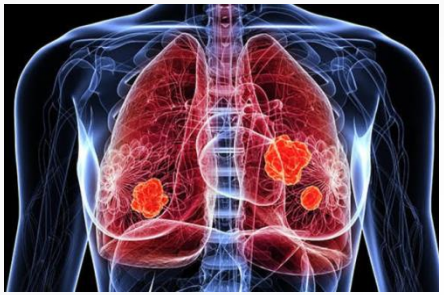

Management of NCSLC with EGFR Mutations

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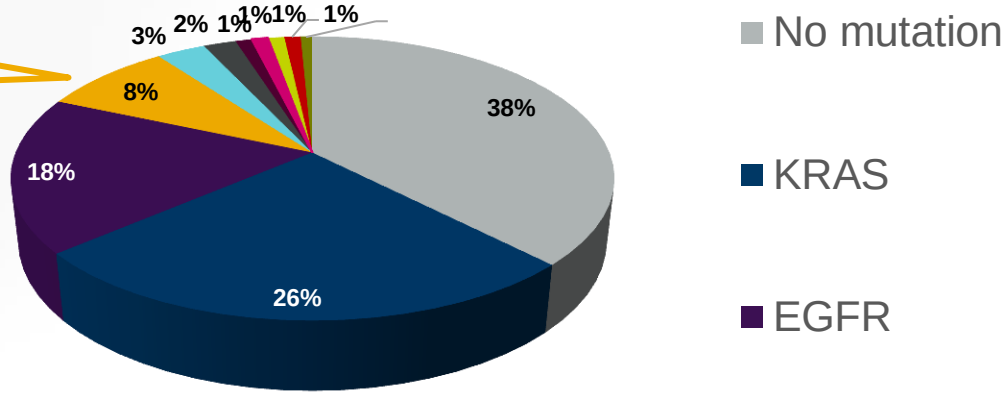
More than 50% of Stage IV NSCLC have biomarkers

Predictive biomarkers are indicative of therapeutic efficacy, because there is an interaction between the biomarker and the therapy on patient outcome

Prognostic biomarkers are indicative of patient survival independent of treatment received because the biomarker is an indicator of the innate tumour aggressiveness

Testing for several genetic mutations and for PD-L1 status is recommended for patients with advanced NSCLC to determine whether they can receive treatment with targeted agents.[1-3]

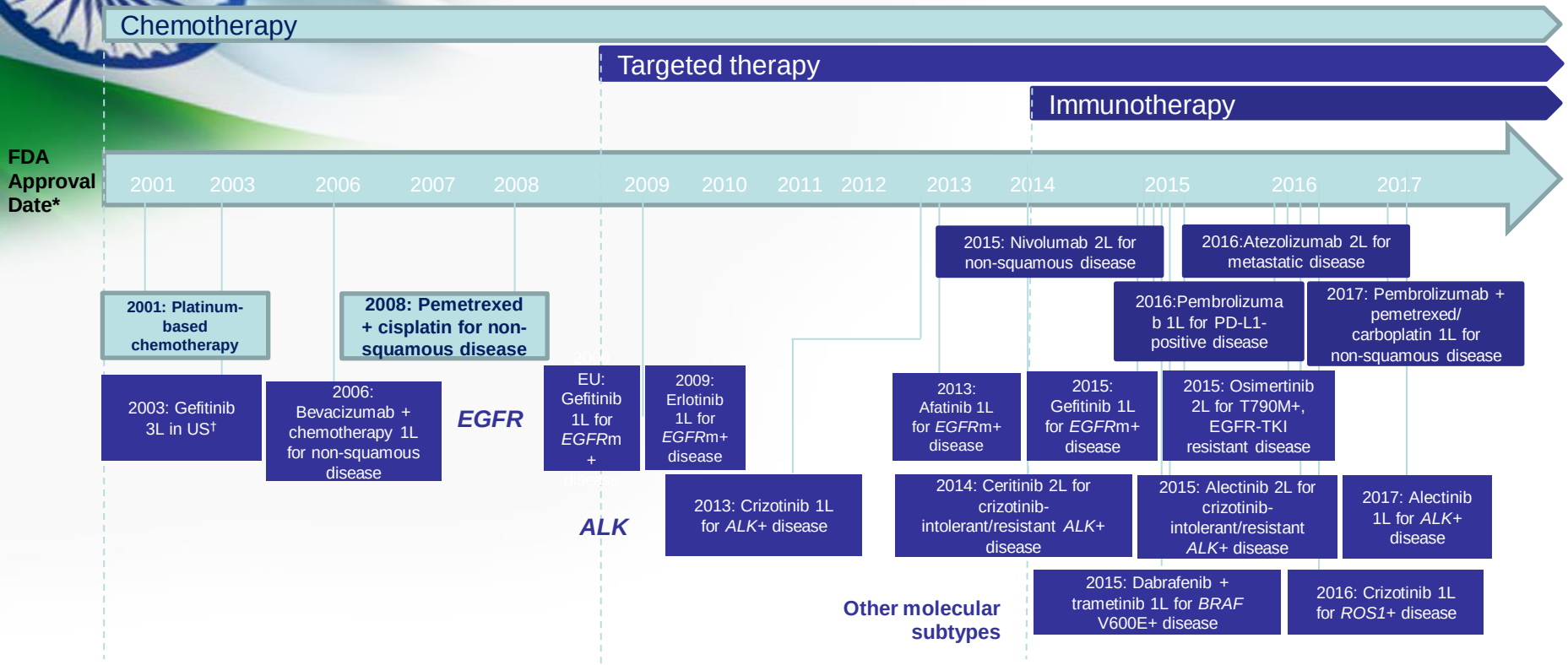
ALK rearrangements are **predictive** of response to ALK inhibitors[2]



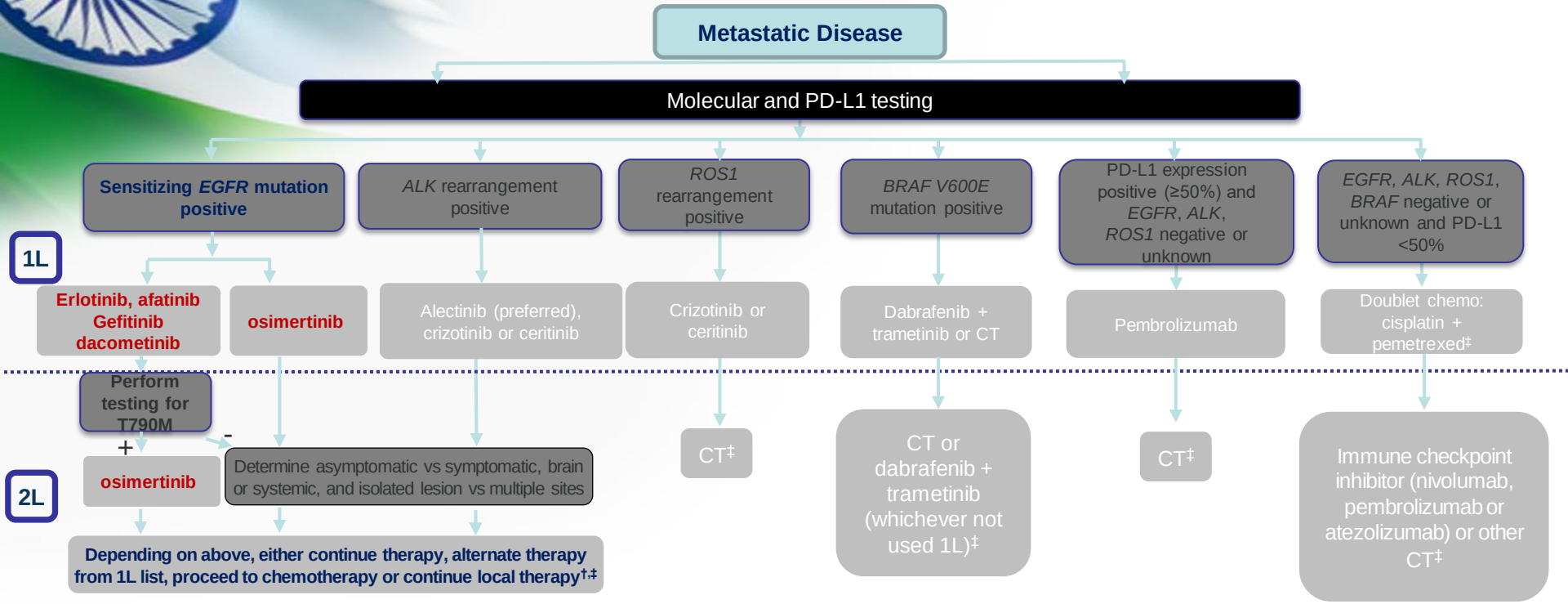
EGFR mutations are **predictive** of response to EGFR-TKIs[2]

KRAS mutations may be **prognostic**[5]

Treatment landscape for Stage IV NSCLC

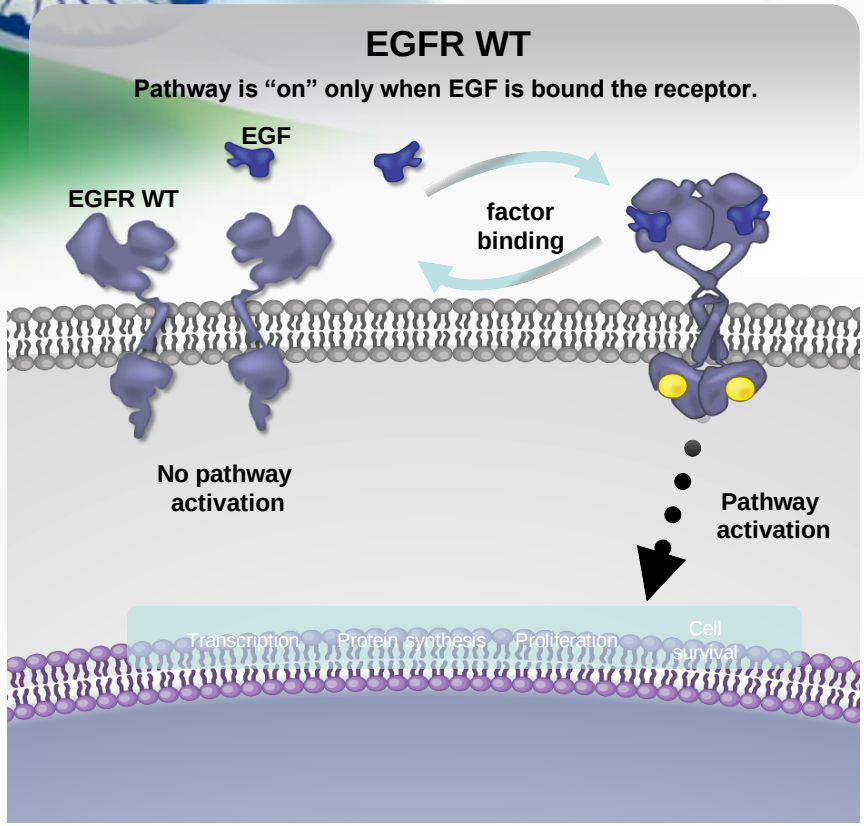


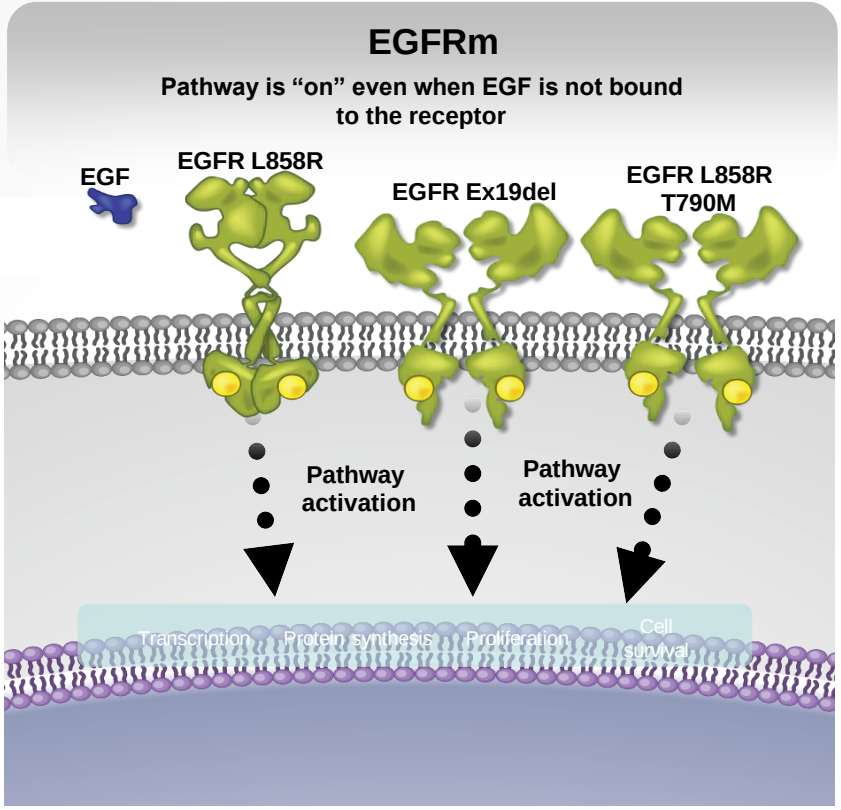
Molecular & PD-L1 testing inform Rx recommendations - NCCN Guidelines



