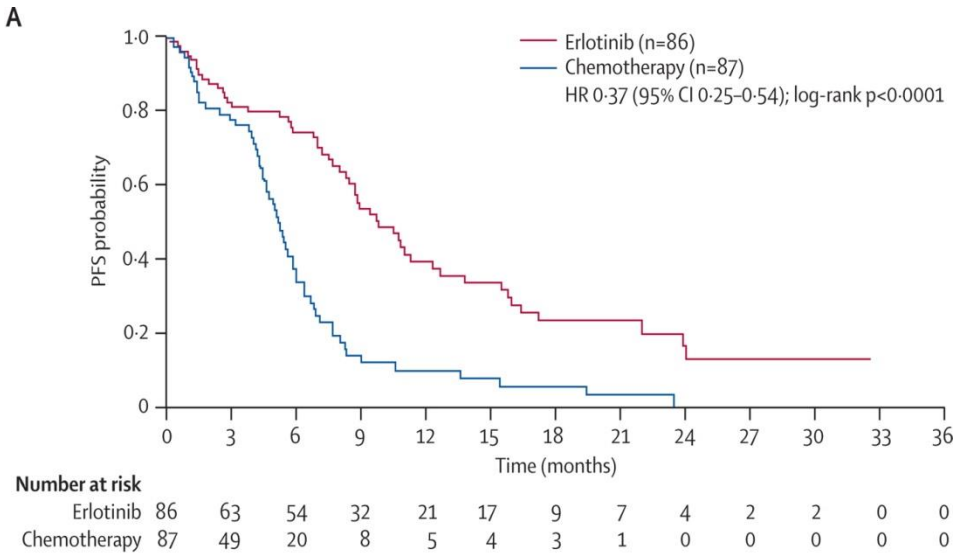
Research Support: Astellas, AstraZeneca

Stockholder : 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

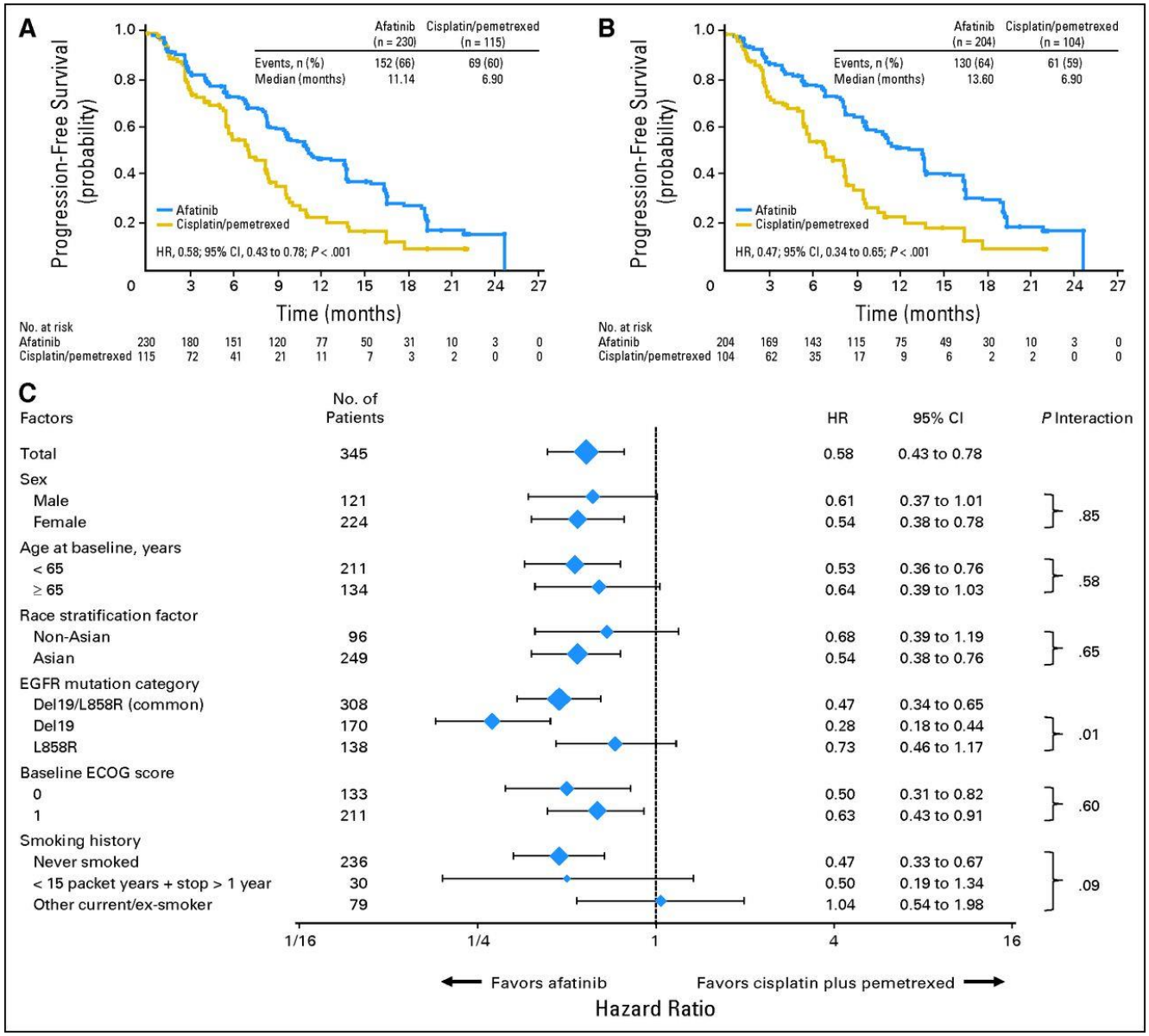
Zhou et al. Lancet Oncol 2011; Rosell et al. Lancet Oncol 2012

