15th ANNUAL MIAMI CANCER MEETING (MCM)

New Frontiers for the Treatment of Solid and Liquid Tumors: Delivering Precision Medicine

Oncology Latin American Association

OLA

15TH ANNUAL MIAMI CANCER MEETING

EGFR & ALK: Where Are We Now?

Edgardo S. Santos, M.D., FACP
Medical Director of Cancer Research
Thoracic and Head and Neck Cancer Programs
Eugene M. & Christine E. Lynn Cancer Institute
Associate Professor of Clinical Biomedical Science
Charles E. Schmidt College of Medicine
Florida Atlantic University
Boca Raton, FL, USA

April 28, 2018

Lynn Cancer Institute
Boca Raton Regional Hospital

Edgardo S. Santos, M.D., FACP

EGFR & ALK: Where Are We Now?

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

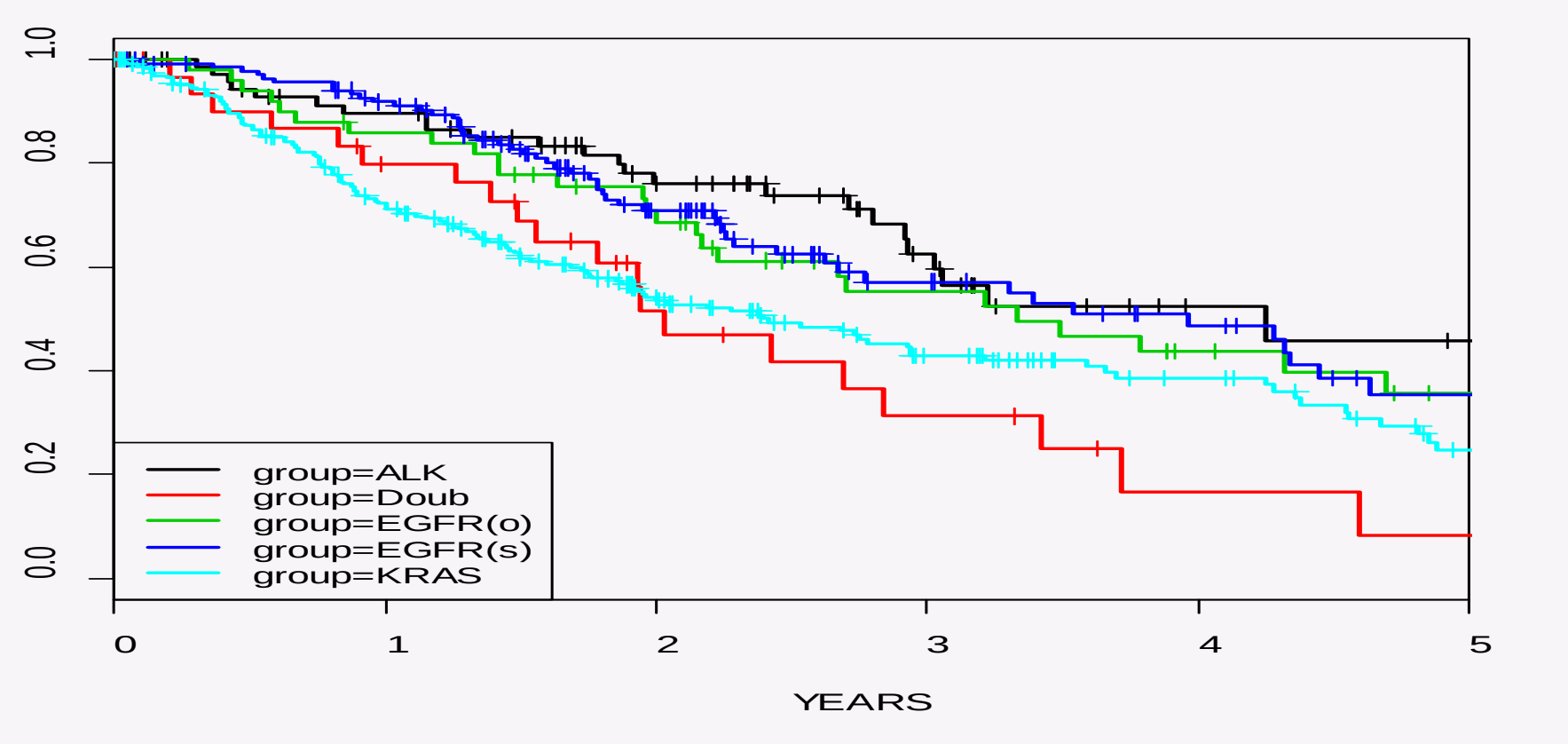
Speakers Bureau: Genentech, Pfizer, Novartis, Merck, Celgene, Amgen, AstraZeneca, Lilly, Takeda, Boehringer-Ingelheim

