Old soldiers never die, just still alive!
(Old soldiers: 2nd-G EGFR-TKIs)

Osaka International Cancer Institute
Motohiro Tamiya

COI

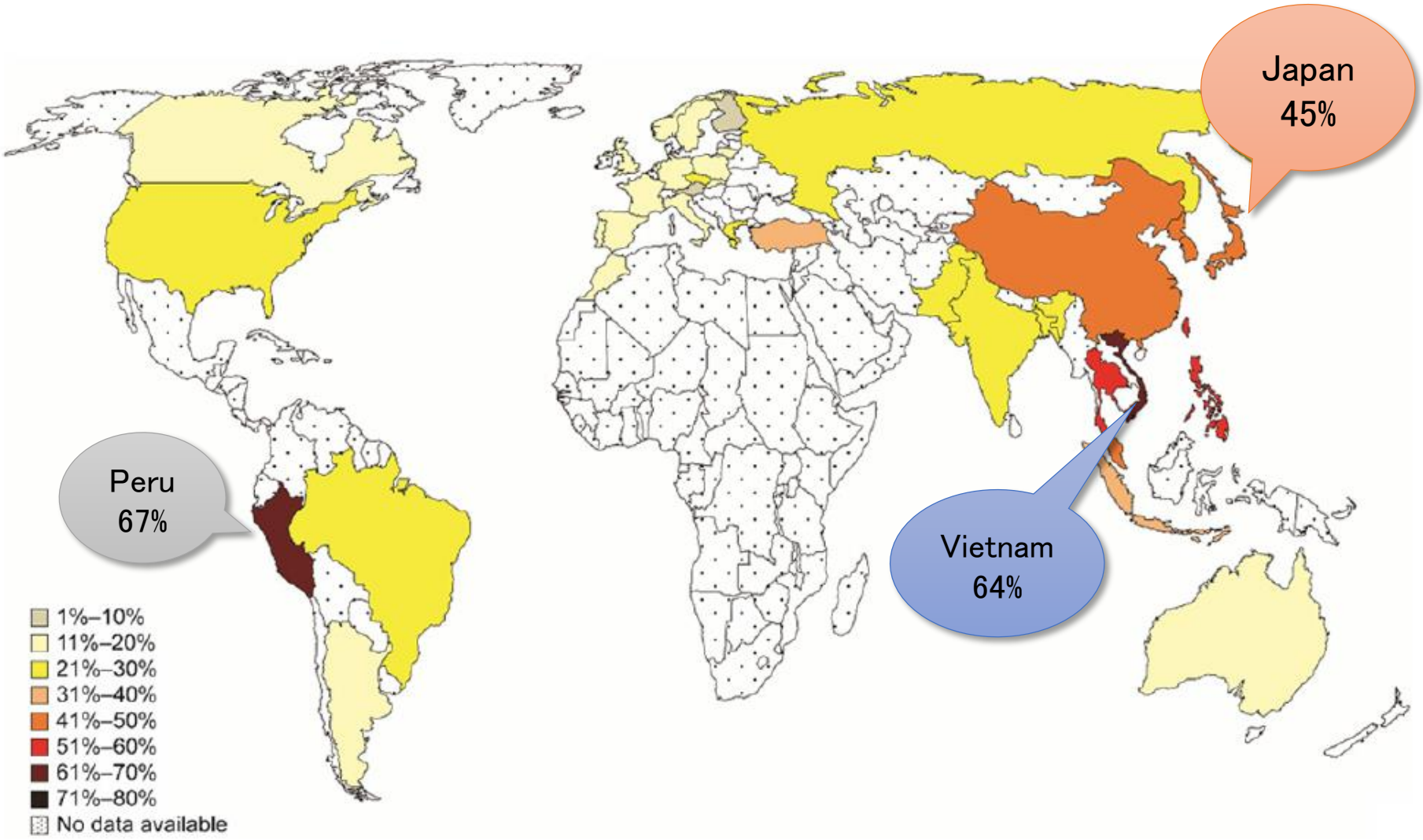
- Lecture

  Boehringer Ingelheim, Chugai Pharmaceutical, AstraZeneca, Taiho Pharmaceutical, Eli Lilly, Asahi Kasei Pharmaceutical, MSD, Ono Pharmaceutical, Bristol-Myers Squibb

- Research

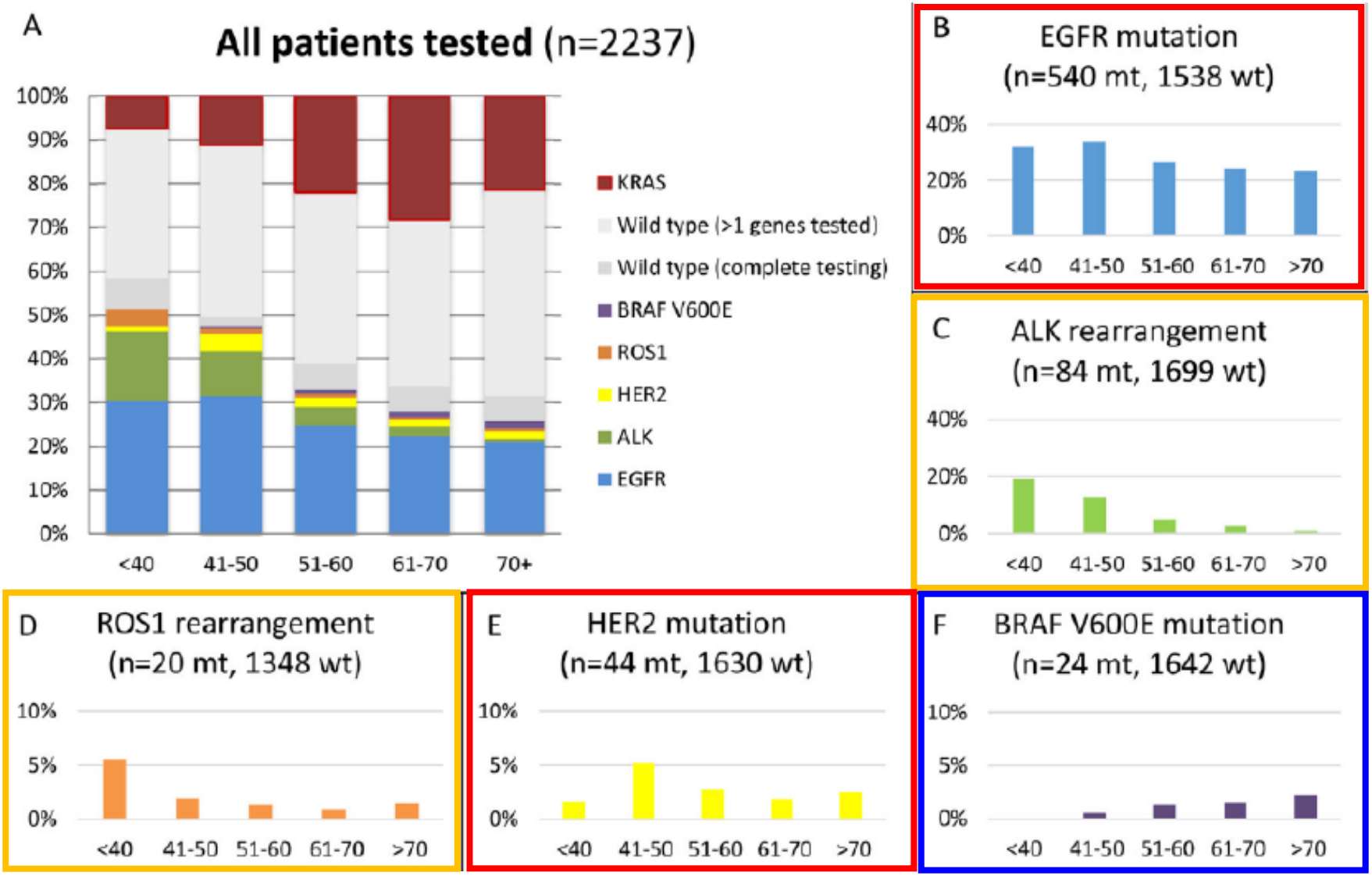
  Boehringer Ingelheim, Ono Pharmaceutical, Bristol-Myers Squibb

Frequency of EGFR mutation in each country (A global *EGFR* mut Map)



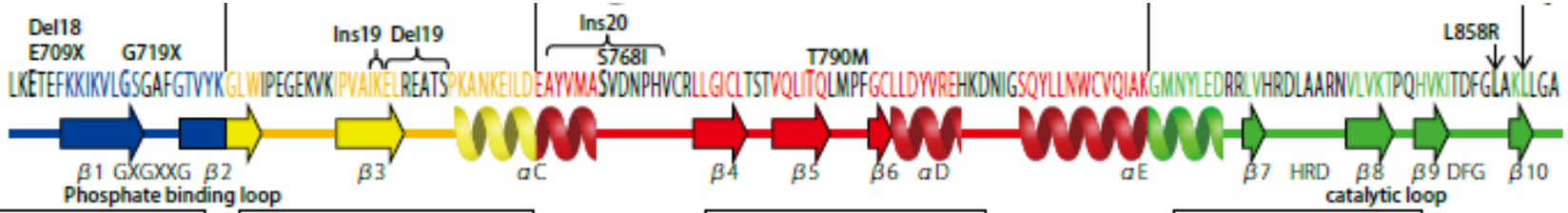
Anita Midha et al. Am J Cancer Res 2015;5(9):2892-2911

Age of onset by driver mutation



JAMA Oncol 2016 5;1;2(3);3113-320

Type and frequency of EGFR mutation



G719X (3.1%)	
G719A	27
G719A+S768I/L861Q/L861R	11
G719S	25
G719S+S768I/L861Q/E709A	13
G719C	12
G719C+S768I/E709K/E709H	9
others	3

E709X (0.3%)	
E709K+G719S/G719C/L858R	44
E709A+G719S/G719E	33
others	22

Del 18 (0.3%)	
delE709_T710insD	100

Del 19 (44.8%)	
delE746_A750	67
delL747_P753insS	8
delL747_T751	5
delL747_A750insP	3
delL747_S752	3
delE746_S752insV	2
delE746_P753insVS	1
delL747_T751insP	1
delE746_T751insA	1
delL747_P753	1
delS752_I759	1
others	8

Ins 19 (0.6%)	
I744_K745insKIPVAI	58
K745_E746insIPVAIK	26
K745_E746insVPVAIK	11
K745_E746insTPVAIK	5

Ins 20 (5.8%)	
V769_D770insASV	20
D770_N771insSVD	19
H773_V774insH	8
A763_Y764insFQEA	7
H773_v774insPH	5
H773_V774insNPH	4
N771_P772insN	3
H773_V774insAH	3
D770delinsGY	2
V774_C775insHV	2
others	25

S768I (1.1%)

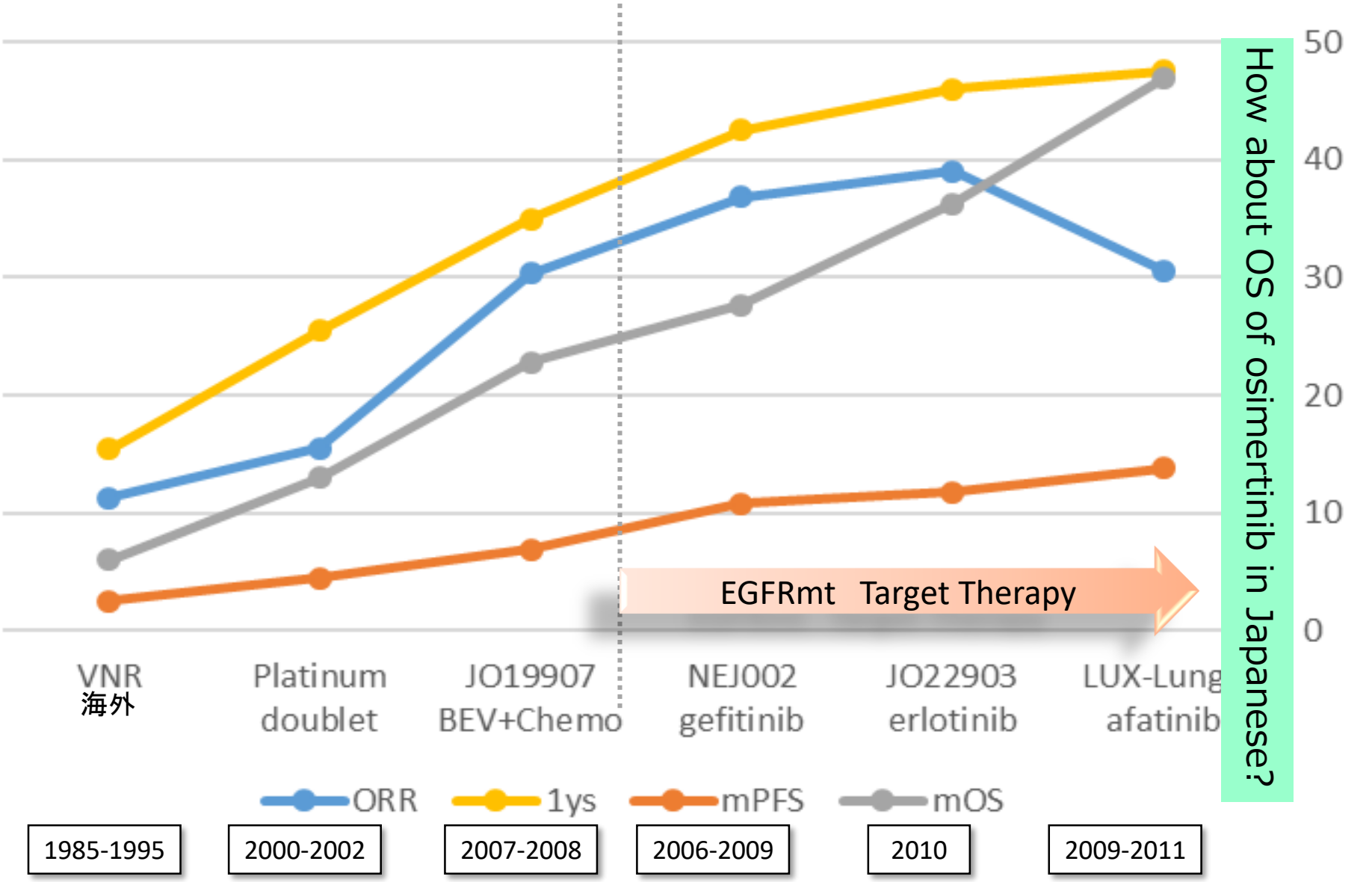
L858R (39.8%)

L861Q (0.9%)

Del19: 44.8%, L858R: 39.8%

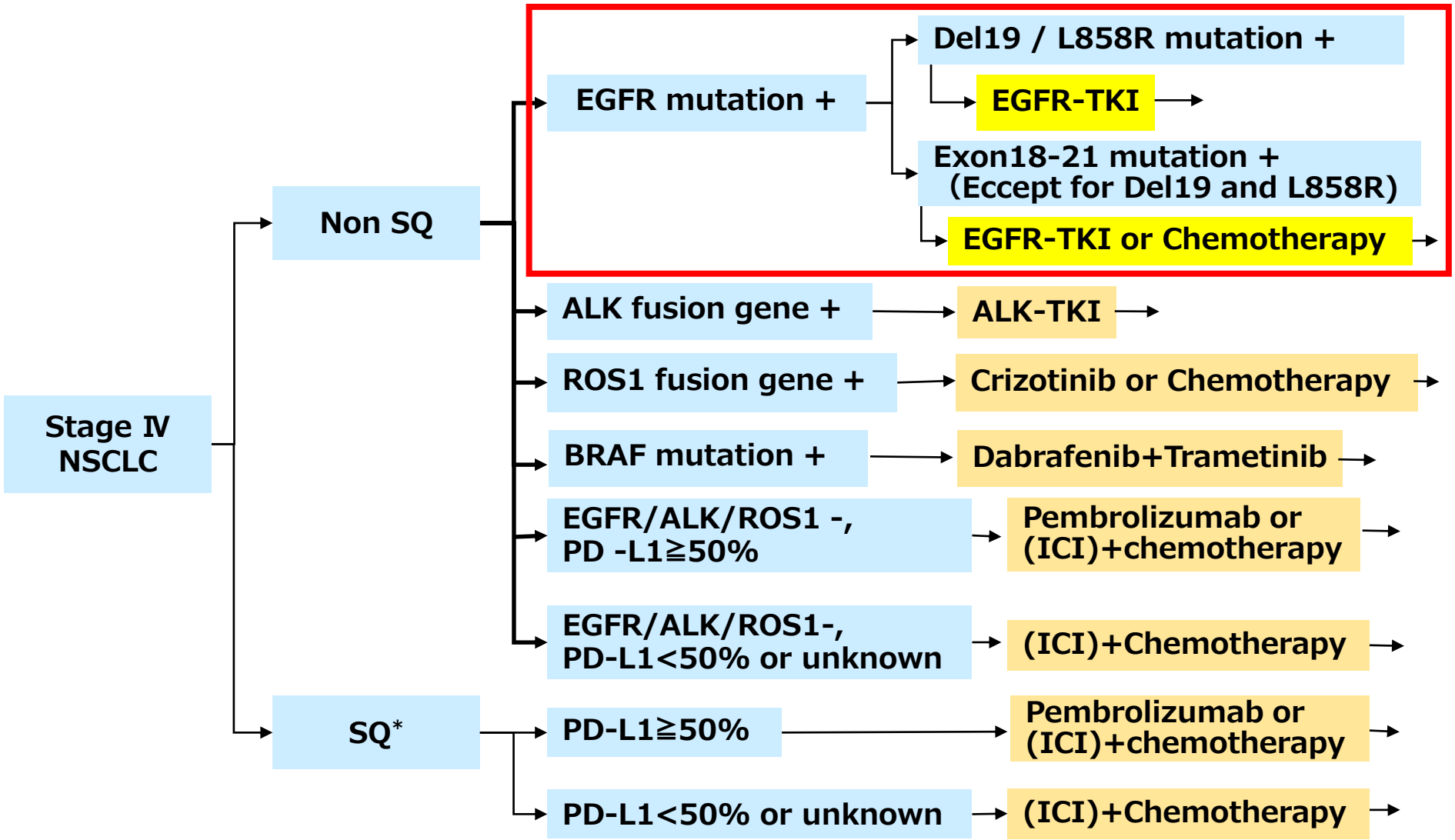
The guideline of EGFR mutation examination: The Japan Lung Cancer Society

The outcome of improved Japanese NSCLC



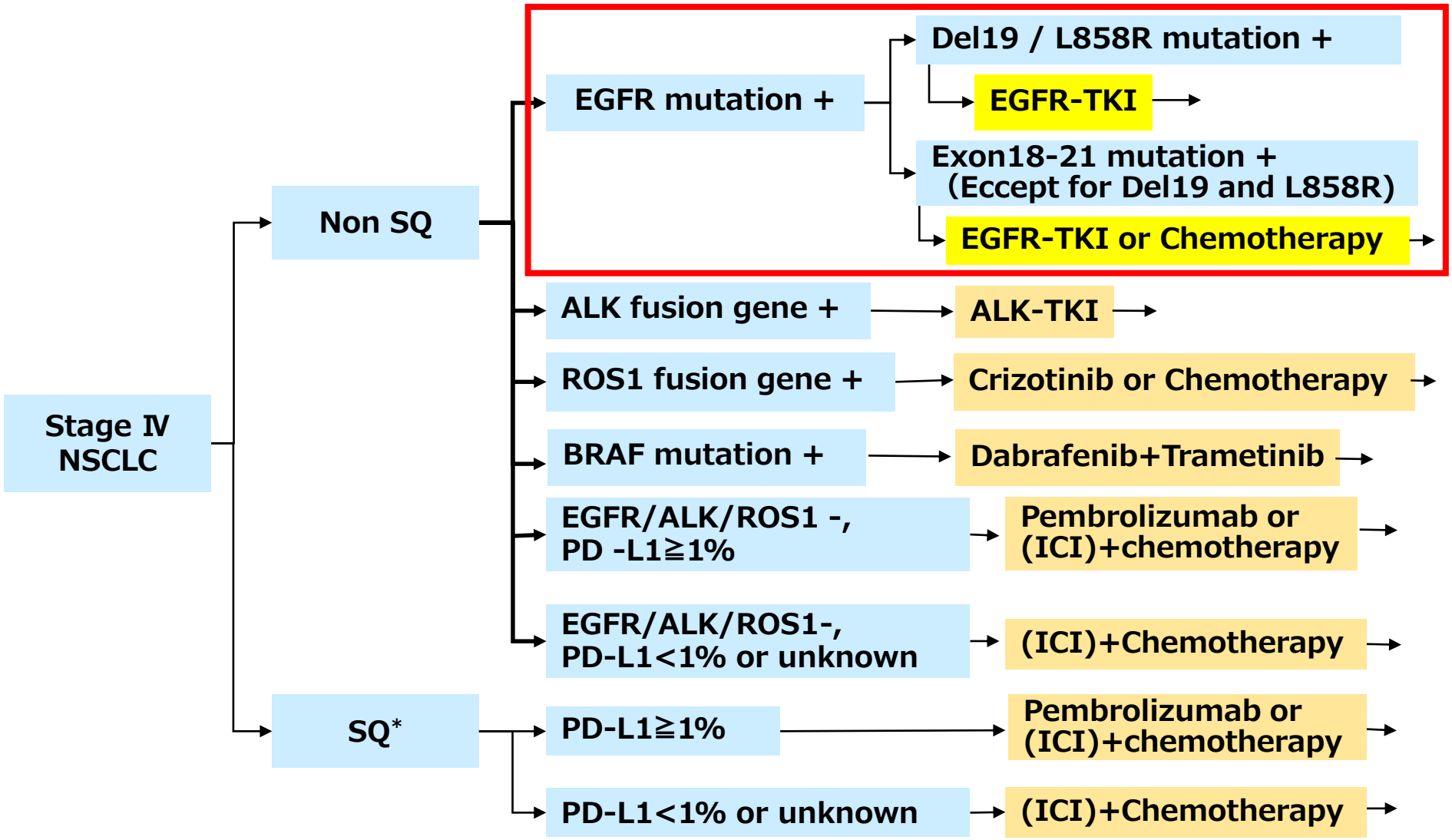
Juian S. Oncologist 2000, Ohe Y. Ann Oncol 2007, Niho S. Lung Cancer 2012, Maemondo M. N Engl J Med 2010
Inoue A. Ann Oncol 2013, Goto K. Lung Cancer 2013, Yamamoto N. Int J Clin Oncol 2016, Kato T. Cancer Sci 2016