Management of EGFR +ve Stage IV NSCLC patients

EGFR-activating mutations result in constant signaling by the EGFR





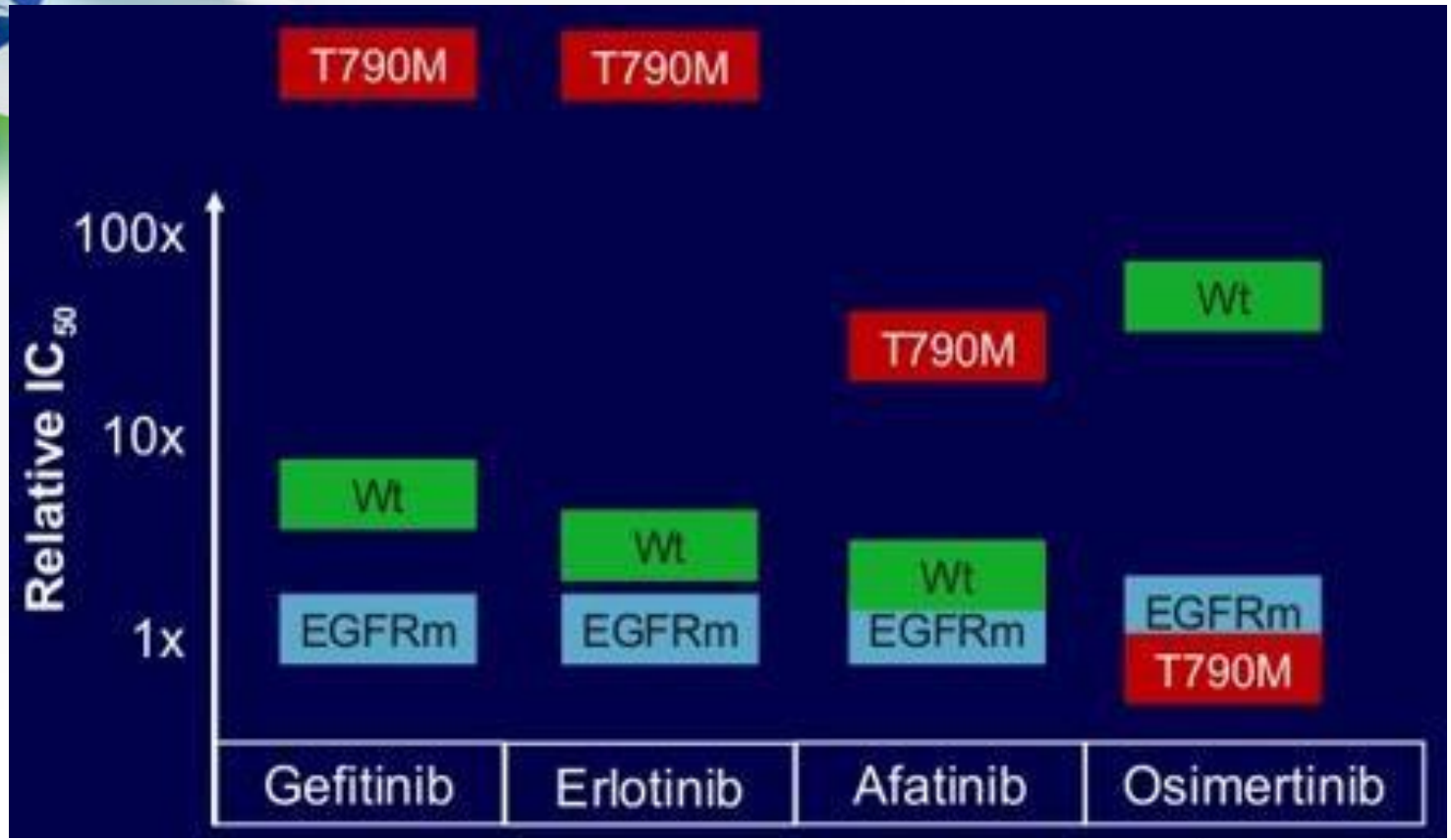
Anti-EGFR TKI

- 1st generation:
  - Gefitinib
  - Erlotinib
- 2nd generation:
  - Afatinib
  - Dacomitinib
- 3rd generation:
  - Osimertinib
  - Rociletinib

Comparative evaluation of EGFR-TKIs

	First-Generation EGFR-TKIs	Second-Generation EGFR-TKIs	Third-Generation EGFR-TKIs
EGFR binding	Reversible	Irreversible	Irreversible
$EGFR^{WT}$	+	+	–
$EGFR^{Del19/L858R}$	+	+ +	+ +
$EGFR^{T790M}$	–	+	+ + +
ErbB2	–	+	–
ErbB4	–	+	–
BBB penetration	+	+	+ + + [c]
Agent	Gefitinib, erlotinib, icotinib	Afatinib, dacomitinib	Osimertinib, rociletinib, HM61713, EGF816, ASP8273

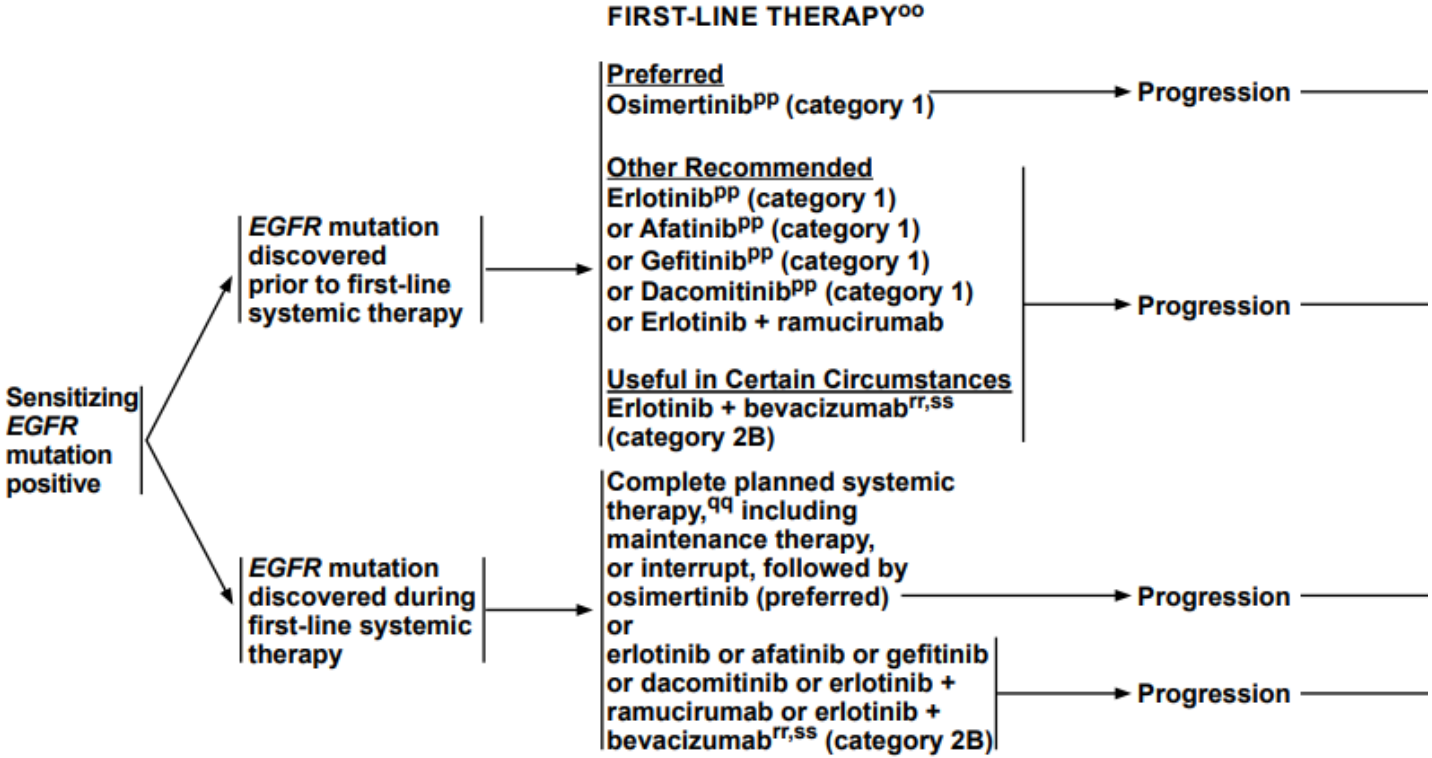
Relative potency of TKIs



National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2020
Non-Small Cell Lung Cancer

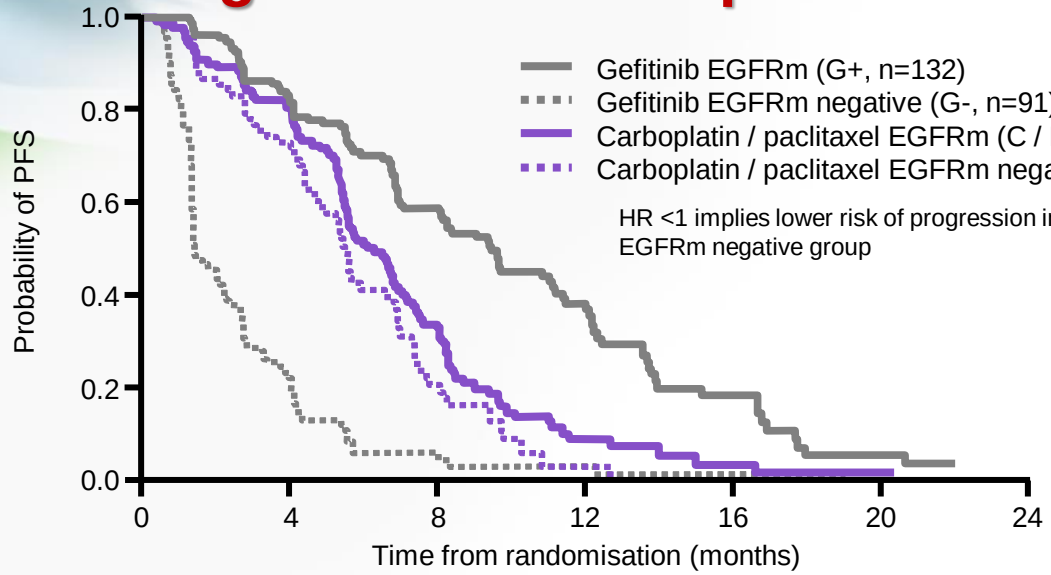
SENSITIZING *EGFR* MUTATION POSITIVE[jj]



1st Gen. TKI v/s chemotherapy

IPASS trial (Gefitinib)

