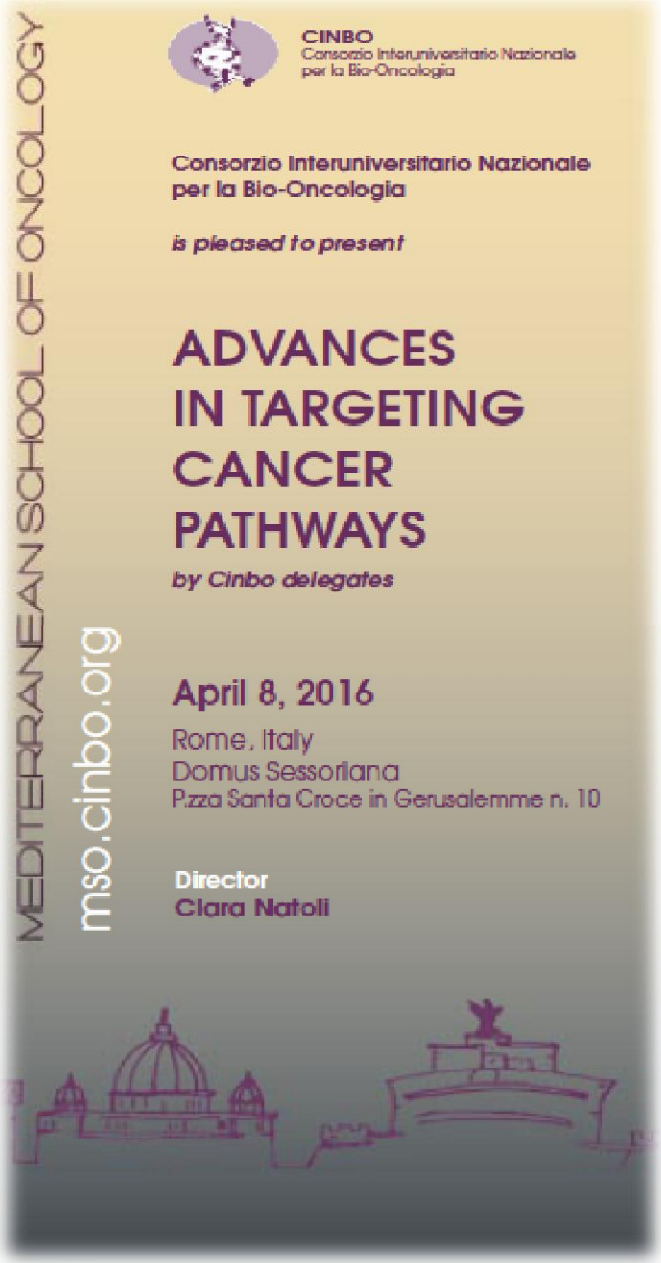


TARGETING EGFR IN NSCLC

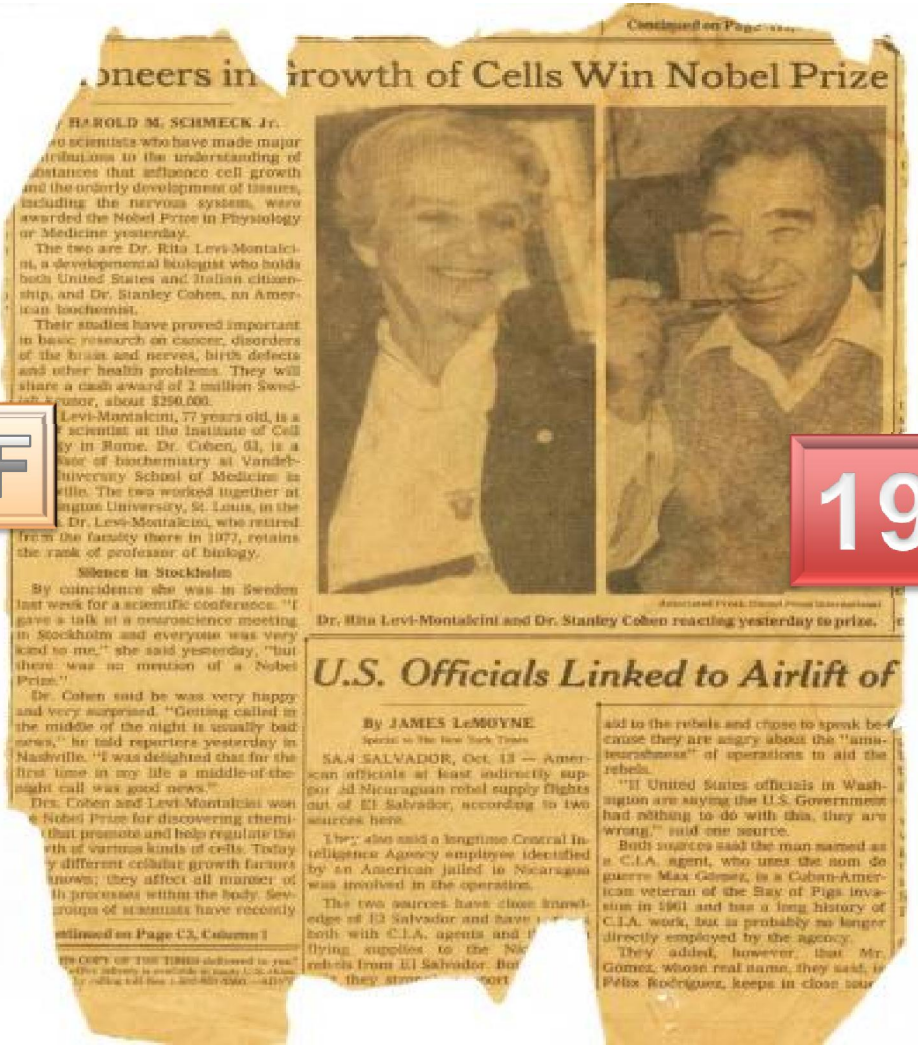
dott.ssa TINDARA FRANCHINA

Dipartimento di Patologia Umana,
Università di Messina
& S.C. Oncologia Medica,A.O. Papardo, Messina

Stanley Cohen's and Rita Levi-Montalcini's Discoveries of Growth Factors Lead to 1986 Nobel in Medicine

1953 NGF

1962 EGF



...oneers in ...rowth of Cells Win Nobel Prize

By HAROLD M. SCHMECK Jr.

...o scientists who have made major ...ributions to the understanding of ...stances that influence cell growth ...and the orderly development of tissues, ...including the nervous system, were awarded the Nobel Prize in Physiology or Medicine yesterday.

The two are Dr. Rita Levi-Montalcini, a developmental biologist who holds both United States and Italian citizenship, and Dr. Stanley Cohen, an American biochemist.

Their studies have proved important in basic research on cancer, disorders of the brain and nerves, birth defects and other health problems. They will share a cash award of 2 million Swed... ...kronor, about $290,000.

...Levi-Montalcini, 77 years old, is a ...scientist at the Institute of Cell ...y in Rome. Dr. Cohen, 63, is a ...ssor of biochemistry at Vanderbilt ...University School of Medicine in ...ville. The two worked together at ...ington University, St. Louis, in the ... Dr. Levi-Montalcini, who retired ...m the faculty there in 1977, retains the rank of professor of biology.

Silence in Stockholm

By coincidence she was in Sweden last week for a scientific conference. "I gave a talk at a neuroscience meeting in Stockholm and everyone was very kind to me," she said yesterday, "but there was no mention of a Nobel Prize."

Dr. Cohen said he was very happy and very surprised. "Getting called in the middle of the night is usually bad news," he told reporters yesterday in Nashville. "I was delighted that for the first time in my life a middle-of-the-night call was good news."

Drs. Cohen and Levi-Montalcini won ...e Nobel Prize for discovering chemi... ...that promote and help regulate the ...th of various kinds of cells. Today ...y different cellular growth factors ...known; they affect all manner of ...n processes within the body. Sev... ...groups of scientists have recently

...ntinued on Page C3, Column 1

Dr. Rita Levi-Montalcini and Dr. Stanley Cohen reacting yesterday to prize.

U.S. Officials Linked to Airlift of

By JAMES LeMOYNE
Special to The New York Times

SAN SALVADOR, Oct. 13 — American officials at least indirectly support ...ld Nicaraguan rebel supply flights out of El Salvador, according to two sources here.

They also said a longtime Central Intelligence Agency employee identified by an American jailed in Nicaragua was involved in the operations.

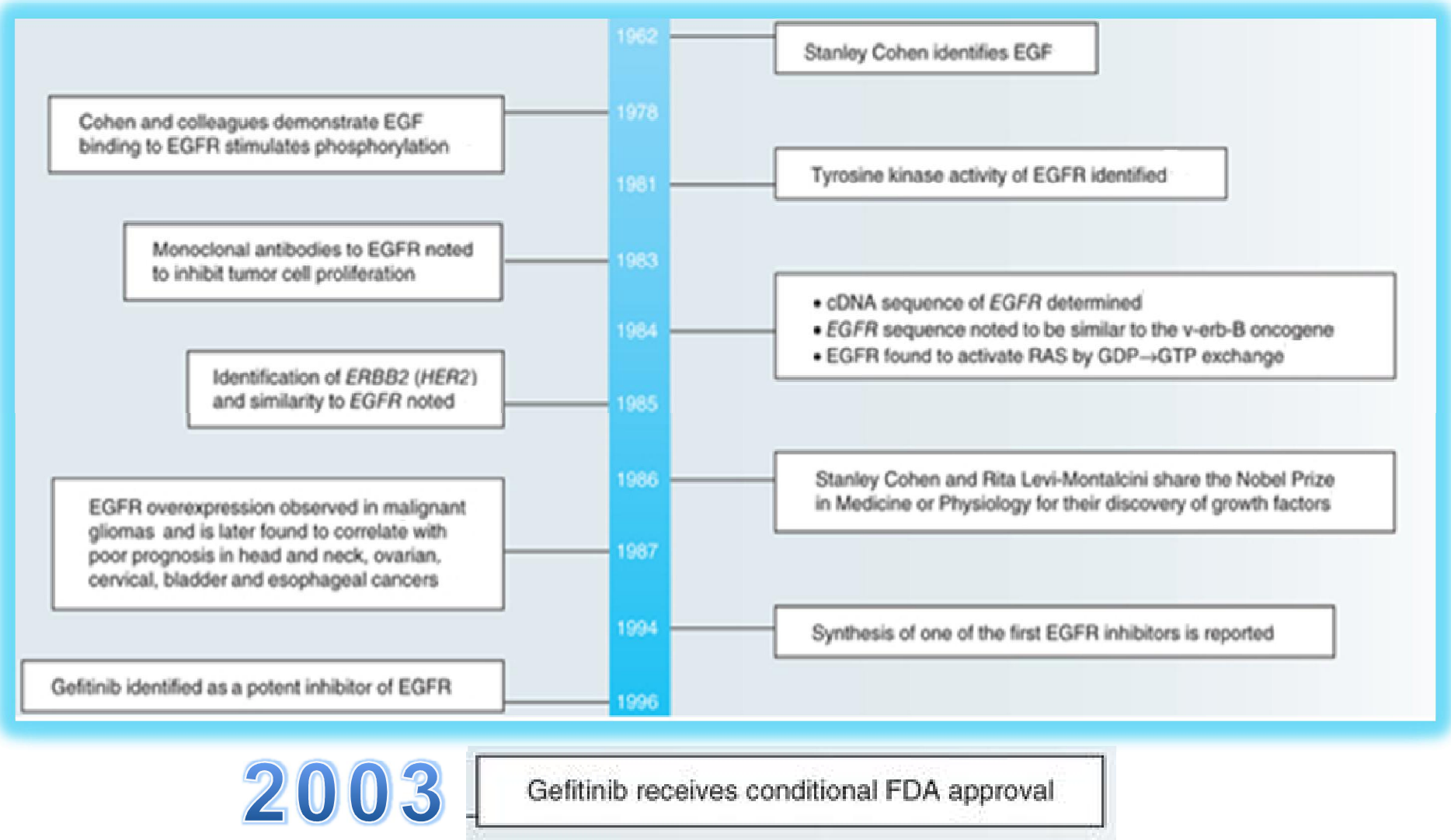
The two sources have close knowledge of El Salvador and have ... both with C.I.A. agents and ... flying supplies to the Nic... rebels from El Salvador. Bo... they stro... port ... aid to the rebels and chose to speak because they are angry about the "amateurishness" of operations to aid the rebels.

"If United States officials in Washington are saying the U.S. Government had nothing to do with this, they are wrong," said one source.

Both sources said the man named as a C.I.A. agent, who uses the nom de guerre Max Gomez, is a Cuban-American veteran of the Bay of Pigs invasion in 1961 and has a long history of C.I.A. work, but is probably no longer directly employed by the agency.

They added, however, that Mr. Gomez, whose real name, they said, ... Felix Rodriguez, keeps in close ...

Timeline of key discoveries in the EGFR field



2003 — Gefitinib receives conditional FDA approval

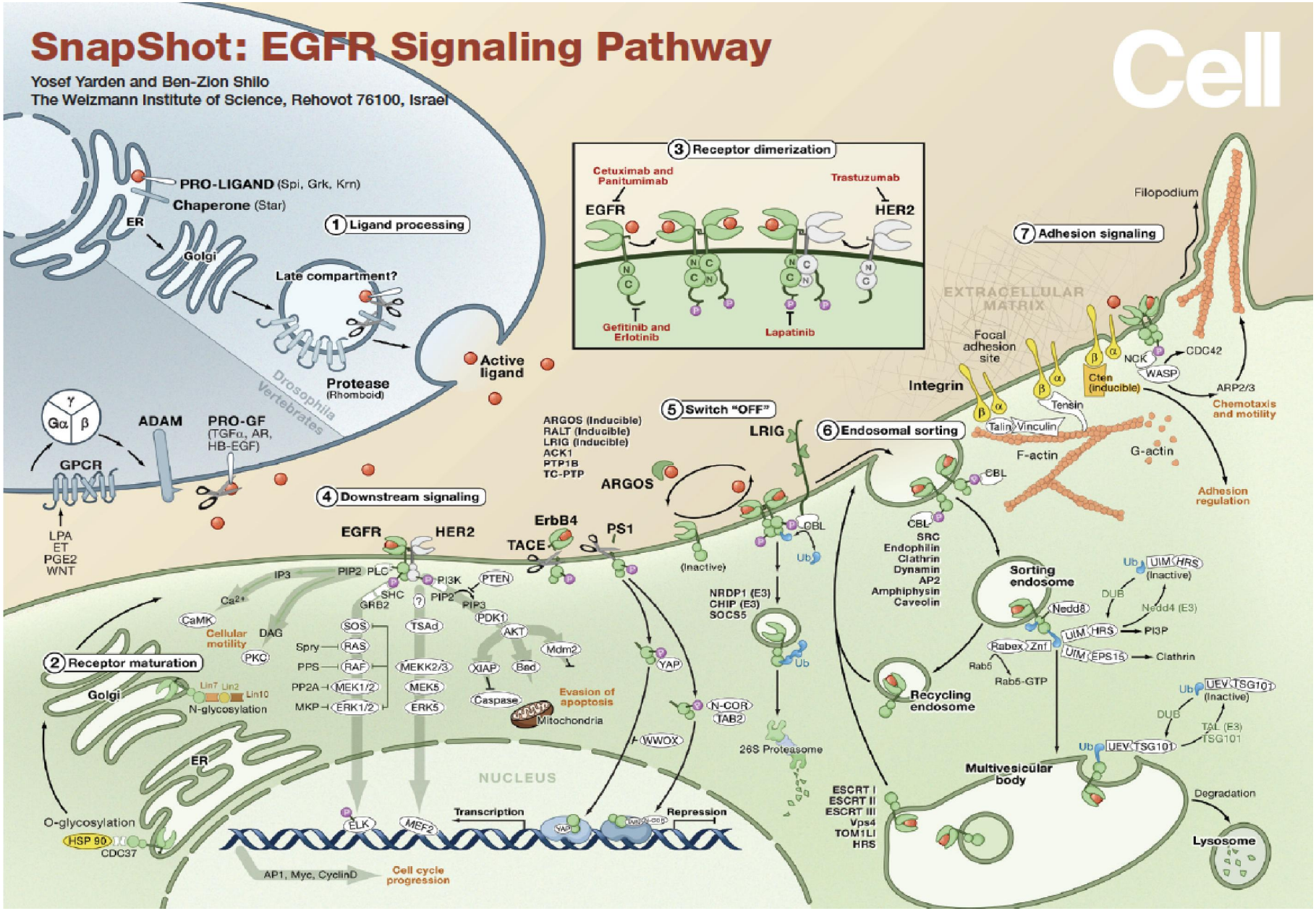
Adapted by Chong CR & Jänne PA, 2013

EGFR signaling pathway in NSCLC

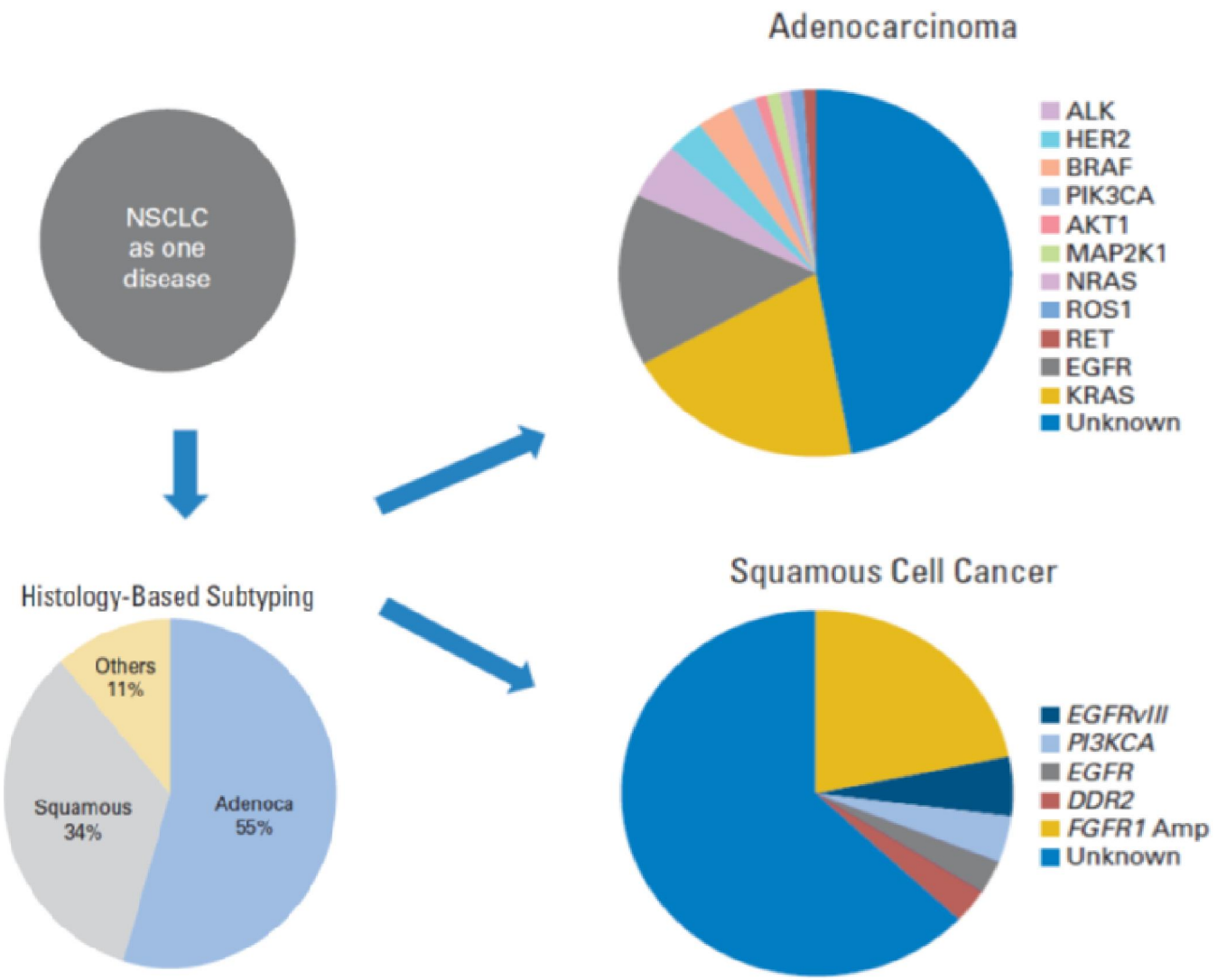
SnapShot: EGFR Signaling Pathway

Yosef Yarden and Ben-Zion Shilo
The Weizmann Institute of Science, Rehovot 76100, Israel

