VII Simpósio Internacional Câncer de PULMÃO

15 e 16 de março de 2019

Hotel Pullman São Paulo Vila Olímpia

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Câncer de pulmão *EGFR* mutado: algoritmo de tratamento e desafios

EGFR mutated lung cancer: treatment algorithm and challenges

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Cancer Center

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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Relevant financial relationships with a commercial interest:

_ Clovis Oncology, research funding (previous 2016)
_ Boehringer Ingelheim Pharm. Inc., consulting/honoraria (previous 2016)
_ Pfizer Inc., consulting/honoraria (previous 2017)
_ Takeda/Millennium Pharmaceuticals, consulting/honoraria (previous 2016-2019)
_ AstraZeneca, consulting/honoraria/research funding (previous 2016-2019)

Non-financial support (institutional research support):

_ Merck Sharp & Dohme Corporation
_ Pfizer
_ Takeda/Millennium Pharmaceuticals
_ Astrazeneca
_ Merrimack Pharmaceuticals

“Off-label” use disclosure relevant to my presentation:

_ gefitinib, erlotinib, afatinib, dacomitinib and osimertinib, off-label use in *EGFR* mutated cancers

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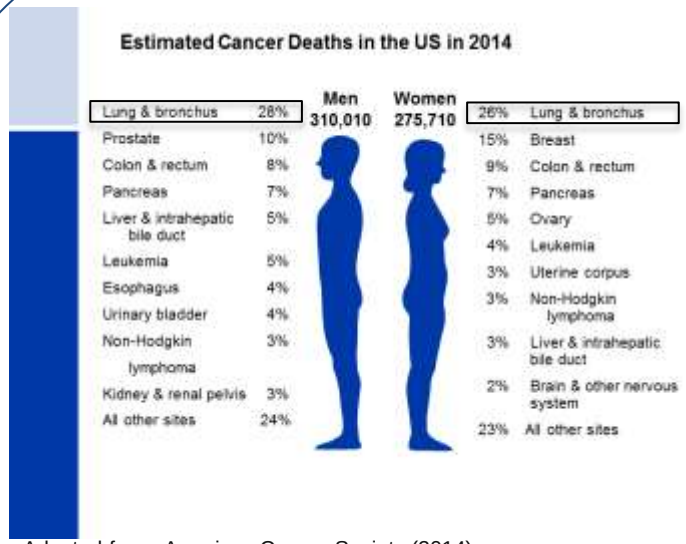
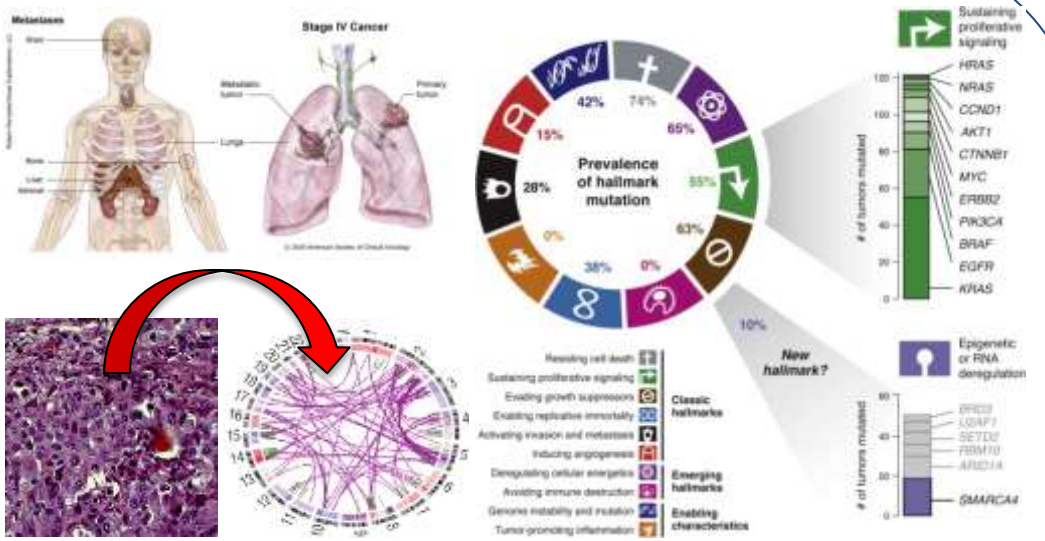
Contemporary View of Lung Cancer in 2019:

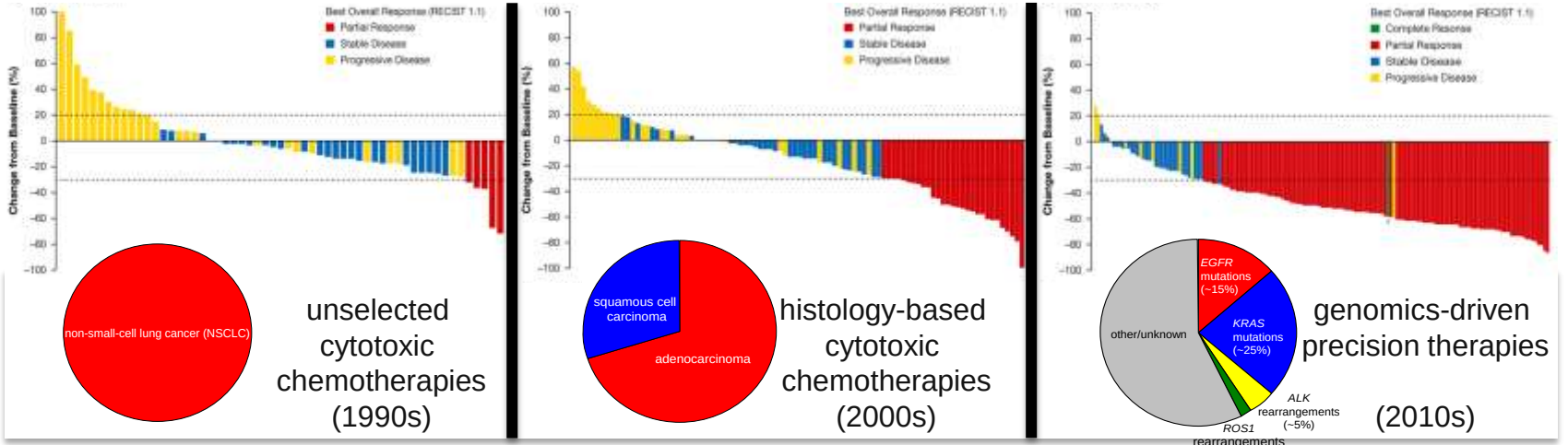
Non-small-cell lung cancers are heterogeneous at the genomic level



Adapted from: American Cancer Society (2014)



Adapted from: Imielinski M. et al. Cell 150, 1107-1120 (2012)



Adapted from: Shaw AT et al. N Engl J Med;368:2385-94 (2013)

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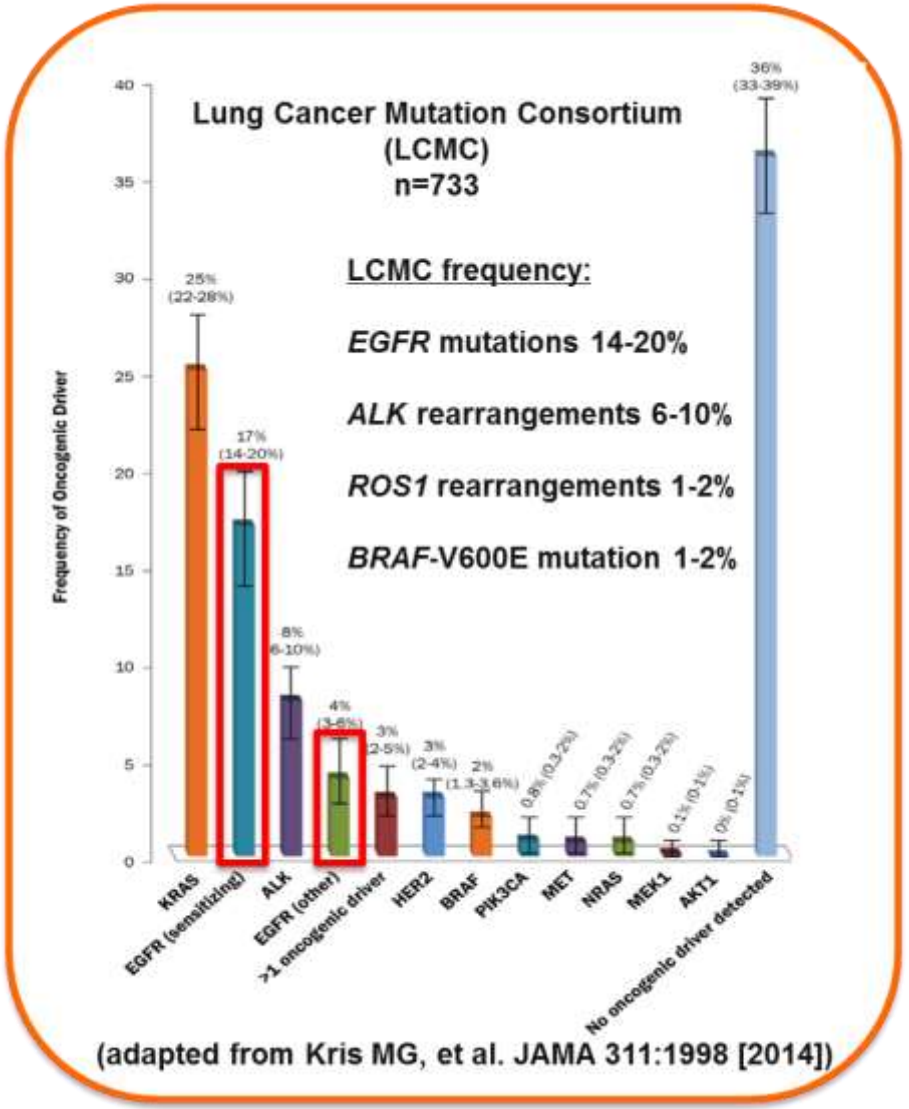
EGFR mutations, *ALK*, *ROS1* rearrangements, *BRAF*-V600E mutation and *NTRK* rearrangements in lung adenocarcinomas (minimal testing required)

CAP, IASLC and AMP recommend rapid testing for *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangement in 2017, *BRAF*-V600E in 2018 and likely *NTRK* rearrangements in 2019 for all patients with advanced stage adenocarcinoma, regardless of sex, race, smoking history or other clinical risk factors

(Lindeman NI, et al. J Thorac Oncol. 2018 Mar;13(3):323-358)

How Rapidly Should Test Results Be Available?

- Specimens with a final histopathologic diagnosis should be submitted for testing within:
  - 24 hours (internal molecular pathology laboratory)
  - 3 business days (external molecular pathology laboratory)
- Test results should be made available within 10 business days of receiving the specimen in the laboratory



(adapted from Kris MG, et al. JAMA 311:1998 [2014])

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Driver oncogene genotypes with kinase inhibitor approval/development (advanced lung adenocarcinoma) in 2019

Genetic aberrations that can modulate targeted or immune therapies:

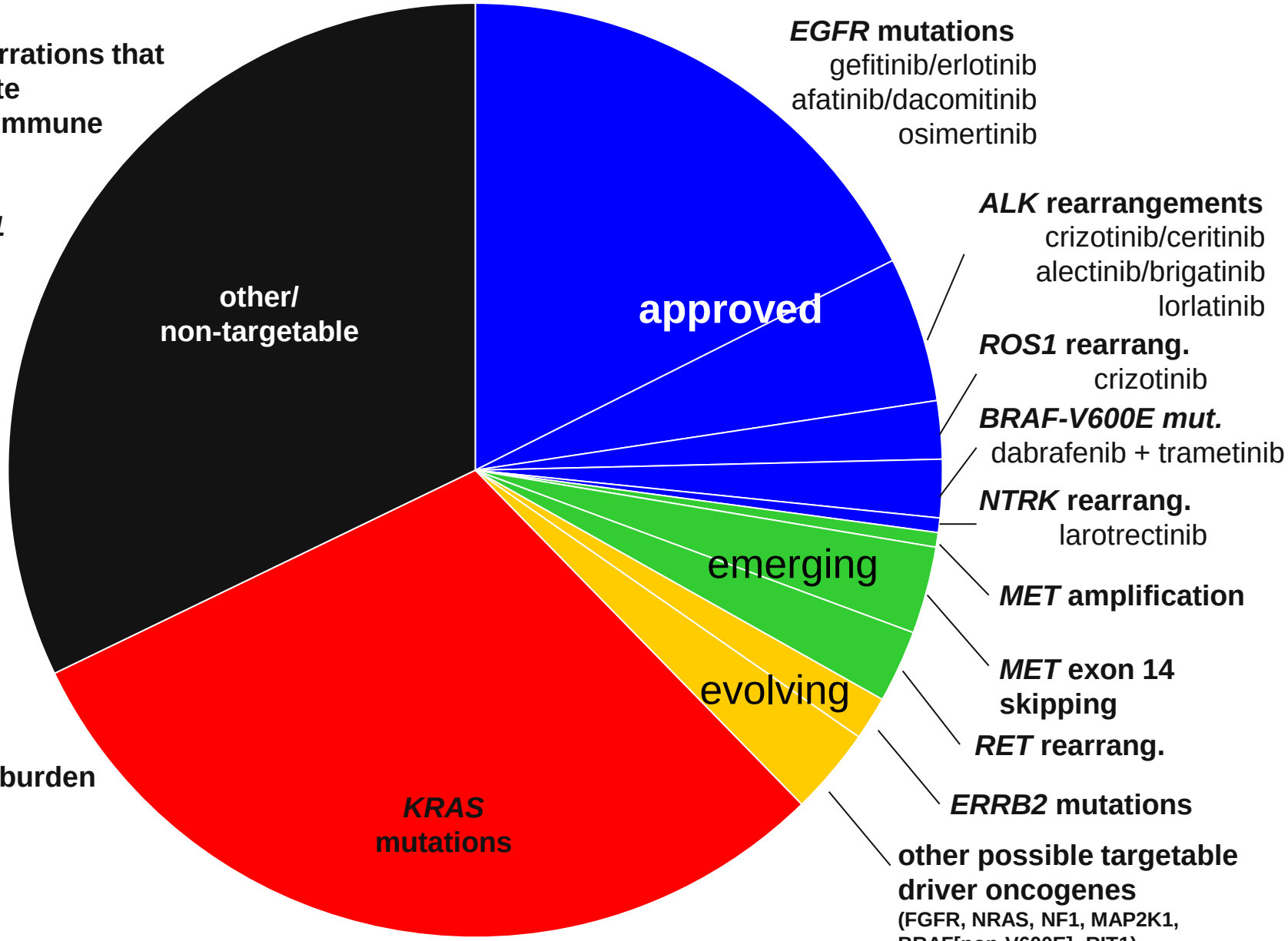
STK11/LKB1
TP53
PIK3CA
RB1

HDR genes (*BRCA1/2* *PALB2*)