PFS is related to EGFRm status in gefitinib-treated patients



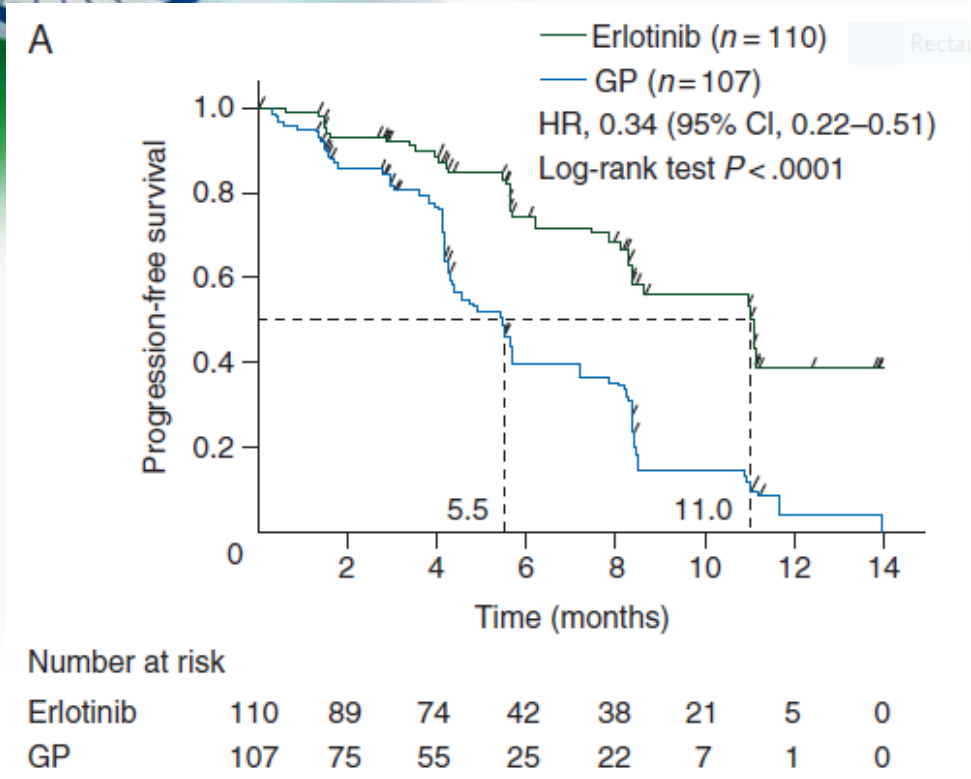
Patients at risk:

G+	132	108	71	31	11	3	0
C / P+	129	103	37	7	2	1	0
G-	91	21	4	2	1	0	0
C / P-	85	58	14	1	0	0	0

Median PFS of 9.5 vs. 6.3 months

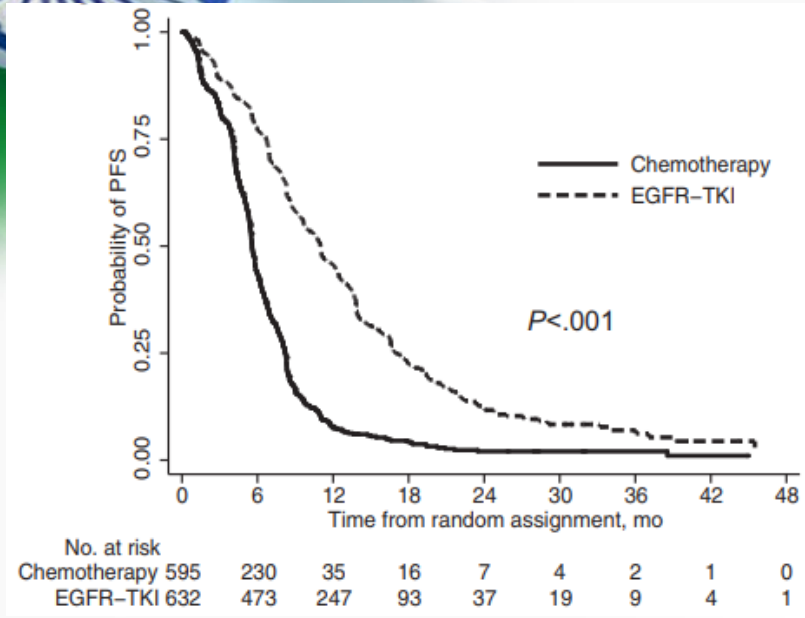
ENSURE (Erlotinib)

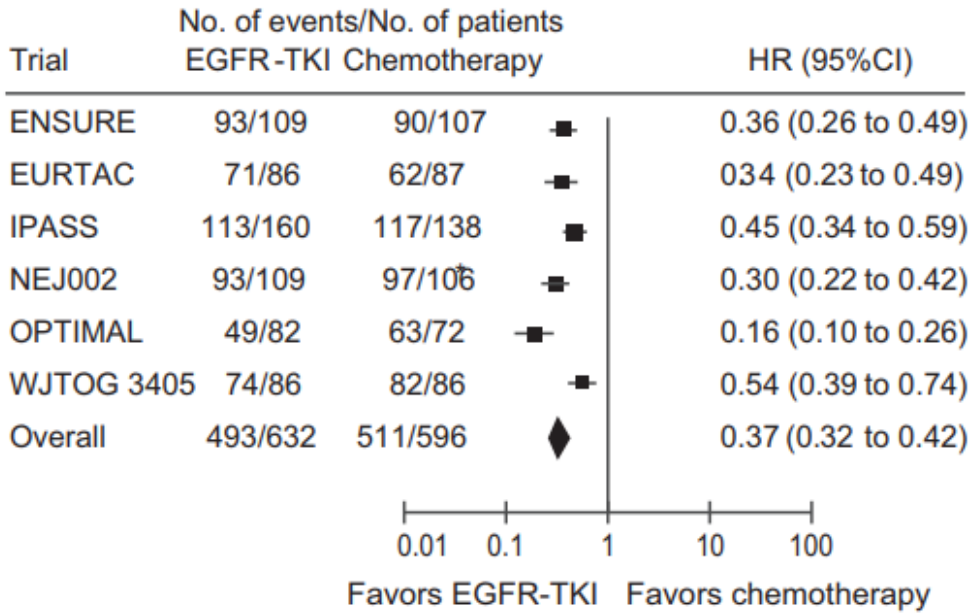
Significantly longer PFS with Erlotinib v/s standard Chemotherapy.



	Median PFS (months)	HR (95% CI)
Erlotinib (n=110)	11.0	0.33 (0.23-0.47) p-value < 0.0001
Chemotherapy(n=107)	5.5	

1st Gen. TKI vs Chemotherapy - PFS

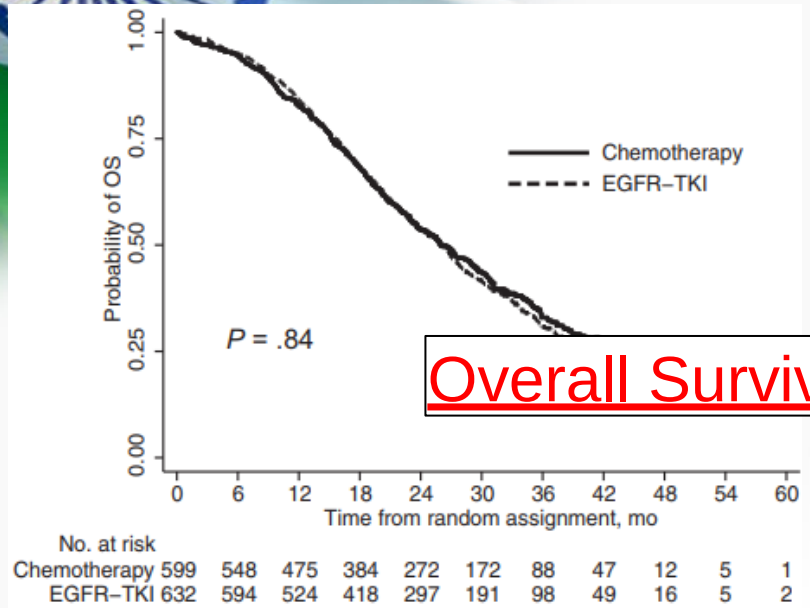


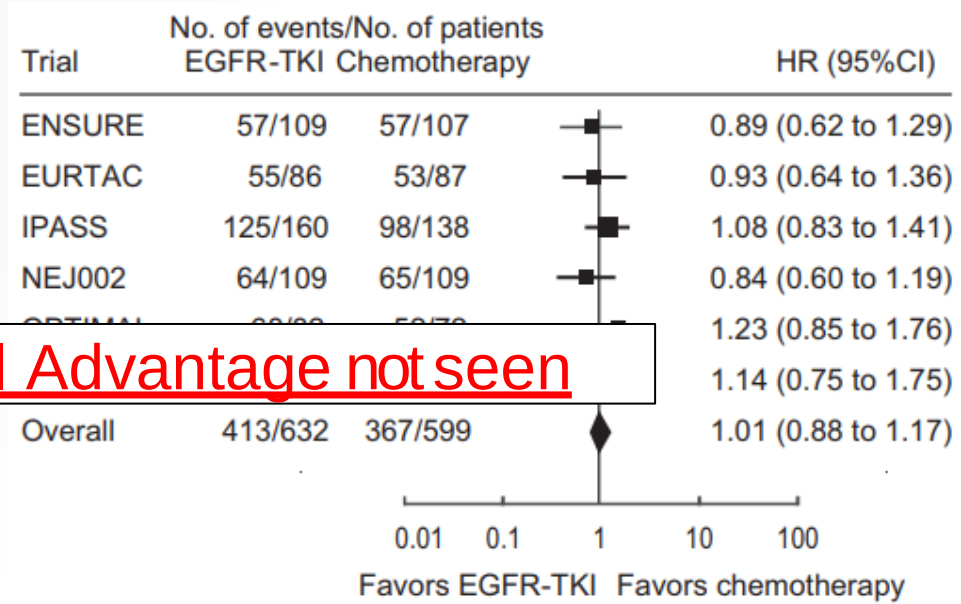


Study Design:- Meta-analysis of 6 trials (N=1,231) comparing efficacy of Gefitinib or Erlotinib vs Chemotherapy in patients with Exon 19 deletion or L858R mutation

Lee CK, Davies L, et al: J Natl Cancer Inst. 2017 01;109(6).

First Generation TKI vs Chemotherapy - OS





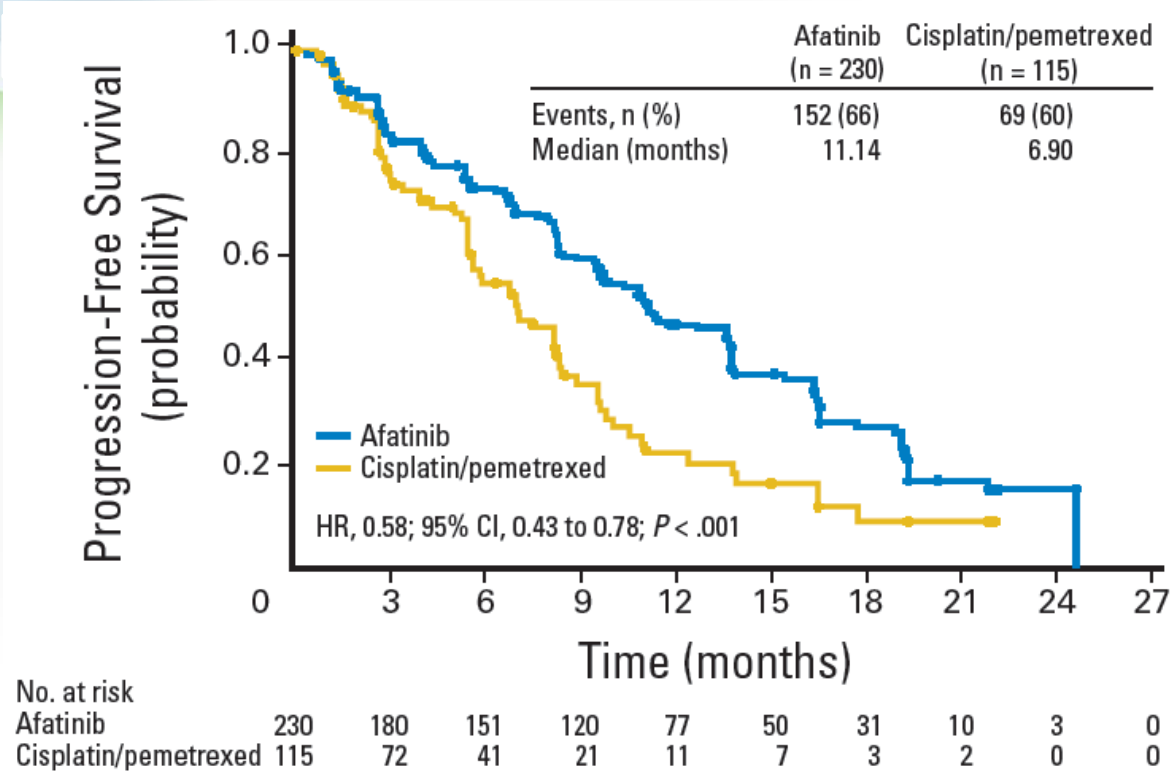
Overall Survival Advantage not seen

Study Design:- Meta-analysis of 6 trials (N=1,231) comparing efficacy of Gefitinib or Erlotinib vs Chemotherapy in patients with Exon 19 deletion or L858R mutation

Lee CK, Davies L, et al: J Natl Cancer Inst. 2017 01;109(6).

