EGFR T790M Inhibitors

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Disclosure Information

Pasi A. Jänne, MD, PhD

Consultant for: Astra Zeneca, Boehringer Ingelheim, Pfizer, Genentech/Roche, Chugai Pharmaceuticals, Merrimack Pharmaceuticals, Ariad, Ignyta, LOXO Oncology

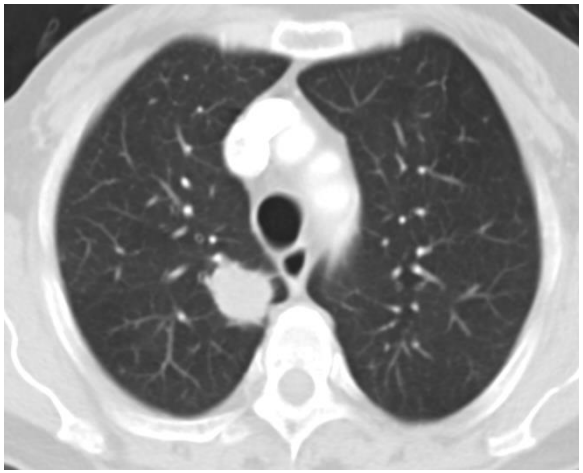
Research Support: Astellas, AstraZeneca, Daiichi-Sankyo, PUMA

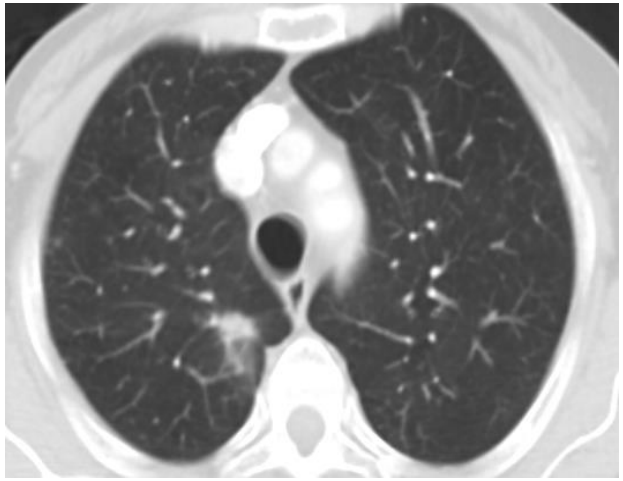
Stockholder in: Gatekeeper Pharmaceuticals

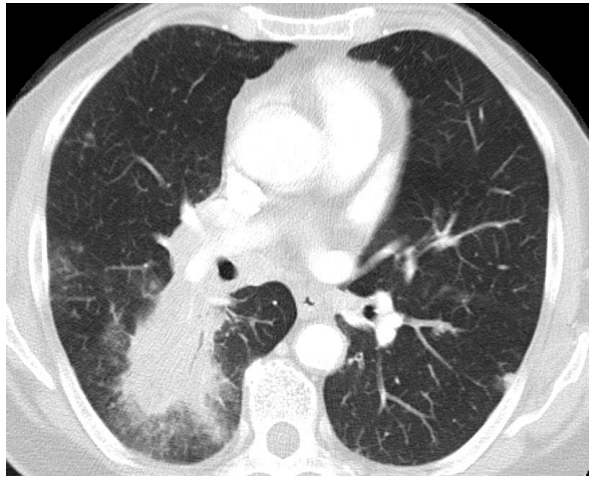
Other: LabCorp – post-marketing royalties from DFCI owned intellectual property on EGFR mutations

Acquired Resistance to Erlotinib

Erlotinib







Diagnosis

EGFR Exon 19 del

3 months

20 months

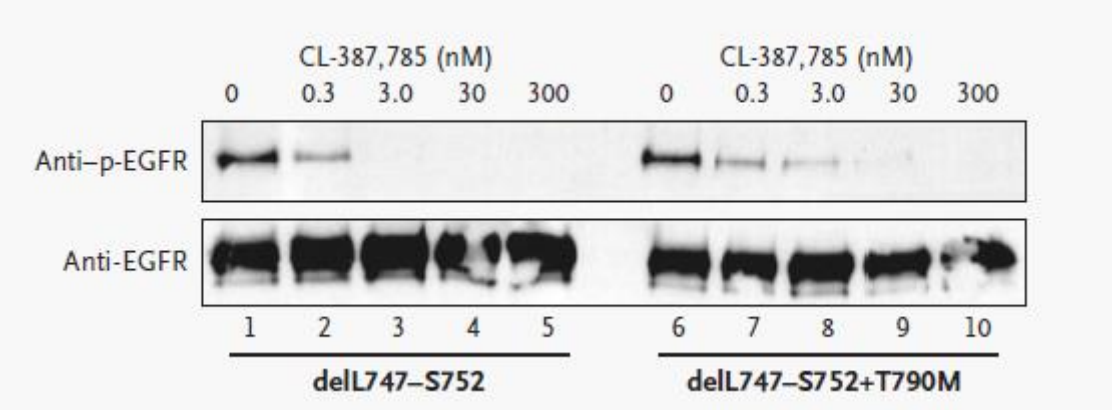
EGFR Exon 19 del
& T790M

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.

