EGFR & ALK: Where Are We Now?

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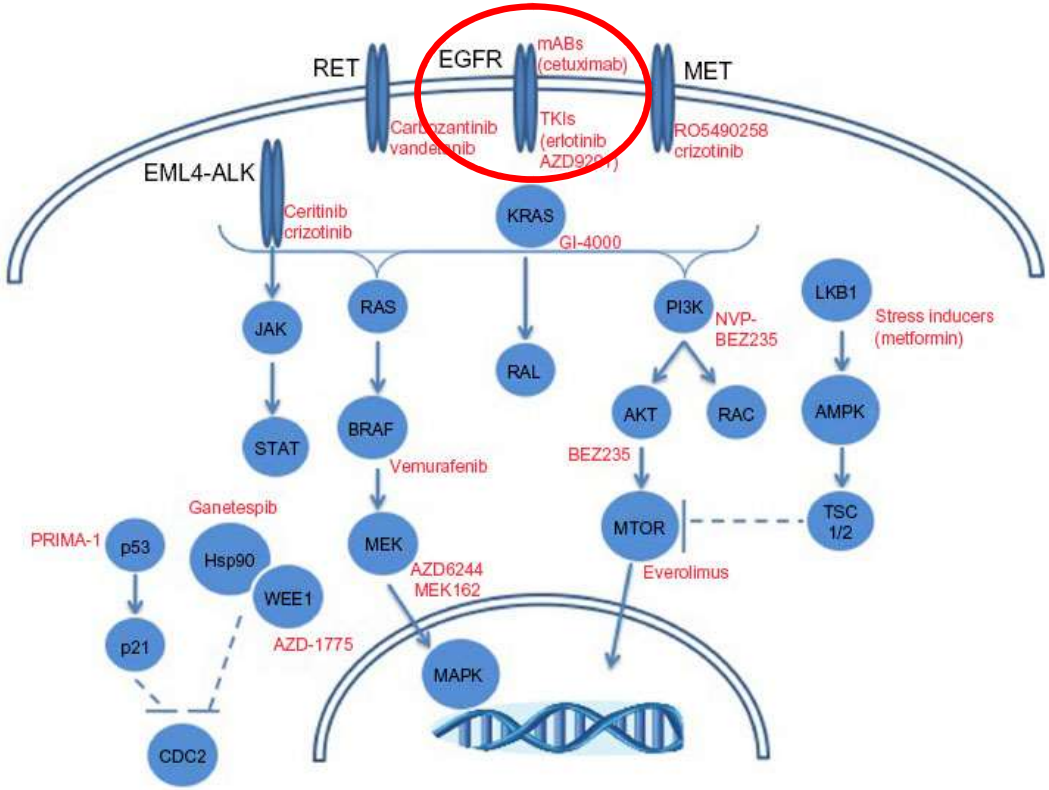
Disclosures

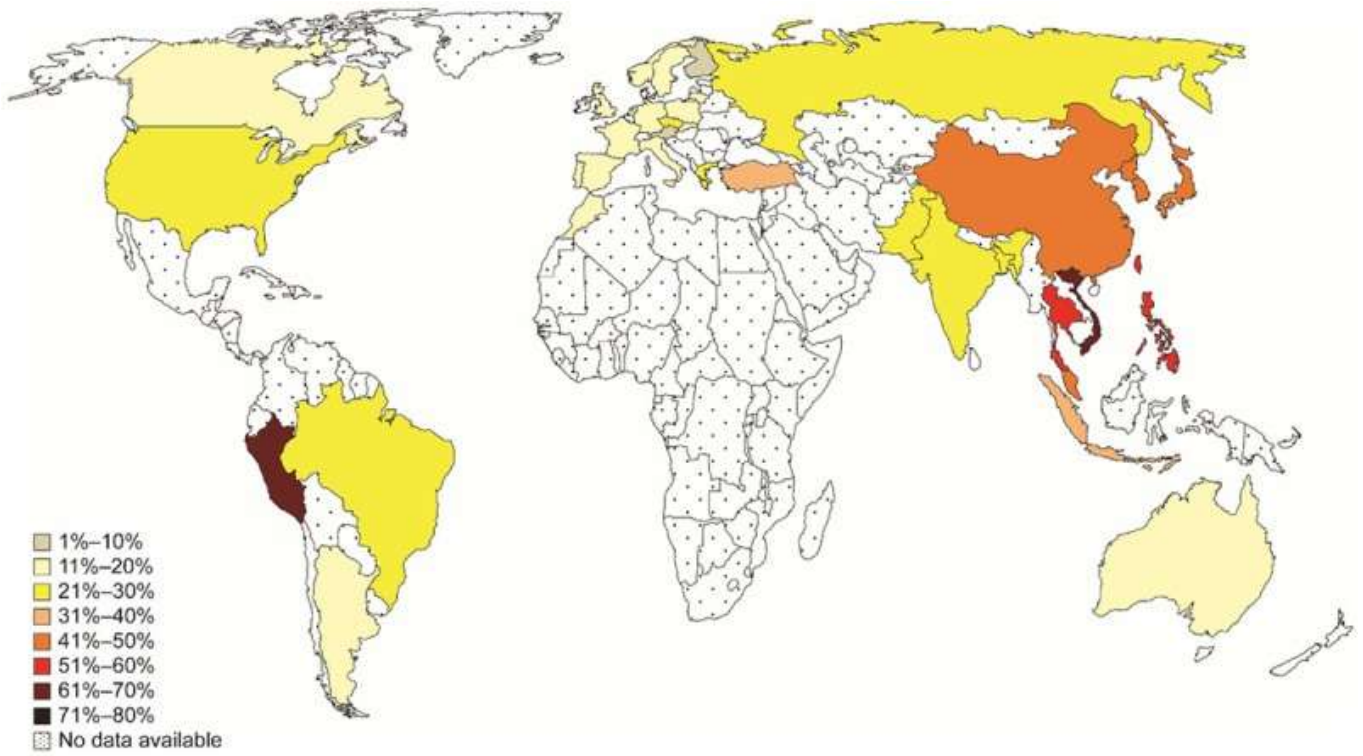
- Advisory Board/Consulting:
  - Loxo, Abbvie, AstraZeneca, Genentech, Incyte, Merck, Celgene, Foundation Medicine

EGFR


RET
EGFR
mABs
(cetuximab)
MET
Cartozantinib
vandetanib
TKIs
(erlotinib
AZD9291)
RO5490258
crizotinib
EML4-ALK
Ceritinib
crizotinib
KRAS
GI-4000
JAK
RAS
RAL
PI3K
NVP-
BEZ235
LKB1
Stress inducers
(metformin)
STAT
BRAF
Vemurafenib
AKT
RAC
AMPK
BEZ235
Ganetespib
PRIMA-1
p53
Hsp90
MEK
MTOR
TSC
1/2
WEE1
AZD6244
MEK162
Everolimus
p21
AZD-1775
MAPK
CDC2

EGFR-mutant NSCLC

- A global problem

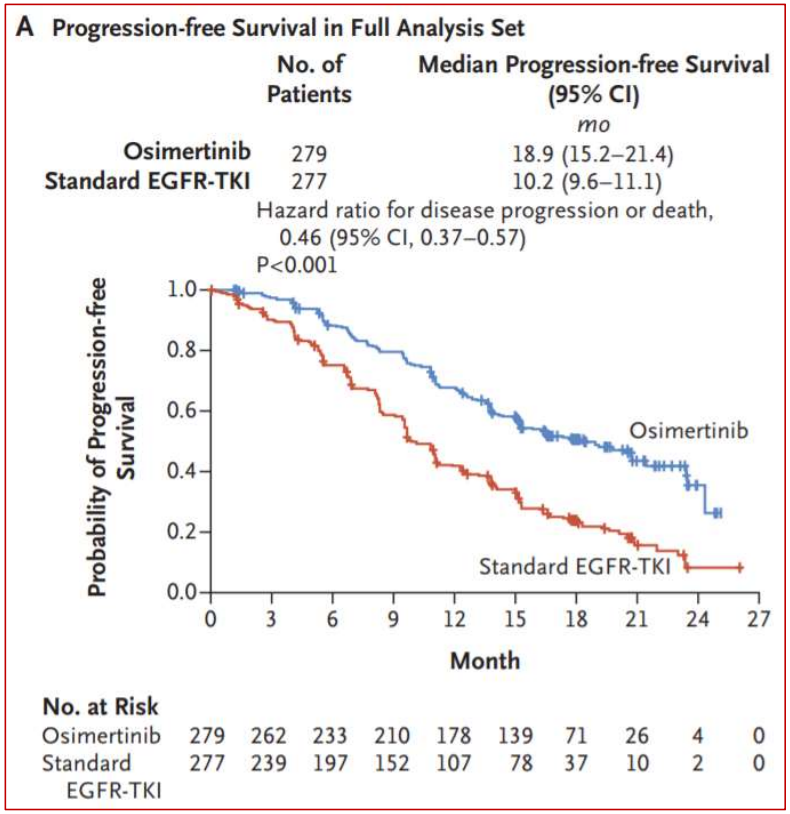


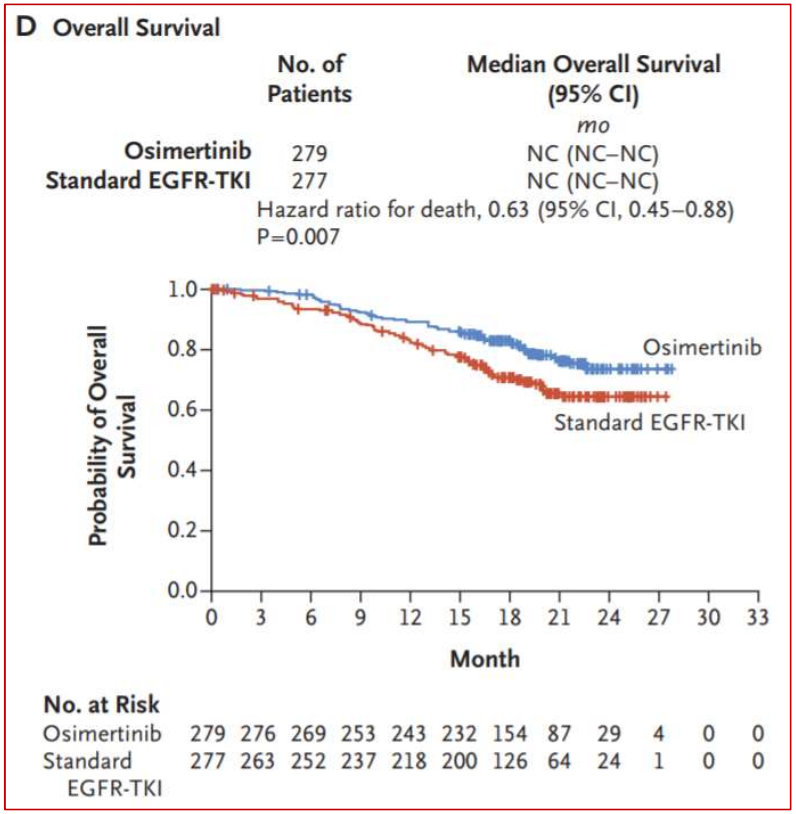
Midha et al, Am J Cancer Res, 2015

EGFR Questions

- Does FLAURA justify frontline osimertinib?
- What is the ideal sequencing?
- Does dacomitinib have a place?

FLAURA





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Soria JC et al. NEJM 2015

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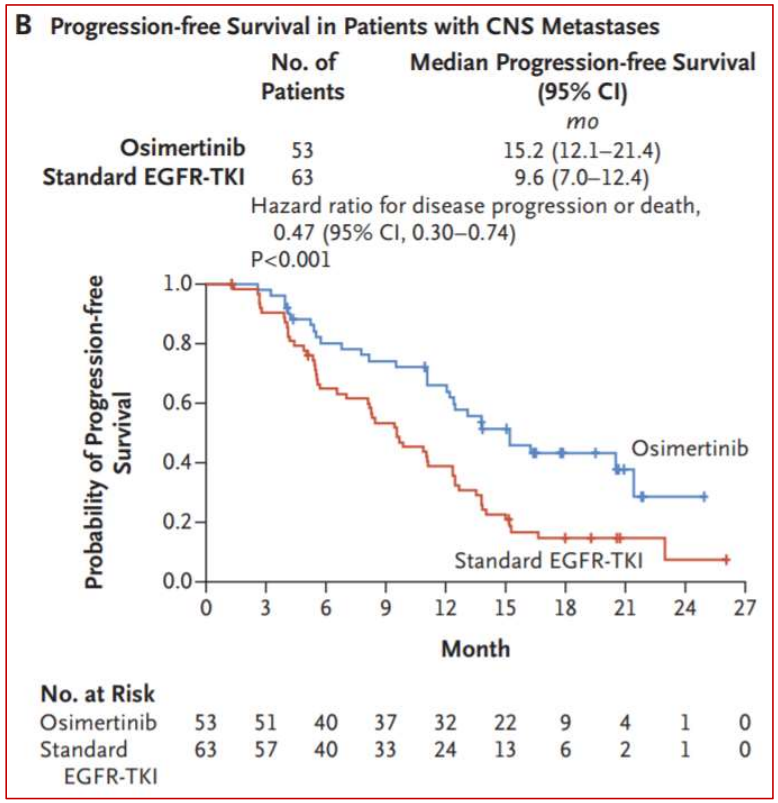
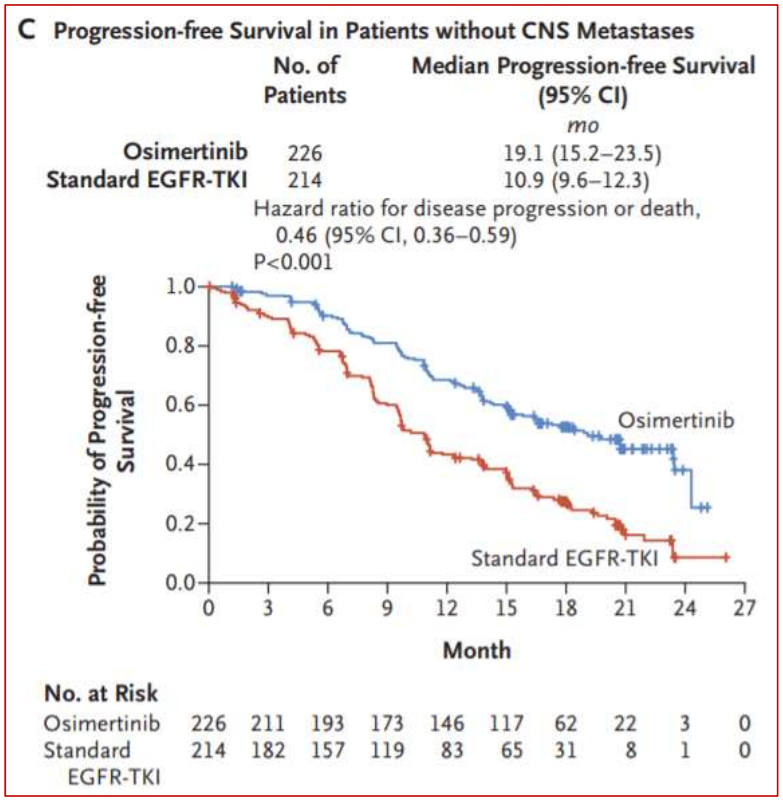
FLAURA (CNS disease)