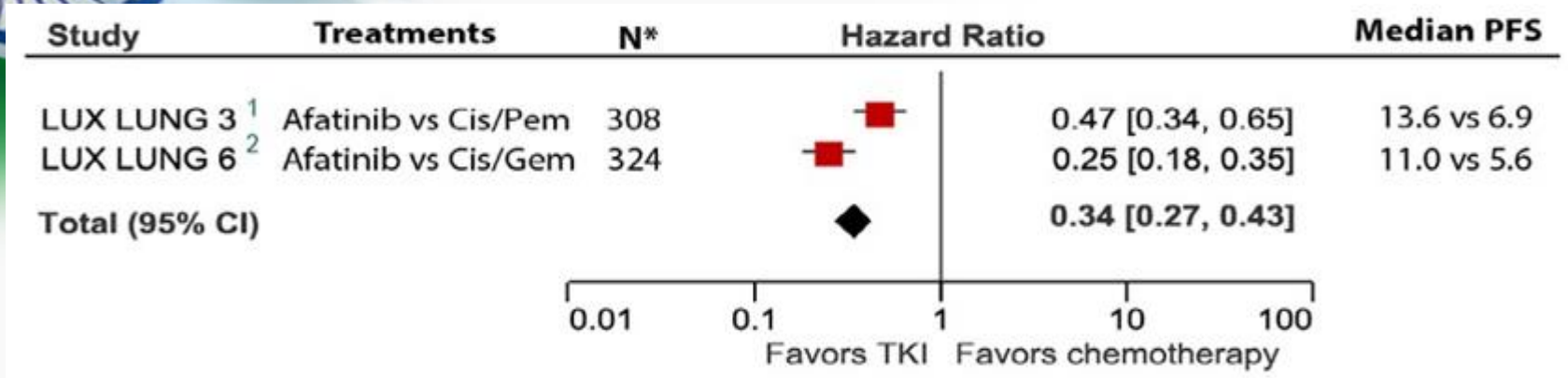
LUX LUNG 3 (Afatinib)

Afatinib - significantly Prolonged PFS v/s standard Chemotherapy.



Sequist et al., J Clin Oncol 2013;DOI: 10.1200/JCO.2012.44.2806

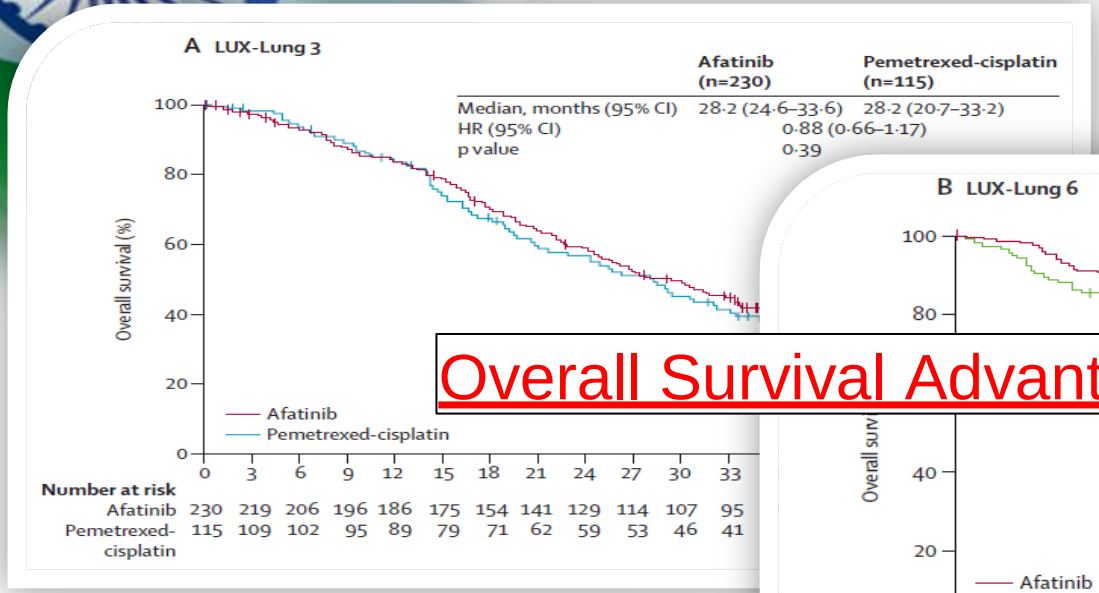
2nd Gen. TKI vs Chemotherapy: PFS



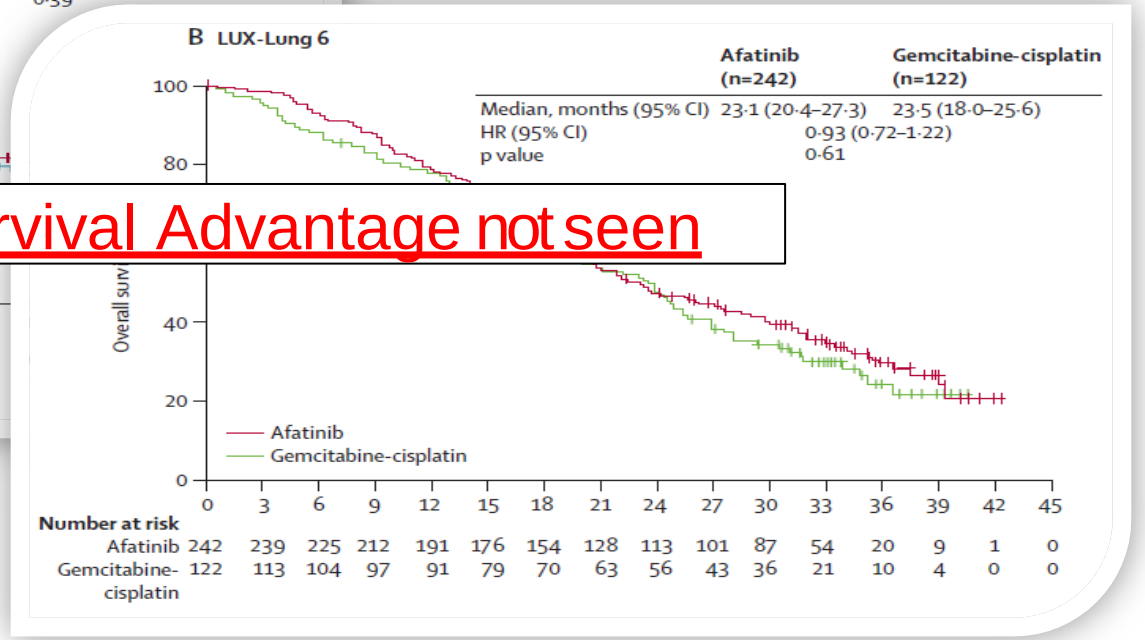
- Treatment naïve *EGFR* +ve stage IIIB or IV lung adenocarcinoma enrolled in LUX-Lung 3 (n=345) and LUX-Lung 6 (n=364).
- Randomly assigned in a 2:1 ratio to receive afatinib or chemotherapy (pemetrexed-cisplatin [LUX-Lung 3] or gemcitabine-cisplatin [LUX-Lung 6]),stratified by *EGFR* mutation (exon 19 deletion [del19], Leu858Arg, or other) and ethnic origin (LUX-Lung 3 only).