The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

The Medical Educator Consortium

15th Annual Miami Cancer Meeting

Survival with the five most frequent oncogenic drivers



Altered Gene	N	Median Survival (95% CI)
EGFR (sensitizing)	140	4.0 years (2.7 to 5.4)
EGFR (other)	50	3.3 years (2.2 to 6.2)
ALK	73	4.3 years (3.0 to NA)
KRAS	231	2.4 years (1.9 to 3.6)
Drivers in Two Genes	32	2.0 years (1.6 to 4.6)

LUNG CANCER MUTATION CONSORTIUM

Matching Patients with the Best Possible Therapies

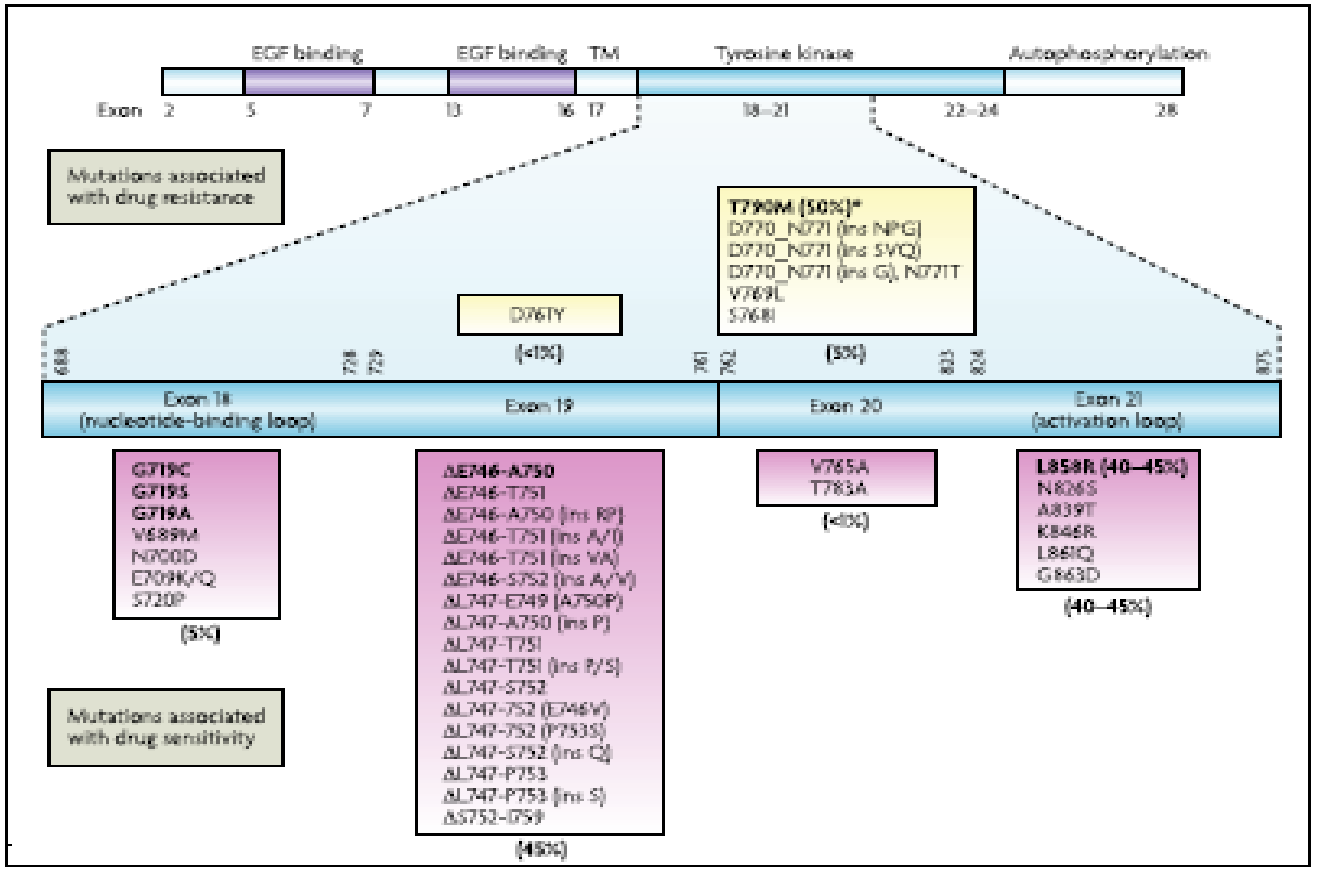
Kris and Johnson; JAMA 2014

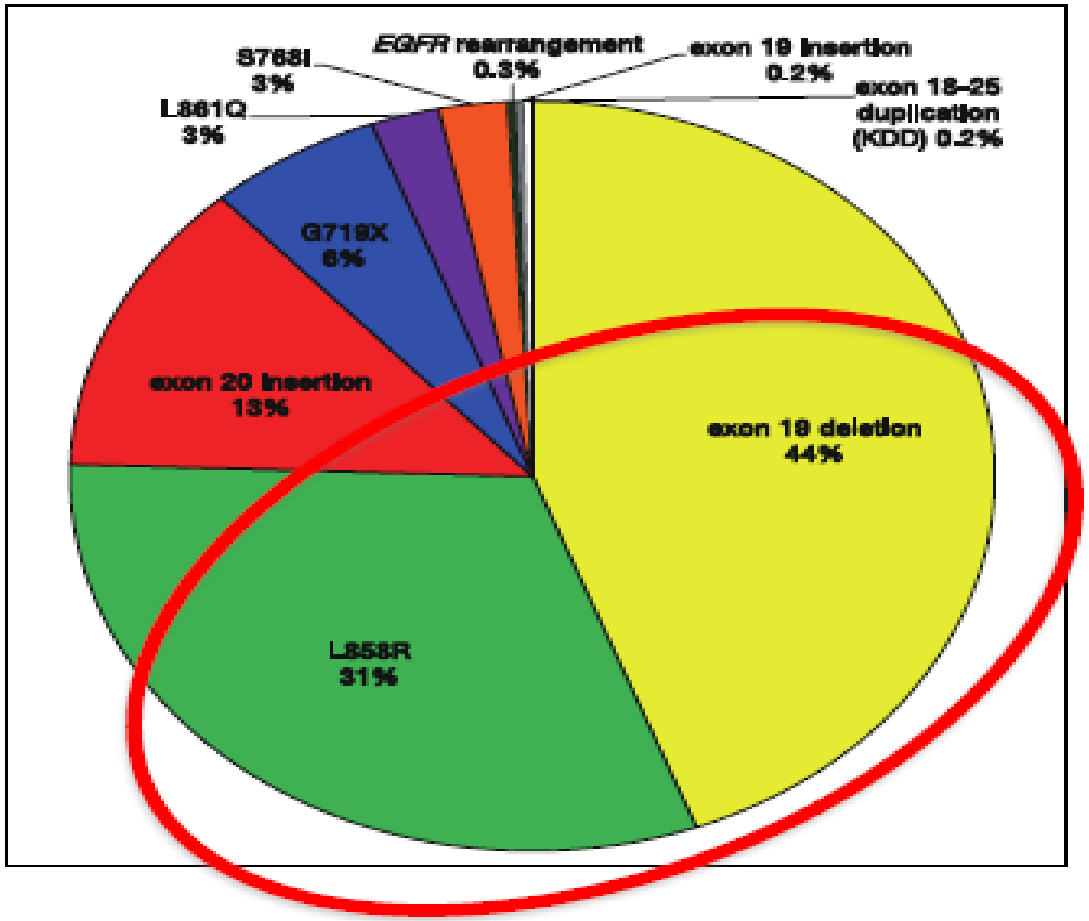
IASLC 2017

What's New From ASCO 2017, ESMO 2017, WCLC 2017, ELCC 2018?