Cell



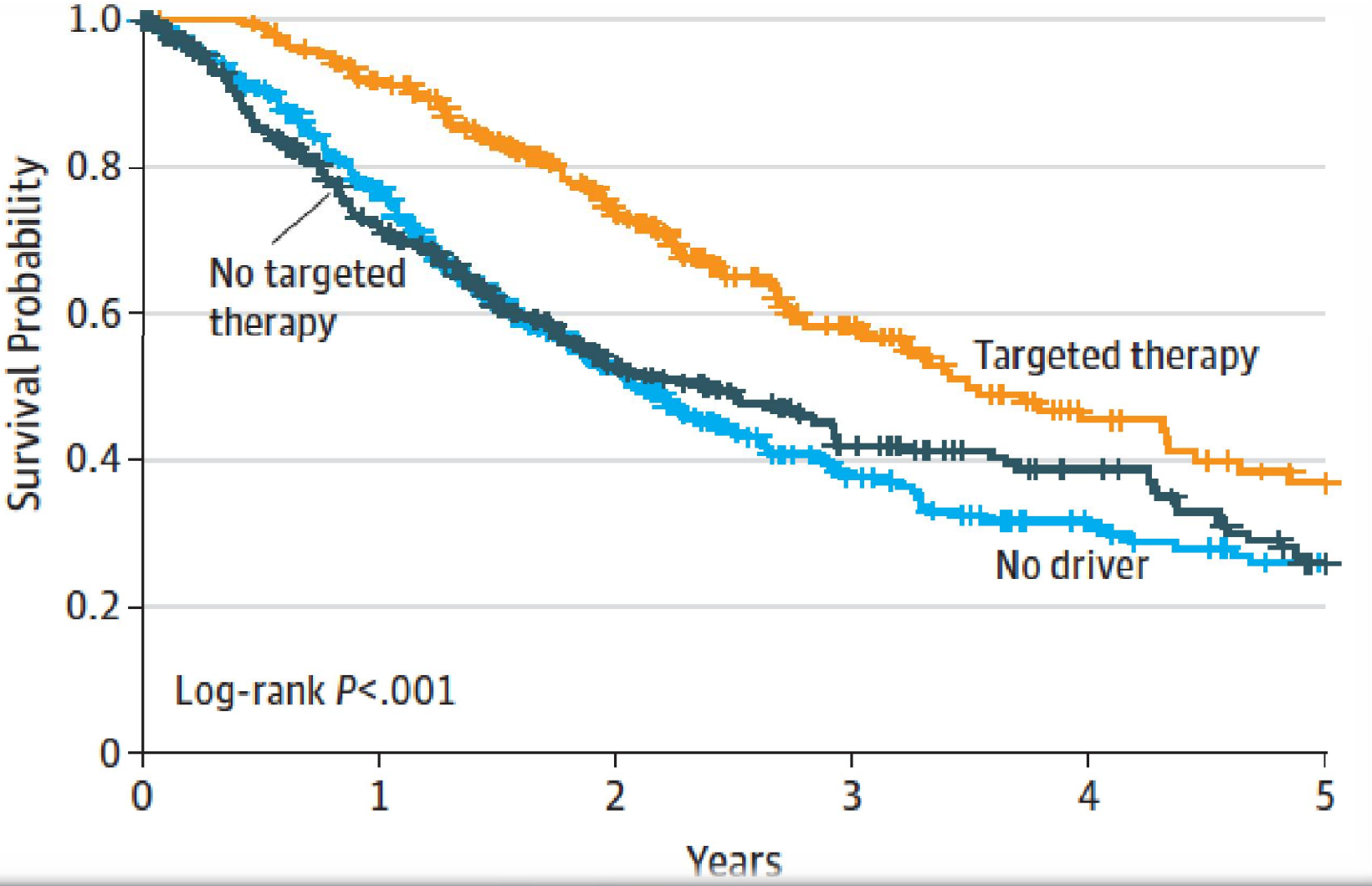
NSCLC: an evolving paradigm
from «one size fits all» to «personalized medicine»



Target	Drug
	Erlotinib (approved)
EGFR	Gefitinib (approved)
	PF299804
	Afatinib (BIBW2992)
ALK	Crizotinib (approved)
	LDK378
	AP26113
	AF802
ROS1	Crizotinib
HER2	PF299804
	Afatinib (BIBW2992)
FGFR	BGJ398
	FP1039 (HGS1036)
	Ponatinib (AP24534)
FGFR/ PDGFRA/ VEGFR	BIBF1120
	Pazopanib
	Lenvatinib (E7080)
	Brivanib (BMS-582,664)
	Dovitinib (TKI258)
PDGFRA	MEDI575
	IMC-3G3
PI3K	BKM120
	PX-866
	GDC-0941
	SAR245408
PI3K/ MTOR	GDC-0980
	BEZ235
	SAR245409
MEK	MEK162
	GDC-0973
	GSK1120212
	MSC1936369B
STAT3	OPB51602
AKT	MK2206

Li T, et al. JCO 2013; Heist RS et al. Cancer Cell 2012

TARGETED THERAPIES IN ONCOGENE ADDICTED NSCLC



Kris MG, et al. JAMA 2014

EGFR TKIs in molecularly-selected NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

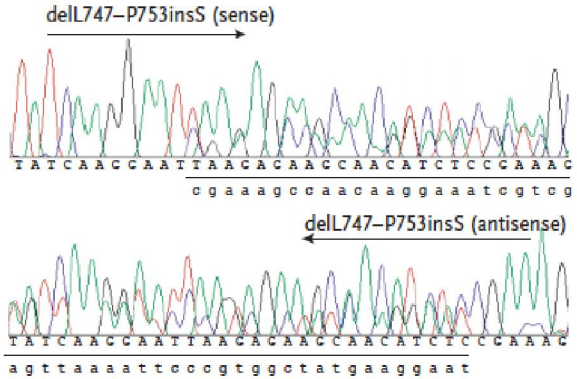
ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

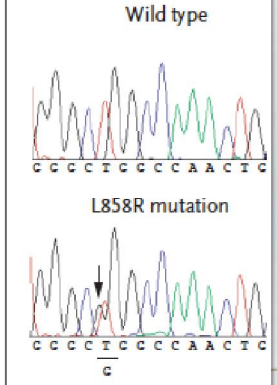
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

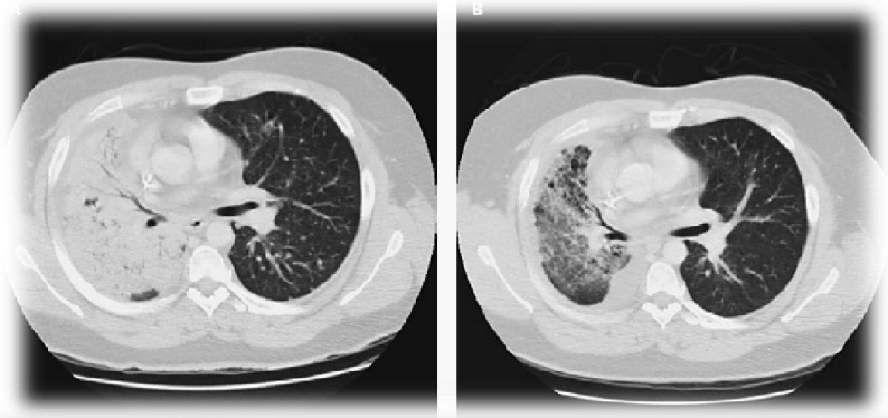
Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

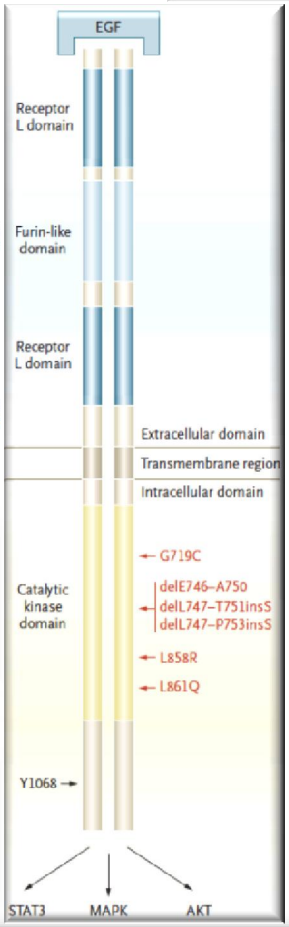
EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

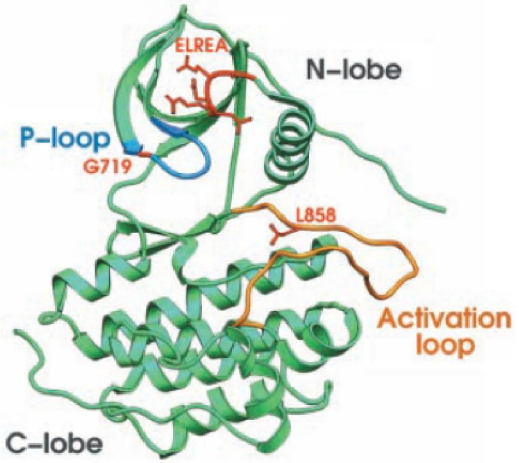
J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

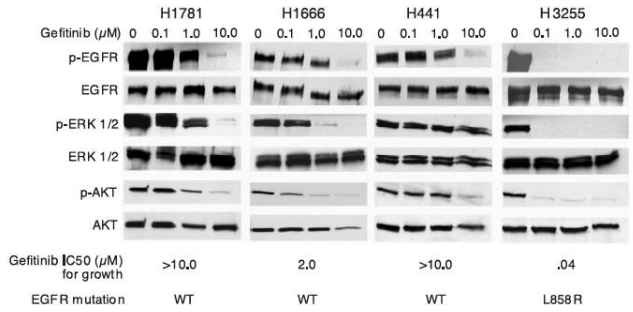






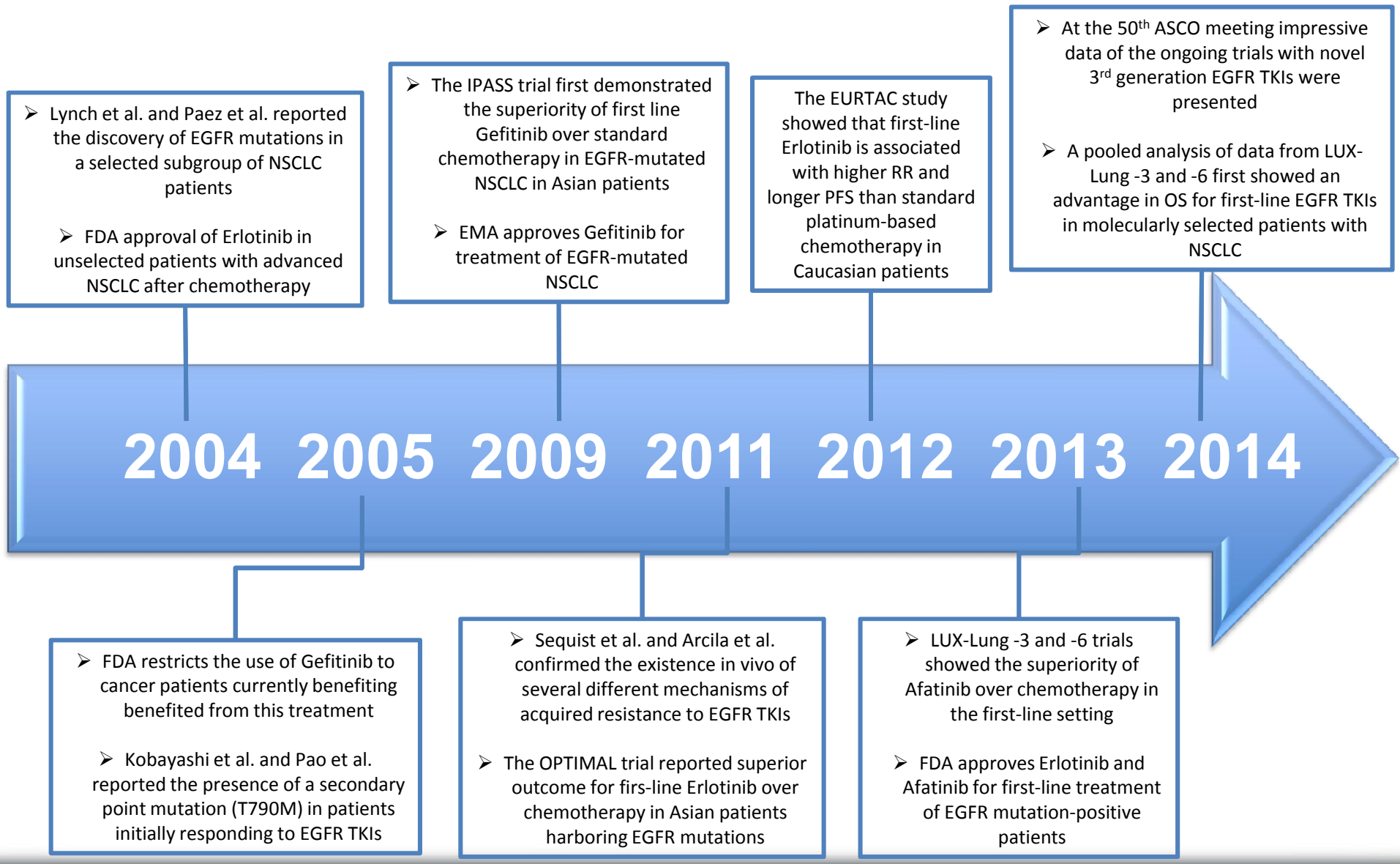






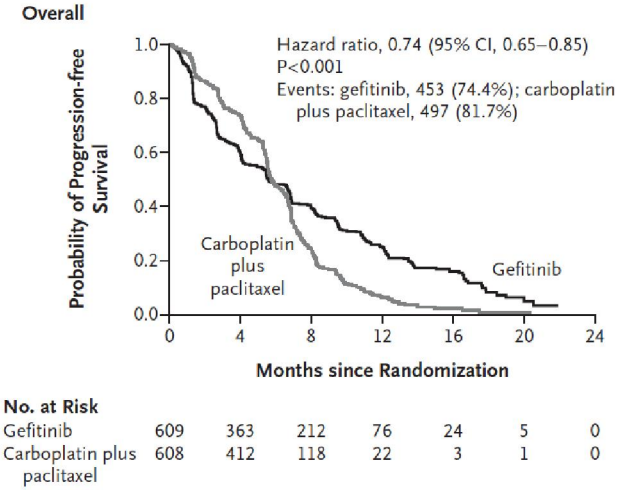
Lynch TJ, et al. NEJM 2004; Paez JG, et al. Science 2004

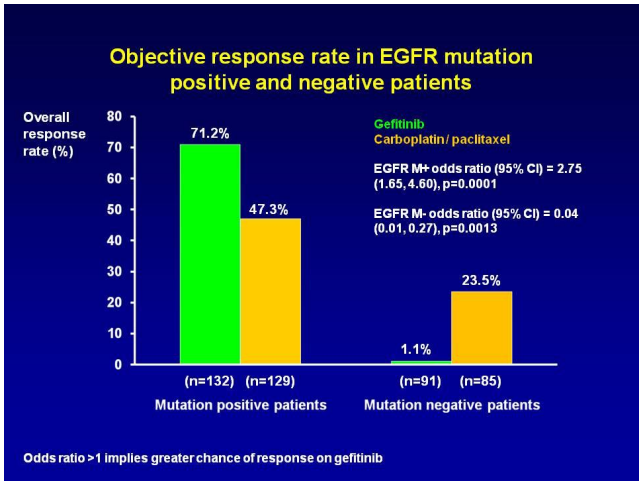
A decade of EGFR inhibition in NSCLC

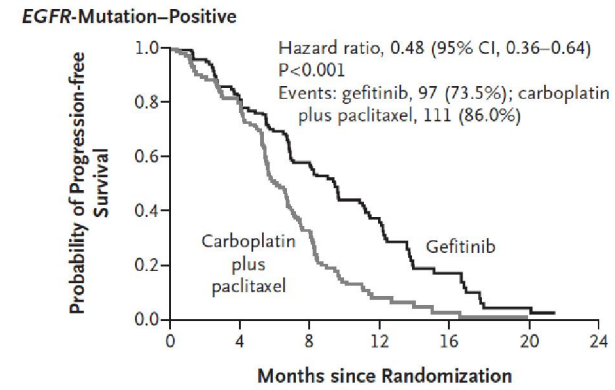


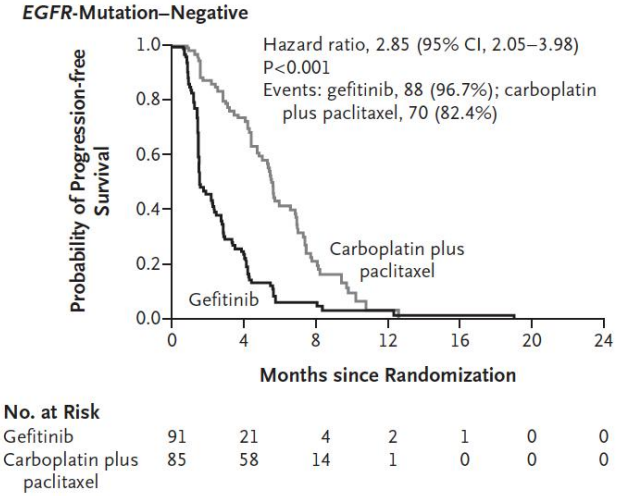
Russo A, Franchina T… Adamo V. Oncotarget 2015