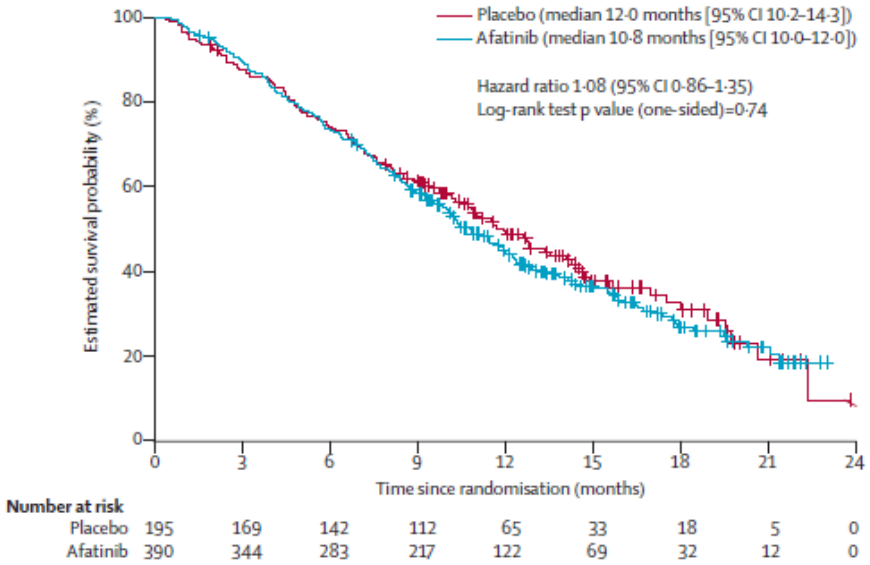


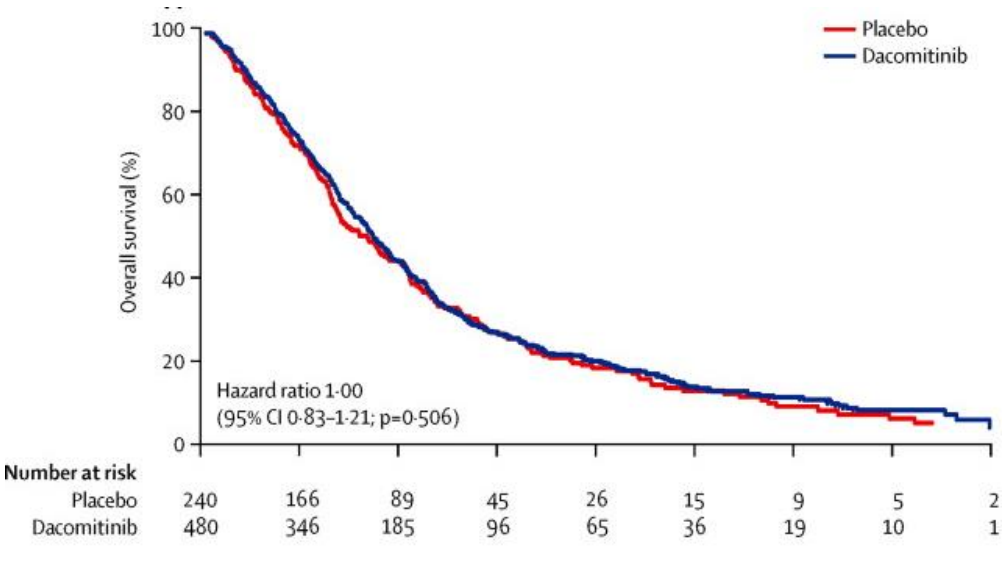
Mechanism: EGFR T790M increases ATP affinity

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 Lung 1 – Afatinib vs Placebo

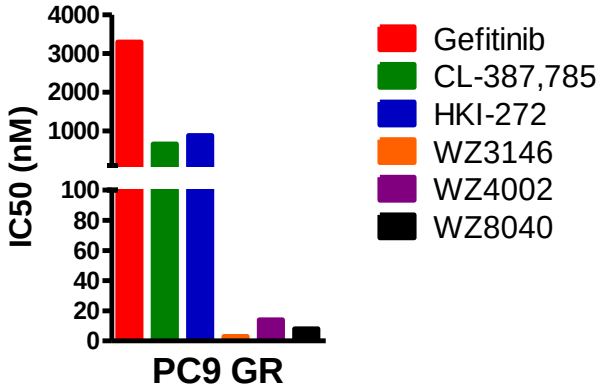
PFS: 3.3 vs. 1.1 months
RR < 10%

BR.26 – Dacomitinib vs Placebo

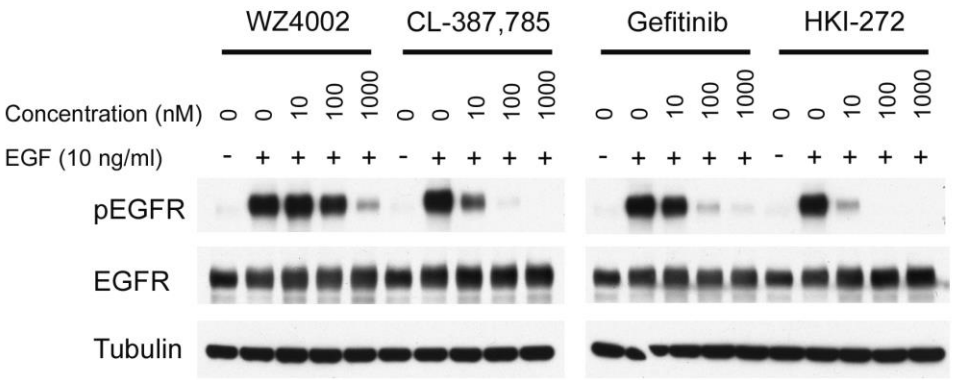
PFS: 2.7 vs. 1.4 months
RR < 10%

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

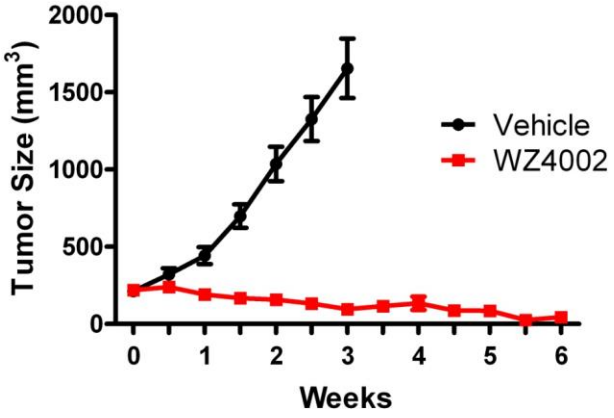
Properties of Mutant Selective EGFR Inhibitors



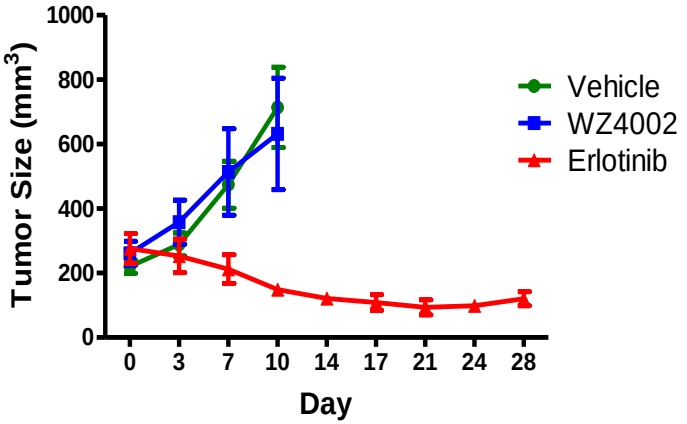
Increased potency in T790M bearing models compared to current clinical agents



Less effective against WT EGFR



PC9 GR (EGFR Del19/T790M)

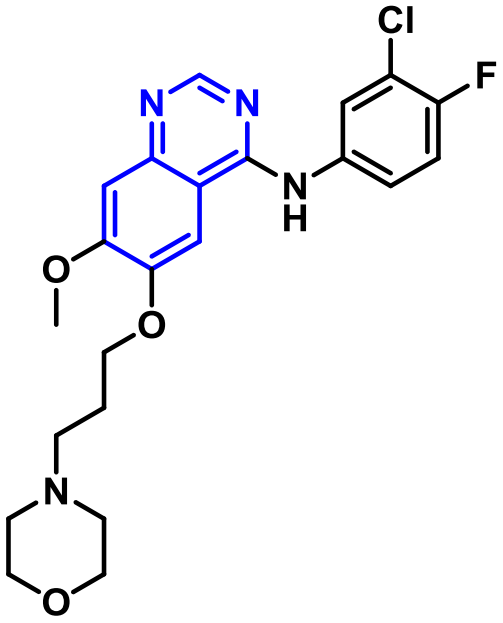


A431 (EGFR WT; amplified)