2nd Gen. TKI vs Chemotherapy: OS

LUX-LUNG-3

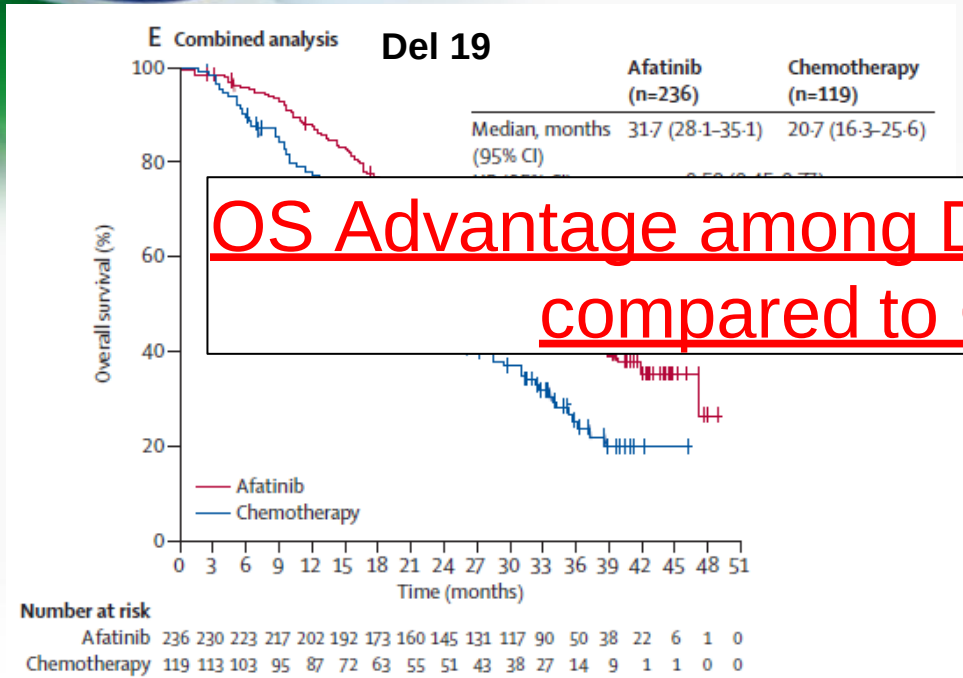


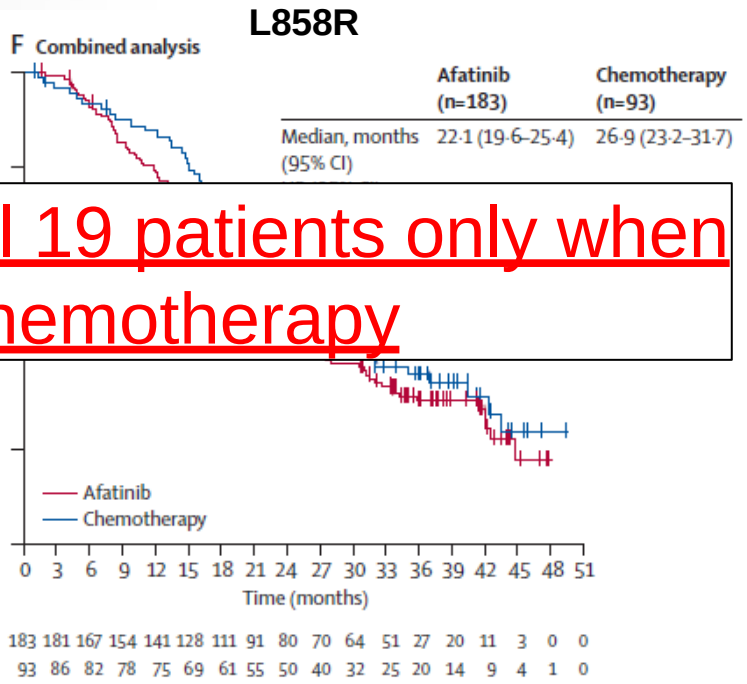
LUX-LUNG-6



Overall Survival Advantage not seen

LUX LUNG 3 & 6
OS according to mutation analysis



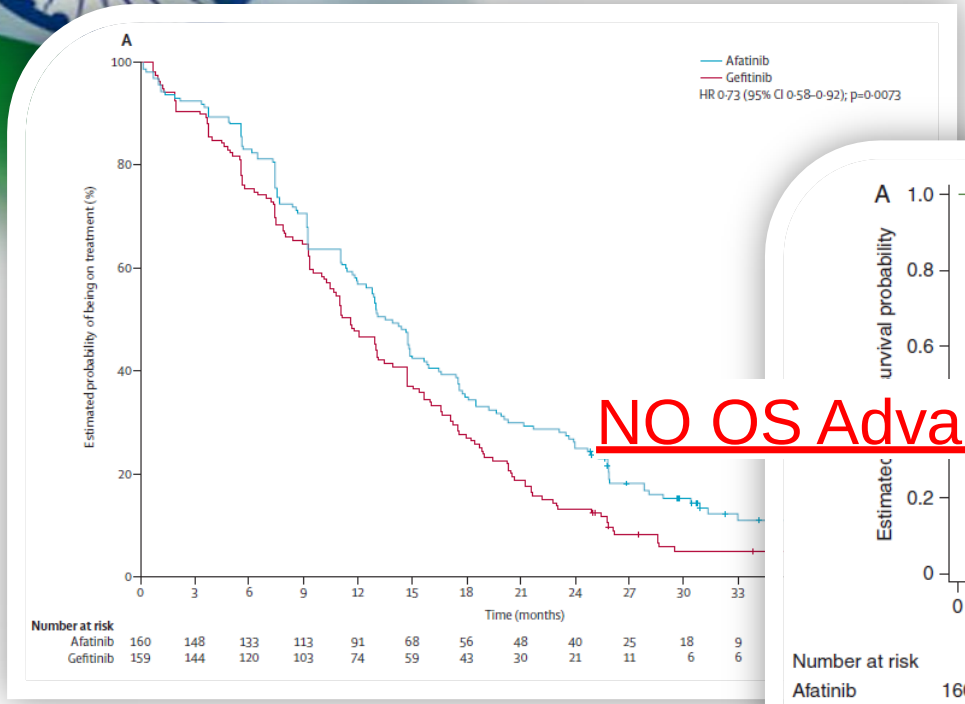


OS Advantage among Del 19 patients only when compared to Chemotherapy

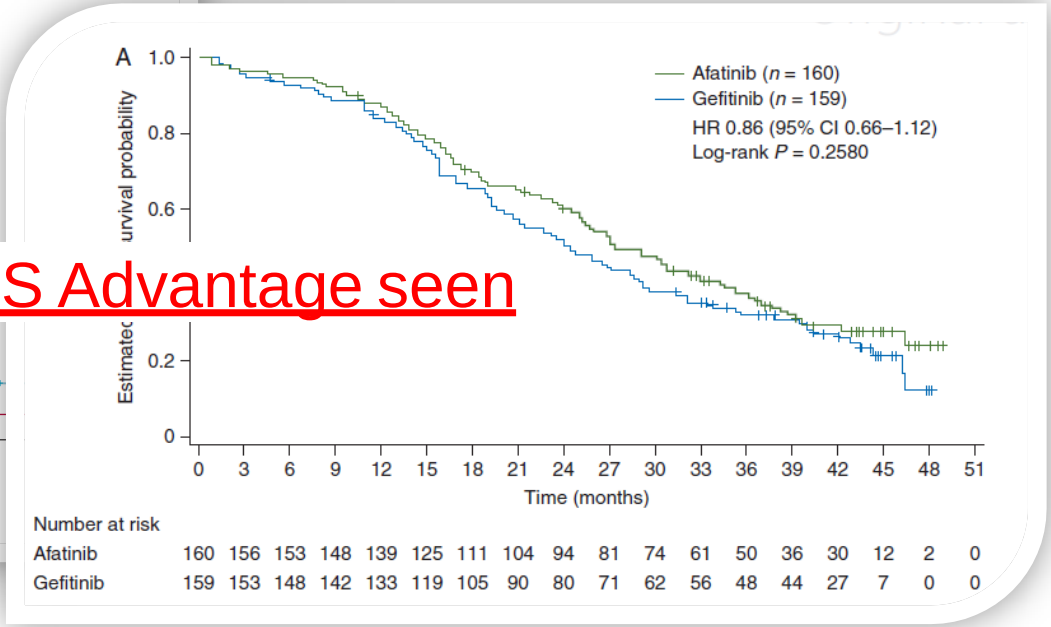
1st Gen. v/s 2nd Gen. TKI

LUX LUNG - 7

Progression Free survival



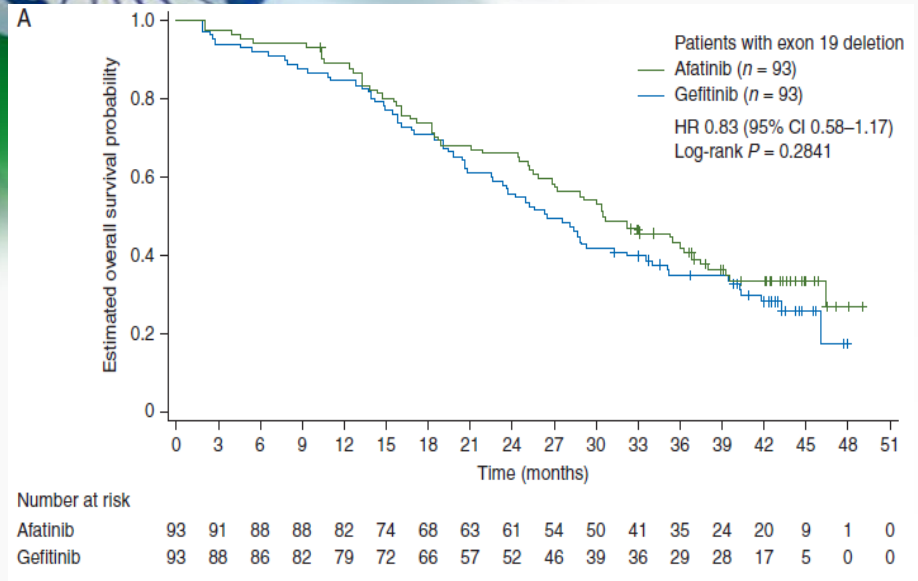
Overall Survival



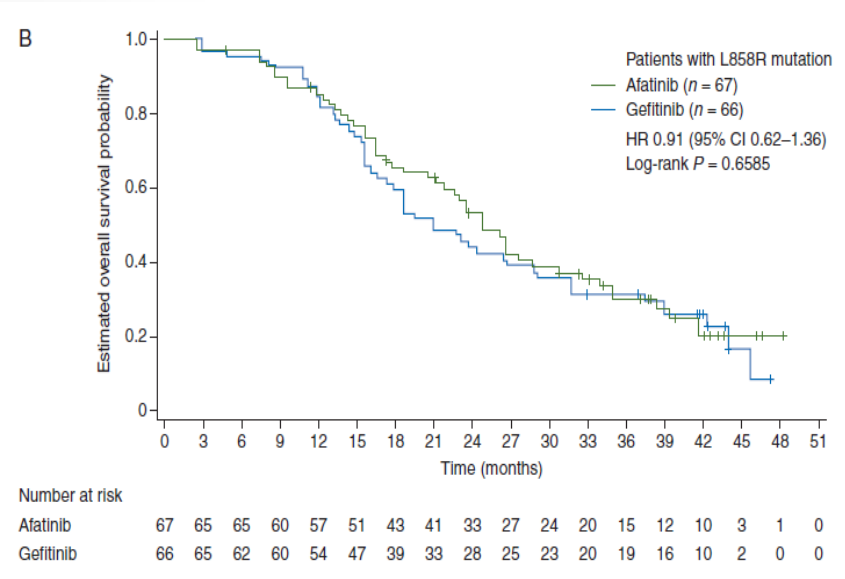
NO OS Advantage seen

LUX LUNG - 7

Del 19



L858R



NO OS Advantage seen as per mutation analysis also

ARCHER 1050: Study Design

Phase III randomized, open-label, study to evaluate dacomitinib as an alternative first-line treatment for patients with advanced NSCLC with an *EGFR*-activating mutation

N=452

Key eligibility criteria:

- Advanced NSCLC with *EGFR*-activating mutation(s)
- Measurable lesion(s) as per RECIST criteria v1.1
- No prior systemic treatment of advanced NSCLC
- No CNS metastasis
- No prior EGFR TKI or other TKI
- ECOG PS 0–1

1:1R ANDOMIZED

- **Dacomitinib 45 mg PO QD (N=227)**
- **Gefitinib 250 mg PO QD (N=225)**

Stratification factors:
Race (incl. Asian vs non-Asian)
EGFR mutation type (exon 19 deletion vs L858R mutation)

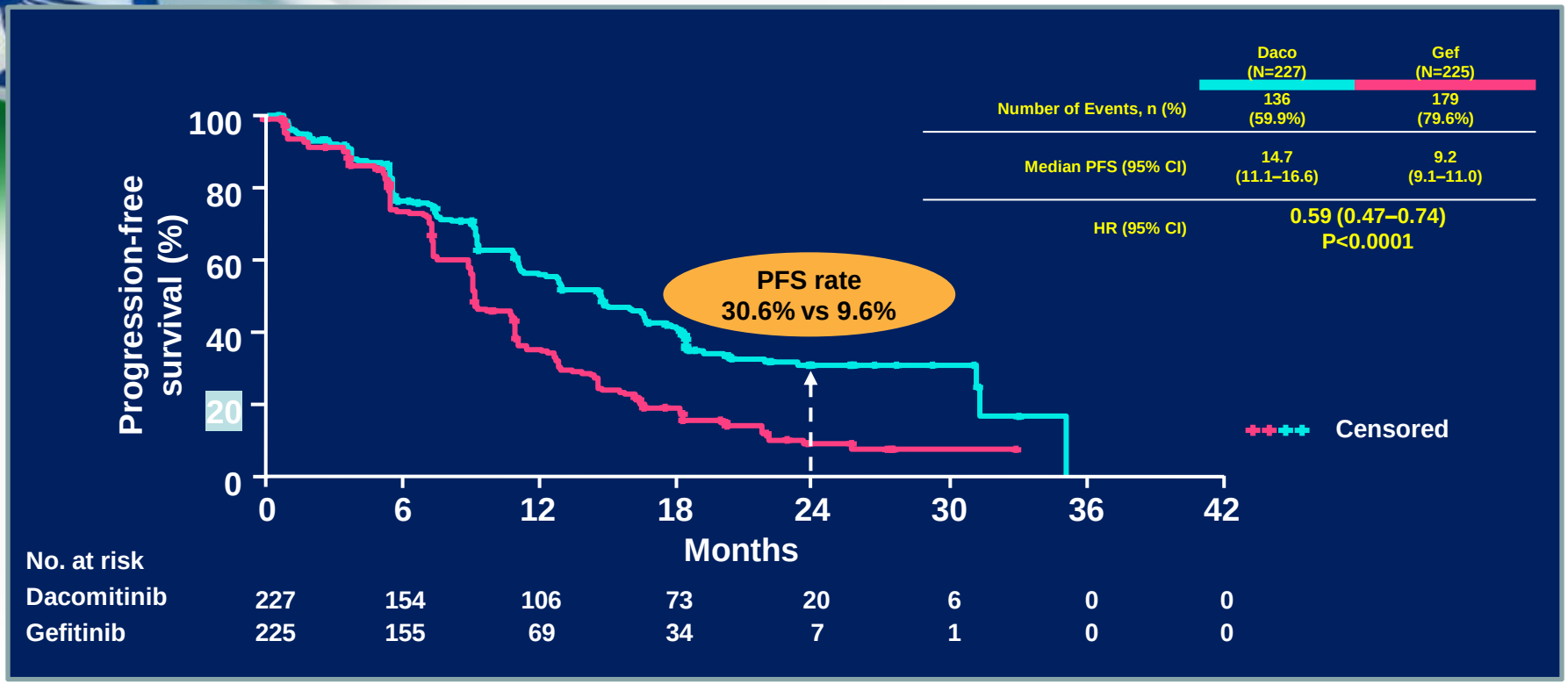
Primary endpoints:

- PFS by blinded IRC in the ITT population

Secondary endpoints:

- PFS (investigator assessed), ORR, DOR, TTF, RMST, OS and OS at 30 months
- Safety and PROs

ARCHER 1050:
PFS by Independent Review – ITT Population

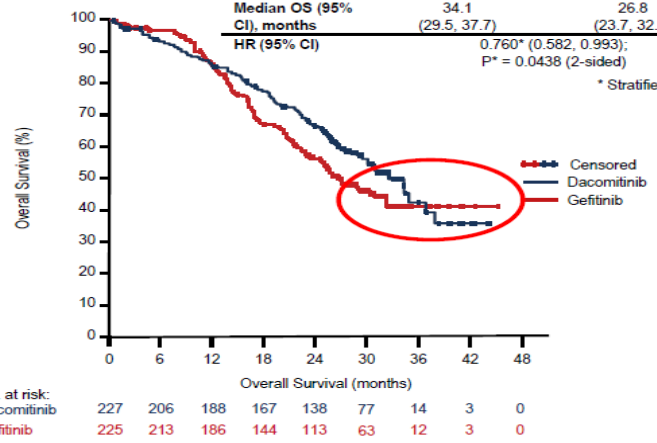


ARCHER 1050: Overall Survival – Intention-to-Treat Population

Overall Survival (Feb. 17, 2017)

	Dacomitinib (n = 227)	Gefitinib (n = 225)
Events, No.	103	117
Median OS (95% CI), months	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR (95% CI)	0.760* (0.582, 0.993); P* = 0.0438 (2-sided)	

* Stratified analysis.