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

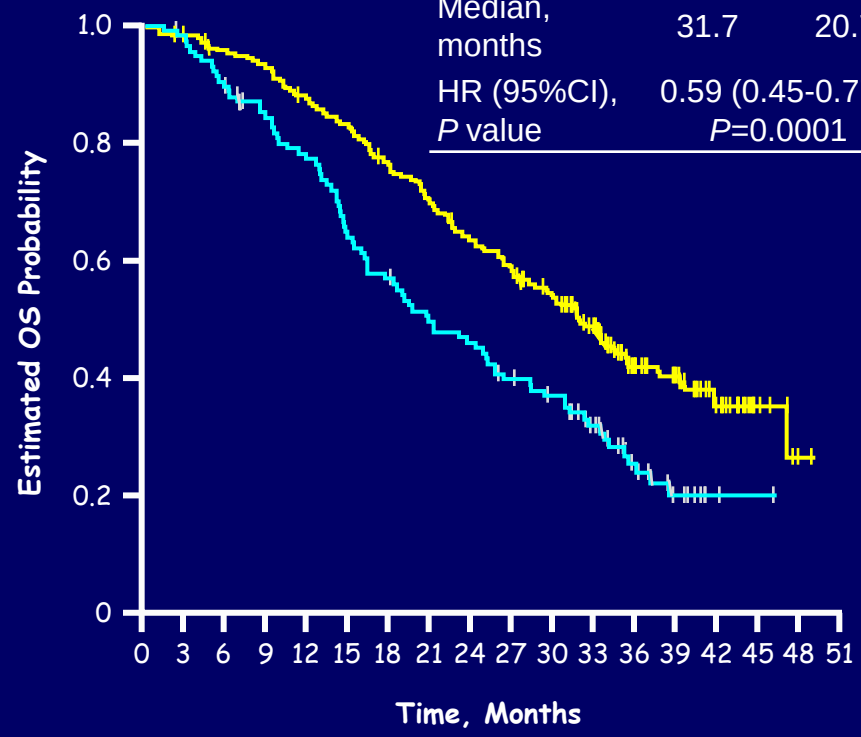
Gefitinib EU Summary of Product Characteristics;
Mitsudomi et al. Lancet Oncol 2010;11:121–1128; Maemondo et al. N Engl J Med 2010;362:2380–2388;
Rosell et al. Lancet Oncol 2012;13:239–246; Zhou et al. J Clin Oncol 2012;30: Abs 7520;
Sequist et al. J Clin Oncol 2013;31:3327–3334; Wu et al. Lancet Oncol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

Phase III Trial of Afatinib vs. Chemotherapy as initial treatment of EGFR mutant NSCLC



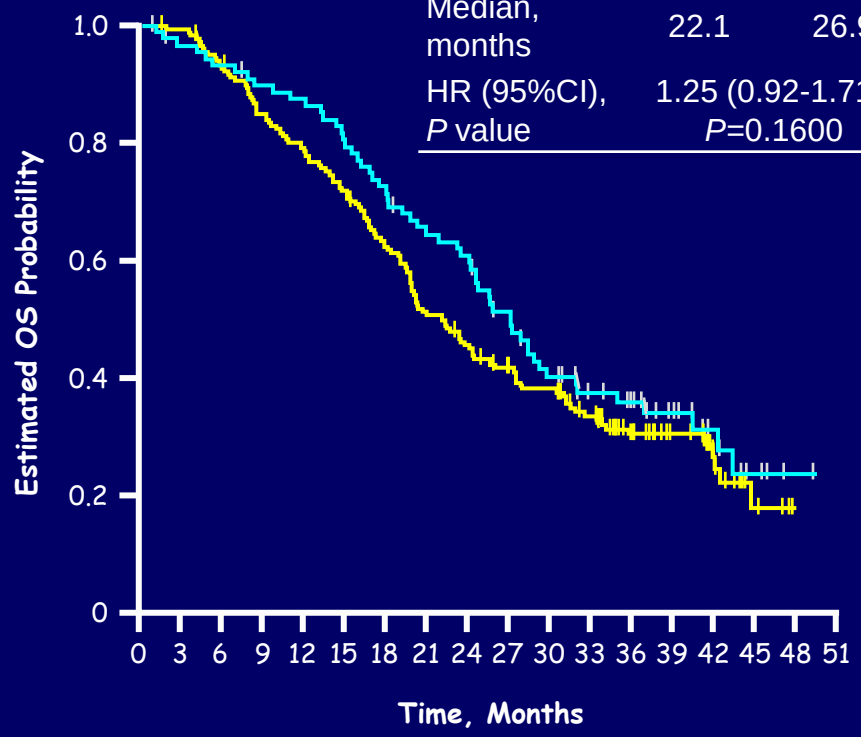
Sequist et al. JCO 2013;31:3327-3334

LUX-Lung 3 and 6: OS Based on Mutation Type – Combined Analysis



Del19	Afatinib (n=236)	Chemo (n=119)
Median, months	31.7	20.7
HR (95%CI), *P* value	0.59 (0.45-0.77), *P*=0.0001	

No of patients																	
Afatinib	236	230	223	217	202	192	173	160	145	131	117	90	50	38	22	6	1	0
Chemo	119	113	103	95	87	72	63	55	51	43	38	27	14	9	1	1	0	0



L858R	Afatinib (n=183)	Chemo (n=93)
Median, months	22.1	26.9
HR (95%CI), *P* value	1.25 (0.92-1.71), *P*=0.1600	

No of patients																	
Afatinib	183	181	167	154	141	128	111	91	80	70	64	51	27	20	11	3	0	0
Chemo	93	86	82	78	75	69	61	55	50	40	32	25	20	14	9	4	1	0