1st line treatment for stage IV NSCLC



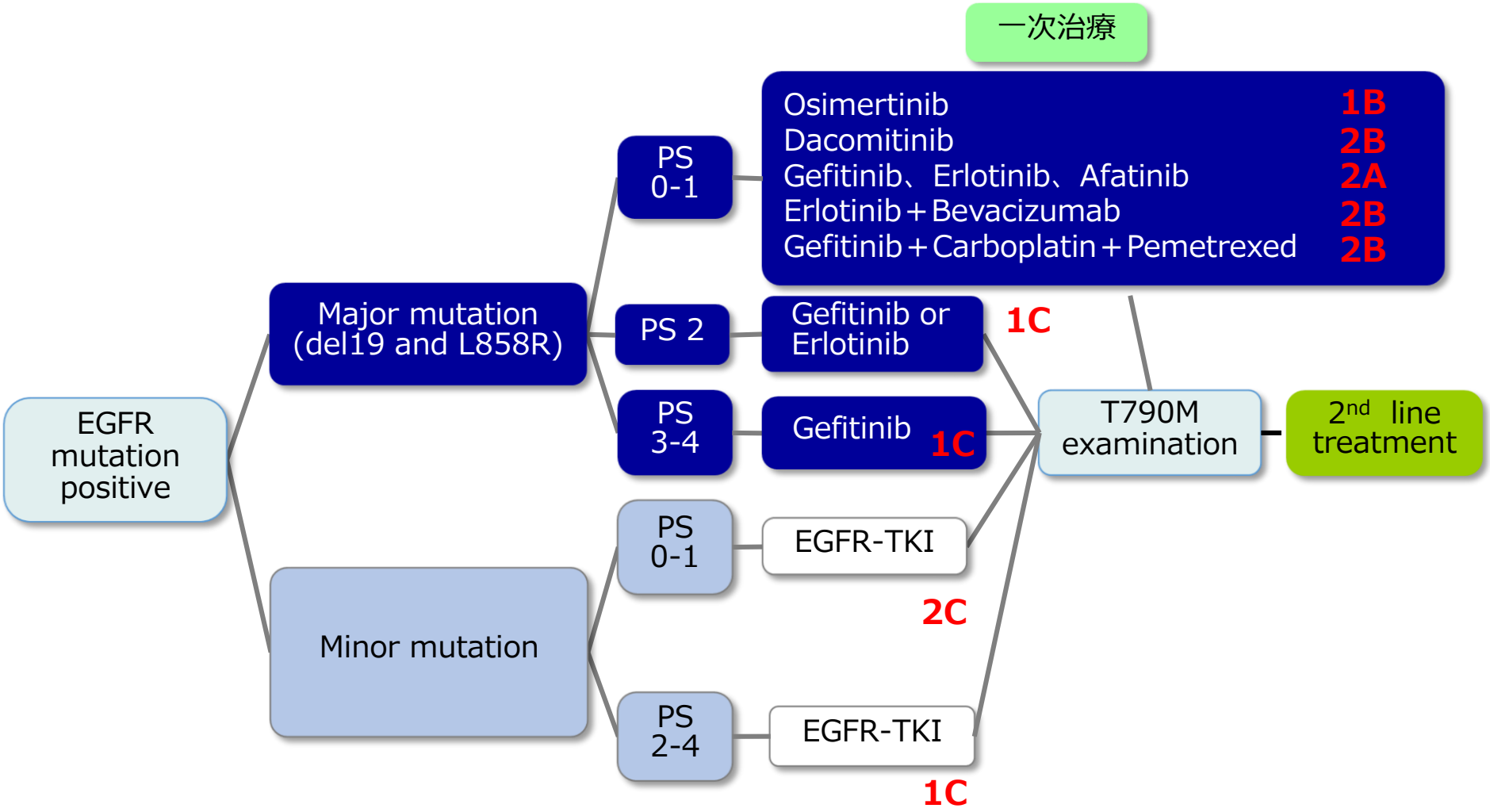
The guideline of lung cancer treatment: The Japan Lung Cancer Society

1st line treatment for stage IV NSCLC



The guideline of lung cancer treatment: The Japan Lung Cancer Society

Lung cancer guideline (StageIV) 2018



Japan Lung Cancer Society. Lung cancer treatment guideline (Stage IV version) 2018

Sensitivities of each EGFR-TKIs

Table 2. Summary of the *in vitro* sensitivities of Ba/F3 cells expressing each EGFR mutation to various TKI

Exon	Category	Mutations	First generation		Second generation			Third generation	
			Gefitinib	Erlotinib	Afatinib	Dacomitinib	Neratinib	Osimertinib	Rociletinib
18	Del18	delE709_T710insD	882	884	1.7	29	27	93	999
	E709X	E709K	187	215	0.7	16	6	62	706
	G719X	G719A	213	167	0.9	6	1.1	53	214
19	Del19	delE746_A750	4.8	4.9	0.9	<1	60	1.1	19
	Del19	delE746_S752insV	306	14	0.2	1.4	86		
	Del19	delL747_A750insP	7.4	13	1	1.6	30		
	Del19	delL747_P753insS	4.1	5.4	2	1.9	38		
	Del19	delS752_I759	35	7.9	0.2	2	6.7		
	Ins19	I744_K745insKIPVAI	400		7				
	Ins19	K745_E746insTPVAIK	100		0.9				
20	Ins20	A763_Y764insFQEA	174	48	3.7			44	673
	Ins20	Y764_V765insHH	>1000	3845	79			237	1730
	Ins20	M766_A767insAI		3403	79				
	Ins20	V769_D770insASV	3100	4400	72	230	48	333	5290
	Ins20	D770_N771insNPG	3356	3700	72		230	42	262
	Ins20	D770_N771insSVD		3187	86				
	Ins20	H773_V774insH		>10 000	268		550		
	S768I	S768I	315	250	0.7			49	
	T790M	T790M+delE746_A750	8300	>10 000	64	140		3	28
	T790M	T790M+L858R	>10 000	>10 000	119	300		21	13
21	L858R	L858R	26	16	4	2.6	1.4	9	140
	L861Q	L861Q	170	103	0.5		3.3	9	
EGFR wild type with interleukin-3			9350	>10 000	>100	>1000	>1000	3078	1549
Plasma drug concentration			(448–2717)	(2717–4040)	(69–130)	(166–238)	(N/A–132)	(400–600)	N/A–N/A

IC50 values (nM) of <10, 10–99, 100–999 and ≥1000 are shown in blue, light blue, yellow and red, respectively. When the exact value was not described in the literature, the approximate number was estimated from each figure. IC90 values are described in del709_T710insD, E709K, G719A and wild type. EGFR, epidermal growth factor receptor; N/A, not availabe TKI, tyrosine kinase inhibitors.

Kobayashi Yoshihisa. et. al. Cancer Science

Today's contents

Considerations in 1st-Line Treatment

- Review FLAURA study and consider of 2nd-G EGFR-TKI potential based on subgroup analysis of FLAURA
- Real world evidence on 1st line EGFR-TKIs treatment on our hospital (Japanese experience) and best sequence of EGFR-TKI.

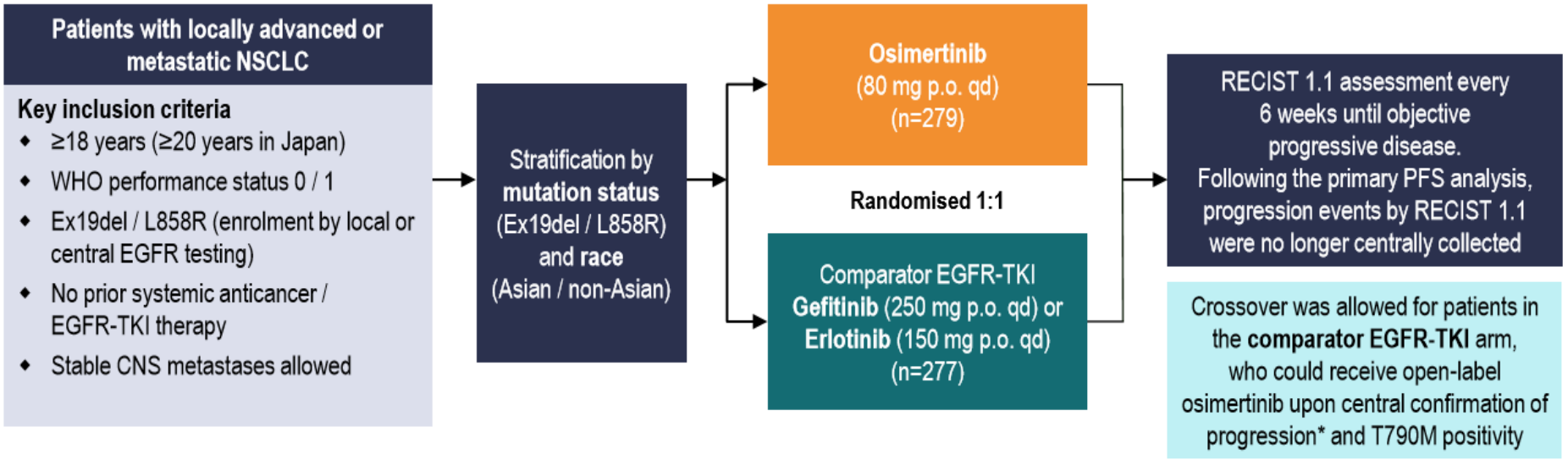
Today's contents

Considerations in 1st-Line Treatment

- Review FLAURA study and consider of 2nd-G EGFR-TKI potential based on subgroup analysis of FLAURA.
- Real world evidence on 1st line EGFR-TKIs treatment on our hospital (Japanese experience) and best sequence of EGFR-TKI.

FLAURA study

FLAURA DOUBLE-BLIND STUDY DESIGN



OS was a key secondary endpoint

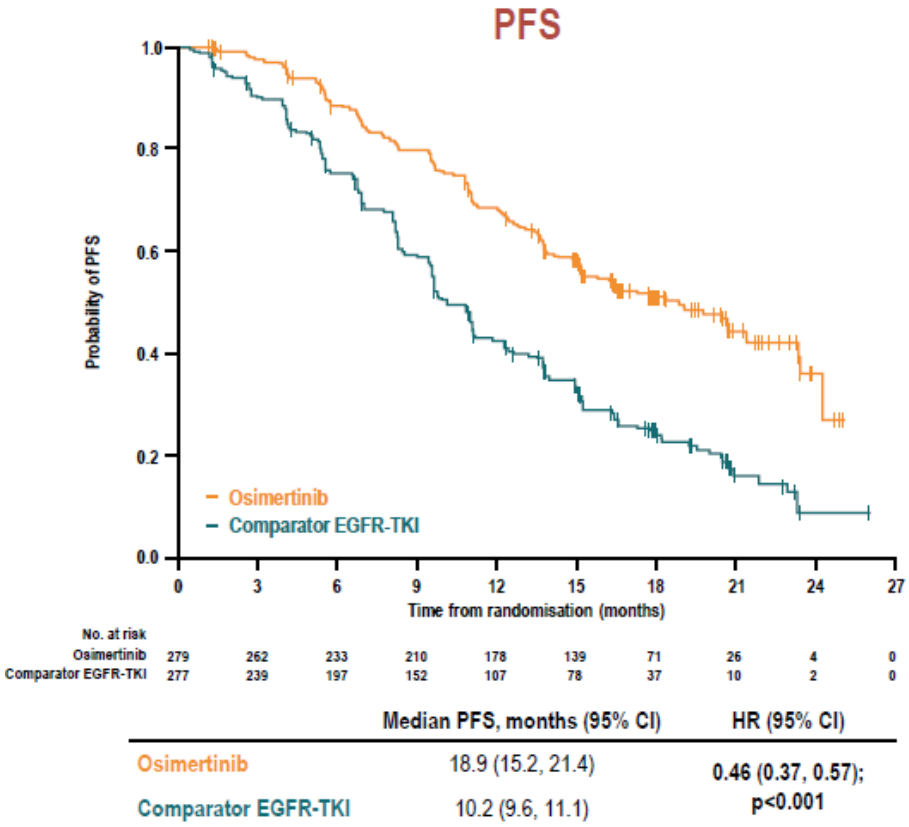
- Final OS analysis planned for when approximately 318 death events had occurred
- For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
  - Alpha spend for interim OS analysis was 0.0015
- At data cut-off, 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatment

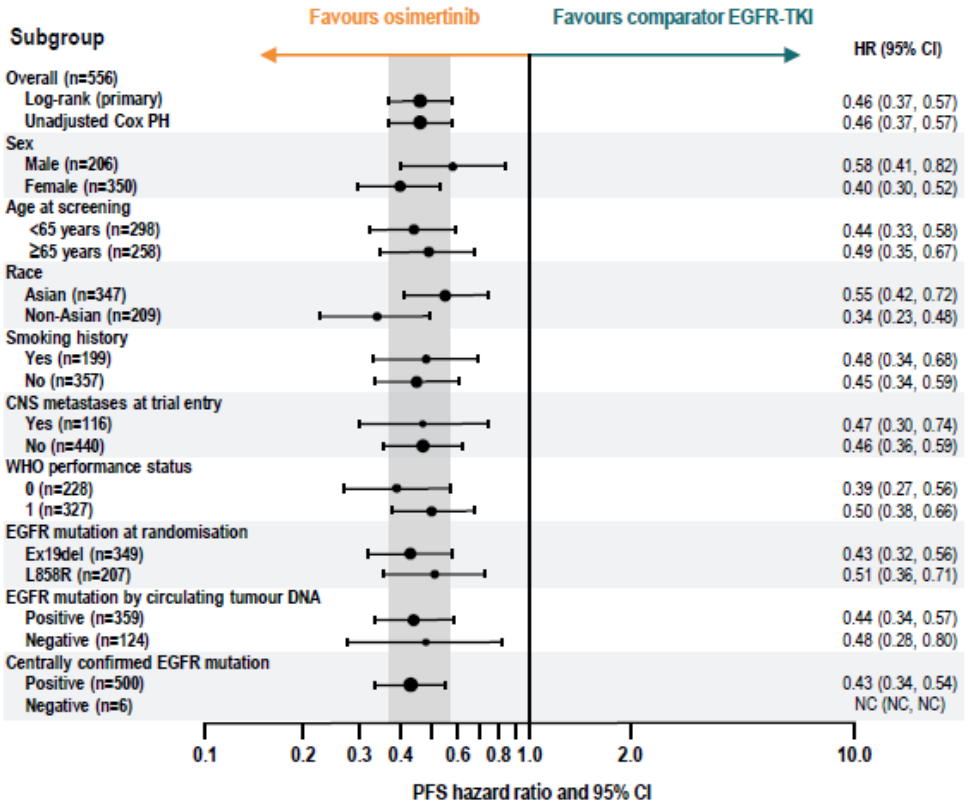
J.-C. Soria, et al. NEJM,2017

FLAURA: PFS［primary endpoint］

	N	Median PFS、M（95% CL）
Osimertinib group	279	18.9 （15.2～21.4）
Standard TKI group	277	10.2 （9.6～11.1）

HR: 0.46（95% CL : 0.37～0.57）
p＜0.001





ESMO2019

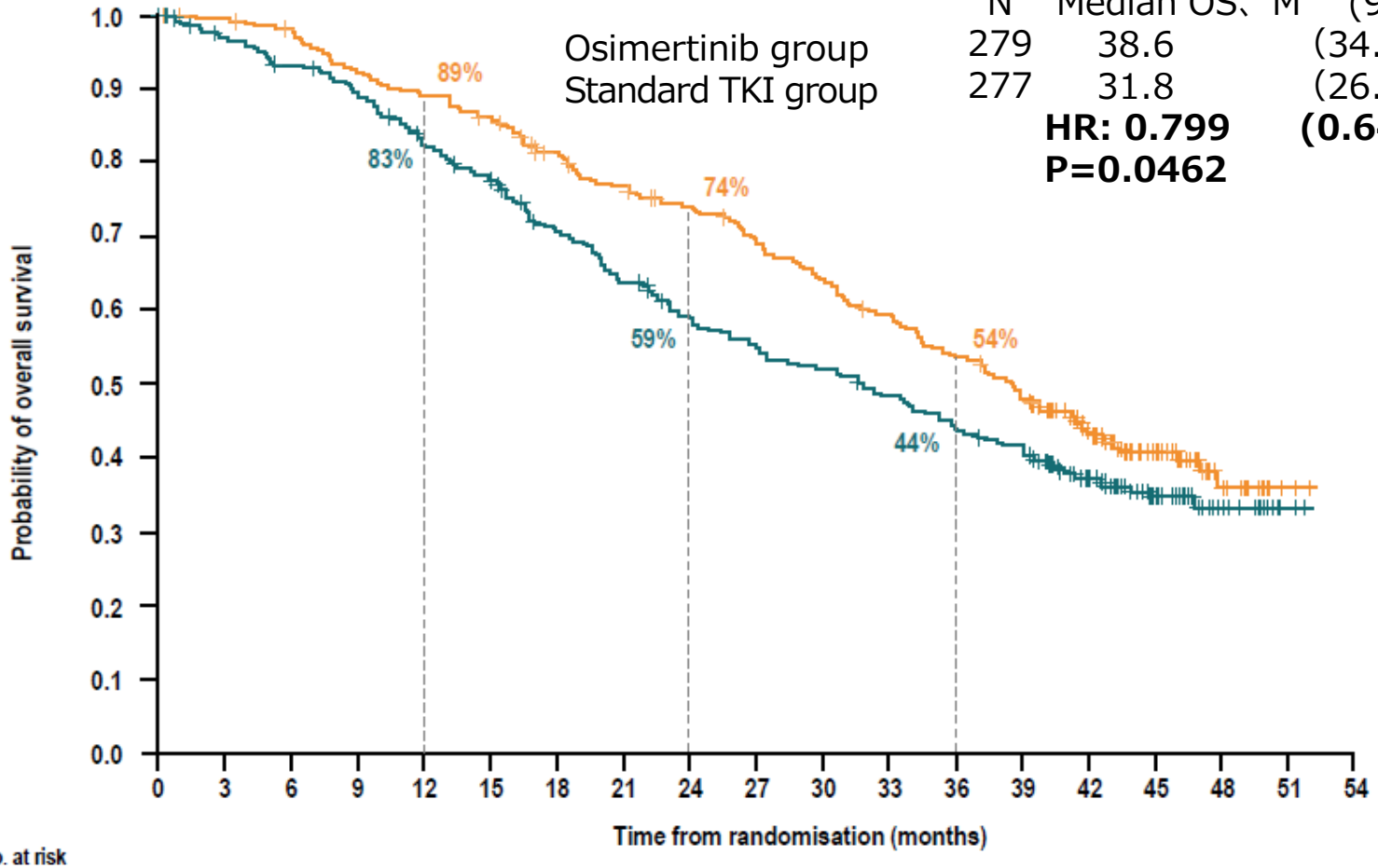
FLAURA study : efficacy rate

Table 2. Secondary Efficacy End Points.*

End Point	Osimertinib (N=279)	Standard EGFR-TKI (N=277)
Type of response — no. (%)†		
Complete	7 (3)	4 (1)
Partial	216 (77)	206 (74)
Stable disease for ≥6 wk	47 (17)	46 (17)
Progression	3 (1)	14 (5)
Death	0	5 (2)
Could not be evaluated	6 (2)	7 (3)
Objective response rate — % of patients (95% CI)	80 (75–85)	76 (70–81)
Disease-control rate — % of patients (95% CI)‡	97 (94–99)	92 (89–95)