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Soria JC et al. NEJM 2015

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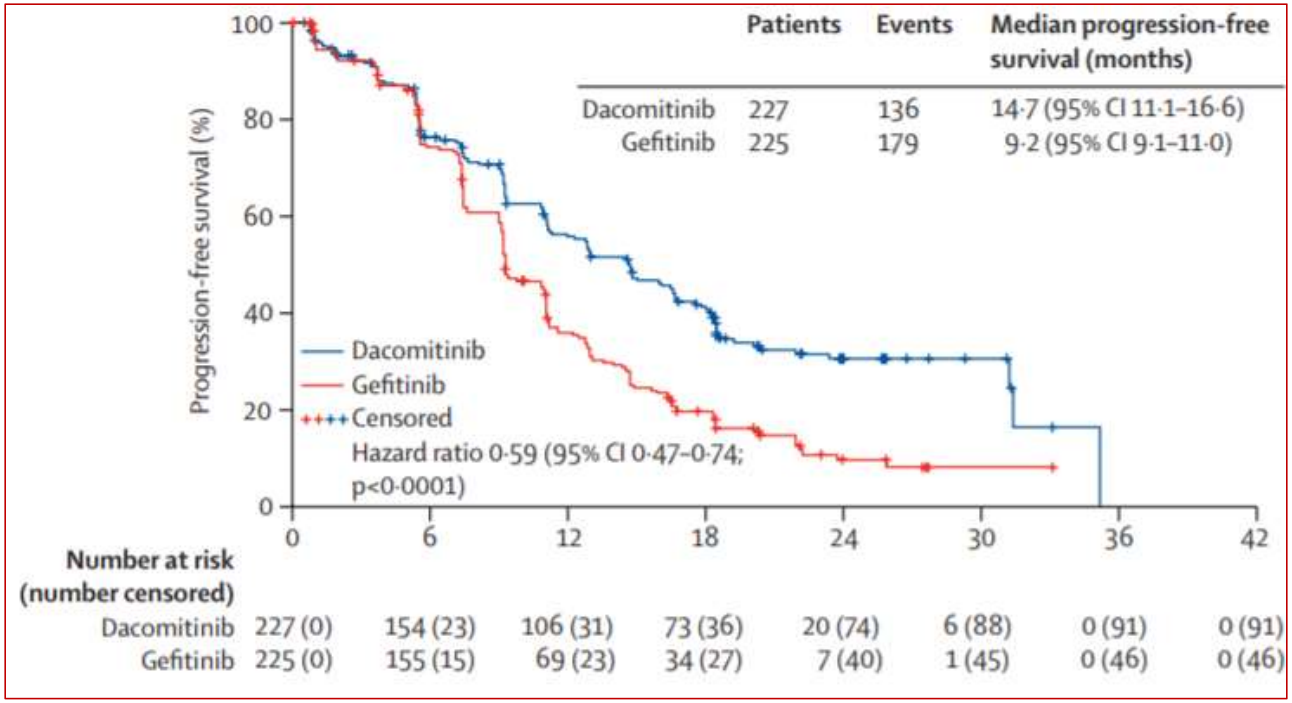
Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial

Yi-Long Wu, Ying Cheng, Xiangdong Zhou, Ki Hyeong Lee, Kazuhiko Nakagawa, Seiji Niho, Fumito Tsuji, Rolf Linke, Rafael Rosell, Jesus Corral, Maria Rita Migliorino, Adam Pluzanski, Eric I Sbar, Tao Wang, Jane Liang White, Sashi Nadanaciva, Rickard Sandin, Tony S Mok

Lancet Oncol 2017; 18: 1454–66

Summary

Background Dacomitinib is a second-generation, irreversible EGFR tyrosine kinase inhibitor. We compared its efficacy



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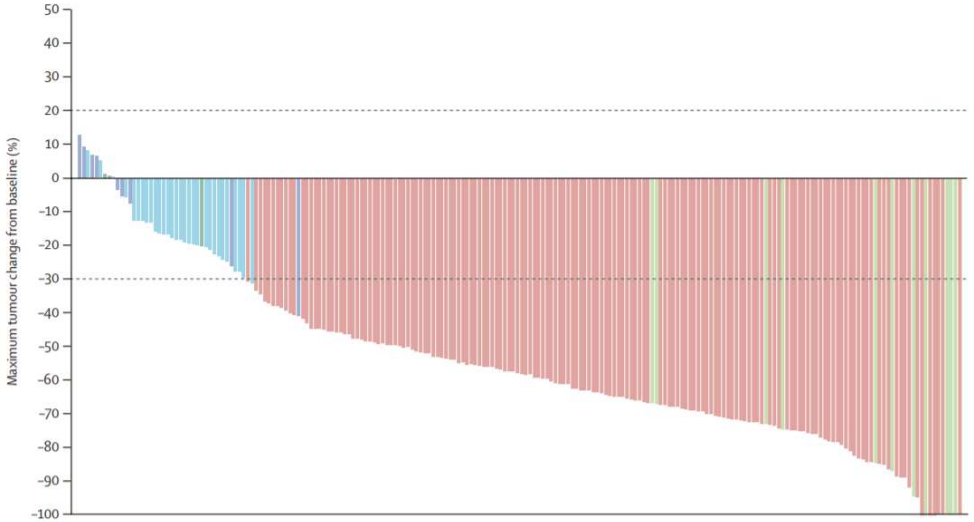
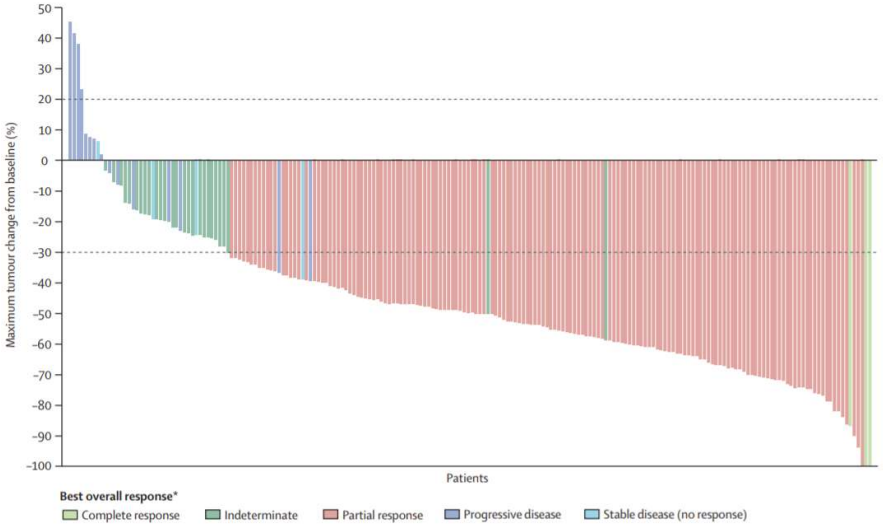
Dacomitinib



Gefitinib



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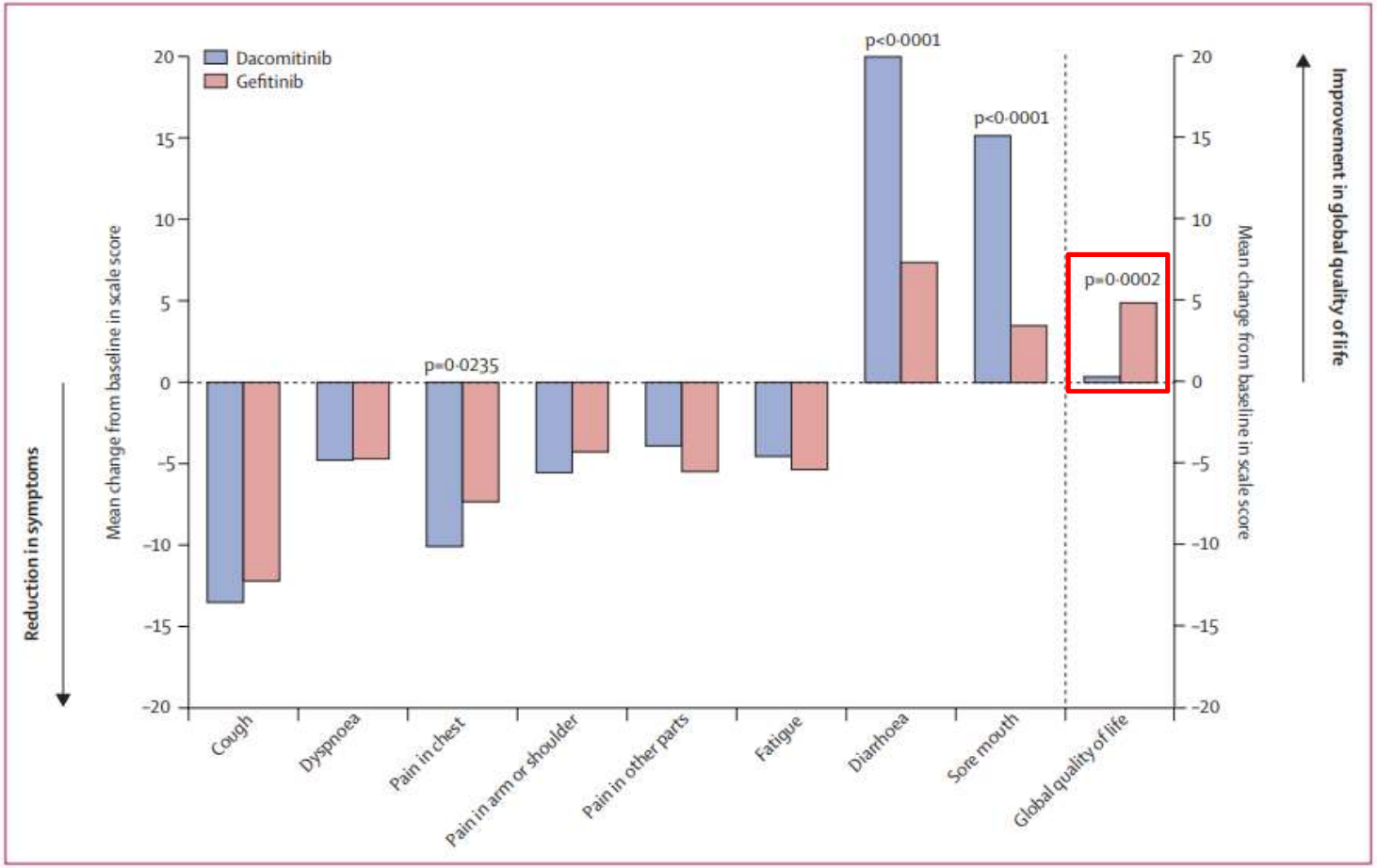
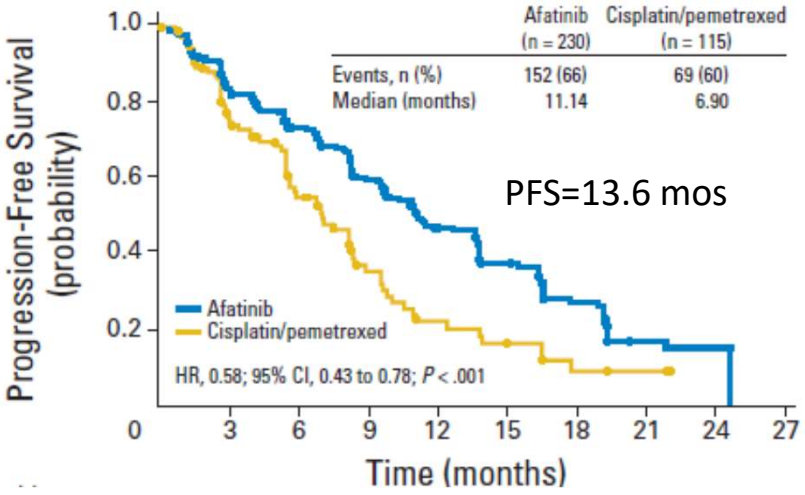
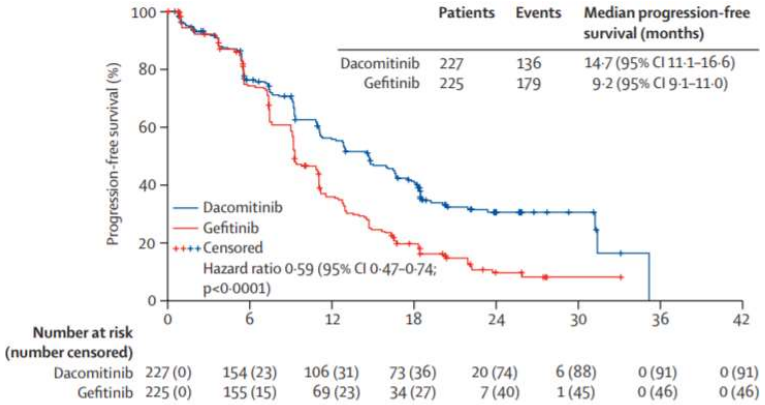


***Figure 5*: Overall change from baseline in key lung cancer-associated symptoms, fatigue, diarrhoea, sore mouth, and global quality of life**
Each scale ranges from 0 to 100, with changes ≥10 points regarded as clinically meaningful. For global quality of life, higher scores indicate better global quality of life; for symptoms, higher scores indicate greater severity of symptoms. p values (unadjusted for multiple testing) are for the between-group comparison of the overall change from baseline, calculated using repeated-measures mixed-effects modelling.

Afatinib

Dacomitinib





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Side Effect Profile

	Dacomitinib (n=227)			
	Grades 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	83 (37%)	116 (51%)	5 (2%)	22 (10%)
Diarrhoea	178 (78%)	19 (8%)	0	1 (<1%)
Paronychia	123 (54%)	17 (7%)	0	0
Dermatitis acneiform	80 (35%)	31 (14%)	0	0
Stomatitis	91 (40%)	8 (4%)	0	0
Decreased appetite	63 (28%)	7 (3%)	0	0
Dry skin	60 (26%)	3 (1%)	0	0
Weight decreased	53 (23%)	5 (2%)	0	0
Alopecia	52 (23%)	1 (<1%)	0	0
Cough	48 (21%)	0	0	0
Pruritus	44 (19%)	1 (<1%)	0	0
ALT increased	42 (19%)	2 (1%)	0	0
Conjunctivitis	43 (19%)	0	0	0
Nausea	40 (18%)	3 (1%)	0	0
AST increased	42 (19%)	0	0	0
Rash	30 (13%)	10 (4%)	0	0
Palmar-plantar erythrodysesthesia syndrome	31 (14%)	2 (1%)	0	0
Pain in extremity	31 (14%)	0	0	0
Dyspnoea	25 (11%)	4 (2%)	1 (<1%)	0
Asthenia	24 (11%)	5 (2%)	0	0
Constipation	29 (13%)	0	0	0
Mouth ulceration	28 (12%)	0	0	0
Maculopapular rash	18 (8%)	10 (4%)	0	0

Table 2. Treatment-Related AEs*

	Afatinib (n = 229)				Cisplatin Plus	
	All Grades		≥ Grade 3		All Grades	
AE	No.	%	No.	%	No.	%
Diarrhea	218	95.2	33	14.4	17	15.3
Rash/acne†	204	89.1	37	16.2	7	6.3
Stomatitis/mucositis†	165	72.1	20	8.7	17	15.3
Paronychia	130	56.8	26	11.4	0	0.0
Dry skin	67	29.3	1	0.4	2	1.8
Decreased appetite	47	20.5	7	3.1	59	53.2
Pruritus	43	18.8	1	0.4	1	0.9
Nausea	41	17.9	2	0.9	73	65.8
Fatigue†	40	17.5	3	1.3	52	46.8
Vomiting	39	17.0	7	3.1	47	42.3
Epistaxis	30	13.1	0	0.0	1	0.9
Cheilitis	28	12.2	0	0.0	1	0.9
Anemia‡	7	3.1	1	0.4	31	27.9
Constipation	6	2.6	0	0.0	21	18.9
Leukopenia‡	4	1.7	1	0.4	21	18.9
Neutropenia‡	2	0.9	1	0.4	35	31.5

Abbreviation: AE, adverse event.
*Events were included if reported in > 10% of patients in either treatment group and if there was ≥ 10% difference betwe
according to incidence in the afatinib group.
†Group term.
‡Numbers are based on AEs reported by the investigator, not derived from laboratory data.

Side Effect Profile

Dacomitinib Grade 3 SAE

Diarrhea 8%

Rash 4%

Dermatitis acneiform 14%

Maculopapular rash 4%

Stomatitis 4%

Paronychia 7%

AST increased	42 (19%)	0	0	0
Rash	30 (13%)	10 (4%)	0	0
Palmar-plantar erythrodysesthesia syndrome	31 (14%)	2 (1%)	0	0
Pain in extremity	31 (14%)	0	0	0
Dyspnoea	25 (11%)	4 (2%)	1 (<1%)	0
Asthenia	24 (11%)	5 (2%)	0	0
Constipation	29 (13%)	0	0	0
Mouth ulceration	28 (12%)	0	0	0
Maculopapular rash	18 (8%)	10 (4%)	0	0

Afatinib Grade 3 SAE

Diarrhea 14.4%

Rash 16.2%

Stomatitis/ mucositis 8.7%

Paronychia 11.4%

Table 2. Treatment-Related AEs*

	Afatinib (n = 229)				Cisplatin Plus	
	All Grades		≥ Grade 3		All Grades	
	No.	%	No.	%	No.	%
Epistaxis	30	13.1	0	0.0	1	0.9
Cheilitis	28	12.2	0	0.0	1	0.9
Anemia‡	7	3.1	1	0.4	31	27.9
Constipation	6	2.6	0	0.0	21	18.9
Leukopenia‡	4	1.7	1	0.4	21	18.9
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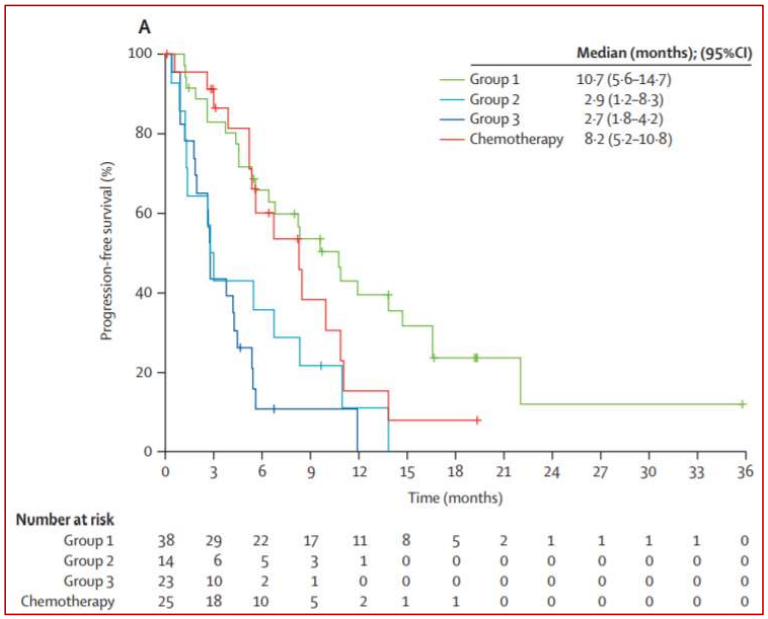
Sequencing?