Yang, et al. Lancet Oncology 2015

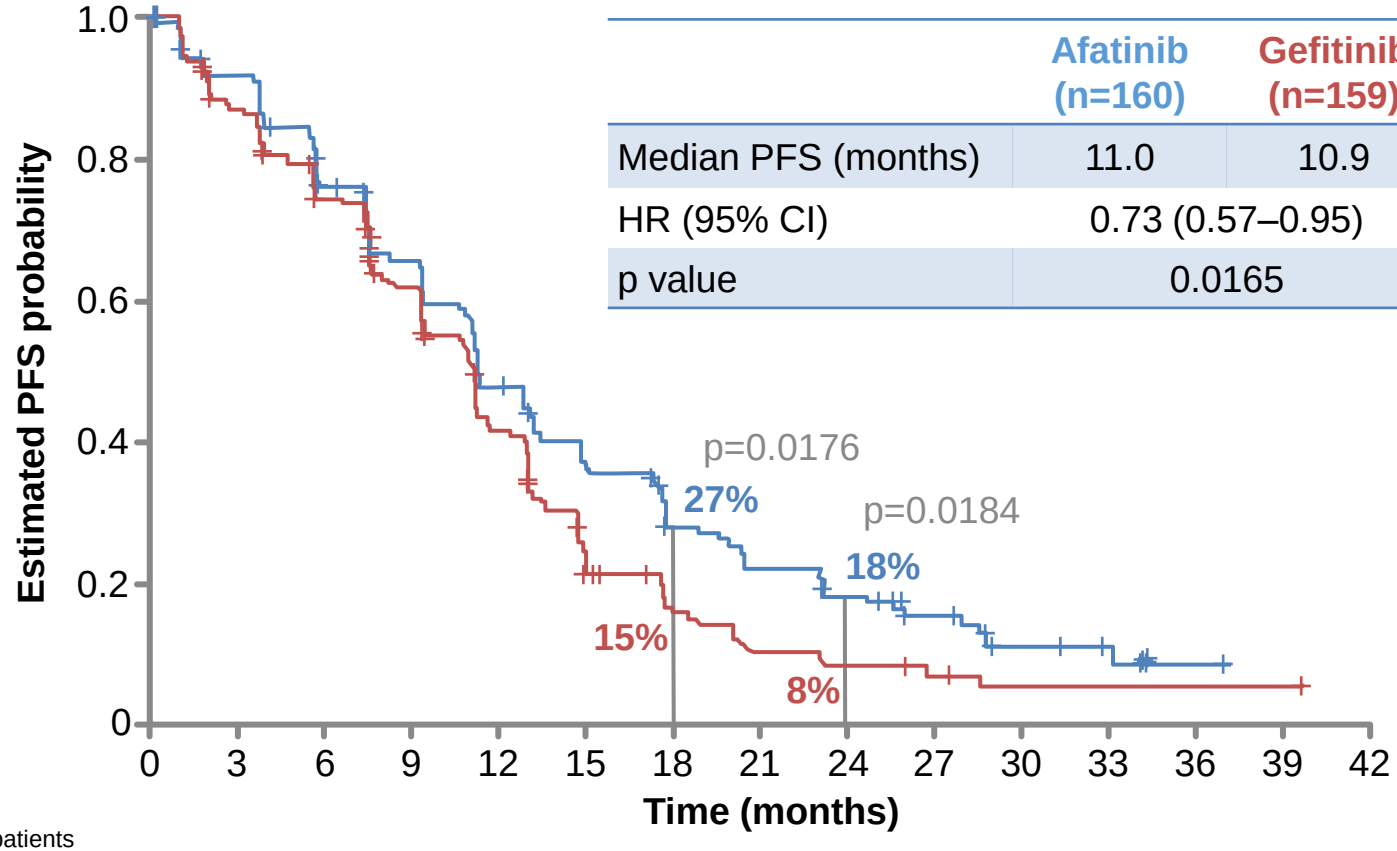
Approved EGFR TKIs

- EGFR mutant; treatment naïve
  - gefitinib, erlotinib, afatinib, icotinib (China)
- Previously treated (non-genotyped)
  - Erlotinib
- EGFR Inhibitor resistant; T790M
  - Osimertinib (US)

Choice of First Line EGFR TKIs

- Balance of efficacy vs. toxicity
- Does choice of first line EGFR TKI impact subsequent treatment ?
  - Are mechanisms of acquired resistance the same as with gefitinib/erlotinib ?
- Cost and convenience

LUX-Lung 7: PFS by Independent Review

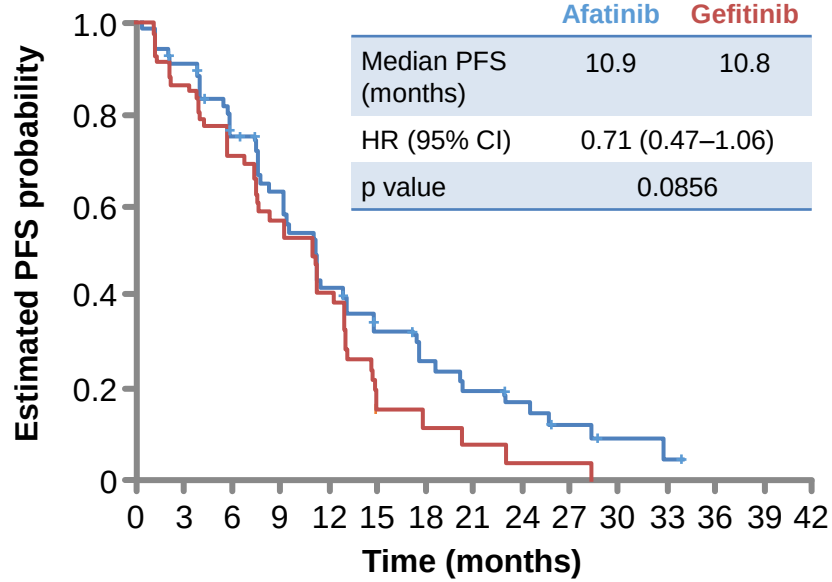


	Afatinib (n=160)	Gefitinib (n=159)
Median PFS (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	

No. of patients															
Afatinib	160	142	112	94	67	47	34	27	21	13	6	3	1	0	0
Gefitinib	159	132	106	83	52	22	14	9	7	5	3	3	1	1	0

Park et al., ESMO Asia 2015

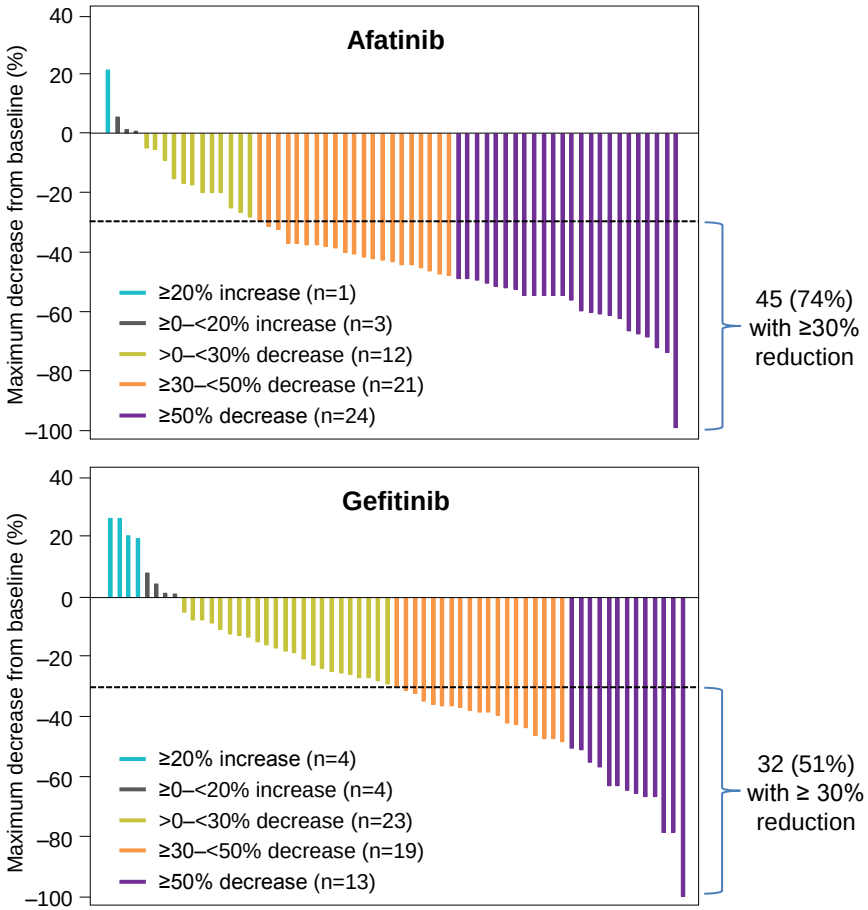
Efficacy in patients with L858R mutation



	Afatinib	Gefitinib
Median PFS (months)	10.9	10.8
HR (95% CI)	0.71 (0.47–1.06)	
p value	0.0856	