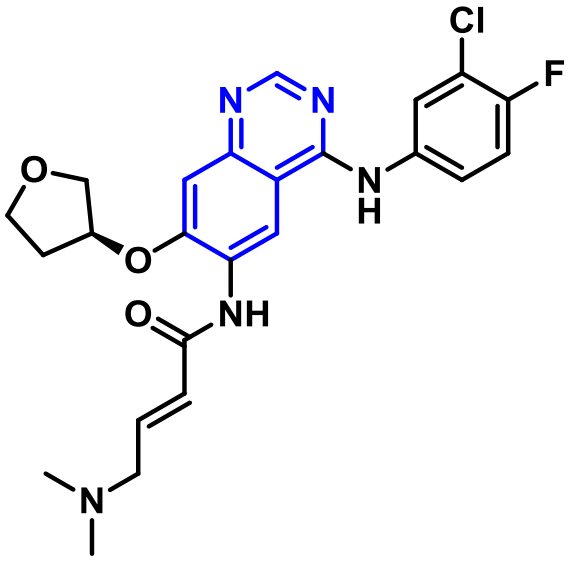
Zhou et al. Nature 2009

Potent and Mutant Selective in vivo

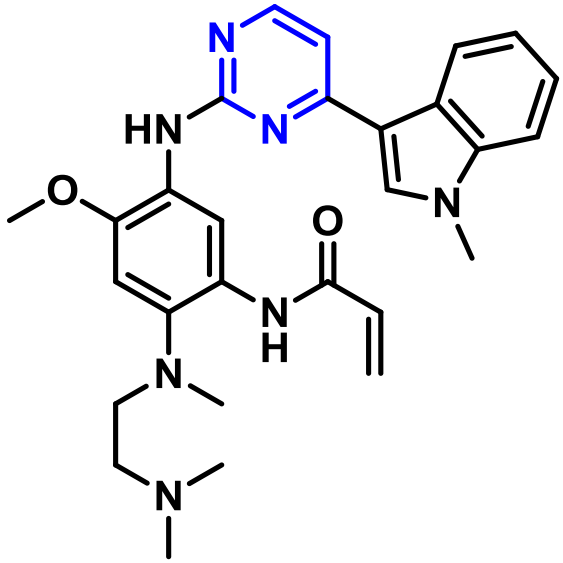
Activity Profiles of EGFR Inhibitors



Gefitinib



Afatinib

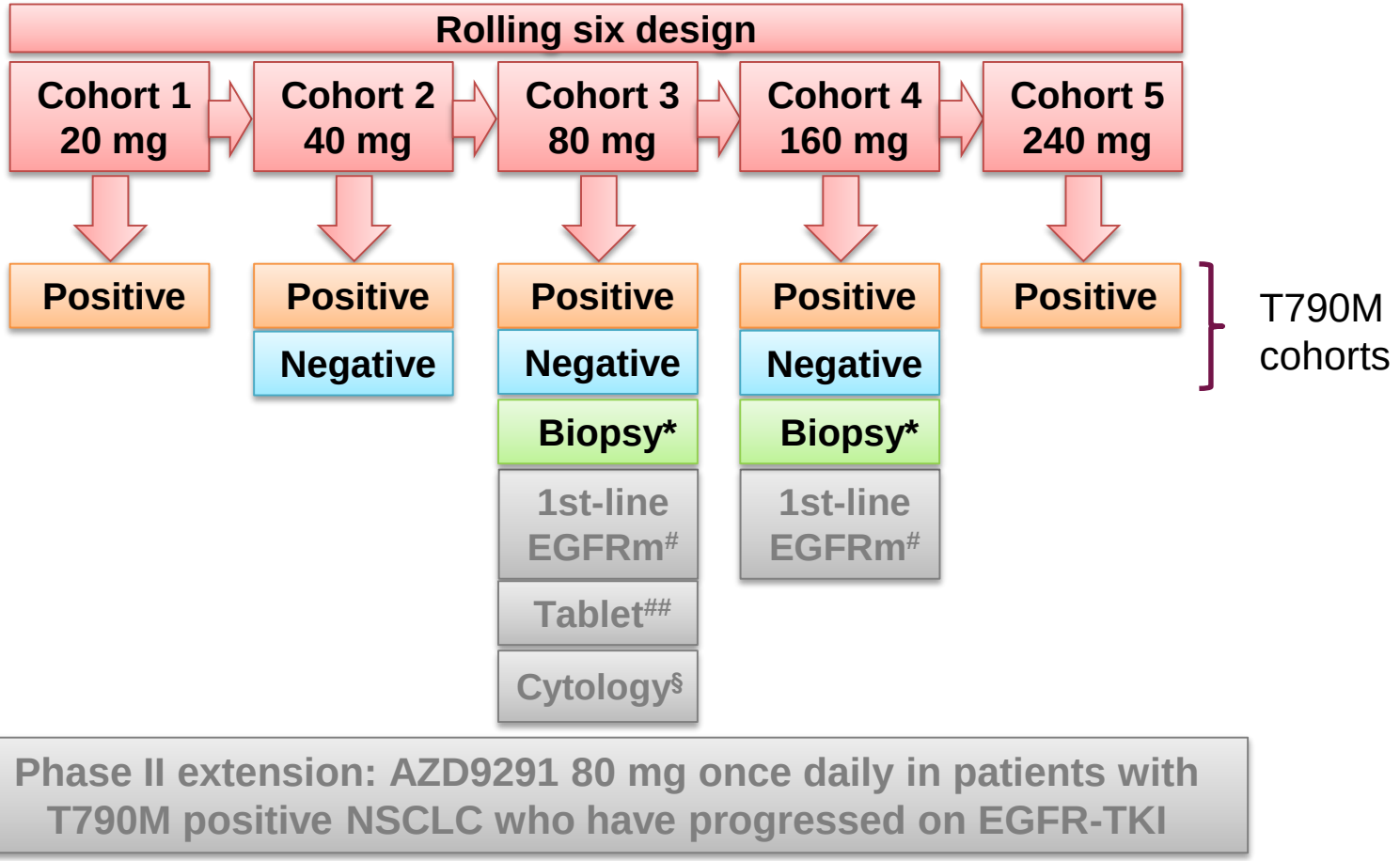


Osimertinib

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

Phase I / II dose escalation / expansion and extension study design

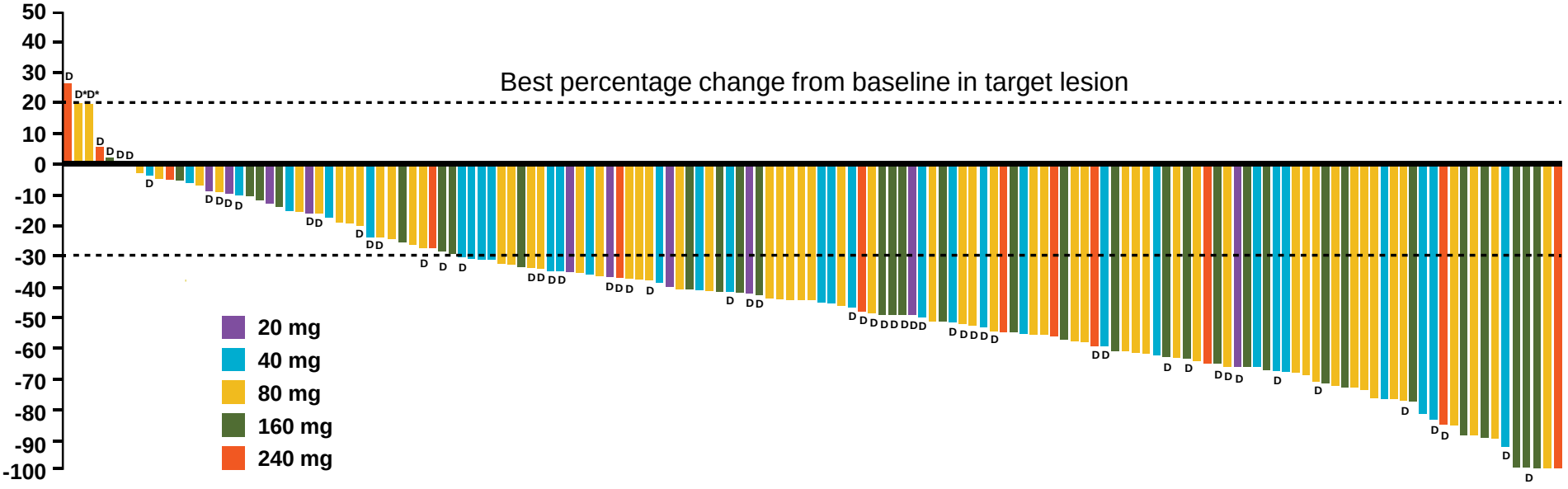
Primary objective – assessment of the safety, tolerability and efficacy (ORR) of AZD9291 in patients with acquired resistance to EGFR-TKIs



*Paired biopsy cohort patients with T790M positive tumours; safety and efficacy data only reported here
#Prior therapy not permissible in this cohort
##Not selected by mutation status, US only
§T790M positive from cytology specimen, Japan only
ORR, objective response rate

Jänne et al. ELCC 2015

Response rate in T790M positive cohorts across all doses



DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