- Osimertinib is the clear first line therapy based on PFS/CNS and side effect profile
- Important to order genomic testing at progression to evaluate for resistance mutations to guide therapy
- No current place for dacomitinib

Afatinib (uncommon EGFR mut)

38 group 1: point mutations and duplications, or both, in exons 18–21
12 Leu861Gln alone
8 Gly719Xaa alone
5 Gly719Xaa + Ser768Ile
3 Gly719Xaa + Leu861Gln
2 Glu709Gly or Val + Leu858Arg
2 Ser768Ile + Leu858Arg
1 Ser768Ile alone
1 Leu861Pro alone
1 Pro848Leu alone
1 Arg776His + Leu858Arg
1 Leu861Gln + del19
1 Lys739_1744dup6



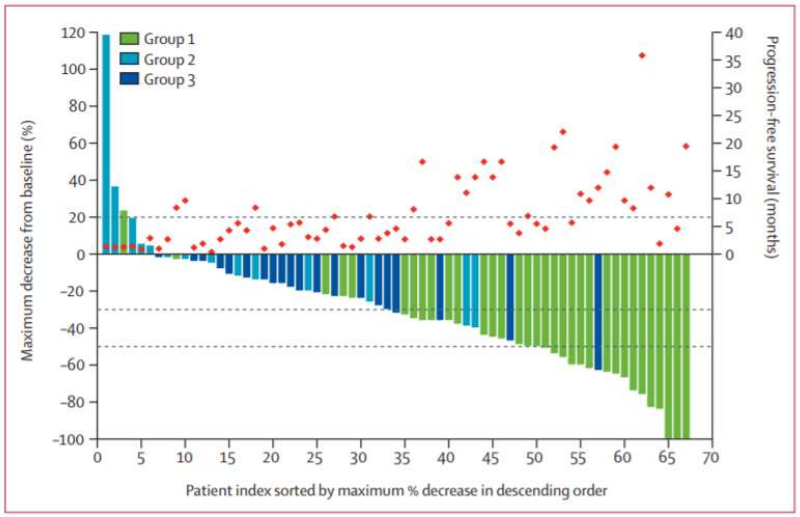


***Figure 2*: Tumour shrinkage per independent review**
67 patients were included (eight had insufficient data). Group 1=point mutations or duplications in exons 18–21; Group 2=de-novo Thr790Met mutations; Group 3=exon 20 insertions.

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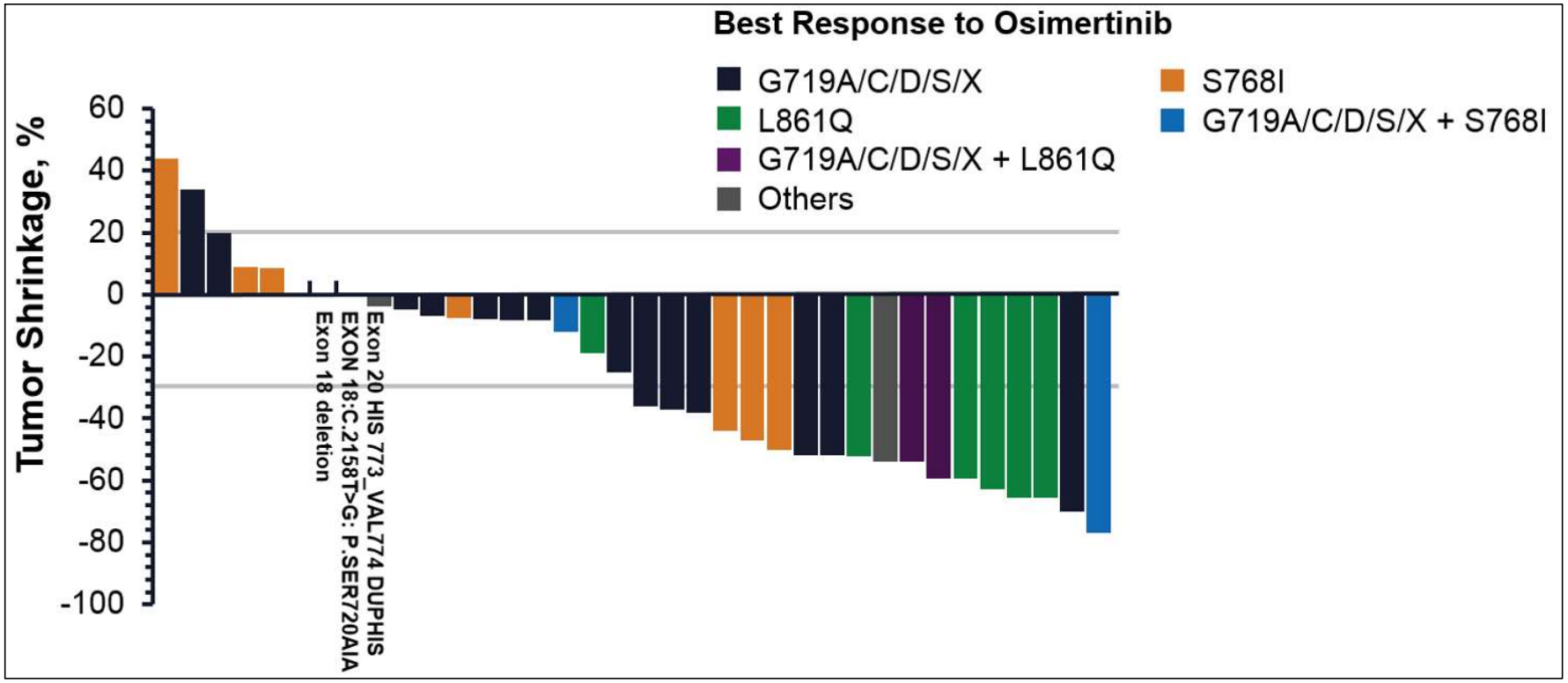
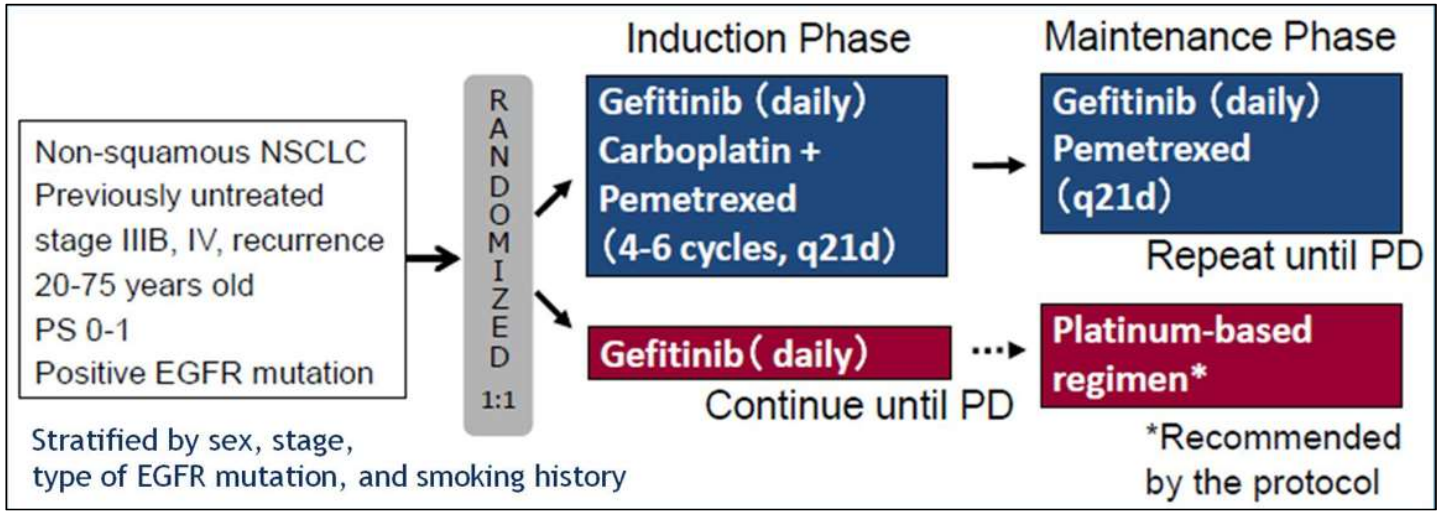
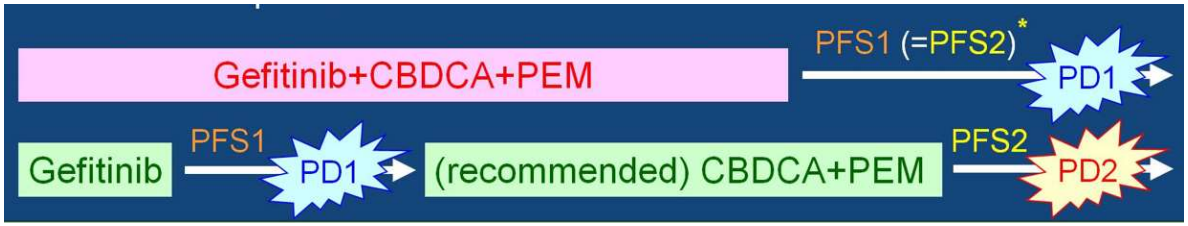
Osimertinib for Uncommon EGFR