Gefitinib in clinically-selected patients: the landmark IPASS trial







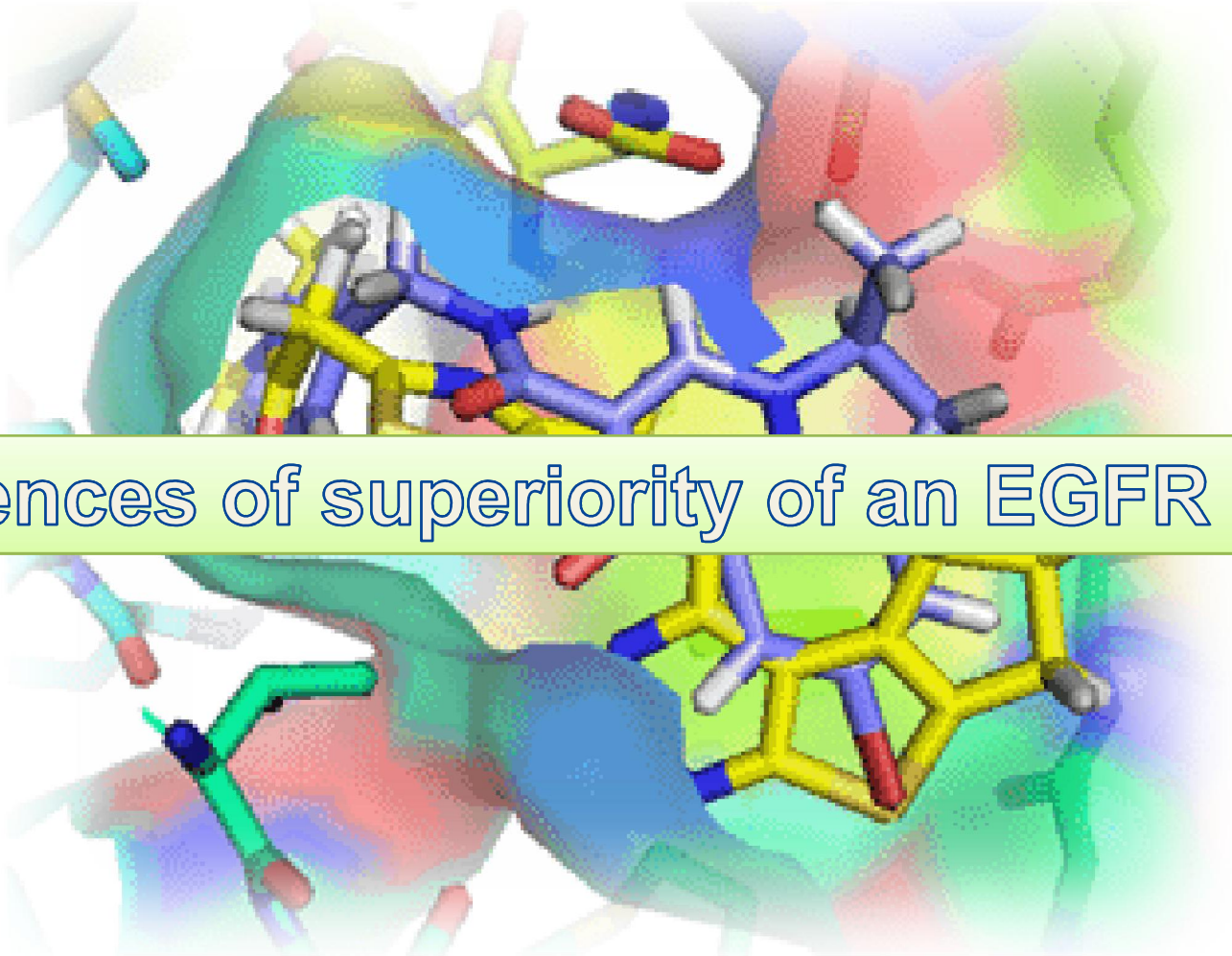


"… this study shows that ***first-line therapy with gefitinib as compared with carboplatin–paclitaxel prolongs progression-free survival, increases the objective response rate, and improves quality of life among clinically selected patients*** *with non–small-cell lung cancer.* ***The presence of an EGFR mutation was a robust predictor of improved progression-free survival with gefitinib****, as compared with carboplatin–paclitaxel, and of the benefit of gefitinib with respect to the objective response rate…"*

Mok TS, et al. N Engl J Med 2009

1st Line EGFR TKIs in EGFR-mut+ NSCLCs: a successful story

Trial	Selection criteria	Treatment	N	RR (%)	PFS (mo)	OS (mo)	Ref
IPASS	East-Asian, light/non-smoker, adenocarcinoma	Gefitinib vs. Carboplatin/Paclitaxel	132 129	71.2 Vs. 47.3	9.6 Vs. 6.3	21.6 Vs. 21.9	Mok TS, et al. NEJM 2009
First-SIGNAL	Korean, non-smoker, adenocarcinoma	Gefitinib Vs. Cisplatin/Gemcitabine	26 16	84.6 Vs. 37.5	8.0 Vs. 6.3	27.2 Vs. 25.6	Han JY, et al. JCO 2012
WJTOG 3405	Japanese, EGFR mutation	Gefitinib Vs. Cisplatin/Docetaxel	86 86	62.1 Vs. 32.1	9.2 Vs. 6.3	35.5 Vs. 38.8	Mitsudomi T, et al. Lancet Oncol 2010
NEJ 002	Japanese, EGFR mutation	Gefitinib vs. Carboplatin/Paclitaxel	114 114	73.7 Vs. 30.7	10.8 Vs. 5.4	27.7 Vs. 26.6	Maemondo M, et al. NEJM 2010
OPTIMAL	Chinese, EGFR mutation	Erlotinib vs. Carboplatin/Gemcitabine	82 72	83 Vs. 36	13.1 Vs. 4.6	22.7 vs. 28.9	Zhou C, et al. Lancet Oncol 2011
ENSURE	Chinese, EGFR mutation	Erlotinib vs. Cisplatin/Gemcitabine	110 107	62.7 vs. 33.6	11.0 vs. 5.5	26.3 vs. 25.5	Wu YL, et al. Ann Oncol 2015
EURTAC	European, EGFR mutation	Erlotinib Vs. Platinum agent + Gemcitabine or Docetaxel	86 87	58 Vs. 15	9.7 Vs. 5.2	19.3 Vs. 19.5	Rosell R, et al. Lancet Oncol 2012
LUX-Lung 3	Asian and European, EGFR mutation	Afatinib Vs. Cisplatin/Pemetrexed	230 115	56.1 Vs. 22.6	11.1 Vs. 6.9	25.8 vs. 24.5	Sequist LV, et al. JCO 2013
LUX-Lung 6	Asian, EGFR mutation	Afatinib Vs. Cisplatin/Gemcitabine	242 122	66.9 Vs. 23.0	11.0 Vs. 5.6		Wu YL, et al. Lancet Oncol 2014
LUX-Lung 7	Asian and European, EGFR mutation	Afatinib vs. Gefitinib	160 159	70 vs. 56%	11.0 vs. 10.9	N.A.	Park K, et al. ESMO Asia 2015



Evidences of superiority of an EGFR TKI?

What is the best in class EGFR TKI in 1st line setting? Indirect comparisons of currently approved TKIs

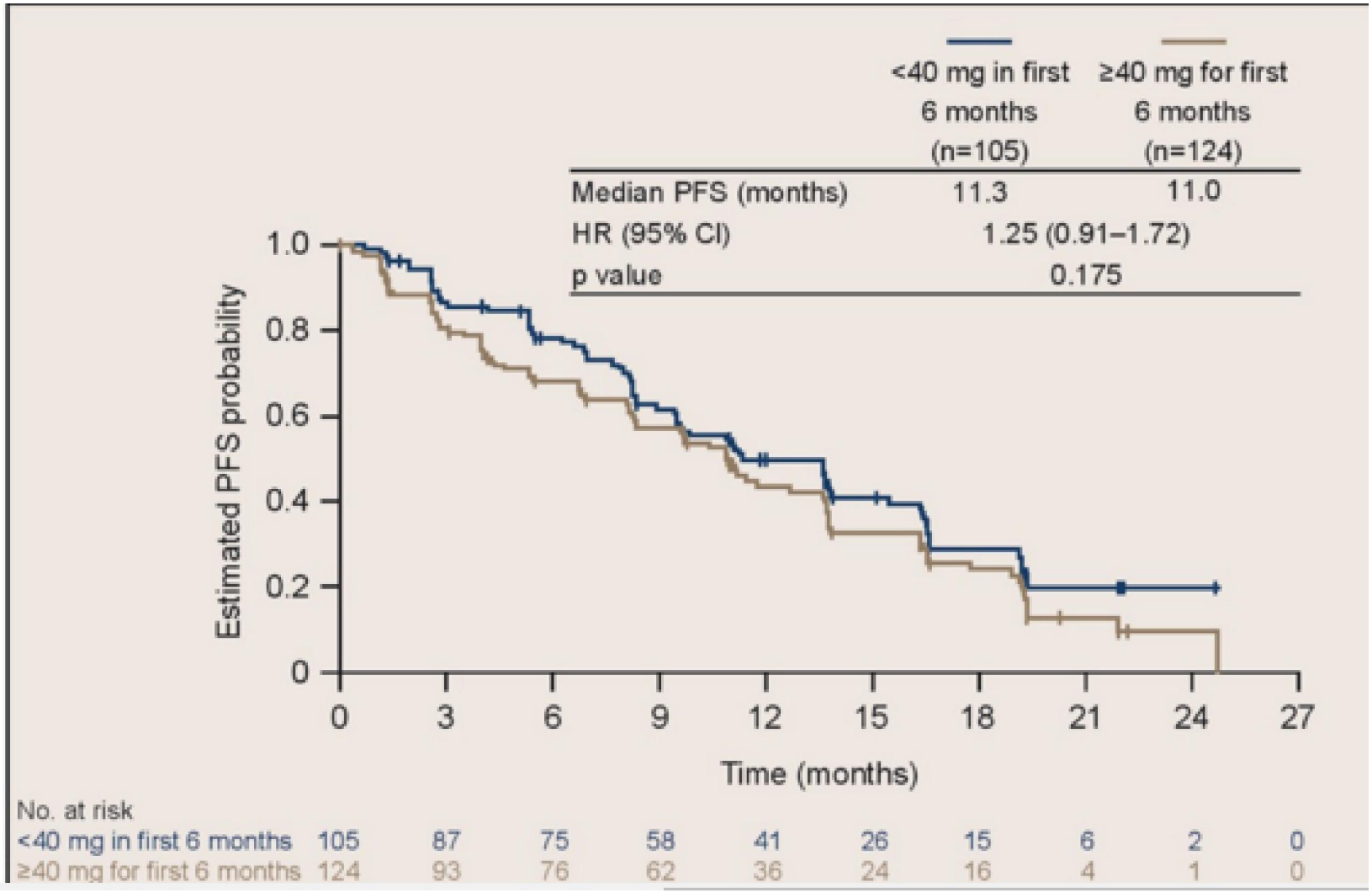
Outcome	Gefitinib *versus* Chemother-apy	Conclusion	Erlotinib *versus* Chemother-apy	Conclusion	Afatinib *versus* chemother-apy	Conclusion	Gefitinib *versus* Afatinib (ind. comp.)	Conclusion	Erlotinib *versus* Afatinib (ind. comp.)	Conclusion	Gefitinib *versus* Erlotinib (ind. comp.)	Conclusion
Progression-free survival												
Hazard ratio (HR)	HR = 0.43	Gefitinib better	HR = 0.32	Erlotinib better	HR = 0.41	Afatinib better	HR = 1.05	No difference	HR = 0.78	No difference	HR = 1.34	No difference
(95% CI)	(0.32, 0.56) I^2 = 54%		(0.16, 0.65) I^2 = 54%		(0.20, 0.82) I^2 = 90%		(0.61, 1.81)		(0.39, 1.55)		(0.63, 2.86)	
Progression-free survival (exon 19 deletion)												
Hazard ratio (HR)	HR = 0.40	Gefitinib better	HR = 0.20	Erlotinib better	HR = 0.24	Afatinib better	HR = 1.67	Afatinib better	HR = 0.83	No difference	HR = 2.00	No difference
(95% CI)	(0.29, 0.55) I^2 = 0%		(0.09, 0.46) I^2 = 76%		(0.17, 0.33) I^2 = 4%		(1.05, 2.64)		(0.35, 2.01)		(0.83, 4.80)	
Progression-free survival (L858R mutation)												
Hazard ratio (HR)	HR = 0.53	Gefitinib better	HR = 0.38	Erlotinib better	HR = 0.49	No difference	HR = 1.08	No difference	HR = 0.78	No difference	HR = 1.39	No difference
(95% CI)	(0.38, 0.76) I^2 = 0%		(0.18, 0.79) I^2 = 64%		(0.22, 1.10) I^2 = 54%		(0.45, 2.60)		(0.26, 2.32)		(0.62, 3.16)	
Overall survival												
Hazard ratio (HR)	HR = 1.00	No difference	HR = 1.11	No difference	HR = 1.01	No difference	HR = 0.91	No difference	HR = 1.10	No difference	HR = 0.90	No difference
(95% CI)	(0.83, 1.20) I^2 = 0%		(0.83, 1.50) I^2 = 0%		(0.77, 1.32) I^2 = 0%		(0.65, 1.26)		(0.74, 1.64)		(0.68, 1.19)	
Objective response rate												
Risk ratio (RR)	RR = 2.45	Gefitinib better	RR = 2.54	Erlotinib better	RR = 2.70	Afatinib better	RR = 0.91	No difference	RR = 0.94	No difference	RR = 0.96	No difference
(95% CI)	(2.03, 2.95) I^2 = 0%		(1.80, 3.59) I^2 = 28%		(2.12, 3.45) I^2 = 0%		(0.67, 1.23)		(0.65, 1.35)		(0.69, 1.34)	
Diarrhea												
Risk ratio (RR)	RR = 2.00	Chemoth. better	RR = 2.55	Chemoth. better	RR = 6.98	Chemoth. better	RR = 0.29	Gefitinib better	RR = 0.36	Erlotinib better	RR = 0.80	No difference
(95% CI)	(1.40, 2.85) I^2 = 80%		(1.42, 4.56) I^2 = 75%		(4.97, 9.81) I^2 = 91%		(0.20, 0.41)		(0.25, 0.54)		(0.63, 1.01)	
Rash												
Risk ratio (RR)	RR = 4.42	Chemoth. better	RR = 4.42	Chemoth. better	RR = 10.90	Chemoth. better	RR = 0.41	Gefitinib better	RR = 0.41	Erlotinib better	RR = 1.00	
(95% CI)	(2.82, 6.92) I^2 = 84%		(1.57, 12.44) I^2 = 93%		(6.89, 17.24) I^2 = 91%		(0.25, 0.65)		(0.25, 0.66)		(0.82, 1.22)	No difference

*"…Our analysis showed that **all treatments had similar efficacy but they differ for toxicities**…"*

Haspinger ER, et al. Crit Rev Oncol Hematol 2015

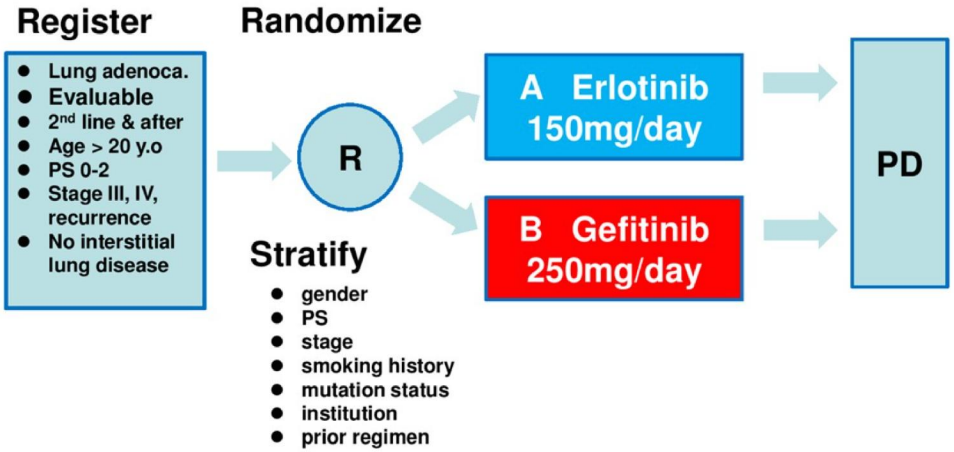
Influence of dose adjustment on afatinib safety and efficacy in patients with advanced *EGFR* mutation-positive NSCLC

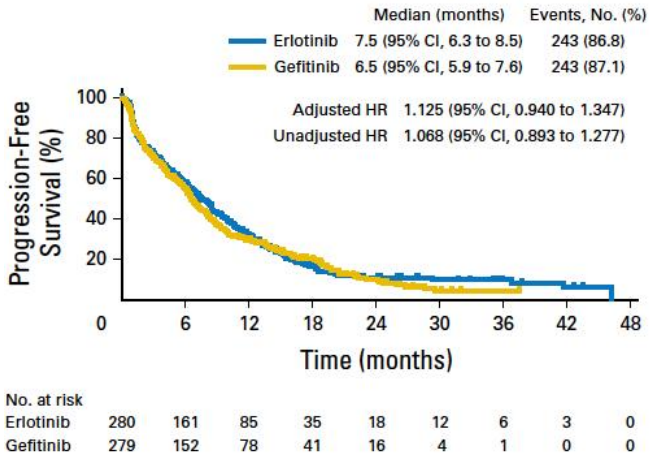
#8073

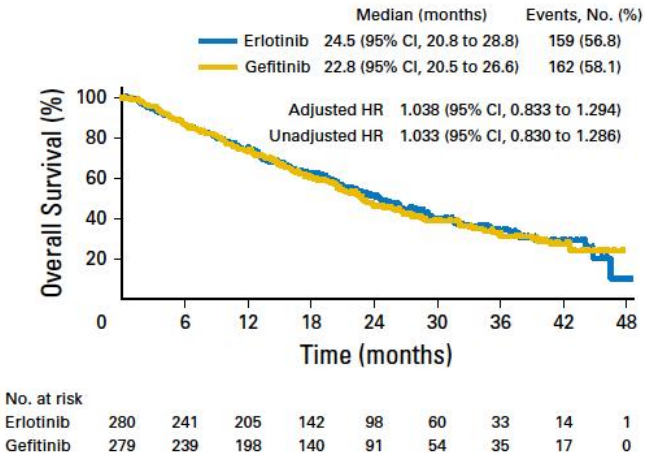


Yang GC, ASCO 2015

What is the best in class EGFR TKI in 1st line setting? Direct comparisons: Gefitinib vs. Erlotinib (WJTOG5108L)