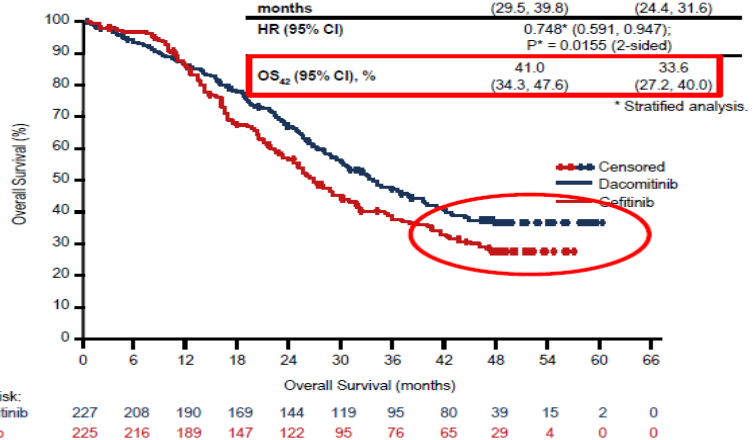
No. at risk:									
Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Mok TS et al. *J Clin Oncol*. 2018;36(22):2244–2250.

Overall Survival (May 13, 2019)

	Dacomitinib (n = 227)	Gefitinib (n = 225)
Events, No.	133	152
Median OS (95% CI), months	34.1 (29.5, 39.8)	27.0 (24.4, 31.6)
HR (95% CI)	0.748* (0.591, 0.947); P* = 0.0155 (2-sided)	
OS_{42} (95% CI), %	41.0 (34.3, 47.6)	33.6 (27.2, 40.0)

* Stratified analysis.



No. at risk:												
Dacomitinib	227	208	190	169	144	119	95	80	39	15	2	0
Gefitinib	225	216	189	147	122	95	76	65	29	4	0	0

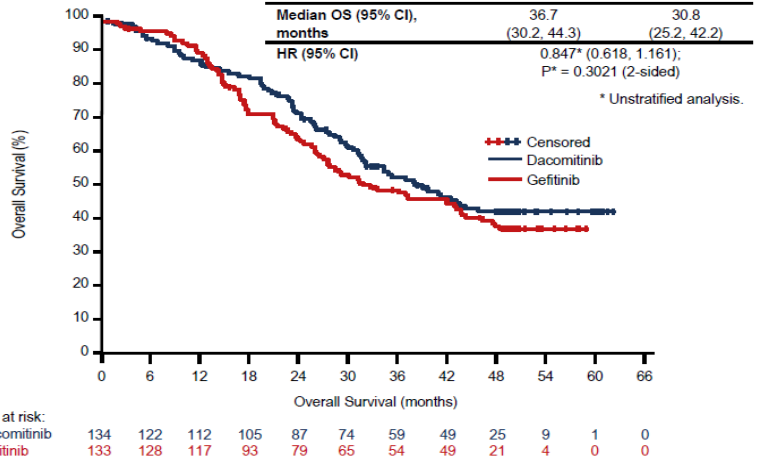
Mok TS, et al. presented at ESMO Asia 2019. 22-24 November, Singapore.

Overall Survival – EGFR Mutational Status

EGFR exon 19 deletion

	Dacomitinib (n = 134)	Gefitinib (n = 133)
Events, No.	73	82
Median OS (95% CI), months	36.7 (30.2, 44.3)	30.8 (25.2, 42.2)
HR (95% CI)	0.847* (0.618, 1.161); P* = 0.3021 (2-sided)	

* Unstratified analysis.

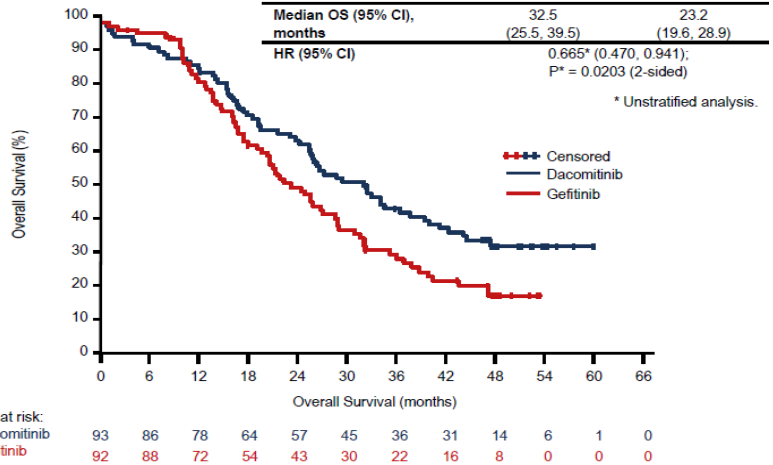


No. at risk:												
Dacomitinib	134	122	112	105	87	74	59	49	25	9	1	0
Gefitinib	133	128	117	93	79	65	54	49	21	4	0	0

EGFR exon 21 L858R

	Dacomitinib (n = 93)	Gefitinib (n = 92)
Events, No.	60	70
Median OS (95% CI), months	32.5 (25.5, 39.5)	23.2 (19.6, 28.9)
HR (95% CI)	0.665* (0.470, 0.941); P* = 0.0203 (2-sided)	

* Unstratified analysis.



No. at risk:												
Dacomitinib	93	86	78	64	57	45	36	31	14	6	1	0
Gefitinib	92	88	72	54	43	30	22	16	8	0	0	0

Mok TS, et al. presented at ESMO Asia 2019. 22-24 November, Singapore.

ARCHER 1050: Serious Adverse Events

	Total incidence of SAEs	Treatment-related SAEs	Permanent discontinuation due to treatment-related AEs	Death related to treatment
Dacomitinib (n=227)	62 (27%)	21 (9%)	22 (10%)	2 (0.9%)
Gefitinib (n=224)	50 (22%)	10 (4%)	15 (7%)	1 (0.4%)

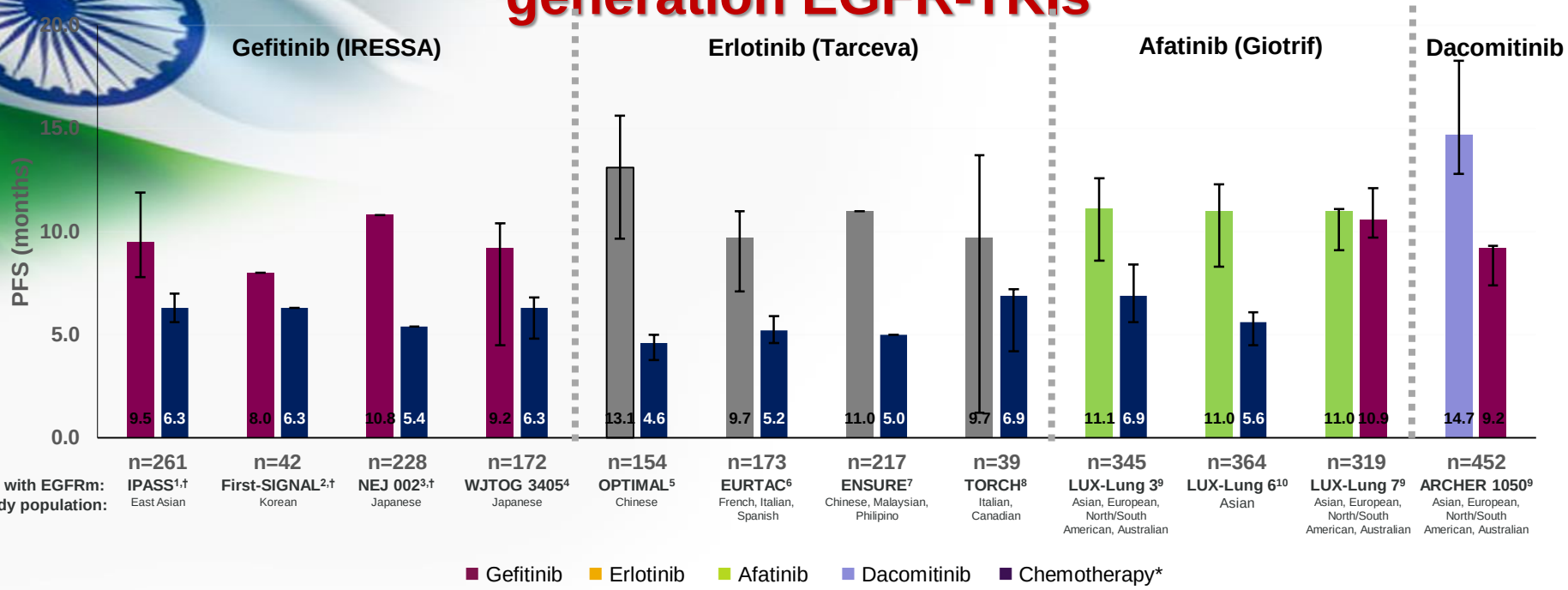
- Causes of death related to treatment:
  - Dacomitinib: 2 (one related to untreated diarrhea, one related to untreated cholelithases/liver disease)
  - Gefitinib: 1 (related to sigmoid colon diverticulitis/rupture complicated by pneumonia)

ARCHER 1050: Dose Modification

- Dacomitinib
  - First dose reduction: 30 mg/day
  - Second reduction: 15 mg/day
- Gefitinib
  - 250 mg every two days

	Median time to first dose reduction	Median duration of dose reduction	Reduction to 30 mg daily	Reduction to 15 mg daily	Total number of patients with dose modification
Dacomitinib (n=227)	2.8 months (IQR 1.3–4.2)	11.3 months (IQR 4.8–18.9)	87 (38%)	63 (28%)	150 (66%)
Gefitinib (n=224)	3.3 months (IQR 2.4–4.2)	5.2 months (IQR 2.5–7.9)	NA	NA	18 (8%)

PFS is plateaued with approved 1st/2nd generation EGFR-TKIs

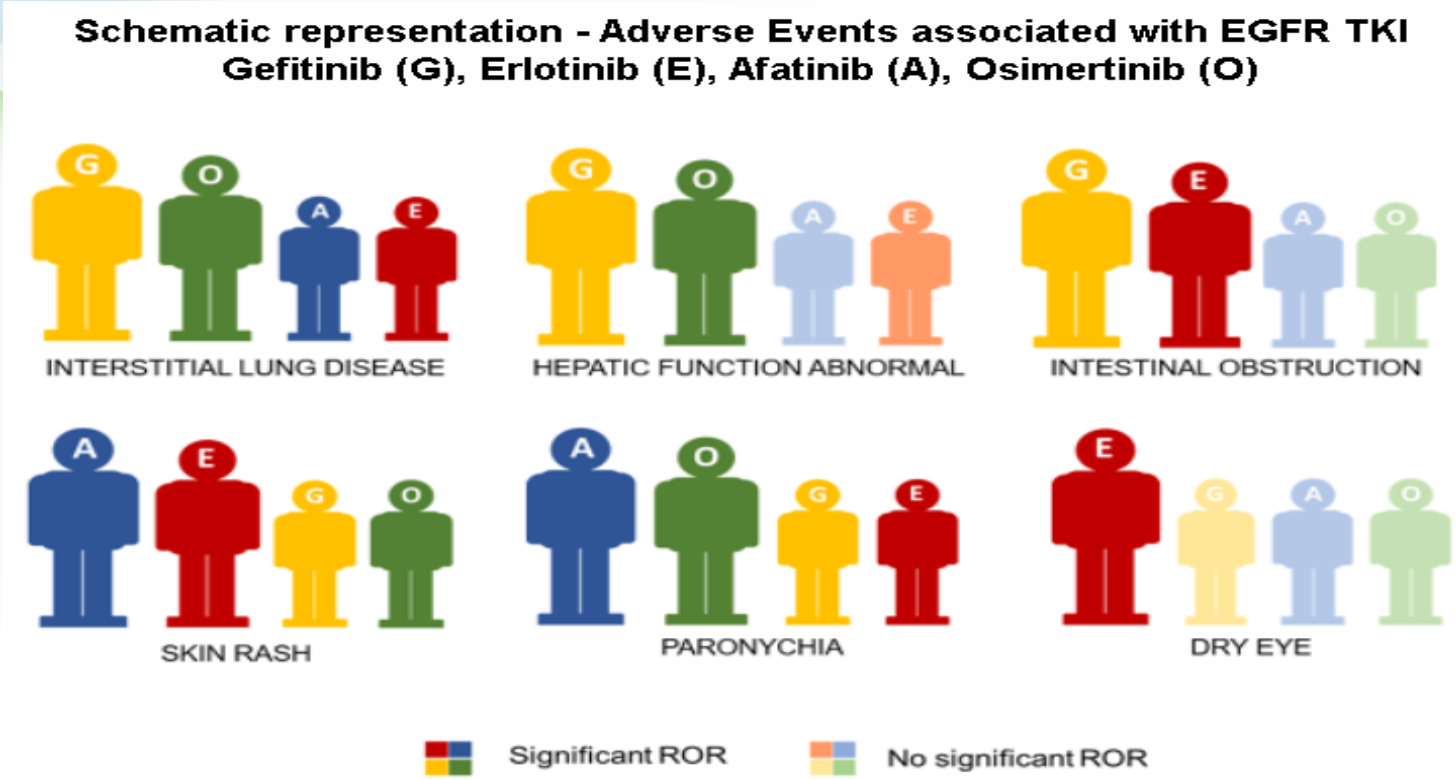


Consistently PFS of 9-12 months have been reported with currently approved EGFR-TKIs in global studies since IPASS