No. of patients

Afatinib	67	59	45	36	24	16	12	9	7	4	2	1	0	0	0
Gefitinib	66	56	42	30	20	5	3	2	1	1	0	0	0	0	0



Exon 19 deletion: ORR (73% vs 66%)

L858R: ORR (66% vs 42%)

Park et al., ESMO Asia 2015

LUX-Lung 7:Overall summary of AEs

Events, %	Afatinib (n=160)	Gefitinib (n=159)
Any AE	98.8	100.0
Drug-related AEs	97.5	96.2
AEs leading to dose reduction*	41.9	1.9*
Drug-related AEs leading to discontinuation	6.3	6.3
Serious AEs	44.4	37.1
Drug-related serious AEs	10.6	4.4†
Drug-related fatal AE	-	0.6‡

*No dose reductions foreseen for gefitinib according to prescribing information
†Including four patients with drug-related ILD (no drug-related ILD on afatinib)
‡One patient died of hepatic failure

AE, adverse event; ILD, interstitial lung disease

Park et al., ESMO Asia 2015

LUX-Lung 7:Drug-related AEs (>10%)

	Afatinib (n=160)		Gefitinib (n=159)	
AE category, %	**All**	**Grade 3**	**All**	**Grade 3**
Diarrhea	90.0	11.9*	61.0	1.3
Rash/acne†	88.8	9.4	81.1	3.1
Stomatitis†	64.4	4.4	23.9	-
Paronychia†	55.6	1.9	17.0	0.6
Dry skin	32.5	-	37.1	-
Pruritus	23.1	-	22.6	-
Fatigue†	20.6	5.6	14.5	-
Decreased appetite	16.3	0.6	11.9	-
Nausea	16.3	1.3	13.8	-
Alopecia	10.6	-	15.1	-
Vomiting	10.6	-	3.8	0.6
ALT increased	9.4	-	23.9	7.5‡
AST increased	6.3	-	20.8	2.5

*Plus 1 case of grade 4 diarrhea
†Grouped terms of AEs
‡Plus 1 case of grade 4 increased ALT
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Park et al., ESMO Asia 2015

Choice of First Line EGFR TKIs

- Balance of efficacy vs. toxicity
- Does choice of first line EGFR TKI impact subsequent treatment ?
  - Are mechanisms of acquired resistance the same as with gefitinib/erlotinib ?
- Cost and convenience

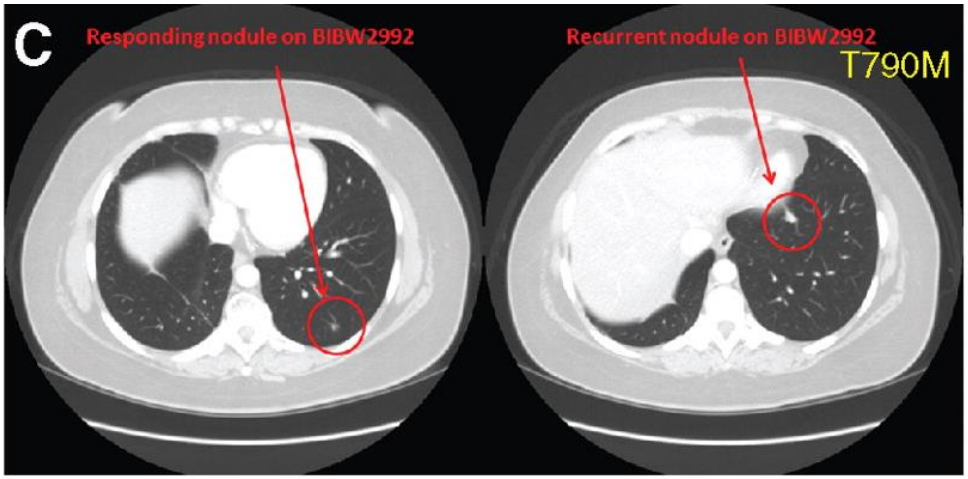
EGFR T790M also occurs as a resistance mechanism to afatinib

Molecular Cancer Therapeutics

Molecular Medicine in Practice

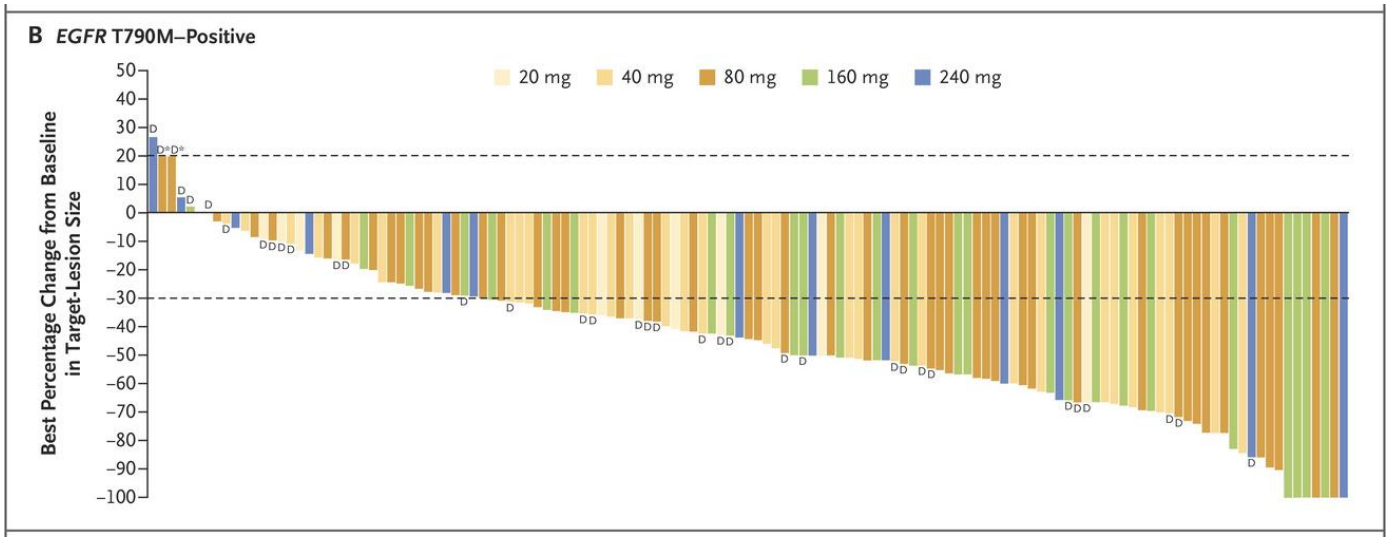
The *EGFR* T790M Mutation in Acquired Resistance to an Irreversible Second-Generation EGFR Inhibitor

Youngwook Kim[1], Jeonghun Ko[1], ZhengYun Cui[1], Amir Abolhoda[3], Jin Seok Ahn[2], Sai-Hong Ou[3], Myung-Ju Ahn[1,2], and Keunchil Park[1,2]