J.-C. Soria, et al. NEJM,2017

FLAURA: OS［FINAL ANALYSIS］



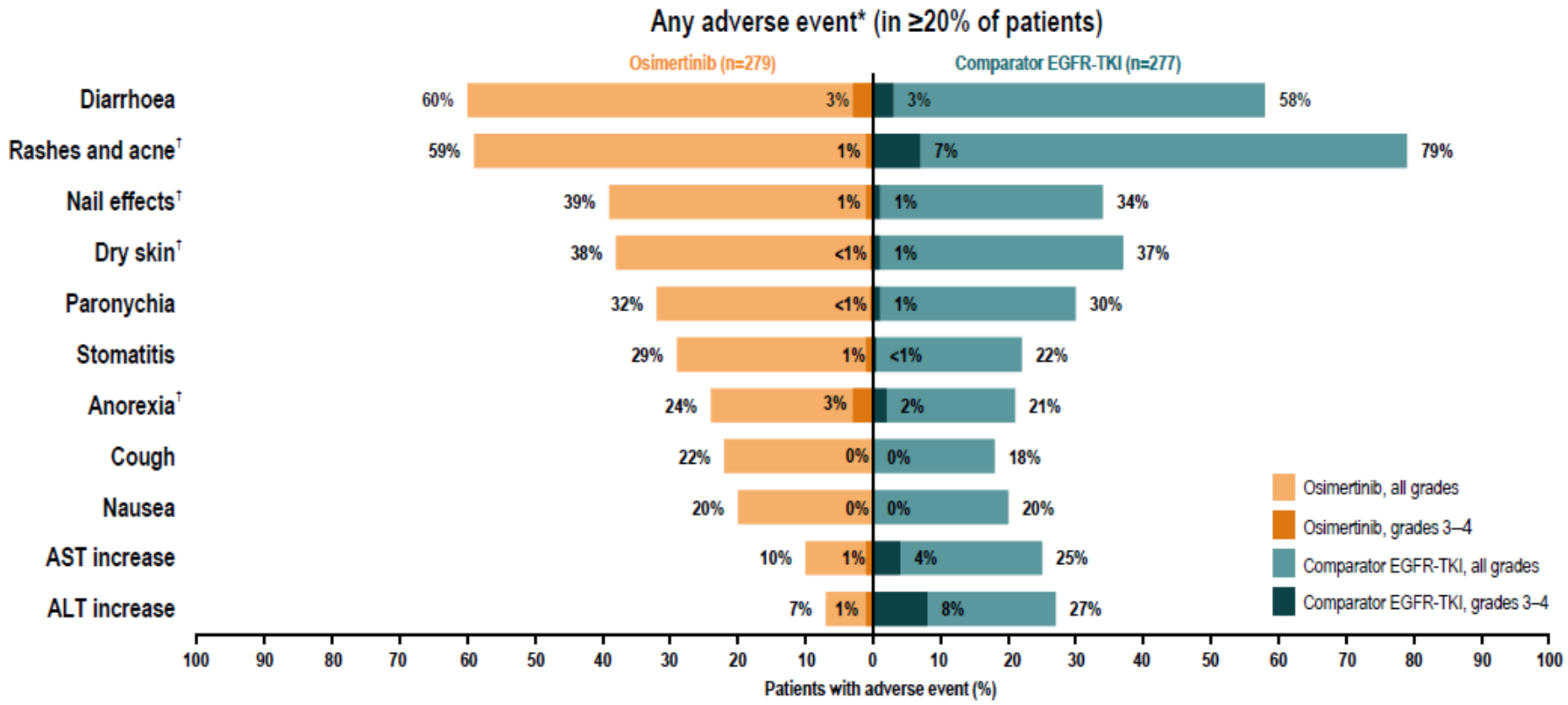
	N	Median OS、M	(95%CI)
Osimertinib group	279	38.6	(34.5~41.8)
Standard TKI group	277	31.8	(26.6~36.0)
		HR: 0.799	**(0.641~0.997)**
		P=0.0462	

No. at risk																		
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

ESMO2019

FLAURA study: side effect

- Median duration of exposure: osimertinib, 20.7 months; comparator EGFR-TKI, 11.5 months
- Grade ≥3 possibly causally related AEs: osimertinib, 51 patients (**18%**); comparator EGFR-TKI, 79 patients (**29%**)



ESMO2019

FLAURA study : interstitial lung disease

		Osimertinib group (n=279)	Standard group (n=277)
SAE of pneumonitis、 N（%） Interstitial lung disease Pneumonitis		11 (4) 6 (2) 5 (2)	6 (2) 4 (1) 2 (1)
Duration until onset、day(range)		106 (9～425)	83.5 (11～253)
Turning、 N	Recovered	7	4
	Improved	4	1
	Unsolved	0	1

Soria, JC., et al.: N. Engl. J. Med., 378（2）, 113, 2018

FLAURA study : safety （Japanese subset)

Duration of treatment : Osimertinib 15.3 M（0.5～25.5 M）、Standard EGFR-TKI 11.0 M（0～25.1 M）

	Osimertinib group（n=65）						Standard EGFR-TKI group（n=55）					
	All grade	Grade1	Grade 2	Grade 3	Grade 4	Grade 5	All grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
All SAE	65（100）	2（3.1）	32（49.2）	30（46.2）	1（1.5）	0	53（96.4）	3（5.5）	19（34.5）	25（45.5）	5（9.1）	1（1.8）
Diarrhea	42（64.6）	33（50.8）	9（13.8）	0	0	0	28（50.9）	24（43.6）	2（3.6）	2（3.6）	0	0
Skin rash	30（46.2）	25（38.5）	5（7.7）	0	0	0	38（69.1）	24（43.6）	11（20.0）	3（5.5）	0	0
Paronychia	33（50.8）	14（21.5）	18（27.7）	1（1.5）	0	0	20（36.4）	10（18.2）	9（16.4）	1（1.8）	0	0
Stomatitis	33（50.8）	27（41.5）	6（9.2）	0	0	0	15（27.3）	11（20.0）	4（7.3）	0	0	0
Dry skin	28（43.1）	21（32.3）	7（10.8）	0	0	0	18（32.7）	16（29.1）	1（1.8）	1（1.8）	0	0
AST increased	7（10.8）	4（6.2）	1（1.5）	2（3.1）	0	0	25（45.5）	11（20.0）	10（18.2）	4（7.3）	0	0
ALT increased	5（7.7）	2（3.1）	2（3.1）	1（1.5）	0	0	27（49.1）	9（16.4）	7（12.7）	8（14.5）	3（5.5）	0
Apetite loss	15（23.1）	5（7.7）	9（13.8）	1（1.5）	0	0	12（21.8）	4（7.3）	5（9.1）	3（5.5）	0	0
Constipation	17（26.2）	15（23.1）	2（3.1）	0	0	0	8（14.5）	8（14.5）	0	0	0	0
Dysgeusia	13（20.0）	8（12.3）	5（7.7）	0	0	0	4（7.3）	3（5.5）	1（1.8）	0	0	0
WBC decreased	14（21.5）	3（4.6）	11（16.9）	0	0	0	1（1.8）	1（1.8）	0	0	0	0
Virus infection	14（21.5）	8（12.3）	6（9.2）	0	0	0	9（16.4）	6（10.9）	3（5.5）	0	0	0
Serious SAE												
QTc prolongation	14（21.5）	6（9.2）	6（9.2）	2（3.1）	0	0	5（9.1）	4（7.3）	1（1.8）	0	0	0
Interstitial lung diseases	8（12.3）	2（3.1）	5（7.7）	1（1.5）	0	0	1（1.8）	0	0	1（1.8）	0	0

Need to be careful with cardio toxicity and pneumonia in osimertinib!

Ohe, Y., et al.: Jpn. J. Clin. Oncol., 49（1）, 29, 2019

ARCHER1050: Dacomitinib vs Gefitinib

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

- Advanced NSCLC with *EGFR*-activating mutation(s)
- No prior systemic treatment of advanced NSCLC
- No CNS metastasis
- No prior EGFR TKI or other TKI
- ECOG PS 0,1

N=452

R
1:1

Dacomitinib
45 mg PO QD
(N=227)

Gefitinib
250 mg PO QD
(N=225)

Primary endpoint

PFS by blinded independent review (IR)

- ≥256 PFS events
- PFS HR≤0.667 (50%↑)
- 90% power
- 1-sided α =0.025
- mPFS: 14.3 vs 9.5 months

Stratification factors

Race (inc. Asian vs non-Asian)

EGFR mutation type (exon 19 vs 21)

Secondary endpoints

PFS (investigator assessed), ORR, DOR,

TTF, OS, Safety, PROs

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01774721

ASCO 2017

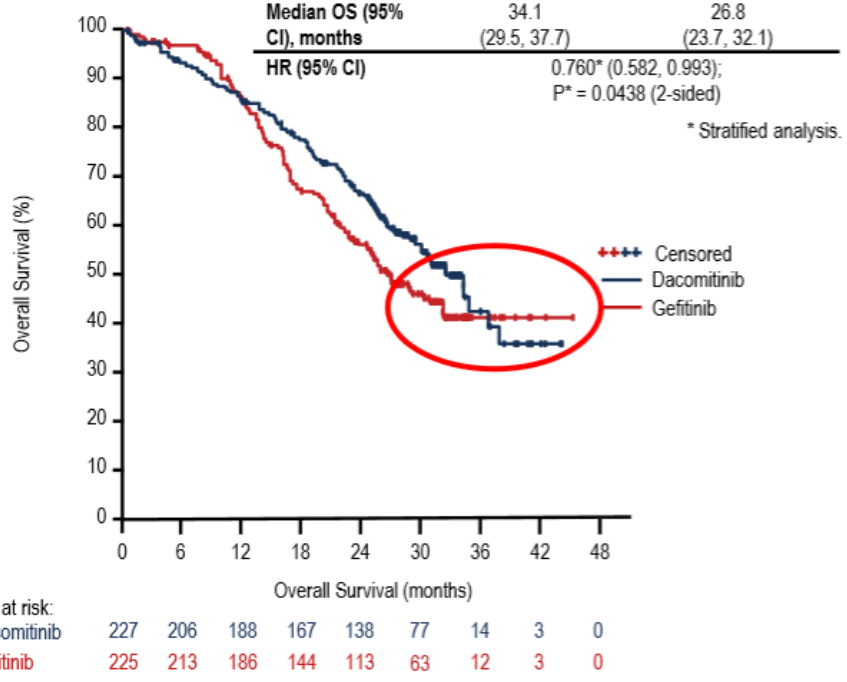
ARCHER1050: Dacomitinib vs Gefitinib

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.

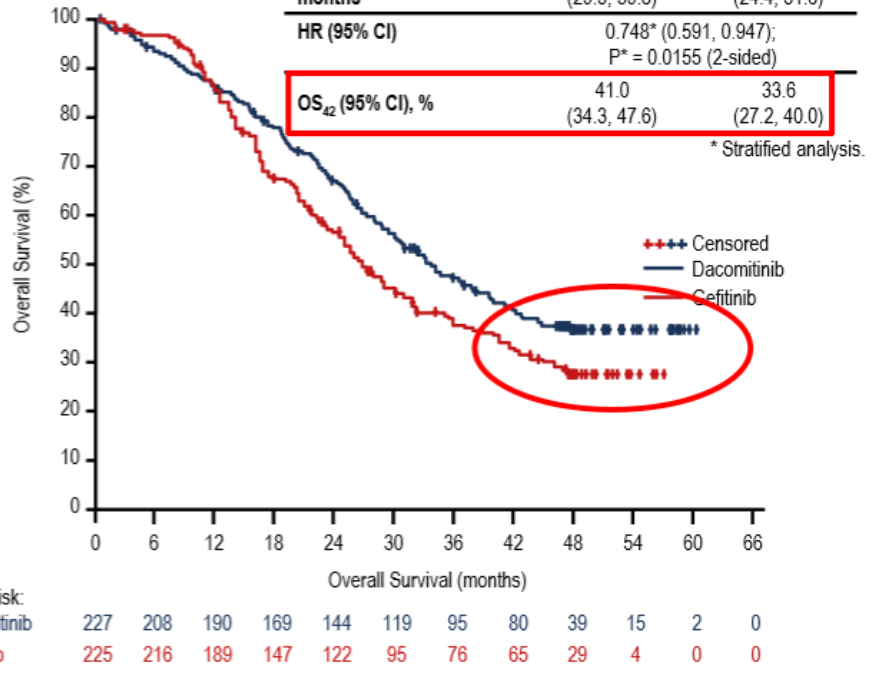


No. at risk:									
Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

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.

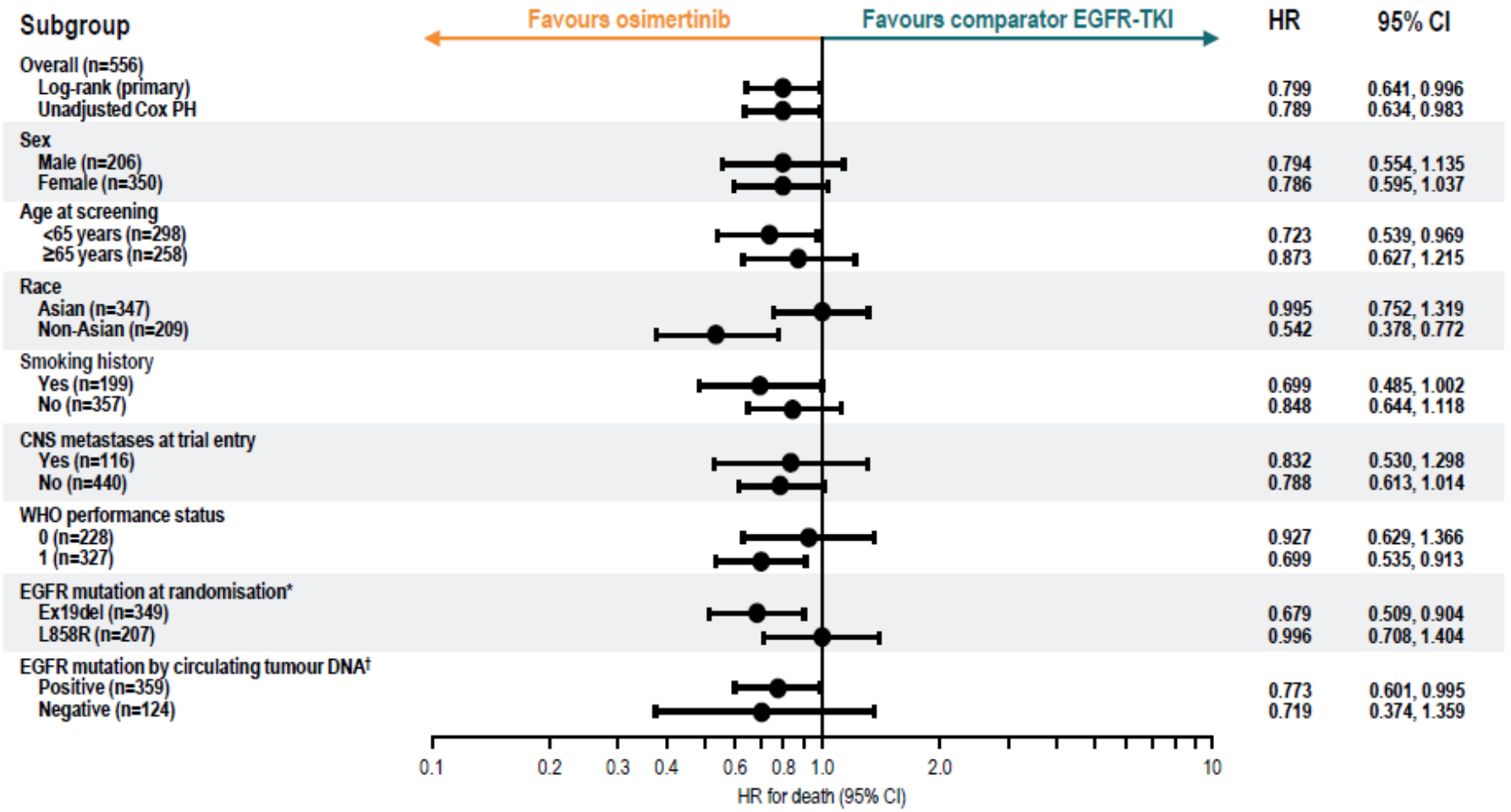


No. at risk:												
Dacomitinib	227	208	190	169	144	119	95	80	39	15	2	0
Gefitinib	225	216	189	147	122	95	76	65	29	4	0	0

2nd-G EGFR TKI potential based on subgroup analysis of FLAURA

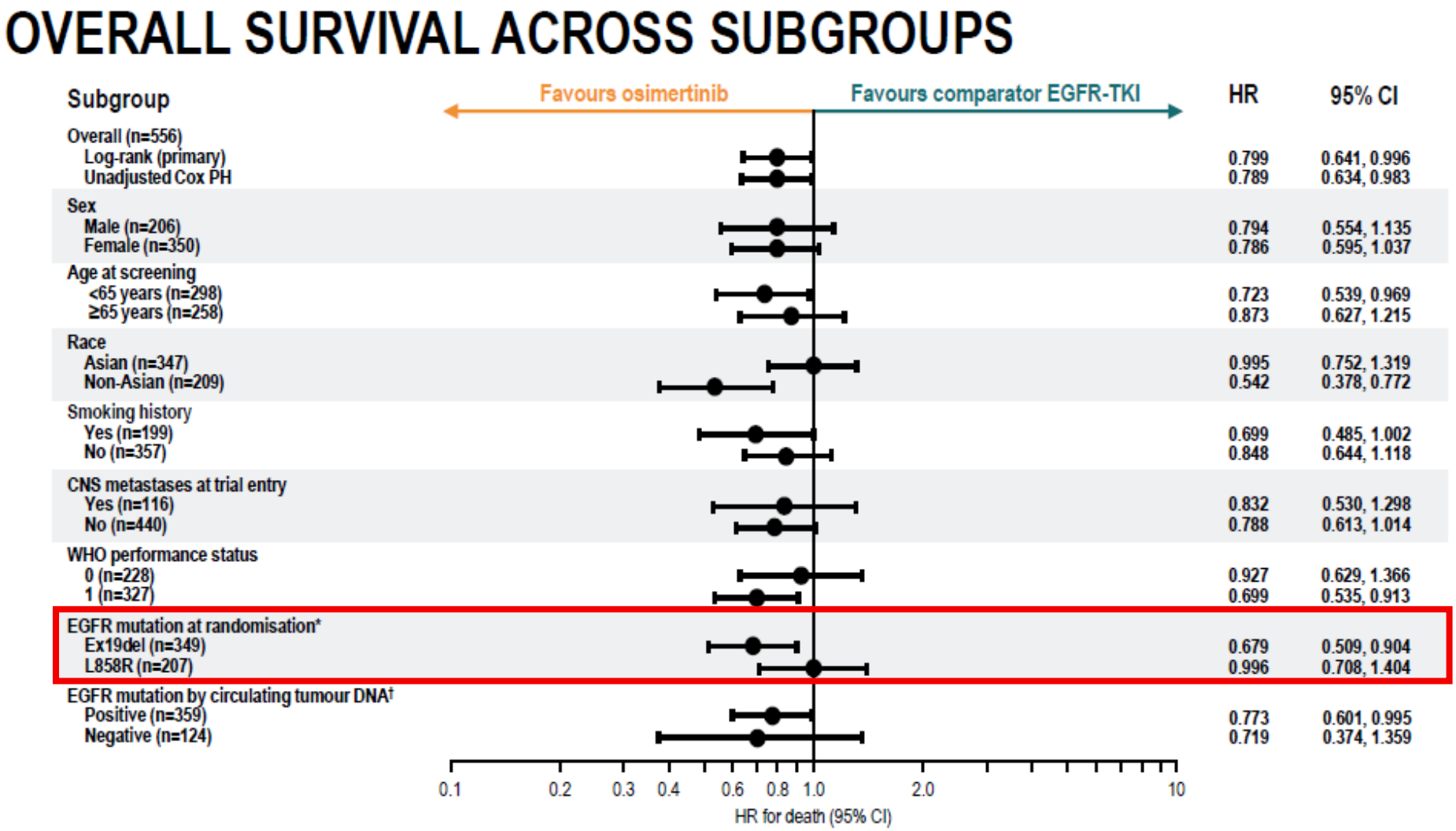
OS subgroup analysis of FLAURA

OVERALL SURVIVAL ACROSS SUBGROUPS



ESMO2019

FLUAURA: EGFR type



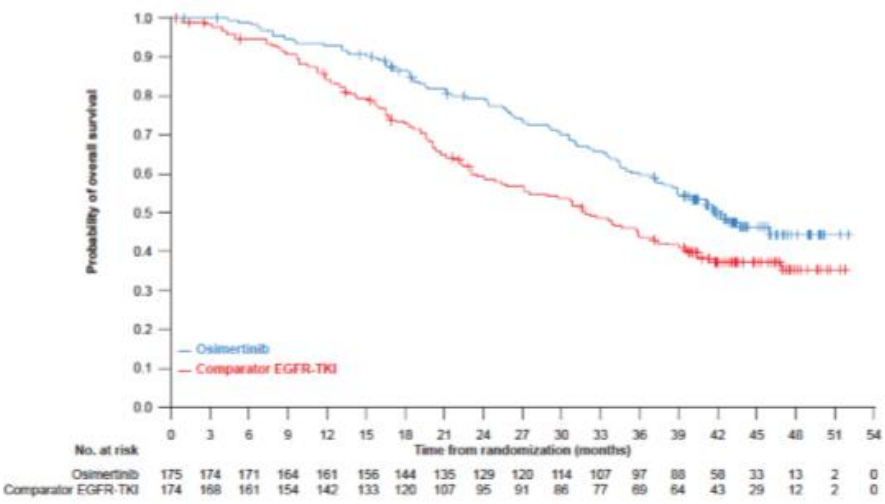
Del19
HR:0.679 (0.509-0.904)

Exon21
HR:0.996 (0.708-1.404)

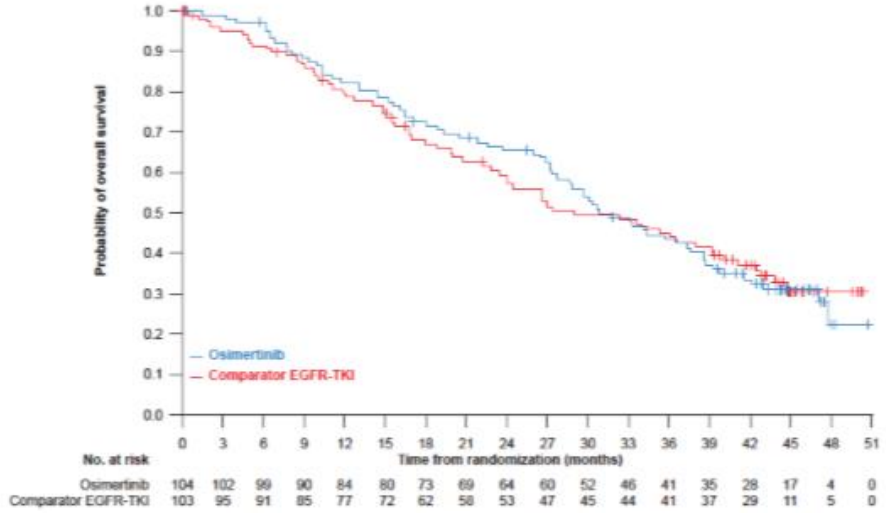
ESMO2019

FLUAURA: EGFR type

Del19
HR:0.679 (0.509-0.904)



Exon21
HR:0.996 (0.708-1.404)



The analysis of the exon21 subgroup of patients were not improved for overall survival analysis!