MSI/MMR genes (*MLH1* *MSH2* *MSH6* *MSI-H*)

Tumor mut. burden (TMB)

PD-L1



***EGFR* mutations**
gefitinib/erlotinib
afatinib/dacomitinib
osimertinib

***ALK* rearrangements**
crizotinib/ceritinib
alectinib/brigatinib
lorlatinib

***ROS1* rearrang.**
crizotinib

BRAF-V600E mut.
dabrafenib + trametinib

***NTRK* rearrang.**
larotrectinib

***MET* amplification**

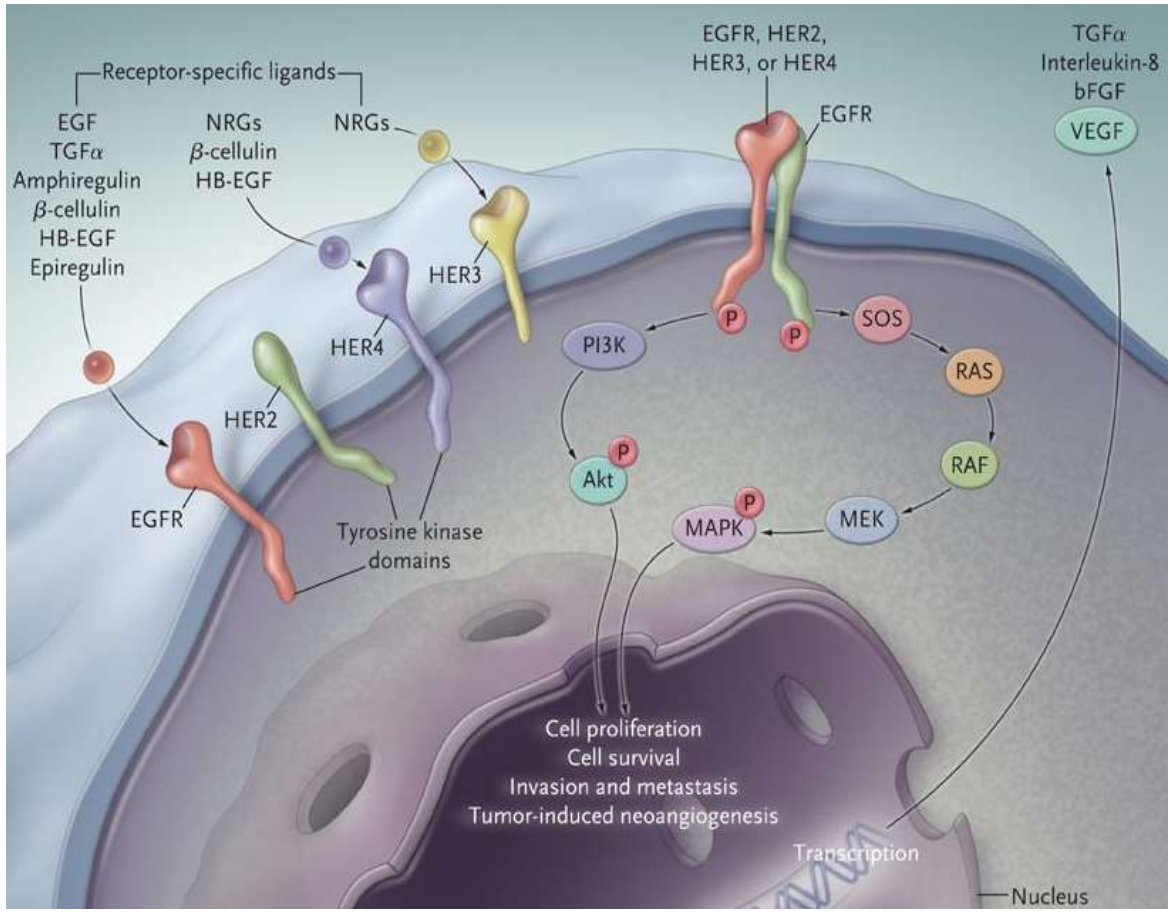
***MET* exon 14 skipping**

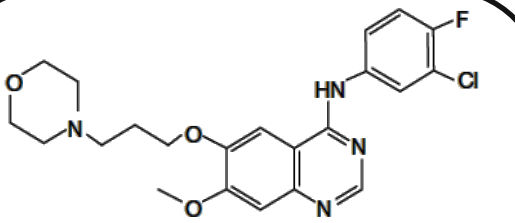
***RET* rearrang.**

***ERRB2* mutations**

other possible targetable driver oncogenes
(FGFR, NRAS, NF1, MAP2K1, BRAF[non-V600E], RIT1)

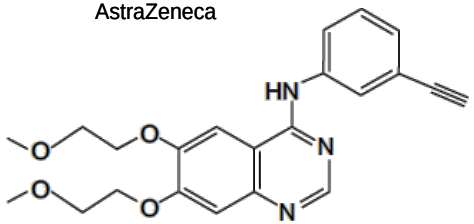
Epidermal growth factor receptor (EGFR) pathway
Initial EGFR tyrosine kinase inhibitors (TKIs)





gefitinib

AstraZeneca



erlotinib

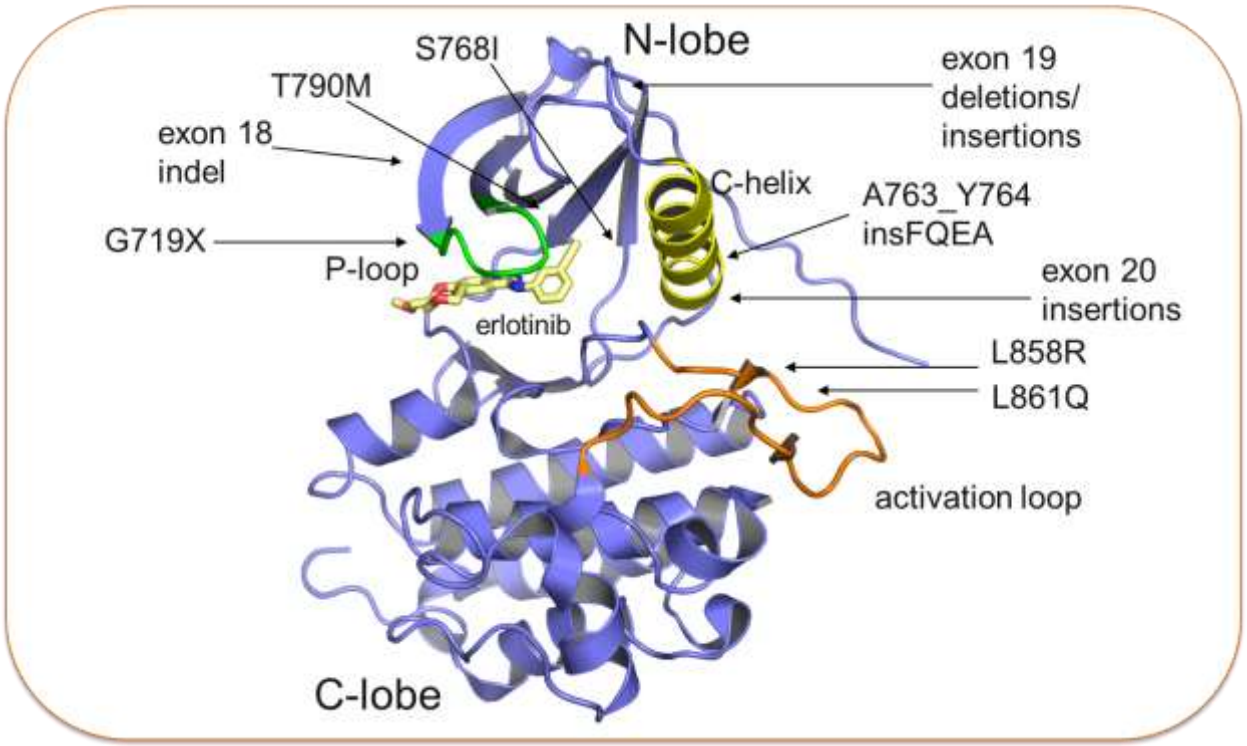
OSI Pharmaceuticals – Genentech - Roche

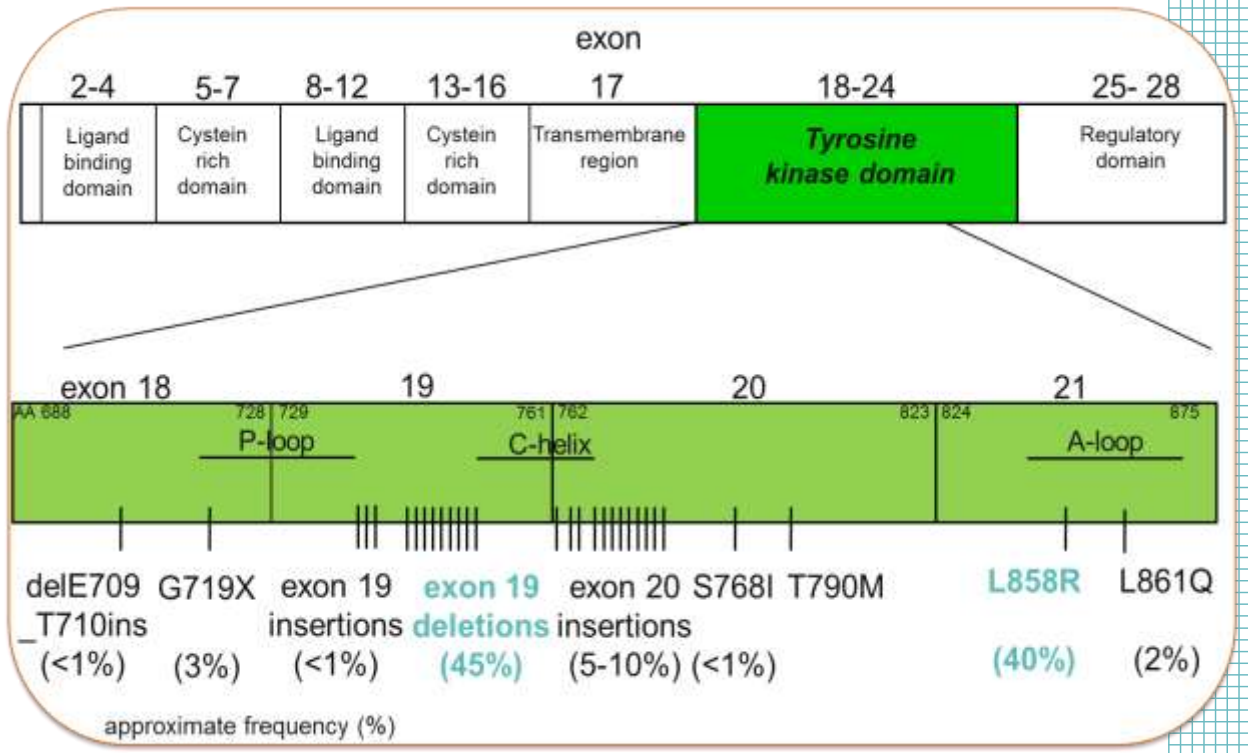
<u>Side-effect profile in humans:</u>

1) Skin rash ~ 50-80% of patients
2) Diarrhea ~ 20-50%
3) Anorexia ~ 10-15%
4) Interstitial Lung Disease <1-5%

Ciardiello F, et al. N Engl J Med; 358:1160-1174. (2008)