Tolerability still remains an issue with 2nd gen EGFR TKIs

EGFR TKIs	Grade 3 or 4 AE	Treatment-related SAE	AE leading to dose modification	AE leading to discontinuation	Most common grade 3 or 4 AE
Erlotinib	40-50%	2-6%	~20%	5-6%	Rash, fatigue, elevation of ALT
Gefitinib	~30%	2-4%	11-15%	4-6%	Rash, diarrhoea, elevation of ALT
Afatinib	26-79%	6-12%	27-70%	6-29%	Rash, diarrhoea
Dacomitinib	27-44%	9%	66%	10%	Diarrhoea

EFGR TKI Toxicities



3rd Gen. TKI

FLAURA

Phase III, double-blind, study conducted across 132 sites in 29 countries

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years*
- WHO performance status 0 / 1
- Exon 19 deletion / L858R No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification Factors

- Exon 19 deletion / L858R
- **Race** (Asian / non-Asian)

Osimertinib (80 mg p.o. qd) **(n=279)** → RECIST 1.1 assessment every 6 weeks¶ until objective PD

Randomised 1:1

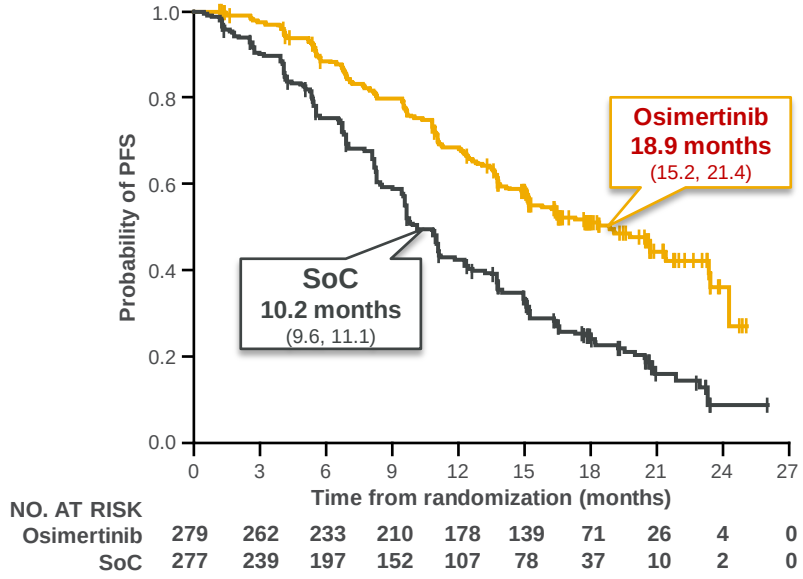
EGFR-TKI SoC#: **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) **(n=277)** → RECIST 1.1 assessment every 6 weeks¶ until objective PD

CROSSOVER was allowed Patients with confirmed PD by BICR on SoC, and T790M+, may begin post-progression open-label osimertinib

Primary endpoint	Secondary endpoints	
• **PFS based on investigator assessment according to RECIST 1.1** (90% powered to detect a hazard ratio of 0.71 at a two-sided alpha-level of 5%)	• Objective response rate • Duration of response • Disease control rate • Depth of response	• Overall survival • Patient reported outcomes • Safety

Osimertinib (FLAURA)
8.7 months longer mPFS than current SoC EGFR TKIs

mPFS (months) (95% CI) with Osimertinib vs gefitinib and erlotinib[1,2]



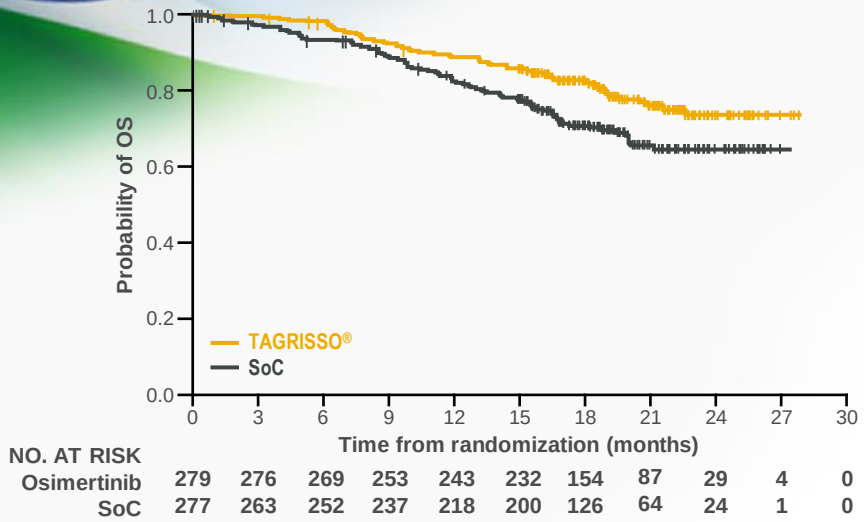
54% REDUCTION IN RISK
of progression or death

HR 0.46
(95% CI: 0.37, 0.57); *P*<0.0001

Clinically meaningful and statistically significant mPFS improvement

With over 2 years of interim data, Osimertinib reduced the risk of death by 37% compared to SoC EGFR TKIs

OS with Osimertinib vs gefitinib and erlotinib



37% REDUCTION IN RISK of death

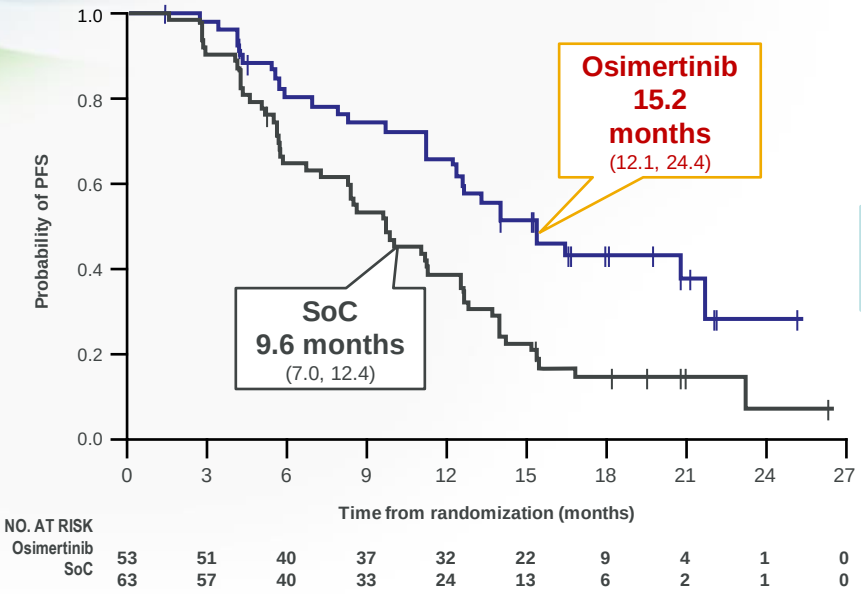
HR 0.63
(95% CI: 0.45, 0.88); *P*<0.0068 (NS)†

Survival	Osimertinib (N=279)	EGFR-TKI SoC (N=277)
Number of deaths	58	83
Survival at 6 months (%)	98.2	93.4
Survival at 12 months (%)	89.1	82.5
Survival at 18 months (%)	82.8	70.9

Interim analysis of OS demonstrated a HR of 0.63 in favor of Osimertinib vs SoC; OS data has not fully matured

PFS benefit for Osimertinib vs SoC is maintained in patients with CNS metastases in FLAURA

mPFS in patients with CNS metastases (n=116)

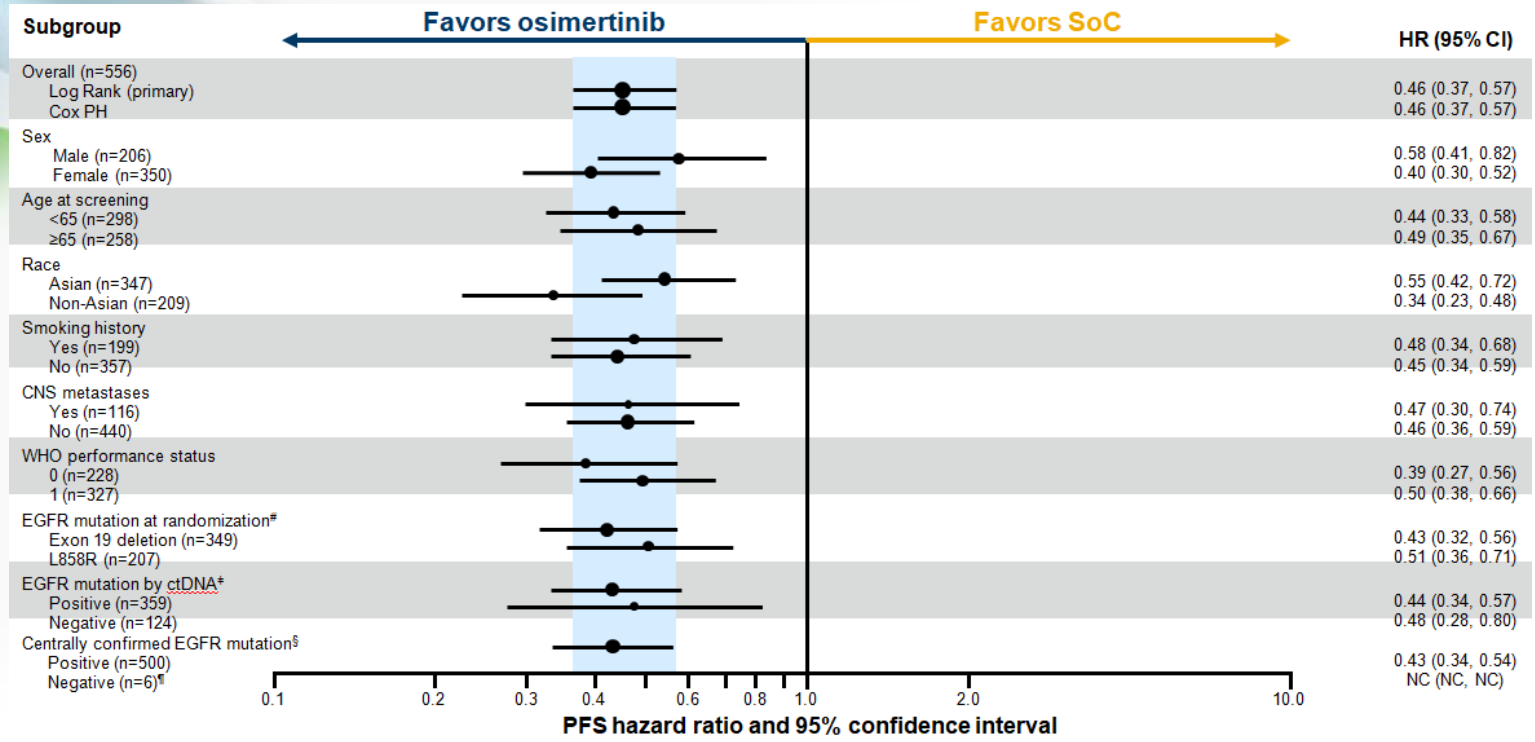


53% REDUCTION IN RISK
of progression or death

HR 0.47
(95% CI: 0.30, 0.74);
P<0.0009

Clinically meaningful and statistically significant mPFS improvement

Efficacy: PFS across subgroups



A consistent benefit of osimertinib over standard EGFR-TKIs with respect to progression-free survival was shown across all predefined subgroups

