Osimertinib or Dacomitinib as first line therapy in EGFR mutated lung cancer

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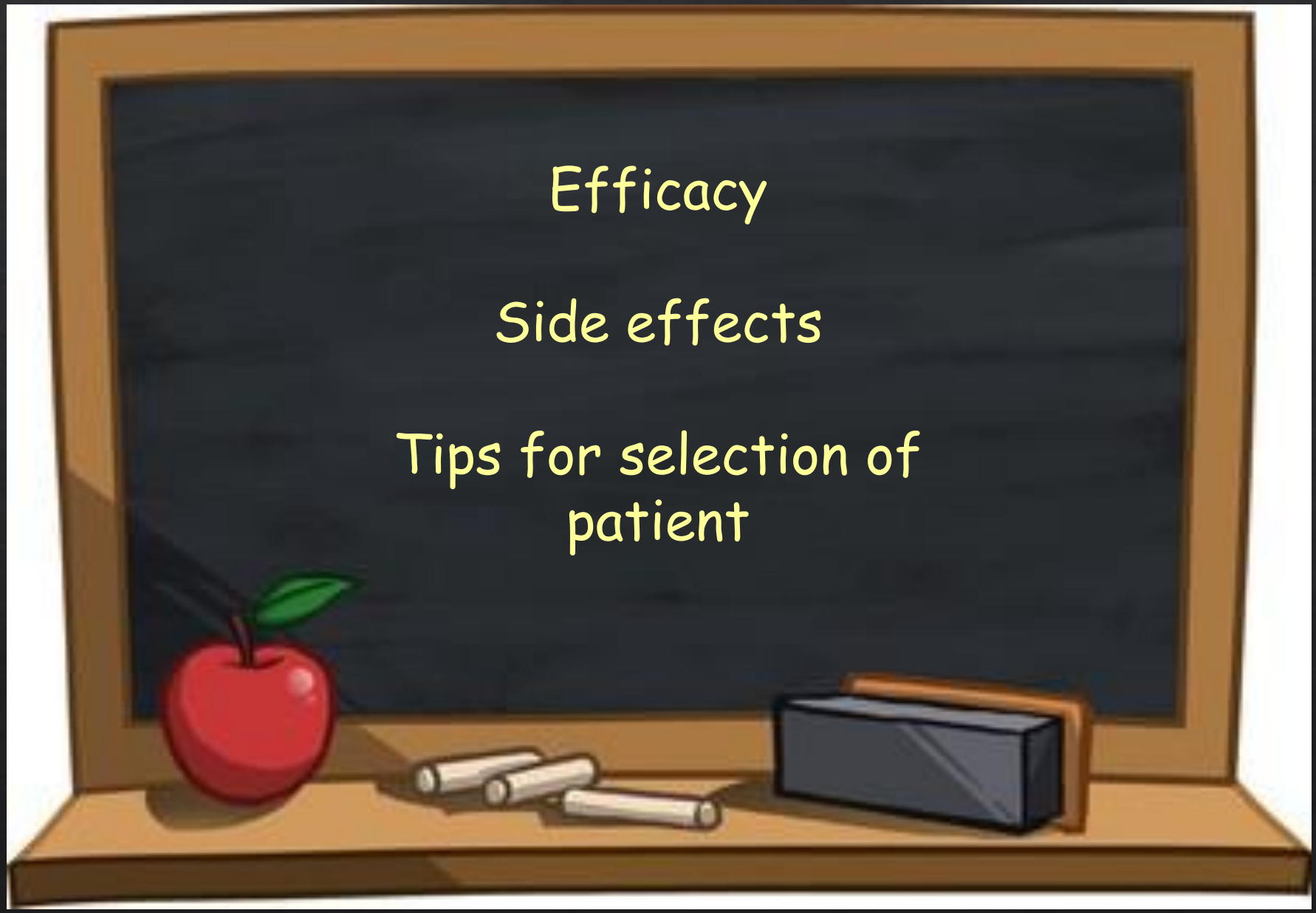
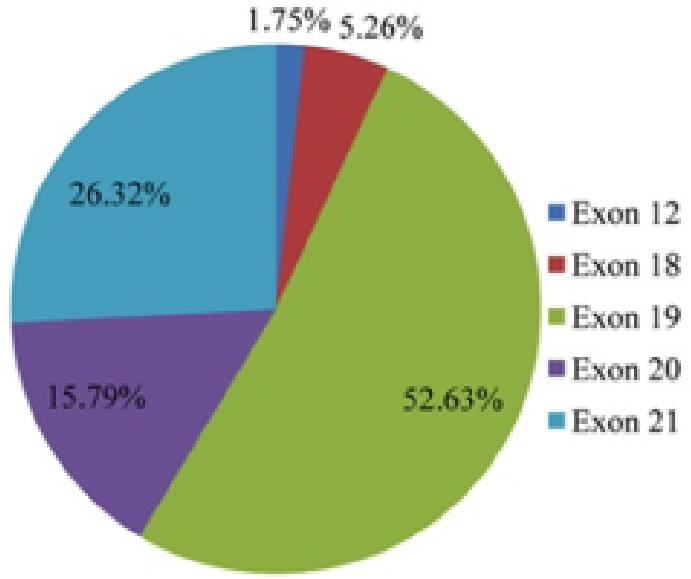

Efficacy
Side effects
Tips for selection of patient

EGFR Mutation-Positive NSCLC: An Overview

- *EGFR* mutations are observed in ~40% and 20% of patients with NSCLC in Asian and non-Asian populations, respectively.[1]
- The incidence rate of *EGFR* mutations among Indian patients is approximately 20%–23%.[2]
- *EGFR* mutations are located in the tyrosine kinase domain and result in increased kinase activity of the EGFR, leading to continued cell proliferation.[1]



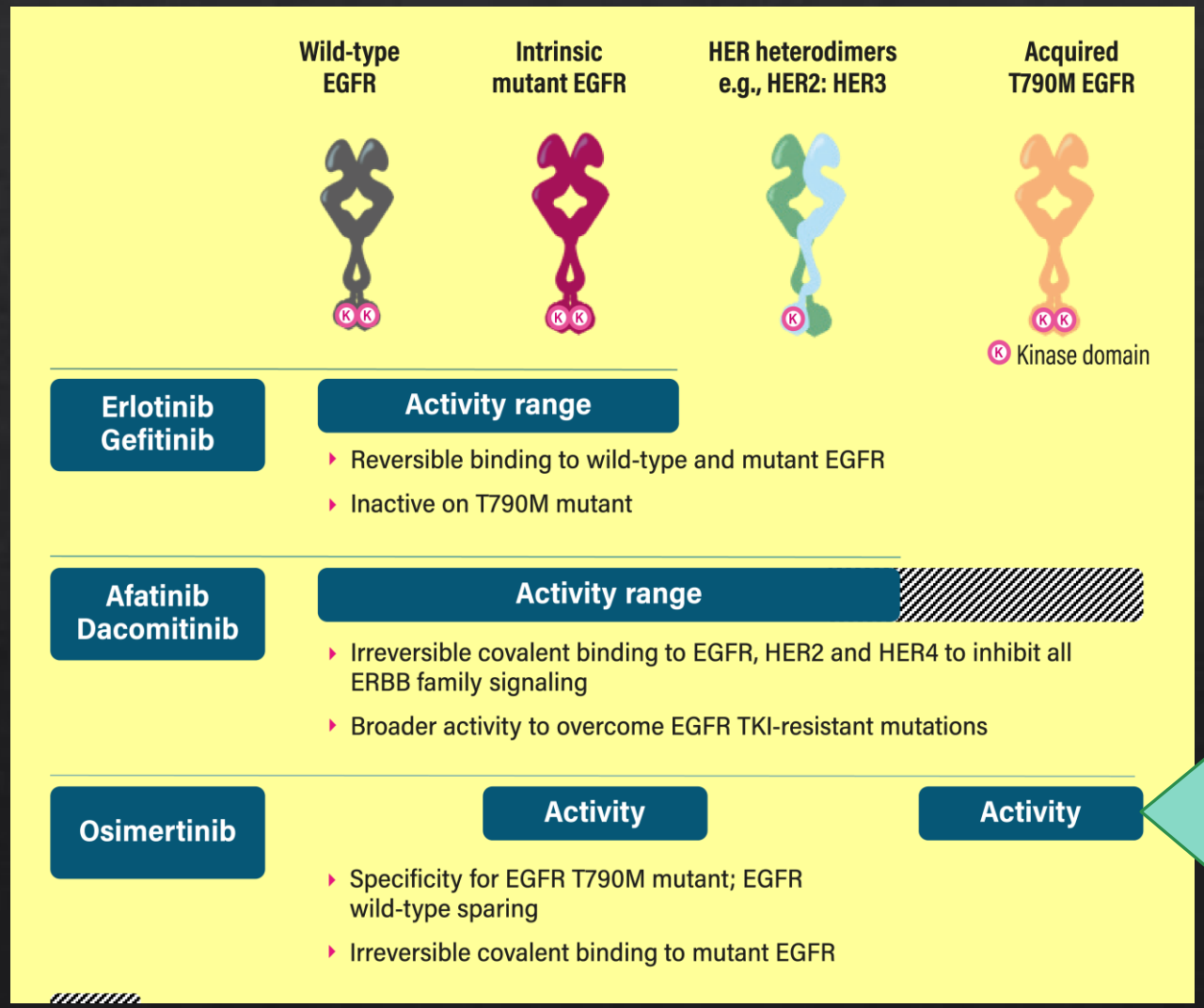
The most common *EGFR* mutations are deletions in exon 19 (Ex19del) and exon 21 L858R point mutation.[1,3]

Gefitinib Afatinib Osimertinib

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

Dacomitinib
Second-generation, irreversible EGFR TKI
activity against all three kinase-active members of the ErbB family (EGFR/HER1, HER2, and HER4

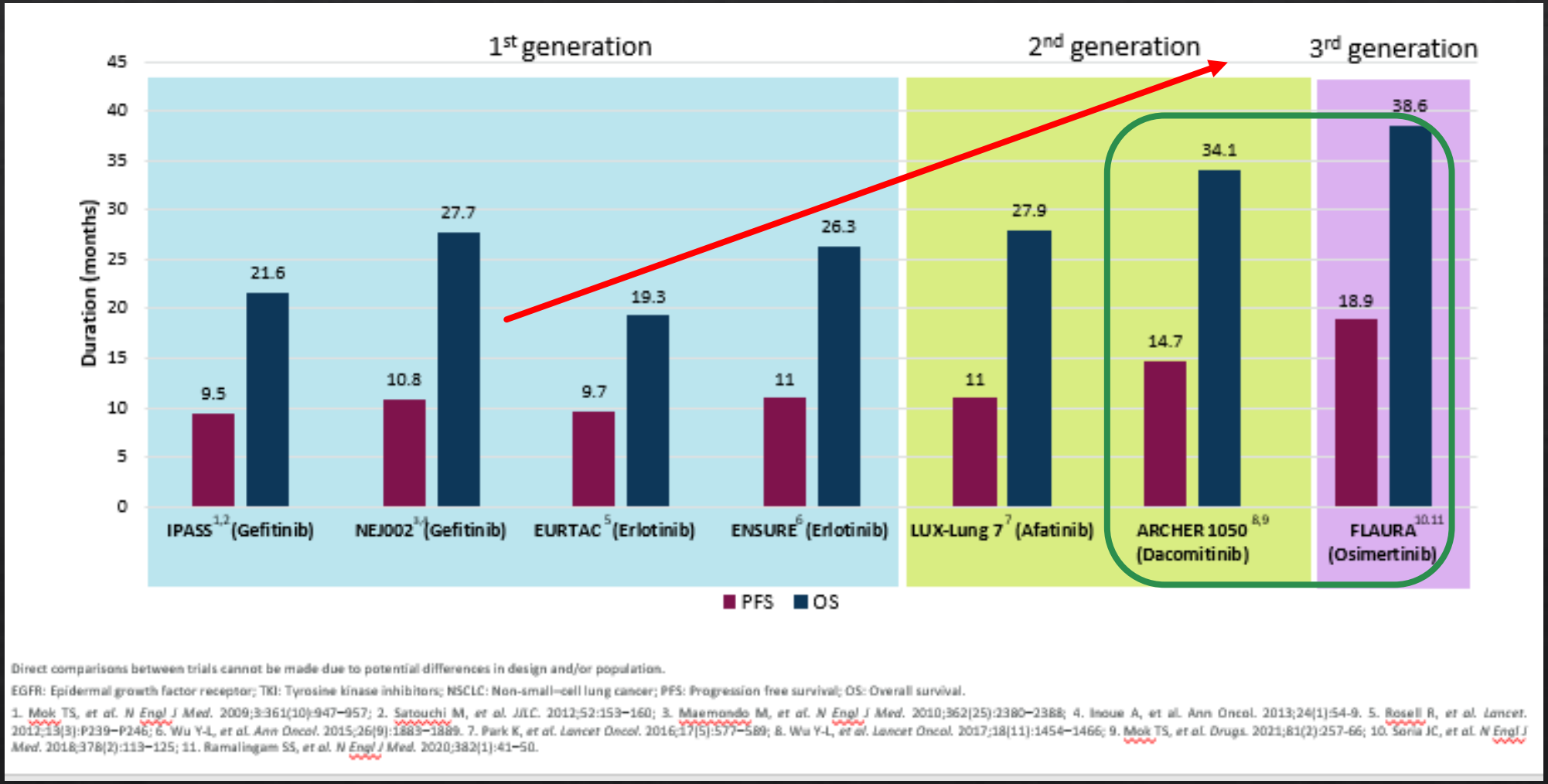
Potential for more complete inhibition of Her signaling