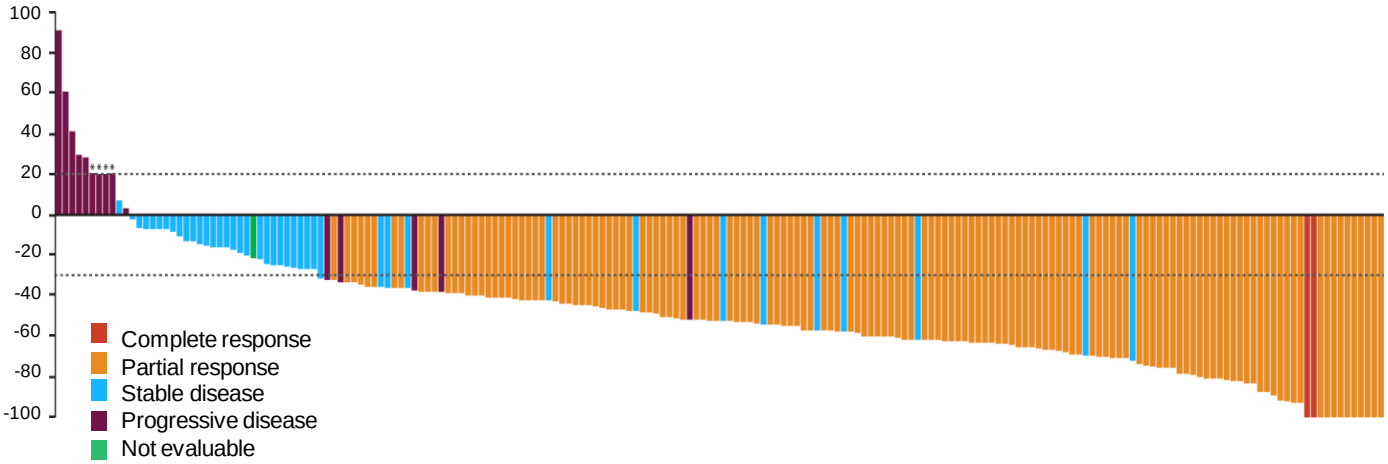
Kim Y et al. Mol Cancer Ther 2012;11:784-791

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)

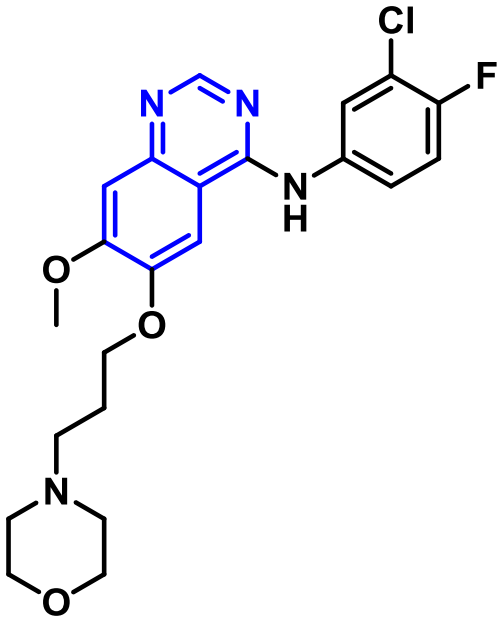
Jänne et al. NEJM 2015; Mitsudomi et al. IASLC 2015

Choice of First Line EGFR TKIs

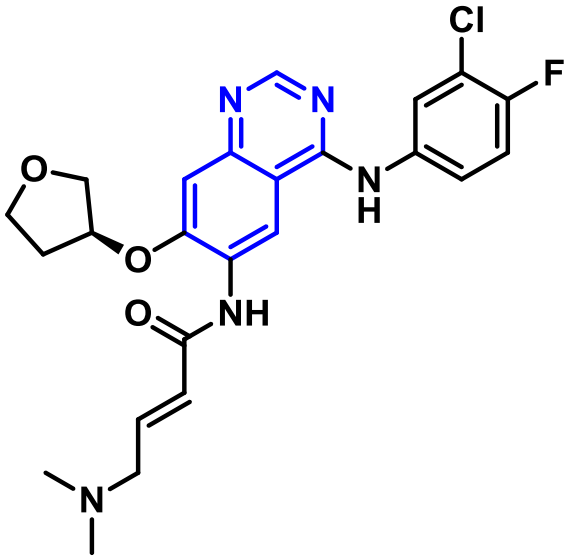
- Balance of efficacy vs. toxicity
- Does choice of first line EGFR TKI impact subsequent treatment ?
  - Are mechanisms of acquired resistance the same as with gefitinib/erlotinib ?
- Cost and convenience

Have we maximized the clinical benefits from single agent quinazoline based EGFR inhibitors ?

Activity Profiles of EGFR Inhibitors



Gefitinib



Afatinib

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

ARCHER 1050: First-line Dacomitinib vs. Gefitinib (Phase 3)

Key eligibility:
- Stage IIIb/IV NSCLC
- EGFR-activating mutation
- ECOG PS 0/1

RANDOMIZE

Dacomitinib 45 mg QD

Gefitinib 250 mg QD

Primary endpoint:
- PFS

Secondary endpoints:
- OS
- OS at 30 months
- PFS by investigator assessment
- Response
- Safety
- PROs

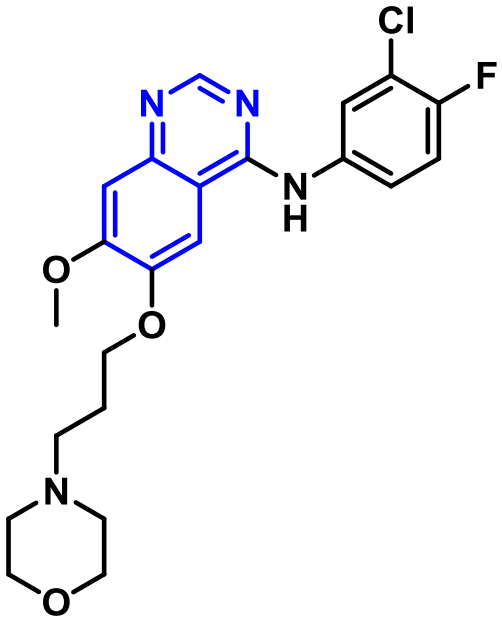
Stratification:
- Race
- EGFR-mutation status (19 vs. 21)