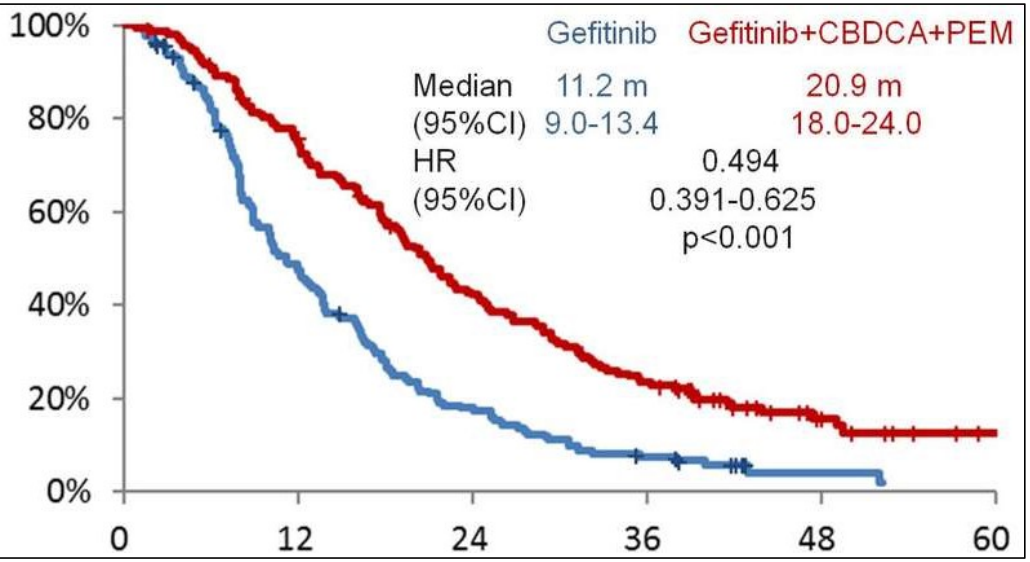
Ahn et al. ASCO 2018

NEJ009 presented at ASCO

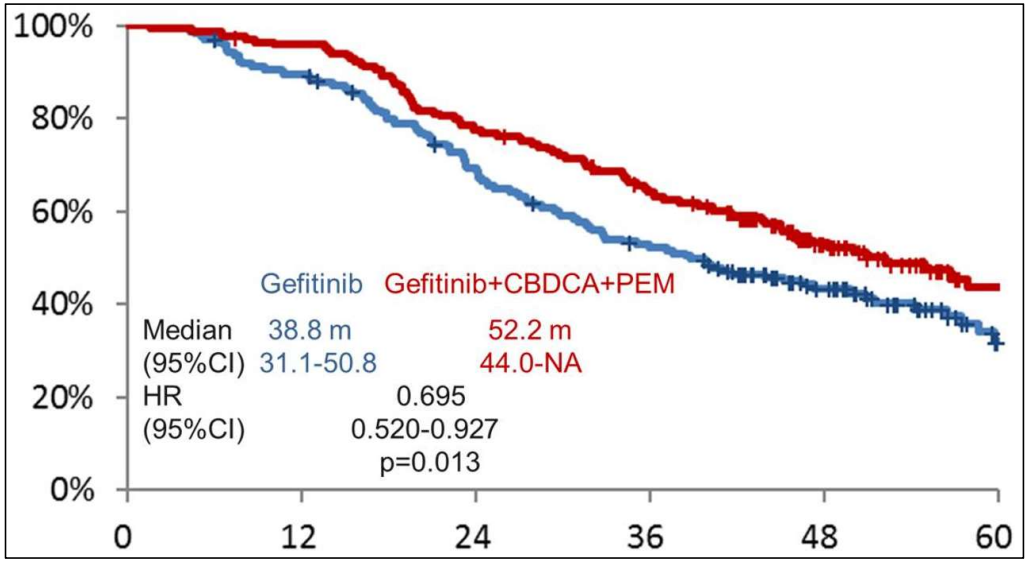




Progression-Free Survival

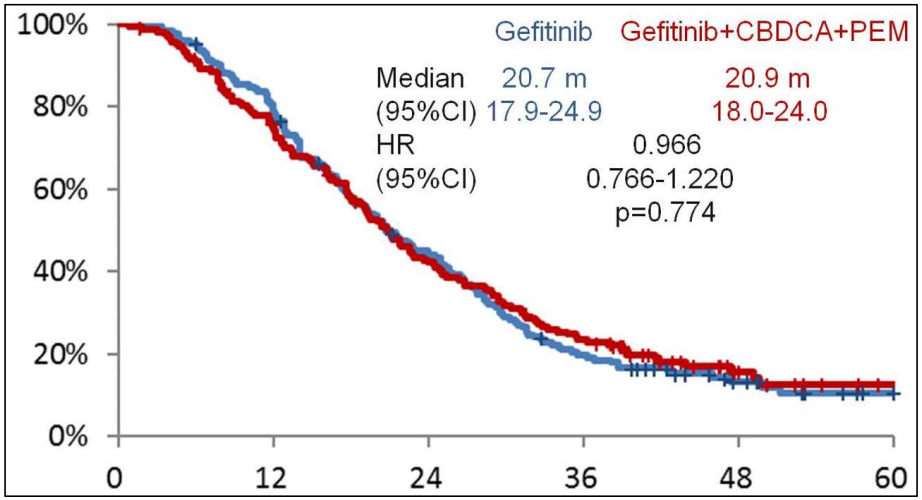


Overall Survival

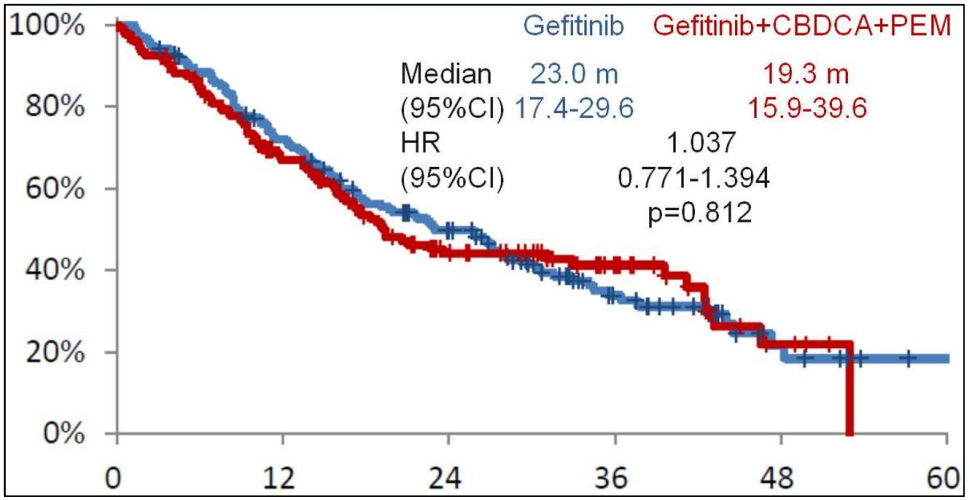


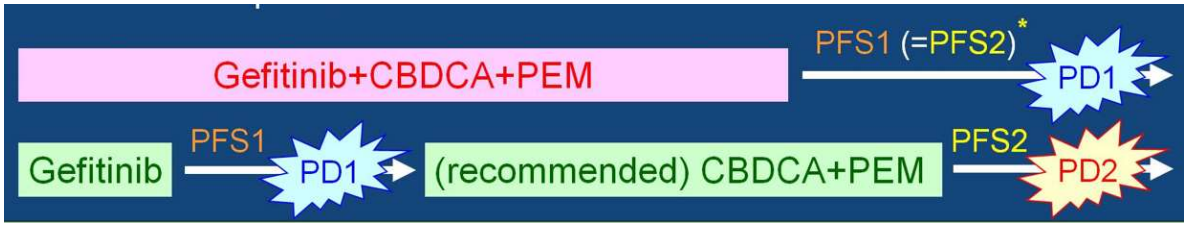
After PD1

Progression-Free Survival 2



Survival beyond 1st Progression





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Nakamura ASCO 2018

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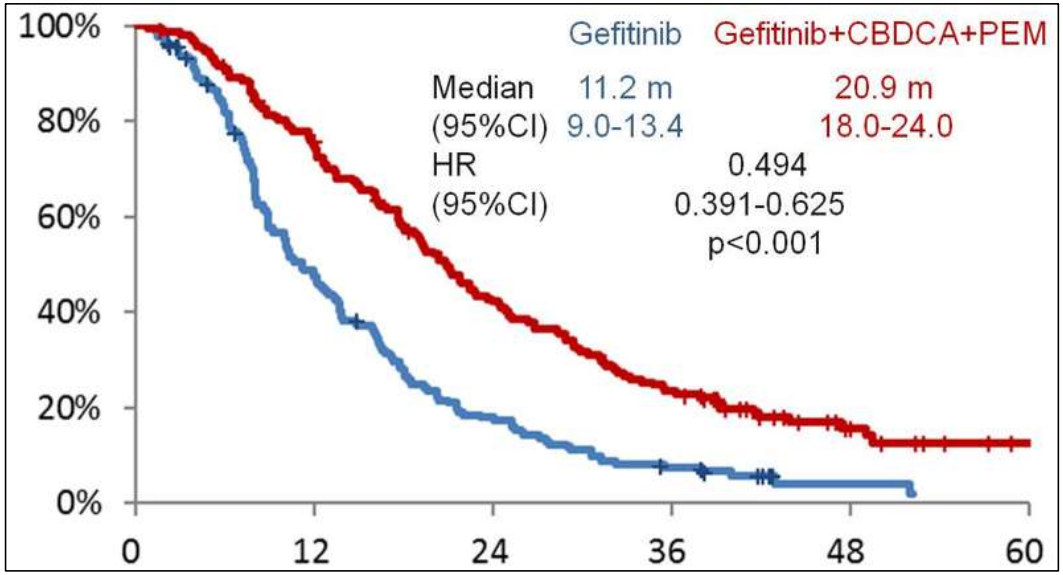
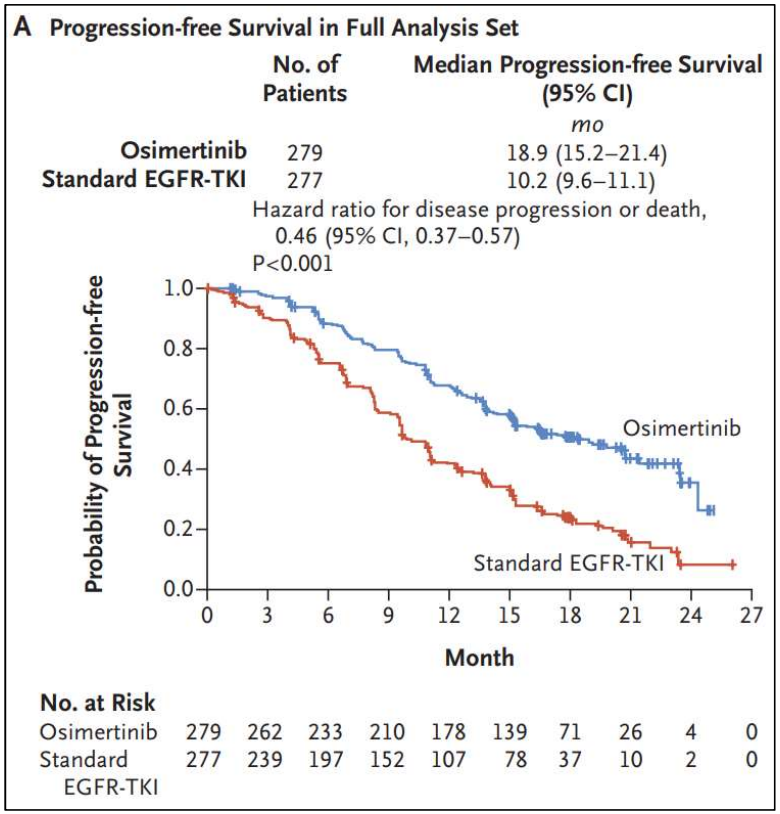
But osimertinib…



Nakamura ASCO 2018



Soria et al. NEJM 2018

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Osimertinib + chemotherapy

Safety of osimertinib plus chemotherapy in EGFR-mutant NSCLC.

Zofia Piotrowska, Stephen V. Liu, Alona Muzikansky, Nicolas Marcoux, Mandeep Banwait, Sara Stevens, Kelly Goodwin, Tracey E Lafferty, Jennifer Ackil, Elizabeth A Krueger, Rebecca Suk Heist, Jessica Jiyeong Lin, Justin F. Gainor, Aaron N. Hata, Alice Tsang Shaw, Lecia V. Sequist

- Retrospective review of data
- All patients had progression on 3rd generation EGFR-TKI monotherapy before the addition of chemo (multiple different regimens)

Adverse Event (n = 25)	Any Grade	Grade ≥ 3
AST/ALT Elevation	9 (36%)	1 (1%)
Anemia	20 (80%)	1 (1%)
Neutropenia	11 (44%)	6 (24%)
Thrombocytopenia	17 (68%)	1 (1%)

Piatrowska et al. JCO abstract 2018

Safety analysis of an open label, randomized phase 2 study of osimertinib alone versus osimertinib plus carboplatin-pemetrexed for patients with non–small cell lung cancer (NSCLC) that progressed during prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy and which harbors a T790M mutation of EGFR.

Morihito Okada, Kentaro Tanaka, Hajime Asahina, Taishi Harada, Kosuke Hamai, Kana Watanabe, Kunihiko Kobayashi, Kenji Sugio, Satoshi Oizumi, Isamu Okamoto

- Randomized Osimertinib +/- carbo/pemetrexed in T790M+
- Toxicity profile in combination arm similar to prior carbo/pem studies

Okada et al. JCO abstract 2018

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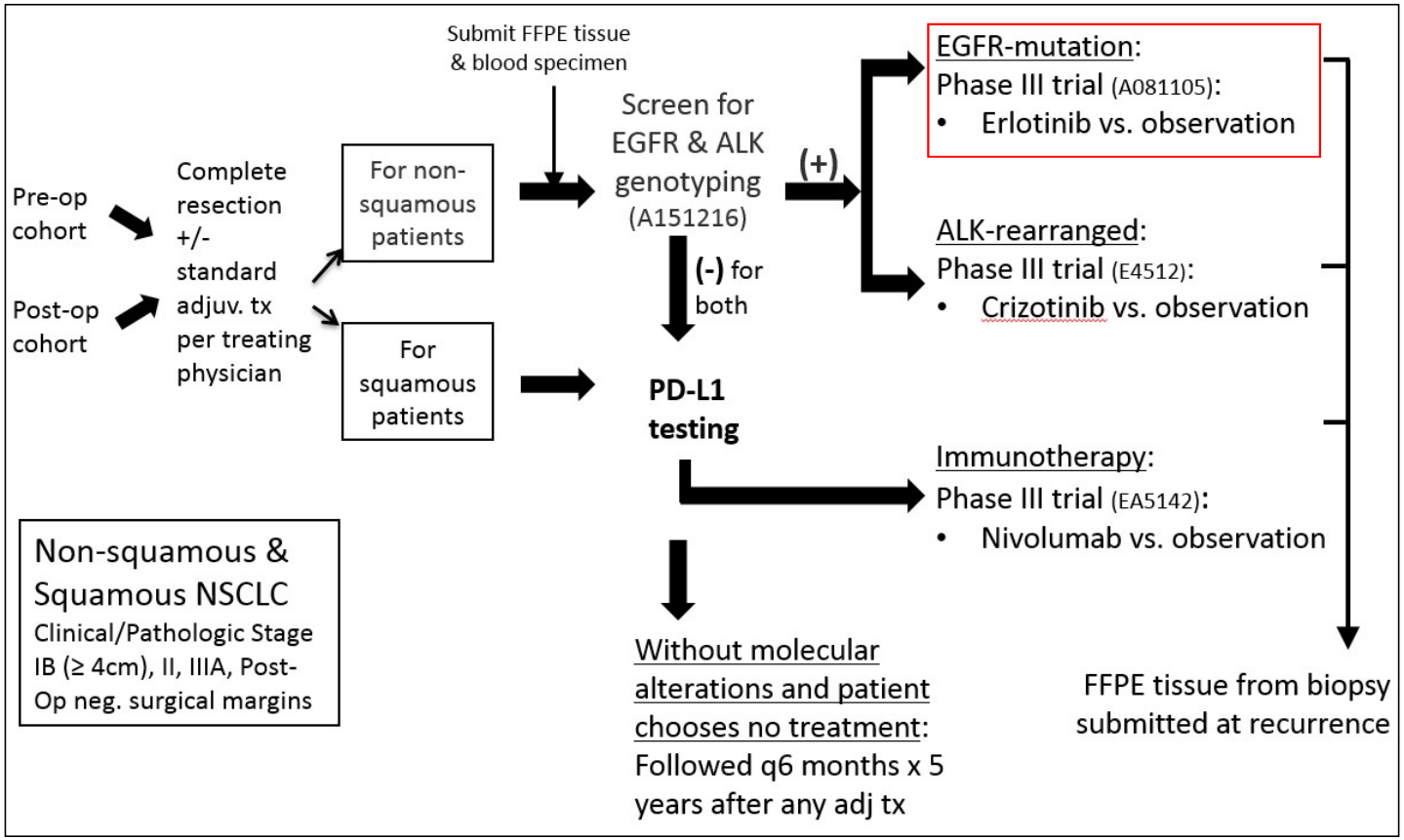
What about early stage???

ALCHEMIST



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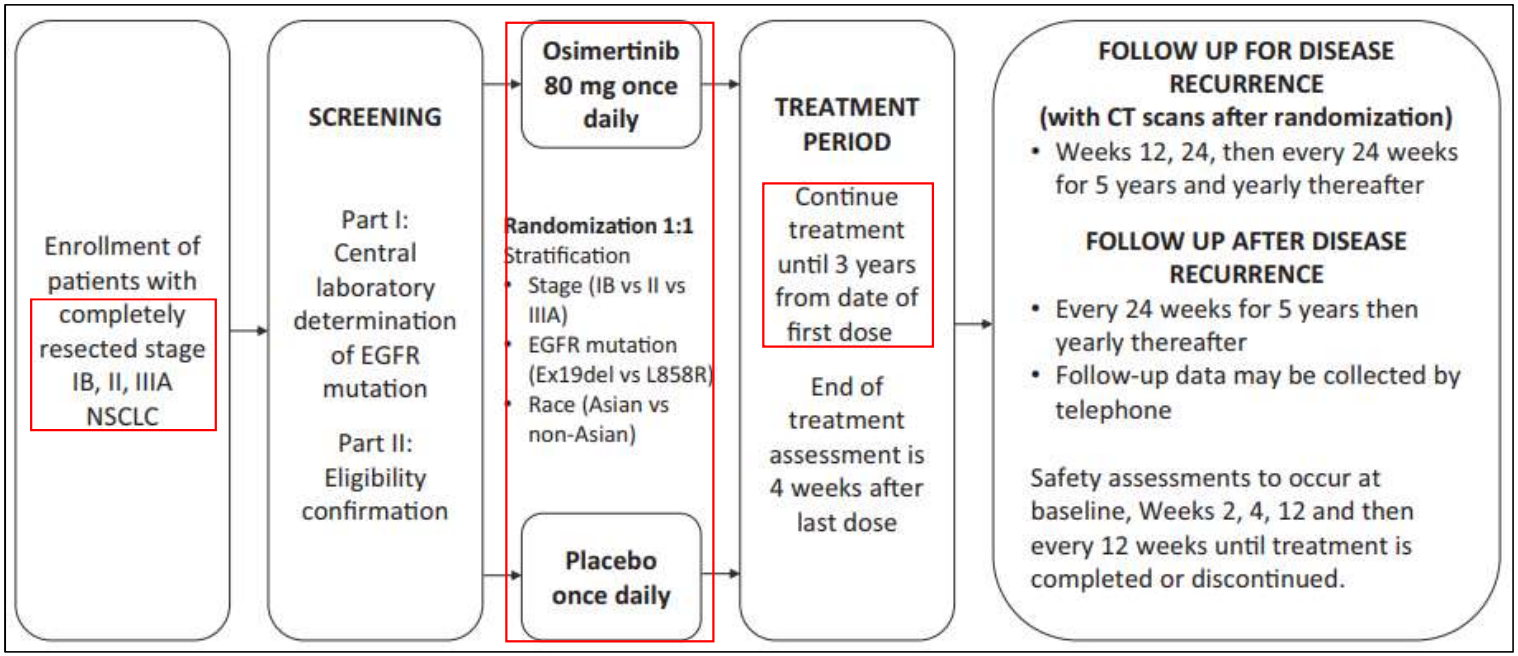
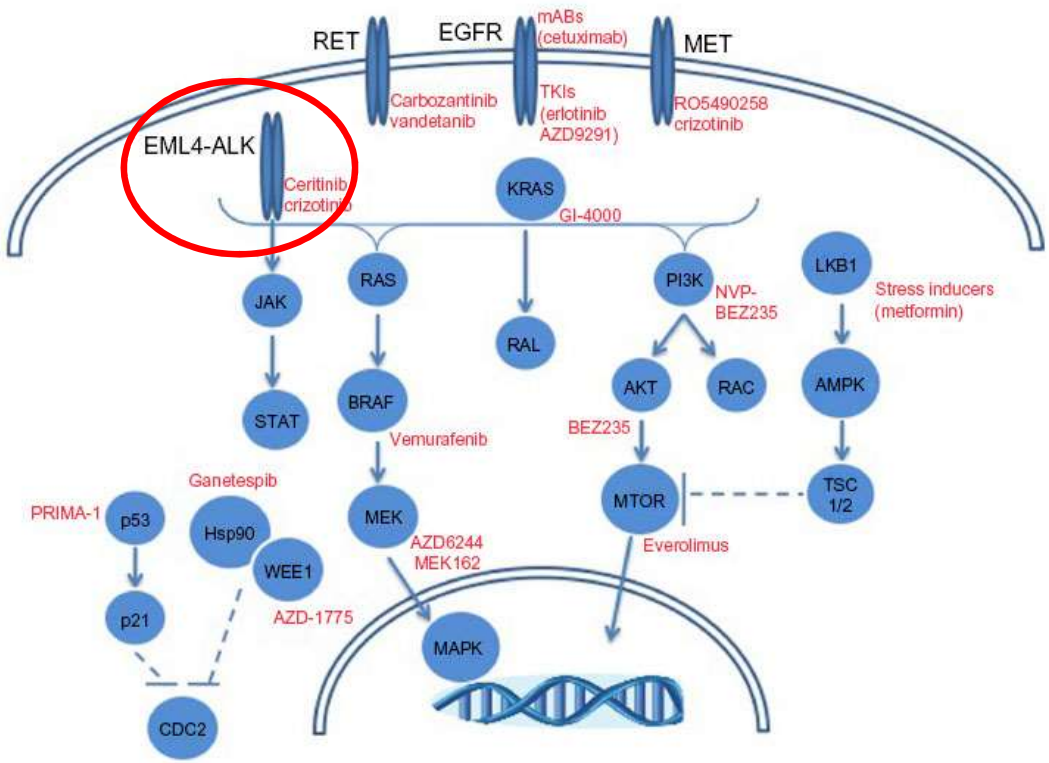
ADAURA


Enrollment of patients with completely resected stage IB, II, IIIA NSCLC
SCREENING
Part I: Central laboratory determination of EGFR mutation
Part II: Eligibility confirmation
Osimertinib 80 mg once daily
Randomization 1:1
Stratification
Stage (IB vs II vs IIIA)
EGFR mutation (Ex19del vs L858R)
Race (Asian vs non-Asian)
Placebo once daily
TREATMENT PERIOD
Continue treatment until 3 years from date of first dose
End of treatment assessment is 4 weeks after last dose
FOLLOW UP FOR DISEASE RECURRENCE
(with CT scans after randomization)
Weeks 12, 24, then every 24 weeks for 5 years and yearly thereafter
FOLLOW UP AFTER DISEASE RECURRENCE
Every 24 weeks for 5 years then yearly thereafter
Follow-up data may be collected by telephone
Safety assessments to occur at baseline, Weeks 2, 4, 12 and then every 12 weeks until treatment is completed or discontinued.