Jänne et al. ELCC 2015

Summary of adverse events, all grades

Patients with an AE, n (%)	20 mg (N=21)	40 mg (N=58)	80 mg (N=103)	160 mg (N=80)	240 mg (N=21)	Total (N=283)
Any AE	21 (100)	56 (97)	102 (99)	78 (98)	21 (100)	278 (98)
Any AE, drug-related*	15 (71)	40 (69)	88 (85)	72 (90)	21 (100)	236 (83)
Any AE ≥ Grade 3	6 (29)	25 (43)	40 (39)	33 (41)	9 (43)	113 (40)
Any AE ≥ Grade 3, drug-related*	3 (14)	3 (5)	14 (14)	23 (29)	4 (19)	47 (17)
Any AE leading to death	2 (10)	2 (3)	5 (5)	0	1 (5)	10 (4)
Any AE leading to death, drug-related*	1 (5)	0	0	0	0	1 (0.4)
Any AE leading to dose interruption	4 (19)	7 (12)	24 (23)	23 (29)	6 (29)	64 (23)
Any AE leading to dose reduction	0	2 (3)	1 (1)	18 (23)	10 (48)	31 (11)
Any AE leading to discontinuation	3 (14)	4 (7)	7 (7)	8 (10)	2 (10)	24 (8)
Any AE leading to discontinuation, drug-related*	2 (10)	0	1 (1)	7 (9)	1 (5)	11 (4)
Any serious AE	5 (24)	13 (22)	26 (25)	20 (25)	5 (24)	69 (24)
Any serious AE, drug-related*	4 (19)	1 (2)	5 (5)	6 (8)	1 (5)	17 (6)