EGFR mutations in NSCLC cluster around the tyrosine kinase domain (ATP binding pocket) of EGFR





Adapted from Yasuda, Kobayashi, Costa DB. Lancet Oncology; 13(1):e23-31. (2012)

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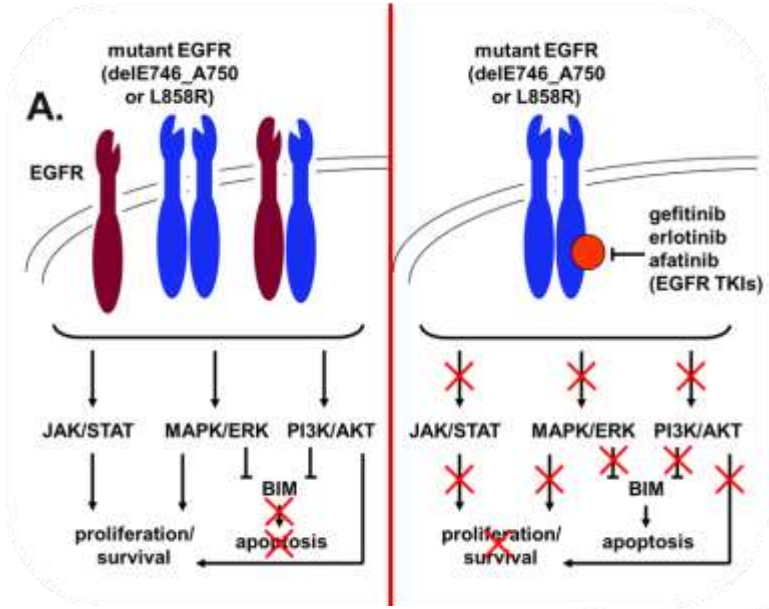
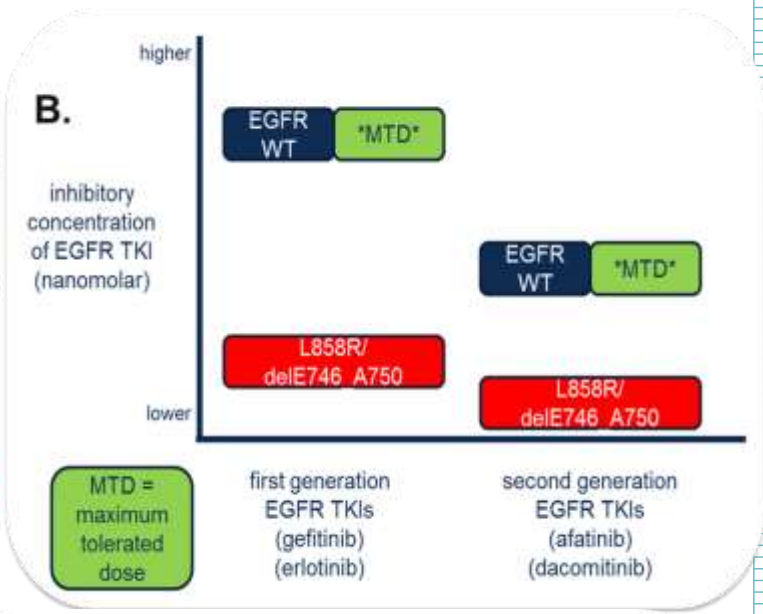
EGFR TKIs as first line therapy for *EGFR* mutated NSCLC: EGFR TKIs vs cytotoxic chemotherapy

Understanding the concepts of:

A. oncogene addiction

B. "therapeutic window"
in relation to EGFR wild-type [WT]





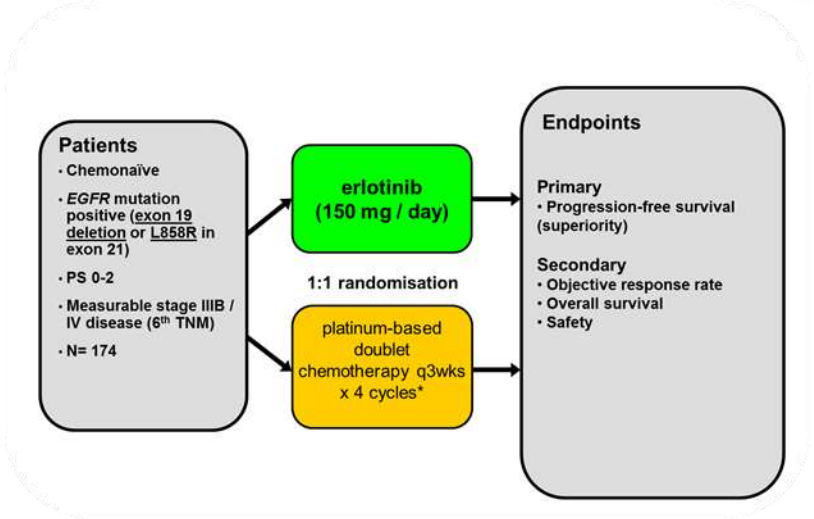
Summary:

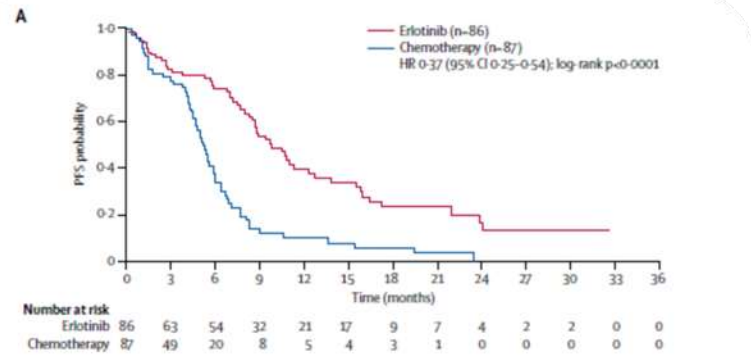
(EGFR-L858R and exon 19 deletions)

ORRs significantly higher for 1st/2nd gen. EGFR TKIs

PFSs were 42-84% longer with EGFR TKIs

No detriment in OS with EGFR TKIs (cross over)





Response rate	erlotinib	chemotherapy
	64.9%	18% (p<0.001)

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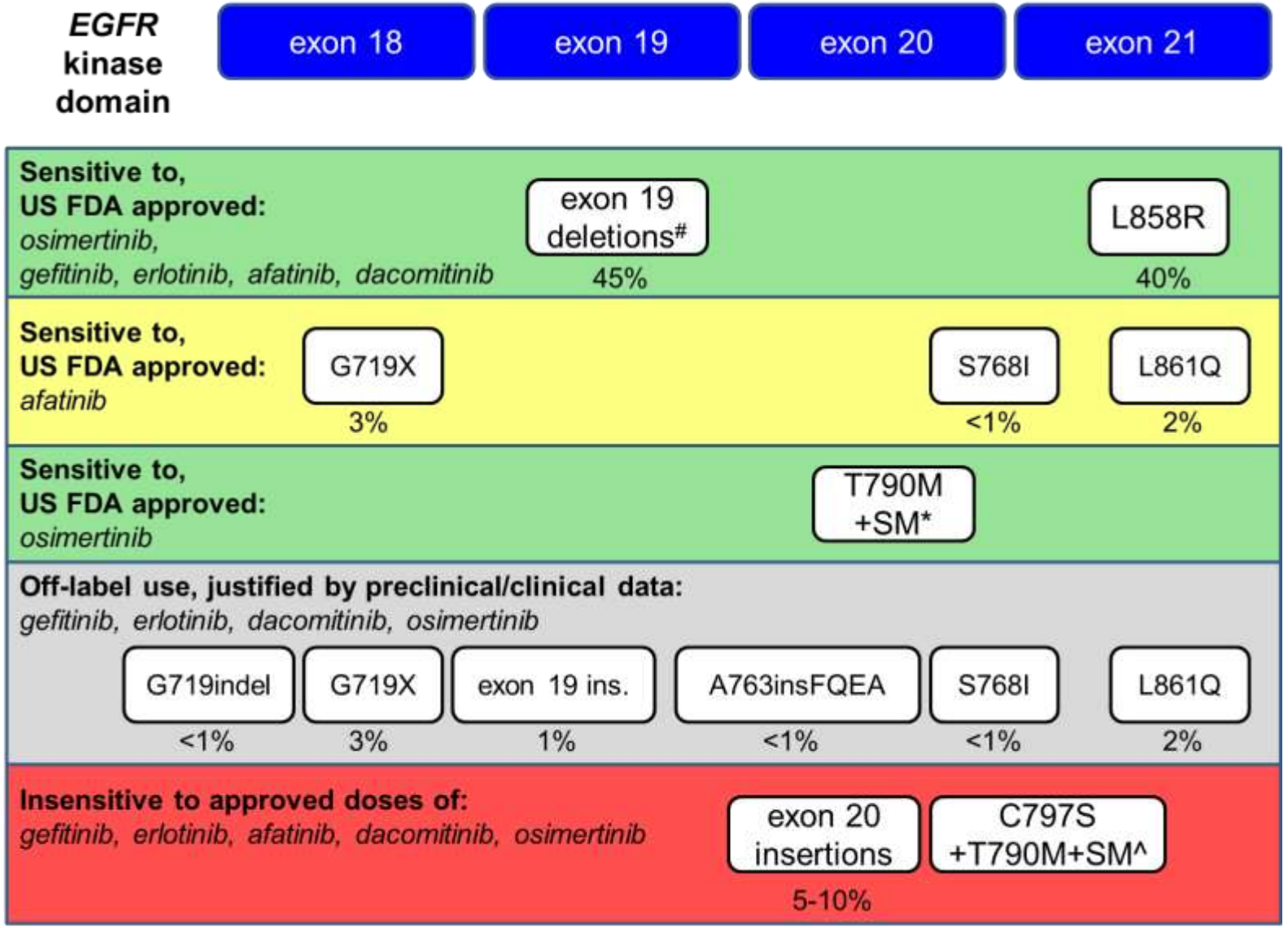
Therapies for advanced *EGFR* mutated lung cancer (March 2019)



"SM" = sensitizing mutation. "X" in G719X = substitution for several different amino acids and is not a stop codon. Approved doses of TKIs are: gefitinib 250mg daily, erlotinib 150mg daily (1st generation TKIs); afatinib 40mg daily (2nd generation TKI); osimertinib 80mg daily (3rd generation TKI).
#Most common exon 19 deletion is delE746_A750 (LREA motif).
***Cause of acquired resistance to gefitinib, erlotinib and afatinib in >50%.**
^Cause of osimertinib resistance in 30%.

Adapted from Sheikine Y, Rangachari D et al. Clin Lung Cancer; 17(6):483. (2016)

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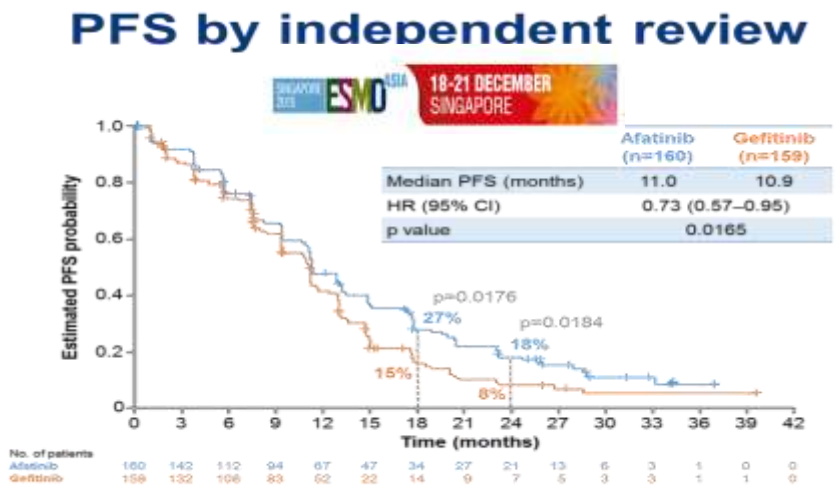
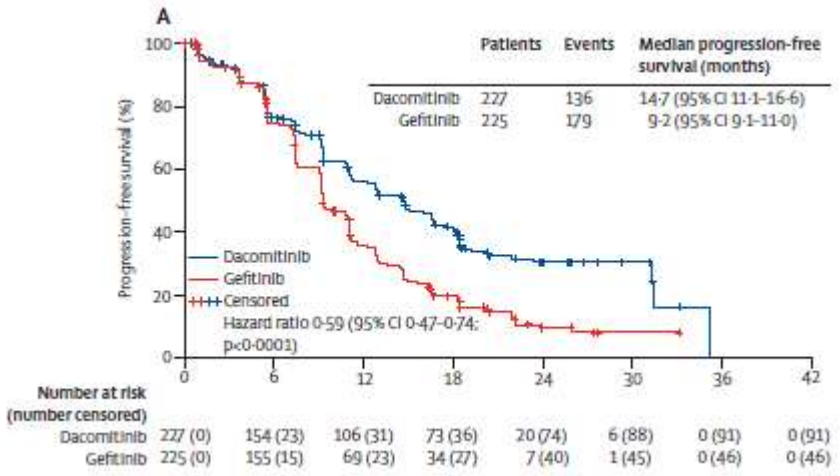
Head-to-head trials of different EGFR TKIs:

2nd generation (afatinib/dacomitinib) vs 1st generation (gefitinib/erlotinib)
3rd generation (osimertinib) vs 1st generation (gefitinib/erlotinib)

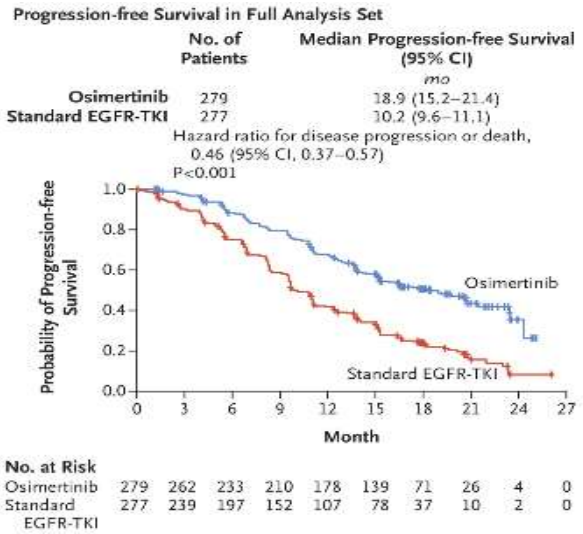
LUX-Lung 7 (afatinib vs gefitinib)



ARCHER 1050 (dacomitinib vs gefitinib)



FL-AURA (osimertinib vs gefitinib/ erlotinib)



	ORR	PFS (m)	OS (m)	CNS activity	Toxicity
afati.	70%	11.0	27.9	+	++++
gefitinib	56%	10.9	24.5	+	++

Lancet Oncol. 2016 May;17(5):577-89.
Ann Oncol. 2017 Feb 1;28(2):270-277

	ORR	PFS (m)	OS (m)	CNS activity	Toxicity
daco.	76%	14.7	34.1		++++
gefitinib	70%	9.2	26.8		++

Lancet Oncol. 2017 Nov;18(11):1454-1466.
J Clin Oncol. 2018 Aug 1;36(22):2244-2250.

	ORR	PFS (m)	OS	CNS activity	Toxicity
osi.	80%	18.9	NR*	+++	+
gef./erl.	76%	10.2	NR	+	++/+++

N Engl J Med. 2018 Jan 11;378(2):113-125.

Preclinical development of covalent pyrimidine EGFR mutant-specific TKIs and clinical development of the current "evidence-based" first line EGFR TKI osimertinib for common EGFR mutants

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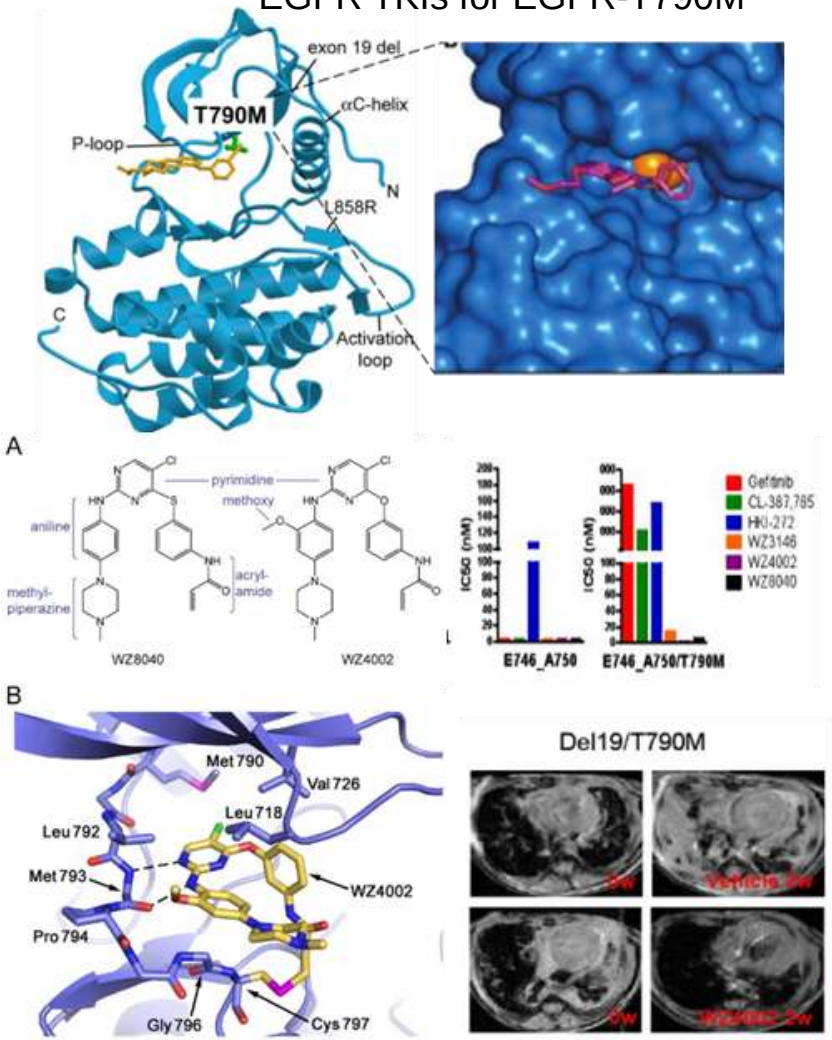
preclinical identification of covalent EGFR TKIs for EGFR-T790M



Significant clinical activity of osimertinib for *EGFR*-T790M+ after 1st/2nd gen. EGFR TKIs

Osimertinib for pretreated *EGFR* Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study

Glenwood Goss, Chun-Ming Tsai, Frances A Shepherd, Lyudmila Bazhenova, Jong Seok Lee, Gee-Chen Chang, Lucio Crino, Miyako Satouchi, Quincy Chu, Toyoaki Hida, Ji-Youn Han, Oscar Juan, Frank Dunphy, Makoto Nishio, Jin-Hyoung Kang, Margarita Majem, Helen Mann, Mirielle Contarini, Serban Ghiorghiu, Tetsuya Mitsudomi

osimertinib – EGFR-T790M positive (rebiopsy)
ORR 70% duration response 11.4 months median PFS 9.9 months 1-yr OS 81%
only 3% participants required dose reductions and 5% discontinued drug from adverse event

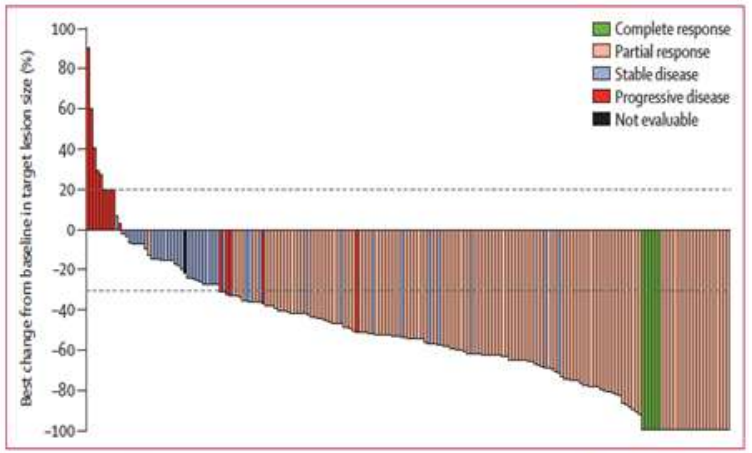


Figure 3: Waterfall plot for best percentage change in target lesion size are shown for all patients
The colour key indicates level of response, as assessed by blinded independent central review. The dashed line at 20% represents the boundary for determination of progressive disease, and the dashed line at –30% represents the boundary for determination of partial response.

Clinical activity of osimertinib in 1st line setting with lesser toxicities and improved CNS control

ORIGINAL ARTICLE

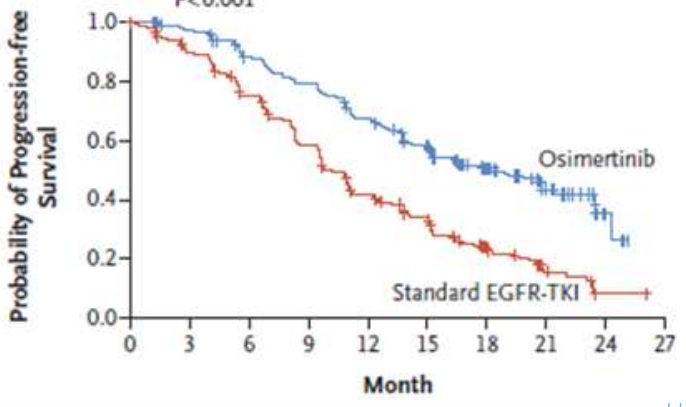
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

Progression-free Survival in Full Analysis Set

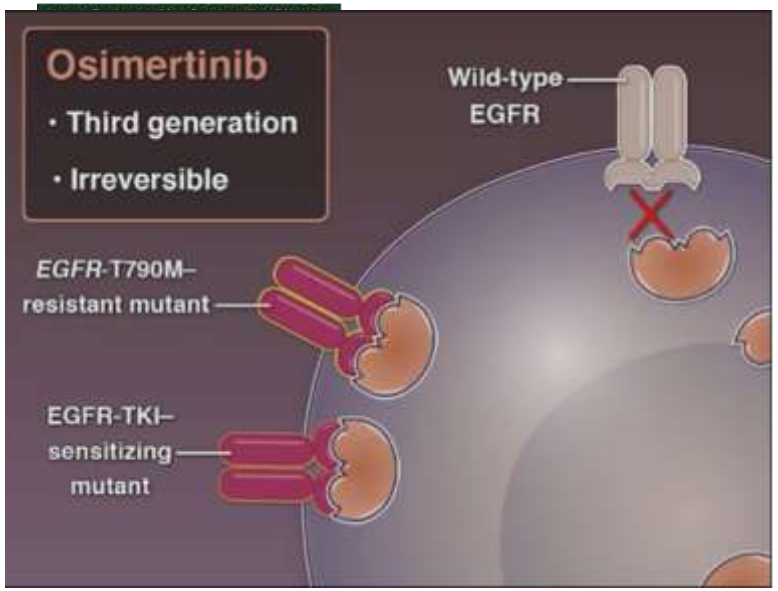
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

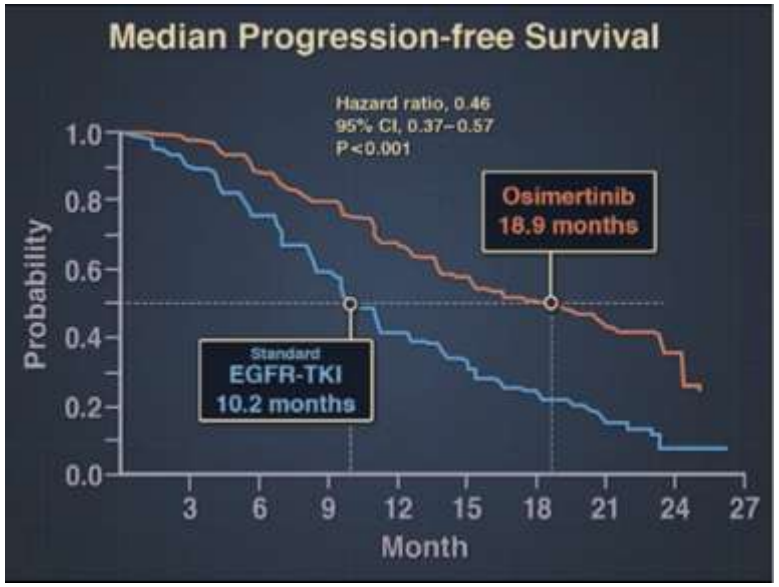
Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

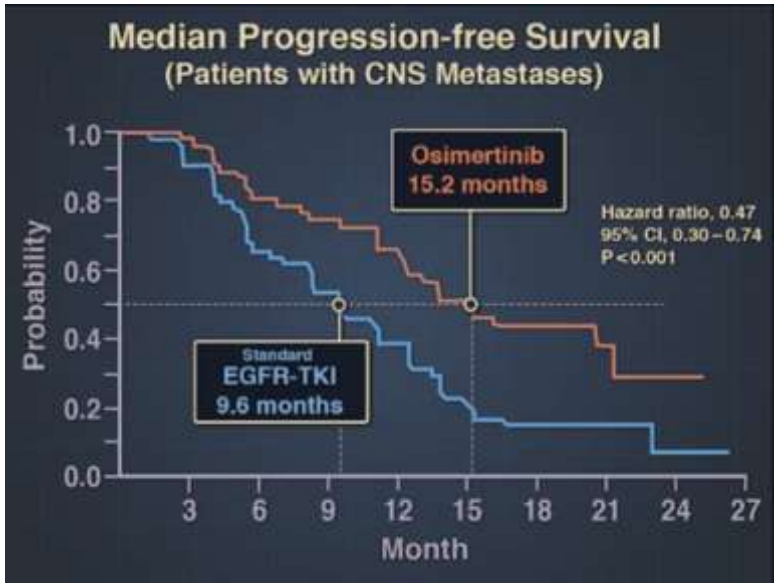


Adapted from Kobayashi S. *NEJM* 352:786 (2005) + Zhou W. *Nature* 462:1070 (2009) + Goss G. *Lancet Oncol* 17:1643 (2016) + Soria JC. et al. *NEJM* 378:113 (2018)

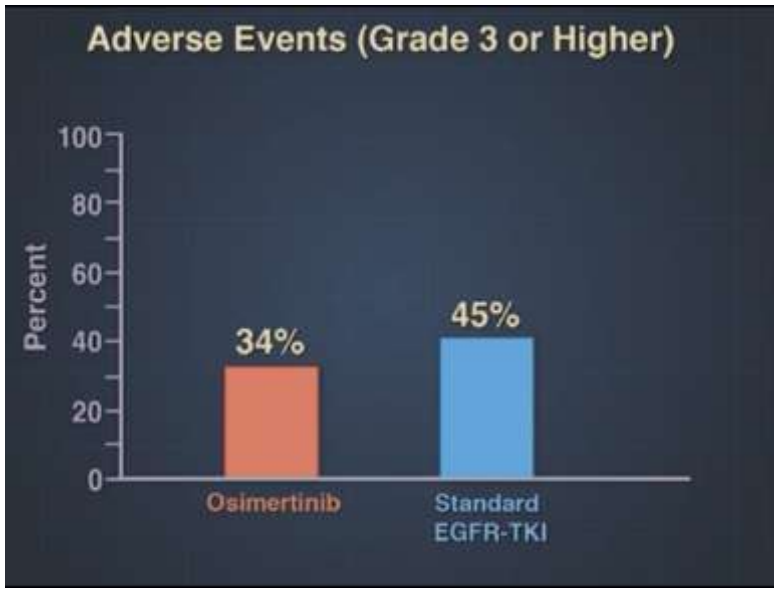
Why is osimertinib the current "evidence-based" first line EGFR TKI for common EGFR mutants (FL-AURA trial)?