Osimertinib
Third-generation EGFR TKI
activity against *EGFR* T790M mutation, and EGFR TKI-sensitizing mutations (exon 19 deletion and exon 21 L858R substitution)

more selectively than wild-type EGFR

Clinical trials of EGFR TKIs in 1st line advanced NSCLC



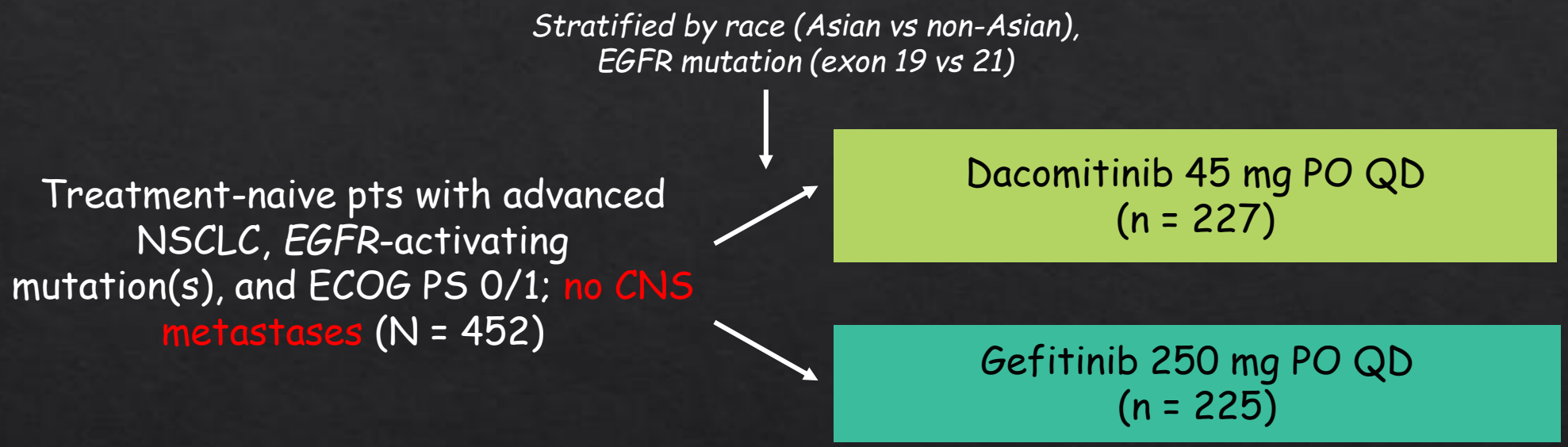
Direct comparisons between trials cannot be made due to potential differences in design and/or population.

EGFR: Epidermal growth factor receptor; TKI: Tyrosine kinase inhibitors; NSCLC: Non-small-cell lung cancer; PFS: Progression free survival; OS: Overall survival.

1. Mok TS, *et al. N Engl J Med.* 2009;3:361(10):947–957; 2. Satouchi M, *et al. JJLC.* 2012;52:153–160; 3. Maemondo M, *et al. N Engl J Med.* 2010;362(25):2380–2388; 4. Inoue A, et al. Ann Oncol. 2013;24(1):54-9. 5. Rosell R, *et al. Lancet.* 2012;13(3):P239–P246; 6. Wu Y-L, *et al. Ann Oncol.* 2015;26(9):1883–1889. 7. Park K, *et al. Lancet Oncol.* 2016;17(5):577–589; 8. Wu Y-L, *et al. Lancet Oncol.* 2017;18(11):1454–1466; 9. Mok TS, *et al. Drugs.* 2021;81(2):257-66; 10. Soria JC, *et al. N Engl J Med.* 2018;378(2):113–125; 11. Ramalingam SS, *et al. N Engl J Med.* 2020;382(1):41–50.

ARCHER 1050: Study Design

- Multicenter, randomized, open-label phase III study



- Primary endpoint: PFS by blinded independent review
- Secondary endpoints: PFS by investigator assessment, ORR, DoR, TTF, OS, safety, pt-reported outcomes

- Prespecified subgroups for subgroup analyses: age (<65 years *vs* ≥65 years), sex, ECOG performance status (0 *vs* 1), race (Asian *vs* non-Asian), smoking history (never *vs* former or current), and *EGFR* mutation type at randomisation (exon 19 deletion *vs* Leu858Arg)

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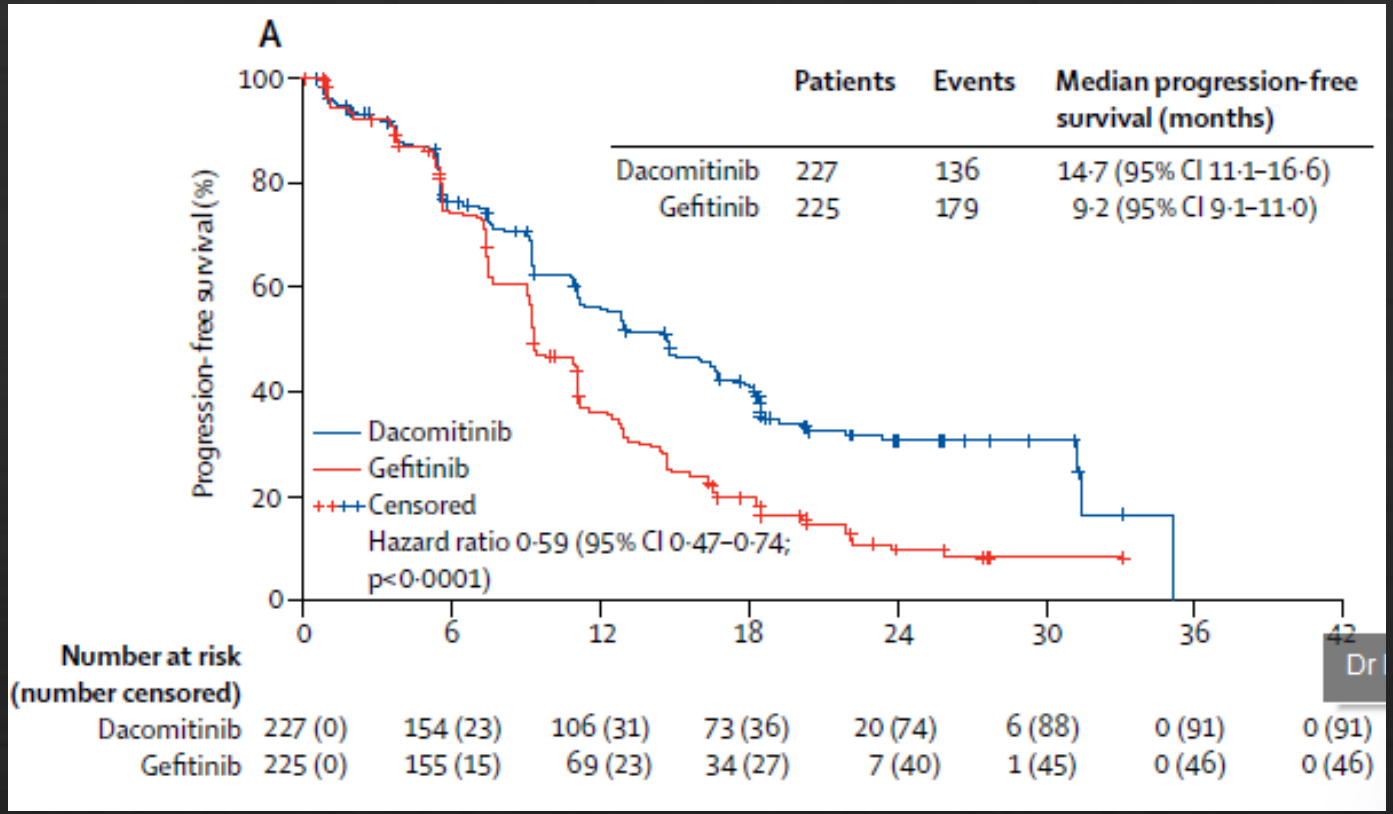
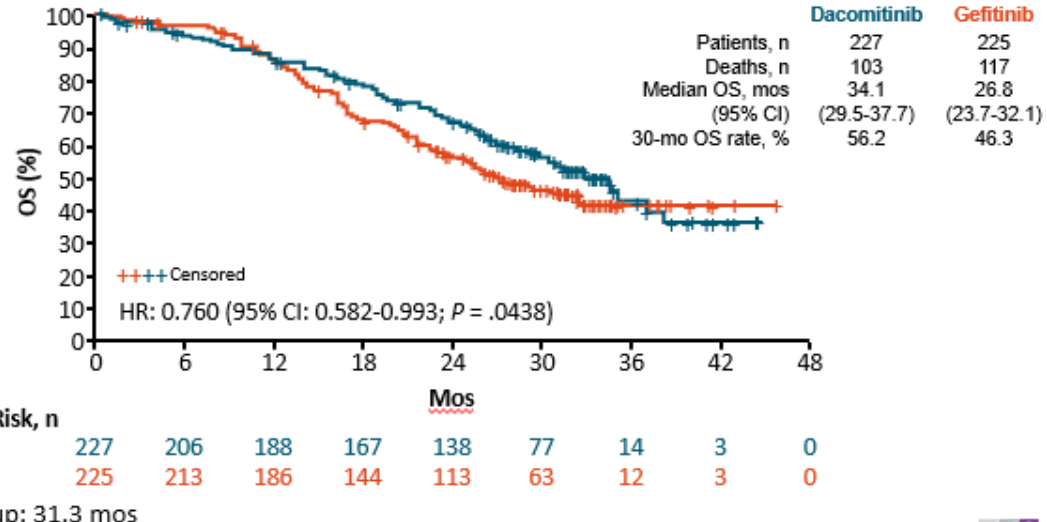
DACOMITINIB EFFICACY



Outcome	Dacomitinib (n = 227)	Gefitinib (n = 225)	HR (95% CI)	*P* Value
Median PFS by investigator assessment, mos (95% CI)	16.6 (12.9-18.4)	11.0 (9.4-12.1)	0.62 (0.50-0.78)	< .0001
ORR, % (95% CI)	74.9 (68.7-80.4)	71.6 (65.2-77.4)	--	.3883
Median DoR, mos (95% CI)	14.8 (12.0-17.4)	8.3 (7.4-9.2)	--	< .0001
Median TTF, mos (95% CI)	11.1 (9.2-14.6)	9.2 (7.6-9.4)	0.67 (0.54-0.83)	< .001

OS was longer in the dacomitinib arm than in the gefitinib arm (HR: 0.748, two-sided *P* = 0.0155)
median OS was 34.1 months versus 27.0 months

ARCHER 1050: Overall Survival



	Dacomitinib	Gefitinib
Patients, n	227	225
Deaths, n	103	117
Median OS, mos	34.1	26.8
(95% CI)	(29.5-37.7)	(23.7-32.1)
30-mo OS rate, %	56.2	46.3

Patients at Risk, n									
Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Median follow-up: 31.3 mos

Mok T, et al. ASCO 2018. Abstract 9004. Mok T, et al. J Clin Oncol. 2018;[Epub ahead of print].