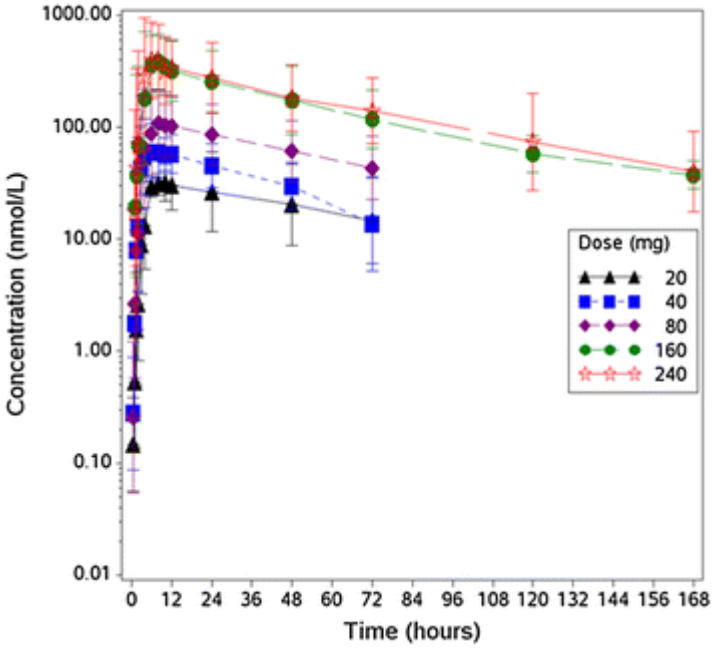
Jänne et al. ELCC 2015

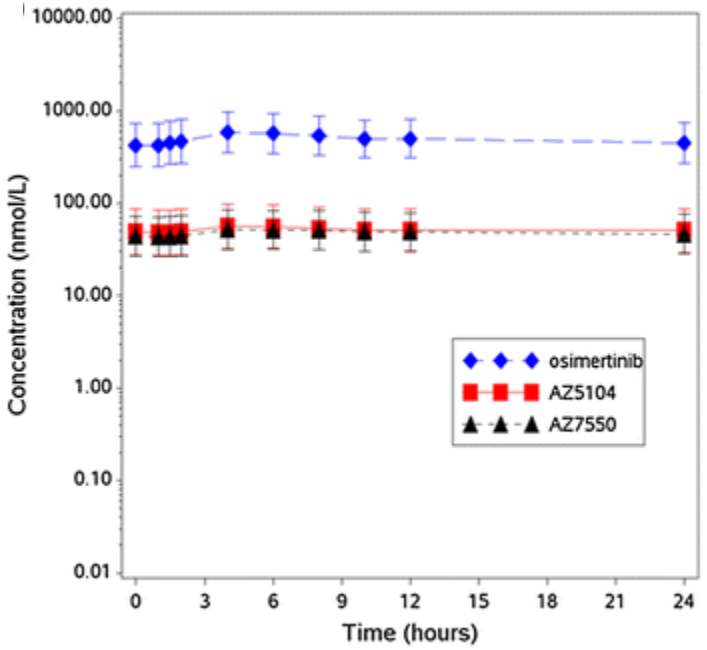
All-causality adverse events

Patients with an AE, %	20 mg (N=21)		40 mg (N=58)		80 mg (N=103)		160 mg (N=80)		240 mg (N=21)		Total (N=283)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3
AE by preferred term, occurring in >15% of patients overall												
Diarrhoea	29	0	47	2	36	1	68	3	76	5	50	2
Rash, grouped terms	24	0	33	0	38	0	63	3	76	5	46	1
Decreased appetite	38	10	19	0	26	3	24	0	33	0	25	2
Nausea	14	5	17	0	18	1	34	1	43	0	24	1
Dry skin	14	0	16	0	15	0	36	0	24	0	22	0
Paronychia	14	0	9	0	21	2	29	4	38	5	22	2
Pruritus	14	0	21	0	19	0	20	0	38	0	21	0
Fatigue	24	5	26	0	16	0	19	0	19	5	19	1
Constipation	5	0	26	0	21	0	18	0	14	0	19	0
Cough	19	0	17	0	13	0	21	0	0	0	16	0
Select AEs of interest												
Hyperglycaemia (n=8)	0	0	3	0	4	0	3	0	0	0	3	0
QT prolongation (n=10)	0	0	2	0	4	1	5	0	5	0	4	0.4
ILD-like events* (n=8)	0	0	0	0	3	2	6	4	0	0	3	2

Jänne et al. ELCC 2015

Single and multiple dose PK of osimertinib



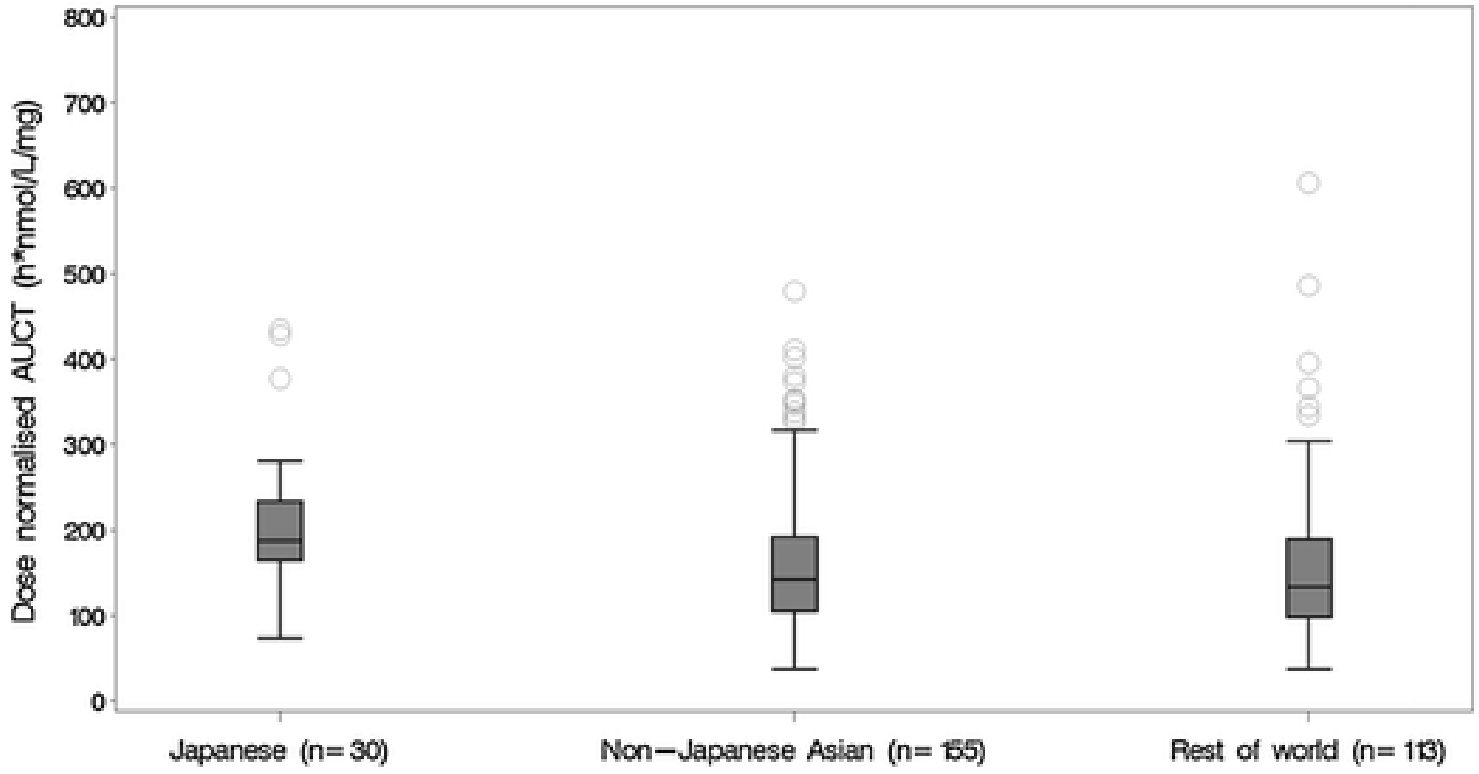


Single dose **Multiple dosing**

Dose proportional increase in exposure
Half life: 48 hours; Steady state reached in 15 days