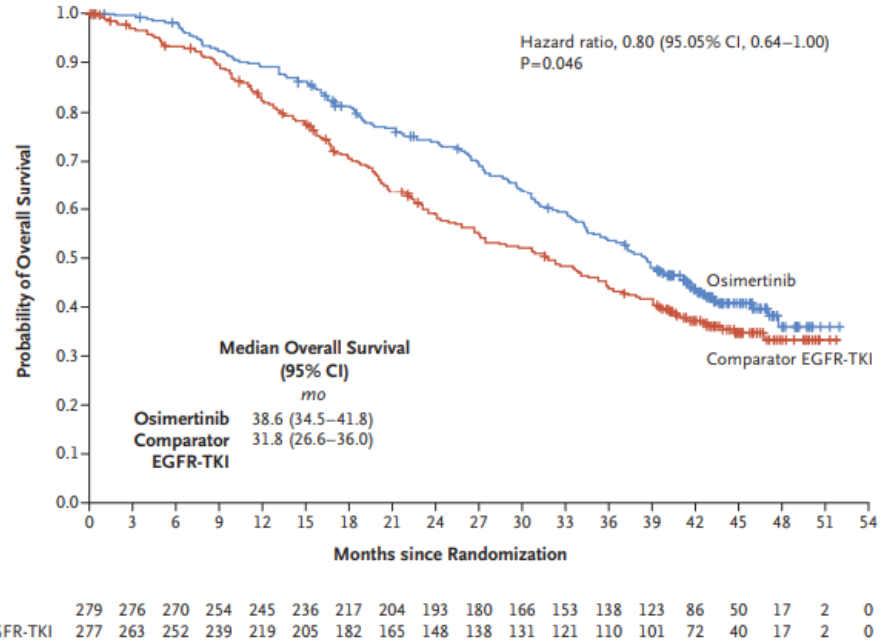
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*

N ENGL J MED 382;1 NEJM.ORG JANUARY 2, 2020



Subsequent treatment

~40% patients did not receive 2L treatment in both arms

Characteristic, %	Osimertinib (n=279)	EGFR-TKI SoC (n=277)	Significance
PFS	**18.9 mts** (95% 15.2-21.4)	**10.2 mts** (95% 9.6-11.1)	**HR 0.46** (95% CI: 0.37, 0.57); P<0.0001
% of patients continuing assigned treatment	141 (51%)	64(23%)	
First subsequent Anticancer treatment % (n)	82 (29%)	129 (47%)	
Chemotherapy	53 (71%)	32 (25%)	
EGFR-Tki therapy	29 (21%)	97 (46%) *	
TFST (Time to first subsequent treatment)	**23.5 mts** (95% CI 22.0 - [NC])	**13.8 mts** (95% CI 12.3 to 15.7)	**HR: 0.51** [95% CI 0.40 to 0.64], p<0.001
PFS2	NC (95% CI 23.7 to NC)	**20.0 mts** (95% CI 18.2 to NC)	**HR 0.58** (95% CI 0.44 to 0.78; P<0.001)
TSST (Time to second subsequent treatment)	NC (95% CI NC-NC)	**25.9 monts** (95% CI 20.0 to NC)	**HR 0.60** (95% CI 0.45 to 0.80; P<0.001)

* 48 patients received Osimertinib on cross-over in SOC arm

Sequencing of TKI

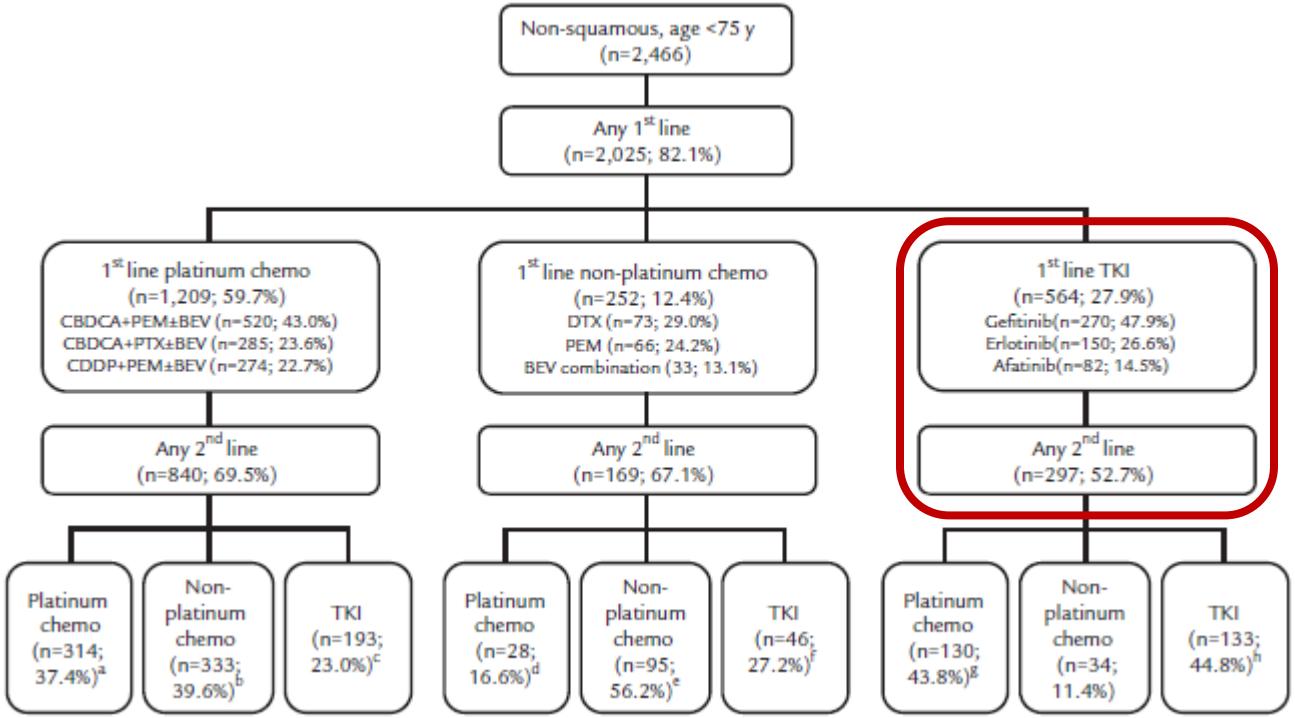
Phase III EGFR TKI trials

~2/3 of patients receive a second therapy after progression

	IPASS n=132	IFUM N=106	NEJ002 N=114	WJTOG 3405 N=86	EURTAC N=86	OPTIMAL N=82	ENSURE N=110	CTONG0901 N=128	N=128	LL3 N=230	LL6 N=242	LL7 N=160	N=159
TKI	**Gefitinib**	**Gefitinib**	**Gefitinib**	**Gefitinib**	**Erlotinib**	**Erlotinib**	**Erlotinib**	**Gefitinib**	**Erlotinib**	**Afatinib**	**Afatinib**	**Afatinib**	**Gefitinib**
OS, months	21.6	19.2	27.7	34.8	19.3	22.8	26.3	20.1	22.9	28.2	23.1	27.9	24.5
Post-TKI treatment*	**76%**	**49%**	**72%**	**88%**	**68%**	**63%**	**66%**	**55%**	**51%**	**71%**	**57%**	**73%**	**77%**

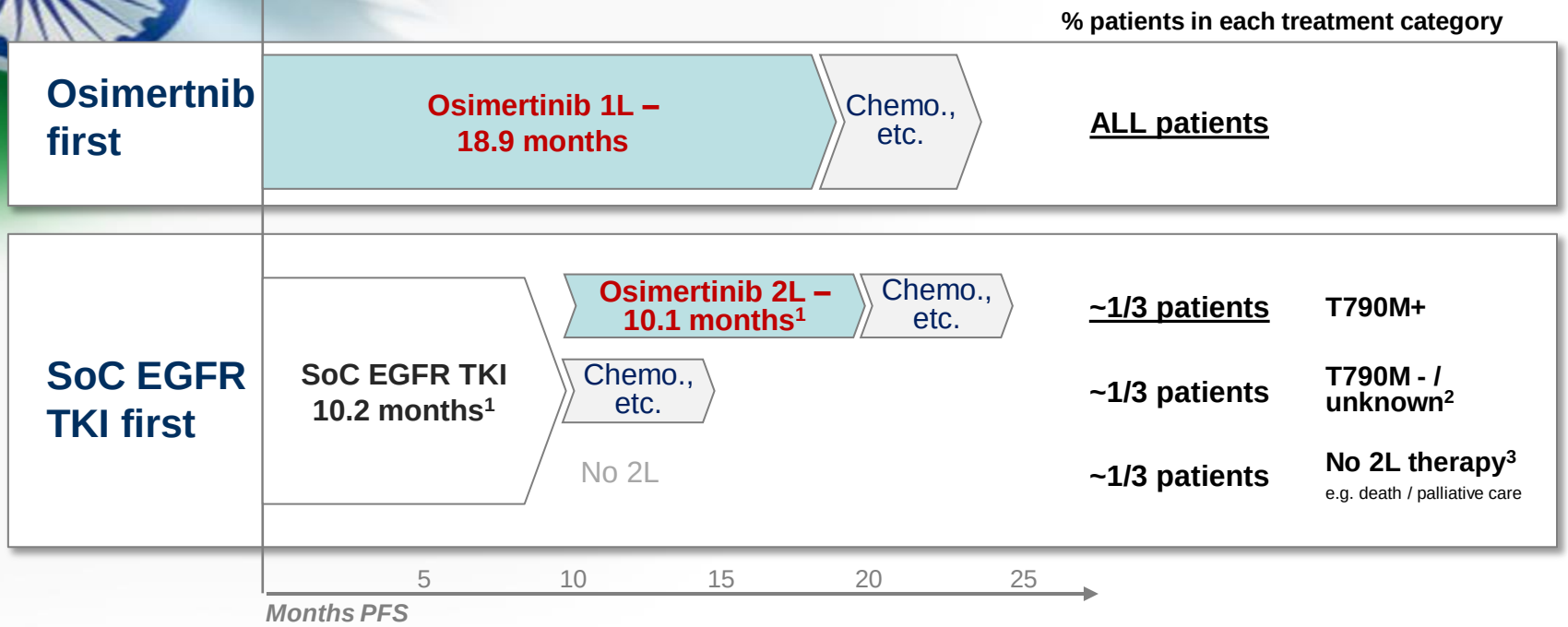
Real-world scenario

~1/2 of patients receive 2L Rx after 1L TKI



Wang F, Mishina S, Takai S, Le TK, Ochi K, Funato K, et al. Systemic Treatment Patterns With Advanced or Recurrent Non–small Cell Lung Cancer in Japan: A Retrospective Hospital Administrative Database Study. Clinical Therapeutics [Internet]. 2017 Jun 1;39(6):1146–60. Available from: http://www.sciencedirect.com/science/article/pii/S014929181730245X

Osimertinib upfront or reserve it for later line?



Sit-at-home Messages!

- Proven benefit of all generation of EGFR TKIs vs Chemotherapy
- No OS benefit seen with 1st or 2nd gen TKI till date, OS benefit with osimertinib
- Safety concerns arises from first to second generation TKIs
- 3rd Generations TKIs (Osimertinib) have shown significant improvement in PFS over SoC
  - Consistent benefit in patients with and without CNS metastases at study entry
  - Interim OS results showed promising survival favoring Osimertinib vs SoC
- Significant fraction of patients do not receive 2L treatment after progressing on 1L TKI.
  - Should consider this while deciding for 1L treatment for EGFRm metastatic NSCLC patient
- Cost of Rx remains major factor in decision making

Thank You!!

Stay Positive, Stay Alert & Stay Safe!!