ALK


RET
EGFR
mABs
(cetuximab)
MET
Carbozantinib
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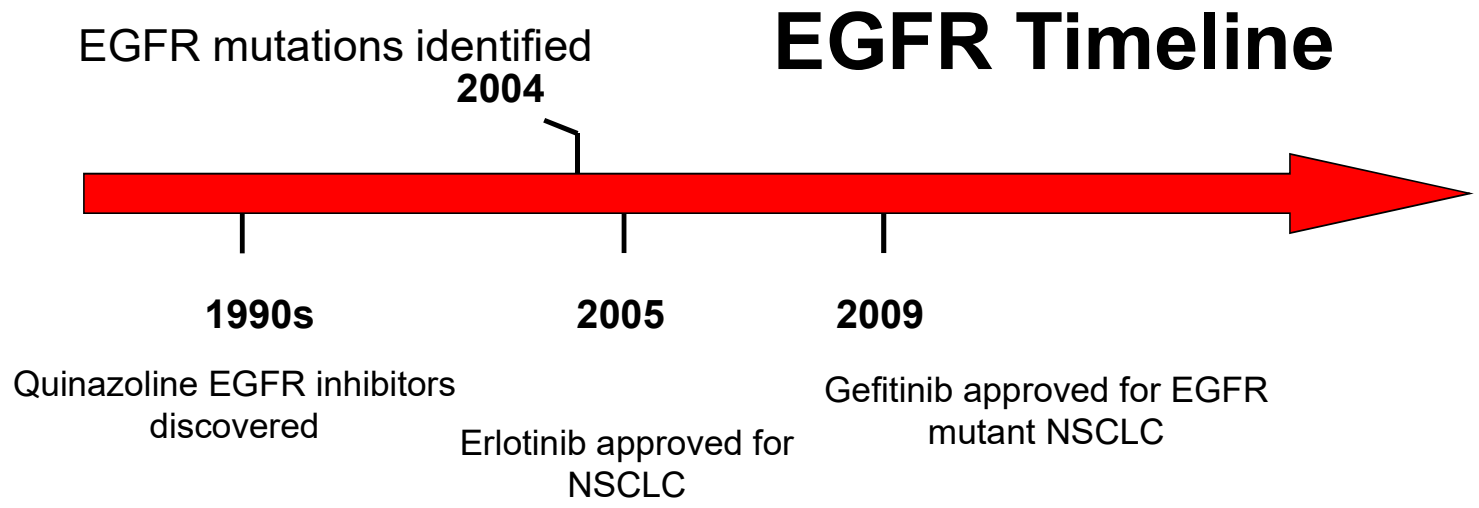
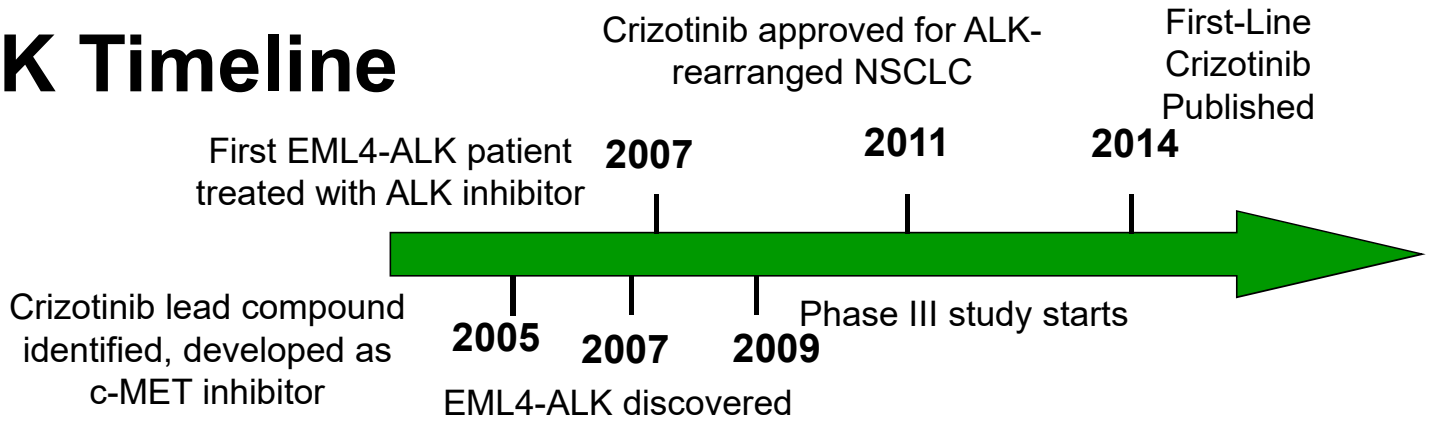
(erlotinib
AZD9291)
RO5490258
crizotinib
EML4-ALK
Ceritinib
crizotinib
KRAS
GI-4000
JAK
RAS
RAL
PI3K
NVP-
BEZ235
LKB1
Stress inducers
(metformin)
STAT
BRAF
Vemurafenib
AKT
RAC
AMPK
BEZ235
Ganetespib
PRIMA-1
p53
Hsp90
MEK
MTOR
TSC
1/2
WEE1
AZD6244
MEK162
Everolimus
p21
AZD-1775
MAPK
CDC2

EGFR Timeline

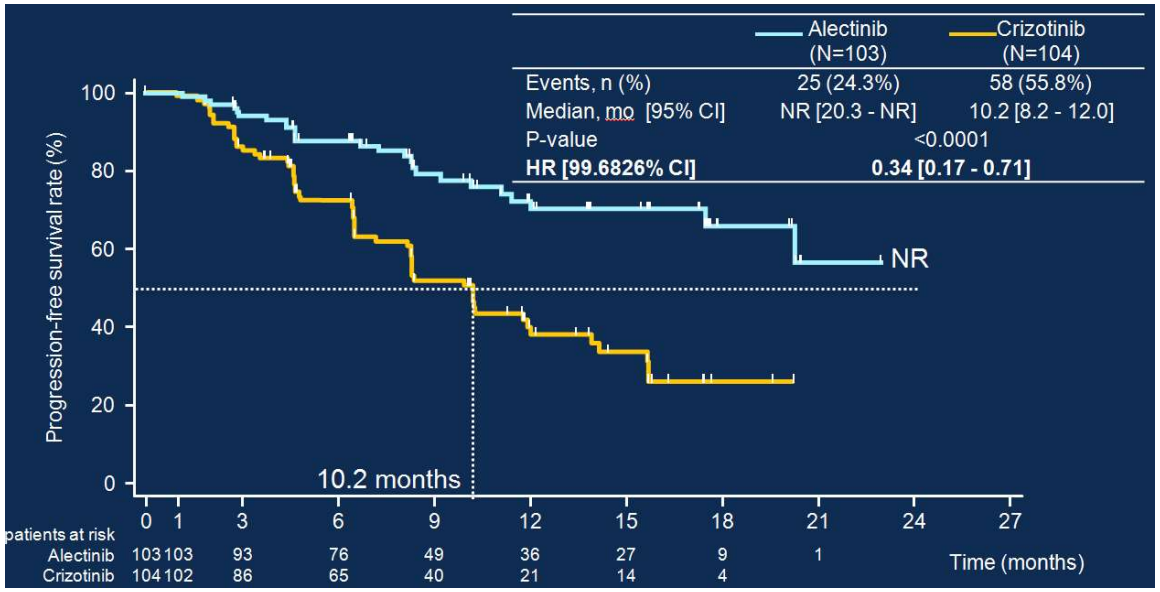


ALK Timeline



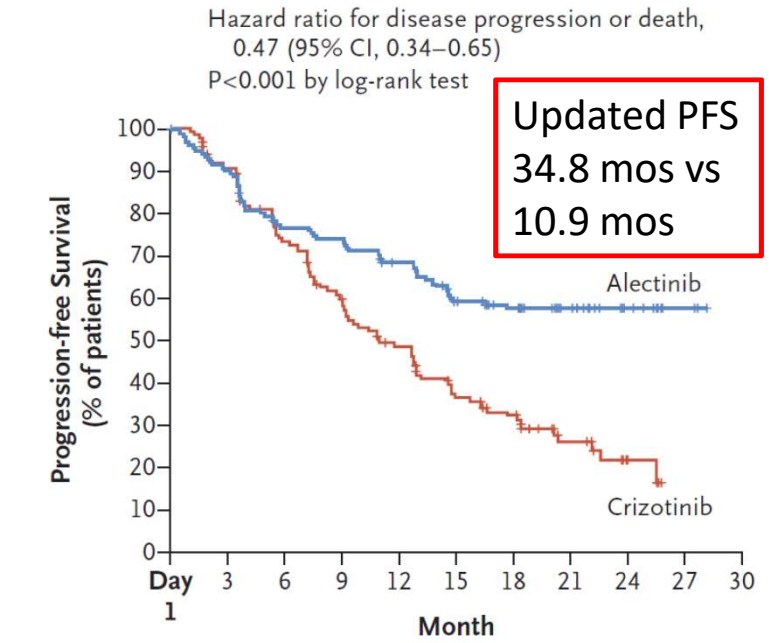
First line alectinib

- J-ALEX trial studied alectinib (300mg BID) versus crizotinib in 200 patients with TKI-naïve ALK+ NSCLC



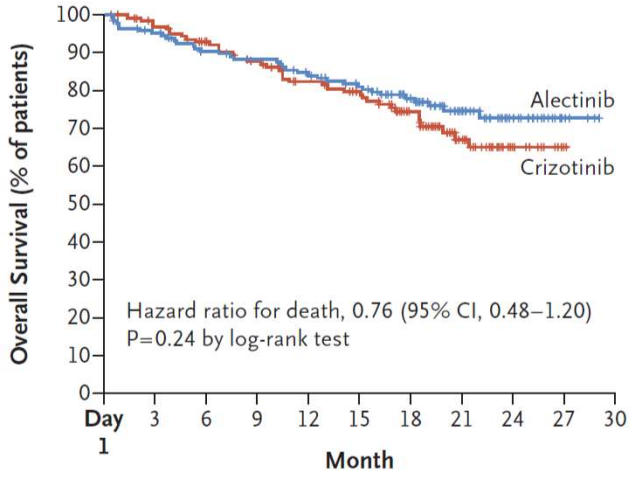
Nokihara et al, ASCO, 2016

First line alectinib



Updated PFS
34.8 mos vs
10.9 mos

No. at Risk										
Alectinib	152	135	113	109	97	81	67	35	15	3
Crizotinib	151	132	104	84	65	46	35	16	5	

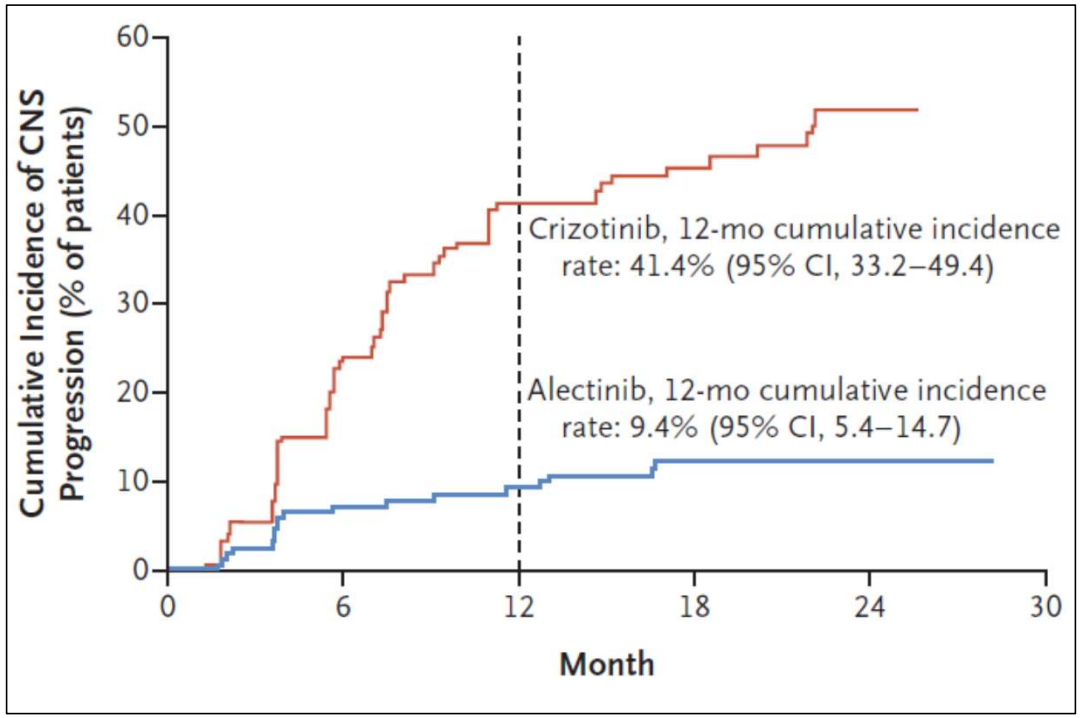


No. at Risk										
Alectinib	152	142	131	127	119	107	87	51	24	5
Crizotinib	151	141	127	115	103	95	73	33	13	1