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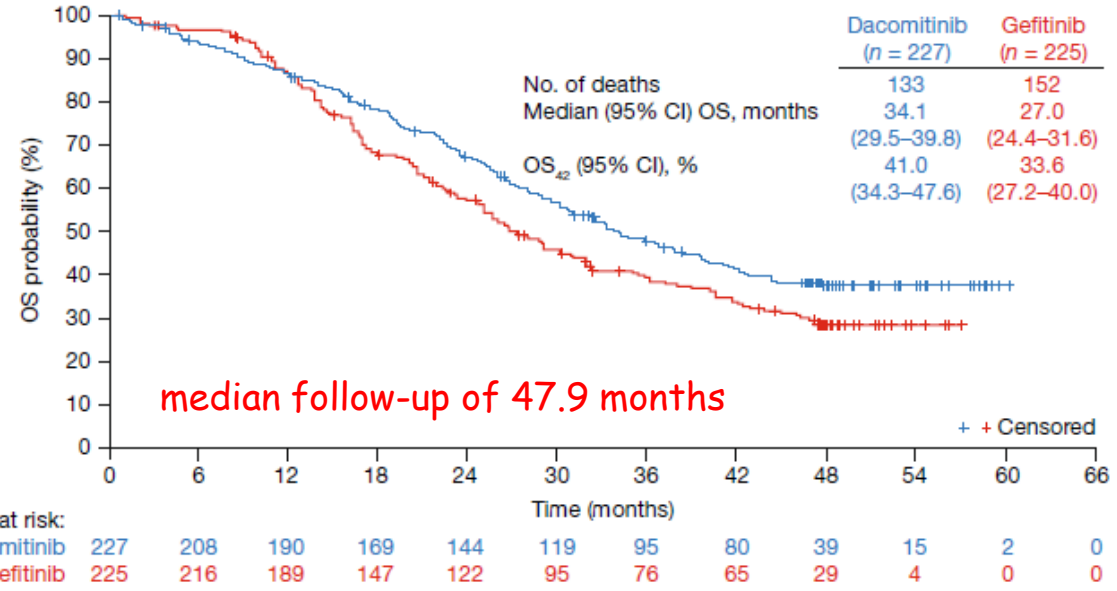
HR, 0.748; 95% CI: 0.591–0.947;
P = 0.0155 (2-sided stratified log-rank test)

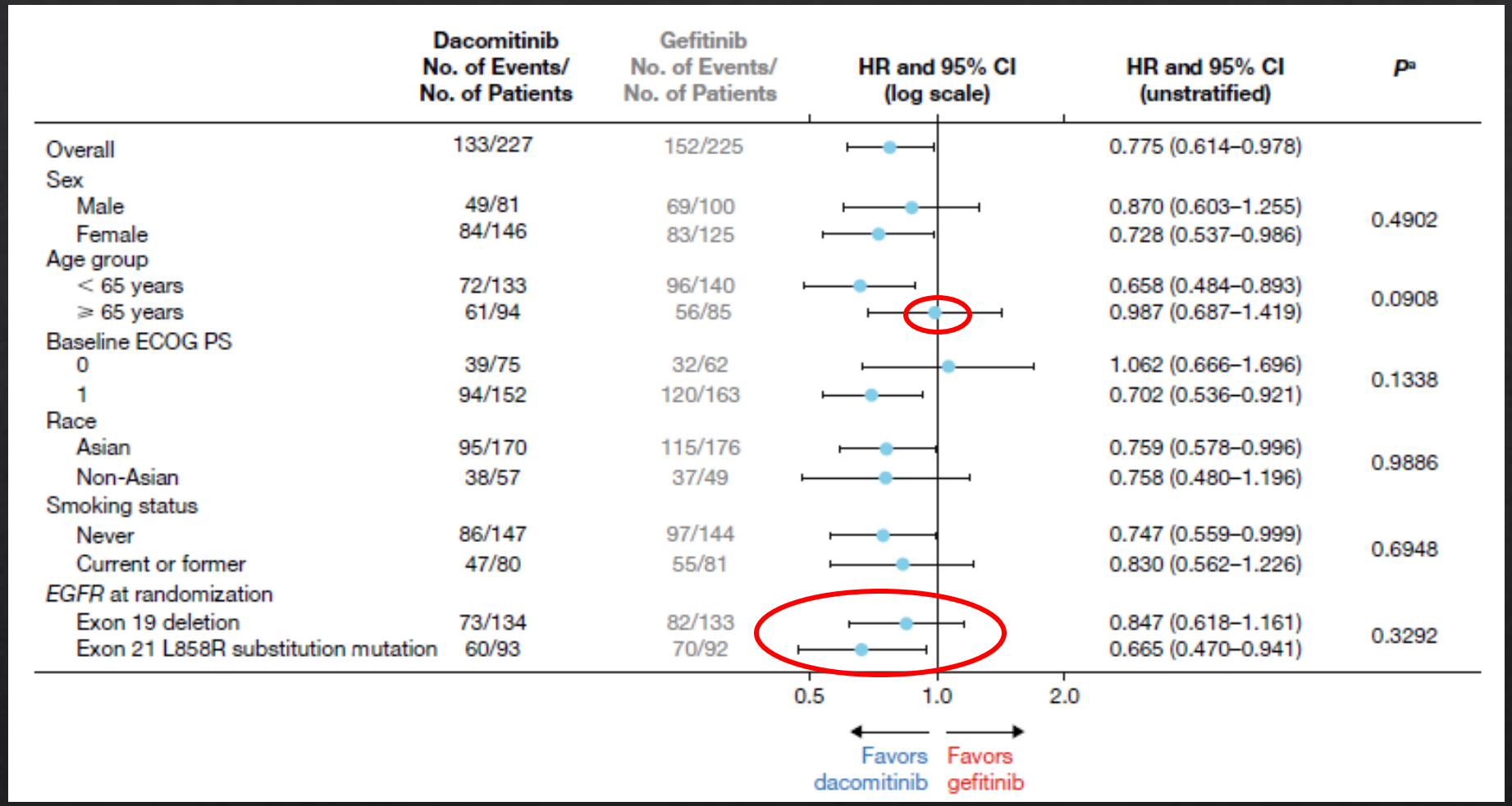


	Dacomitinib (*n* = 227)	Gefitinib (*n* = 225)
No. of deaths	133	152
Median (95% CI) OS, months	34.1 (29.5–39.8)	27.0 (24.4–31.6)
OS_{42} (95% CI), %	41.0 (34.3–47.6)	33.6 (27.2–40.0)

median follow-up of 47.9 months

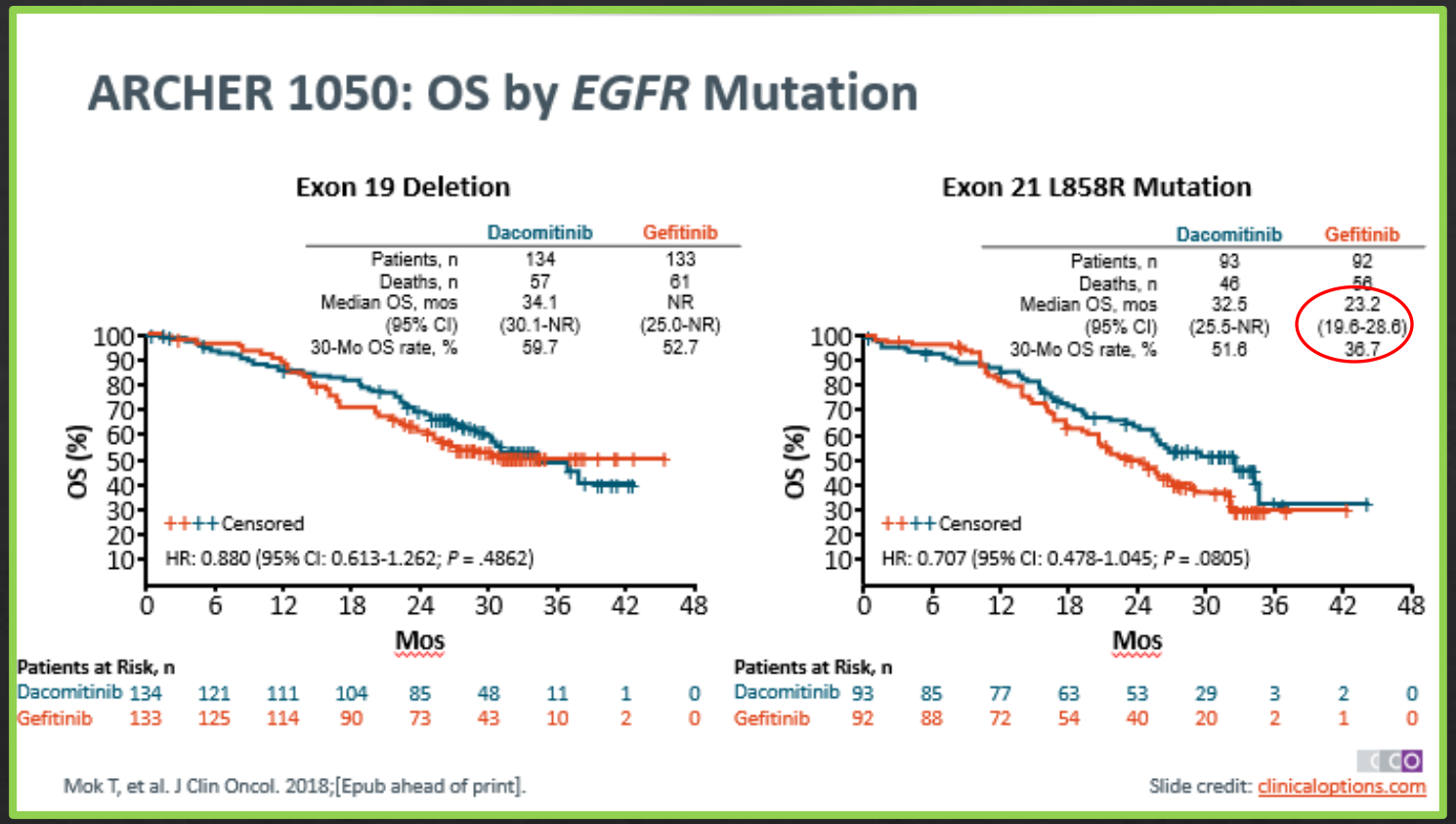
No. at risk:												
Dacomitinib	227	208	190	169	144	119	95	80	39	15	2	0
Gefitinib	225	216	189	147	122	95	76	65	29	4	0	0

The hierarchical statistical testing order was PFS → ORR → OS.
While the updated OS result was statistically significant when assessed on its own, since the gate-keeping procedure stopped at the testing of ORR (per BIRC review) as ORR was not statistically significant, the statistical significance of OS improvement could not be formally assessed. [1,2]



One patient of the dacomitinib group progressed in the brain compared to eleven patients in the gefitinib group (0.44% vs 4.9%)

biologically, EGFR Del 19 mutations are so sensitive to any EGFR TKI that any attempt to further improve OS outcome may be difficult

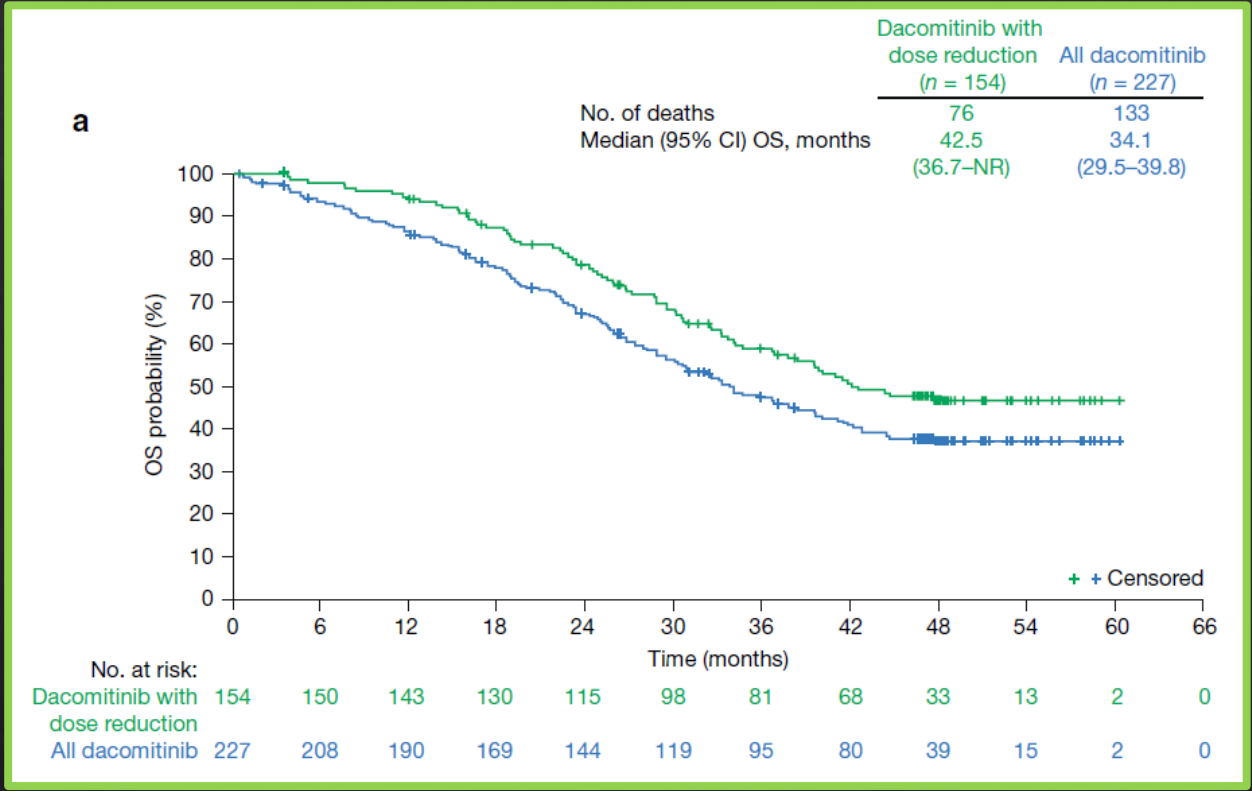


reflection of the poor outcome for gefitinib in patients with exon 21 L858R substitution mutation

exon 19 deletion mutation:
HR for OS with dacomitinib versus gefitinib, 0.847
median OS 36.7 months versus 30.8 months: Benefit not significant

exon 21 L858R substitution :
HR for OS with dacomitinib versus gefitinib 0.665
median OS 32.5 months versus 23.2 months