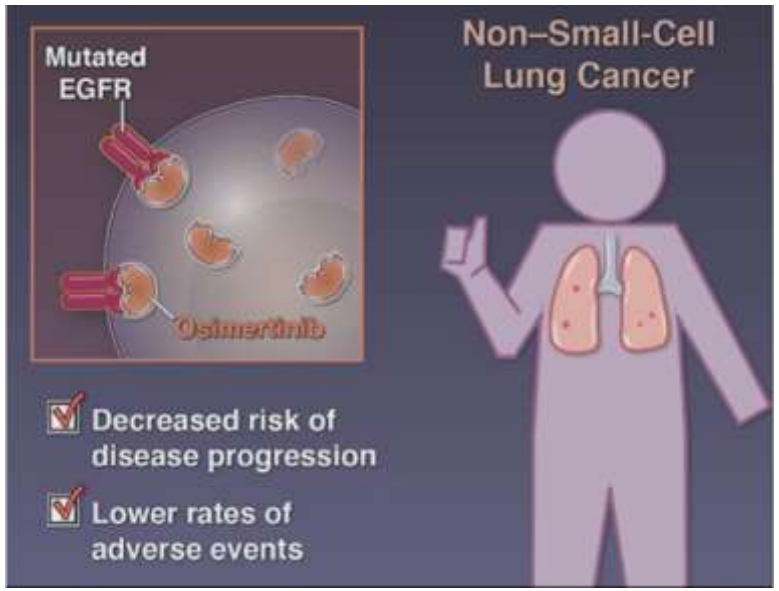






NEJM QuickTake





Adapted from Soria JC. et al. *NEJM* 378:113 (2018) – NEJM QuickTake (https://www.nejm.org/do/10.1056/NEJMdo005241/full/?requestType=popUp&relatedArticle=10.1056%2FNEJMoa1713137)

Covalent/irreversible (EGFR-C797 binding) EGFR mutant-specific TKIs and their clinical development status: do we need a better EGFR TKI than osimertinib for the most common EGFR mutants?

EGFR inhibitor	Current approval status (*EGFR* mutation subtype)	Preclinical EGFR-del19, L858R and T790M activity	Clinical efficacy/toxicity superior to osimertinib (EGFR-del19 or L858R)	Ongoing clinical trial EGFRm 1st line with osimertinib as control arm (ClinicalTrials.gov)	Combination studies in TKI-naïve orTKI-resistant tumors (ClinicalTrials.gov)
osimertinib	**approved 80 mg/day (T790M) (exon 19 deletions + L858R)**	**Yes**	**-**	**-**	**Yes (MET inhibitor, BH3 mimetic, MEK inhibitor, 1st generation EGFR TKI, EGFR Ab, others)**
afatinib	approved 40 mg/day (exon 19 deletions + L858R + L861Q + G719X + S768I)	No	No	-	-
dacomitinib	approved (exon 19 deletions + L858R)	No	No	-	-
rociletinib	**not approved (T790M)**	**Yes**	**No**	**No** (drug program terminated)	**-**
poziotinib	**not approved (exon 20 insertions)**	**Yes**	**No**	**No** (drug program terminated EGFR-del19, L858R, T790M)	**-**
naquotinib (ASP8273)	**not approved (790M)**	**Yes**	**No**	**No** (1st line trial vs gefitinib/erlotinib withdrawn)	**No**
nazartinib (EGF816)	**not approved (T790M)**	**Yes**	**No**	**No** (1st line trial vs gefitinib/erlotinib withdrawn)	**Yes (MEK inhibitor, MET inhibitor, others)**
olmutinib (HM61713)	**approved 800 mg/day (T790M) [South Korea]**	**Yes**	**No**	**No**	**No**

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Other strategies that predate 1st line osimertinib such as EGFR TKI + bevacizumab and EGFR TKI + chemotherapy, and why they may not be warranted in routine practice

EGFR TKI + VEGF inhibition

Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring *EGFR* mutations (JO25567): an open-label, randomised, multicentre, phase 2 study

Takashi Seto, Terufumi Kato, Makoto Nishio, Koichi Goto, Shinji Atagi, Yukio Hosomi, Nobaru Yamamoto, Toyoaki Hida, Makoto Maemondo, Kazuhiko Nakagawa, Setsuko Nagase, Isamu Okamoto, Takeharu Yamanaka, Kosei Tajima, Ryosuke Harada, Masahiro Fukuoka, Nobuyuki Yamamoto

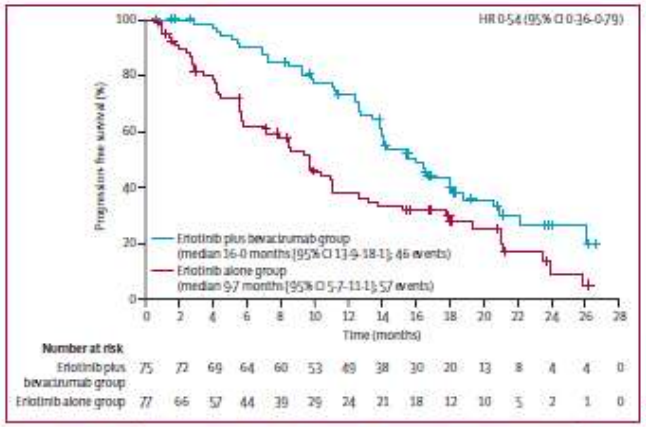


Figure 2: Progression-free survival, as determined by independent review committee, in the modified intention-to-treat population
HR=hazard ratio.

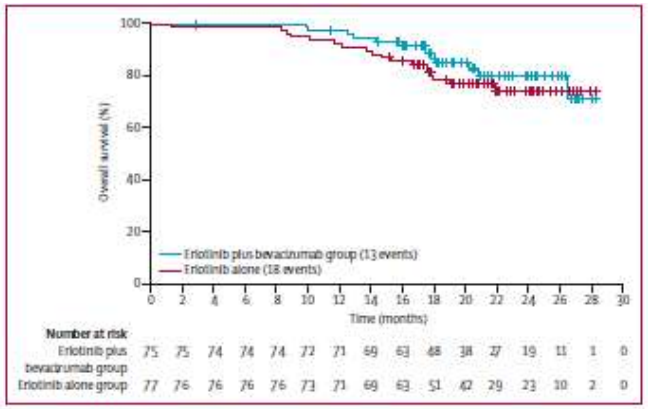


Figure 5: Overall survival, as determined by independent review committee, in the modified intention-to-treat population

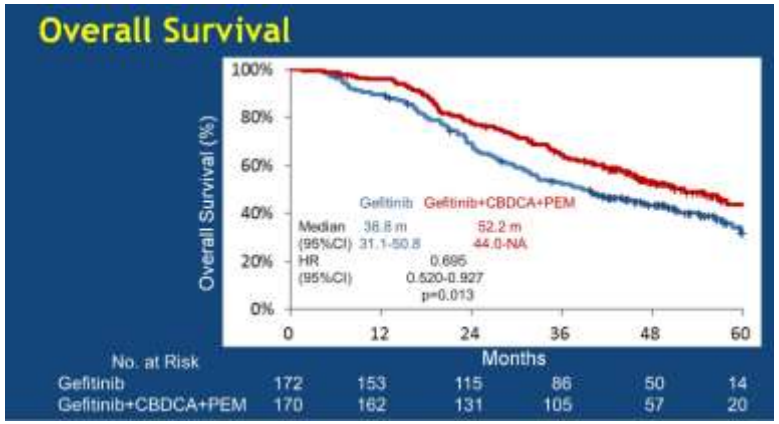
ORR similar
PFS improved (but below osimertinib obtained levels)
Toxicities higher/Costs higher
OS not improved
Strategy doesn't prevent development of *EGFR*-T790M

Lancet Oncol. 2014 Oct;15(11):1236-44.

EGFR TKI + carboplatin/pemetrexed

Phase III Study Comparing Gefitinib Monotherapy to Combination Therapy with Gefitinib, Carboplatin, and Pemetrexed for Untreated Patients with Advanced Non-Small Cell Lung Cancer with EGFR Mutations (NEJ009)

Atsushi Nakamura[1], Akira Inoue[2], Satoshi Morita[3], Yukio Hosomi[4], Terufumi Kato[5]



ORR, PFS and OS higher with combination
Toxicities higher/Costs higher
Prior US studies did not show advantage of 1st gen. EGFR TKI + chemotherapy
Doesn't prevent development of *EGFR*-T790M

J Clin Oncol 36, 2018 (suppl; abstr 9005)

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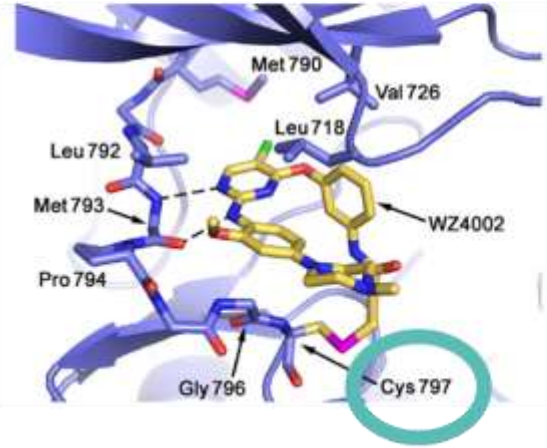
Mechanisms of resistance to covalent pyrimidine EGFR inhibitors such as osimertinib (preclinical models and initial clinical studies of cfDNA/re-biopsy)

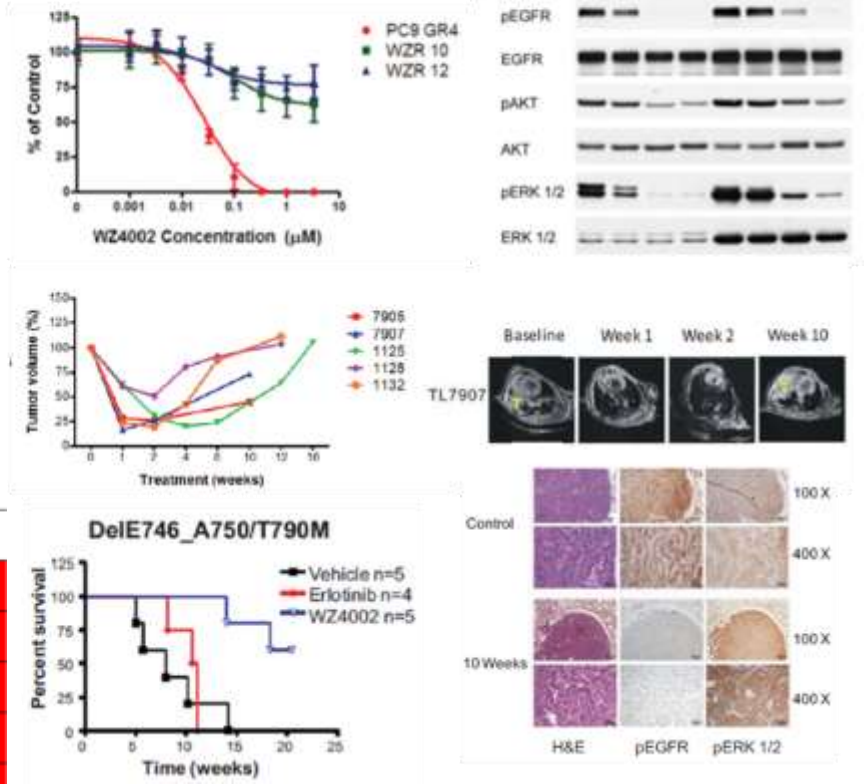
EGFR-C797 mutation

specific interactions of covalent inhibitors with EGFR-Cys797 are critical to the activity of the drug