N= 440

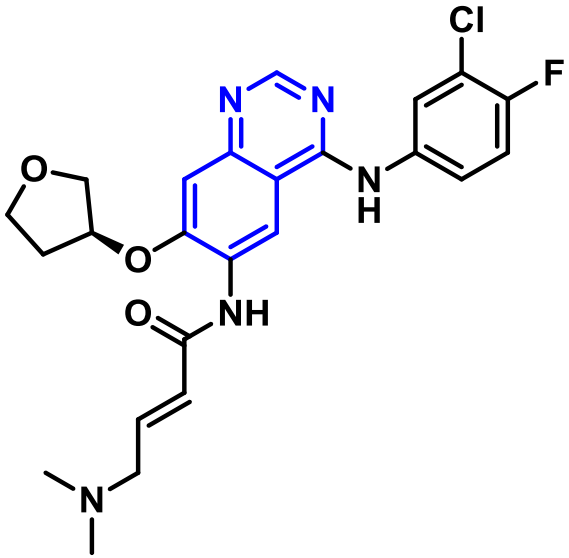
* Per blinded IRC review. Ha: HR≤ 0.667(50%↑)

www.clinicaltrials.gov: NCT01774721

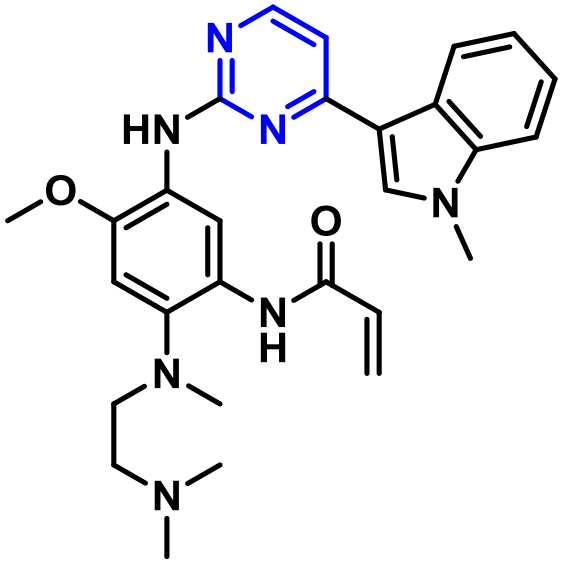
Activity Profiles of EGFR Inhibitors



Gefitinib



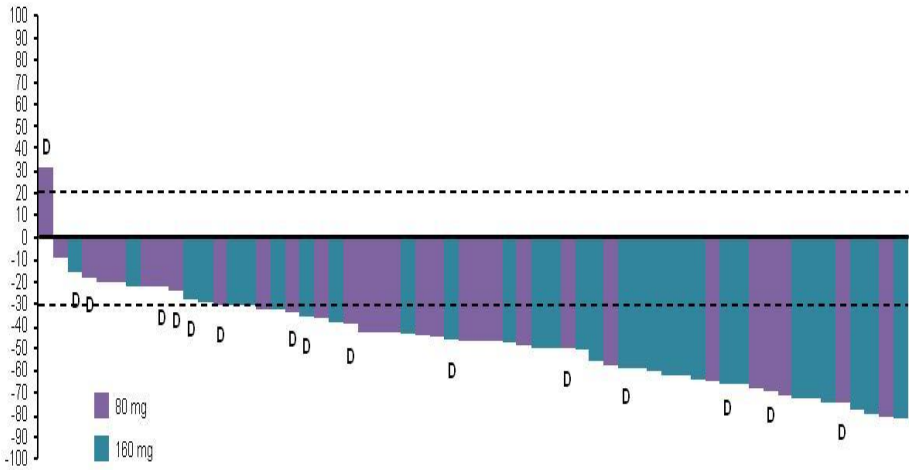
Afatinib

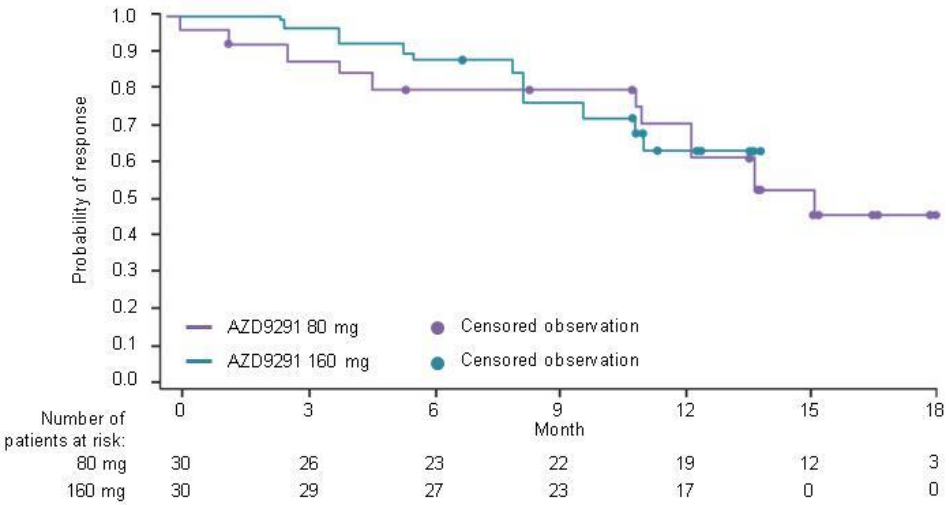


Osimertinib

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

Osimertinib in EGFR TKI naïve EGFR mutant NSCLC

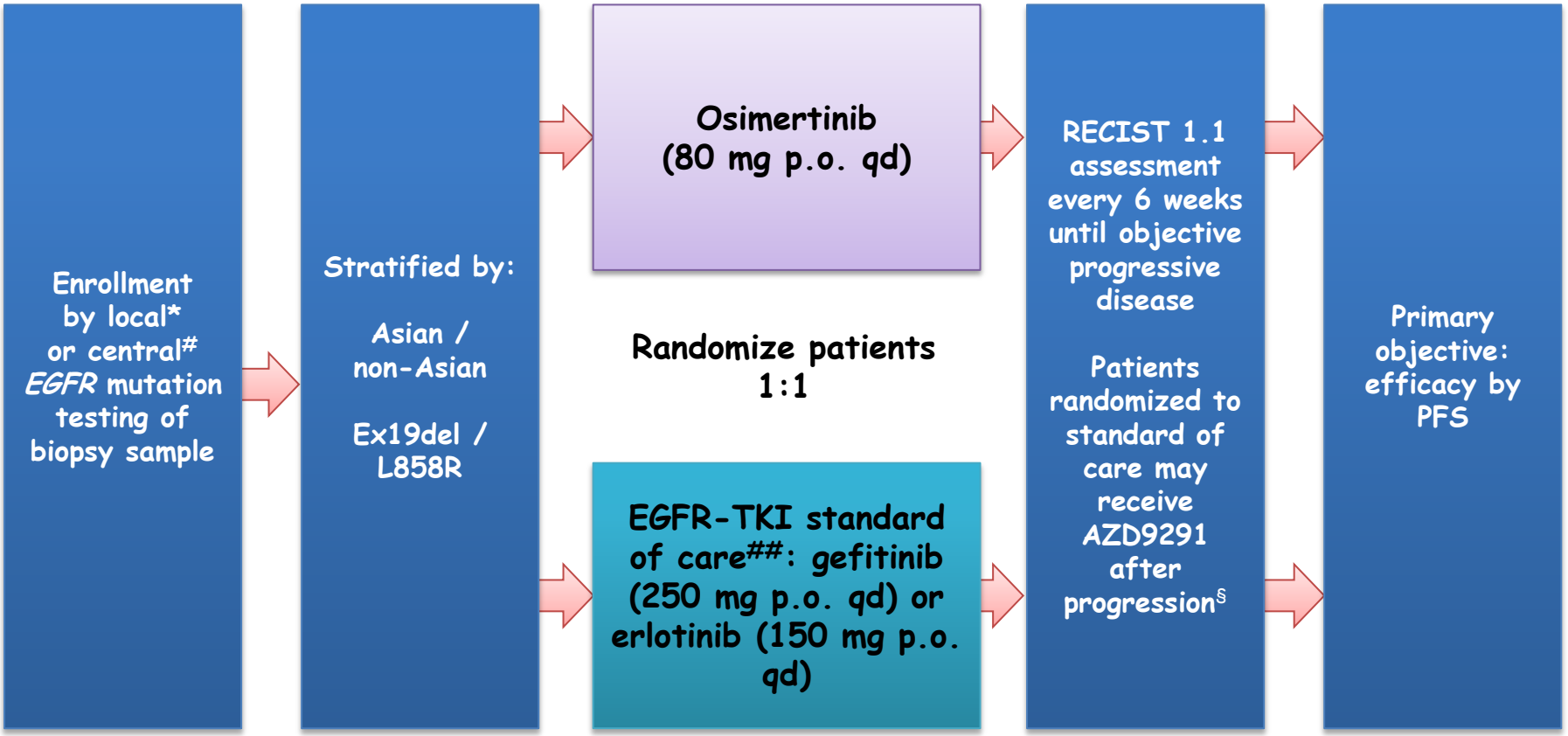




	80 mg N=30	160 mg N=30	Total N=60