Maintained benefit of dacomitinib over gefitinib in terms of PFS and OS in patients who received dose reductions



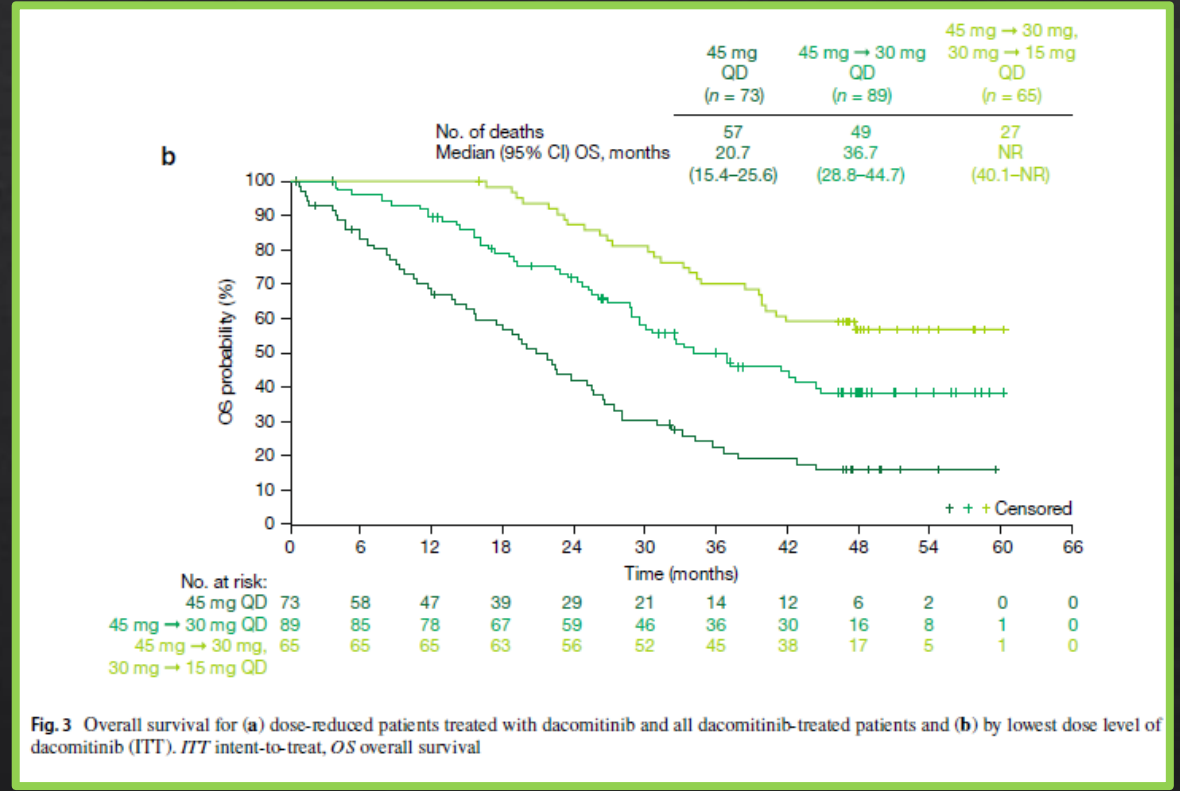


Fig. 3 Overall survival for (**a**) dose-reduced patients treated with dacomitinib and all dacomitinib-treated patients and (**b**) by lowest dose level of dacomitinib (ITT). *ITT* intent-to-treat, *OS* overall survival

HR for OS in patients with dose reduction(s) in the dacomitinib arm compared with all patients in the gefitinib arm: 0.554

Median OS: 42.5 months for patients with dose reduction(s) in the dacomitinib arm vs 34 months

Table 1 All causality treat-emergent adverse events in ≥ 20% of patients (any grade) and/or ≥ 2% grade 3 or 4 (safety population)

	Dacomitinib (n = 227)			Gefitinib (n = 224)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Diarrhea	199 (87.7)	19 (8.4)	0	125 (55.8)	2 (0.9)	0
Paronychia	140 (61.7)	18 (7.9)	0	45 (20.1)	3 (1.3)	0
Dermatitis acneiform	112 (49.3)	31 (13.7)	0	64 (28.6)	0	0
Stomatitis	99 (43.6)	8 (3.5)	0	41 (18.3)	1 (0.4)	0
Decreased appetite	74 (32.6)	8 (3.5)	0	57 (25.4)	2 (0.9)	0
Weight decreased	67 (29.5)	7 (3.1)	0	43 (19.2)	1 (0.4)	0
Dry skin	64 (28.2)	3 (1.3)	0	39 (17.4)	0	0
ALT increased	53 (23.3)	2 (0.9)	0	90 (40.2)	19 (8.5)	1 (0.4)
Alopecia	53 (23.3)	0	0	29 (12.9)	0	0
AST increased	49 (21.6)	1 (0.4)	0	84 (37.5)	10 (4.5)	1 (0.4)
Cough	47 (20.7)	0	0	45 (20.1)	2 (0.9)	0
Pruritus	47 (20.7)	1 (0.4)	0	32 (14.3)	3 (1.3)	0
Conjunctivitis	46 (20.3)	0	0	10 (4.5)	0	0
Rash	41 (18.1)	10 (4.4)	0	26 (11.6)	0	0
Asthenia	32 (14.1)	5 (2.2)	0	30 (13.4)	4 (1.8)	0
Dyspnea	32 (14.1)	5 (2.2)	1 (0.4)	31 (13.8)	4 (1.8)	0
Rash maculopapular	29 (12.8)	12 (5.3)	0	27 (12.1)	1 (0.4)	0
Dermatitis	25 (11.0)	5 (2.2)	0	9 (4.0)	1 (0.4)	0
Hypokalemia	25 (11.0)	10 (4.4)	2 (0.9)	13 (5.8)	4 (1.8)	0
Rash pustular	15 (6.6)	8 (3.5)	0	3 (1.3)	0	0
Pleural effusion	6 (2.6)	5 (2.2)	0	6 (2.7)	1 (0.4)	0
Lymphocyte count decreased	5 (2.2)	5 (2.2)	0	3 (1.3)	0	0
Hypertension	19 (8.4)	4 (1.8)	0	21 (9.4)	7 (3.1)	0
Anemia	27 (11.9)	3 (1.3)	0	18 (8.0)	5 (2.2)	0
Hepatic function abnormal	5 (2.2)	2 (0.9)	0	8 (3.6)	5 (2.2)	0

ALT alanine aminotransferase, *AST* aspartate aminotransferase

most frequently reported AEs of any grade in patients on Dacomitinib

diarrhea 87.7%
paronychia 61.7%
dermatitis acneiform 49.3%
stomatitis 43.6%

ARCHER 1050 toxicity

most frequently reported AEs of any grade in patients on gefitinib

diarrhea, 55.8%
alanine aminotransferase (ALT) increased 40.2%
aspartate aminotransferase (AST) increased 37.5%

ARCHER 1050 Safety

Parameter	Dacomitinib (n = 227)	Gefitinib (n = 224)
Median time to dose reduction, mos (range)	2.8 (0.3-20.3)	3.3 (1.2-25.7)
Median duration of dose reduction, mos (range)	11.3 (0.1-33.6)	5.2 (0.3-17.8)
Dacomitinib reduction to 30 mg/day,* n (%)	88 (38.8)	NA
Dacomitinib reduction 15 mg/day,† n (%)	63 (27.8)	NA
Patients with dose reduction, n (%)	150 (66.5)	18 (8.0)
permanent discontinuation, n (%)	22 (10)	15 (6.7)

Patients were permitted to increase the dose after tolerating the lower dose and six patients had dose re-escalation

ARCHER 1050: Impact on Next Treatment

Survival With Next Therapy*	Dacomitinib (n = 227)	Gefitinib (n = 225)
Chemotherapy		
▪ Patients, n (%)	63 (27.8)	80 (35.6)
▪ Deaths, n/N (%)	35/63 (55.6)	47/80 (58.8)
▪ Median OS, mos (95% CI)	29.5 (25.1-37.7)	24.6 (21.3-29.1)
Third-generation EGFR TKI†		
▪ Patients, n (%)	22 (9.7)	25 (11.1)
▪ Deaths, n/N (%)	8/22 (36.4)	4/25 (16.0)
▪ Median OS, mos (95% CI)	36.7 (30.1-NR)	NR (NR-NR)
Other EGFR TKI		
▪ Patients, n (%)	20 (8.8)	19 (8.4)
▪ Deaths, n/N (%)	10/20 (50.0)	10/19 (52.8)
▪ Median OS, mos (95% CI)	34.7 (15.6-NR)	32.1 (20.5-NR)

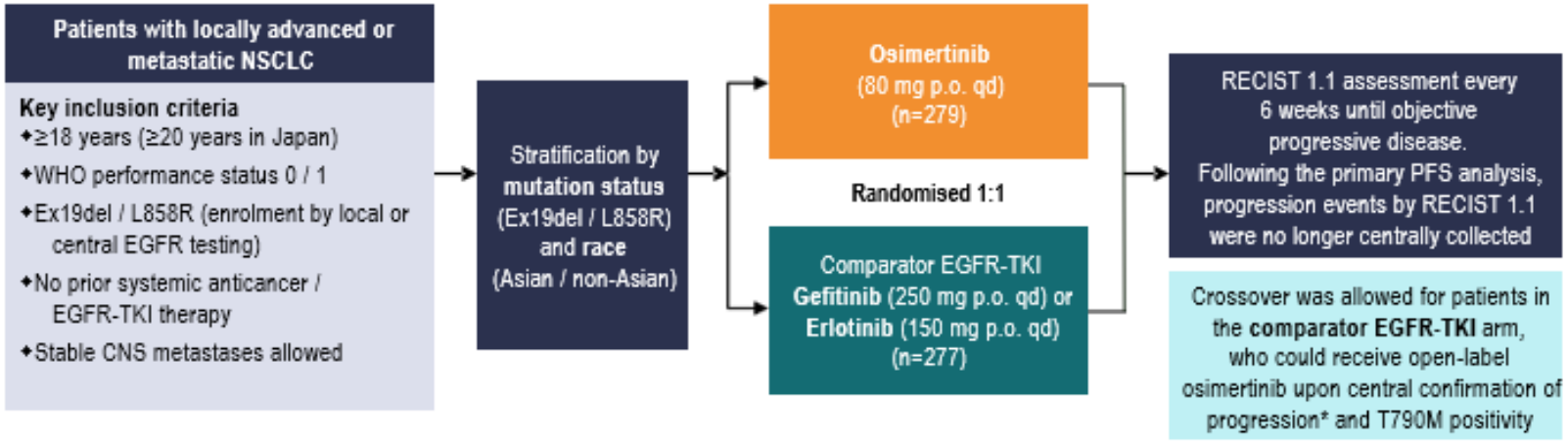
*Patient data censored after first subsequent treatment. Not prespecified subgroups.
†Includes osimertinib, olmutinib, rociletinib, avitinib, TAS-121, and unspecified.

Subsequent systemic therapies were received by 130 (57.3%) patients in the dacomitinib arm and 146 (64.9%) in the gefitinib arm