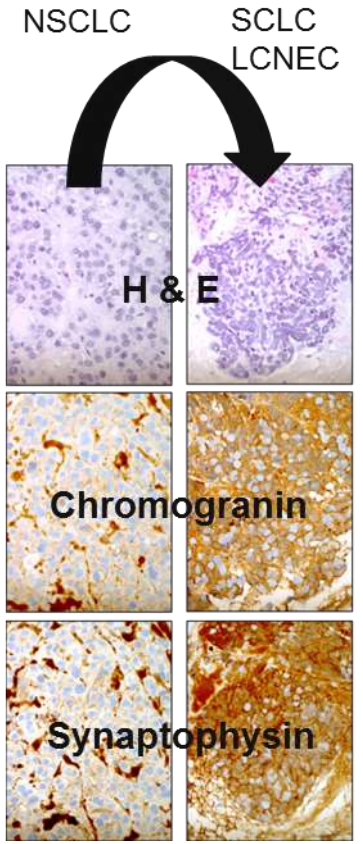


EGFR inhibitor	EGFR mutant type (preclinical model prediction)			
	exon 19 deletion (del19)	del19 + C797S	del19 + T790M	del19 + T790M + C797S
gefitinib (1st gen. reversible)				
erlotinib (1st gen. reversible)				
afatinib (2nd gen. irreversible)				
dacomitinib (2nd gen. irreversible)				
osimertinib (3rd gen. irreversible)				
		resistant	sensitive	

MAPK/ERK bypass activation
ERBB2 amplification
MET amplification



neuroendocrine transformation



Adapted from Ercan D. *Cancer Discov*; 2:934. (2012) + Schwartz PA. *PNAS*; 111:173. (2014) + Zhou W. *Bioorg Med Chem Lett*; 21:638 (2011)

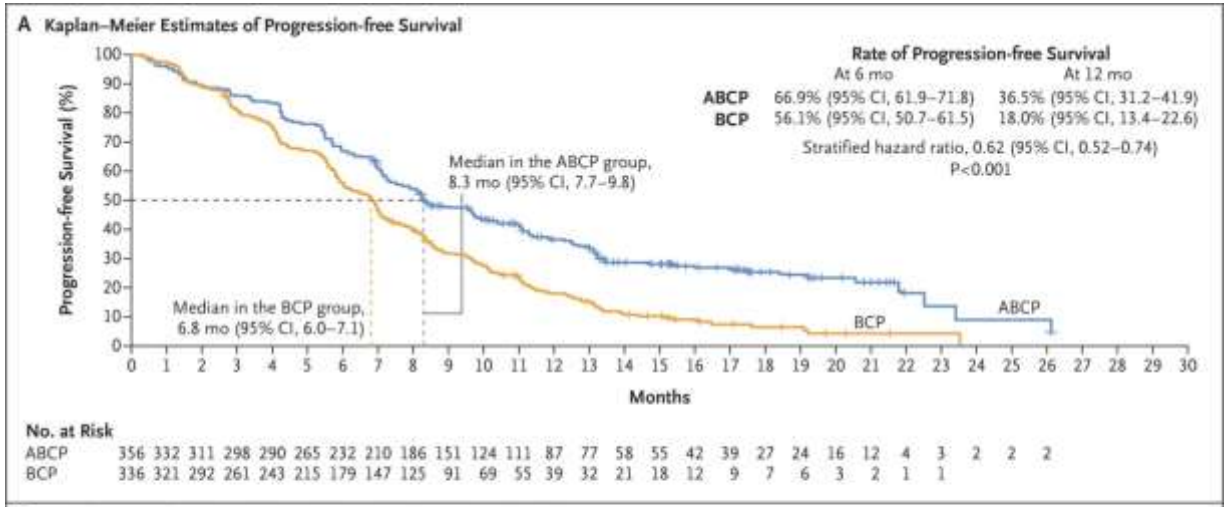
Management of osimertinib-resistant *EGFR* mutated NSCLC when a potentially actionable mechanism of acquired resistance (*EGFR*-C797S, *MET*, *BRAF*, SCLC etc) is not present: Standard platinum-based chemotherapy or chemo-immunotherapy? (1)

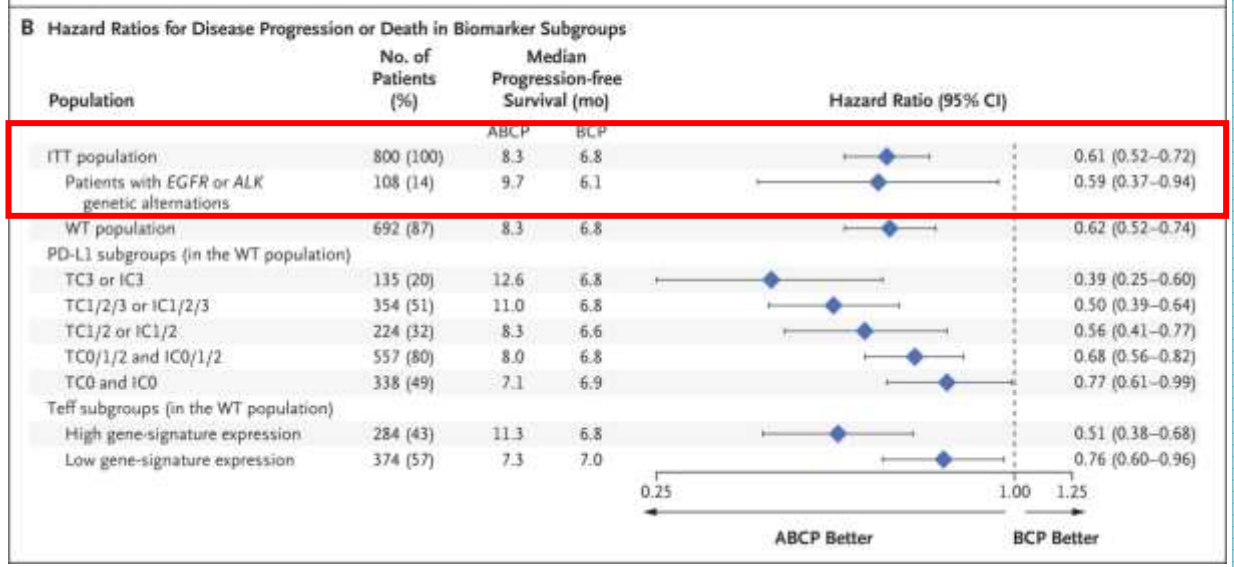
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

M.A. Socinski, R.M. Jotte, F. Cappuzzo, F. Orlandi, D. Stroyakovskiy, N. Nogami, D. Rodríguez-Abreu, D. Moro-Sibilot, C.A. Thomas, F. Barlesi, G. Finley, C. Kelsch, A. Lee, S. Coleman, Y. Deng, Y. Shen, M. Kowanetz, A. Lopez-Chavez, A. Sandler, and M. Reck, for the IMpower150 Study Group*





- Platinum-doublets are the vetted “standard”
- One can extrapolate data from IMpower150
- Reasonable to consider Keynote-189 scheme (carboplatin, pemetrexed, pembrolizumab)
- Unclear role of immune biomarkers (PD-L1 IHC TPS, TMB, MSI-H, *TP53*, others)
- Ongoing clinical trials trying to answer if chemo-immunotherapy appropriate plus if continuation osimertinib is beneficial/safe with IO

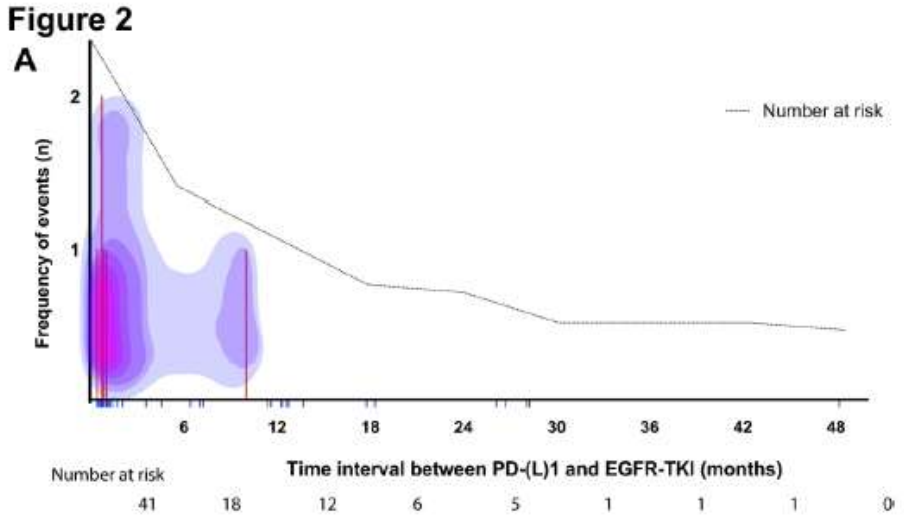
Management of osimertinib-resistant *EGFR* mutated NSCLC when a potentially actionable mechanism of acquired resistance (*EGFR*-C797S, *MET*, *BRAF*, SCLC etc) is not present: Standard platinum-based chemotherapy or chemo-immunotherapy? (2)

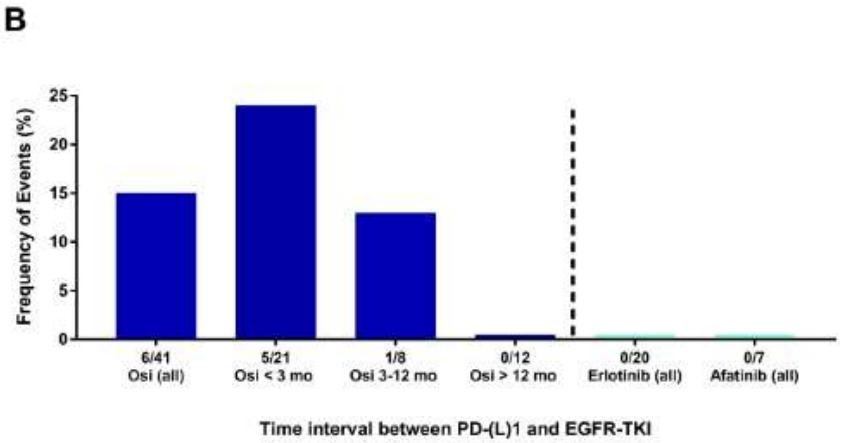
TITLE: Severe immune related adverse events are common with sequential PD-(L)1 blockade and osimertinib

AUTHORS: A. J. Schoenfeld[1], K. C. Arbour[1], H. Rizvi[1], A.N. Iqbal[1], S. M. Gadgeel[2], J. Girshman[3], M.G. Kris[1], G. J. Riely[1], H. A. Yu[1*], M. D. Hellmann[1*]

[1]Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

***Annals of Oncology*, mdz077, Published: 07 March 2019**





- **Safety concerns of using PD-1/PD-L1 antibodies before osimertinib. Increased immune-mediated adverse events and pneumonitis/ILD**

- **No significant adverse event signature if PD-1/PD-L1 antibodies used after osimertinib**

What we have learned from the development of EGFR inhibitors in *EGFR* mutated lung cancers that applies to other oncogene-driven tumors

1. The need to identify an oncogene, its variants (types of mutations), prove in preclinical models that the oncogene drives tumor dependence and can be inhibited with pathway-specific inhibitors, and then develop a clinical test to allow for diagnosis in routine pathology specimens in a timely fashion;

2. The need to prove in clinical trials high response rate, that then can translate into improved outcomes against previously established evidence-based cytotoxic chemotherapy +/- immunotherapy;

3. The need to then develop/test more potent inhibitors (for both systemic disease and central nervous system penetration) and less toxic oral monotherapies that become newest evidence-based backbones for future attempts to improve palliative therapies in advanced disease or be used in the adjuvant setting to attempt to improve cure rates;

4. The understanding that combination therapies to delay/prevent resistance will be part of the clinical trial portfolio for treatment-naïve oncogene-driven tumors within the next decade.