- ✓ ***First prospective randomized phase III study to directly compare two first-generation EGFR TKIs**, gefitinib and erlotinib, in pretreated patients;*
- ✓ *The study was **unable to demonstrate statistical noninferiority in PFS between erlotinib and gefitinib;***
- ✓ *Subset analysis including **mutation status did not reveal any populations with noteworthy differences in clinical efficacy** between gefitinib and erlotinib.*
- ✓ *This suggests that, **although not demonstrated to be statistically noninferior, gefitinib could be therapeutic option, considering the milder adverse effects in patients with EGFR mutation–positive** adenocarcinoma.*

Katakami N, et al. ASCO 2014; Urata Y, et al. JCO 2016

AFATINIB VS. GEFITINIB: LUX-Lung 7 trial

Study design

- 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)

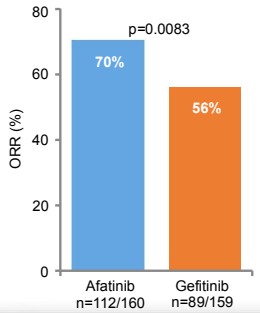
Primary endpoints:
- PFS (independent)
- TTF
- OS

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

- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter

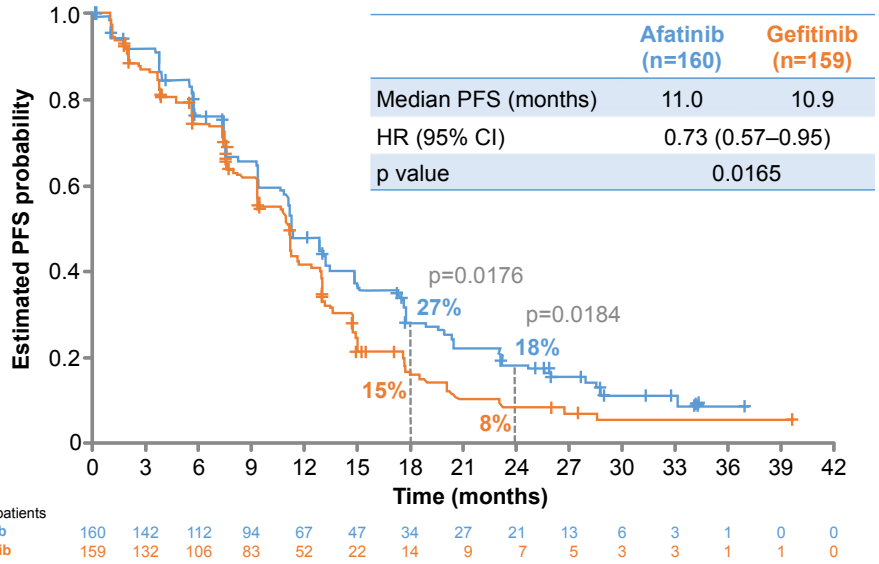
*Central or local test
†Dose modification to 50, 30, 20 mg permitted in line with prescribing information

Objective response and duration of response (independent review)



	Afatinib (n=112)	Gefitinib (n=89)
Median DoR (months)	10 .1	8.4
95% CI	(7.8–11.1)	(7.4–10.9)

PFS by independent review



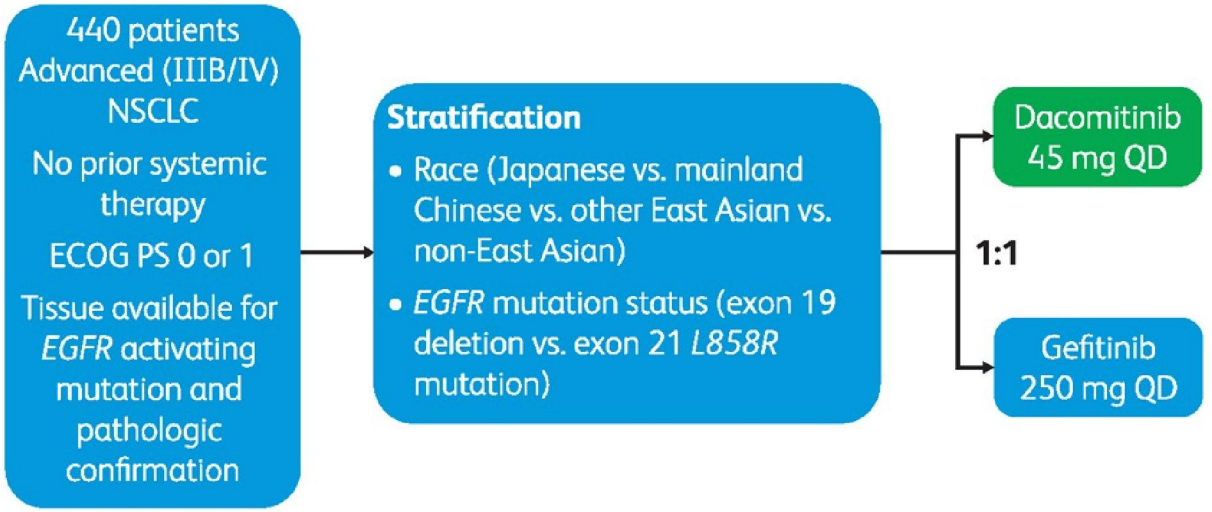
	Afatinib (n=160)	Gefitinib (n=159)
Median PFS (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	

*"….**Afatinib significantly improved PFS** of patients with EGFRm+ NSCLC relative to gefitinib. **Results are consistent across subgroups**… The improvement in efficacy was observed **in both Del19 and L858R** populations…**OS data immature** (current HR: 0.87, 95%CI: 0.66–1.15)…"*

DACOMITINIB vs. GEFITINIB: ARCHER 1050

Ongoing

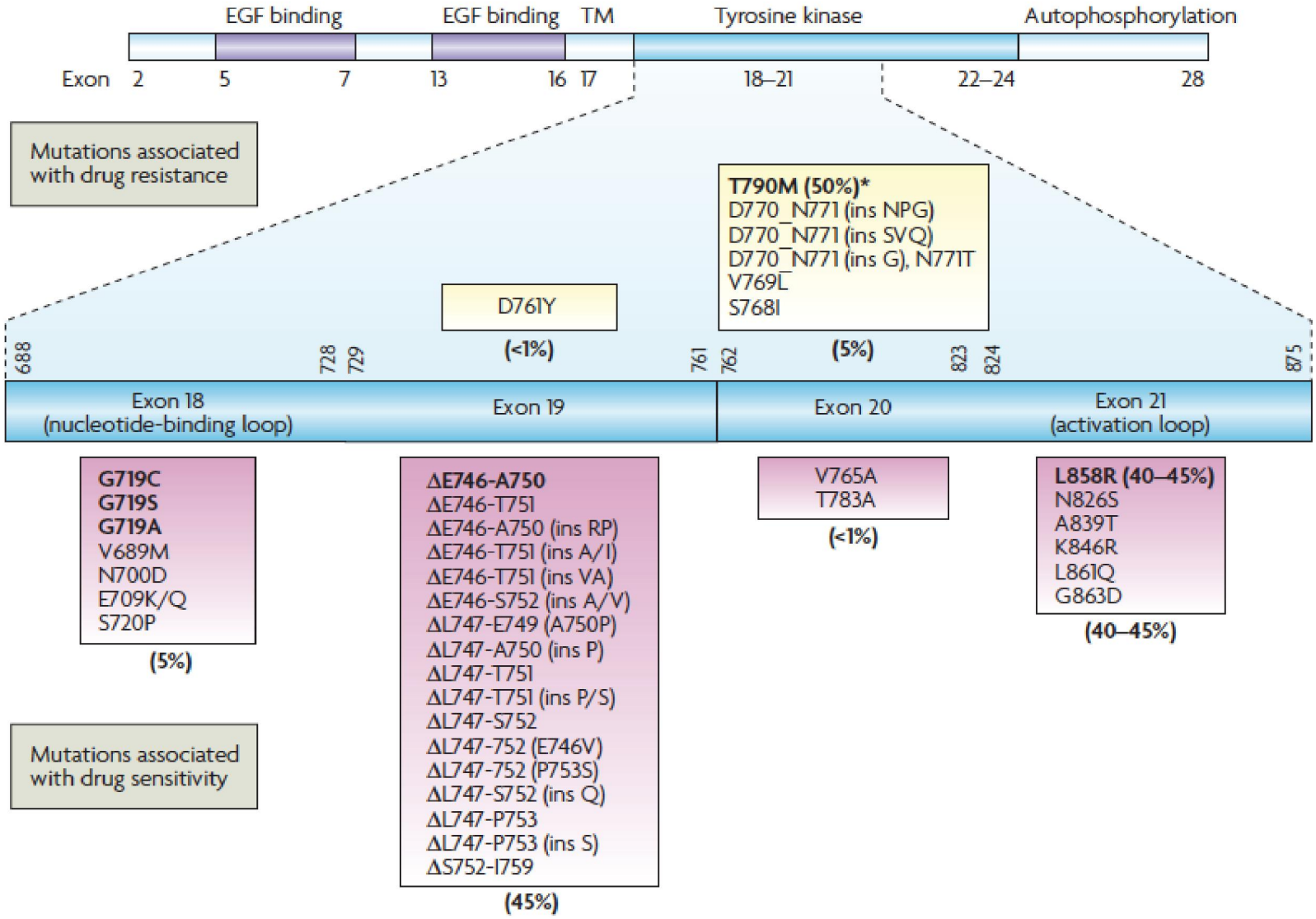
Trial design	Endpoints	Study sites
Open-label, randomized, phase III, global	Primary: PFS (IRC review) Secondary: OS, OS at 30 months, PFS (investigator assessment), BOR, DR, safety, PRO, PK	**Global** Japan, China, Hong Kong, Korea, Spain, Italy and Poland



BOR, best overall response; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent radiologic central; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcomes

Mok TS, et al. ASCO 2013

NOT ALL EGFR MUTATIONS ARE CREATED EQUAL



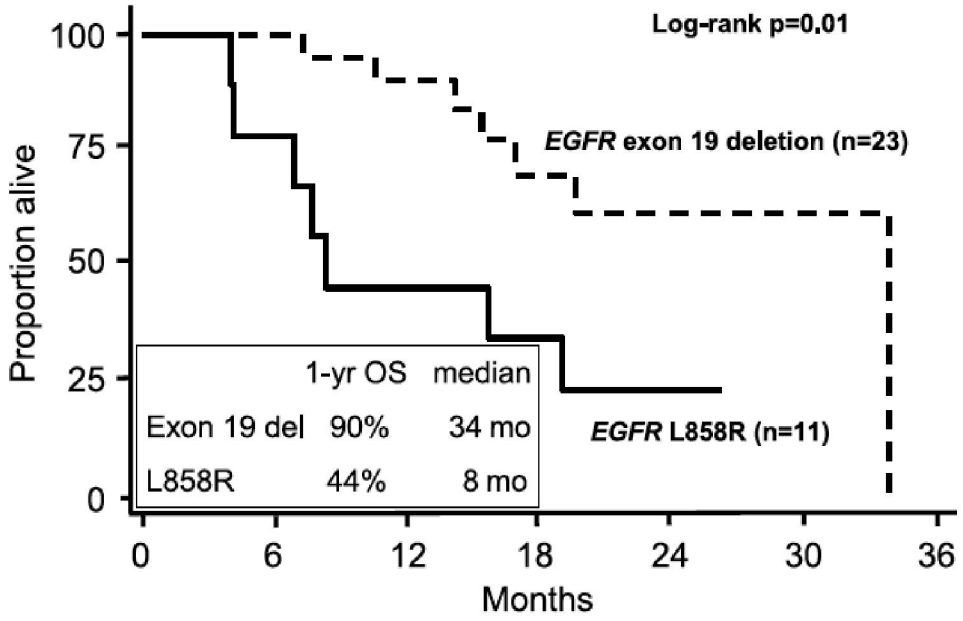
Sharma SV, et al. Nat Rev Cancer 2007

Exon 19 vs. L858R: where the story begins

Cancer Therapy: Clinical

Clinical Course of Patients with Non–Small Cell Lung Cancer and Epidermal Growth Factor Receptor Exon 19 and Exon 21 Mutations Treated with Gefitinib or Erlotinib

Gregory J. Riely,[1] William Pao,[1,4] DuyKhanh Pham,[2] Allan R. Li,[3] Naiyer Rizvi,[1] Ennapadam S. Venkatraman,[5] Maureen F. Zakowski,[3] Mark G. Kris,[1] Marc Ladanyi,[3] and Vincent A. Miller[1]

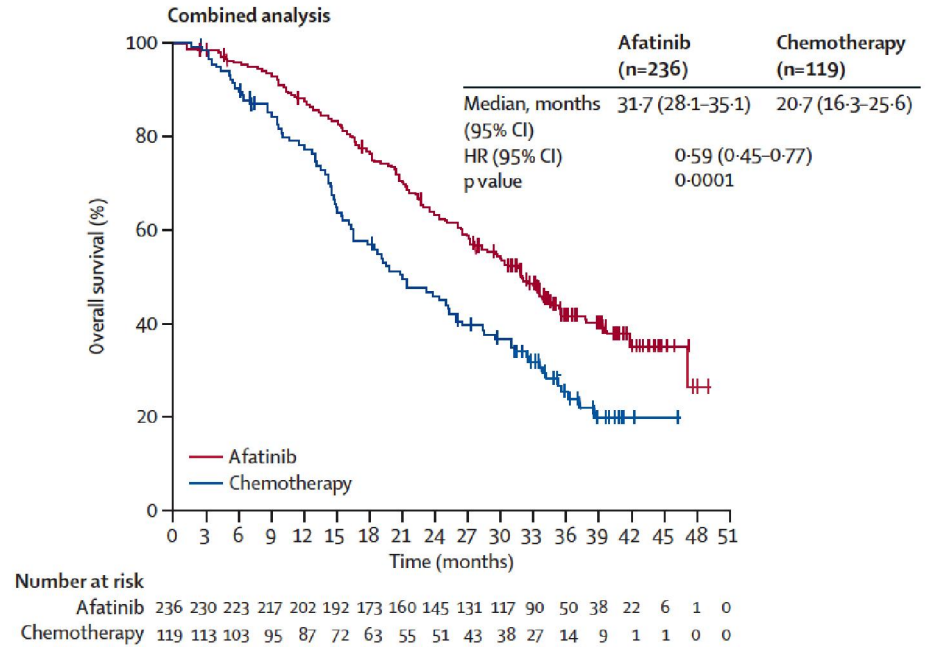


"…EGFR mutations in exons 19 or 21 are correlated with clinical factors predictive of response to gefitinib and erlotinib. Those with ***EGFR exon 19 deletion mutations had a longer median survival than patients with EGFR L858R point mutation****…"*

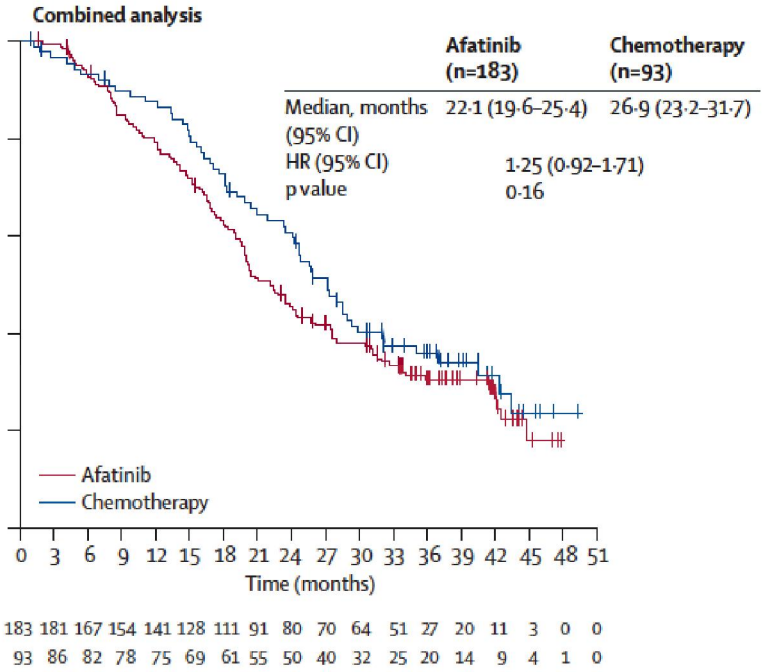
Riely GJ, et al. Clin Cancer Res 2006

LUX-Lung 3 & 6 combined analysis

Exon 19 del



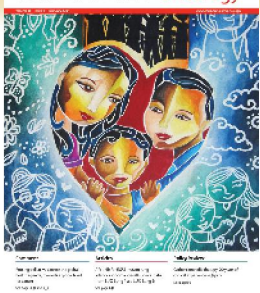
L858R



"…Although afatinib did not improve overall survival in the whole population of either trial, overall survival was improved with the drug for patients with del19 EGFR mutations. The absence of an effect in patients with Leu858Arg EGFR mutations suggests that ***EGFR del19-positive disease might be distinct from Leu858Arg-positive disease and that these subgroups should be analysed separately in future trials****…"*