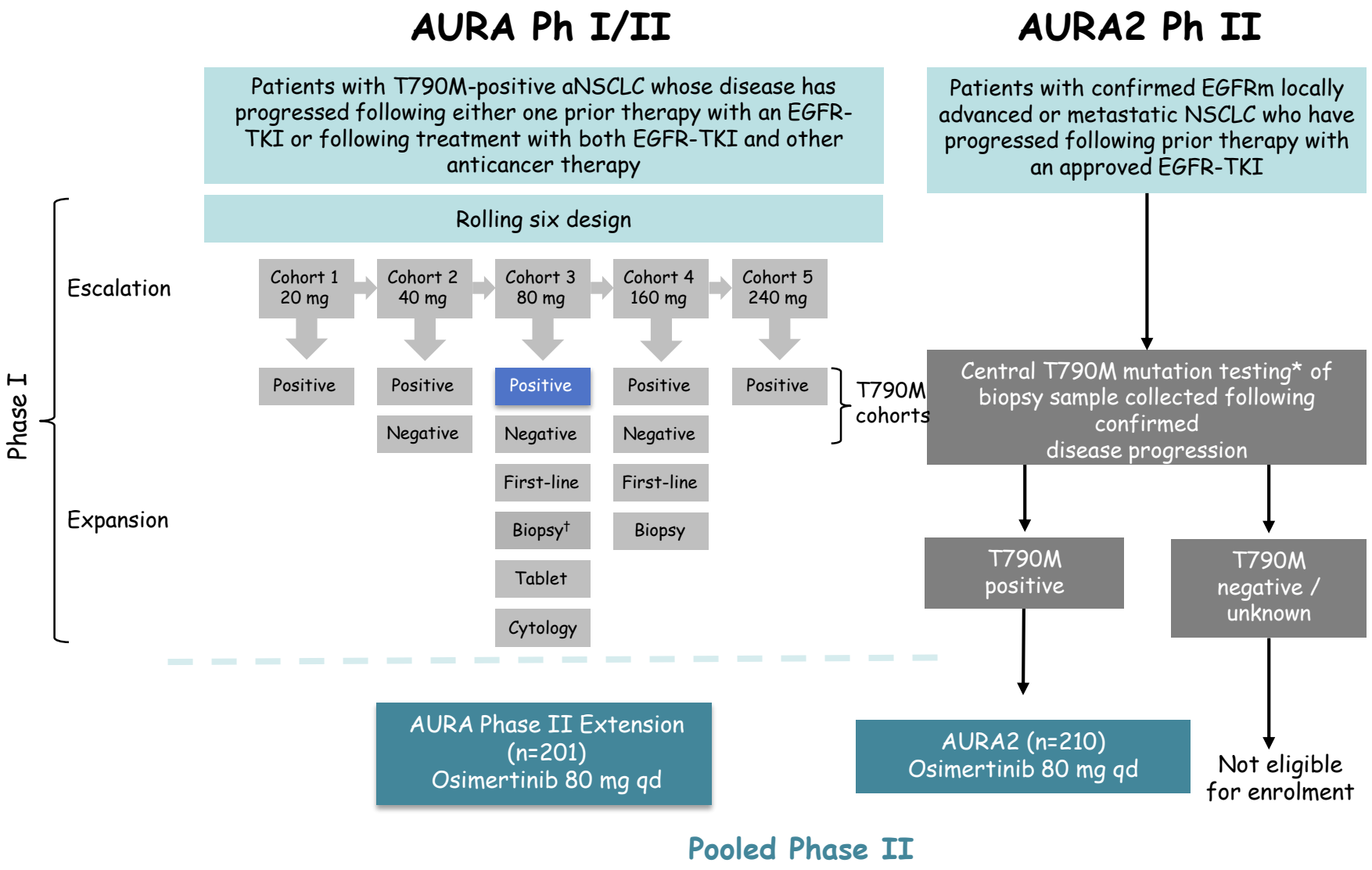
Planchard et al. Cancer Chemother Pharmacol 2016

Osimertinib exposure in different ethnic populations

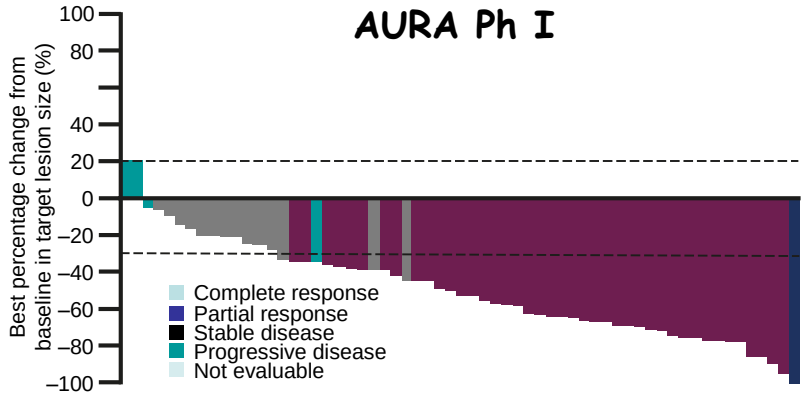


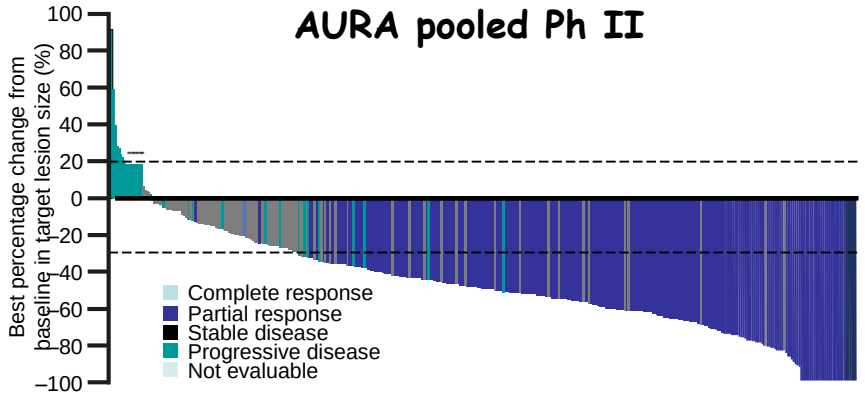
Planchard et al. Cancer Chemother Pharmacol 2016