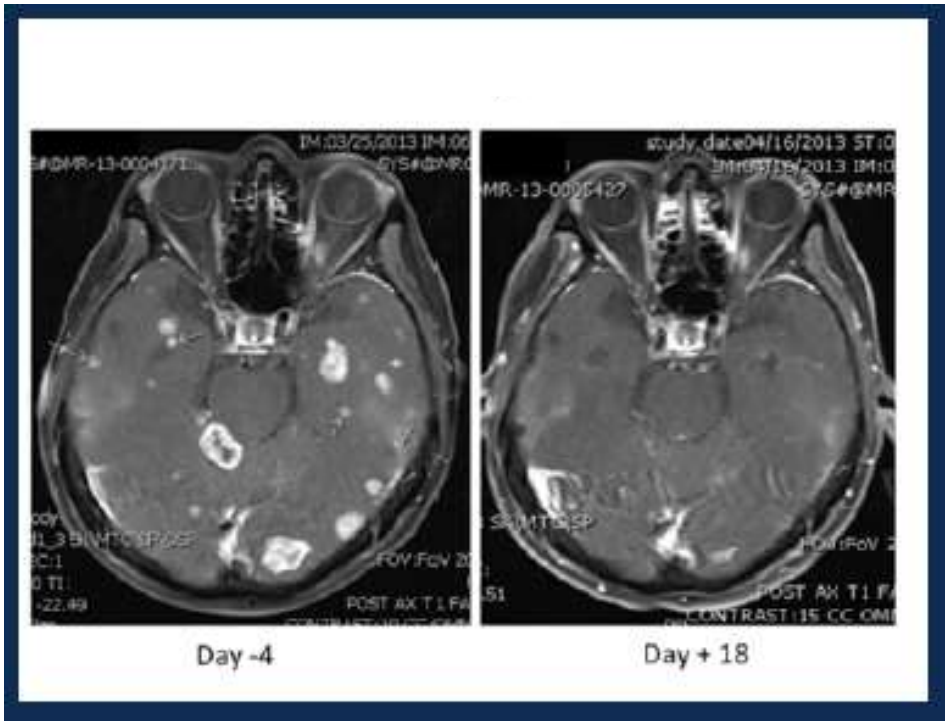
Peters et al. NEJM 2017

CNS Efficacy

- Significant responses and improvement in PFS with alectinib

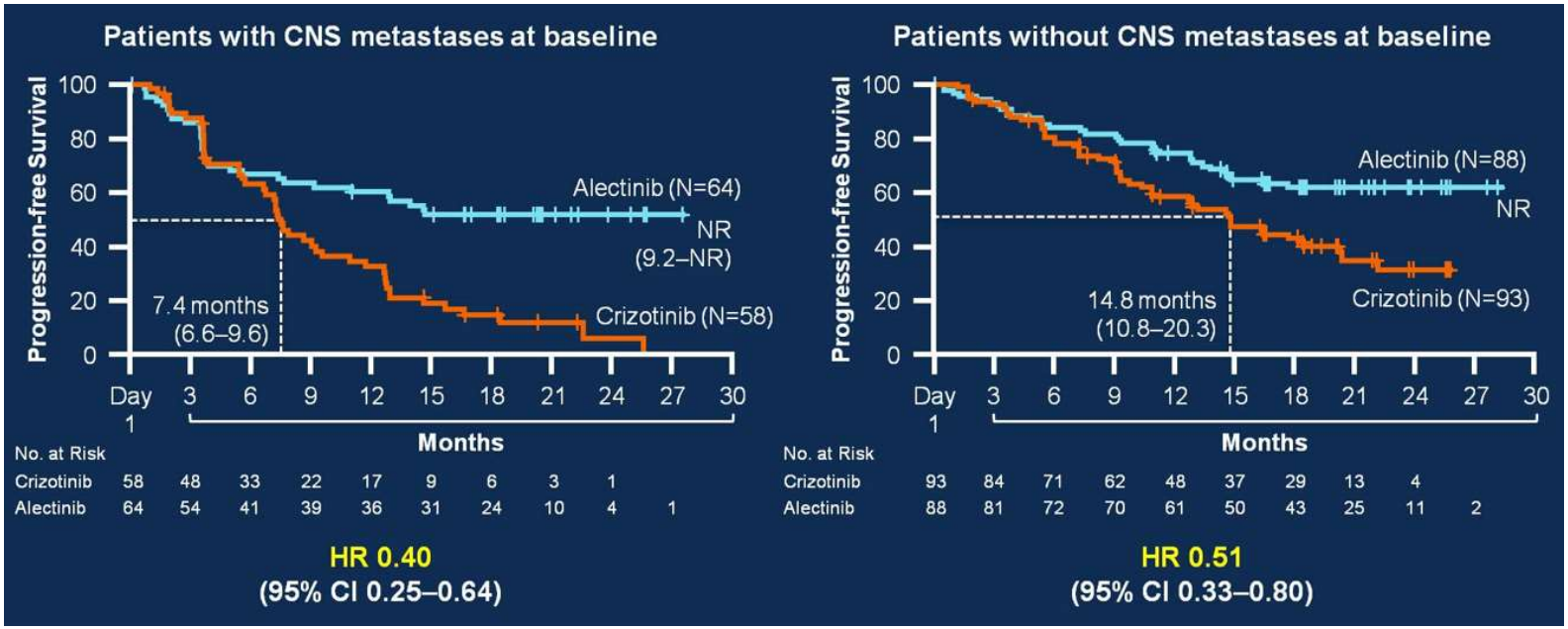


Peters et al. NEJM 2017



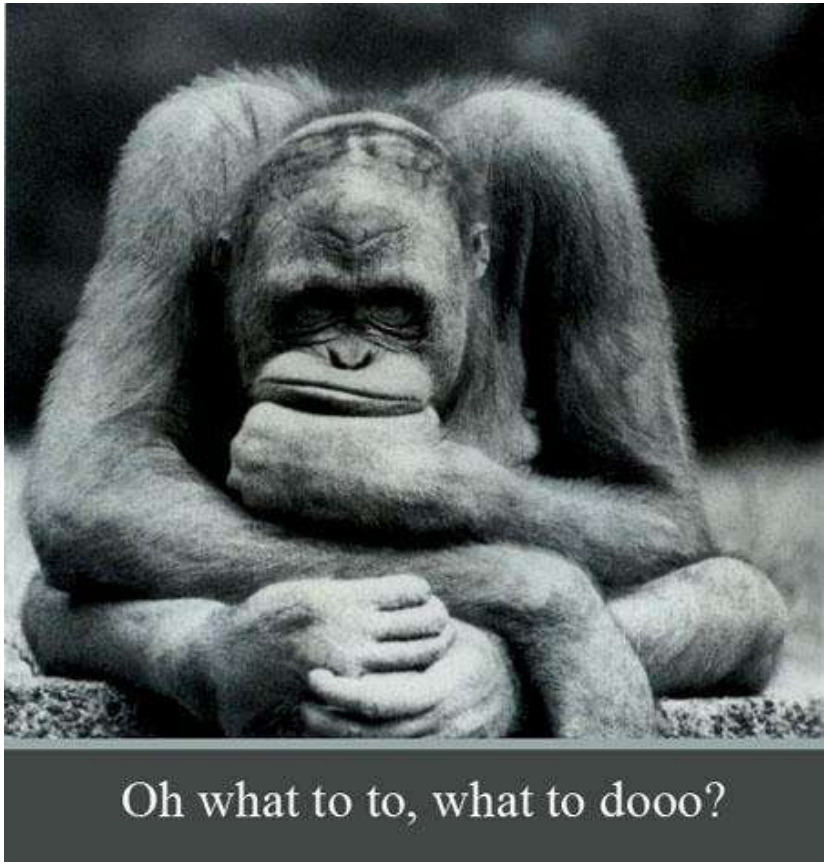
Ou et al, WCLC, 2013

CNS Efficacy



Slide from Alice Shaw ASCO 2017

At Progression…



Lots of ALK Inhibitors

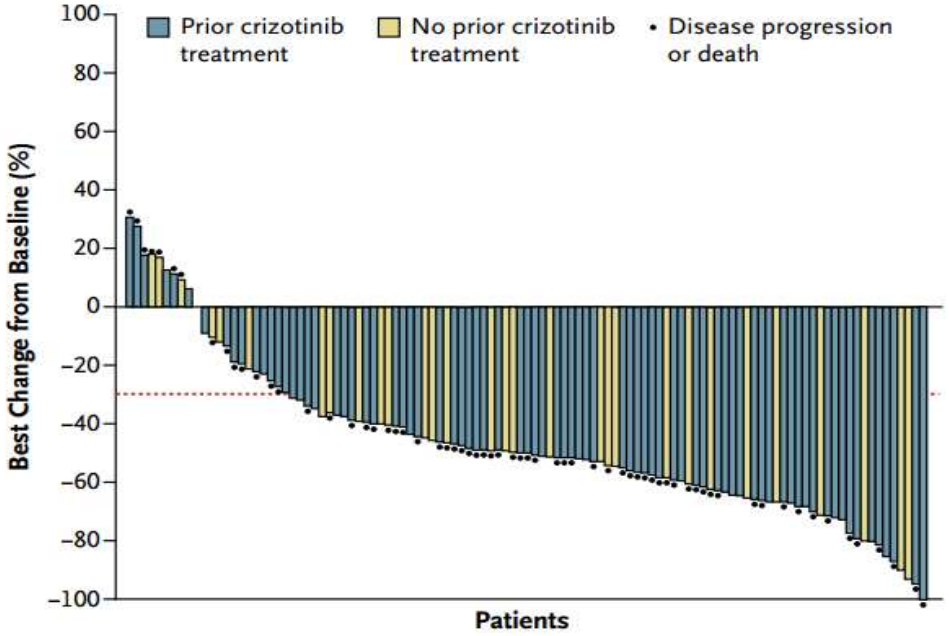
	Crizotinib	Ceritinib	Alectinib	Brigatinib
Indication	ALK+ NSCLC	ALK resistance	ALK resistance	ALK resistance
Highly active	Yes	Yes	Yes	Yes
Tolerability	Good	Moderate	Good	Good
CNS activity	Some	Good	Good	Good
Potency against resistance	Poor	Moderate	Moderate	Good

- **All of these agents are highly active against ALK**
- **Other characteristics must be compared when selecting the optimal treatment for ALK+ patients.**

Kwak et al, NEJM, 2010; Awad et al, Clin Adv Hematol Oncol, 2014
[1]Kodama et al, MCT, 2014; [2]Costa et al, JCO, 2015

Ceritinib

- Phase I trial of ceritinib in ALK+ NSCLC
  - 67% RR in 114 patients on >400mg daily



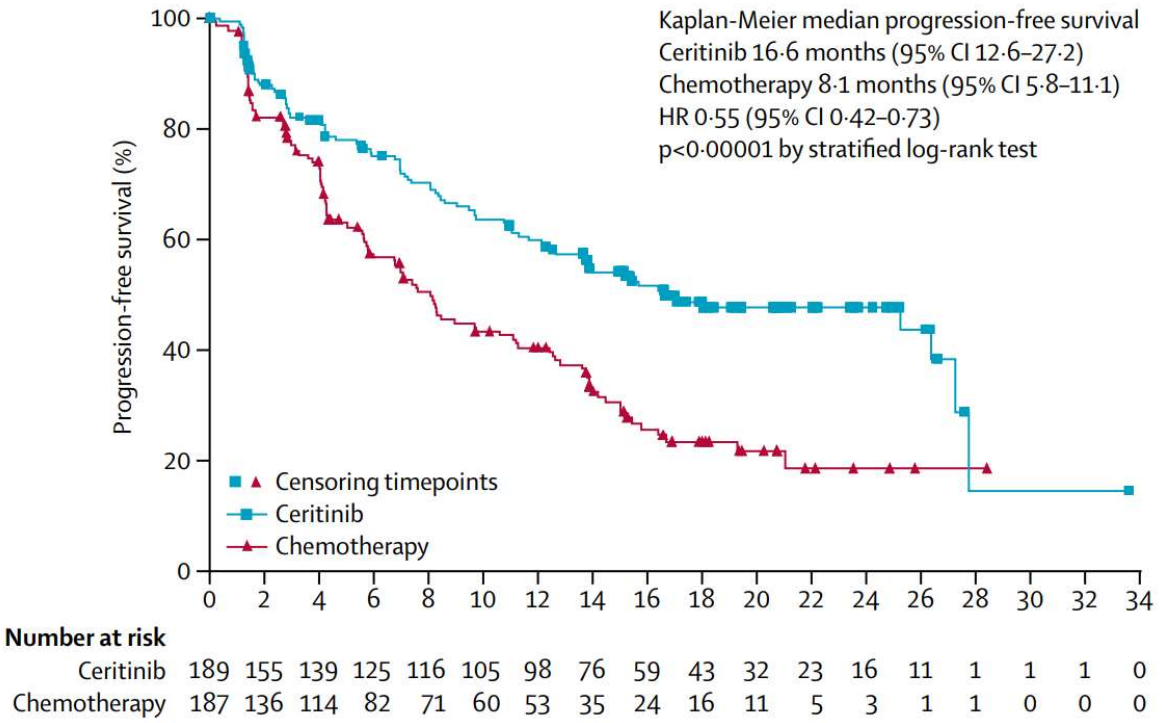
Shaw et al, NEJM, 2014

Ceritinib

- Phase I trial of ceritinib in ALK+ NSCLC
  - 67% RR in 114 patients on >400mg daily
- Phase II trial in 140 patients with crizotinib resistance (ASCEND-2): reported 38% RR and 5.7mos median PFS
  - 45% intracranial response rate
- At full dose (750mg daily), 62% of patients require dose reduction, generally due to nausea, diarrhea, anorexia, LFT elevation

Shaw et al, NEJM, 2014; Mok et al, ASCO, 2015

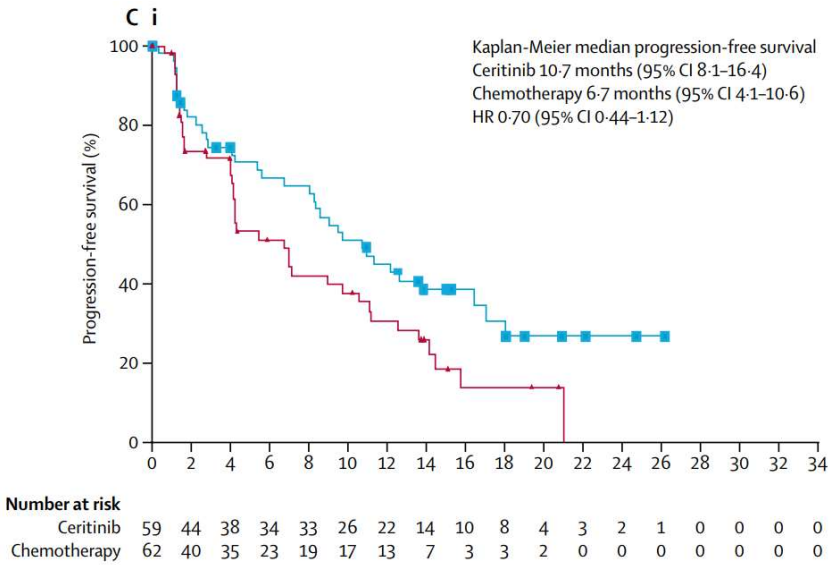
Ceritinib First Line



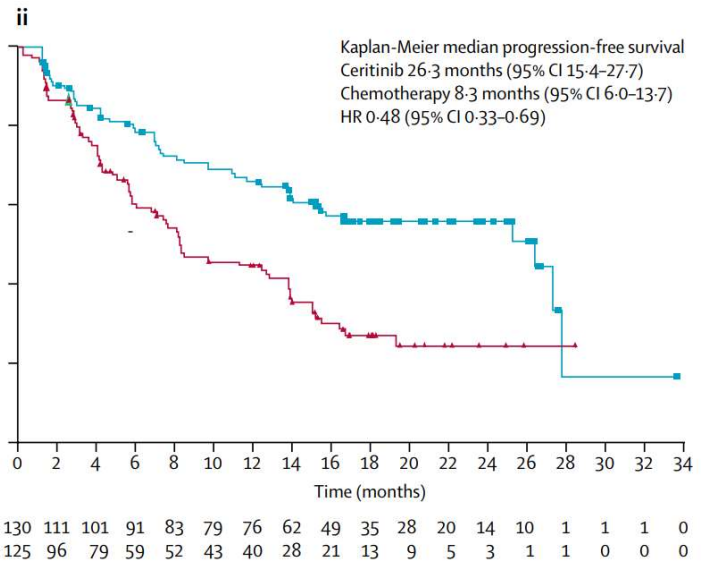
Shaw et al, NEJM, 2014; Mok et al, ASCO, 2015

Ceritinib First Line

Baseline brain mets



Baseline no CNS disease



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	Ceritinib (n=189)		Chemotherapy (n=175)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse event	189 (100%)	148 (78%)	170 (97%)	108 (62%)
Diarrhoea	160 (85%)	10 (5%)	19 (11%)	2 (1%)
Nausea	130 (69%)	5 (3%)	97 (55%)	9 (5%)
Vomiting	125 (66%)	10 (5%)	63 (36%)	10 (6%)
Alanine aminotransferase increased	114 (60%)	58 (31%)	38 (22%)	5 (3%)
Aspartate aminotransferase increased	100 (53%)	32 (17%)	34 (19%)	3 (2%)
Gamma-glutamyltransferase increased	70 (37%)	54 (29%)	18 (10%)	3 (2%)
Decreased appetite	64 (34%)	2 (1%)	55 (31%)	2 (1%)
Blood alkaline phosphatase increased	55 (29%)	14 (7%)	8 (5%)	1 (1%)
Fatigue	55 (29%)	8 (4%)	52 (30%)	5 (3%)
Abdominal pain	47 (25%)	4 (2%)	13 (7%)	0
Cough	46 (24%)	0	28 (16%)	0
Weight decreased	45 (24%)	7 (4%)	26 (15%)	1 (1%)
Blood creatinine increased	42 (22%)	4 (2%)	17 (10%)	0
Upper abdominal pain	39 (21%)	3 (2%)	10 (6%)	0
Non-cardiac chest pain	38 (20%)	2 (1%)	17 (10%)	1 (1%)
Back pain	36 (19%)	3 (2%)	32 (18%)	4 (2%)
Constipation	36 (19%)	0	38 (22%)	0
Pyrexia	34 (18%)	0	24 (14%)	2 (1%)
Asthenia	33 (17·5)	5 (3%)	36 (21%)	6 (3%)
Headache	31 (16%)	0	21 (12%)	2 (1%)
Dyspnoea	29 (15%)	4 (2%)	35 (20%)	11 (6%)
Anaemia	28 (15%)	4 (2%)	62 (35%)	13 (7%)
Neutropenia	9 (5%)	1 (1%)	38 (22%)	19 (11%)
White blood cell count decreased	7 (4%)	0	31 (18%)	7 (4%)

Data are n (%).