S.S. Ramalingam, et al. N Engl J Med. DOI: 10.1056/NEJMoa1913662

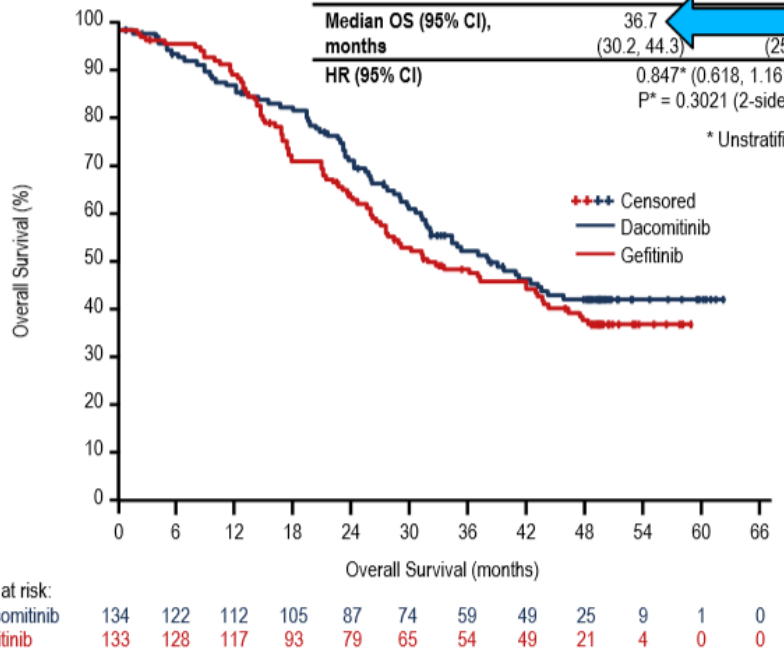
ARCHER1050: Dacomitinib vs Gefitinib

Overall Survival – *EGFR* Mutational Status (At Randomization)

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)	(25.2, 42.2)
HR (95% CI)	0.847* (0.618, 1.161); P* = 0.3021 (2-sided)	

* Unstratified analysis.

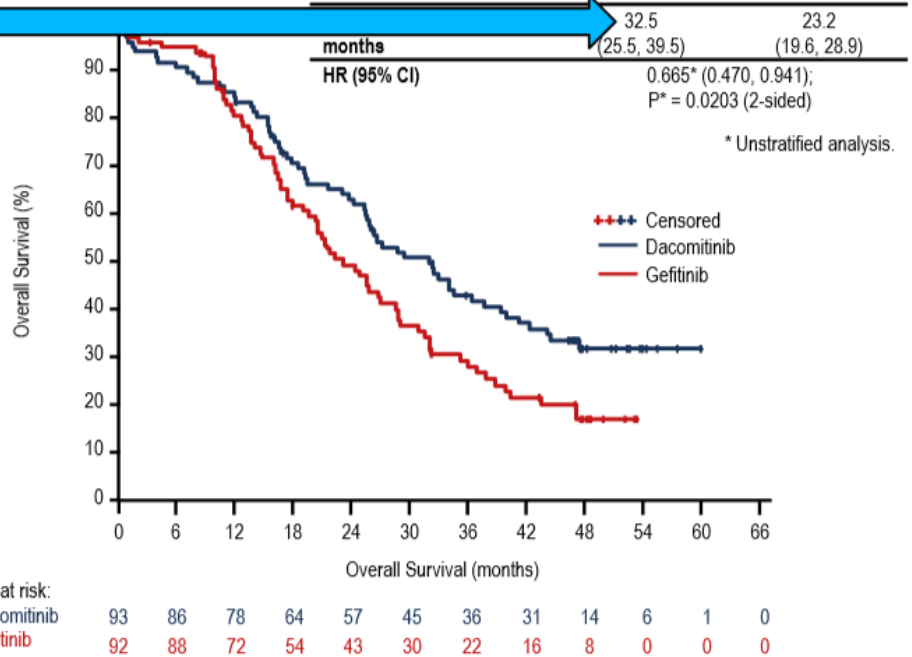


No. at risk:												
Dacomitinib	134	122	112	105	87	74	59	49	25	9	1	0
Gefitinib	133	128	117	93	79	65	54	49	21	4	0	0

EGFR exon 21 L858R

	Dacomitinib (n = 93)	Gefitinib (n = 92)
Events, No.	60	70
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.



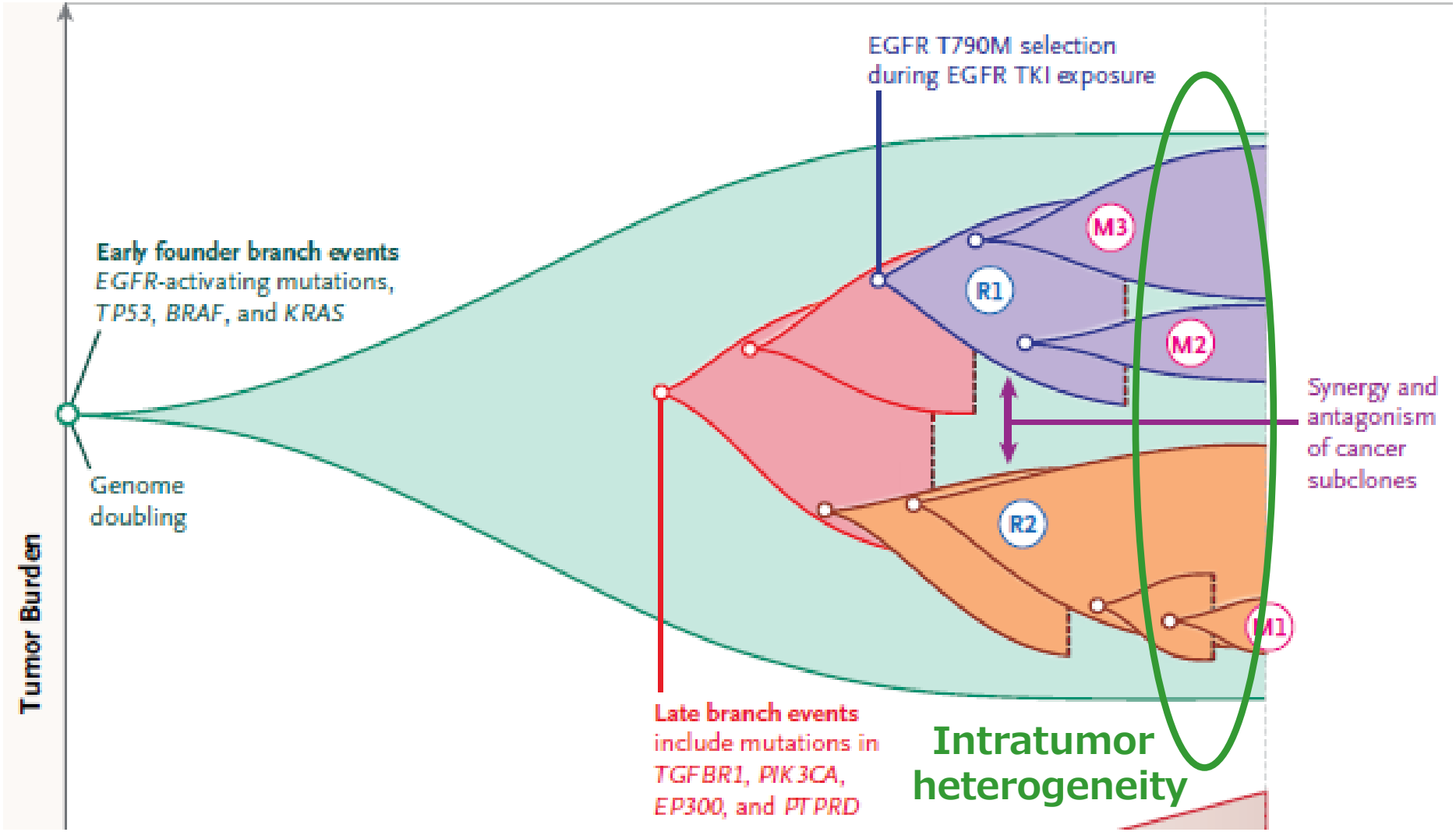
No. at risk:												
Dacomitinib	93	86	78	64	57	45	36	31	14	6	1	0
Gefitinib	92	88	72	54	43	30	22	16	8	0	0	0

Del19
HR:0.847 (0.618-1.161)

Exon21
HR:0.665 (0.470-0.941)

ESMO ASIA2019

Evolutionary Trajectory of an Adenocarcinoma



Jamal-Hanjani M. et al. : Clin Cancer Res 21（6）, 1258, 2015

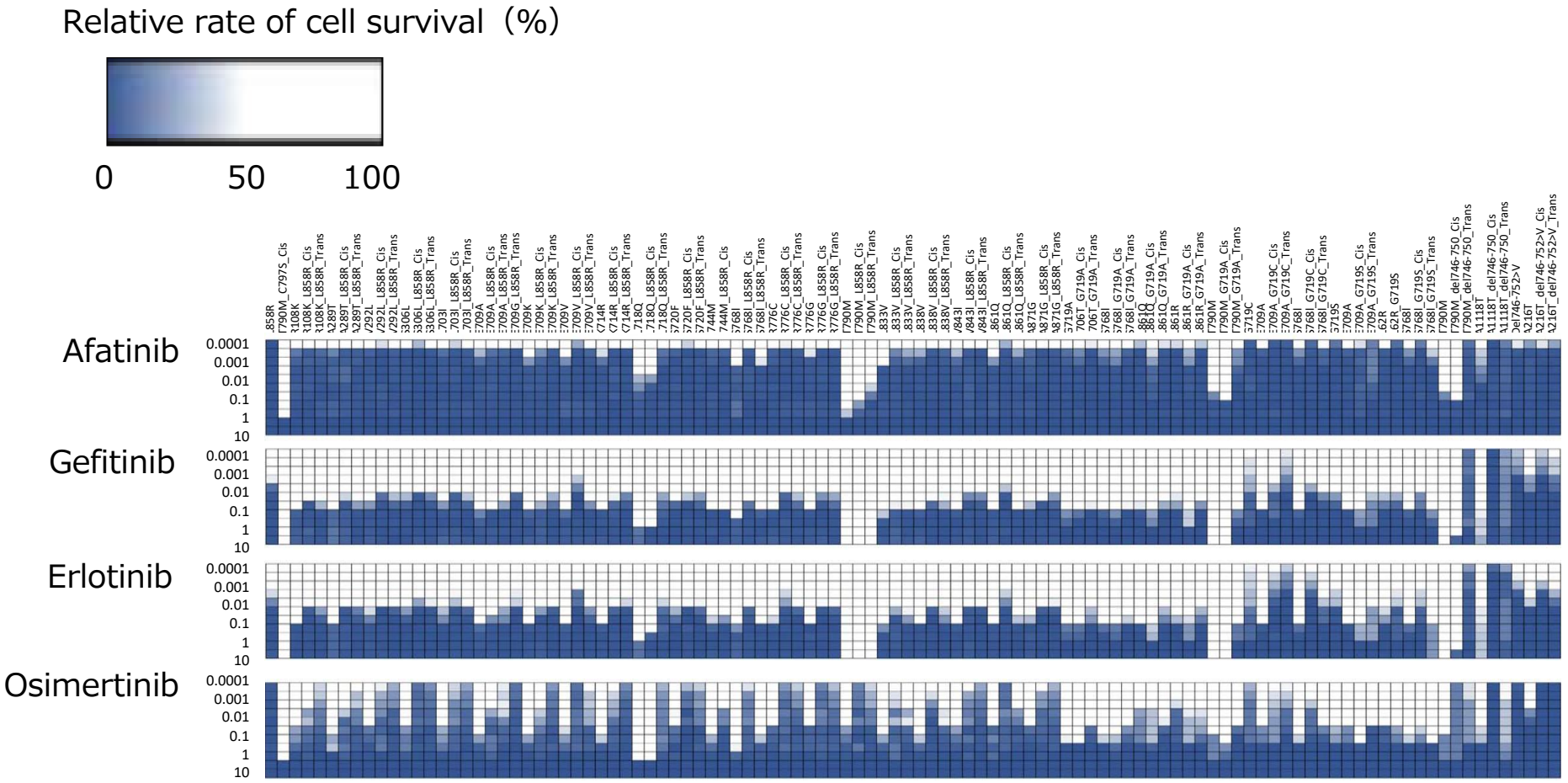
Charles Swanton, et. al. NEJM 2016

The frequency of compound mutation

	L858R	Del19	G719X	L861Q	Total
Compound mut + (N)	38	8	14	4	62
Compound mut - (N)	157	163	1	7	328
Total (N)	195	171	15	11	390
Frequency (%)	19.5	4.7	93.3	36.4	15.9

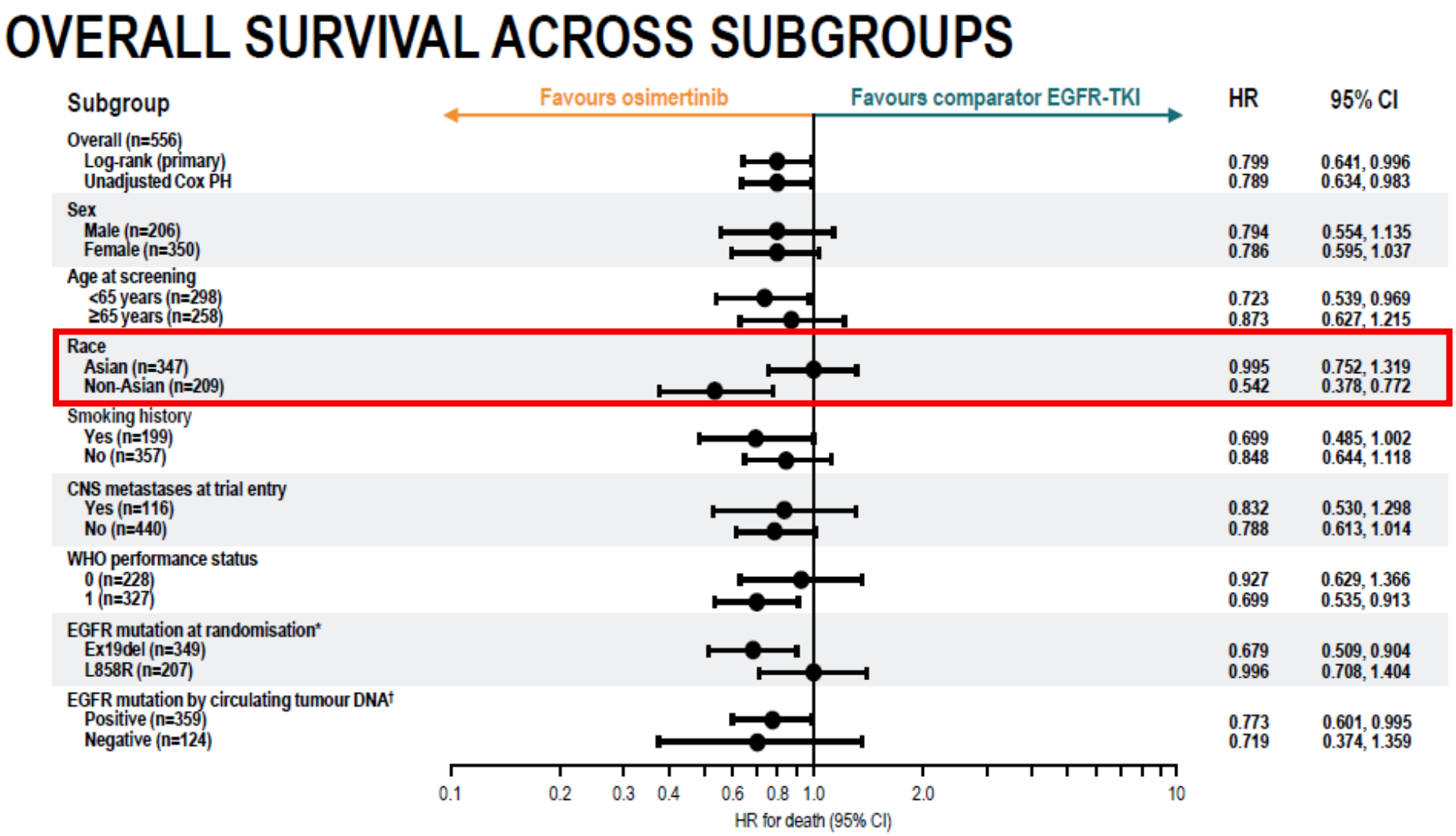
Kosaka S, et al. Sci. Transl. Med. 9 (416)

Efficacy of EGFR-TKI for compound mutation



Mano H. et al. : Sci Transl Med 9（416）, Nov 15, 2017

FLUAURA: Race

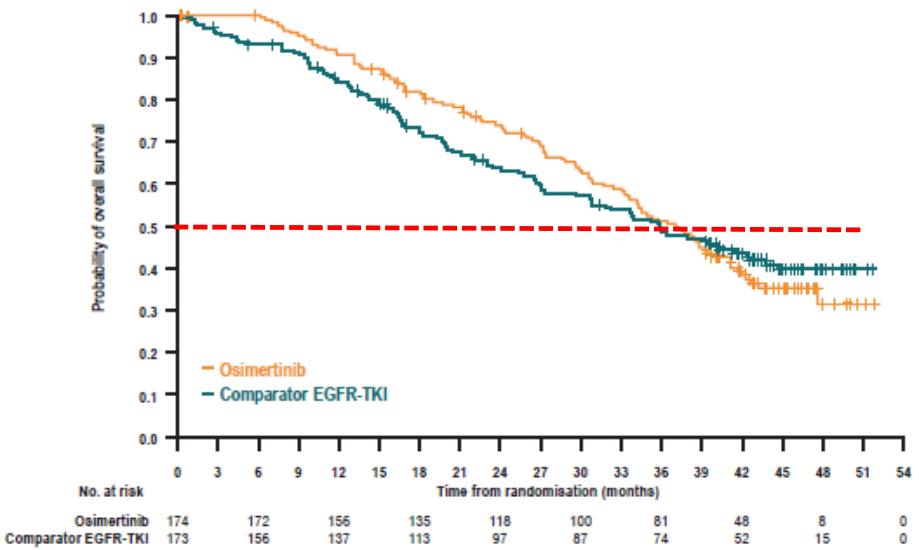


ESMO2019

FLUAURA: Race

OVERALL SURVIVAL IN ASIAN AND NON-ASIAN PATIENTS

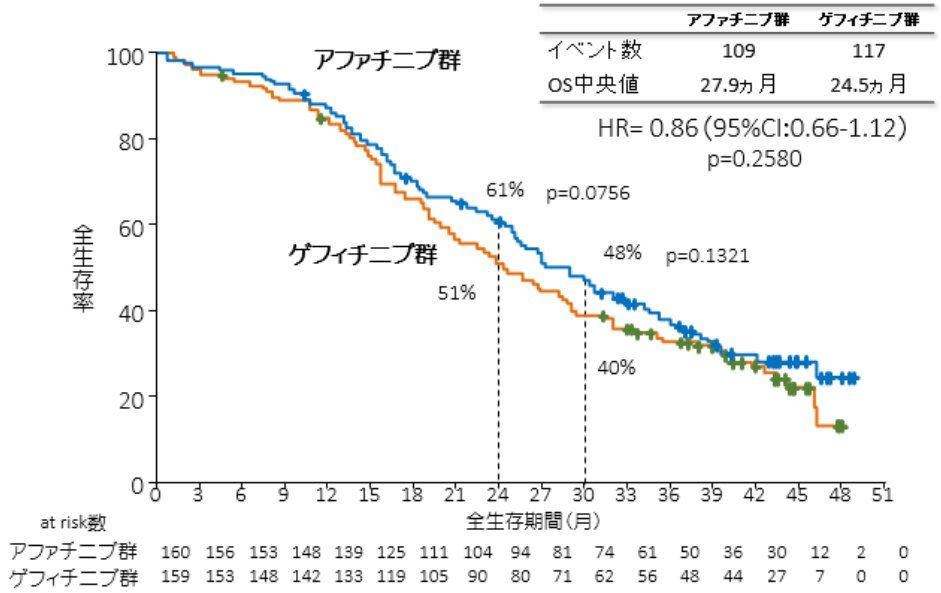
Asian patients



HR:0.995 (0.752-1.319)

Japanese included in35% of all in FLAURA.