Confirmed objective response rate	**67% (95% CI 47, 83)**	**83% (95% CI 65, 94)**	**75% (95% CI 62, 85)**
Disease control rate	93% (95% CI, 78, 99)	100% (95% CI 88, 100)	97% (95% CI 89, 100)
Median PFS, months (95% CI)	NC (12.3, NC) Maturity: 40%	NC (11.1, NC) Maturity: 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

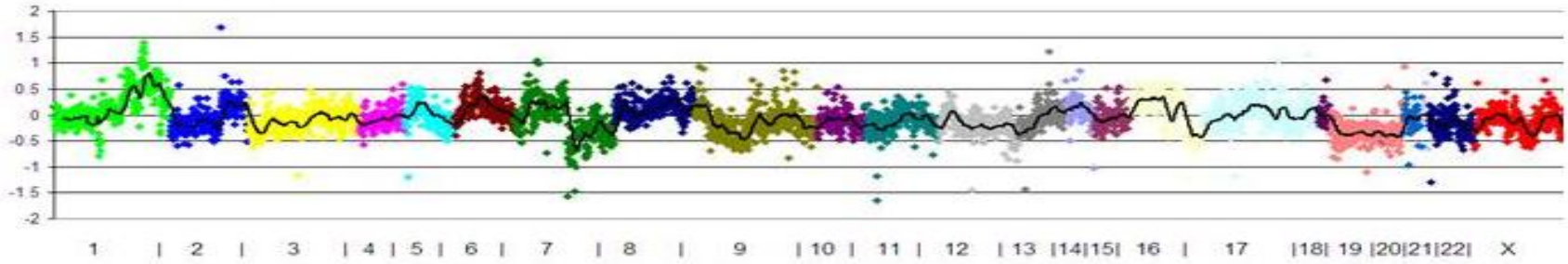
How do we move forward to improve the outcome of patients with EGFR mutant lung cancer ?

Are EGFR mutant cancers a homogenous disease ?