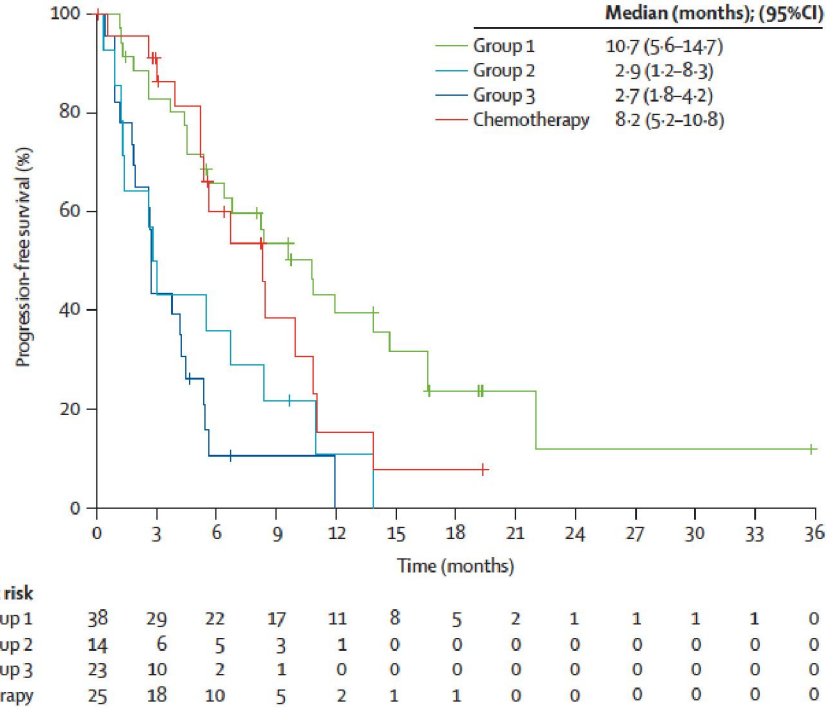
Yang JC, et al. Lancet Oncol 2015

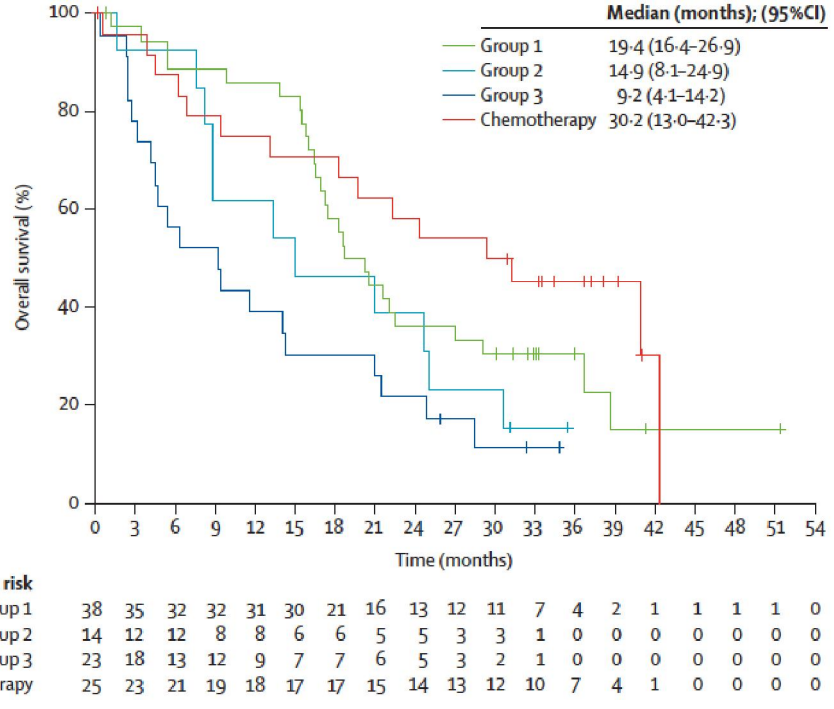
THE LANCET Oncology



Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

James C-H Yang, Lecia V Sequist*, Sarayut Lucien Geater, Chun-Ming Tsai, Tony Shu Kam Mok, Martin Schuler, Nobuyuki Yamamoto, Chong-Jen Yu, Sai-Hong I Ou, Caicun Zhou, Daniel Massey, Victoria Zazulina, Yi-Long Wu*





*"…We found a **high degree of molecular heterogeneity in this uncommon EGFR mutation population**…**High afatinib activity was recorded in patients with the uncommon EGFR mutations Gly719Xaa, Leu861Gln, and Ser768Ile**; these are the three most frequently detected types of uncommon EGFR mutations in lung adenocarcinoma…we noted p**oor activity for patients with de-novo Thr790Met and exon 20 insertion mutations, for whom treatment with chemotherapy might be considered rather than EGFR inhibitors**…"*

Is there a role for EGFR TKIs in EGFR Wild Type Patients?

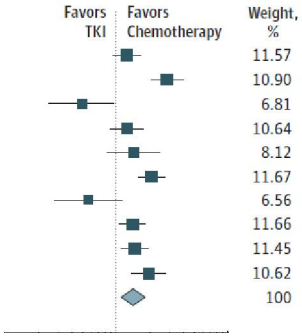
Original Investigation

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors vs Conventional Chemotherapy in Non–Small Cell Lung Cancer Harboring Wild-Type Epidermal Growth Factor Receptor
A Meta-analysis

June-Koo Lee, MD; Seokyung Hahn, PhD; Dong-Wan Kim, MD, PhD; Koung Jin Suh, MD; Bhumsuk Keam, MD; Tae Min Kim, MD, PhD; Se-Hoon Lee, MD, PhD; Dae Seog Heo, MD, PhD

Progression-Free Survival From the 10 Randomized Controlled Trials Comparing EGFR TKI With Chemotherapy

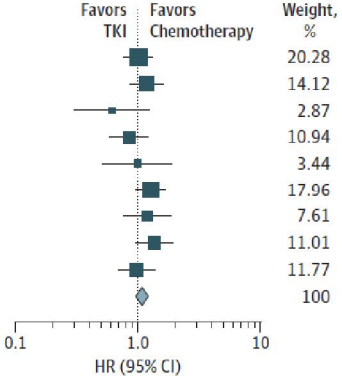
Source	No. of Patients With WT *EGFR* TKI	No. of Patients With WT *EGFR* Chemotherapy	Progression-Free Survival, HR (95% CI)	Weight, %
INTEREST,[12,27] 2008 and 2010	106	123	1.24 (0.94-1.64)	11.57
IPASS,[5,28] 2009 and 2011	91	85	2.85 (2.05-3.98)	10.90
ML20322,[29] 2012	21	15	0.50 (0.25-0.97)	6.81
TITAN,[13] 2012	75	74	1.25 (0.88-1.78)	10.64
First-SIGNAL,[30] 2012	27	27	1.42 (0.82-2.47)	8.12
TORCH,[14] 2012	119	117	2.07 (1.58-2.71)	11.67
KCSG-LU08-01,[31] 2012	18	20	0.56 (0.28-1.13)	6.56
TAILOR,[15] 2013	109	110	1.39 (1.06-1.82)	11.66
DELTA,[33] 2013	109	90	1.45 (1.09-1.94)	11.45
CTONG-0806,[34] 2013	81	76	1.96 (1.37-2.78)	10.62
Overall: I^2=79.1%; P<.001	756	737	1.41 (1.10-1.81)	100



PFS significantly longer with CT (HR 1.41)

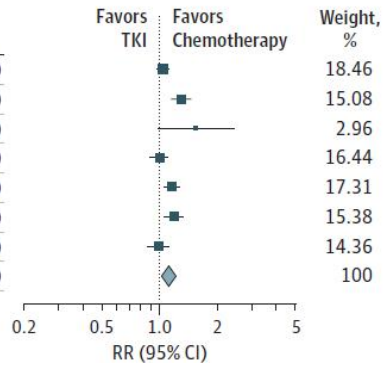
Overall survival

Source	No. of Patients With WT *EGFR* TKI	No. of Patients With WT *EGFR* Chemotherapy	HR (95% CI)	Weight, %
INTEREST,[12,27] 2008 and 2010	119	134	1.02 (0.78-1.33)	20.28
IPASS,[5,28] 2009 and 2011	91	85	1.18 (0.86-1.63)	14.12
ML20322,[29] 2012	21	15	0.62 (0.30-1.24)	2.87
TITAN,[13] 2012	75	74	0.85 (0.59-1.22)	10.94
First-SIGNAL,[30] 2012	27	27	1.00 (0.52-1.91)	3.44
TORCH,[14] 2012	119	117	1.29 (0.97-1.71)	17.96
CT/06.05,[32] 2013	55	57	1.19 (0.77-1.84)	7.61
TAILOR,[15] 2013	109	110	1.28 (0.95-1.96)	11.01
DELTA,[33] 2013	109	90	0.98 (0.69-1.39)	11.77
Overall: I^2=0%; P=.496	725	709	1.08 (0.96-1.22)	100



No statistically significant difference in OS (HR 1.08)

Source	No. of Patients With WT *EGFR* TKI Event[a]	TKI Total	Chemotherapy Event[a]	Chemotherapy Total	RR[a] (95% CI)	Weight, %
INTEREST,[12,27] 2008 and 2010	99	106	111	123	1.03 (0.96-1.12)	18.46
IPASS,[5,28] 2009 and 2011	90	91	65	85	1.29 (1.15-1.46)	15.08
First-SIGNAL,[30] 2012	20	27	13	27	1.54 (0.98-2.41)	2.96
CT/06.05,[32] 2013	51	55	53	57	1.00 (0.90-1.11)	16.44
TAILOR,[15] 2013	97	100	82	97	1.15 (1.05-1.26)	17.31
DELTA,[33] 2013	100	106	68	85	1.18 (1.05-1.32)	15.38
CTONG-0806,[34] 2013	64	75	65	75	0.98 (0.87-1.12)	14.36
Overall: I^2=71.7%; P=.002	521	560	457	549	1.11 (1.02-1.21)	100



ORR was significantly higher with CT (16.8% vs. 7.2%)

Conclusions

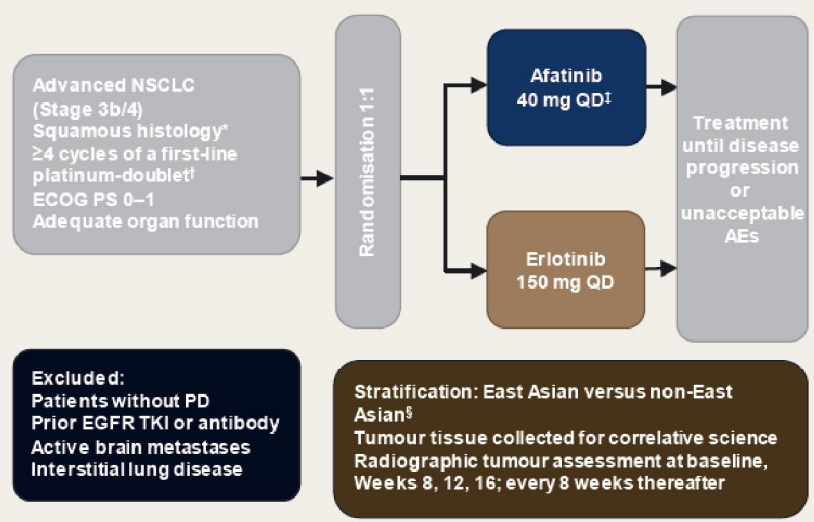
In patients with advanced NSCLC harboring WT *EGFR* tumors, conventional chemotherapy was associated with improvement in PFS and a higher objective response rate, compared with first-generation EGFR TKI. However, there was no statistically significant difference in terms of overall survival between the 2 treatment groups.

Lee JK, et al. JAMA 2014

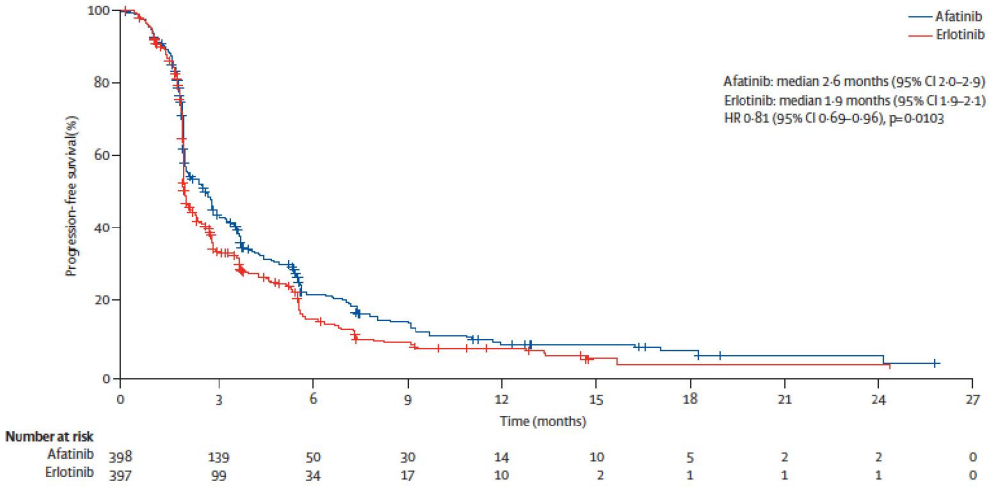
THE LANCET Oncology

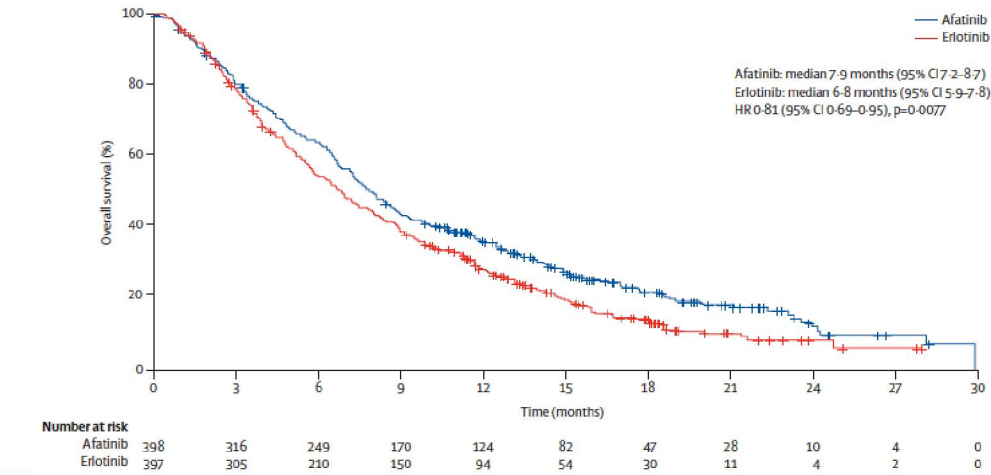
Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial

Jean-Charles Soria, Enriqueta Felip, Manuel Cobo, Shun Lu, Konstantinos Syrigos, Ki Hyeong Lee, Erdem Göker, Vassilis Georgoulias, Wei Li, Dolores Isla, Salih Z Guclu, Alessandro Morabito, Young J Min, Andrea Ardizzoni, Shirish M Gadgeel, Glenwood D Goss, for the LUX-Lung 8 Investigators



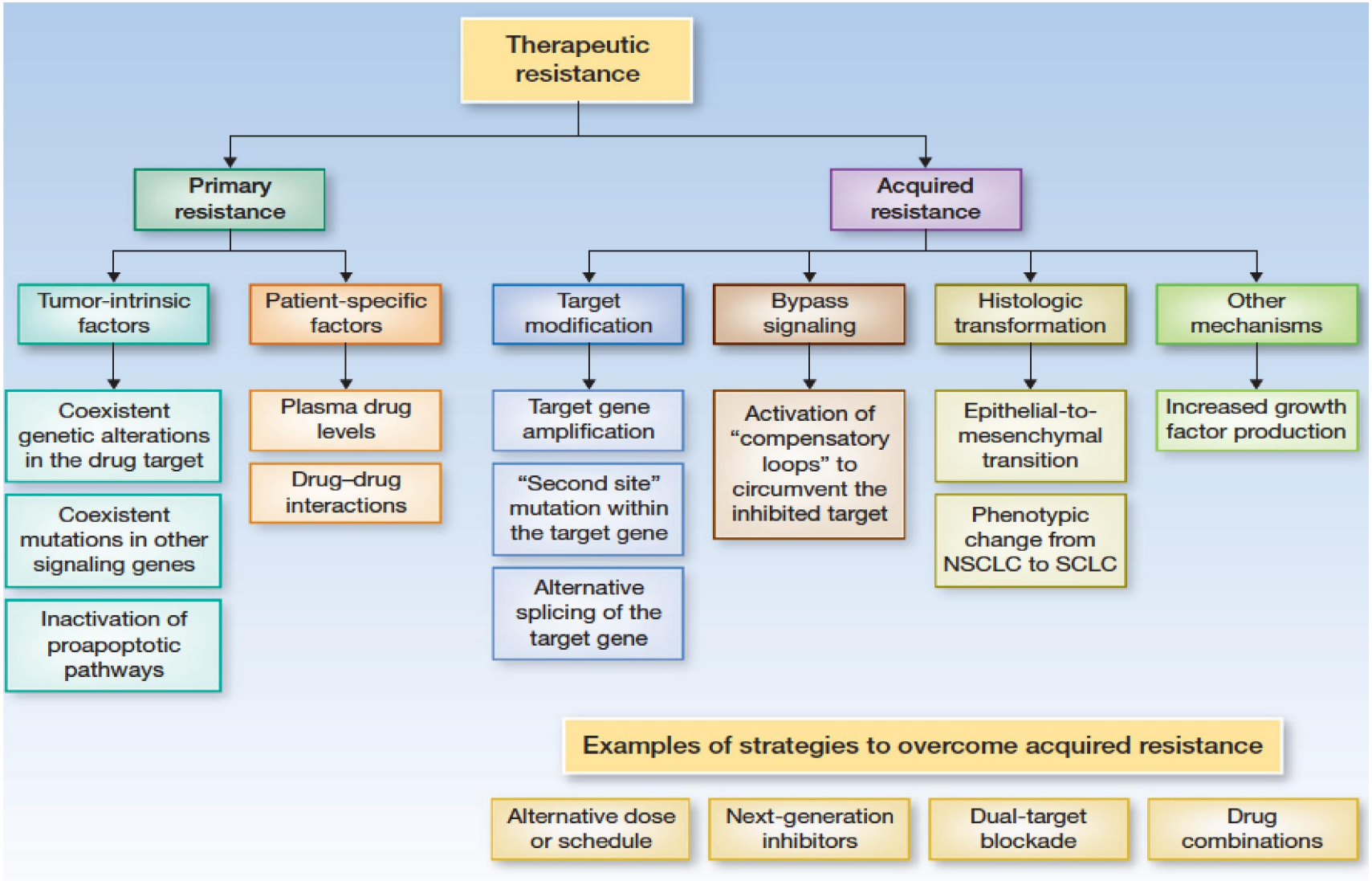
	Afatinib (n=398)	Erlotinib (n=397)	p value
Disease control	201 (51%)	157 (40%)	0·0020
Excluding patients with NN*	146 (37%)	114 (29%)	0·0170
Objective response	22 (6%)	11 (3%)	0·0551
CR	1 (<1%)	0 (0%)	..
PR	21 (5%)	11 (3%)	..
SD†	124 (31%)	103 (26%)	..
NN*†	55 (14%)	43 (11%)	..
PD	133 (33%)	169 (43%)	..
NE	64 (16%)	71 (18%)	..