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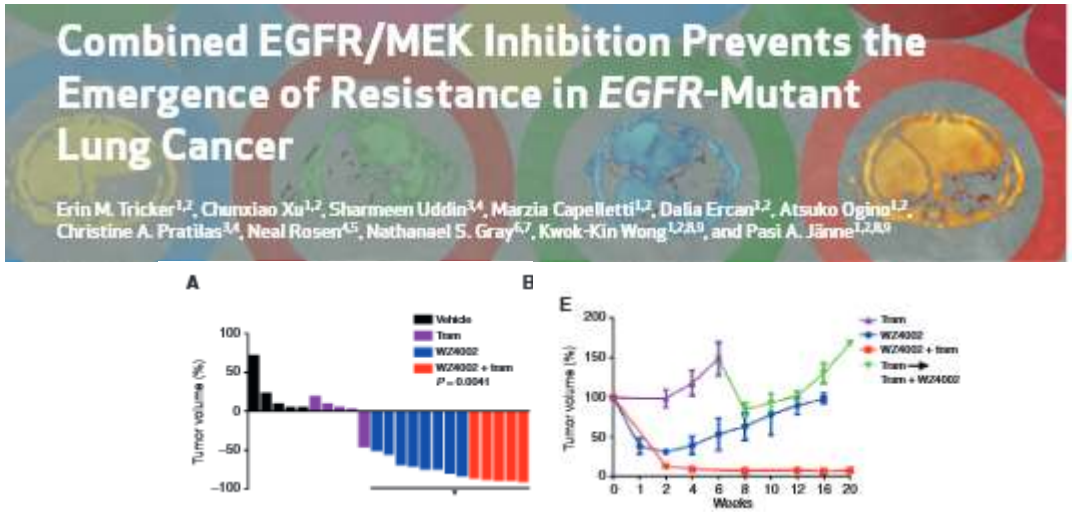
The future for covalent pyrimidine EGFR inhibitors such as osimertinib: combinations therapies to delay/prevent resistance (↑PFS/OS)

Osimertinib + MEK inhibitors delay multiple types of resistance in preclinical models



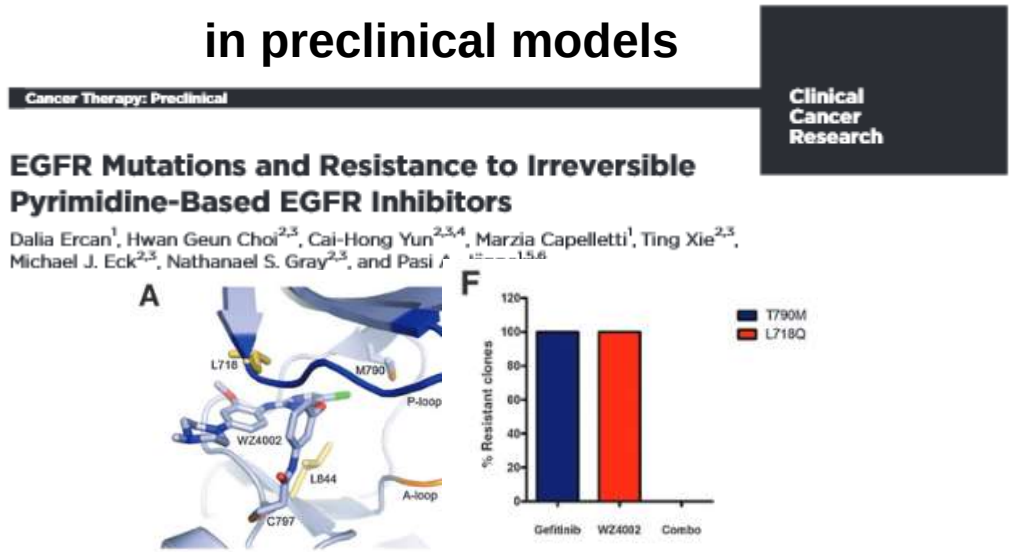
Osimertinib in Combination With Selumetinib in EGFR Inhibitor naïve Advanced *EGFR* Mutant Lung Cancer

(Phase 2)

ClinicalTrials.gov Identifier: NCT03392246

Overall PI:
Pasi A. Jänne, MD, PhD
Dana-Farber Cancer Institute

Osimertinib + gefitinib prevent *EGFR*-T790M and *EGFR*-C797S in preclinical models



Osimertinib and Gefitinib in EGFR Inhibitor naïve Advanced *EGFR* Mutant Lung Cancer

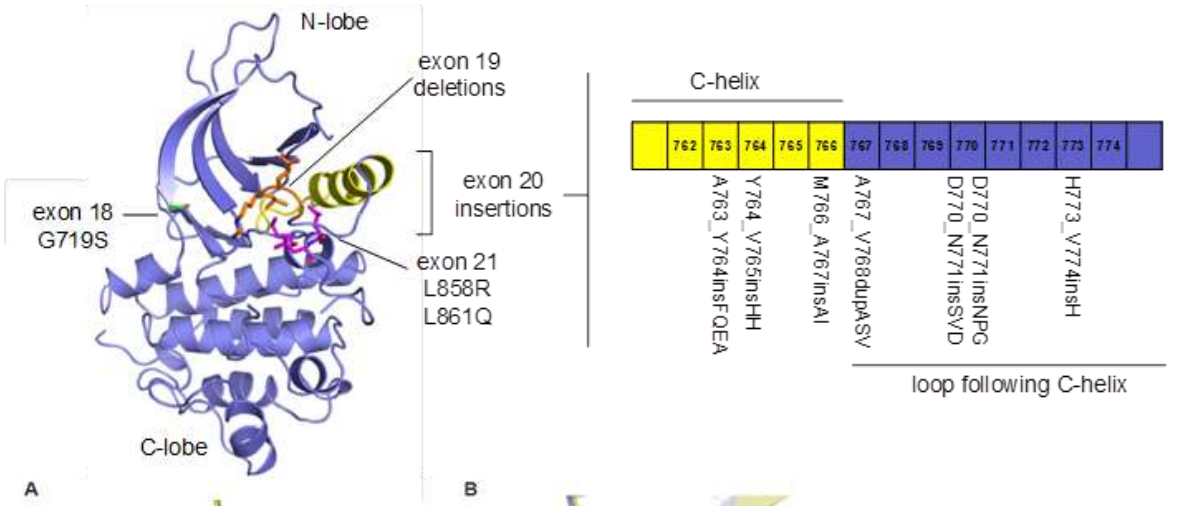
(Phase 1/2)

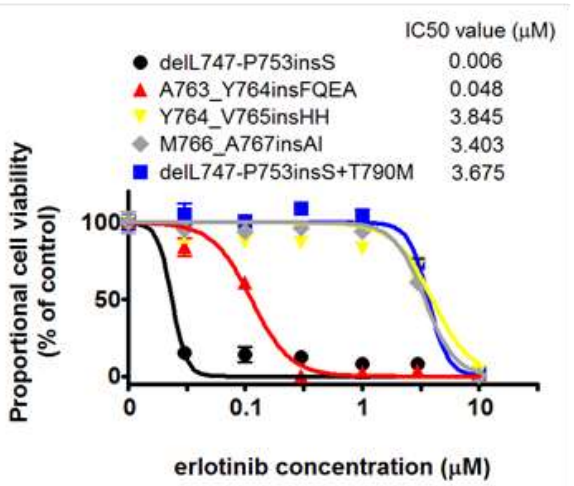
ClinicalTrials.gov Identifier: NCT03122717

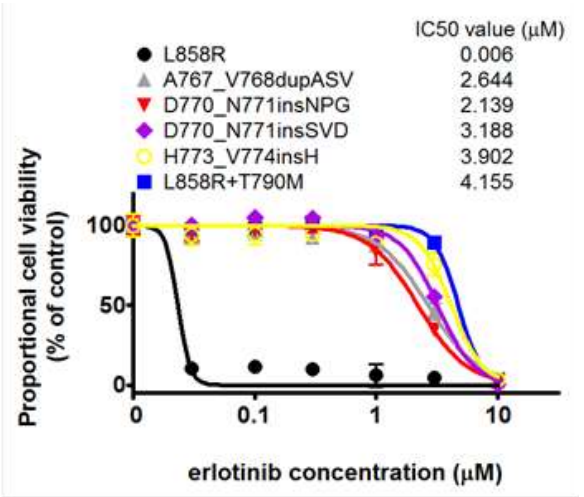
Overall PI:
Pasi A. Jänne, MD, PhD
Dana-Farber Cancer Institute

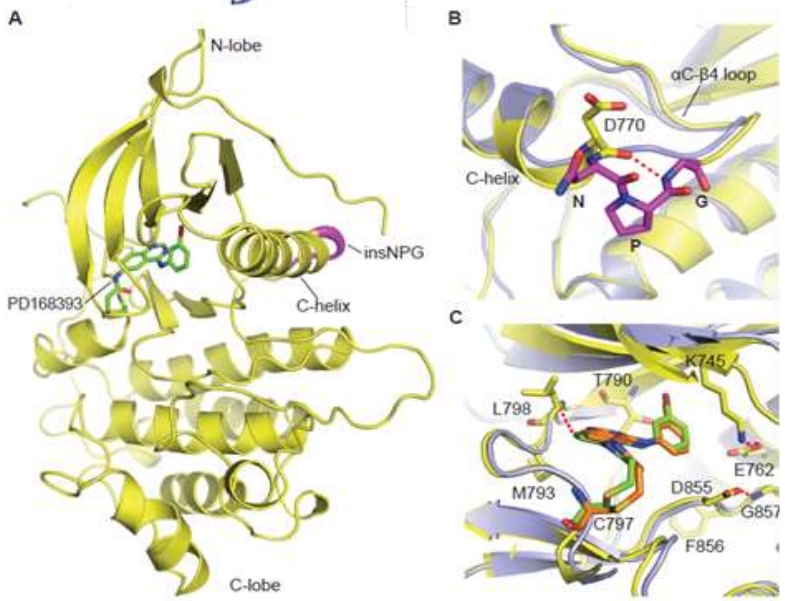
EGFR exon 20 insertion mutations: lack of inhibition by 1st/2nd generation EGFR TKIs *in vitro* and *in vivo*

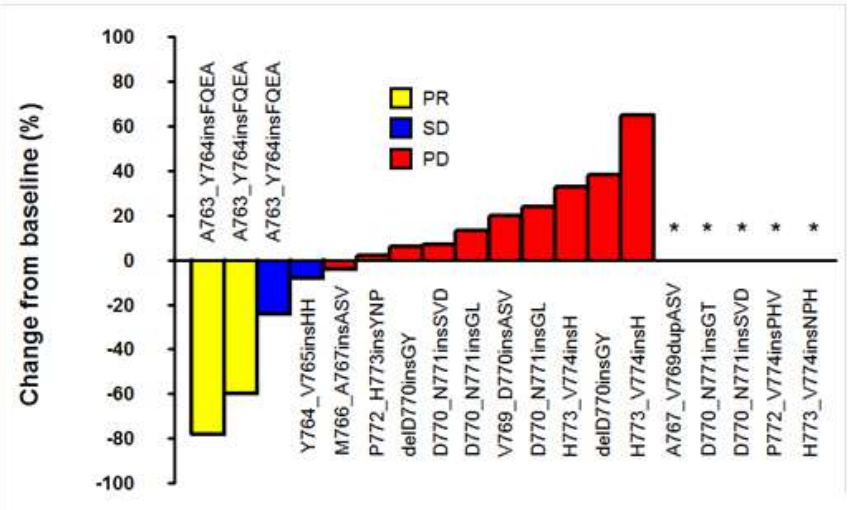
All exon 20 insertions, outside A763_Y764insFQEA, are insensitive to approved 1st/2nd generation EGFR TKIs











	Best response to reversible EGFR TKI				
***EGFR* mutation**	**drug**	**PR**	**SD**	**PD**	**RR [%]**
A763_Y764insFQEA	erlotinib	2	1	-	66.6%
Y764_V765insHH	gefitinib	-	1	-	0%
M766_A767insASV	erlotinib	-	-	1	0%
A767_V769dupASV	gefitinib	-	-	1	0%
V769_D770insASV	erlotinib	-	-	1	0%
D770_N771insGL	erlotinib	-	-	2	0%
D770_N771insGT	erlotinib	-	-	1	0%
D770_N771insSVD	erlotinib	-	1	1	0%
delD770insGY	erlotinib	-	-	2	0%
P772_H773insYNP	gefitinib	-	-	1	0%
P772_V774insPHV	erlotinib	-	-	1	0%
H773_V774insH	gefitinib/ erlotinib	-	-	2	0%
H773_V774insNPH	erlotinib	-	-	1	0%

Adapted from: Yasuda et al. *Sci Trans Med*. 5:216ra177 (2013)

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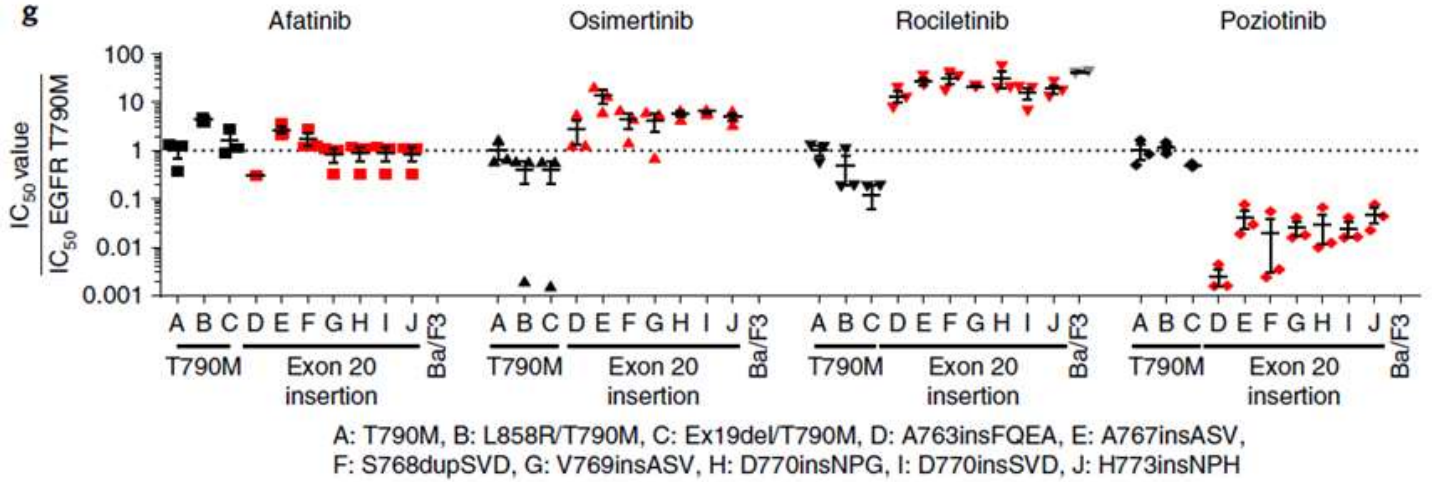
Development of novel EGFR/ERBB2 exon 20 mutant-specific therapies: poziotinib