LuxLung7: Afatinib vs Gefitinib



HR:0.86 (0.66-1.12)

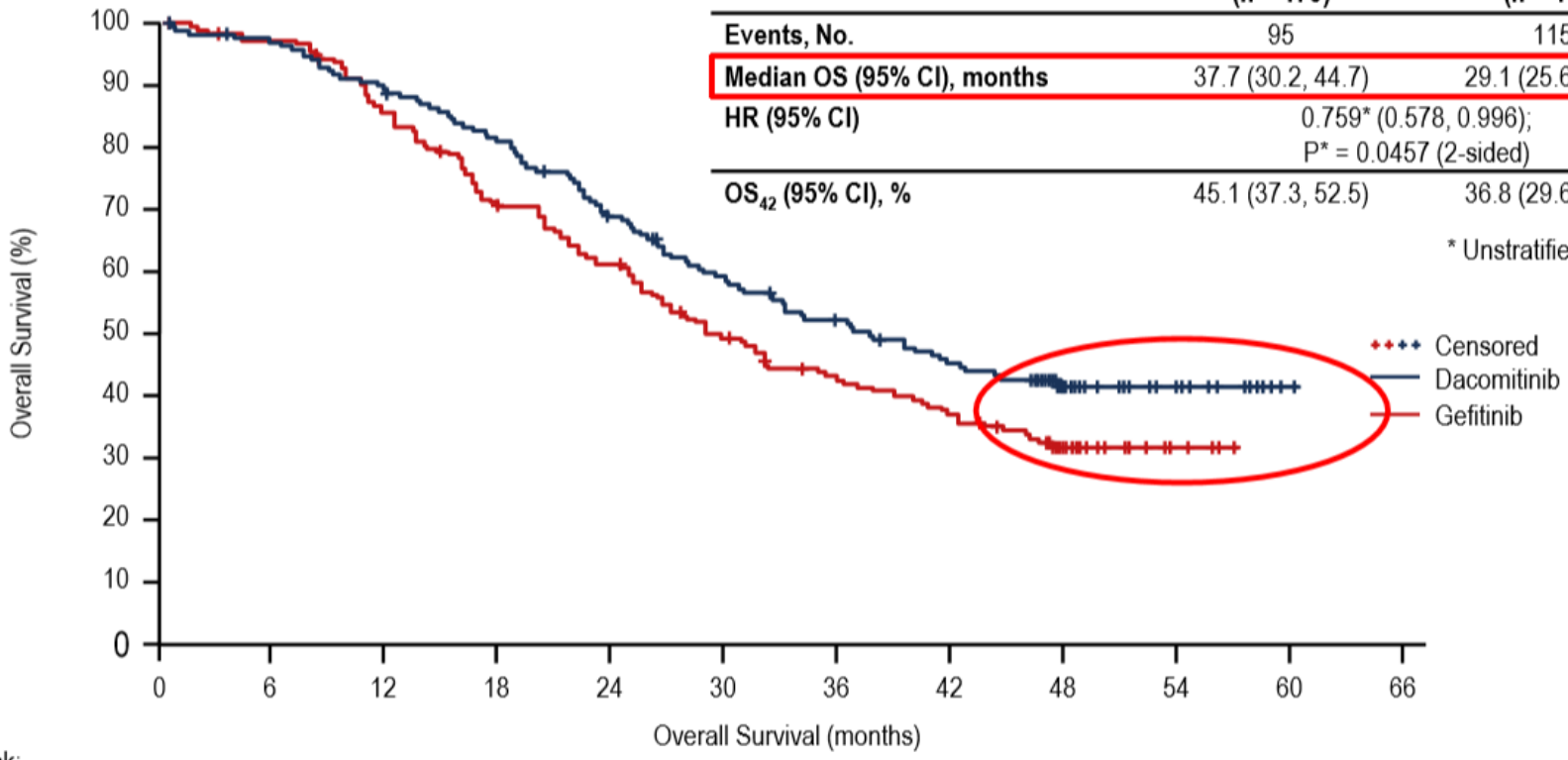
Japanese did not included at all In LUX LUNG7

ARCHER1050: Race

Overall Survival – Asian

	Dacomitinib (n = 170)	Gefitinib (n = 176)
Events, No.	95	115
Median OS (95% CI), months	37.7 (30.2, 44.7)	29.1 (25.6, 36.0)
HR (95% CI)	0.759* (0.578, 0.996); P* = 0.0457 (2-sided)	
OS_{42} (95% CI), %	45.1 (37.3, 52.5)	36.8 (29.6, 44.1)

* Unstratified analysis.



No. at risk:												
Dacomitinib	170	163	149	135	113	95	82	70	33	15	2	0
Gefitinib	176	170	148	120	104	83	69	59	25	4	0	0

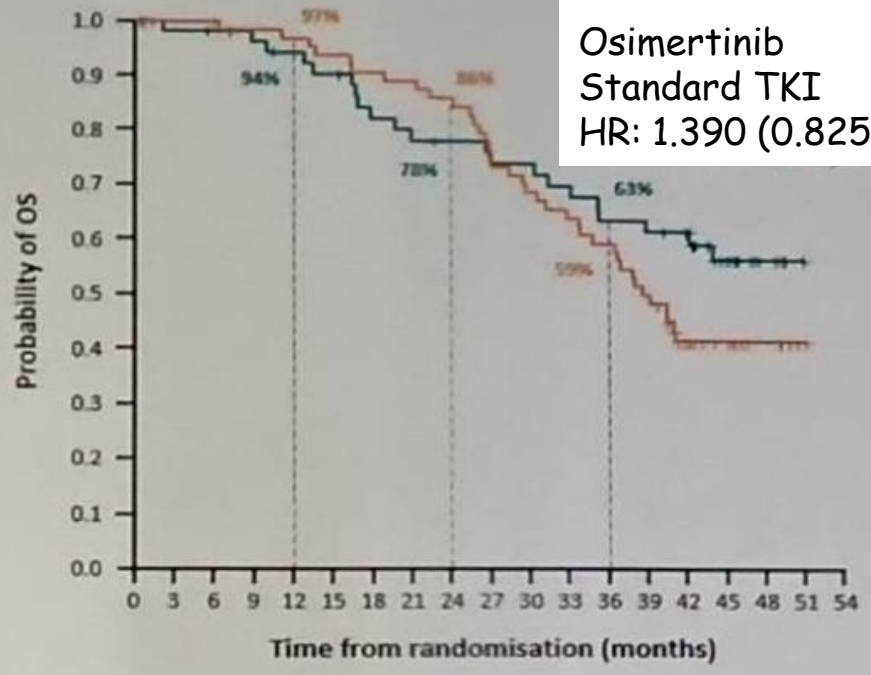
FLUAURA: Japanese subset

This data was presented today's afternoon
in the Japan Lung Cancer Society meeting!

Exploratory post-hoc analysis of overall survival in Japanese patients

	median OS (Months)	(0.95CL)
Osimertinib	39.3	(34.2-Infinity)
Standard TKI	not reached	(35.8-Infinity)

HR: 1.390 (0.8259-2.3381)



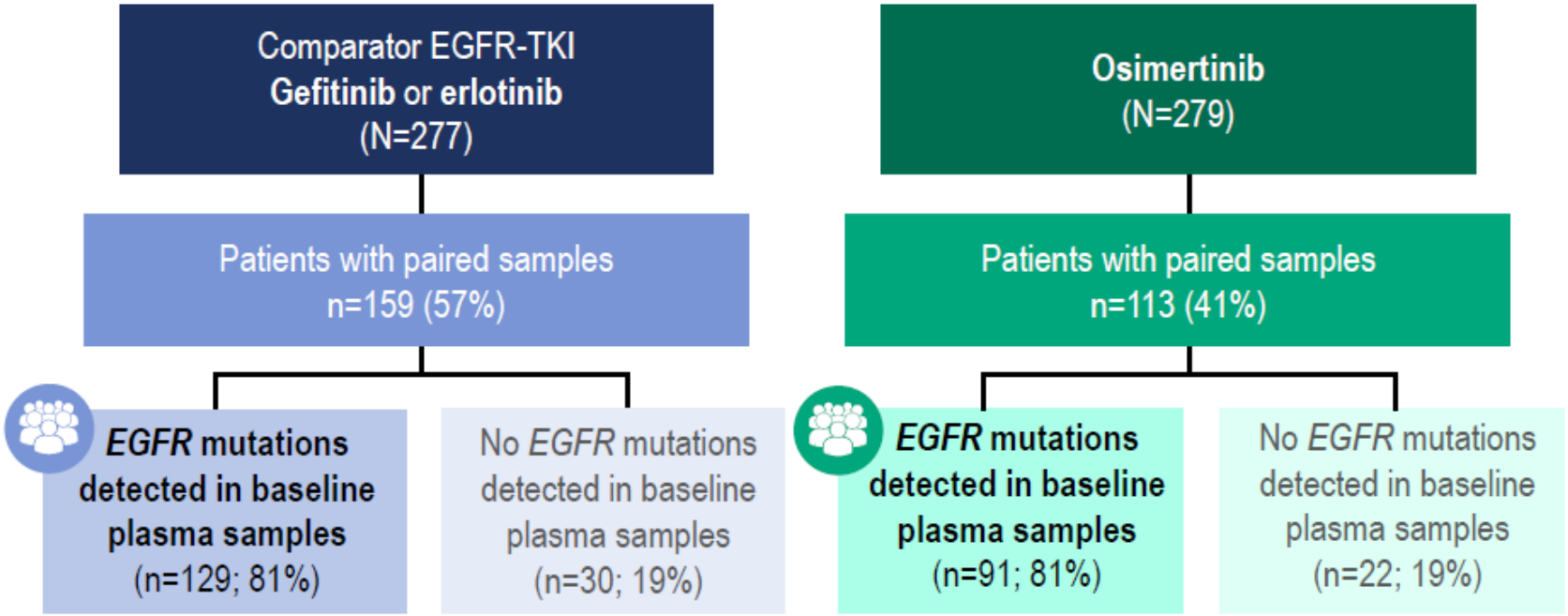
The 60th Annual Meeting of the Japan Lung Cancer Society

Data cut-off: 25 June 2019.
Tick marks indicate censored data.

Resistance mechanism of Osimertinib

PATIENT DISPOSITION IN PATIENTS WITH PAIRED PLASMA SAMPLES

Patients with detectable plasma sensitising EGFRm (ex19del/L858R) at baseline (shedding) were evaluable



MUNICH 2018 ESMO congress

EGFR mutations included exon 19 deletion or L858R

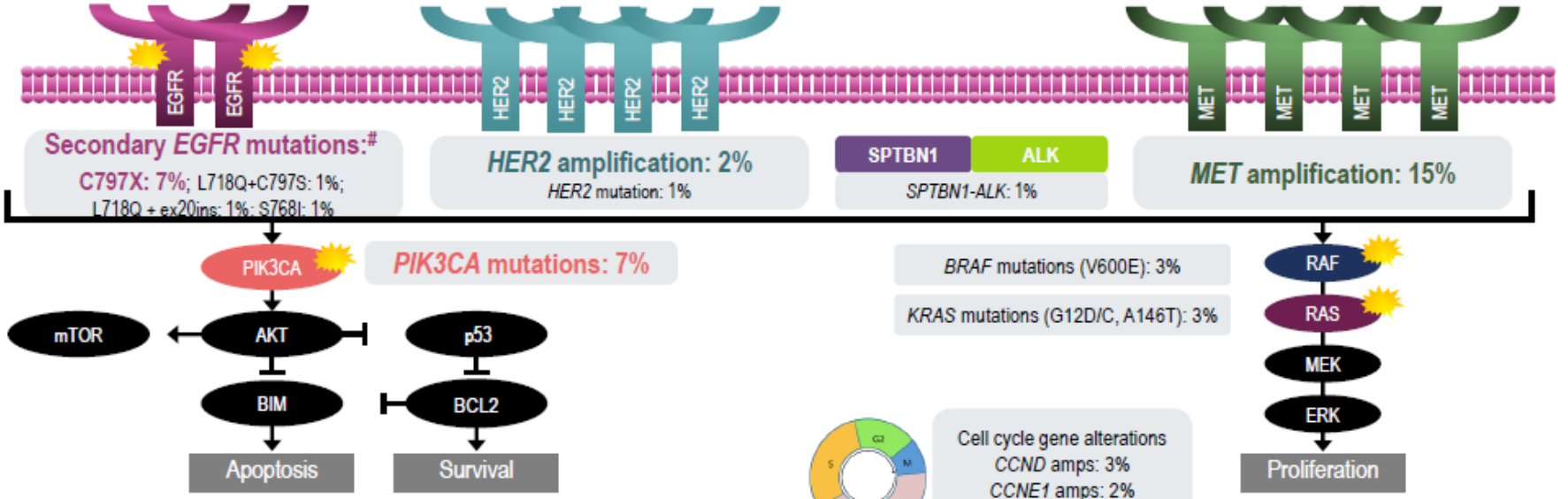
*Samples were restricted to those patients with disease progression and/or discontinuation samples, and patients who provided informed consent.

p.o., orally; qd, once daily

Resistance mechanism of Osimertinib

RESULTS: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were *MET* amplification and EGFR C797S mutation
  - Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations

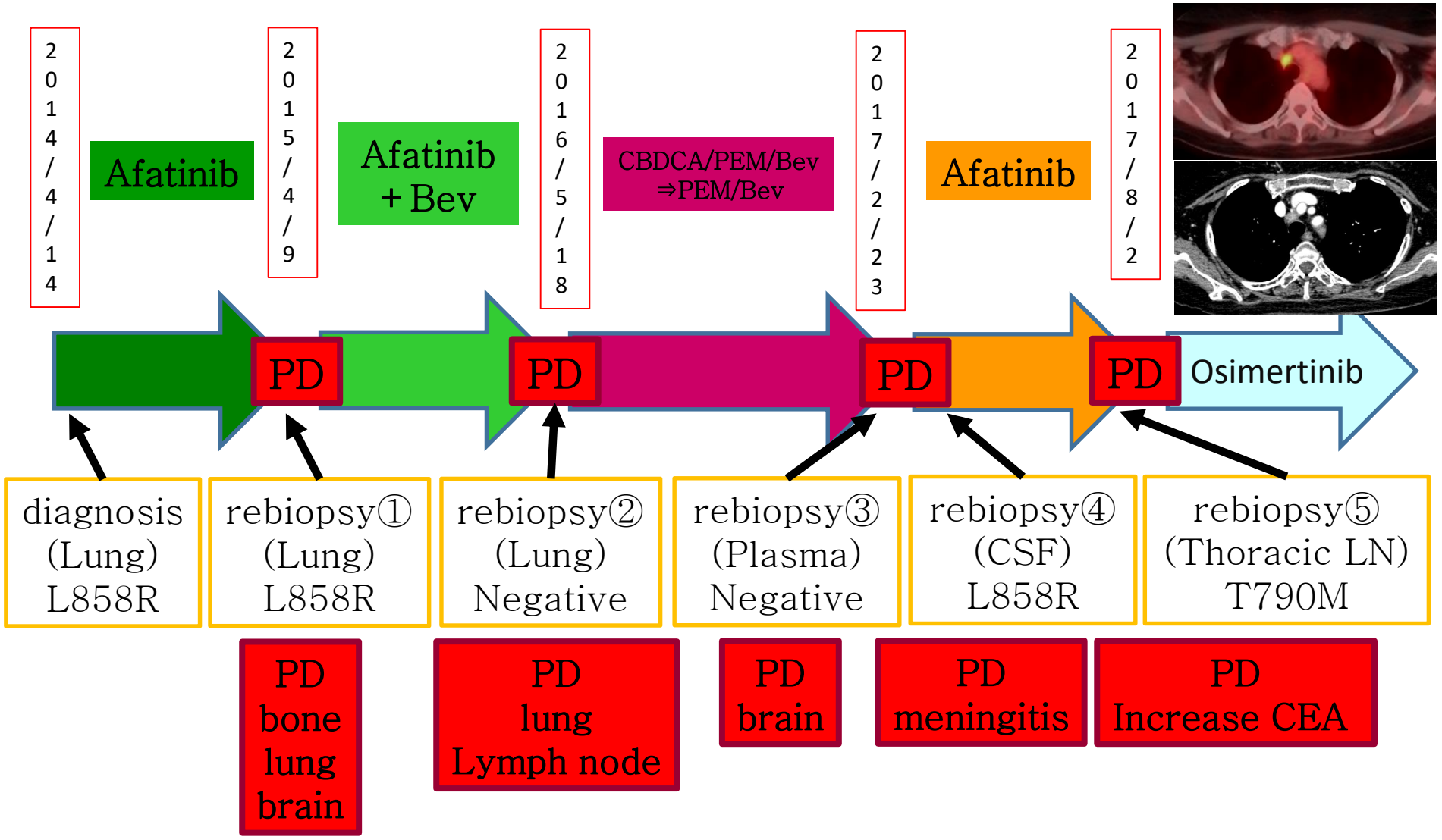


MUNICH 2018 ESMO congress

*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

There are a few treatment after osimertinib failure because of unknown resistance mechanism

Case-2: 61 y.o. Female, stage4, Ad with L858R



Summary of subset analysis

- For exon 21, osimertinib is similar to 1st G EGFR-TKIs and osimertinib may be inferior to 2nd G EGFR-TKIs.
- 1st and 2nd G EGFR-TKIs for Asian people tend to be better than non-Asian people, however osimertinib for Asian people tend to be worse than non Asian people.
- The mechanism of between EGFR of 1st / 2nd G EGFR-TKIs and osimertinib may be different depending on race.

Today's contents

Considerations in 1st-Line Treatment

- Review the primary endpoint of main RCT.
- Real world evidence on 1st line EGFR-TKIs treatment on our hospital (Japanese experience) and best sequence of EGFR-TKI.