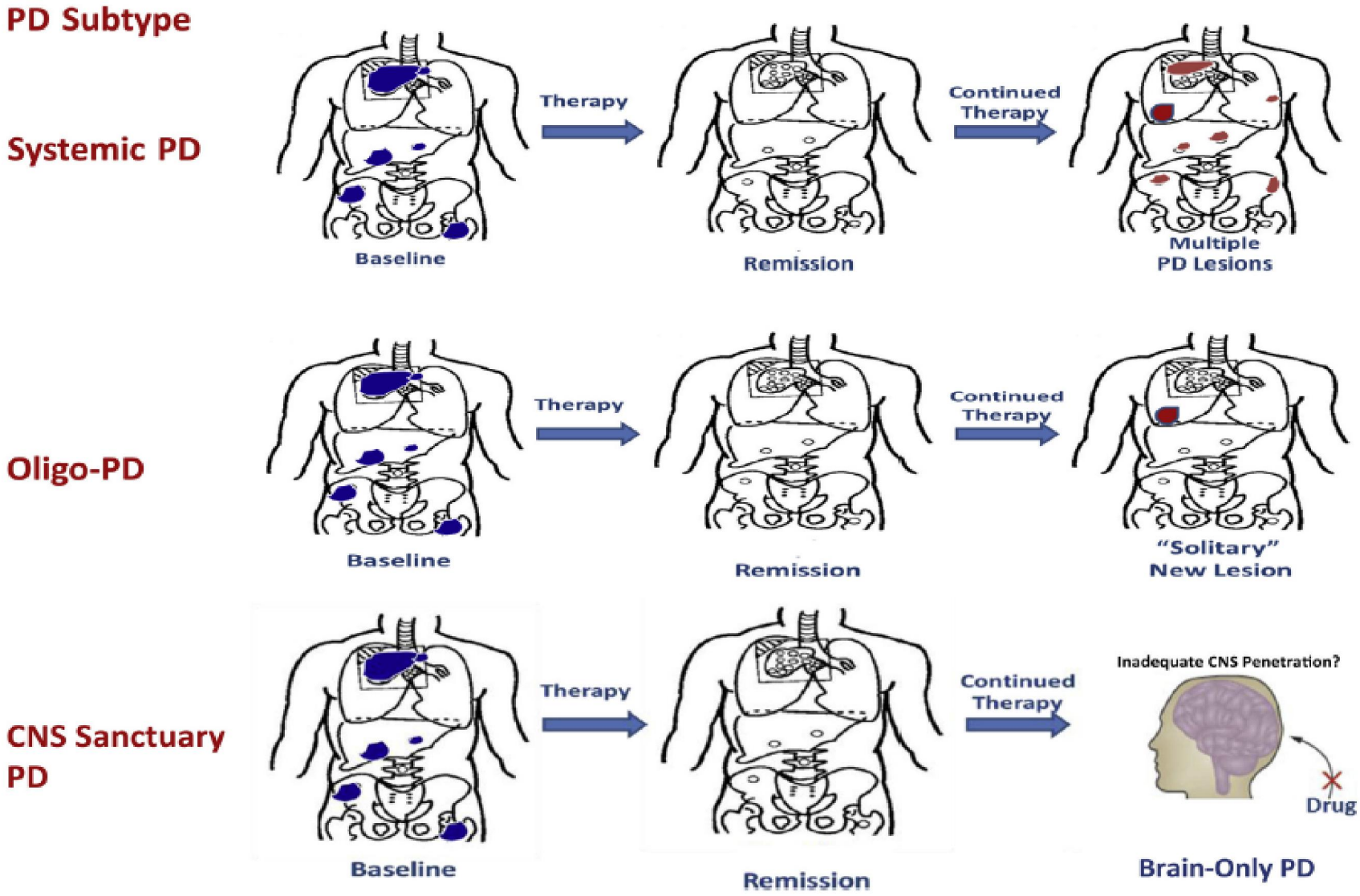
Mechanisms of Acquired Resistance and strategies for overcoming it

Resistance to EGFR inhibition



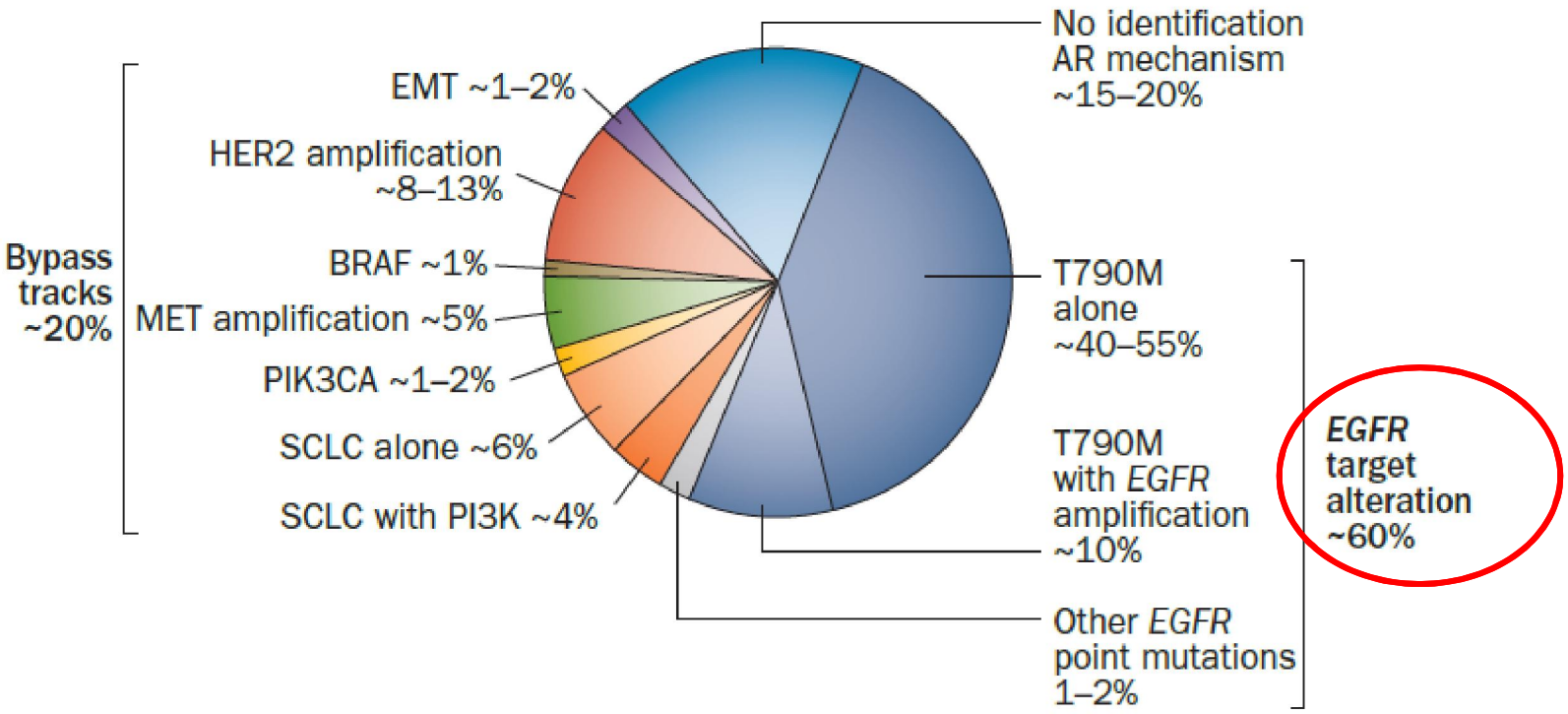
Lovly CM & Shaw AT. Clin Cancer Res 2014

CLINICAL MODES OF EGFR TKI FAILURE



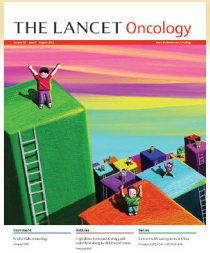
Gandara DR, et al. Clin Lung Cancer 2013

MECHANISMS OF ACQUIRED RESISTANCE TO EGFR TKIs



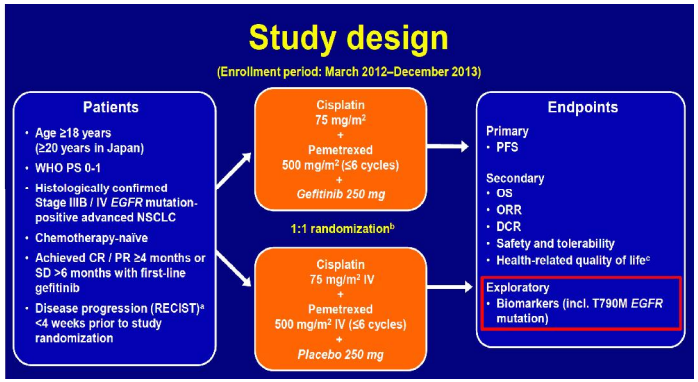
Camidge DR, Pao W, Sequist LV. Nat Rev Clin Oncol 2014

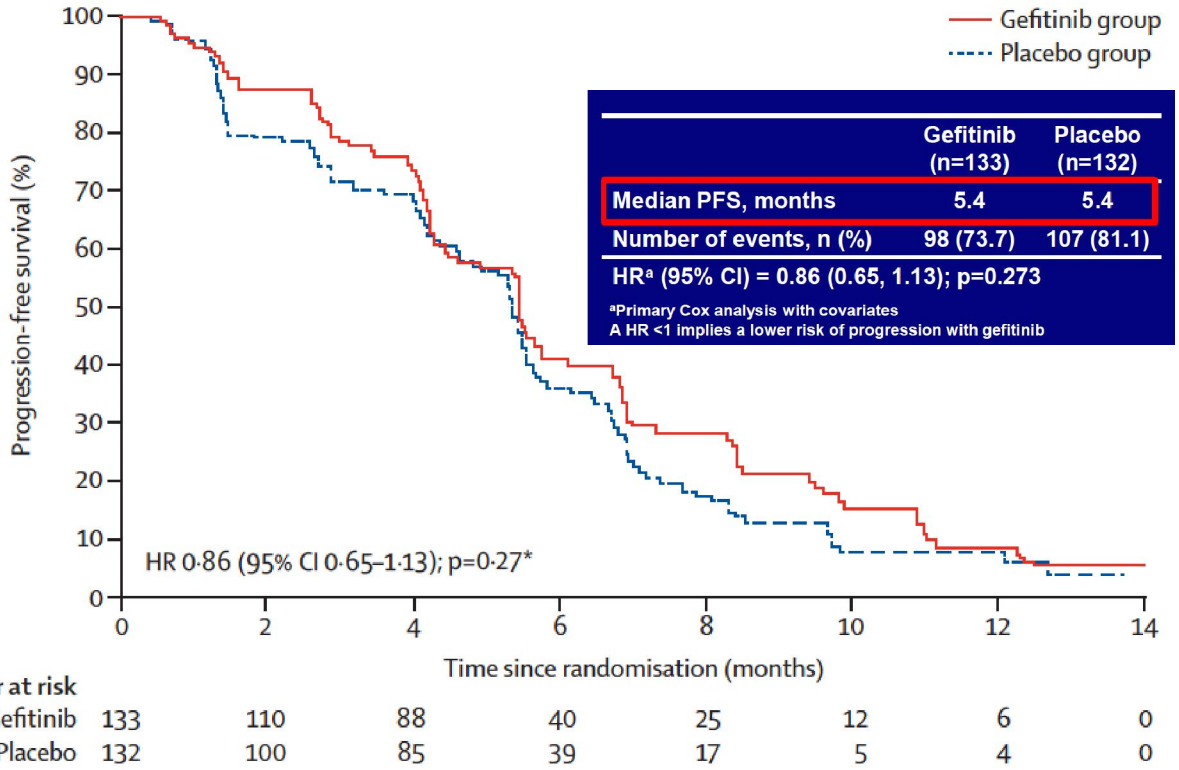
Treatment beyond progression



Gefitinib plus chemotherapy versus placebo plus chemotherapy in *EGFR*-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial

Jean-Charles Soria, Yi-Long Wu, Kazuhiko Nakagawa, Sang-We Kim, Jin-Ji Yang, Myung-Ju Ahn, Jie Wang, James Chih-Hsin Yang, You Lu, Shinji Atagi, Santiago Ponce, Dae Ho Lee, Yunpeng Liu, Kiyotaka Yoh, Jian-Ying Zhou, Xiaojin Shi, Alan Webster, Haiyi Jiang, Tony S K Mok





	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		

[a]Primary Cox analysis with covariates
A HR <1 implies a lower risk of progression with gefitinib

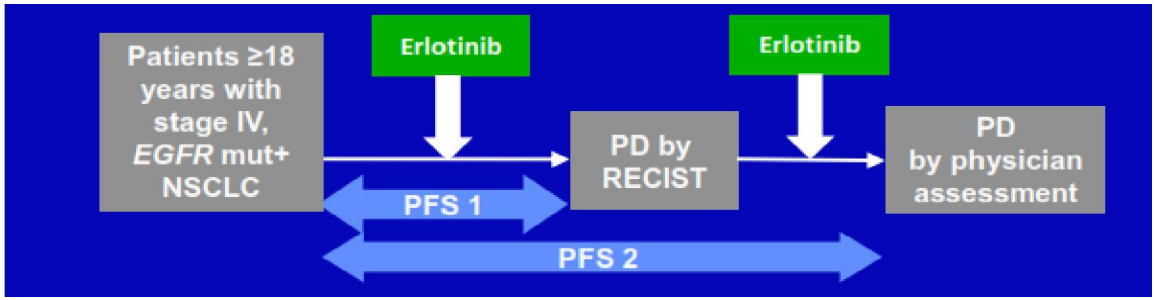
*"…**Continuation of gefitinib after radiological disease progression on first-line gefitinib did not prolong progression-free survival in patients** who received platinum-based doublet chemotherapy as subsequent line of treatment. Platinum-based doublet chemotherapy remains the standard of care in this setting…"*

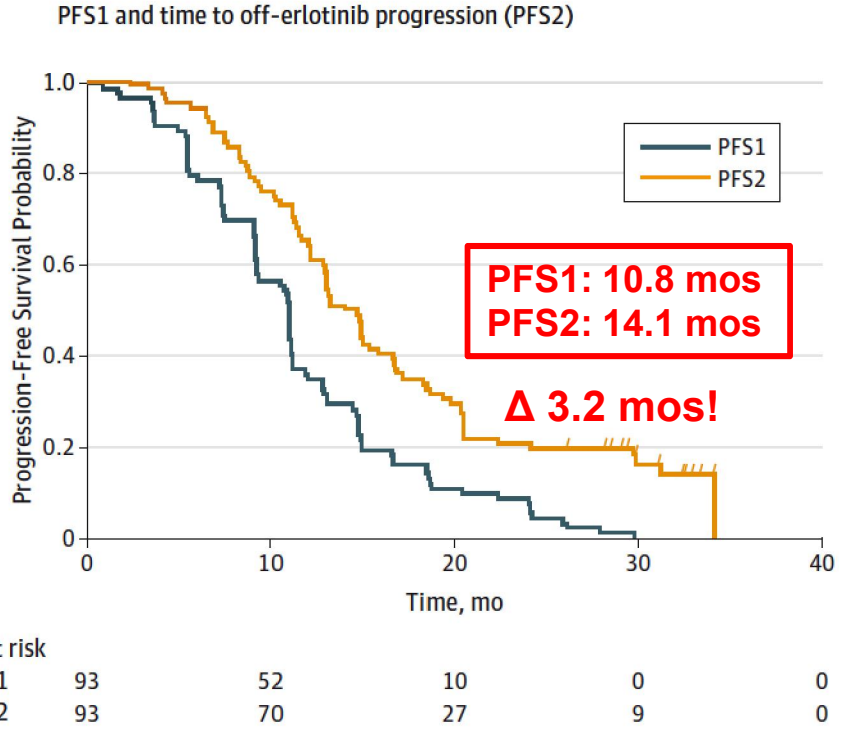
Soria JC, et al. Lancet Oncol 2015; Mok TS, et al. WCLC 2015

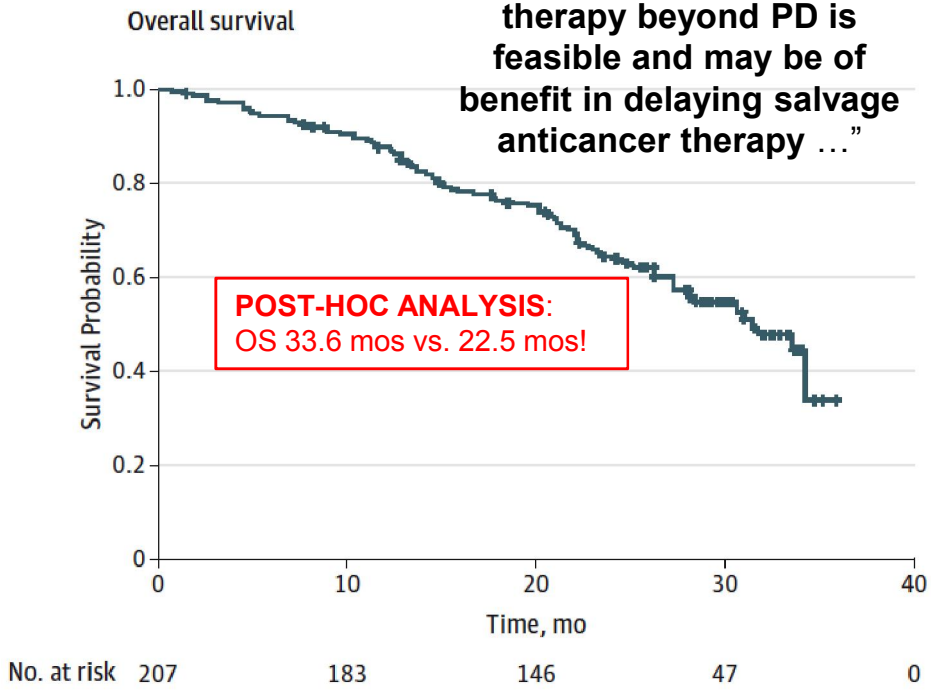
Original Investigation

First-Line Erlotinib Therapy Until and Beyond Response Evaluation Criteria in Solid Tumors Progression in Asian Patients With Epidermal Growth Factor Receptor Mutation–Positive Non–Small-Cell Lung Cancer
The ASPIRATION Study

Keunchil Park, MD; Chong-Jen Yu, MD; Sang-We Kim, MD; Meng-Chih Lin, MD; Virote Sriuranpong, MD; Chun-Ming Tsai, MD; Jong-Seok Lee, MD; Jin-Hyoung Kang, PhD; K. C. Allen Chan, MD; Pablo Perez-Moreno, MD; Peter Button, MSc; Myung-Ju Ahn, MD; Tony Mok, MD