Only 10% patients received a subsequent third generation EGFR TKI

Osimertinib Efficacy

FLAURA DOUBLE-BLIND STUDY DESIGN

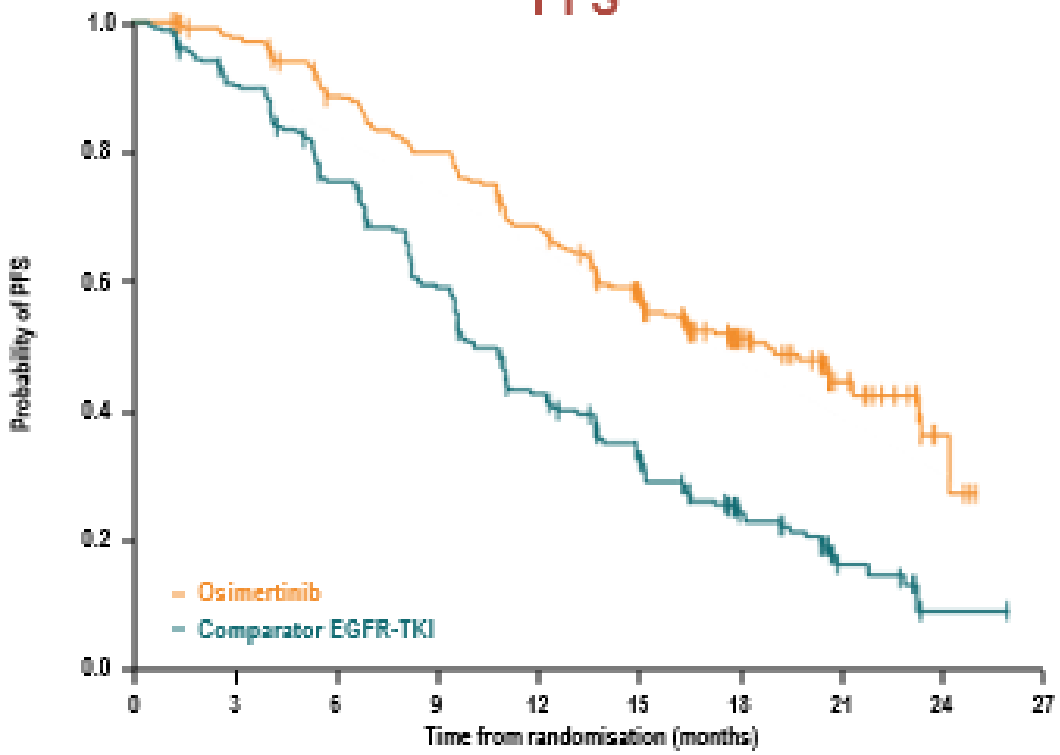


OS was a key secondary endpoint

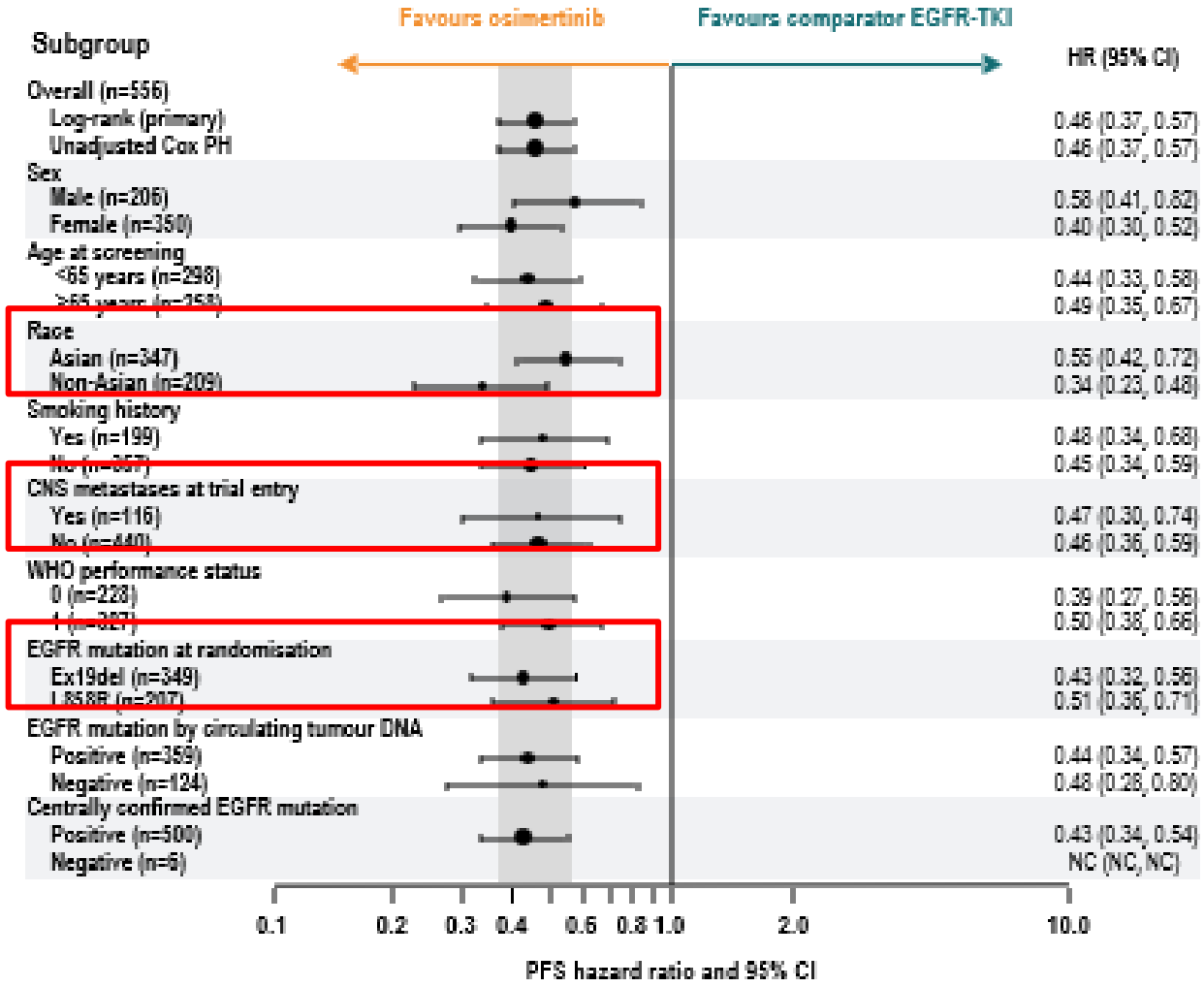
- Final OS analysis planned for when approximately 318 death events had occurred
- For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
  - Alpha spend for interim OS analysis was 0.0015
- At data cut-off, 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatmen t

Data cut-off: 25 June 2019
Soria et al. N Engl J Med 2018;378:113-25
*By investigator assessment if disease progression occurred after the primary analysis data cut-off
p.o., orally; qd, once daily; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

PFS



	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	18.9 (15.2, 21.4)	0.46 (0.37, 0.57); p<0.001
Comparator EGFR-TKI	10.2 (9.6, 11.1)	



Data cut-off: 12 June 2017

Soria et al. N Engl J Med 2018;378:113-25

CI, confidence interval; ctDNA, circulating tumour DNA; NC, not calculable; PH, proportional-hazards

FLAURA: Overall Survival

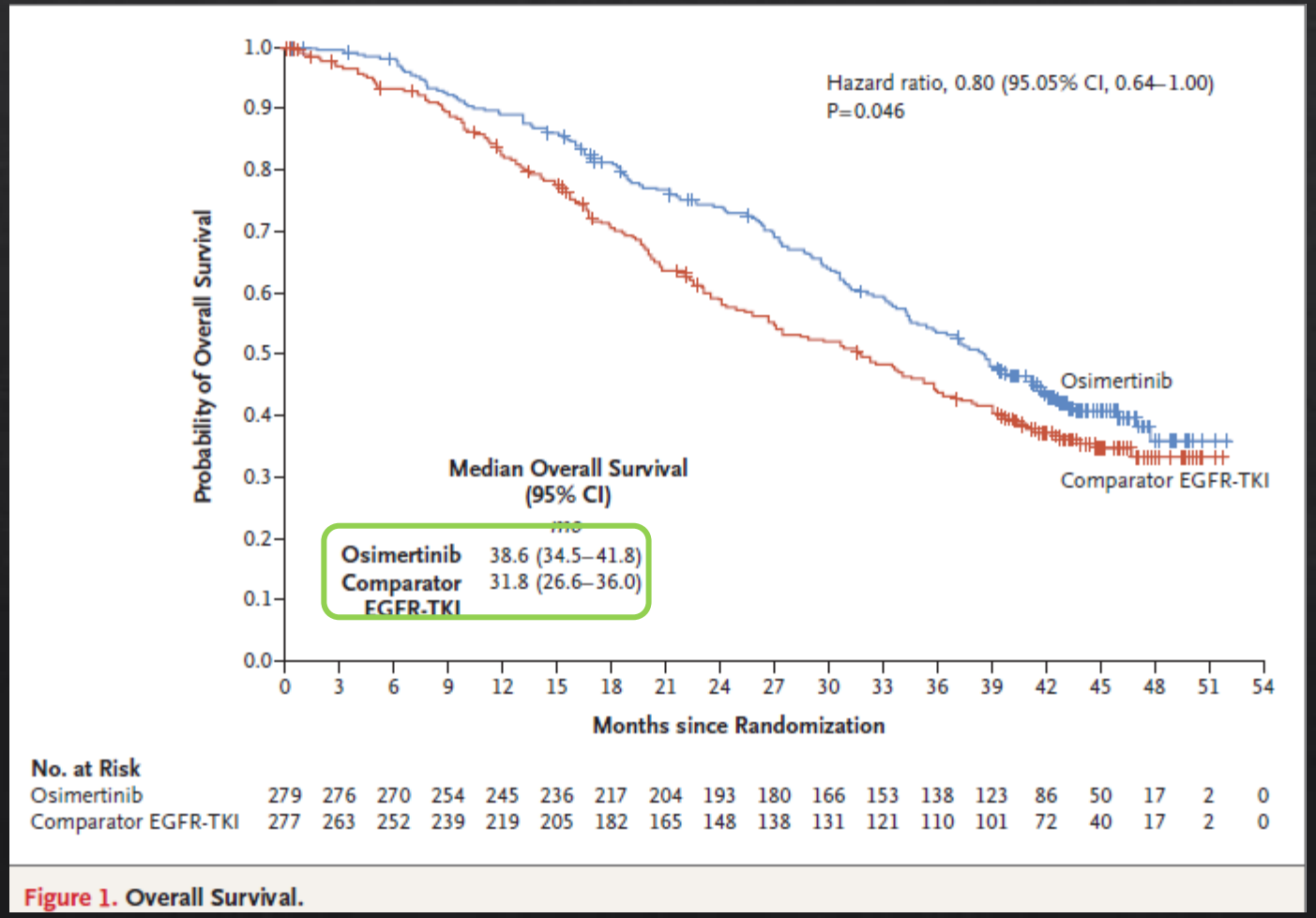


Figure 1. Overall Survival.

Table 1. Overall Survival and Continuation of First-Line Trial Drug.*

Variable	Osimertinib (N=279)	Comparator EGFR-TKI (N=277)
Overall survival — % (95% CI)		
At 12 mo	89 (85–92)	83 (77–87)
At 24 mo	74 (69–79)	59 (53–65)
At 36 mo	54 (48–60)	44 (38–50)
Patients continuing to receive first-line trial drug — no. (%)		
At 12 mo	194 (70)	131 (47)
At 24 mo	118 (42)	45 (16)
At 36 mo	78 (28)	26 (9)

* In the comparator group, patients received one of two tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR-TKI): gefitinib or erlotinib.

20% lower risk of death, even in the presence of crossover from the comparator group to the osimertinib group