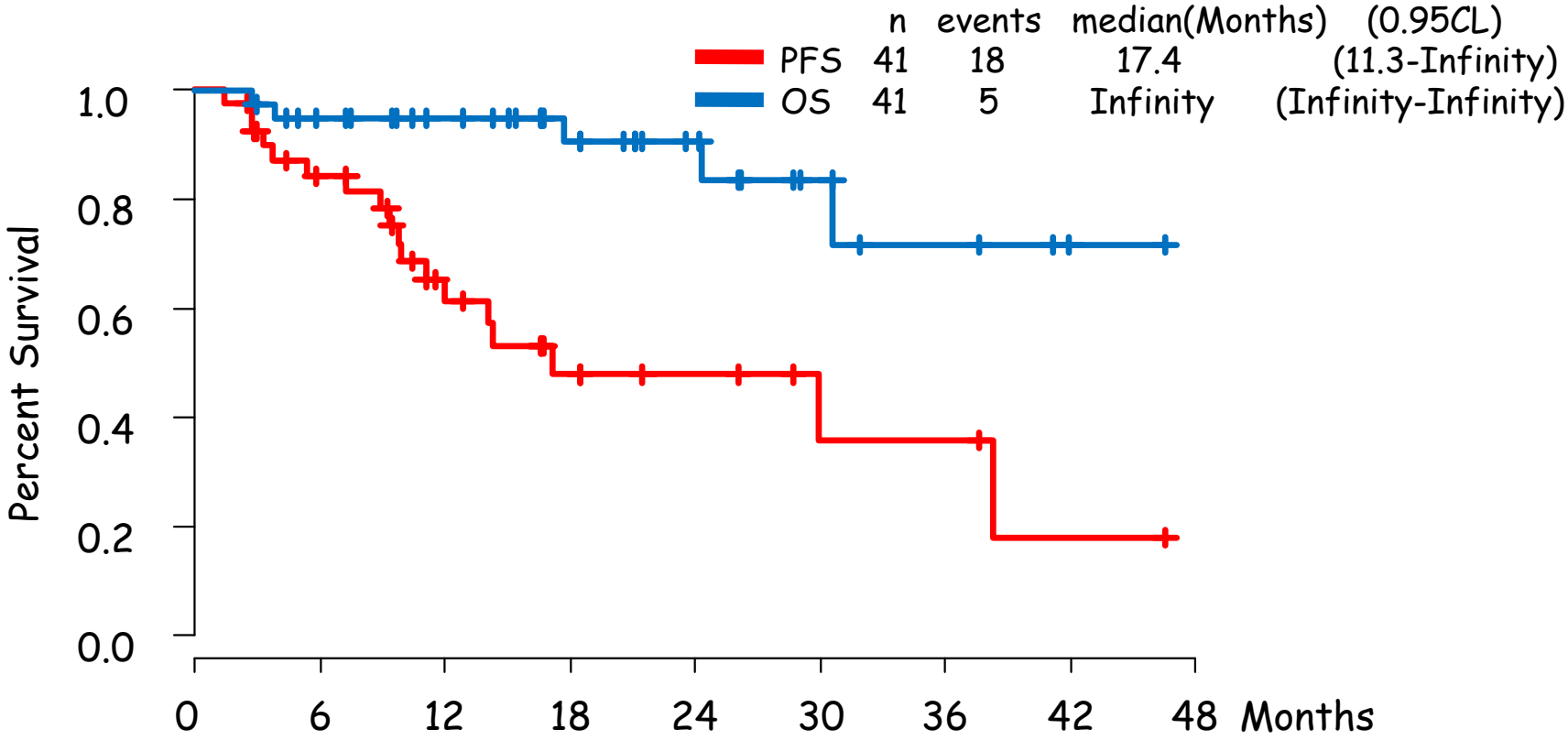
Patients demographics in our hospital data

1st line treatment with Afatinib for EGFR (+) NSCLC patients

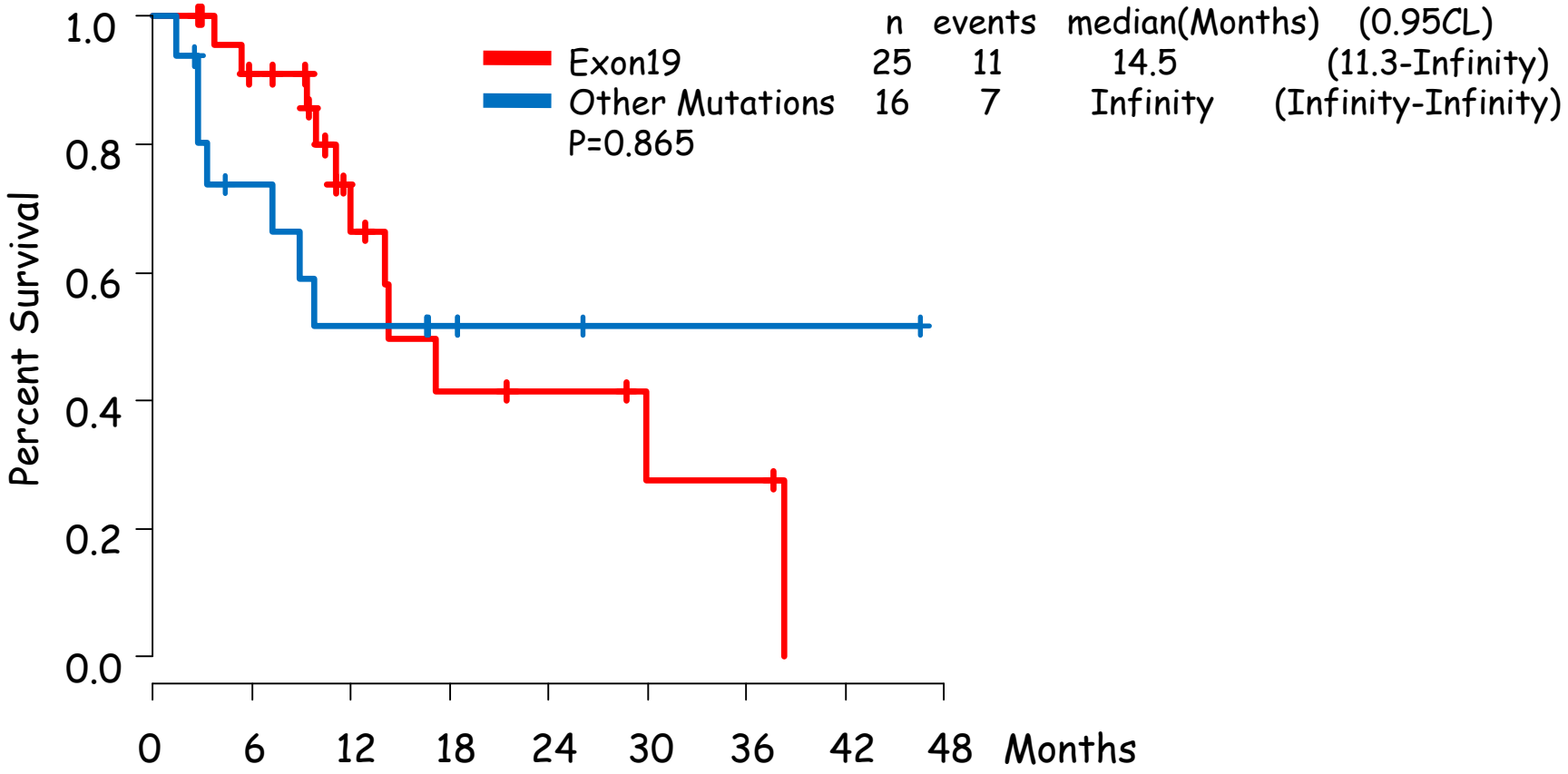
	n=41
Median age (year old)	64 (40-83)
Male / Female	19 / 22
Smoking: Non-smoker / Smoker	21 / 20
Performance status: 0 / 1 / 2 / 3	12 / 25 / 3 / 1
Mutation type: Exon19 / L858R / Minor	25 / 11 / 5
Stage: IIIB / IV / post ope	1 / 23 / 17
First dose (mg) of Afatinib: 40 / 30 / 20	36 / 3 / 2
Brain metastasis: + / -	5 / 32

Response Rate

Best response of 1st line afatinib in our hospital					
Best response	CR	PR	SD	PD	Response rate
All lesions	2	32	2	5	82.9%
Intracranial	0	3	0	2	60%



PFS between Exon19 and Other mutations



Prophylactic management of Adverse Events in our hospital

Upon prescription of afatinib

afatinib 40 mg 1T at the time of getting up	
biofermin 3T after each meal	Proactive of diarrhea
loperamide 2C at diarrhea (Until 3 times a day)	Treatment of diarrhea
azulene coughing five times a day	Oral care
heparin lotion 0.3% for face or neck some times	Moisturizing
heparin cream for the body some time	Moisturizing
minocycline100mg 1T after breakfast	Proactive of skin rash

Prophylactic management of Adverse Events in our hospital

When AEs are further aggrevated

afatinib 40mg		
biofermin		
loperamic (Until 3 ti		
azulene coughing		
heparin lotion 0.3%		
heparin cream	for the body	some times a day
steroid ointment (strongest)	for face or body	some times a day
steroid DP lotion (very strong)	for scalp	some times a day
Minocycline 100 mg	2T	twice a day

We use more strong steroid ointment and lotion.
Increase in quantity of minocycline.

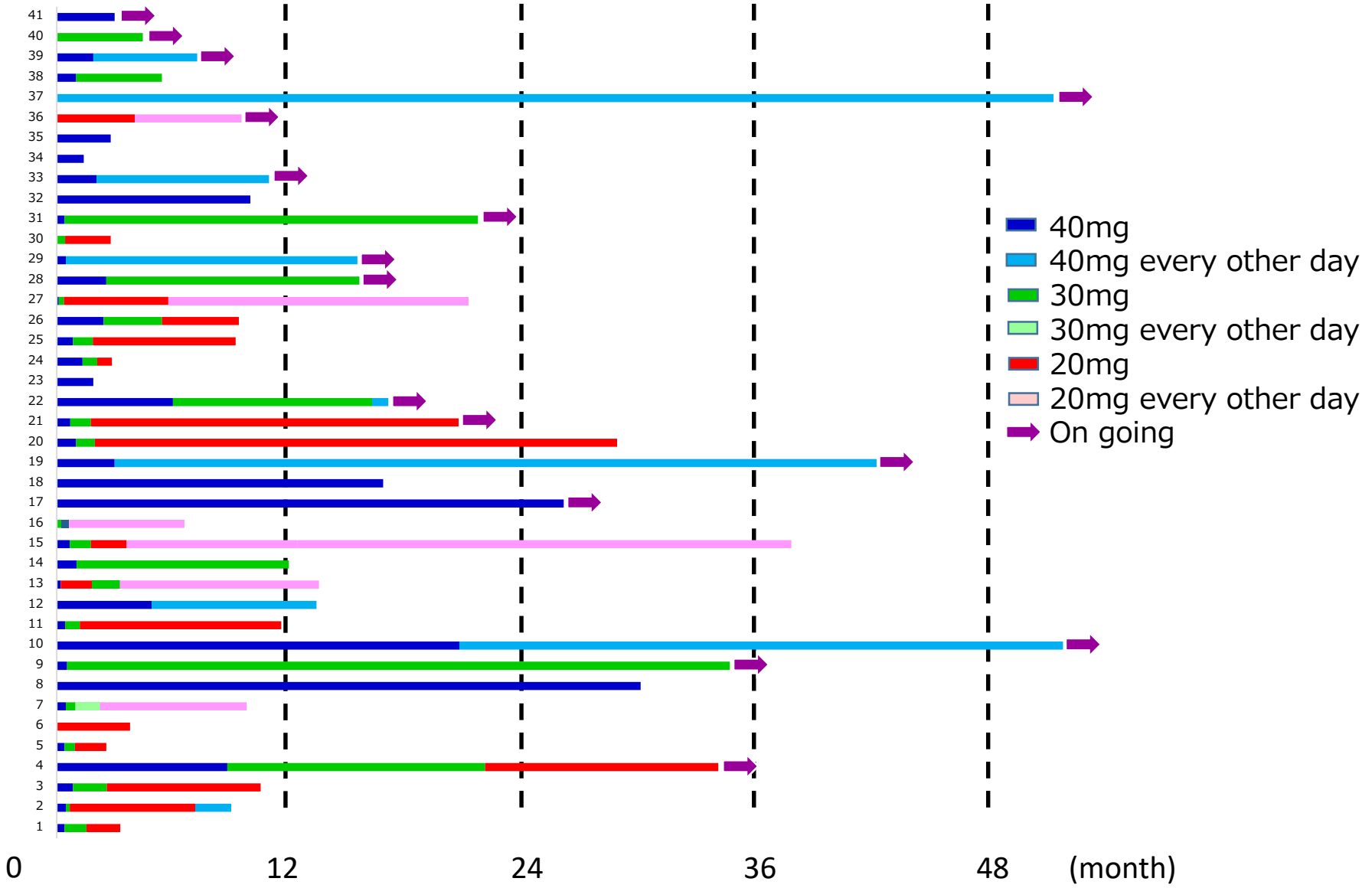
Safety in our data

Afatinib of side effects （N=41）

	LUX-Lung study data All Grade（≧G3）	Our data All Grade（≧G3）
Skin Rash	98.1%（20.4%）	80.5%（9.8%）
Paronychia	88.9%（24.1%）	73.2%（4.9%）
Stomatitis	88.9%（7.4%）	75.6%（7.3%）
Diarrea	100%（20.4%）	85.4%（9.8%）
Anorexia	46.9%（5.5%）	28.3%（9.8%）

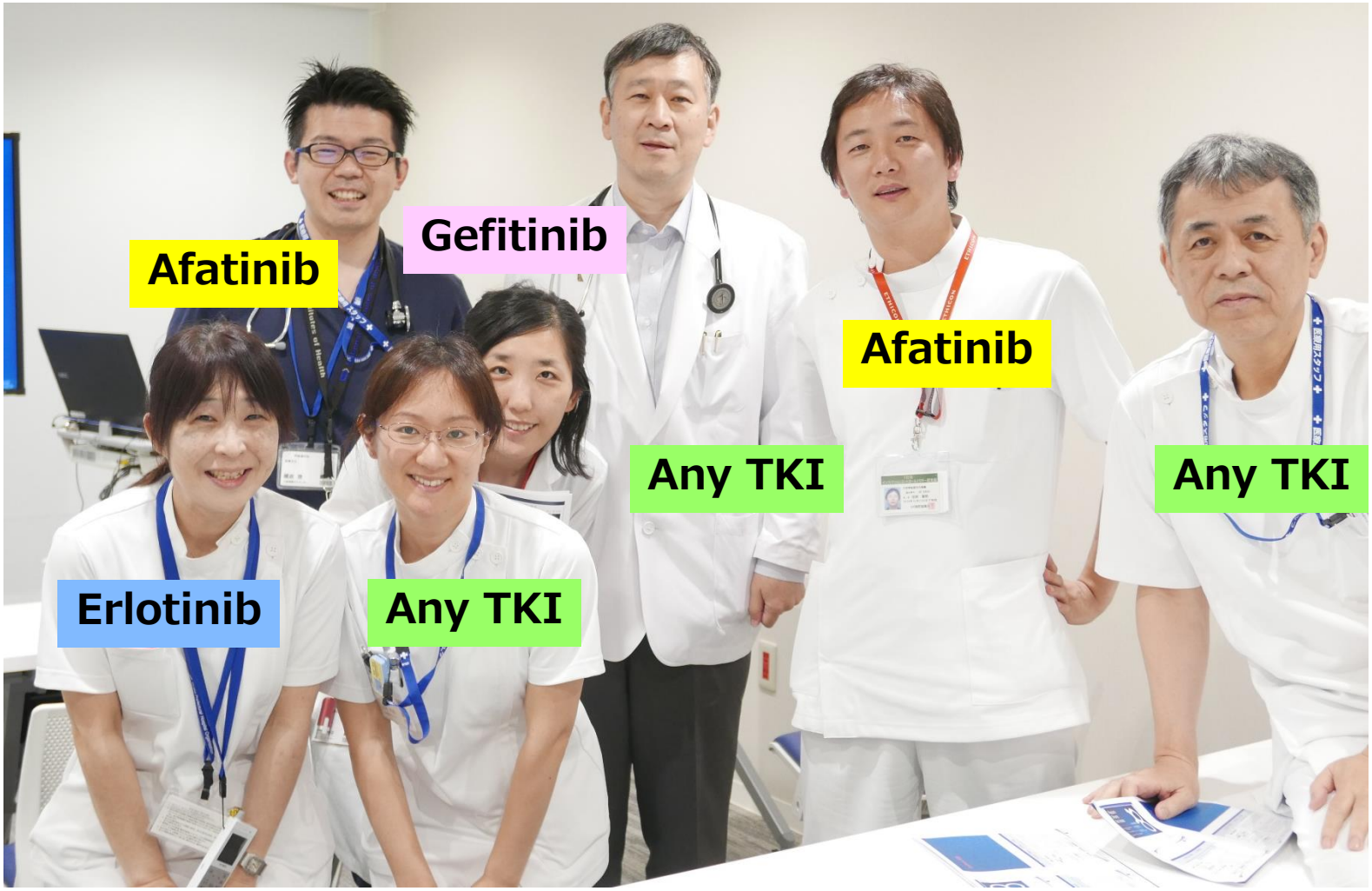
Number of dose reduction	31 (75.6%)
median duration time until dose reduction	36 days (11-628 days)

The flow of treatment dose



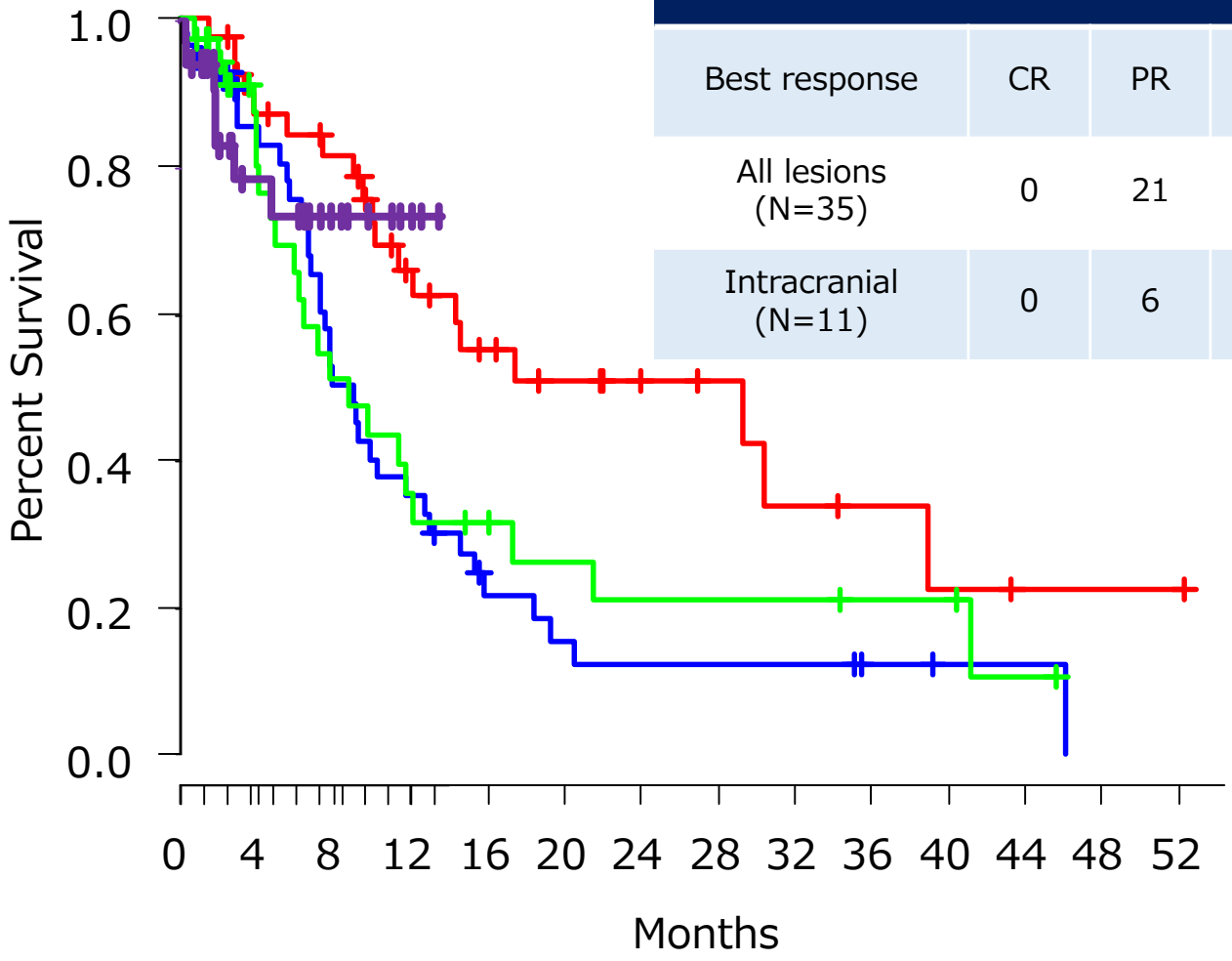
1st line treatment with EGFR-TKIs for EGFR (+) NSCLC patients

2014.4～2017.8 in our hospital



PFS of 1st line treatment with EGFR-TKIs for EGFR (+) NSCLC patients

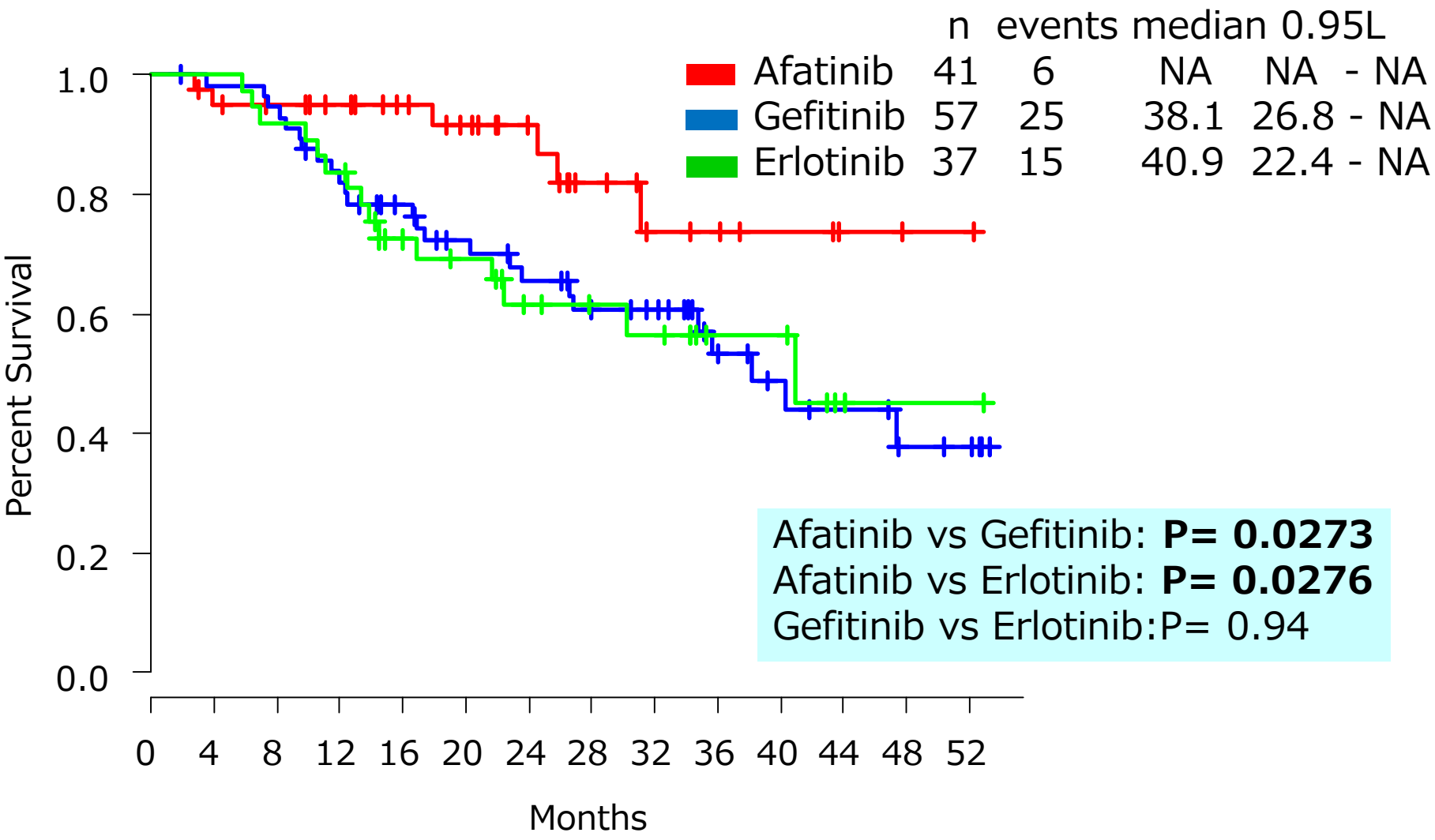
2014.4～2017.8 in our hospital



Best Response of 1st-Line Osimertinib in Our Hospital						
Best response	CR	PR	SD	PD	NE	Response rate
All lesions (N=35)	0	21	3	6	5	60.0%
Intracranial (N=11)	0	6	1	0	4	54.5%

OS of 1st line treatment with EGFR-TKIs for EGFR (+) NSCLC patients

2014.4～2017.8 in our hospital



Considerations in 1st-Line Treatment

What are the important factors in choosing the EGFR-TKI for EGFR mutation–positive patients?