Osimertinib Phase I & II studies



Osimertinib – phase I and phase II studies

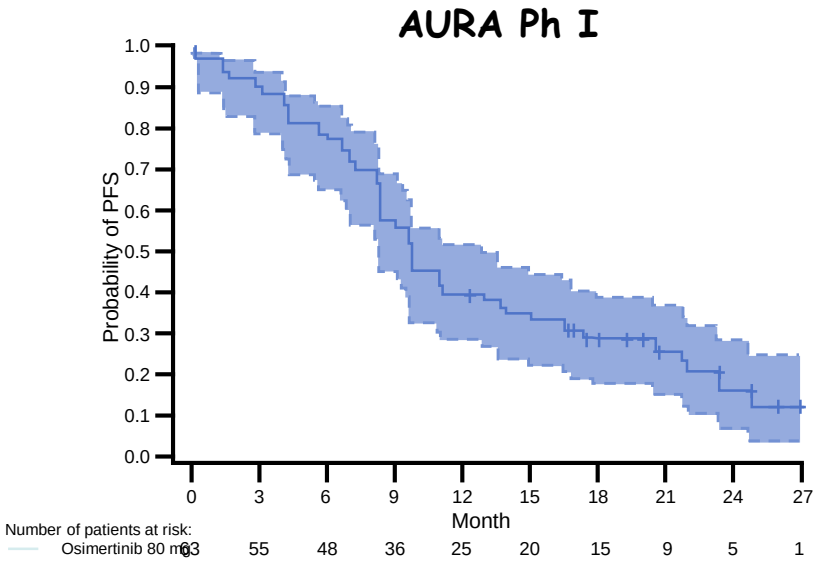


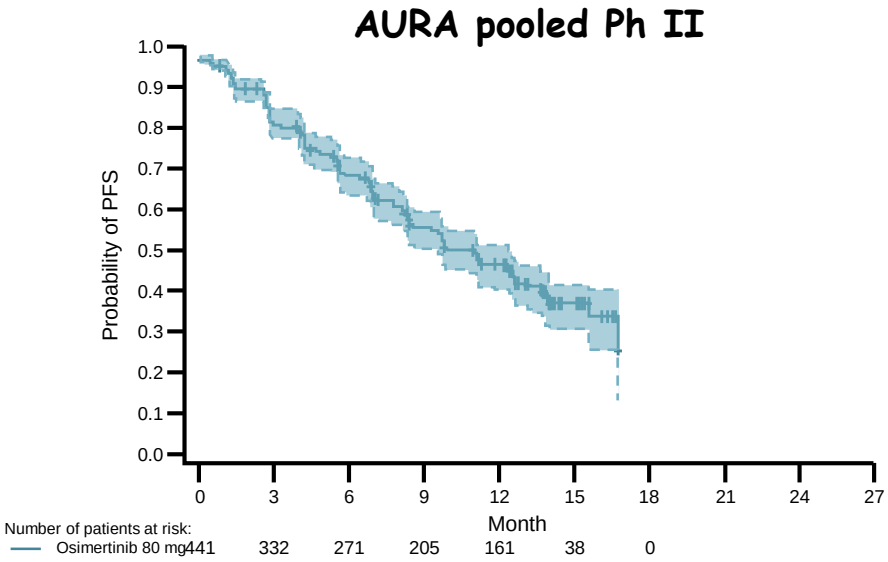


	AURA Ph I (80 mg) N=61	AURA pooled Ph II (80 mg) N=397
Confirmed ORR	71% (95% CI 57, 82)	66% (95% CI 61, 71)
Disease control rate†	93% (95% CI 84, 98)	91% (95% CI 88, 94)
Best objective response		
Complete response	1	6
Partial response	42	256
Stable disease ≥6 weeks	14	99
Progressive disease	2	25

Yang et al. ELCC 2016

Progression-free survival with osimertinib



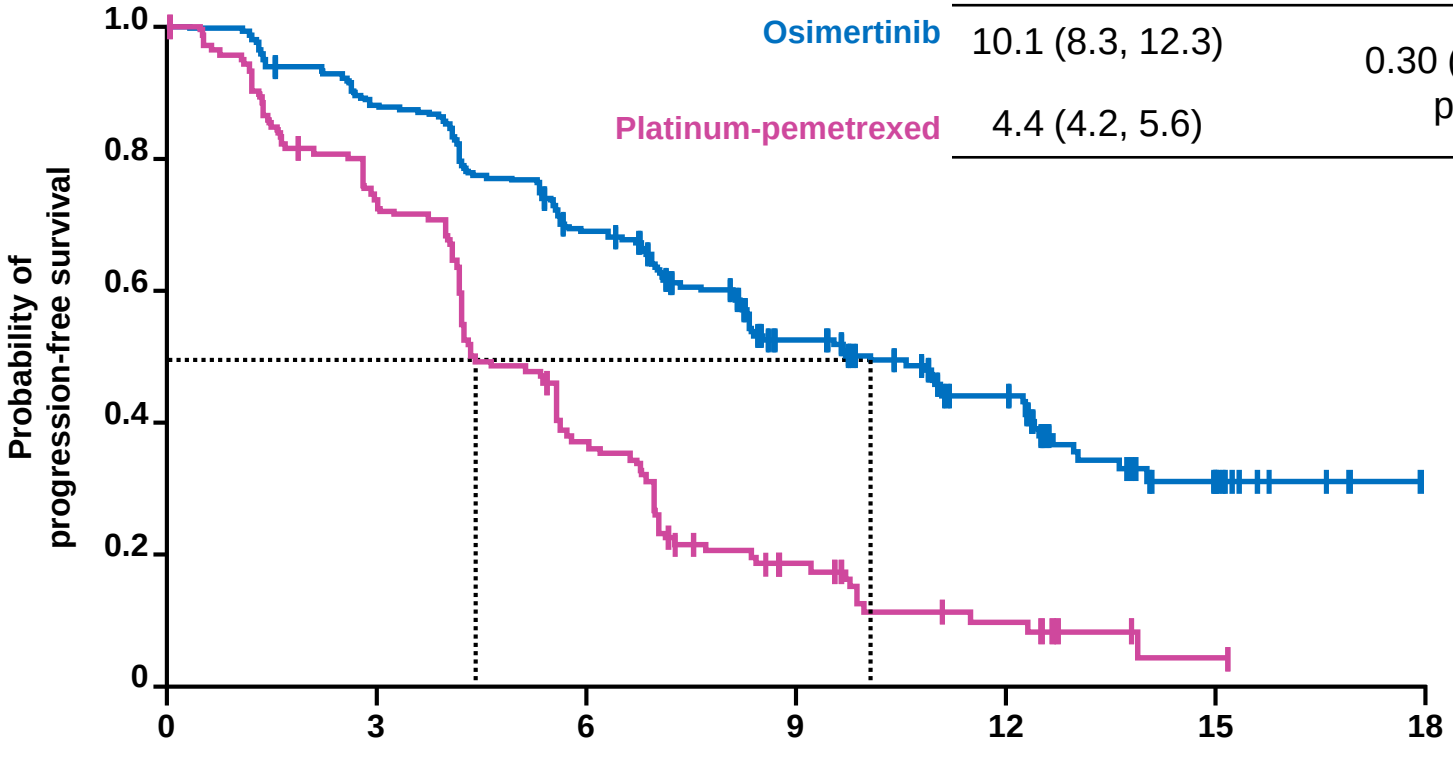


	AURA Ph I (80 mg) N=63	AURA pooled Ph II (80 mg) N=411
Median PFS,* months (95% CI)	9.7 (8.3, 13.6)	11.0 (9.6, 12.4)
Remaining alive and progression-free,† % (95% CI)		
12 months	41 (29, 53)	48 (42, 53)
18 months	29 (18, 41)	NC
24 months	17 (8, 30)	NC