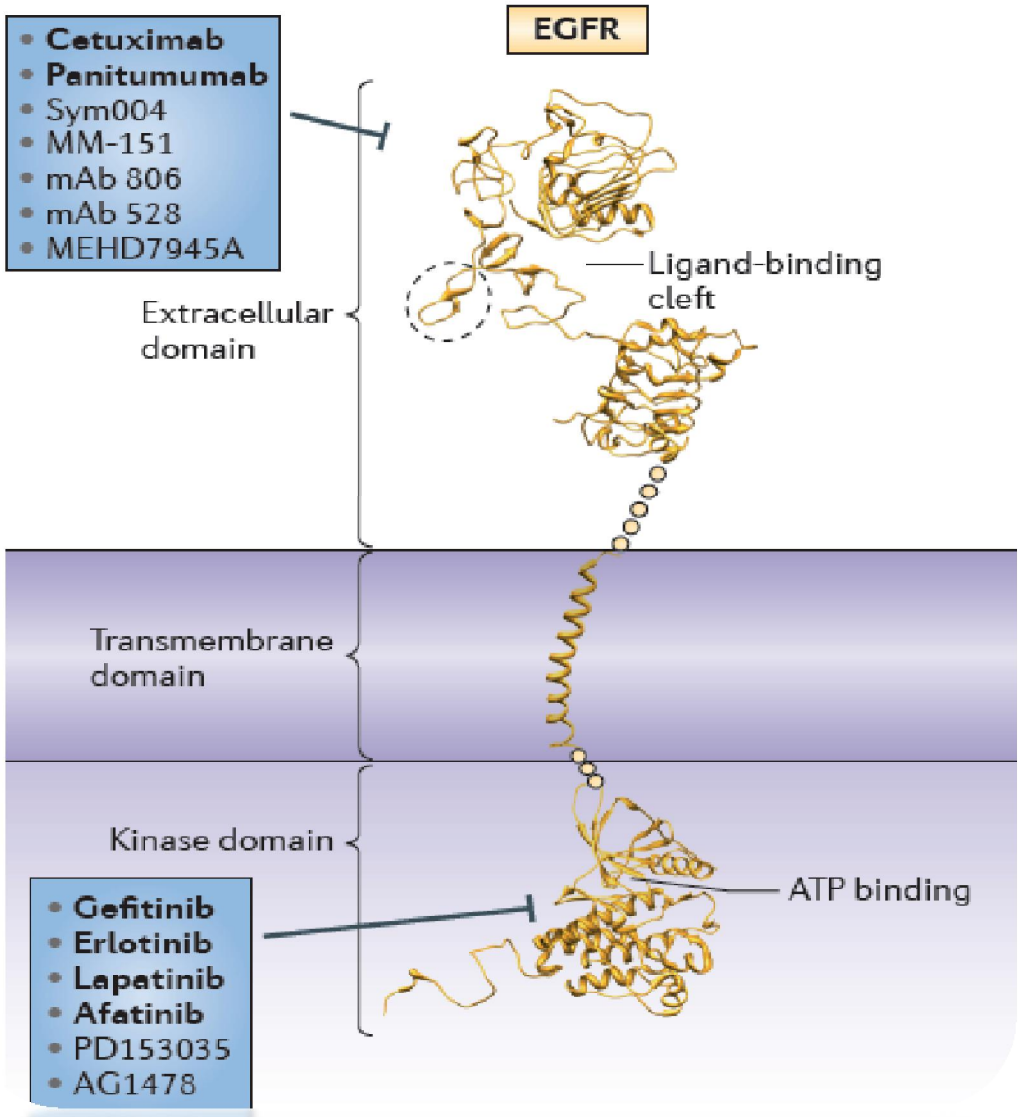




"…The prospective ASPIRATION study **supports the efficacy of first-line erlotinib therapy in Asian patients** with EGFR mutation–positive NSCLC and **that continuing Erlotinib therapy beyond PD is feasible and may be of benefit in delaying salvage anticancer therapy** …"

Park K, et al. ESMO 2014; Park K, et al. JAMA Oncol 2016

VERTICAL BLOCKAGE OF EGFR



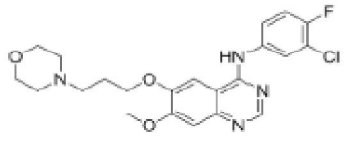
Tebbutt N, et al. Nat Rev Cancer 2013

3rd generation EGFR inhibitors

The discovery of selective irreversible inhibitors for EGFR-T790M

"quinazoline-based"

1st generation TKI



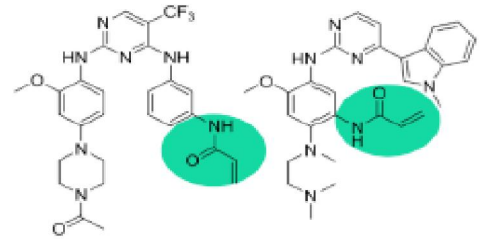
gefitinib

2nd generation TKI

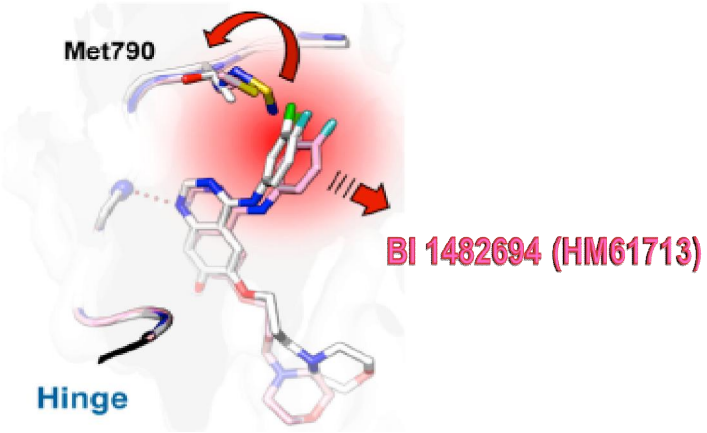
afatinib

"aminopyrimidine-based"

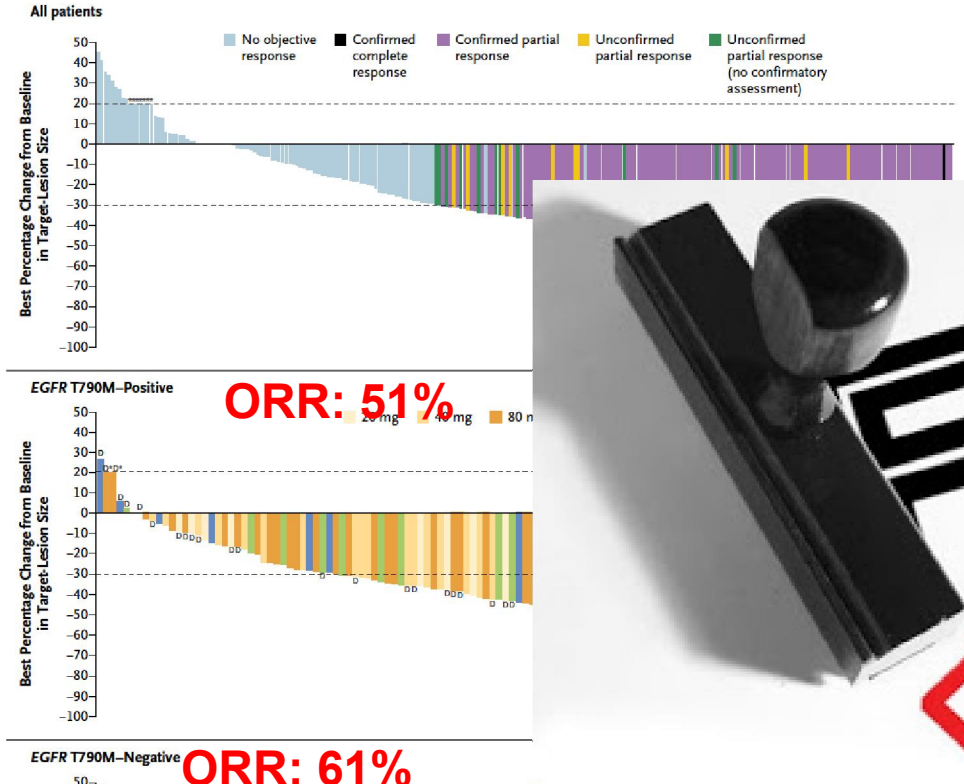
3rd generation TKI



CO-1686 AZD9291

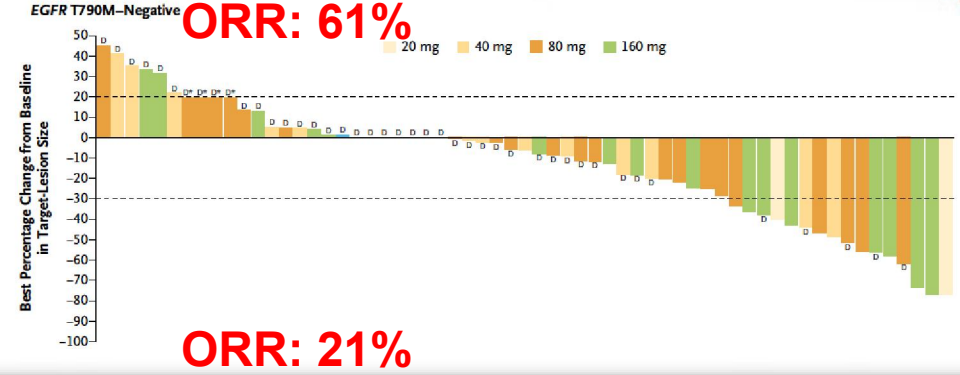


Osimertinib: preliminary data from the phase I AURA trial



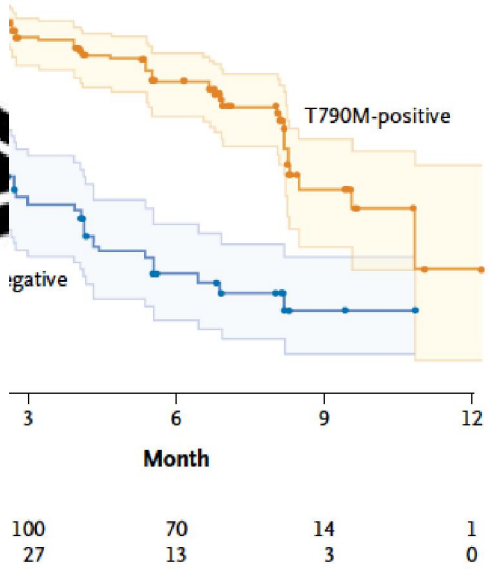
ORR: 51%

ORR: 61%



ORR: 21%

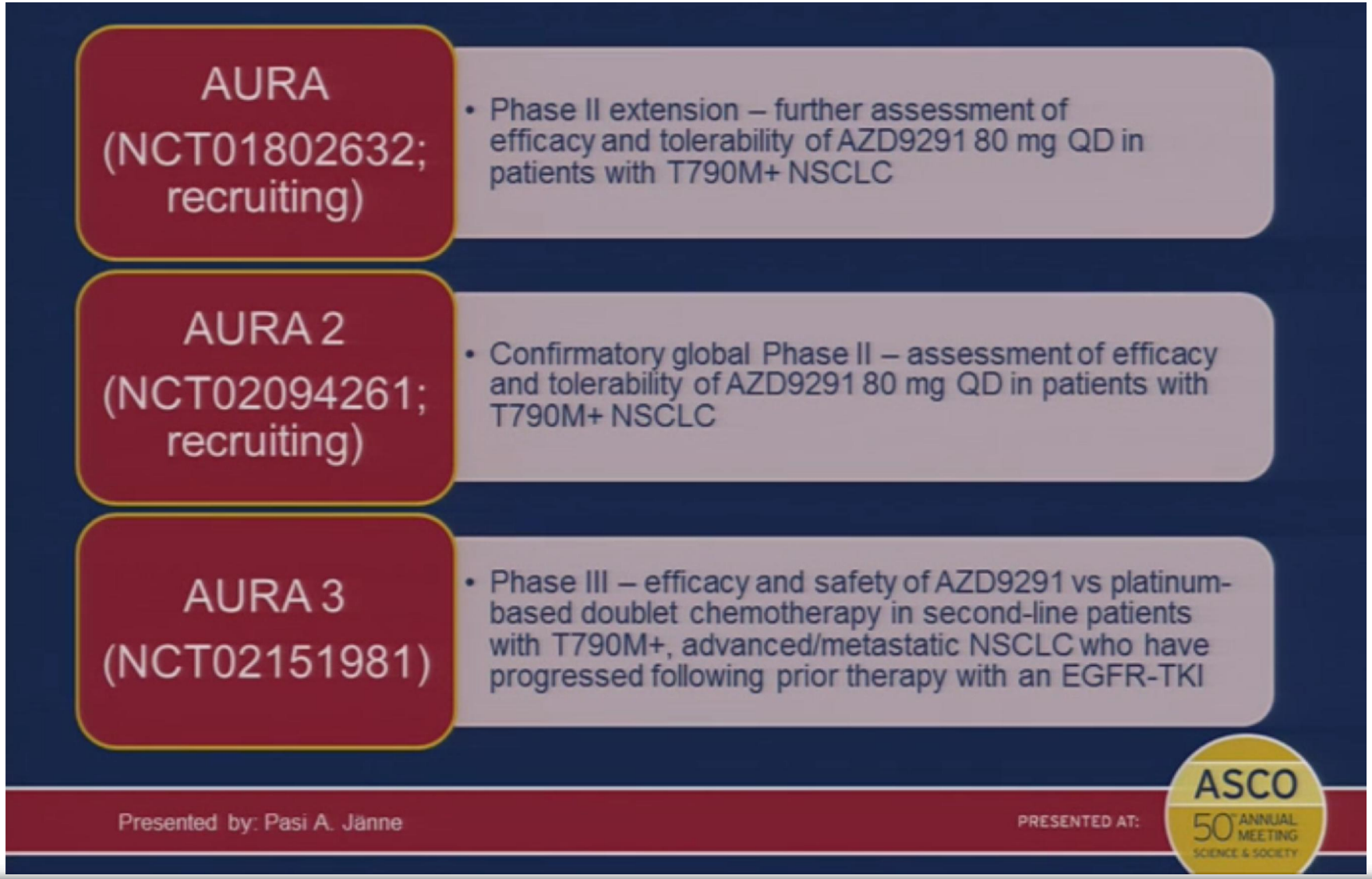
PFS: 9.6 (T790M+) vs. 2.8 months (T790M-)



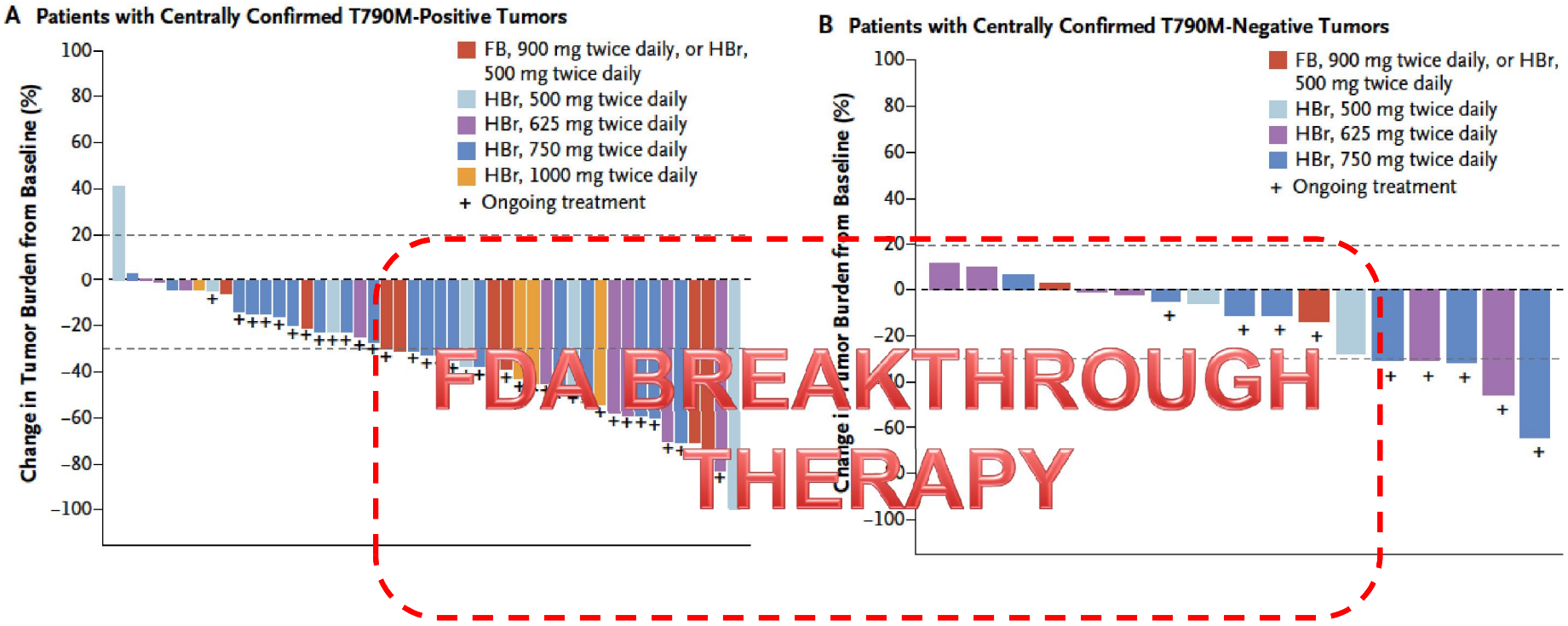
"…AZD9291 was highly active in patients with lung cancer with the EGFR T790M mutation who had had disease progression during prior therapy with EGFR tyrosine kinase inhibitors…"