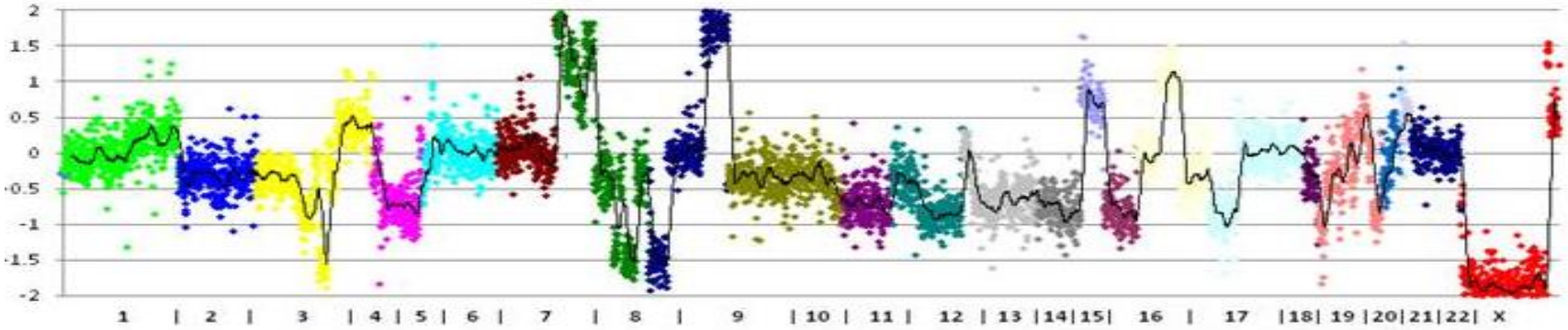
EGFR L858R or Exon 19 deletion

Concurrent mutations
Tumor suppressor alterations
Copy number changes

A tale of two (EGFR L858R) patients

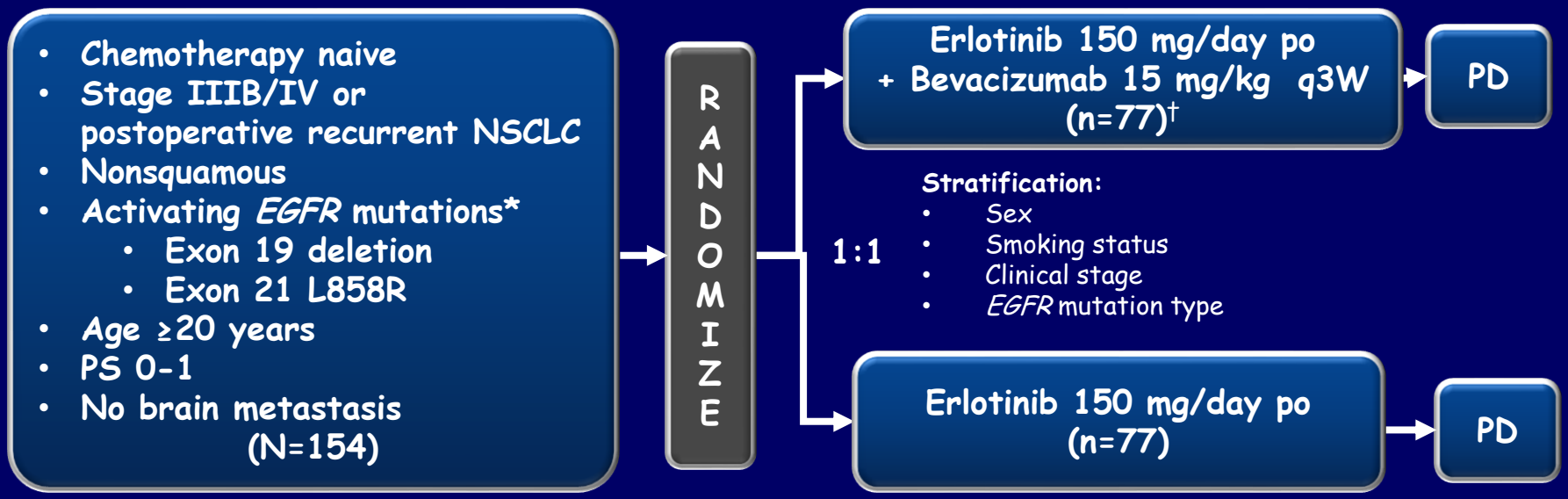


53 yo Asian male light smoker (1 pack year) with no significant past medical history



65 yo Asian male never-smoker with no significant past medical history

Phase II A+T Study: Erlotinib ± Bevacizumab in *EGFR* Mutation–Positive NSCLC – Study Design



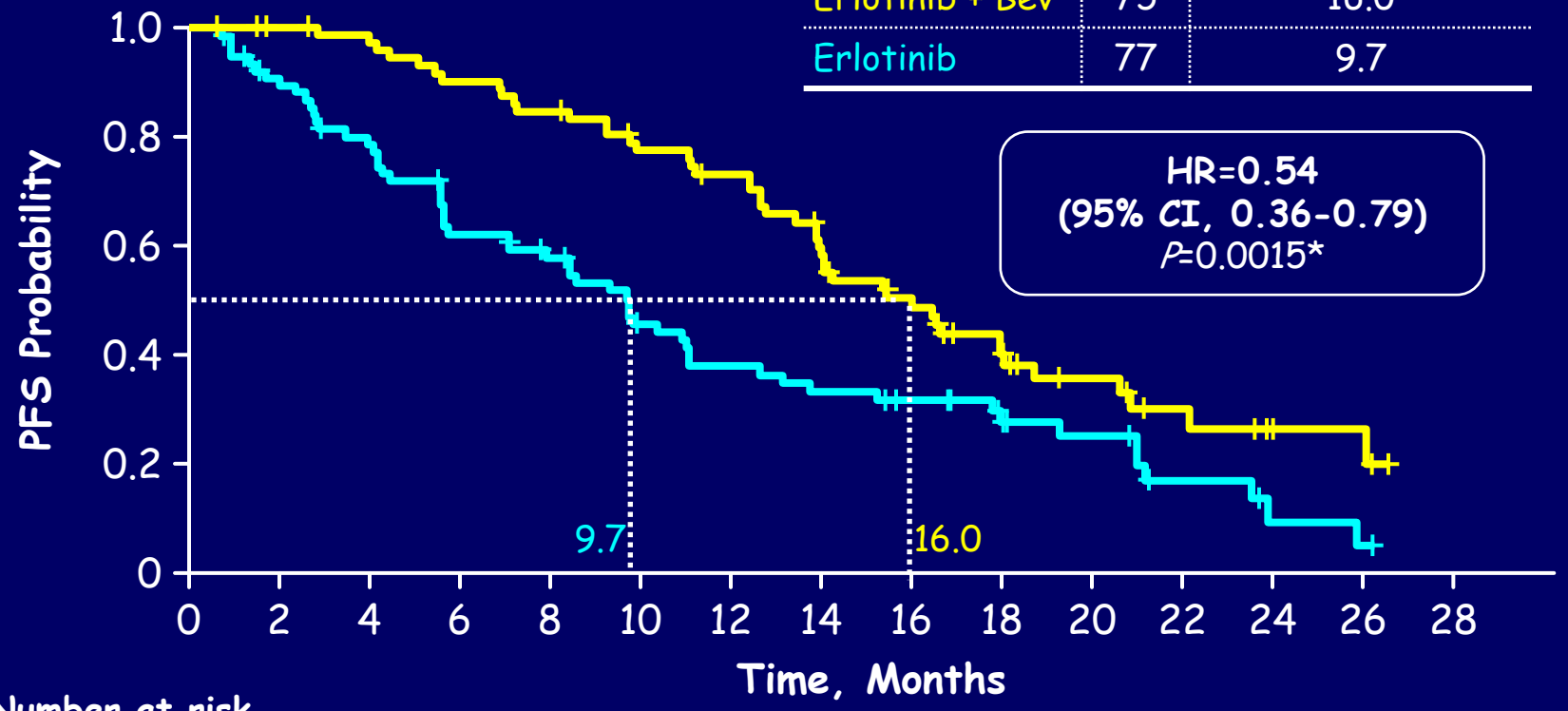
Primary endpoint: PFS (RECIST v1.1, independent review)
Secondary endpoints: OS, tumor response, QOL, safety
Correlative research: biomarker assessment

*T790M excluded.
†2 patients withdrew before treatment.

Seto et al. Lancet Oncology 2014

Erlotinib vs. Erlotinib/Bevacizumab: PFS

	n	Median, Months
Erlotinib + Bev	75	16.0
Erlotinib	77	9.7



Number at risk

E+B	75	72	69	64	60	53	49	38	30	20	13	8	4	4	0
E	77	66	57	44	39	29	24	21	18	12	10	5	2	1	0

*Log-rank test, two-sided.

Seto et al. Lancet Oncology 2014

LUX-Lung 7 Conclusions

- Afatinib remains a choice as a first line EGFR TKI for EGFR mutant NSCLC

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- Afatinib remains a choice as a first line EGFR TKI for EGFR mutant NSCLC
- Choice of first line EGFR TKI therapy must balance efficacy with toxicity
- Therapeutic landscape is evolving
  - Structurally divergent EGFR inhibitors
  - Combination therapies

LUX-Lung 7 Conclusions

- Afatinib remains a choice as a first line EGFR TKI for EGFR mutant NSCLC
- Choice of first line EGFR TKI therapy must balance efficacy with toxicity
- Therapeutic landscape is evolving
  - Structurally divergent EGFR inhibitors
  - Combination therapies
- Develop most effective/tolerable strategy to prevent/delay resistance