EGFR MUTANT TUMORS

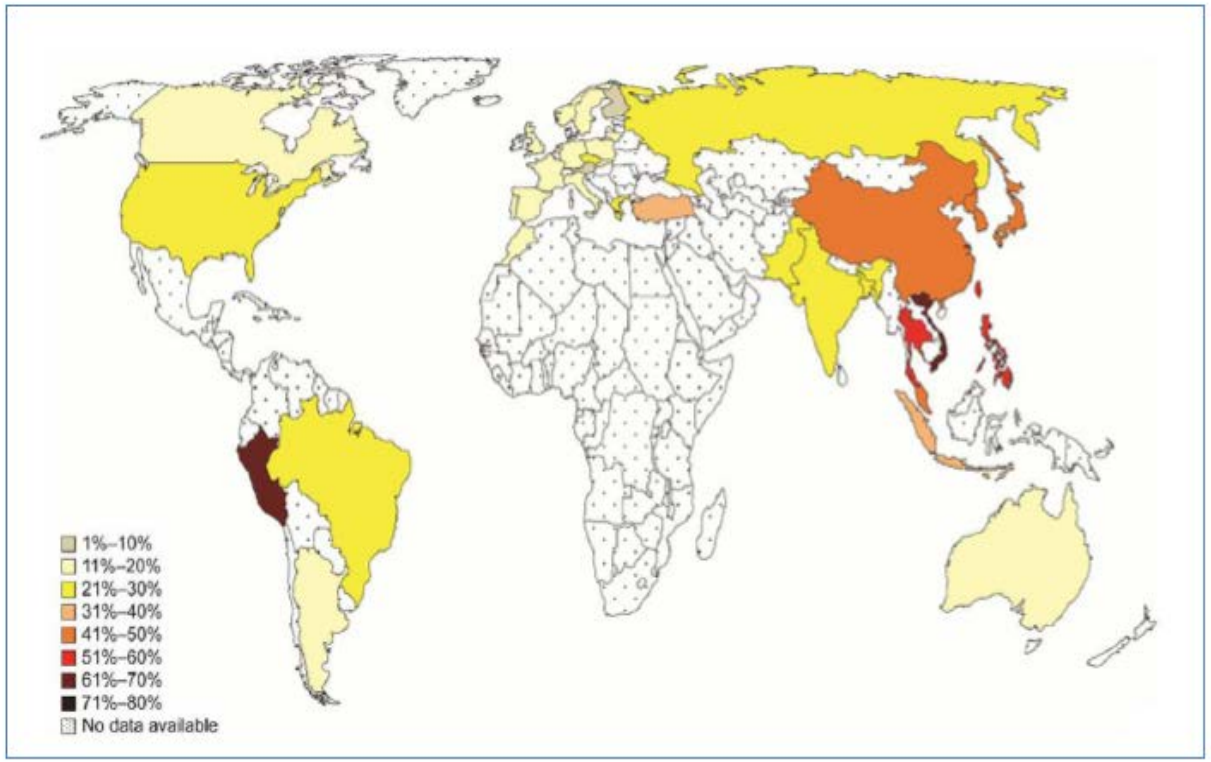
Activating mutations in the EGFR kinase domain confer therapeutic vulnerability to EGFR TKIs





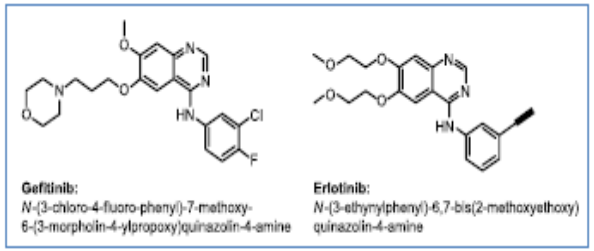
Sharma et al, Nature Rev Cancer 2007; Konduri et al, Cancer Disc. 2016

The prevalence of EGFR mut. lung adenocarcinoma varies between different countries



Midha et al, Am J Cancer Res 2015

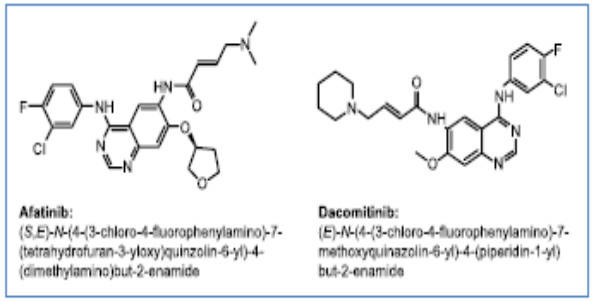
Different types of EGFR TKIs have been developed