Jänne PA, et al. NEJM 2015

AURA TRIAL PROGRAM



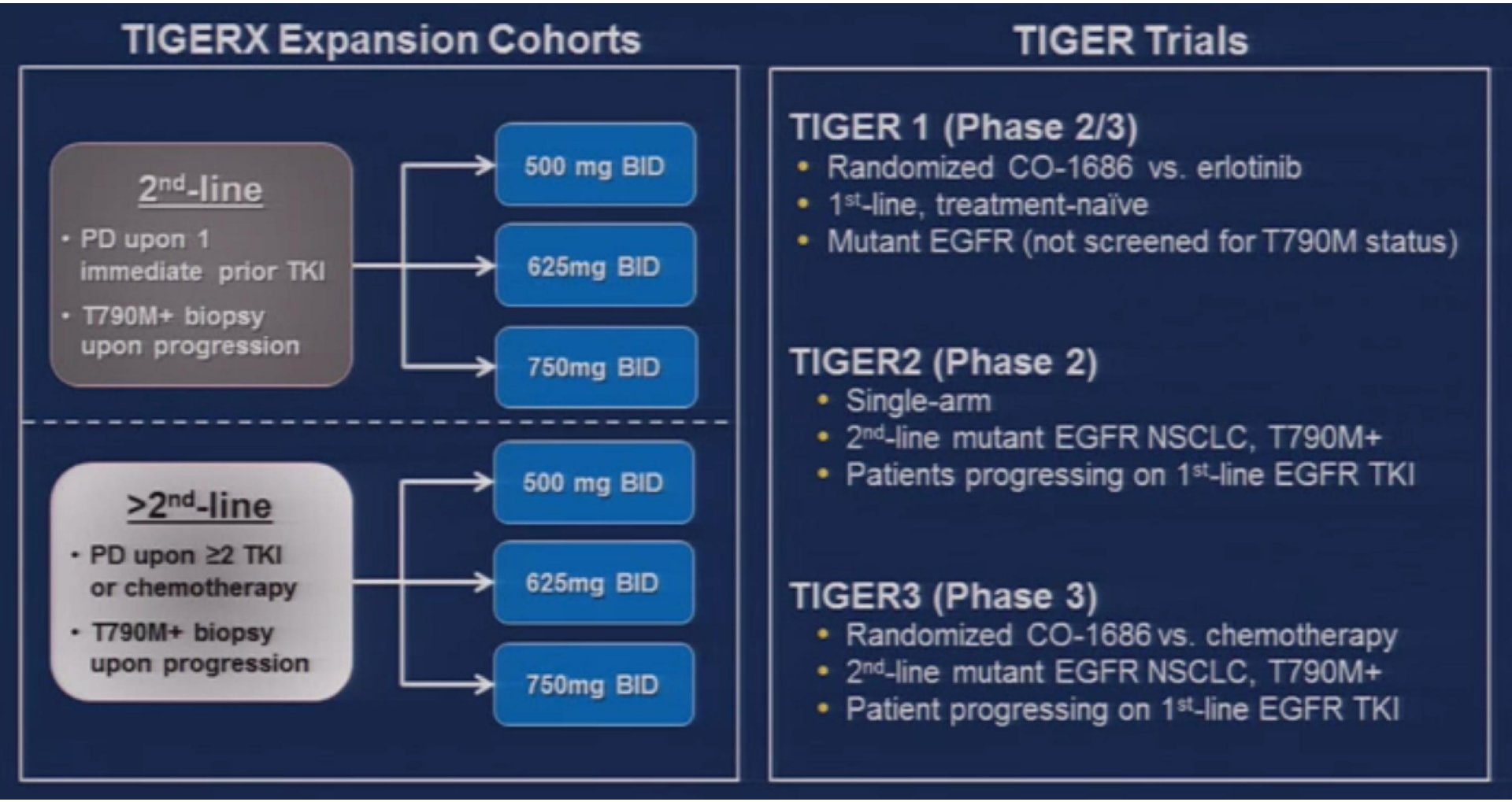
Rociletinib: preliminary data from the phase I TIGER-X trial



"…Rociletinib was active in patients with EGFR -mutated NSCLC associated with the T790M resistance mutation…"

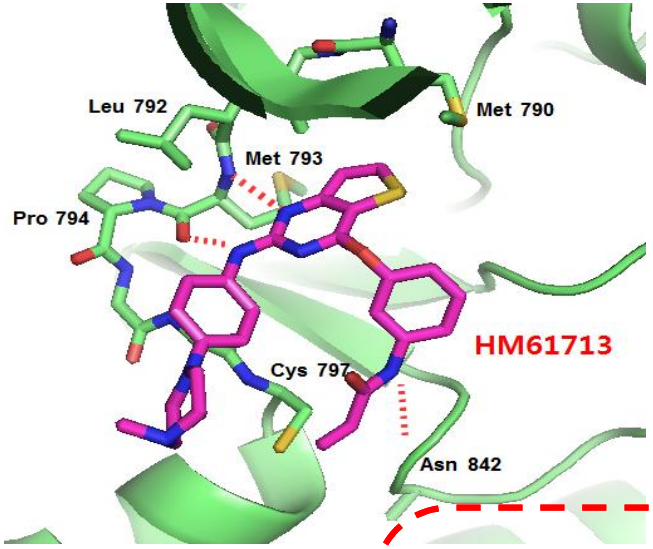
Sequist LV, et al. NEJM 2015

TIGER PROGRAM



Sequist LV, et al. ASCO 2014

ELUXA TRIAL PROGRAM



BI 1482694 (HM61713)

FDA BREAKTHROUGH THERAPY

Recruiting →	Phase I/II [illegible] NSCLC
Recruiting →	Phase II Korean study in 1st [illegible] NSCLC
Recruiting →	Phase II global study in ≥ 2 line patients with EGFR ^{T790M} positive NSCLC
Planned →	Phase III randomized trials

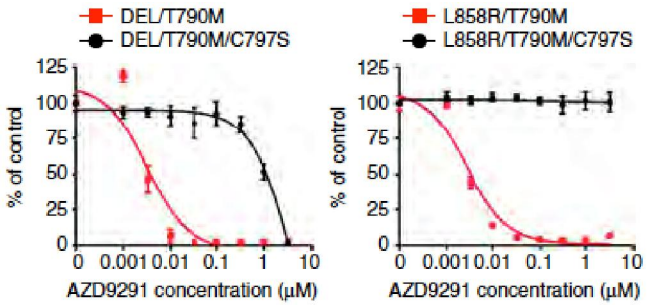
NOVEL CHALLENGES POSED BY 3rd GEN EGFR TKIs

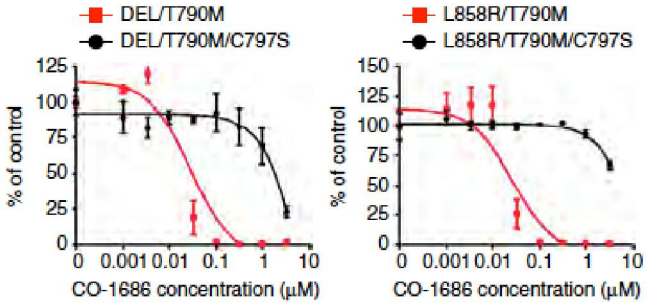
Acquired Resistance to 3rd generation EGFR TKIs: tertiary mutations

nature medicine

Acquired *EGFR* C797S mutation mediates resistance to AZD9291 in non–small cell lung cancer harboring *EGFR* T790M

Kenneth S Thress[1], Cloud P Paweletz[2,3], Enriqueta Felip[4,5], Byoung Chul Cho[6], Daniel Stetson[1], Brian Dougherty[1], Zhongwu Lai[1], Aleksandra Markovets[1], Ana Vivancos[4], Yanan Kuang[2,3], Dalia Ercan[2], Sarah E Matthews[2], Mireille Cantarini[7], J Carl Barrett[1], Pasi A Jänne[2,3] & Geoffrey R Oxnard[2]



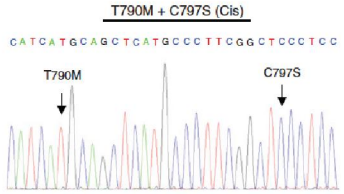


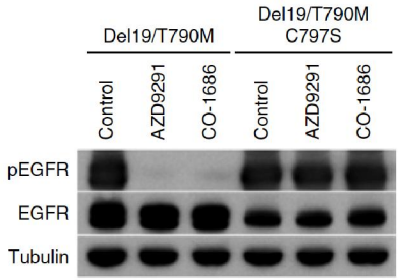
Cancer Therapy: Preclinical

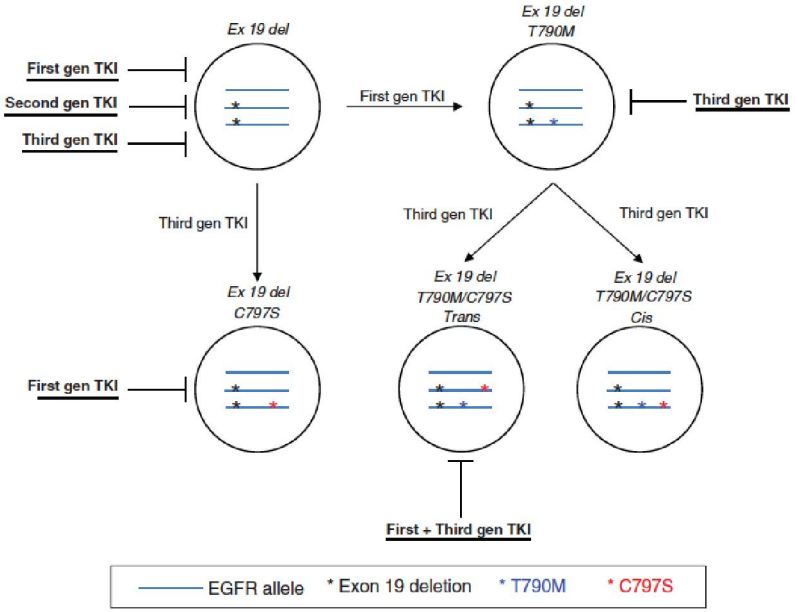
Clinical Cancer Research

The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies

Matthew J. Niederst[1,2], Haichuan Hu[1,2], Hillary E. Mulvey[1,2], Elizabeth L. Lockerman[1,2], Angel R. Garcia[1,2], Zofia Piotrowska[1,2], Lecia V. Sequist[1,2], and Jeffrey A. Engelman[1,2]

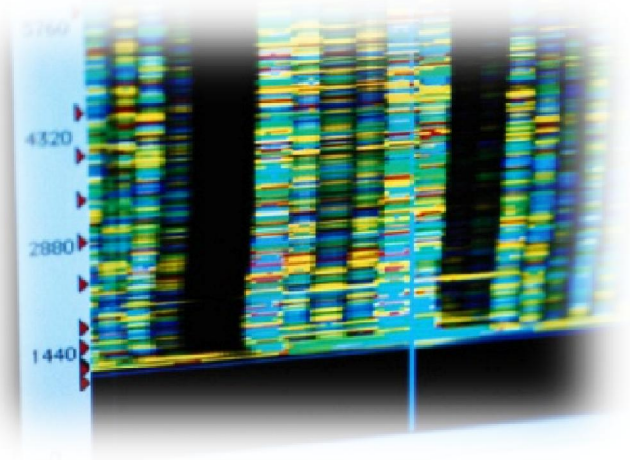




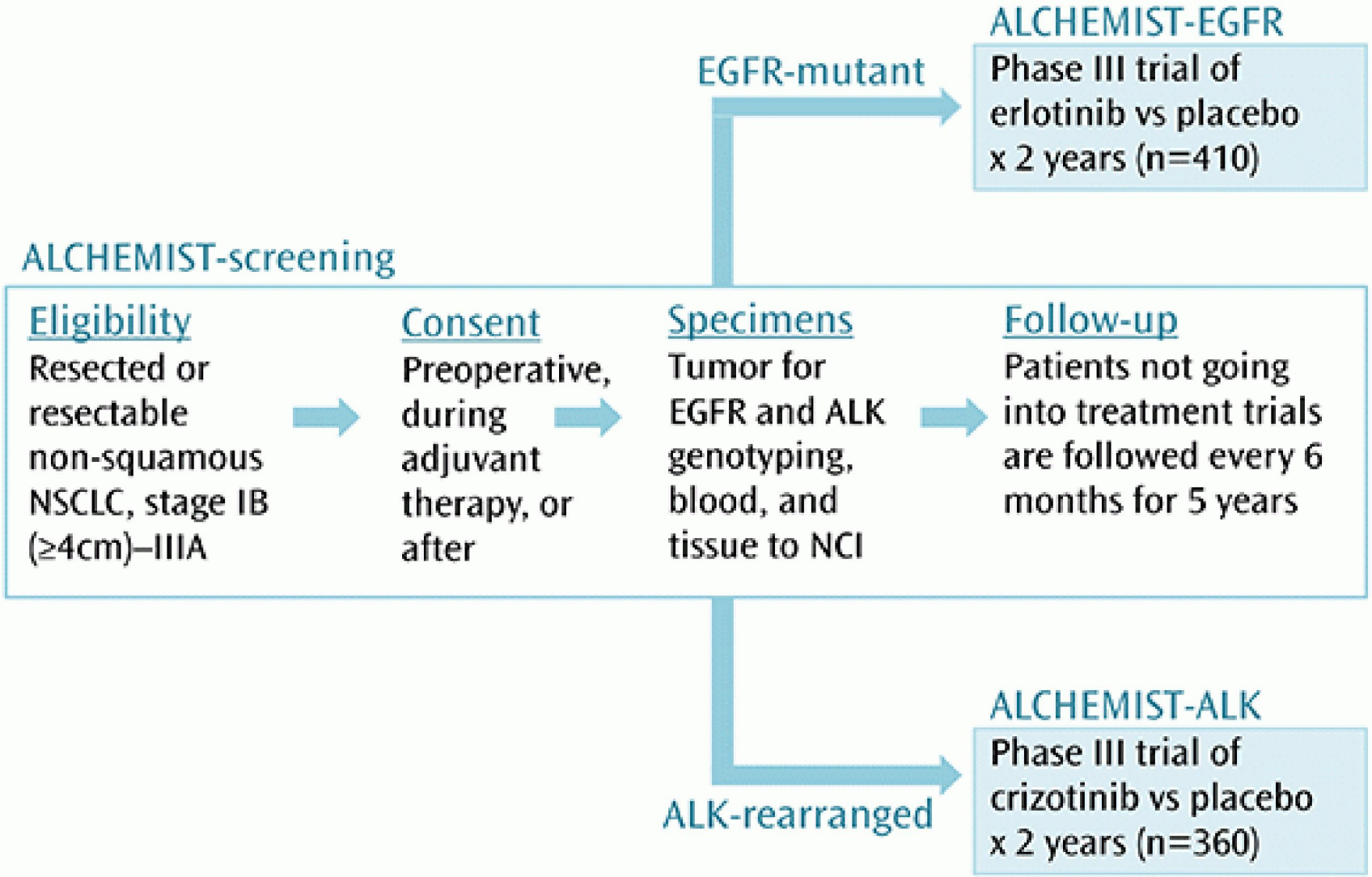


Thress KS, et al. Nat Med 2015; Niederst MJ, et al. Clin Cancer Res 2015

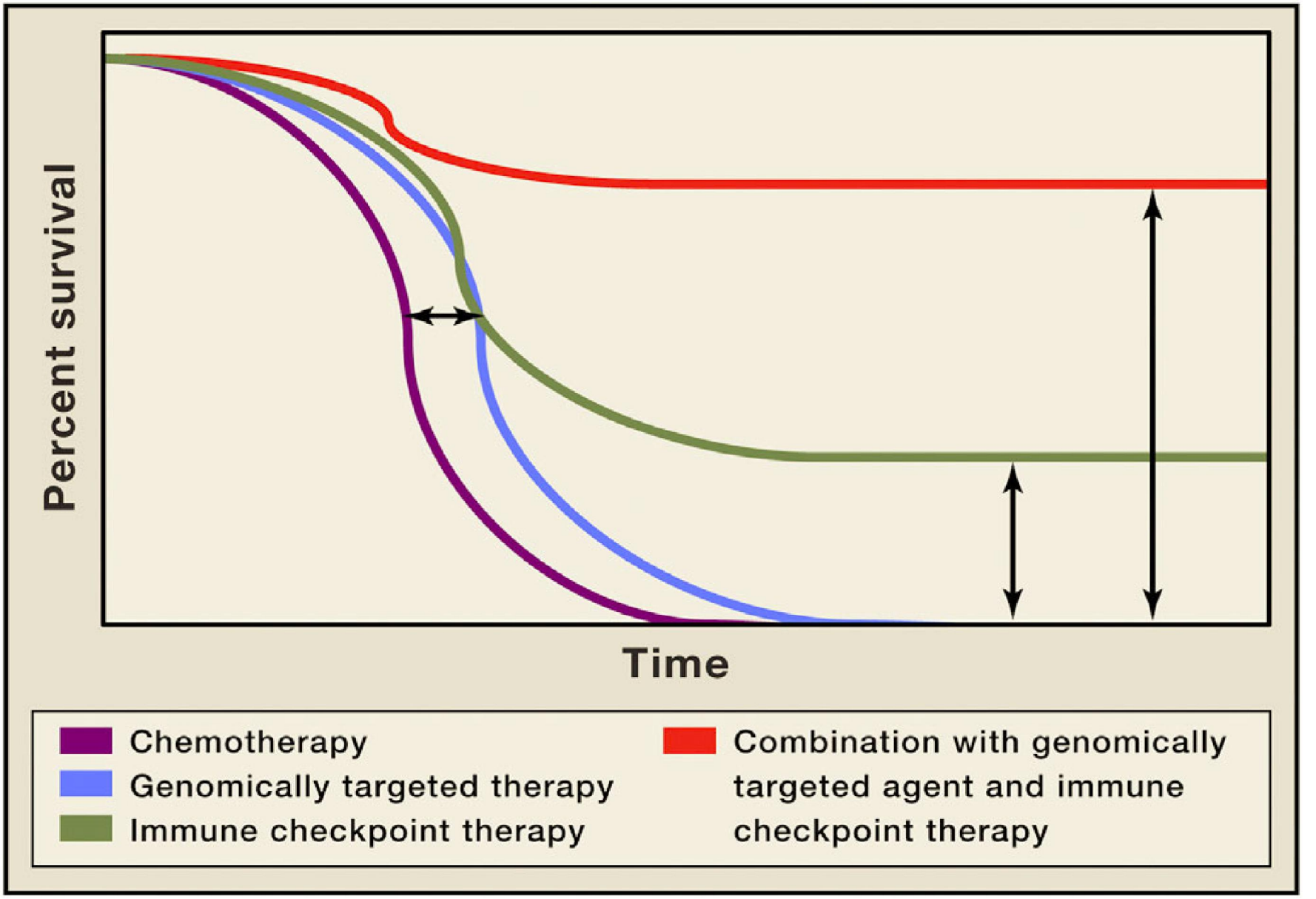
Future perspectives



Biomarker-driven adjuvant targeted therapy for NSCLC—the ALCHEMIST trials



The future? INTEGRATION...



TAKE HOME MESSAGES

- EGFR-mutated NSCLC is a distinct molecular subtype with peculiar clinic-pathological characteristics
- First-line EGFR TKIs is the mainstay of treatment in EGFR-mut+ NSCLC
- Treatment of EGFR-mutant NSCLCs is an evolving paradigm: ongoing prospective, comparative trials will provide the definitive conclusions on the best EGFR TKI in 1st line
- Mutant-selective EGFR TKIs expand our therapeutic armamentarium, but poses novel and attractive challenges
- Moving anti-EGFR treatment in early stage NSCLC may change the disease course in radically-resected patients

TAKE HOME MESSAGE

Target is target