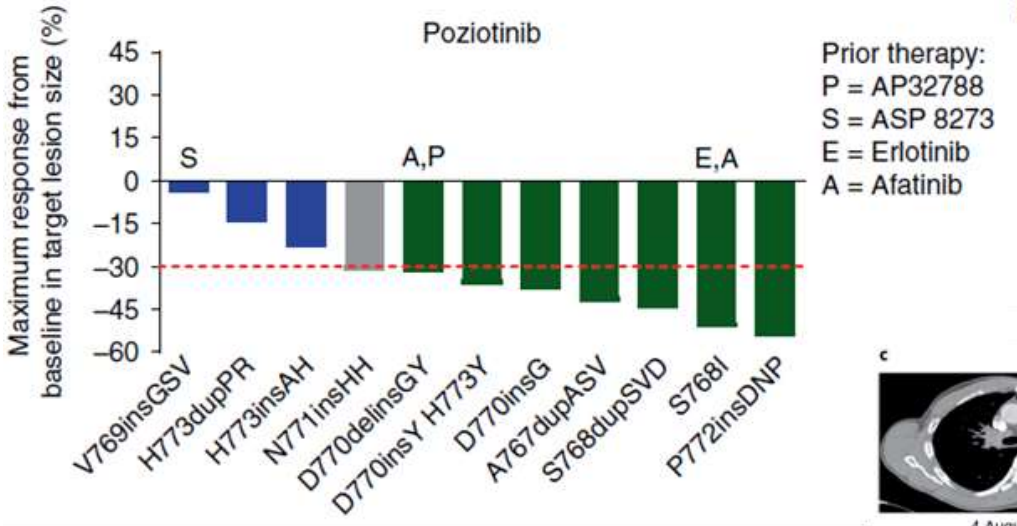
(formerly HM781-36B [Hamni Pharm.], a pan-ErbB TKI that had limited activity in the setting of tumors with *EGFR*-L858R and -del19 with enhancement for *EGFR*-T790M)

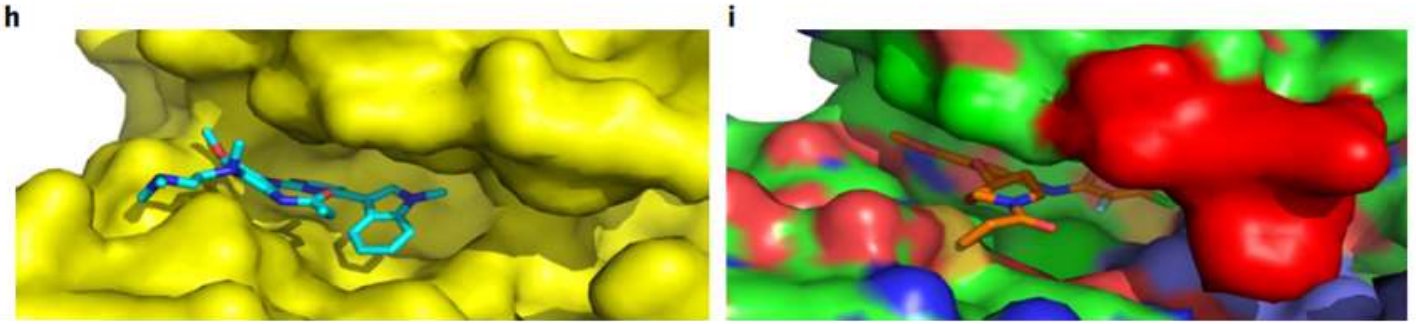
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-018-0007-9

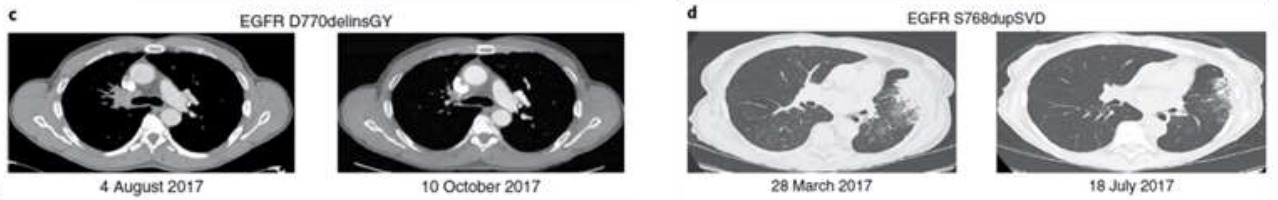
Mechanisms and clinical activity of an EGFR and HER2 exon 20–selective kinase inhibitor in non–small cell lung cancer

Jacqulyne P. Robichaux[1], Yasir Y. Elamin[1], Zhi Tan[2], Brett W. Carter[3], Shuxing Zhang[2], Shengwu Liu[4], Shuai Li[4], Ting Chen[4], Alissa Poteete[1], Adriana Estrada-Bernal[5], Anh T. Le[5], Anna Truini[6], Monique B. Nilsson[1], Huiying Sun[1], Emily Roarty[1], Sarah B. Goldberg[6,7], Julie R. Brahmer[8], Mehmet Altan[1], Charles Lu[1], Vassiliki Papadimitrakopoulou[1], Katerina Politi[6,7,9], Robert C. Doebele[5], Kwok-Kin Wong[10] and John V. Heymach[1]*









Adapted from Robichaux J.P., *Nature Med*; 24(5):638-646 (2018)

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Different EGFR mutations and sensitivity to EGFR inhibitors

Table 1 Types, frequency and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor sensitivity of *EGFR* kinase domain mutations in lung cancer

EGFR mutation		EGFR TKI [*in vitro* sensitivity and expected overall response rate (ORR)]		
EGFR TKI sensitivity type	Approximate frequency (%)	1st generation Gefitinib 250 mg Erlotinib 150 mg	2nd generation Afatinib 40 mg	3rd generation Osimertinib 80 mg
Sensitizing				
Exon 19 deletion	45.0	++++ (ORR >70%)	++++ (ORR >75%)	++++ (ORR >70%)
L858R	35.0	++++ (ORR >60%)	++++ (ORR >70%)	++++ (ORR >60%)
G719X	3.0	++ (ORR >55%)	+++ (ORR >65%)	++ (ORR ?)
L861Q	3.0	++ (ORR >55%)	++ (ORR >55%)	++ (ORR ?)
S768I	<1.5	+ (ORR >45%)	++ (ORR >55%)	? (ORR ?)
Exon 18 indel/E709X	<0.5	++ (ORR >55%)	+++ (ORR >65%)	++ (ORR ?)
Exon 19 insertion	<0.5	++ (ORR >55%)	++ (ORR ?)	++ (ORR ?)
A763_Y764insFQEA	<0.5	++ (ORR >55%)	++ (ORR ?)	++ (ORR ?)
Exon 18–25 duplication (*EGFR*-KDD)	<0.5	++ (ORR >55%)	+++ (ORR >65%)	++ (ORR ?)
Rearrangement (*EGFR-RAD51*)	<0.5	++ (ORR >55%)	+++ (ORR ?)	++ (ORR ?)
Insensitizing				
Exon 20 insertion	>7.0	– (ORR <5%)	– (ORR <10%)	– (ORR ?)
T790M inherited	<1.0	– (ORR ~0%)	– (ORR ~0%)	++++ (ORR >60%)
Others	>2.0	? (ORR ?)	? (ORR ?)	? (ORR ?)
Acquired resistance				
T790M + sens.	>50.0 (1st/2nd gen. TKI)	– (ORR ~0%)	– (ORR <5%)	++++ (ORR >60%)
C797X + T790M + sens.	<50.0 (osimertinib)	– (ORR ~0%)	– (ORR ~0%)	– (ORR ~0%)

++++, maximum inhibition; +++, moderate inhibition; ++, adequate inhibition; +, minimal inhibition; –, no significant inhibition beyond the therapeutic window of wild-type EGFR; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ?, unknown; sens, sensitizing mutation; gen., generation.

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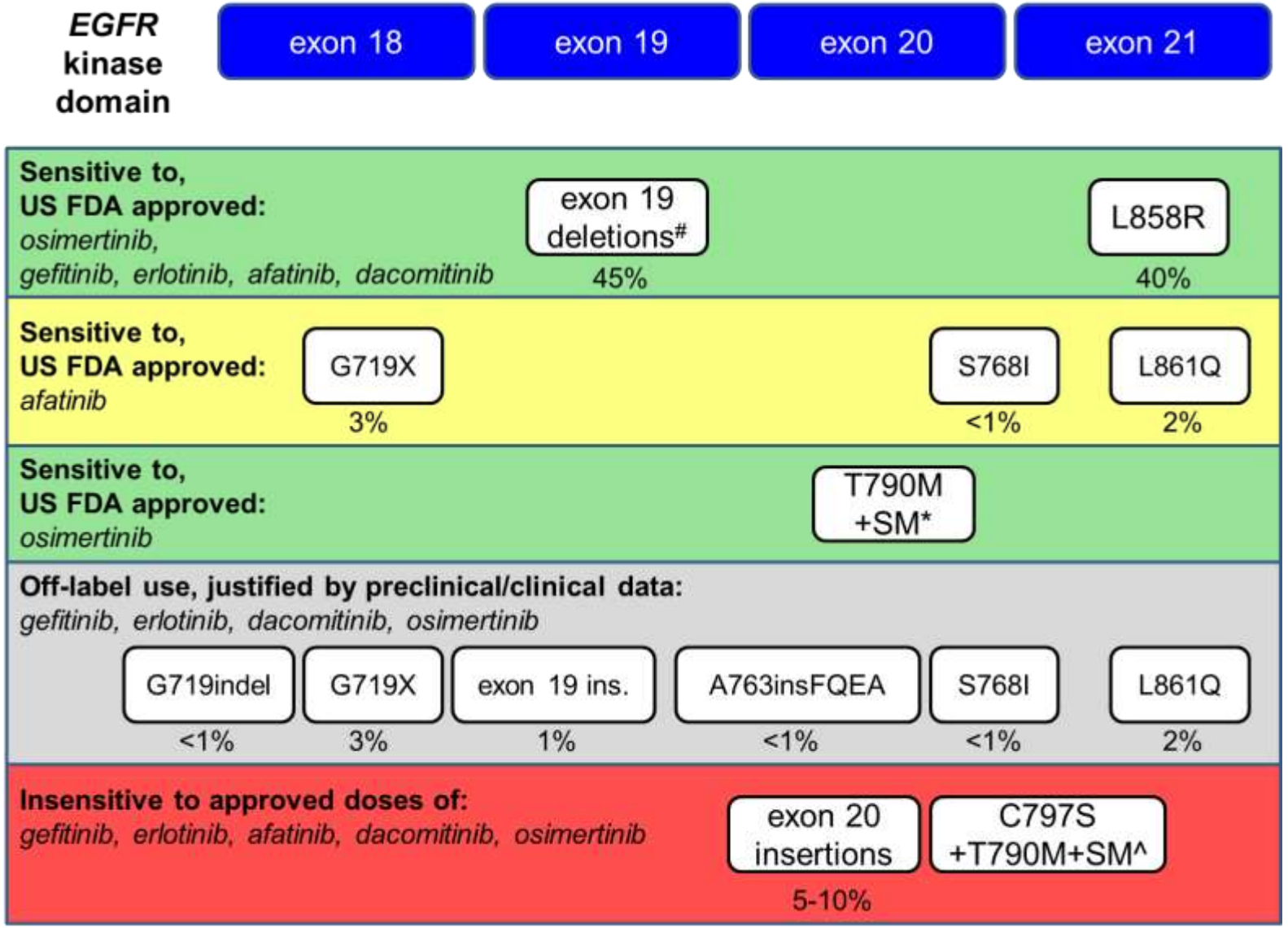
Therapies for advanced *EGFR* mutated lung cancer (March 2019)



"SM" = sensitizing mutation. "X" in G719X = substitution for several different amino acids and is not a stop codon. Approved doses of TKIs are: gefitinib 250mg daily, erlotinib 150mg daily (1st generation TKIs); afatinib 40mg daily (2nd generation TKI); osimertinib 80mg daily (3rd generation TKI).
#Most common exon 19 deletion is delE746_A750 (LREA motif).
***Cause of acquired resistance to gefitinib, erlotinib and afatinib in >50%.**
^Cause of osimertinib resistance in 30%.

Adapted from Sheikine Y, Rangachari D et al. Clin Lung Cancer; 17(6):483. (2016)

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Q&A