***Table 3*: Adverse events regardless of study drug relationship in the safety set (>15% of patients in either group)**

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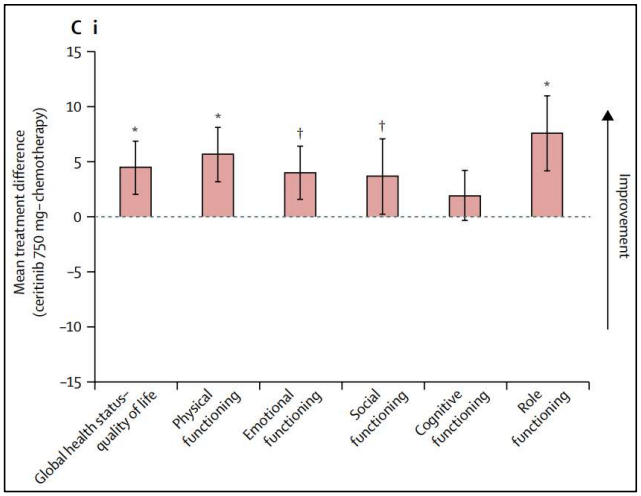
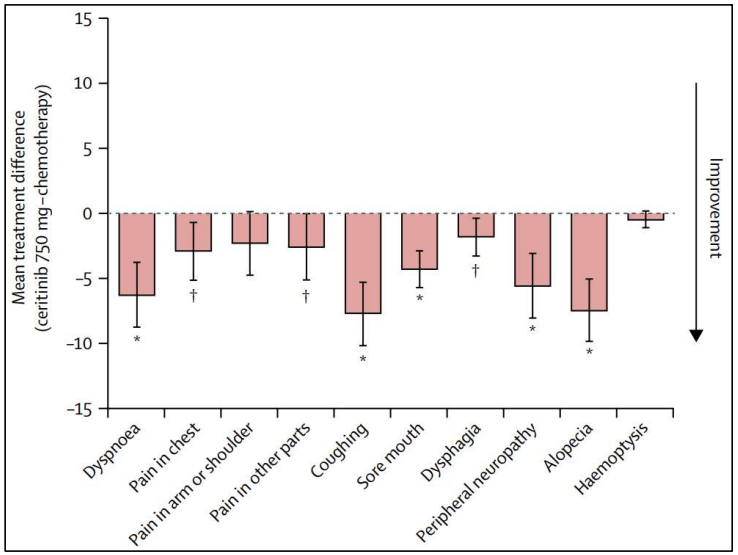
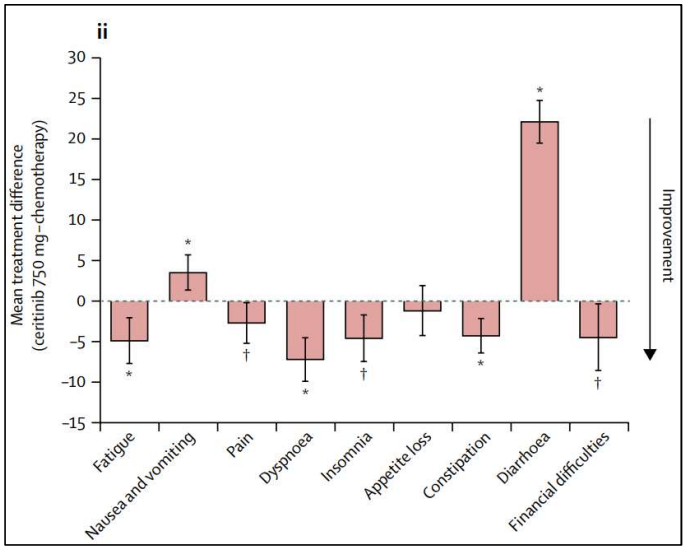
Ceritinib QOL







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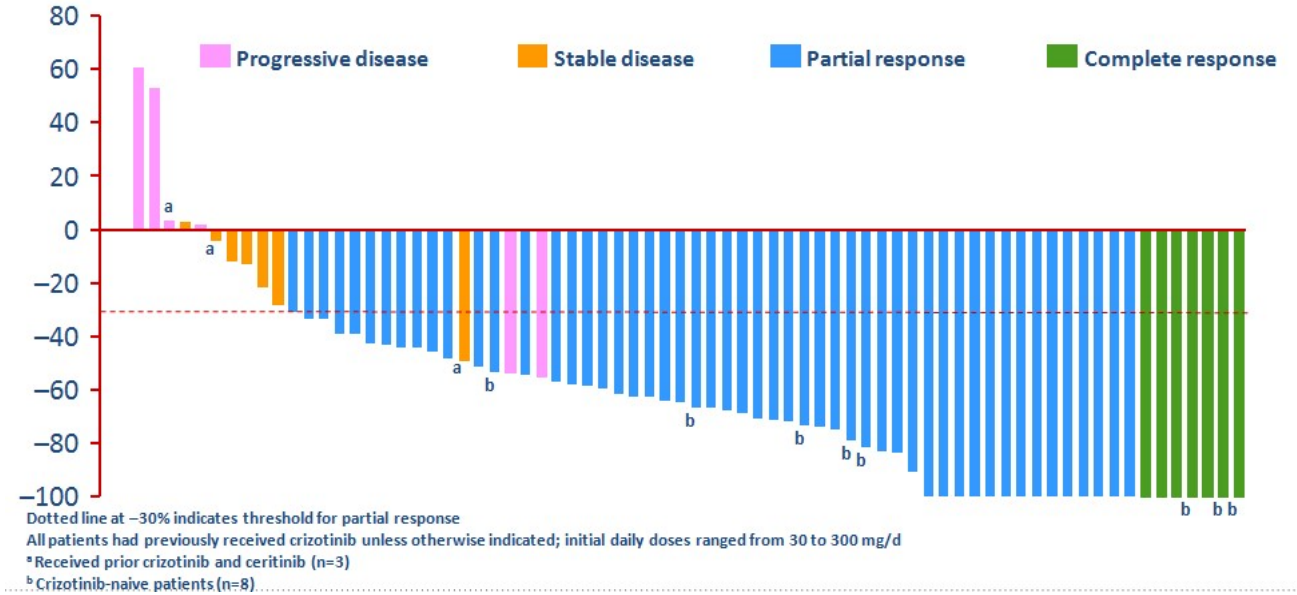
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Brigatinib

- Received breakthrough status for 72% RR in crizotinib-resistant patients



Langer et al, ASCO, 2016

Brigatinib

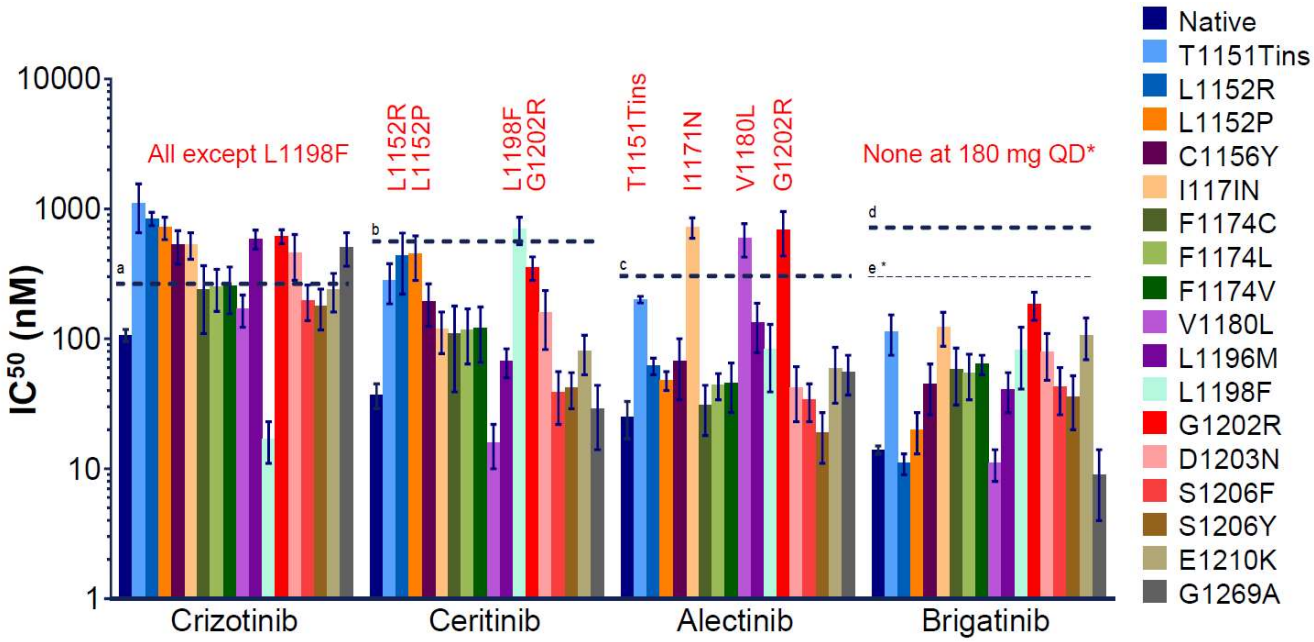
- Received breakthrough status for 72% RR in crizotinib-resistant patients
- FDA-approved April 28, 2017 post crizotinib

- Early pulmonary toxicity (cough, hypoxia, infiltrates) is seen within 1-2 weeks in a small number of patients, resulting in an atypical dosing strategy:
  - 90mg daily x1 week
  - Then 180mg daily until progression

Langer et al, ASCO, 2016

Brigatinib

- Developed for activity against a wide range of resistance mutations



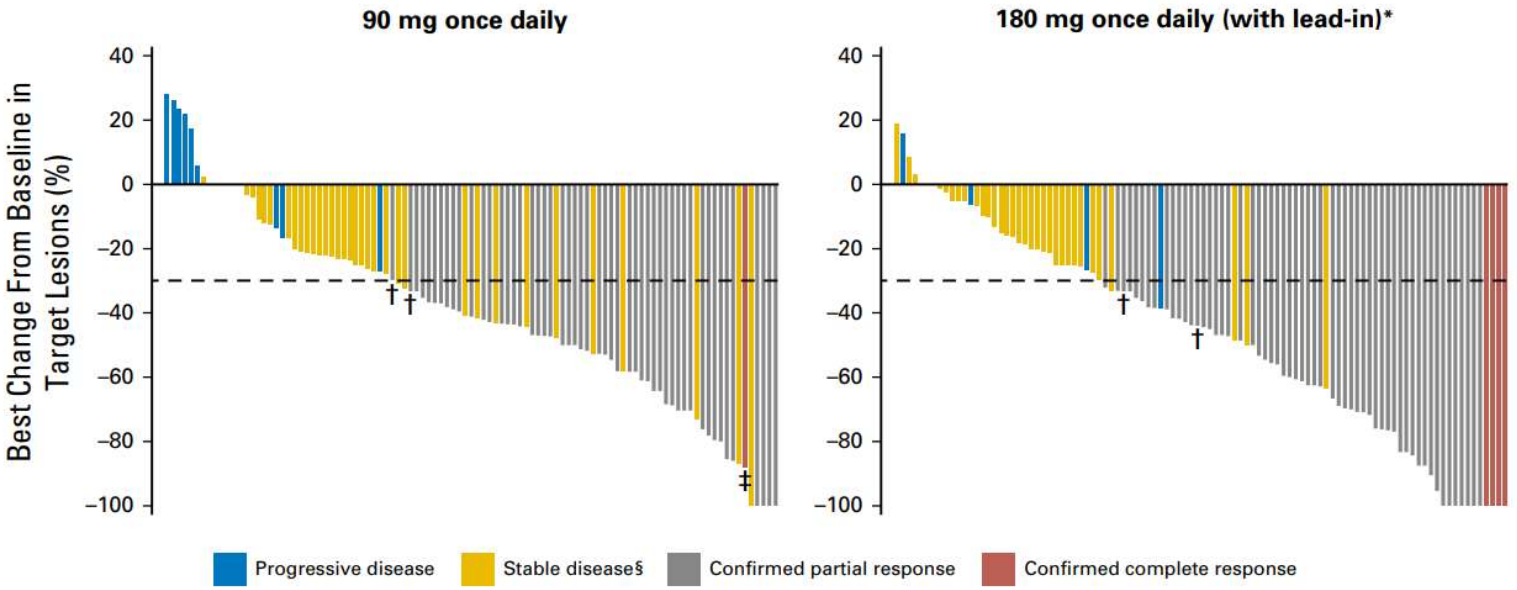
Gettinger et al, ASCO, 2016

Brigatinib

- ALTA trial randomized 222 NSCLC patients with crizotinib-resistance to 2 different doses of brigatinib
  - Early pulmonary toxicity seen in 6% of pts (3% grade 3, patients often could be re-challenged at lower dose)

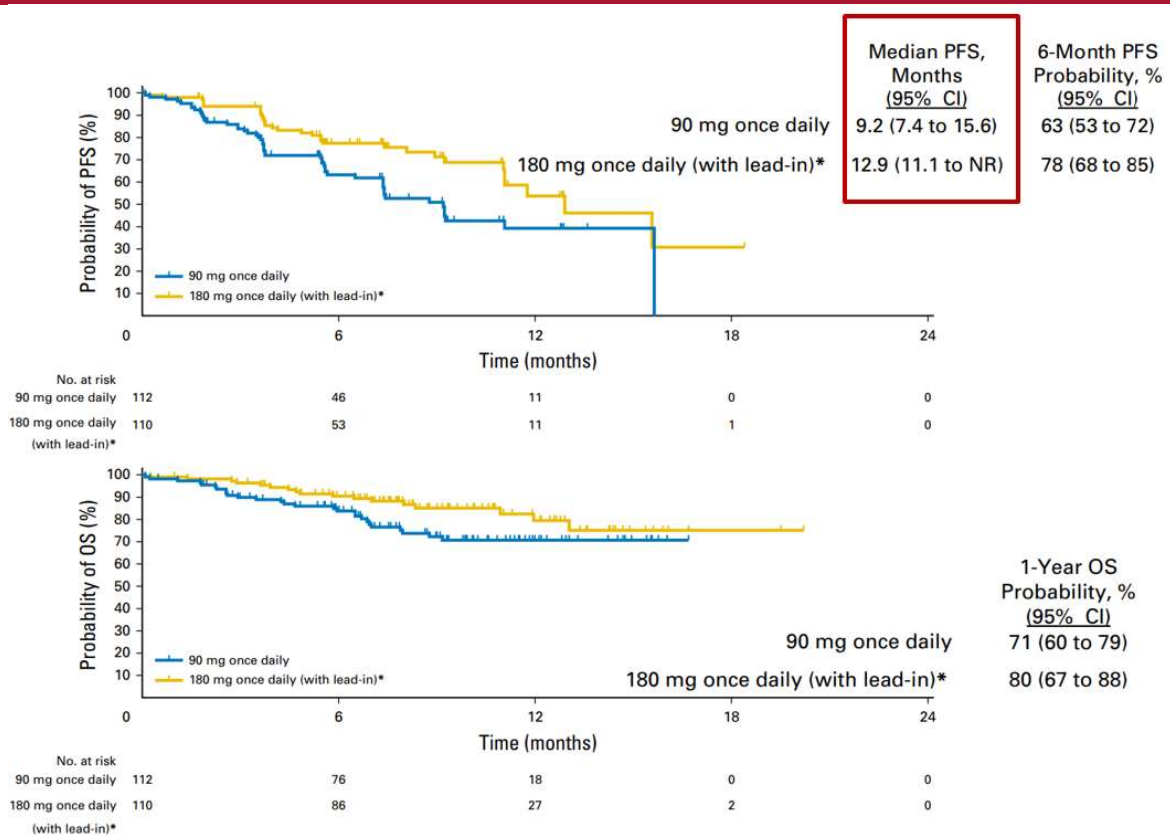
Kim et al, ASCO, 2016

Brigatinib



Kim et al, JCO, 2017

Brigatinib



Kim et al, JCO, 2017

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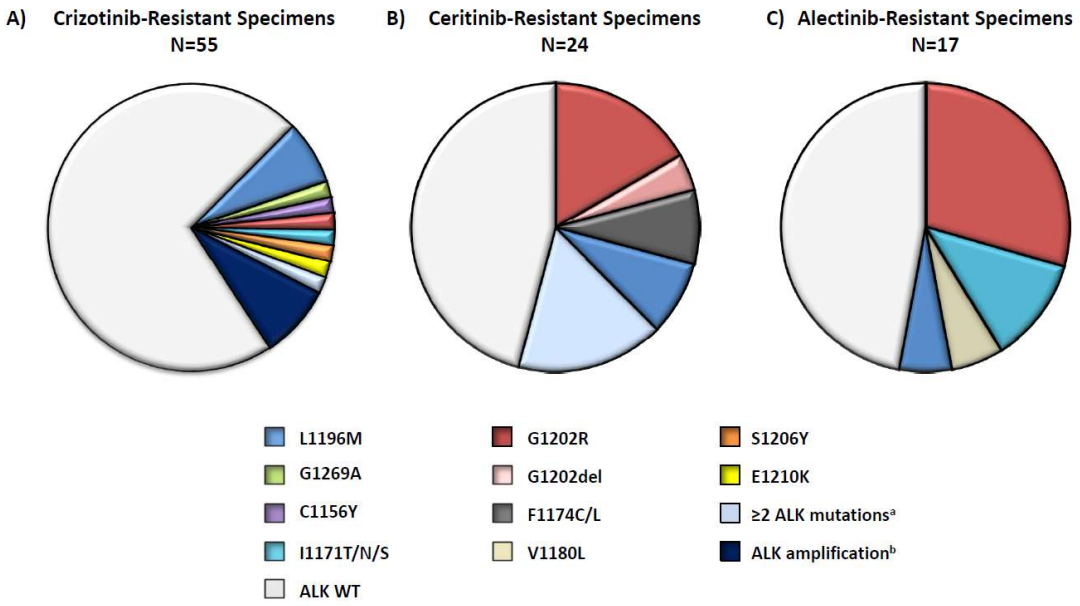
ALK Resistance