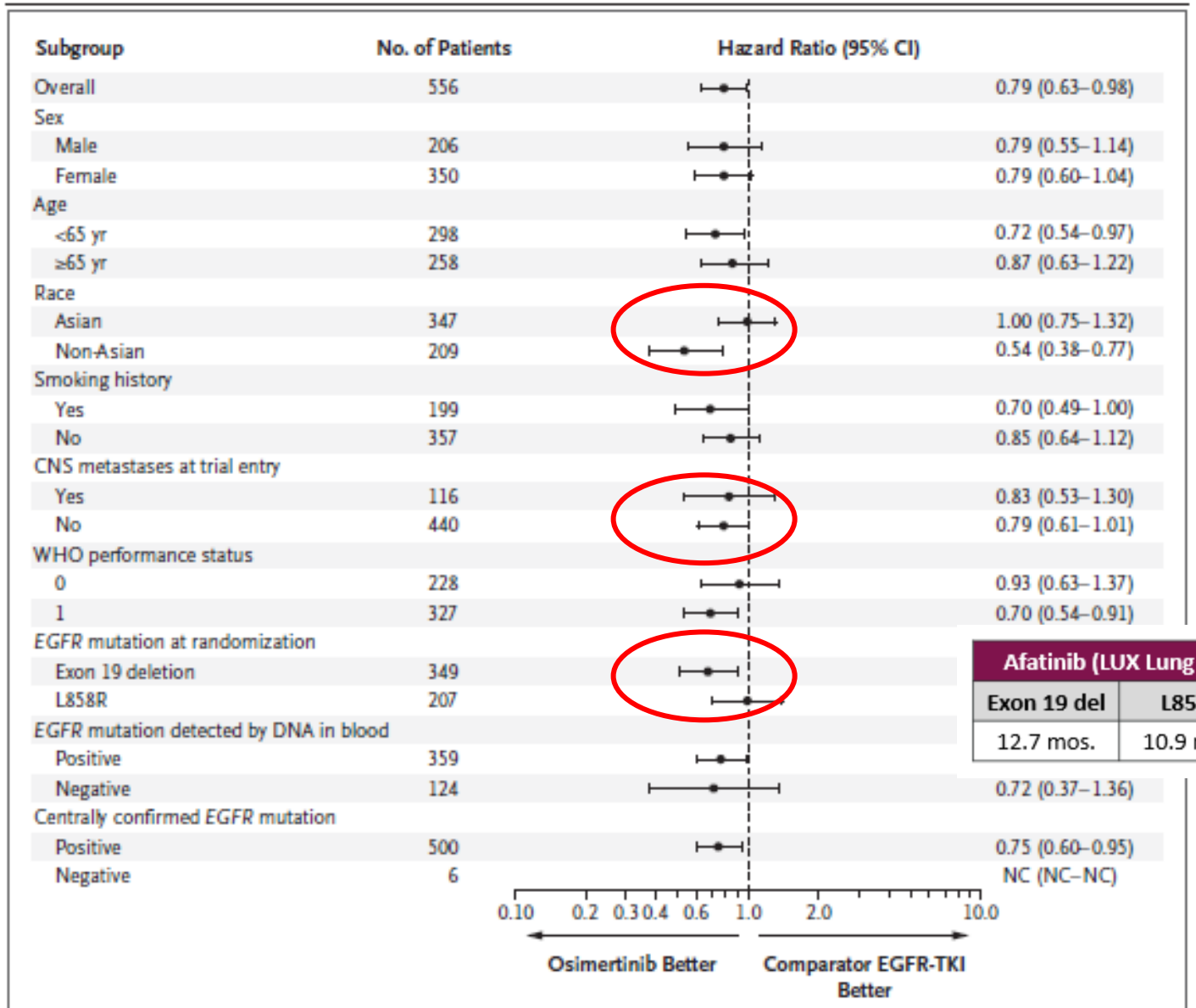


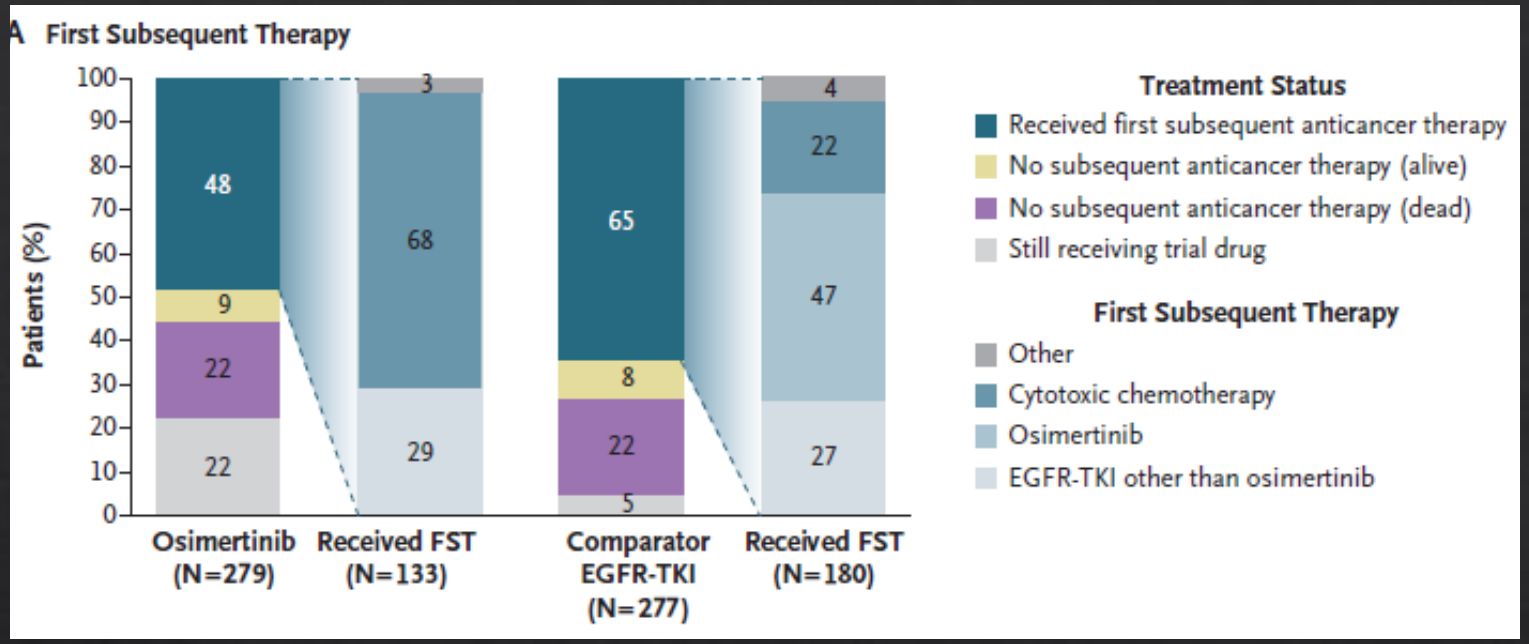
Figure 2. Subgroup Analyses of Overall Survival.

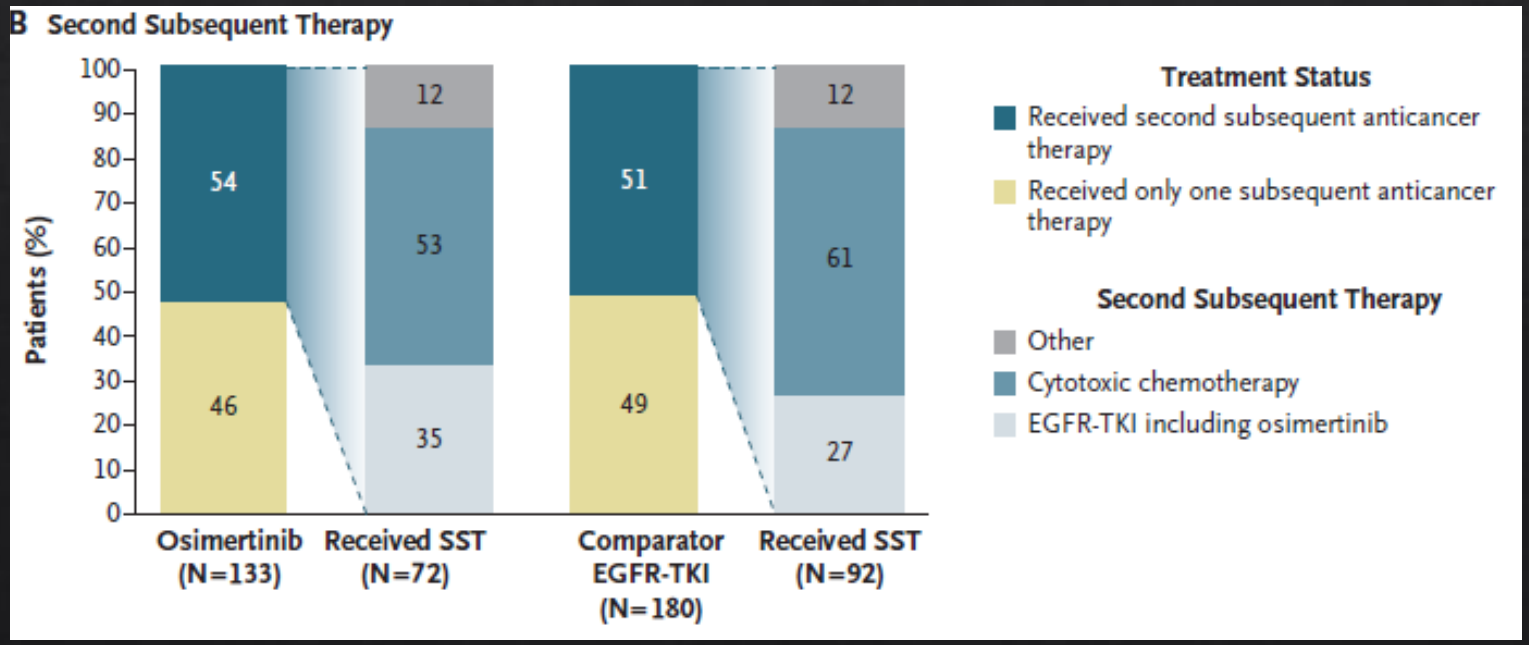
As a secondary end point, the trial and the analysis of the Asian subgroup of patients were not powered for overall survival analysis

Afatinib (LUX Lung 7) [1]	
Exon 19 del	L858R
12.7 mos.	10.9 mos.

Dacomitinib (ARCHER 1050) [2]	
Exon 19 del	L858R
16.5 mos.	12.3 mos.

Osimertinib (FLAURA) [3]	
Exon 19 del	L858R
21.4 mos.	**14.4 mos.**





Osimertinib arm: nearly 50% patients received 1st subsequent therapy: nearly 70% of those received chemotherapy

1st Gen EGFR TKI arm: 65% patients received 1st subsequent therapy, 47% received osimertinib

overall only 30% received osimertinib

50% patients in both arms went on to receive 2nd subsequent therapy

Osimertinib Toxicity

Most commonly reported adverse events :
rash or acne, diarrhea and dry skin

Adverse events of grade 3 or higher
42% of the patients in the osimertinib
47% of those in the comparator group

Rates of treatment discontinuation:
similar in the two groups, despite the longer duration of exposure to osimertinib

Table 2. Adverse Events.*

Adverse Event	Osimertinib (N=279)				Comparator EGFR-TKI (N=277)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
	number of patients (percent)							
Diarrhea	167 (60)	119 (43)	41 (15)	7 (3)	162 (58)	118 (43)	35 (13)	7 (3)
Rash or acne†	164 (59)	132 (47)	29 (10)	3 (1)	219 (79)	111 (40)	88 (32)	20 (7)
Nail effects†	108 (39)	61 (22)	45 (16)	2 (1)	95 (34)	58 (21)	35 (13)	2 (1)
Dry skin†	106 (38)	89 (32)	16 (6)	1 (<1)	102 (37)	78 (28)	21 (8)	3 (1)
Stomatitis	82 (29)	66 (24)	14 (5)	1 (<1)	60 (22)	51 (18)	8 (3)	1 (<1)
Decreased appetite	66 (24)	32 (11)	27 (10)	7 (3)	58 (21)	29 (10)	24 (9)	5 (2)
Cough	60 (22)	42 (15)	18 (6)	0	50 (18)	33 (12)	17 (6)	0
Nausea	55 (20)	37 (13)	18 (6)	0	55 (20)	31 (11)	23 (8)	0
Constipation	51 (18)	42 (15)	9 (3)	0	39 (14)	29 (10)	10 (4)	0
Pruritus	50 (18)	41 (15)	8 (3)	1 (<1)	44 (16)	30 (11)	14 (5)	0
Renal symptoms‡	50 (18)	32 (11)	13 (5)	3 (1)	32 (12)	24 (9)	7 (3)	1 (<1)
Fatigue	45 (16)	25 (9)	17 (6)	3 (1)	35 (13)	23 (8)	10 (4)	2 (1)
Anemia	44 (16)	22 (8)	15 (5)	7 (3)	27 (10)	19 (7)	5 (2)	3 (1)
Dyspnea	42 (15)	28 (10)	12 (4)	2 (1)	22 (8)	10 (4)	9 (3)	3 (1)
Vomiting	41 (15)	32 (11)	9 (3)	0	32 (12)	24 (9)	4 (1)	4 (1)
Headache	39 (14)	29 (10)	8 (3)	2 (1)	25 (9)	17 (6)	8 (3)	0
Back pain	36 (13)	22 (8)	14 (5)	0	29 (10)	15 (5)	14 (5)	0
Upper respiratory tract infection	36 (13)	20 (7)	16 (6)	0	23 (8)	12 (4)	11 (4)	0
Pyrexia	32 (11)	28 (10)	4 (1)	0	12 (4)	9 (3)	2 (1)	1 (<1)
Insomnia	31 (11)	23 (8)	8 (3)	0	21 (8)	12 (4)	9 (3)	0
Nasopharyngitis	31 (11)	17 (6)	14 (5)	0	16 (6)	11 (4)	5 (2)	0
Prolonged QT interval	28 (10)	12 (4)	12 (4)	4 (1)	12 (4)	7 (3)	3 (1)	2 (1)
Increase in aspartate aminotransferase	28 (10)	19 (7)	7 (3)	2 (1)	69 (25)	39 (14)	18 (6)	12 (4)
Musculoskeletal pain	28 (10)	19 (7)	9 (3)	0	14 (5)	8 (3)	6 (2)	0
Alopecia	22 (8)	18 (6)	4 (1)	0	35 (13)	31 (11)	4 (1)	0
Increase in alanine aminotransferase	19 (7)	11 (4)	6 (2)	2 (1)	74 (27)	30 (11)	19 (7)	21 (8)

* Listed are adverse events that were reported in at least 10% of the patients in either trial group. The safety analyses included all the patients