1. Efficacy (response rate, PFS)
   Osimertinib≥Afatinib > Erlotinib = Gefitinib
   (OS)
   (Osimertinib= Afatinib)? > Erlotinib = Gefitinib

2. Toxicities
   Diarrhoea, skin toxicities: Afatinib > Erlotinib > Gefitinib = Osimertinib
   AST/ALT elevation: Gefitinib > Erlotinib > = Osimertinib ≥ Afatinib
   ILD: Osimertinib≥ Gefitinib = Erlotinib = Afatinib

3.

Considerations in 1st-Line Treatment

What are the important factors in choosing the EGFR-TKI for EGFR mutation–positive patients?

1. Efficacy (response rate, PFS)
   Osimertinib≥Afatinib > Erlotinib = Gefitinib
   (OS)
   (Osimertinib= Afatinib)? > Erlotinib = Gefitinib

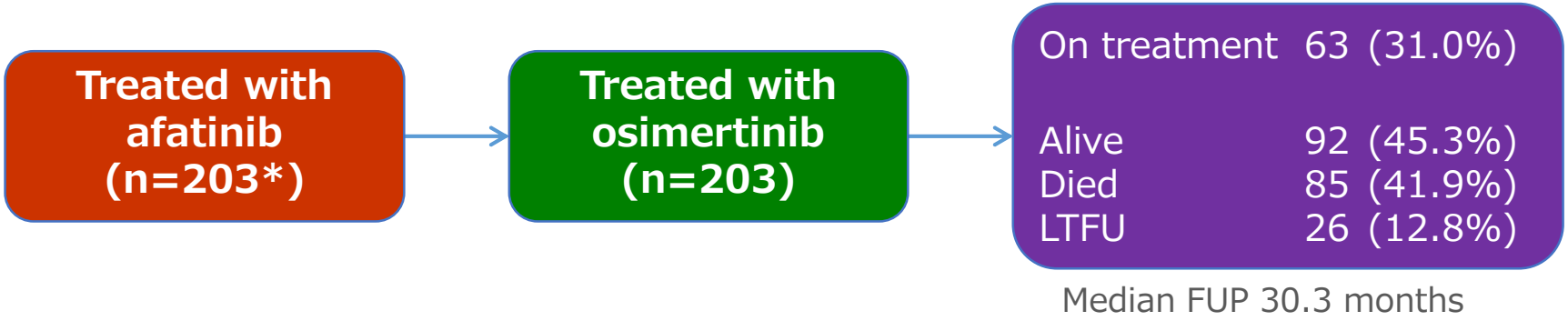
2. Toxicities
   Diarrhoea, skin toxicities: Afatinib > Erlotinib > Gefitinib = Osimertinib
   AST/ALT elevation: Gefitinib > Erlotinib > = Osimertinib ≥ Afatinib
   ILD: Osimertinib≥ Gefitinib = Erlotinib = Afatinib

3. **How to connect EGFR-TKI to osimertinib**

GIO-TAG trial

- 204 patients from 10 countries
  Austria: 8, Canada: 4, Israel: 5, Italy: 18, Japan: 12, Singapore: 1, Slovenia: 5, Spain: 7, Taiwan: 15, USA: 129

- Recruitment (documentation period): 28 Dec 17 – 31 May 2018



Future Oncol. 2019 Sep;15(25):2905-2914. Epub 2019 Aug 2.

GIO-TAG trial: patients characteristics

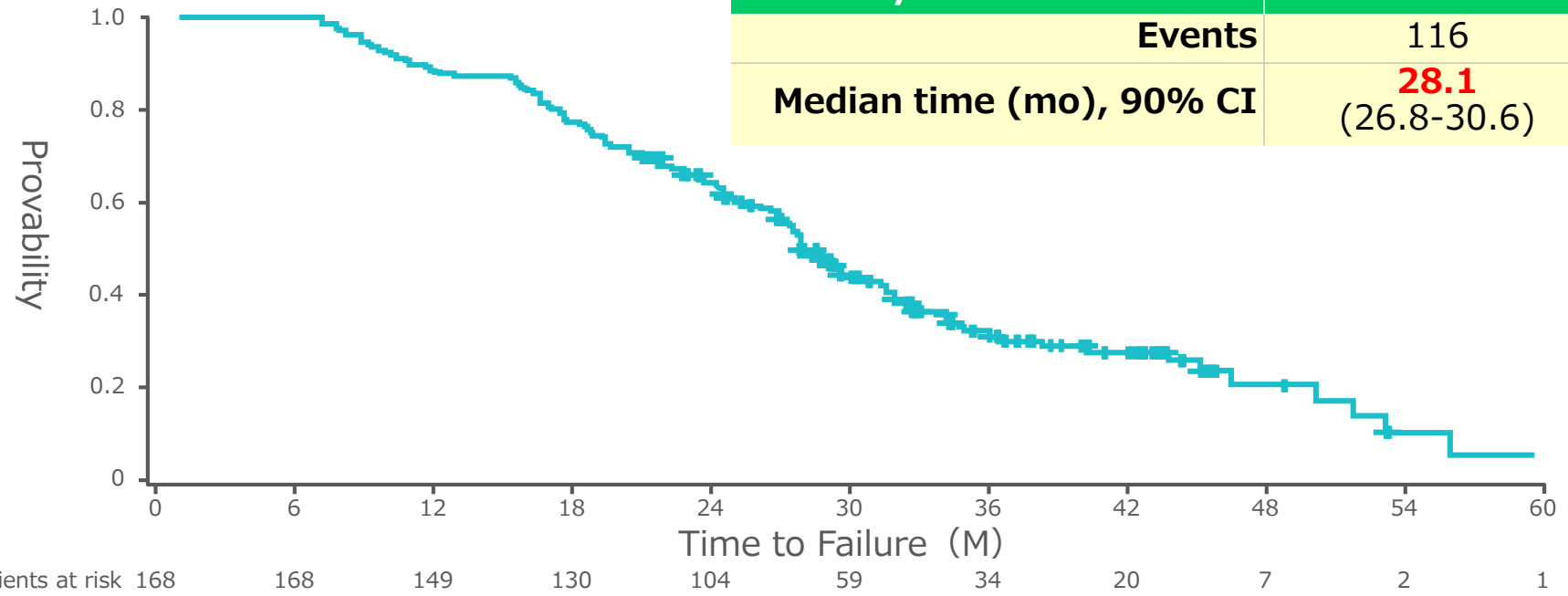
		Non-Asian (n=138) N (%)	Asian (n=50) N (%)
	Female	65 (47.1)	33 (66.0)
Median (range)	Age (years)	61.0 (30 – 86)	60.5 (35 – 78)
	Weight (kg)	74.4 (48 -115)	61.2 (37 -79)
	BMI (kg/m²)	25.8 (18.6 – 39.1)	23.3 (15.0 – 33.8)
ECOG	0	22 (16.1)	16 (32.0)
	1	72 (52.6)	29 (58.0)
	2/3	26 (19.0)	3 (6.0)
EGFR	Del19	108 (78.3)	31 (62.0)
	L858R	29 (21.0)	19 (38.0)
	Del19 + L858R	1 (0.7)	0 (0.0)
	Brain mets	12 (8.7)	8 (16.0)

Future Oncol. 2019 Sep;15(25):2905-2914. Epub 2019 Aug 2.

GIO-TAG trial

Patients Who Started With Afatinib 40 mg （TTF）

Afatinib followed by osimertinib	N=168
Events	116
Median time (mo), 90% CI	**28.1** (26.8-30.6)

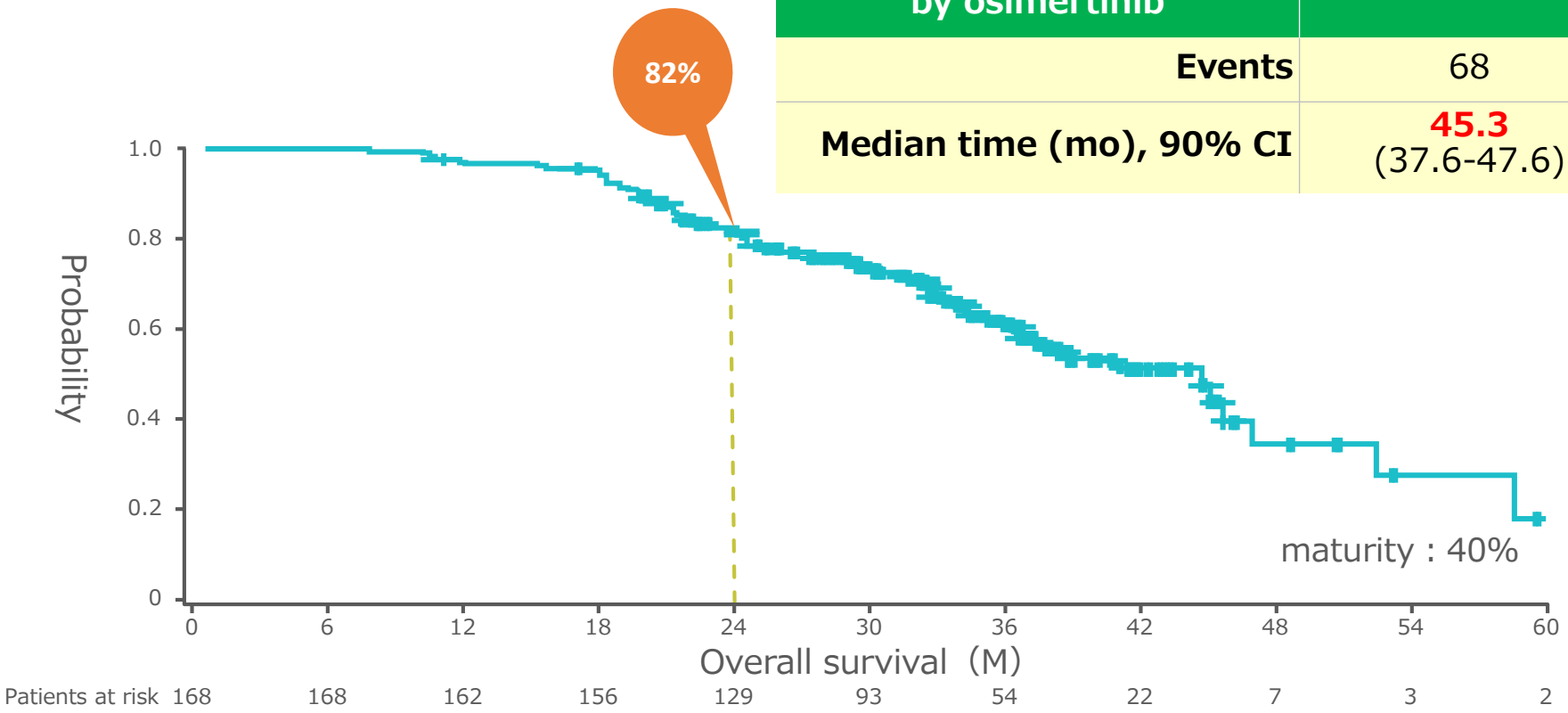


Future Oncol. 2019 Sep;15(25):2905-2914. Epub 2019 Aug 2.

GIO-TAG trial

Patients Who Started With Afatinib 40 mg (OS)

Afatinib followed by osimertinib	N=168
Events	68
Median time (mo), 90% CI	**45.3** (37.6-47.6)



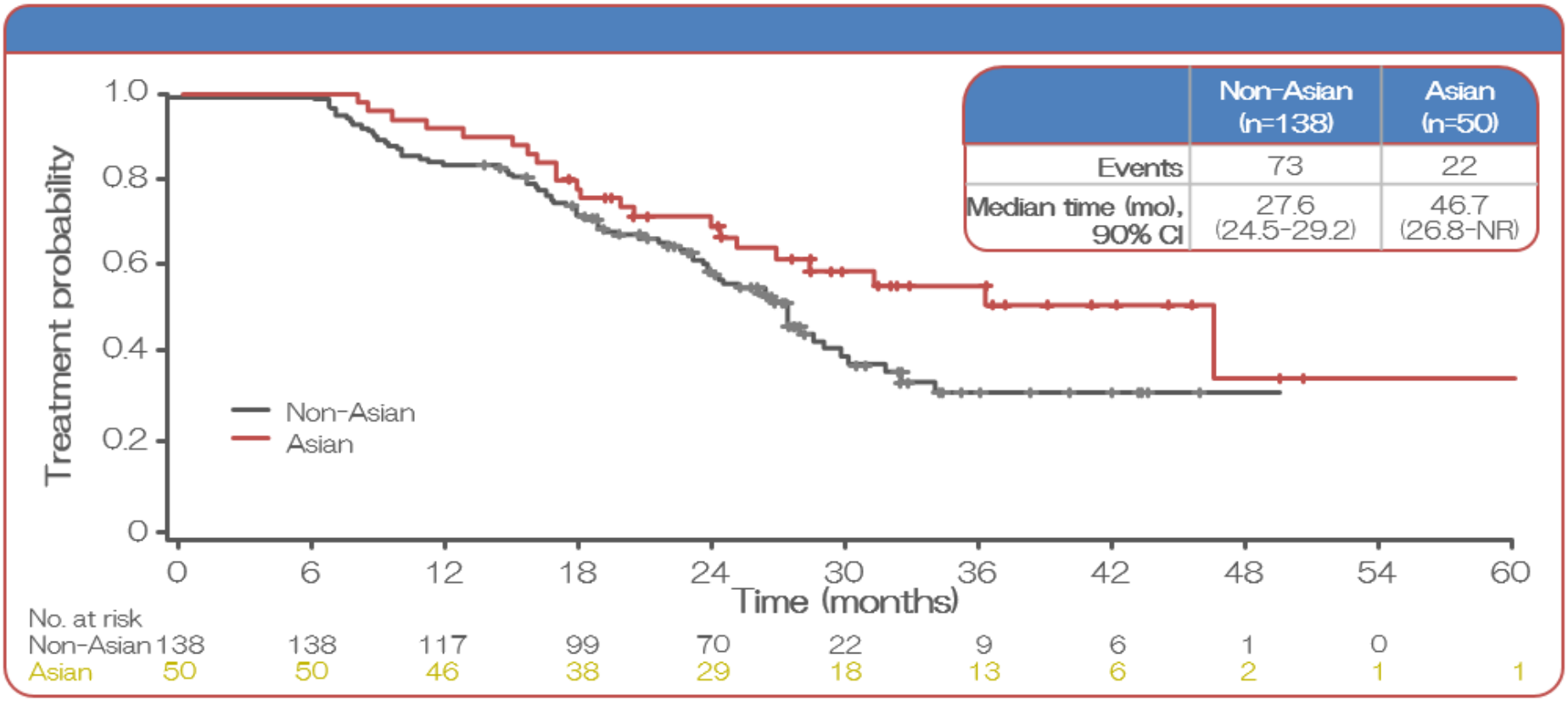
Future Oncol. 2019 Sep;15(25):2905-2914. Epub 2019 Aug 2.

GioTag trial: Race

[primary endpoint] Time to Treatment:
From start of afatinib to finish of osimertinib or death

afatinib ⇨ osimertinib

Time to Treatment of sequence



	Non-Asian (n=138)	Asian (n=50)
Events	73	22
Median time (mo), 90% CI	27.6 (24.5-29.2)	46.7 (26.8-NR)

Future Oncol. 2019 Sep;15(25):2905-2914. Epub 2019 Aug 2.

Comparison Between 1st- and 2nd-Gen EGFR-TKI Followed by Osimertinib

【Retrospective analysis of medical records】

- Osaka International Cancer Institute
- Osaka Habikino Medical Center
- National Hospital Organization Kinki-Chuo Chest Medical Center

Tamiya M, Tamiya A, et al. Anticancer Research 2019

Osimertinib Response Comparison Between the Last Administration of 1st- and 2nd-Gen EGFR-TKI

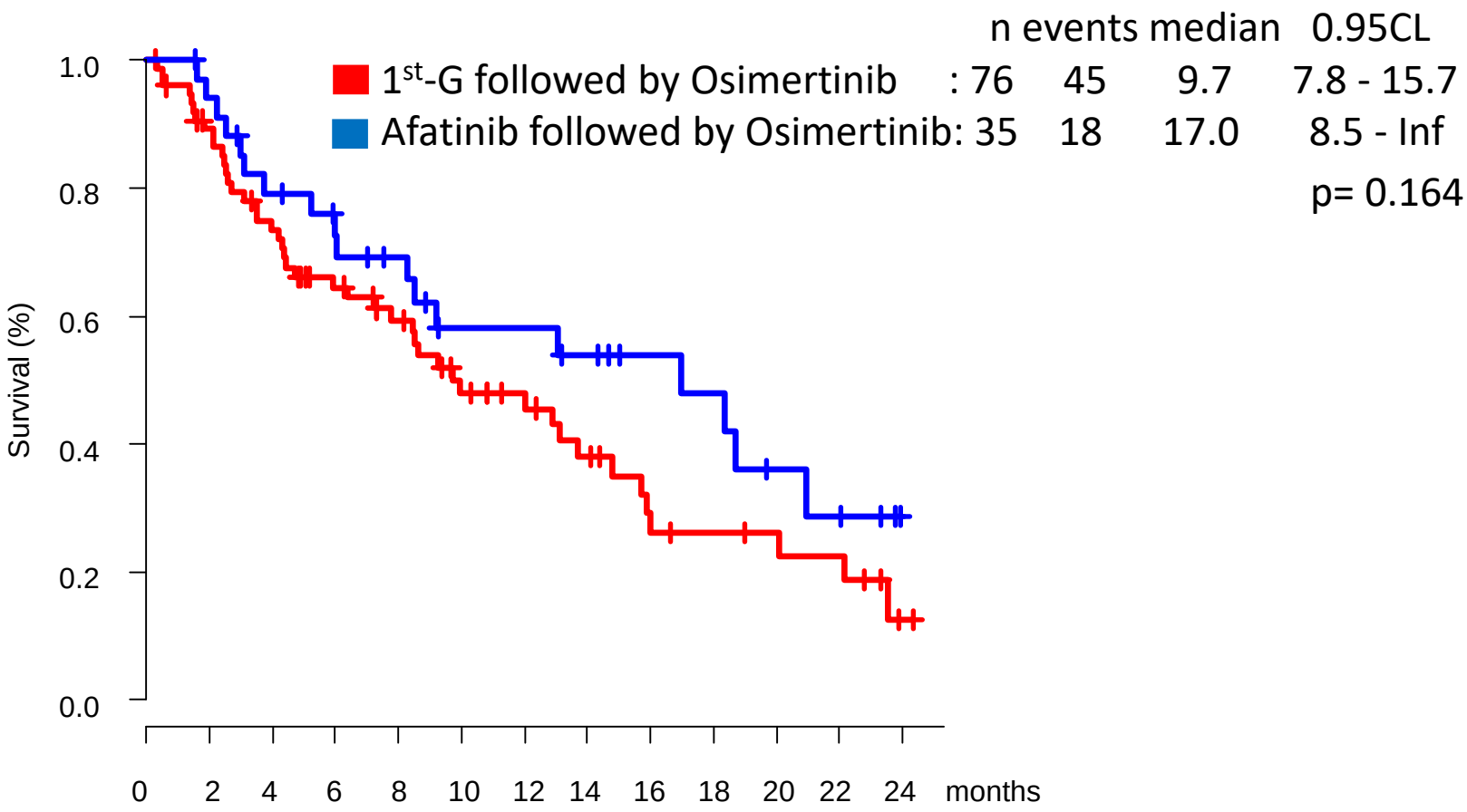
	n	RR (%)	DCR (%)	CR (%)	PR (%)	SD (%)	PD (%)	NE (%)
All patients	111	63.1%	78.4%	2 1.8%	68 61.3%	17 15.3%	17 15.3%	7 6.3%
Afa >> Osime	35	82.9%	91.4%	2 5.7%	27 77.1%	3 8.6%	3 8.6%	0 0%
1st-gen >> Osime	76	53.9%	72.4%	0 0%	41 53.9%	14 18.4%	14 18.4%	7 9.2%