Yang et al. ELCC 2016

Phase III Osimertinib vs. Chemotherapy - 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)	

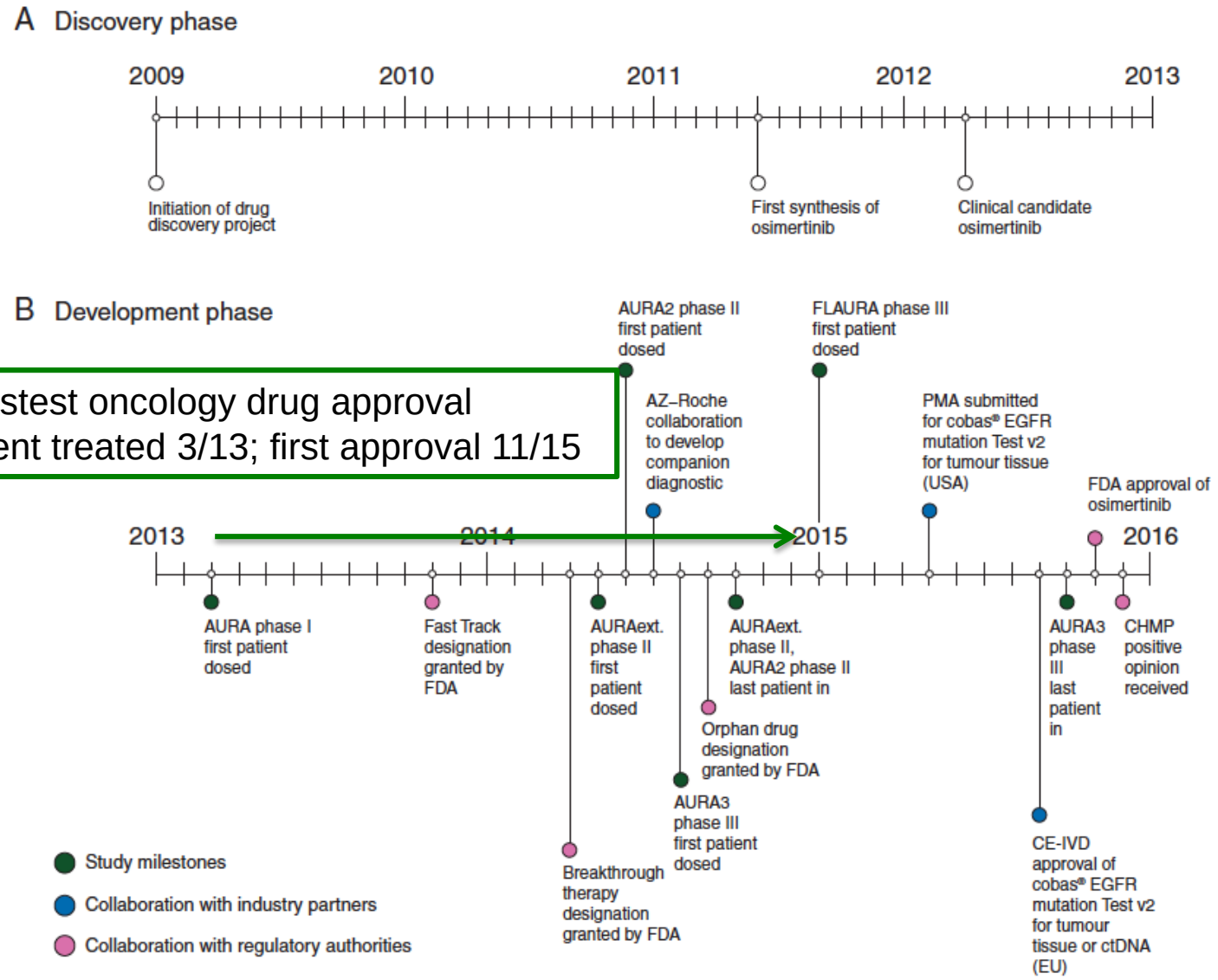


No. at risk							
Osimertinib	279	240	162	88	50	13	0
Platinum-pemetrexed	140	93	44	17	7	1	0

- 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.

Mok et al. NEJM 2016

Osimertinib Development Timeline



Yver Ann Oncol 2016

Osimertinib – Subsequent Development

- Significant activity in EGFR TKI naïve patients
  - RR 77%; PFS 19.3 months
  - Phase III trial vs. gefitinib/erlotinib in EGFR TKI naïve patient completed enrollment
- Phase III trial vs. placebo in surgically resected EGFR mutant NSCLC patients
  - Enrollment ongoing
- Activity in patients with brain metastases and leptomeningeal carcinomatosis
  - Independent of EGFR T790M

Efficacy and Toxicity of 3rd Generation EGFR TKIs

Drug	T790M RR	PFS	Toxicities
Osimertinib[1,2]	66-71%	9.7-11.0	ILD, rash
Rociletinib[3,4]	~ 30%	5.0	Hyperglycemia, QTc, cataracts
HM61713[5]	55%	Too early	Palmar Plantar Erythema, rash
ASP8273[6,7]	36%-50%	Too early	Hyponatremia, neuropathy
EGF816[8]	50%	Too early	Rash, diarrhea
AC0010[9]	50%	Too early	Diarrhea, rash, transaminitis
PF-06747775	?	?	?

[1]Jänne NEJM 2015; [2]Yang ELCC 2016; [3]Sequist NEJM 2015; [4]Wakelee ASCO2016; [5]Park ASCO 2015; [6]Yu et al. ASCO 2015; [7]Goto ASCO 2015; [8]Tan ASCO 2015; Wu IASLC 2016

Rociletinib (CO-1686) Clinical Development

- Clinical Development began in late 2011

Rociletinib (CO-1686) Activity & Toxicity

- Initial report of 59% RR & PFS 13.1 months
  - Presentations were not transparent; changing denominator
  - Subsequently revealed that RR based on unconfirmed RR
    - Confirmed RR ~ 30%; PFS 5.0 months

HM61713 (Olmutinib)

- Developed by Hanmi Pharmaceuticals
  - Approved in South Korea in 2016
  - Response rate of ~ 50%
- Worldwide clinical development by Boehringer Ingelheim
  - Phase II global clinical trial initiated
  - Plans for several phase III clinical trials
  - Sep 2016 – development returned to Hanmi
    - “Decision is based on a re-evaluation of all available clinical data…”
    - Reports of toxic epidermal necrolysis and Stevens Johnson Syndrome including a drug related death

EGFR T790M Inhibitors

- Effective against most common mechanism of acquired drug resistance
- Also great inhibitors of EGFR activating mutations
  - Trials in EGFR TKI naïve patients underway
- Additional CNS activity of osimertinib
- Open up the possibility to develop combination therapies (lack of EGFR WT activity)
  - Previously not possible with erlotinib or afatinib