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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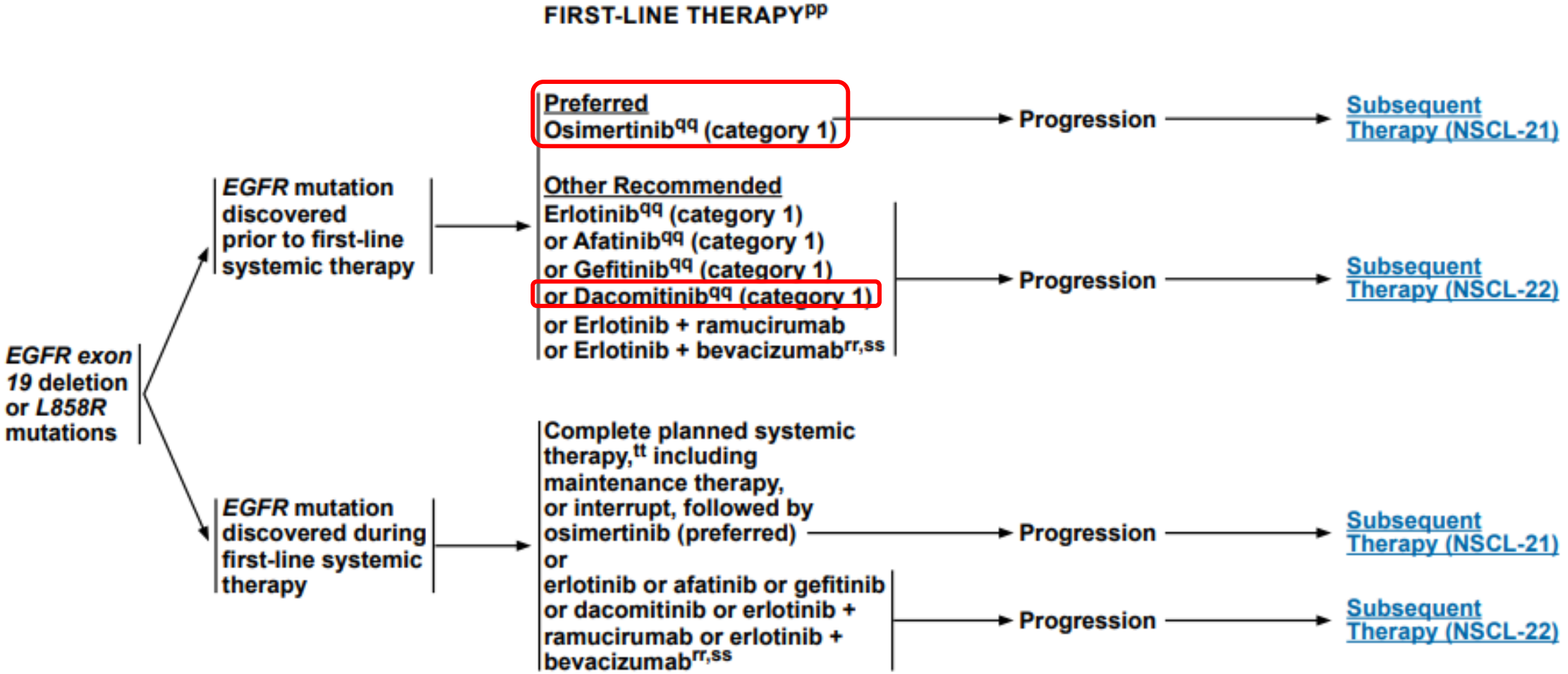
Discussion

EGFR EXON 19 DELETION OR *L858R* MUTATIONS[mm]



How to select patients ??? Which Approach?? Which Drug First ???

MORE QUESTIONS THAN ANSWERS

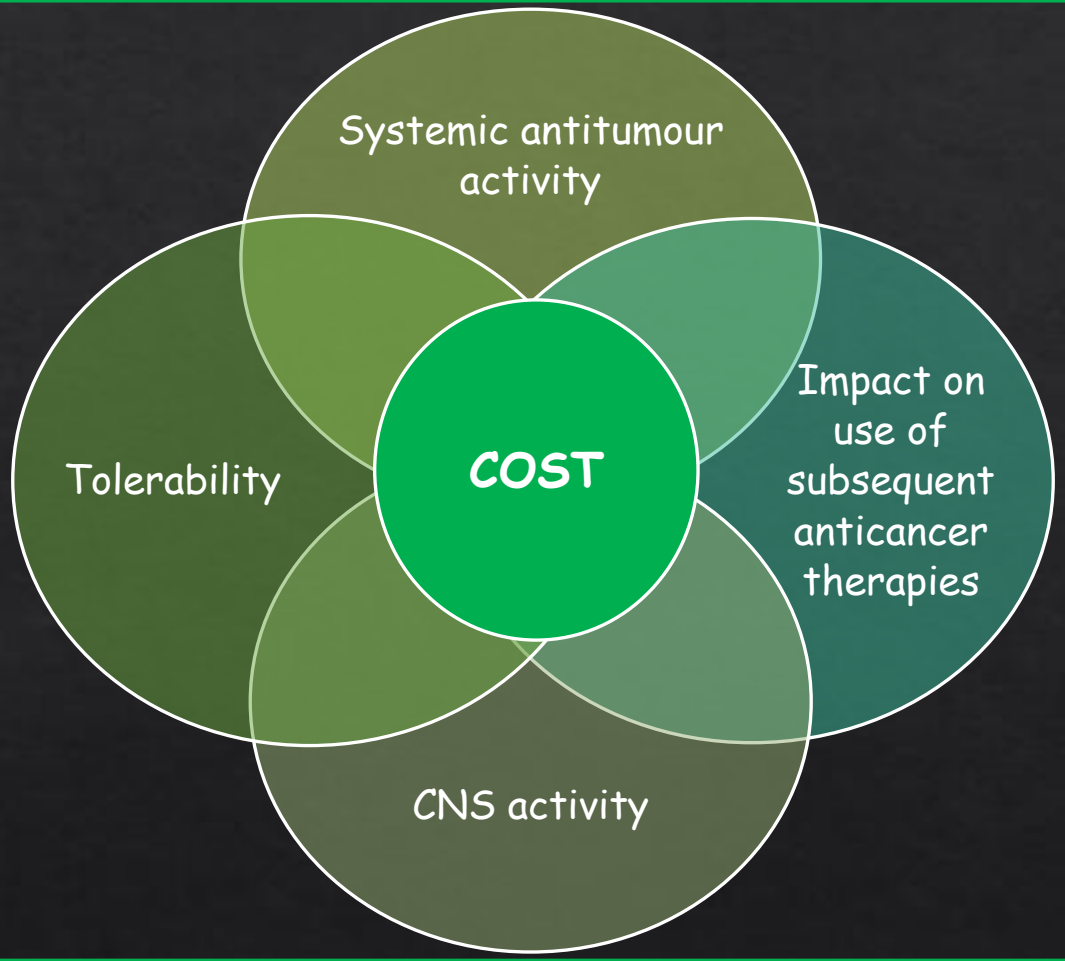
No one right answer

- Lack of a Randomised control trial comparing 2nd vs 3rd Generation EGFR TKIs
- Longer follow up of already completed pivotal Phase three trials may not add more information

- Sequential 2nd Gen TKI F/B 3rd Gen TKI versus upfront 3rd generation TKI approach
- Results of trials of Bi specific antibodies (and other drugs) after progression on all generation TKIs may further shed light on this

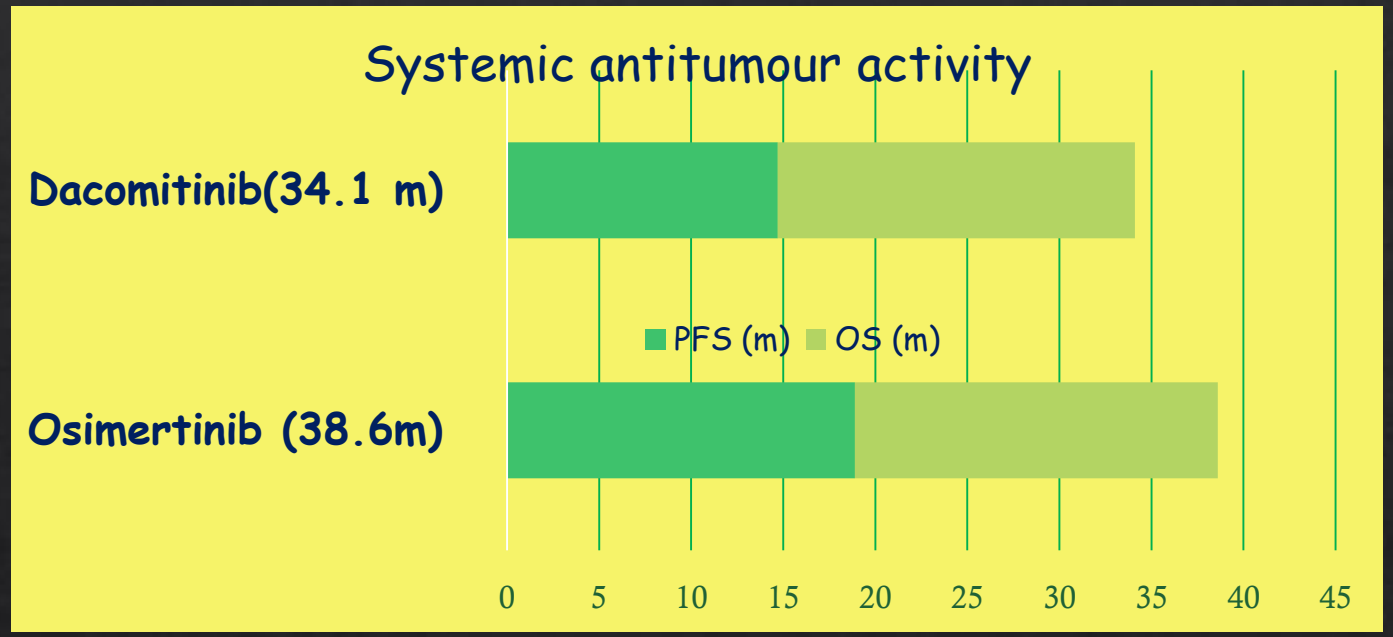
How do we decide the optimal first line agent ?

ECOG P/S
Age
Comorbidities
Drug interaction

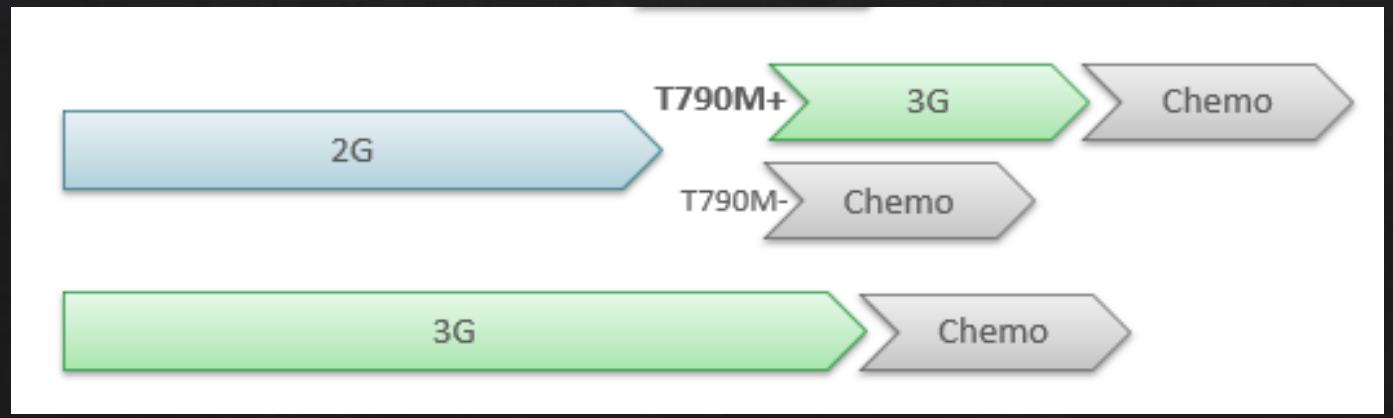


PERSONALISED APPROACH IS KEY !!!

Systemic anti tumour activity and impact on use of subsequent anticancer therapies

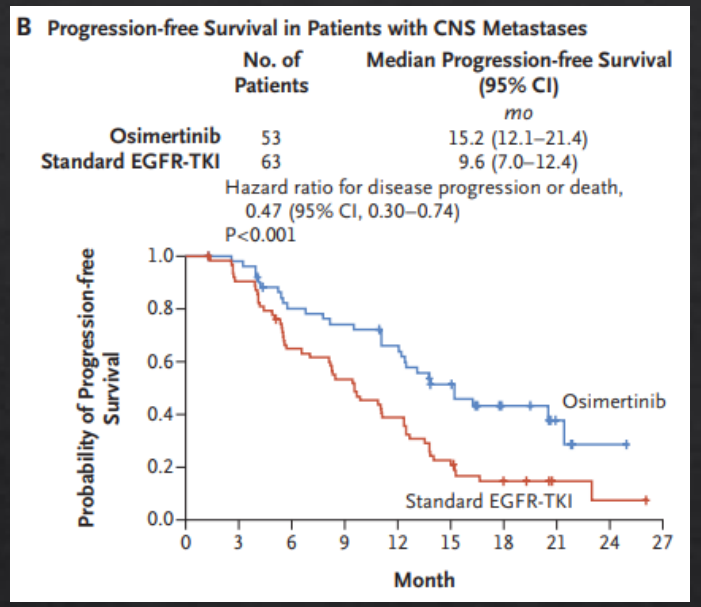


ORR 75% vs 80%



Only 10% patients received a subsequent third generation EGFR TKI !!

CNS activity



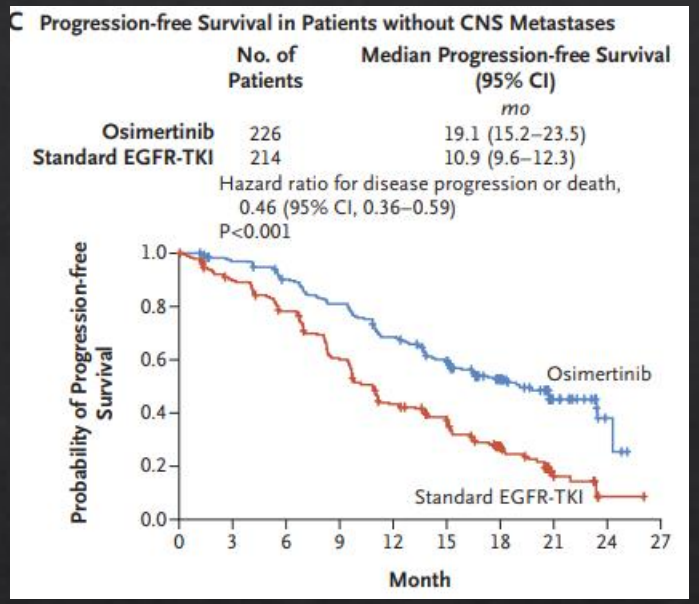
Progression-free survival at 18 months among patients with CNS metastases

58% in the osimertinib group

40% in the comparator group

hazard ratio for disease progression or death, 0.48; 95% CI, 0.26 to 0.86

Leptomeningeal: Which dose of Osimertinib??