The objective response and disease control rates were significantly higher in Afa followed by osime than in those with 1st-G EGFR TKI followed by osime

RR : 82.9% vs 53.9% (p=0.0065), DCR: 91.4% vs 71.1% (p=0.032)

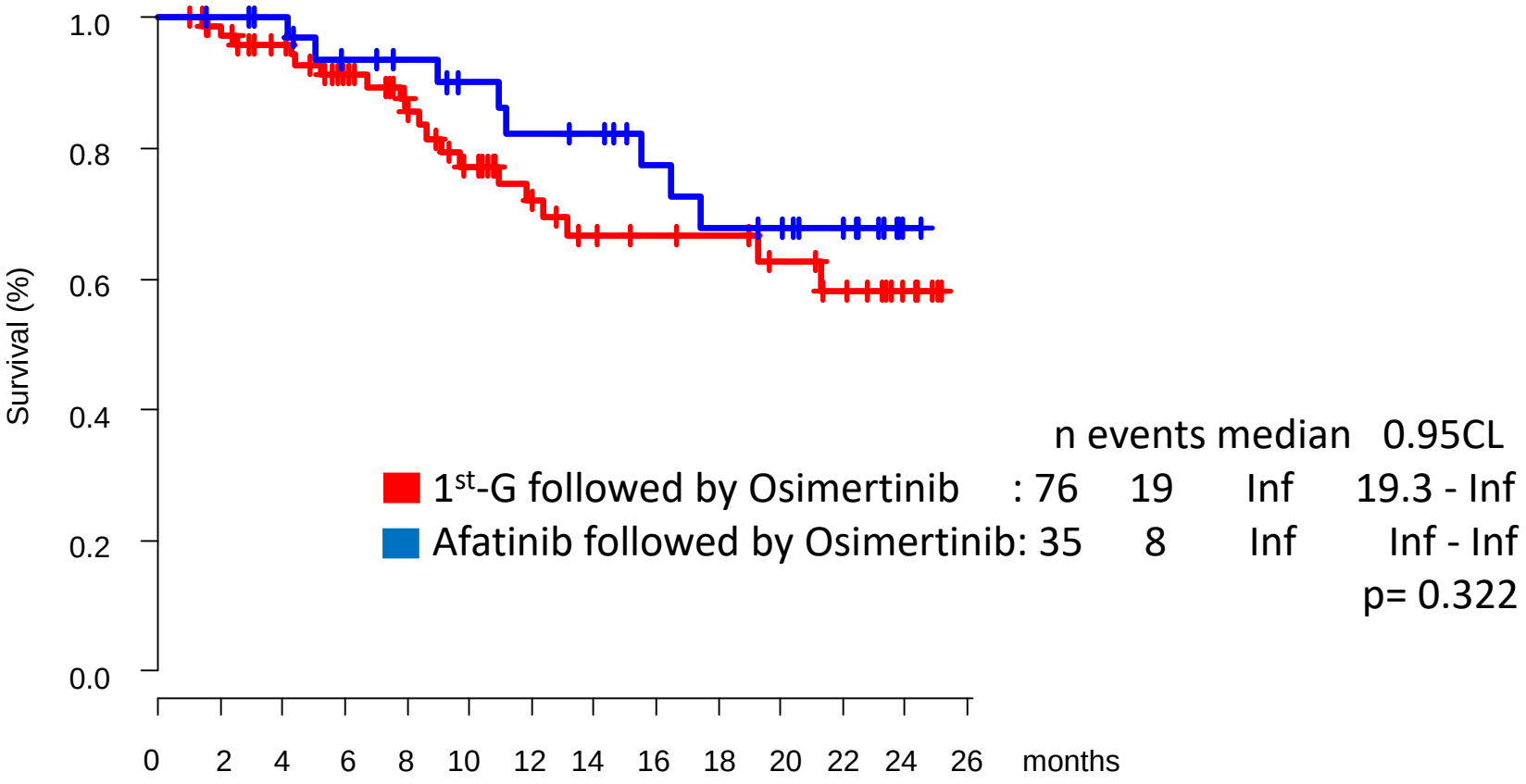
Tamiya M, Tamiya A, et al. Anticancer Research 2019

Osimertinib PFS
Comparison between the last administration of 1st and 2nd gen EGFR-TKI



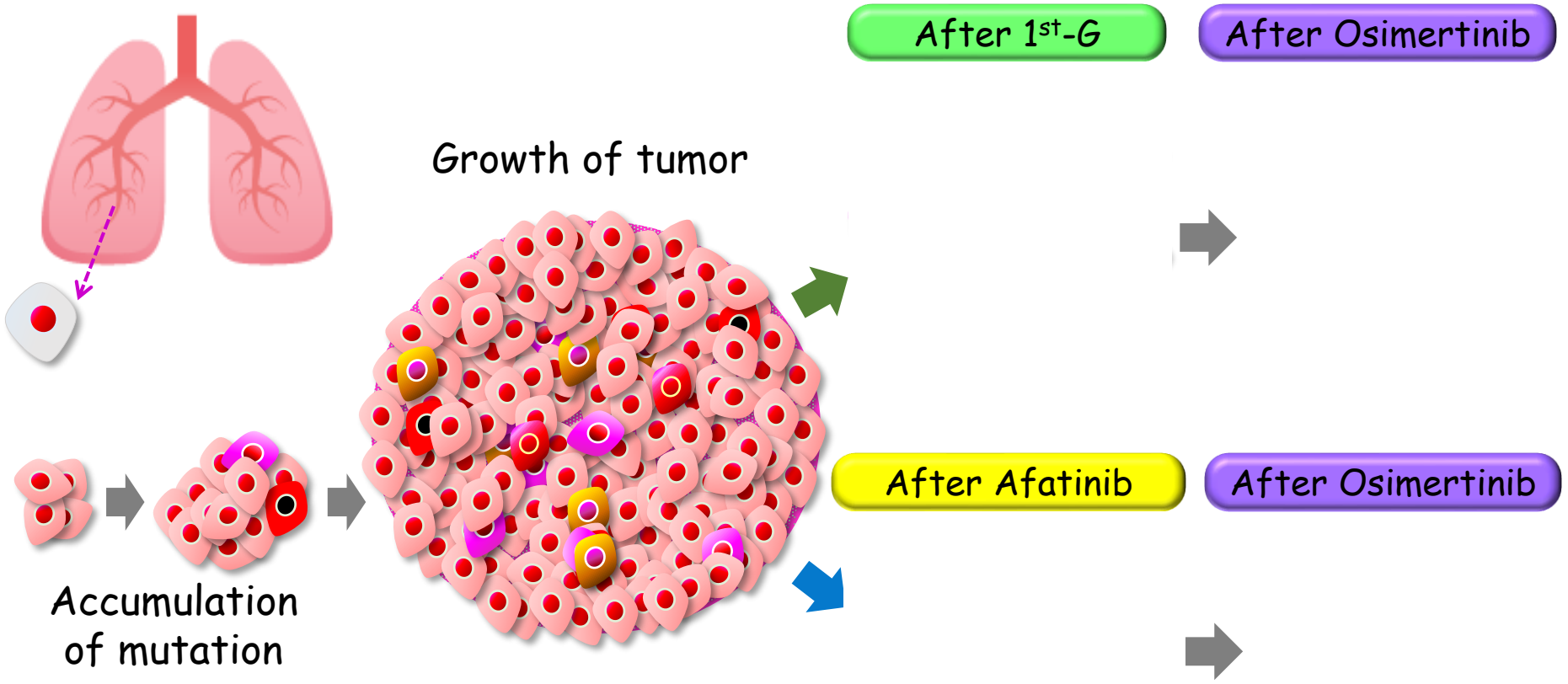
Tamiya M, Tamiya A, et al. Anticancer Research 2019

Osimertinib OS
Comparison between the last administration of 1st and 2nd gen EGFR-TKI



Tamiya M, Tamiya A, et al. Anticancer Research 2019

More efficacy of Osimertinib after afatinib



Purify to T790M colony
⇒ More effective for Osimertinib ?

Considerations in 1st-Line Treatment

What are the important factors in choosing the EGFR-TKI for EGFR mutation–positive patients?

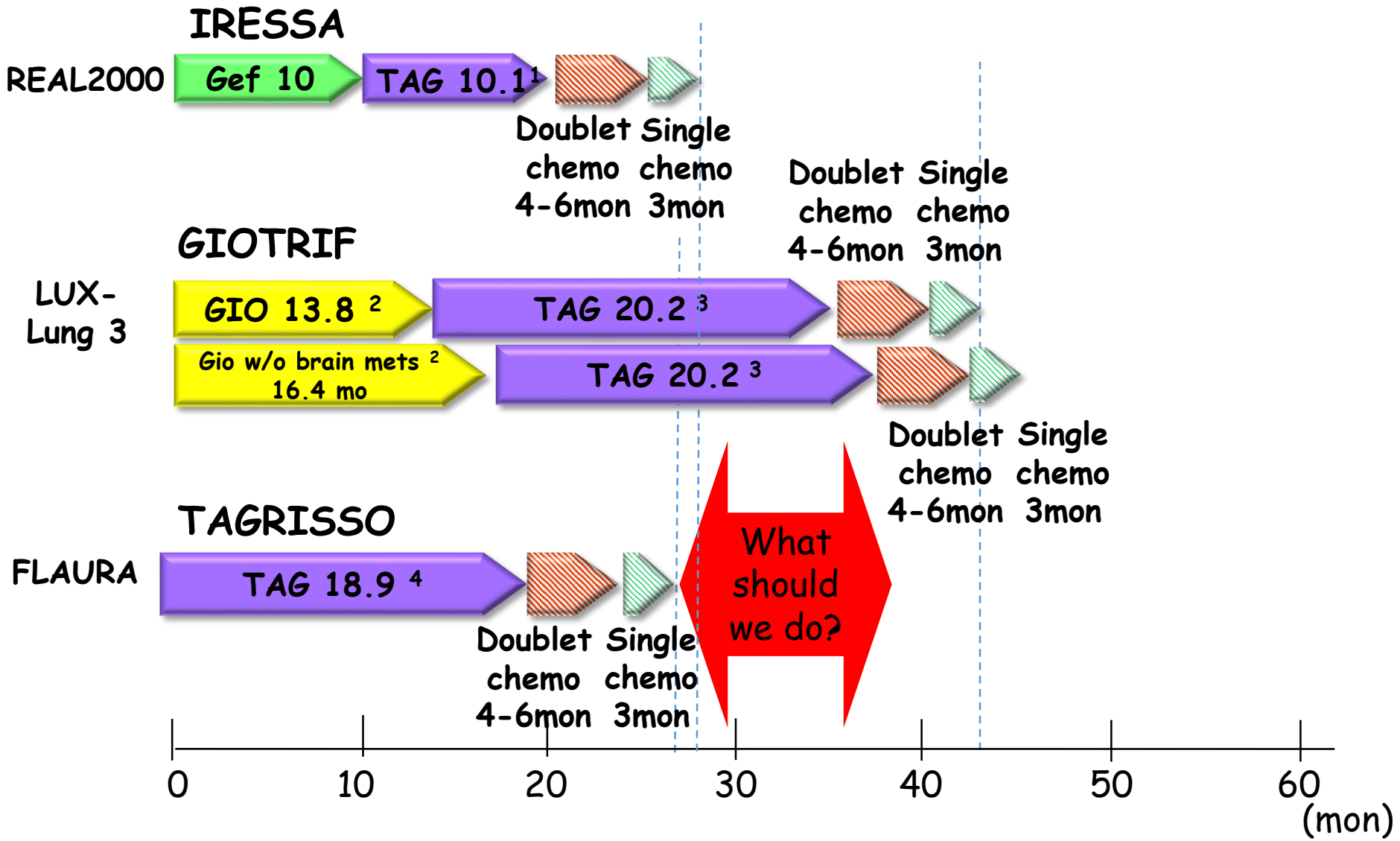
1. Efficacy (response rate, PFS)
   Osimertinib≥Afatinib > Erlotinib = Gefitinib
   (OS)
   (Osimertinib= Afatinib)? > Erlotinib = Gefitinib

2. Toxicities
   Diarrhoea, skin toxicities: Afatinib > Erlotinib > Gefitinib = Osimertinib
   AST/ALT elevation: Gefitinib > Erlotinib > = Osimertinib ≥ Afatinib
   ILD: Osimertinib≥ Gefitinib = Erlotinib = Afatinib

3. How to connect EGFR-TKI to osimertinib

Afatinib > Erlotinib = Gefitinib

Treatment Sequence (Overall survival)



1) Mok TS, et al. N Engl J Med 2017;376(7): 629. 3) Sequist L, et al. ESMO 2017 #1349P.
2) Kato T, et al. Cancer Sci 2015;106(9):1202-1211. 4) Ramalingam S, et al. ESMO 2017 LBA2.

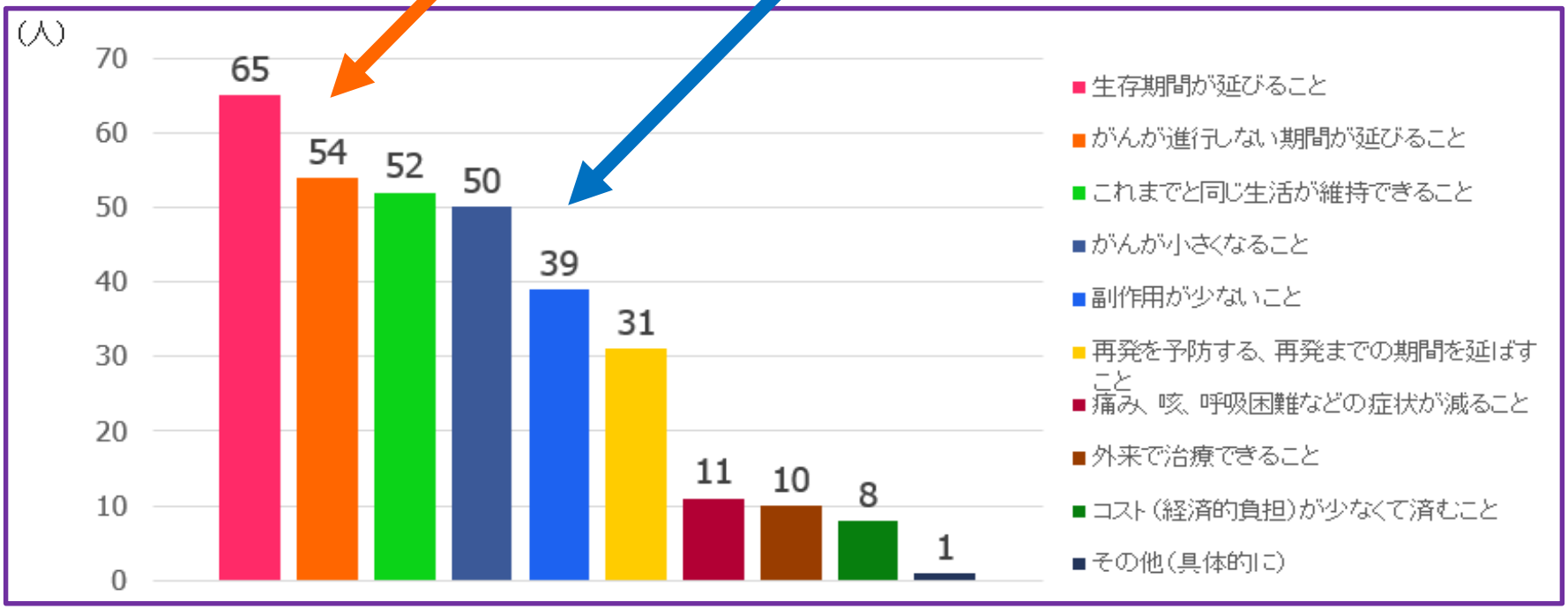
The wish of patients

Patients' thought about efficacy and toxicity (for patients who experienced the chemotherapy)

Extended of overall survival

Extended of progression free survival

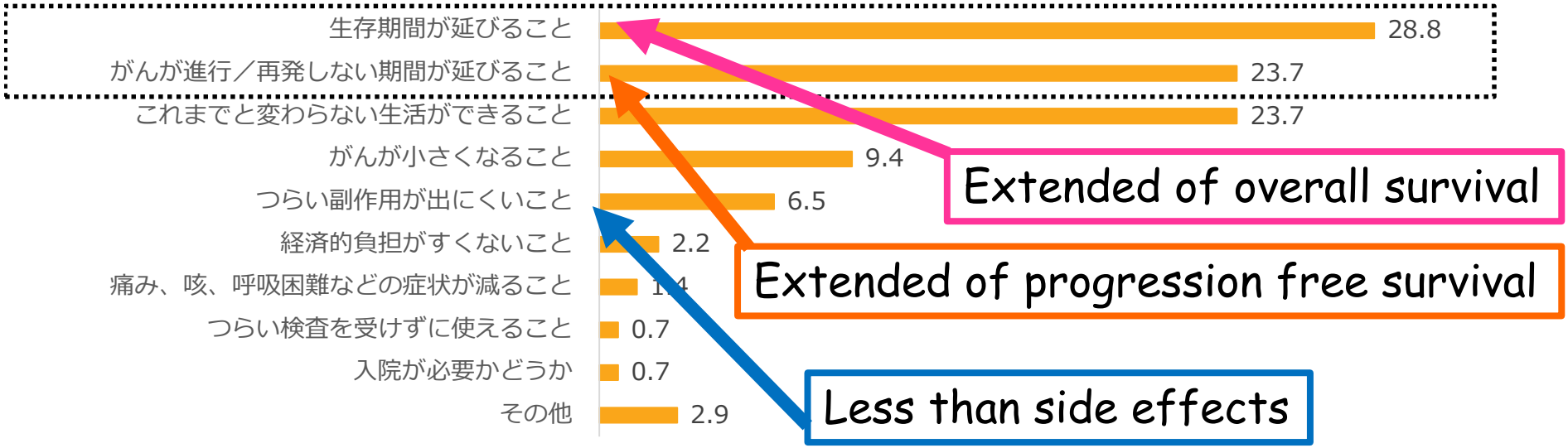
Less than side effects



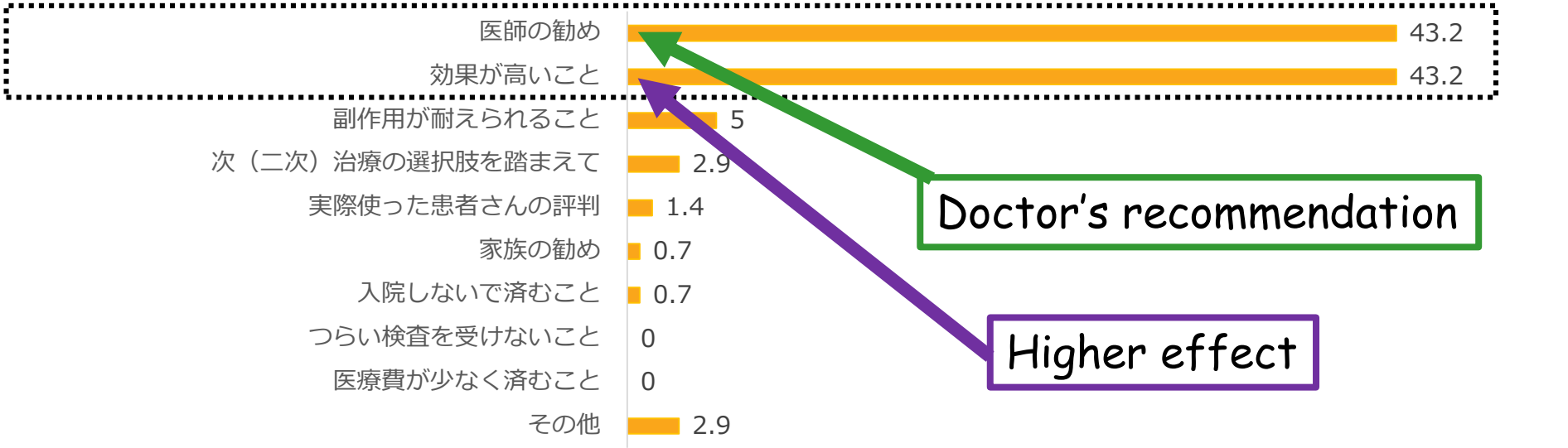
The result of questionnaire for Lung Cancer Patients by Cancer net Japan

Wish of patients who experienced the chemotherapy

●What does patients wish when we start to treat?



●What are the major factors to decide the treatment options?



https://www.boehringer-ingelheim.jp/sites/jp/files/documents/press_release_doc/201905_01.pdf

Take home message

- Afatinib is effective and well-tolerated for EGFR(+) NSCLC patients as a first line treatment.
  (RR:82.9%, Median PFS: 17.4 months in our hospital)

- Afatinib demonstrates good response to intracranial lesions.

- Prophylactic management of side effects can avoid severe toxicities.

- Afatinib before osimertinib is one of the option even if we can use osimertinib as a first line therapy.

THANK YOU
for your
ATTENTION!