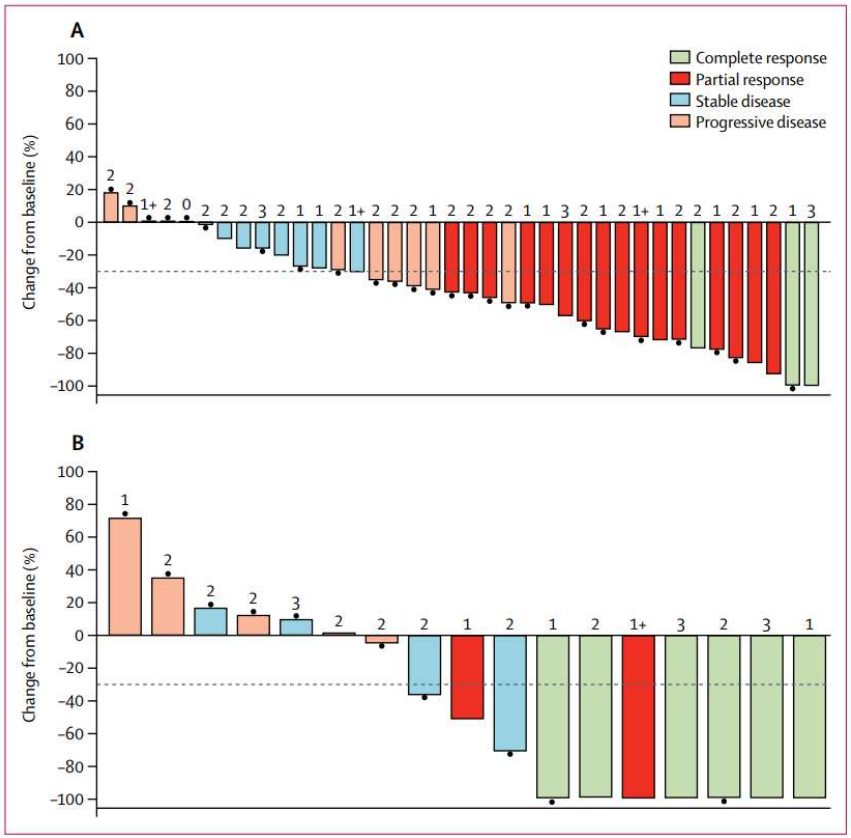
- Emerging data suggests that newer ALK inhibitors alter the spectrum of resistance mutations, inducing more ALK resistance mutations



Gainor et al, Cancer Disc, 2016

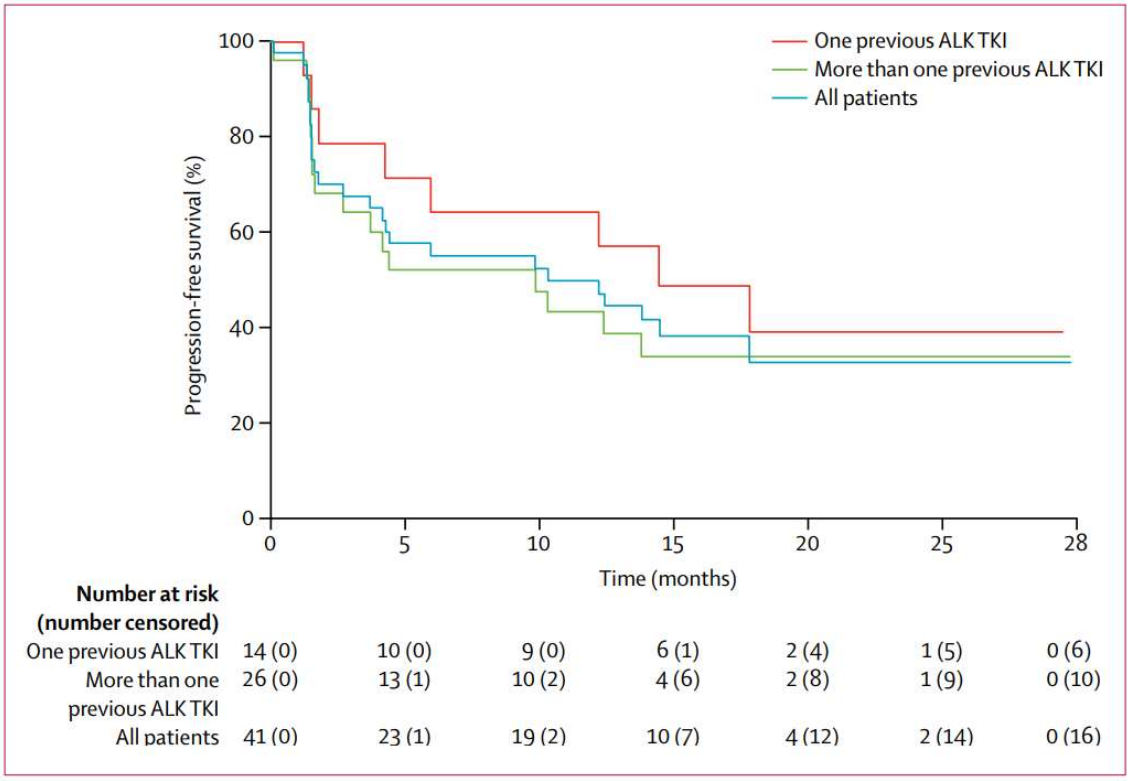
Lorlatinib

- Phase I Study
  - ALK or ROS1
- Previous ALK or ROS1 TKI
  - None: 6 (11%)
  - One: 20 (37%)
  - ≥Two: 28 (52%)



Shaw et al. Lancet Oncol 2017

Lorlatinib

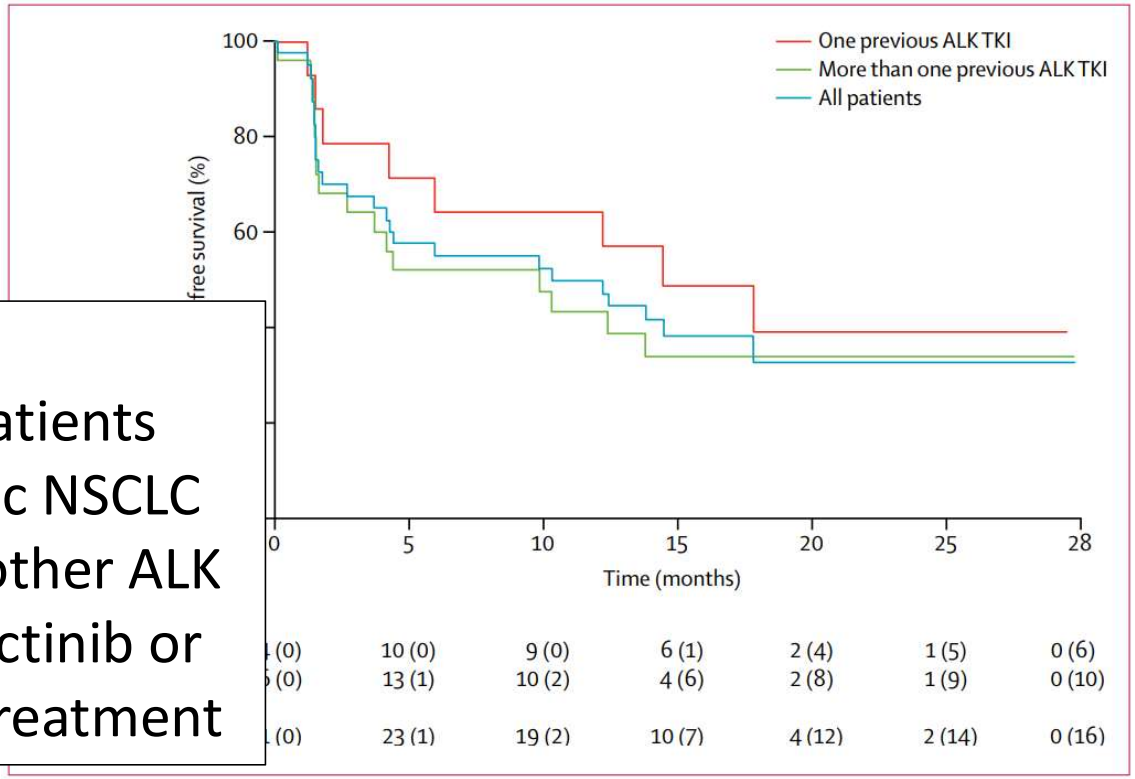


Number at risk (number censored)							
One previous ALK TKI	14 (0)	10 (0)	9 (0)	6 (1)	2 (4)	1 (5)	0 (6)
More than one previous ALK TKI	26 (0)	13 (1)	10 (2)	4 (6)	2 (8)	1 (9)	0 (10)
All patients	41 (0)	23 (1)	19 (2)	10 (7)	4 (12)	2 (14)	0 (16)

Shaw et al. Lancet Oncol 2017

Lorlatinib

11/2/2018
FDA approved for patients with ALK+ metastatic NSCLC post crizotinib + another ALK inhibitor or post alectinib or ceritinib as 1st line treatment



Shaw et al. Lancet Oncol 2017

ALK Sensitivies

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

Gainor et al. Cancer Disc 2016

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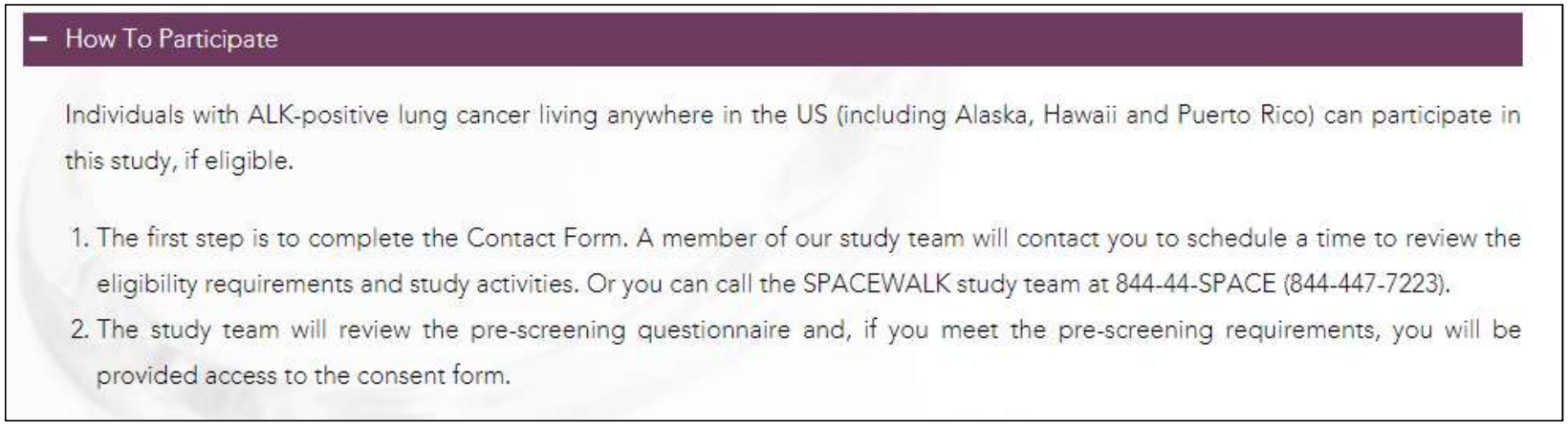
SPACEWALK

- Cell-free DNA analysis at time of progression on ALK inhibitor to look for other actionable resistance mutations.
  - https://alcmi.net/research/spacewalk/



How To Participate

Individuals with ALK-positive lung cancer living anywhere in the US (including Alaska, Hawaii and Puerto Rico) can participate in this study, if eligible.

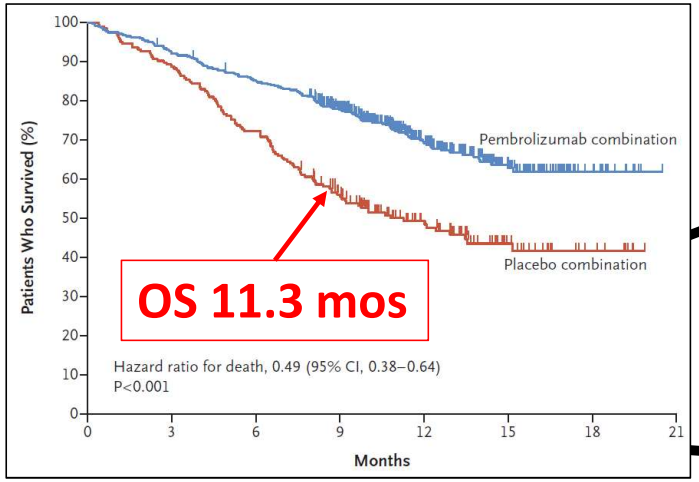
1. The first step is to complete the Contact Form. A member of our study team will contact you to schedule a time to review the eligibility requirements and study activities. Or you can call the SPACEWALK study team at 844-44-SPACE (844-447-7223).
2. The study team will review the pre-screening questionnaire and, if you meet the pre-screening requirements, you will be provided access to the consent form.

Where we were 10 years ago: 2009

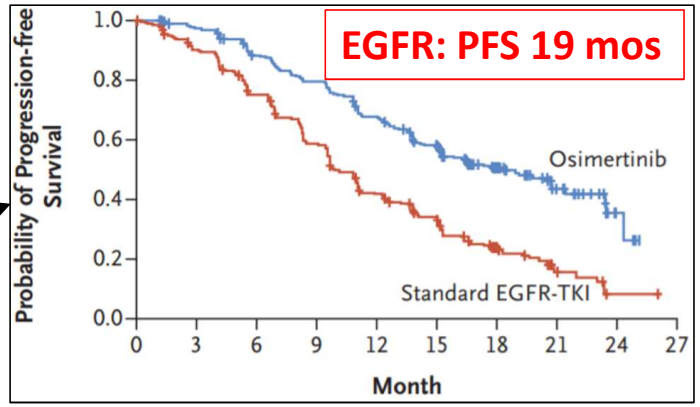
- IPASS published: The first time a targeted monotherapy demonstrated significantly longer PFS than doublet chemotherapy

Where are we now?

- EGFR
  - Osimertinib, dacomitinib, erlotinib, gefitinib, afatinib
- ALK
  - Alectinib, crizotinib, brigatinib, ceritinib, lorlatinib

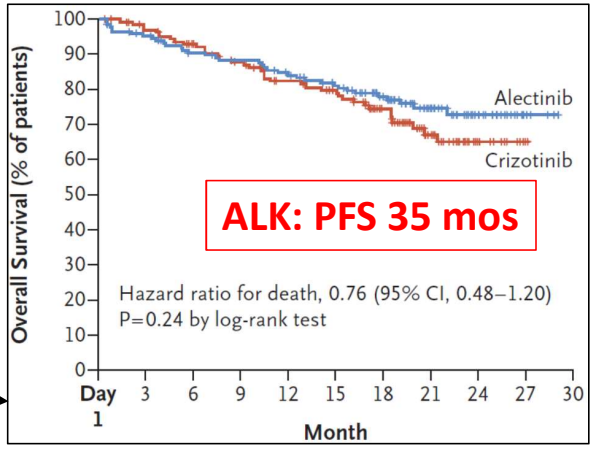


Gandhi et al. NEJM 2018



Soria JC et al. NEJM 2015

Peters et al. NEJM 2017



Take Home Points

- EGFR
  - Osimertinib is 1st line therapy
  - At progression, it is important to do genomics testing
  - Early stage studies available
- ALK
  - Alectinib 1st line
    - Consider SPACEWALK at progression!
  - Lorlatinib next line option
- Important to get full panel NGS testing!

Thank you