Trial	LUX-Lung 7 (Afatinib)[1]	ARCHER 1050 (Dacomitinib)[2]	FLAURA (Osimertinib)[3]
Patients with CNS metastases	Included (16%)	Excluded	Included (~19%)
Median PFS	**7.2** vs 7.4 months (HR 0.76 ,p=0.93)	**Excluded**	**15.2** vs 9.6 months (HR=0.47, p<0.001)

Trial	N	Grade 3	Grade 4	Grade 5	Most common grade ≥3 AEs
LUX-Lung 7 (Afatinib)[1]	160	29%	2%	0	Diarrhoea, 13% Rash/acne, 9% Fatigue, 6%
ARCHER (Dacomitinib)[2]	227	51%	2%	10%	Acne, 14% Diarrhea, 8%
FLAURA (Osimertinib)[3]	279	30%	2%	N/A	Diarrhea, 2% Decreased appetite, 2%

Tolerability

Trial	Frequency of dose reductions
LUX-Lung 7 (Afatinib)[1]	41.9%
ARCHER 1050 (Dacomitinib)[2]	38% (Dose reduced to 30 mg)
	28% (Dose reduced to 15 mg)
FLAURA (Osimertinib)[3]	4%

Trial	Tx Discontinuation due to AE
LUX-Lung 7 (Afatinib)[1]	6%
ARCHER 1050 (Dacomitinib)[2]	10%
FLAURA (Osimertinib)[3]	13%


Tips & Tricks

Situation	Osimertinib	Dacomitinib
Pantoprazole/ PPI interaction	No interaction	Avoid concomitant use
Hydroxychloroquine	Increase QTc: avoid 4 months	No interaction
ATT	More interactions: use with caution/consider modification	No significant interaction
Relationship with food	With or without food	With or without food
Cardiac dysfunction	Needs more frequent monitoring	----
Uncommon mutations Afatinib is the only EGFR TKI currently approved for three types of uncommon EGFR mutations (p.G718X, p.S768I and p.L861Q) by the US FDA	Has activity in particular in the major uncommon alterations (G719X, L861Q and S768I) and can be considered as an alternative treatment	Further data needed for confirmation of activity, seems to benefit: one patient with a D770delinsGY mutation had PR and three patients had SD (Exon 20). In another trial, 1 pt exon 18 G719C and exon 20 S768I mutations had an objective response

Dacomitinib toxicity management

Interstitial lung disease (ILD) *[see Warnings and Precautions (5.1)]*	Any Grade	• Permanently discontinue VIZIMPRO.
Diarrhea *[see Warnings and Precautions (5.2)]*	Grade 2	• Withhold VIZIMPRO until recovery to less than or equal to Grade 1; then resume VIZIMPRO at the same dose level. • For recurrent Grade 2 diarrhea, withhold until recovery to less than or equal to Grade 1; then resume VIZIMPRO at a reduced dose.
	Grade 3 or 4	• Withhold VIZIMPRO until recovery to less than or equal to Grade 1; then resume VIZIMPRO at a reduced dose.
Dermatologic Adverse Reactions *[see Warnings and Precautions (5.3)]*	Grade 2	• Withhold VIZIMPRO for persistent dermatologic adverse reactions; upon recovery to less than or equal to Grade 1, resume VIZIMPRO at the same dose level. • For recurrent persistent Grade 2 dermatologic adverse reactions, withhold until recovery to less than or equal to Grade 1; then resume VIZIMPRO at a reduced dose.
	Grade 3 or 4	• Withhold VIZIMPRO until recovery to less than or equal to Grade 1; then resume VIZIMPRO at a reduced dose.
Other	Grade 3 or 4	• Withhold VIZIMPRO until recovery to less than or equal to Grade 2; then resume VIZIMPRO at a reduced dose.

Dacomitinib: other important clinical points

- Pregnancy: use effective contraception during treatment and for at least 17 days after the final dose

- Geriatric: higher incidence of Grade 3 and 4 adverse reactions (67% versus 56%, respectively), more frequent dose interruptions (53% versus 45%, respectively), and more frequent discontinuations (24% versus 10%, respectively) for adverse reactions in patients 65 years or older

- Renal impairment: Recommended dose has not been established for patients with severe renal impairment (CLcr <30 mL/min)
- Liver impairment: No dose adjustment is recommended in patients with mild (total bilirubin ≤ upper limit of normal [ULN] with AST > ULN or total bilirubin > 1 to 1.5 × ULN with any AST) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment. The recommended dose has not been established for patients with severe hepatic impairment (total bilirubin > 3 to 10 × ULN and any AST)

Osimertinib toxicity management

Table 1 Recommended Dose Modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	QTc[↑] interval greater than 500 msec on at least 2 separate ECGs[b]	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.
	QTc interval prolongation with signs/symptoms of life threatening arrhythmia	Permanently discontinue TAGRISSO.
	Asymptomatic, absolute decrease in LVEF[c] of 10% from baseline and below 50%	Withhold TAGRISSO for up to 4 weeks. • If improved to baseline LVEF, resume. • If not improved to baseline, permanently discontinue.
	Symptomatic congestive heart failure	Permanently discontinue TAGRISSO.
Other	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).

Osimertinib: other important clinical points

- Cardiac: Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval.
- Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation, 3 month intervals while on treatment

- Pregnancy: Advise females of reproductive potential to use effective contraception during treatment and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Geriatric: Exploratory analysis suggest a higher incidence of Grade 3 and 4 adverse reactions (32% versus 25%) and more frequent dose modifications for adverse reactions (23% versus 17%) in patients 65 years or older as compared to those younger than 65 years

- Renal: no recommended dose for patients with severe renal impairment (CLcr <30 mL/min) or end-stage-renal disease
- Hepatic: no recommended dose for TAGRISSO for patients with moderate or severe hepatic impairment
- Liquid diet or through RT: Disperse tablet in 4 tablespoons (approximately 50 mL) of non-carbonated water only. Stir until tablet is completely dispersed and swallow or administer through naso-gastric tube immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube

Patient education regarding toxicities: information sheets

General Precautions for Skin Care to be followed

- Avoid exposure to sunlight
- Wear protective clothing (including hat, sunglasses, etc.).
- Use broad-spectrum sunscreen with an SPF of ≥30 and reapply as necessary. UVA light can penetrate glass; therefore, sunscreen should also be worn indoors and in vehicles if exposed to direct sunlight. In case of oily skin, to consider using water based sunscreens
- Apply skin moisturizer on dry areas of the body regularly after bathing, and as needed
    - Creams and ointments are preferred over gels, lotions and oils, e.g. Venusia max cream.
    - Use alcohol-free moisturizing creams
    - Apply moisturizer to nails as well
- Avoid habits/products that can produce dry skin (e.g., hot water, alcohol-based cosmetics)
    - Use lukewarm water when bathing, and limit showers to 15 minutes or less.
    - Use fragrance-free soaps to wash your skin, moisturizers to prevent dryness, and detergents to wash clothes.
    - Avoid washing dishes by hand. If you must, try to wear rubber gloves while doing so
    - Avoid Hand sanitizer
- Wear soft shoes that are not tight on your toes. Avoid activities that could injure your fingers or toes
- During Shaving
    - Avoid excessive beard growth
    - Shave with regular shaving razor, sharp multiblade: change frequently, keep clean
    - Use pre-shaving cream emollients and moisturizing aftershave
    - Don't use alcohol and aftershave or electric shaver

In case of development of loose stools

Dietary modification:

- stop milk and milk products
- drink 8 to 10 glasses of clear fluids/ ORS/ water daily
- stop protein supplements (if taking)
- eat soft, frequent bland meals (banana, rice, toast, khichdi etc)

General precautions:

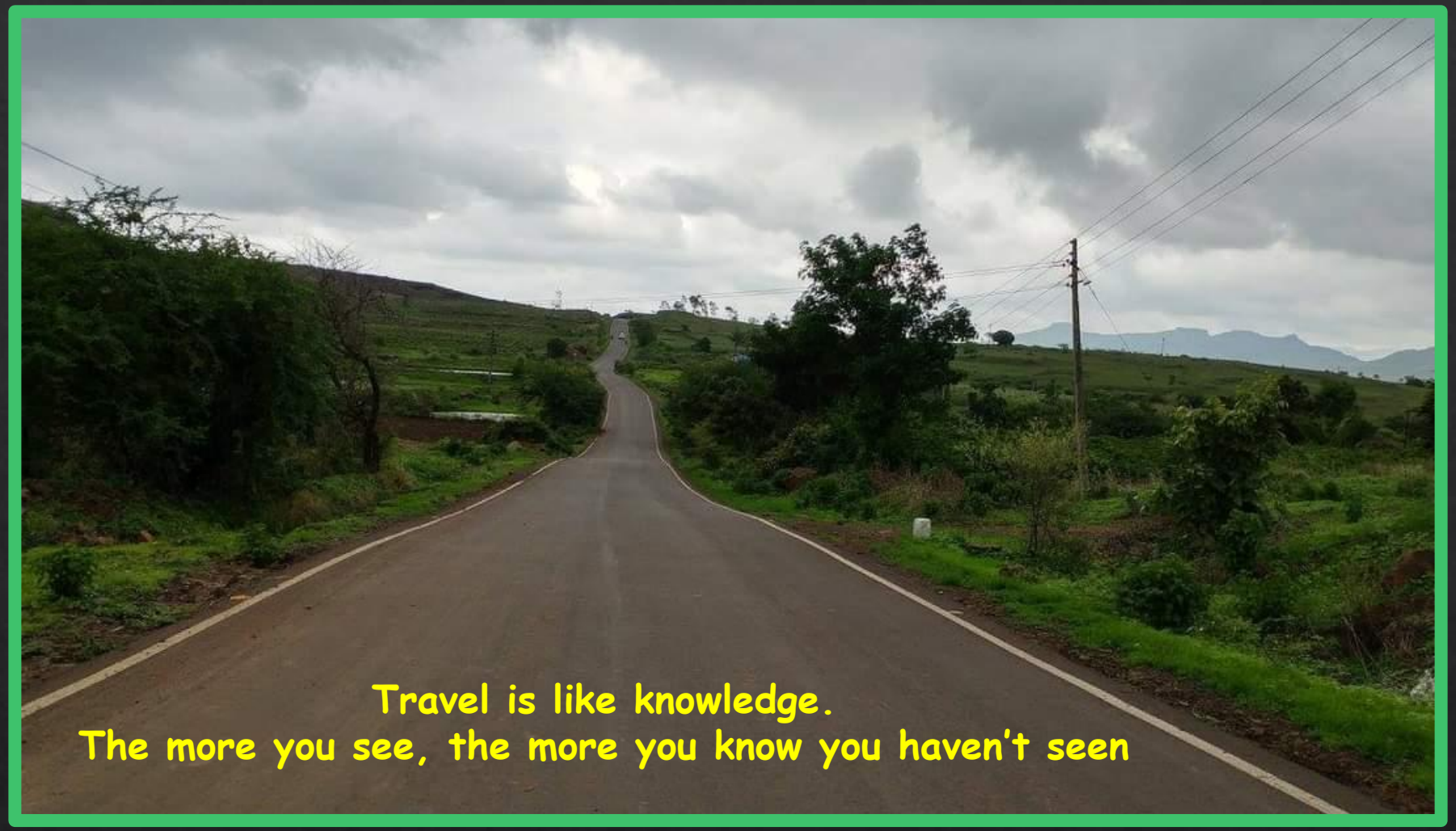
- Inform study physician/ coordinator immediately
- Monitor stool frequency and urine output
- Watch for dizziness, other danger signs as below: to rush to hospital if any of the signs present

Medications:

- Tab Immodium (loperamide) 4 mg at first loose stool, F/B 2 mg every 4 hours after each unformed stools
- Econorm sachet twice a day x 3 days
- Please note: to take Immodium only if none of the below mentioned danger signs are present. To rush to hospital if and danger signs develop
- If no improvement after 3 doses or if any danger signs develop: to stop immodium and review with investigator/ casualty
- Tab Rifagut 200 mg thrice a day x 3 days
- Tab Graniset 1 mg once a day x 3 days then as needed (for nausea)
- Cap Redotril 100 mg thrice a day x 3 days, then as needed

Danger signs:

- Pain abdomen/ cramping abdomen
- Fever
- Blood in stools
- Decreased urine outp
- More than 2 episodes of vomiting


Travel is like knowledge.
The more you see, the more you know you haven't seen

Thank you