1st gen. (erlotinib, gefitinib)

4-Anilino-quinazoline

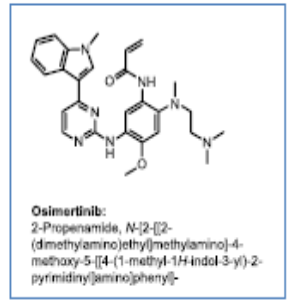
> reversible, non covalent binding



2nd gen. (afatinib, dacomitinib)

Anilino-quinazoline

> covalent, irreversible binding



3rd gen. (osimertinib)

Mono-anilino-pyrimidine

> covalent, irreversible binding

Wang et al, Oncotargets and Therapy 2016

Oncology Latin American Association
OLA

Is There A Controversy? Yes or No

SHOULD OSIMERTINIB BE THE FIRST LINE THERAPY IN EGFR SENSITIVE MUTATION?

Osimertinib > Gefitinib/Erlotinib (FLAURA study; phase III)

Afatinib vs Osimertinib? (no data)

Afatinib > Gefitinib (LUX-Lung 7; phase IIb)

Dacomitinib > Gefitinib (ARCHER 1050; phase III trial)

"Sequence vs No Sequence" …. ⟵ **The question?**

THIS IS NOW!!! APRIL 28, 2018

Oncology Latin American Association
OLA

April 18,2018

US FDA approves *Osimertinib* as *1st-line treatment* for EGFR-mutated non-small cell lung cancer

First line use of Osimertinib offers potential new standard of care; Osimertinib delivered unprecedented median progression-free survival of 18.9 months versus 10.2 months compared with current standard of care

AstraZeneca today announced that the US Food and Drug Administration (FDA) has approved Osimertinib for the 1st-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations, (exon 19 deletions or exon 21 L858R mutations), as detected by an FDA-approved test. The approval is based on results from the Phase III FLAURA trial, which were presented at the European Society of Medical Oncology 2017 Congress and published in the New England Journal of Medicine.

MADRID 2017 ESMO congress

OSIMERTINIB VS STANDARD-OF-CARE EGFR-TKI AS FIRST-LINE TREATMENT IN PATIENTS WITH EGFRm ADVANCED NSCLC: FLAURA

Ramalingam SS[1], Reungwetwattana T[2], Chewaskulyong B[3], Dechaphunkul A[4], Lee KH[5], Imamura F[6], Nogami N[7], Ohe Y[8], Cheng Y[9], Cho BC[10], Cho EK[11], Vansteenkiste J[12], Voon PJ[13], Zhou C[14], Gray JE[15], Hodge R[16], Rukazenkov Y[16], Soria JC[17]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [3]Oncology Unit, Department of Medicine, Chiang Mai University, Chiang Mai, Thailand; [4]Prince of Songkla University, Songkhla, Hat-Yai, Thailand; [5]Division of Medical Oncology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheong-ju, Korea; [6]Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan; [7]Department of Thoracic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [8]Department of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan; [9]Jilin Provincial Cancer Hospital, Changchun, China; [10]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [11]Division of Hematology and Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea; [12]University Hospital KU Leuven, Leuven, Belgium; [13]Hospital Umum Sarawak, Kuching, Malaysia; [14]Pulmonary Hospital of Tongji University, Shanghai, China; [15]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [16]AstraZeneca, Cambridge, United Kingdom; [17]Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France

Presented by SS Ramalingam at the European Society of Medical Oncology Congress 2017

MADRID 2017 ESMO congress

FLAURA DOUBLE-BLIND STUDY DESIGN

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years*
- WHO performance status 0 / 1
- Exon 19 deletion / L858R (enrolment by local# or central‡ EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification by **mutation status** (Exon 19 deletion / L858R) and **race** (Asian / non-Asian)

Randomised 1:1

Osimertinib (80 mg p.o. qd) (n=279)

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 progressive disease

Crossover was allowed for patients in the **SoC** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

Endpoints

- **Primary endpoint**: PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints**: objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

FLAURA data cut-off: 12 June 2017; NCT02296125

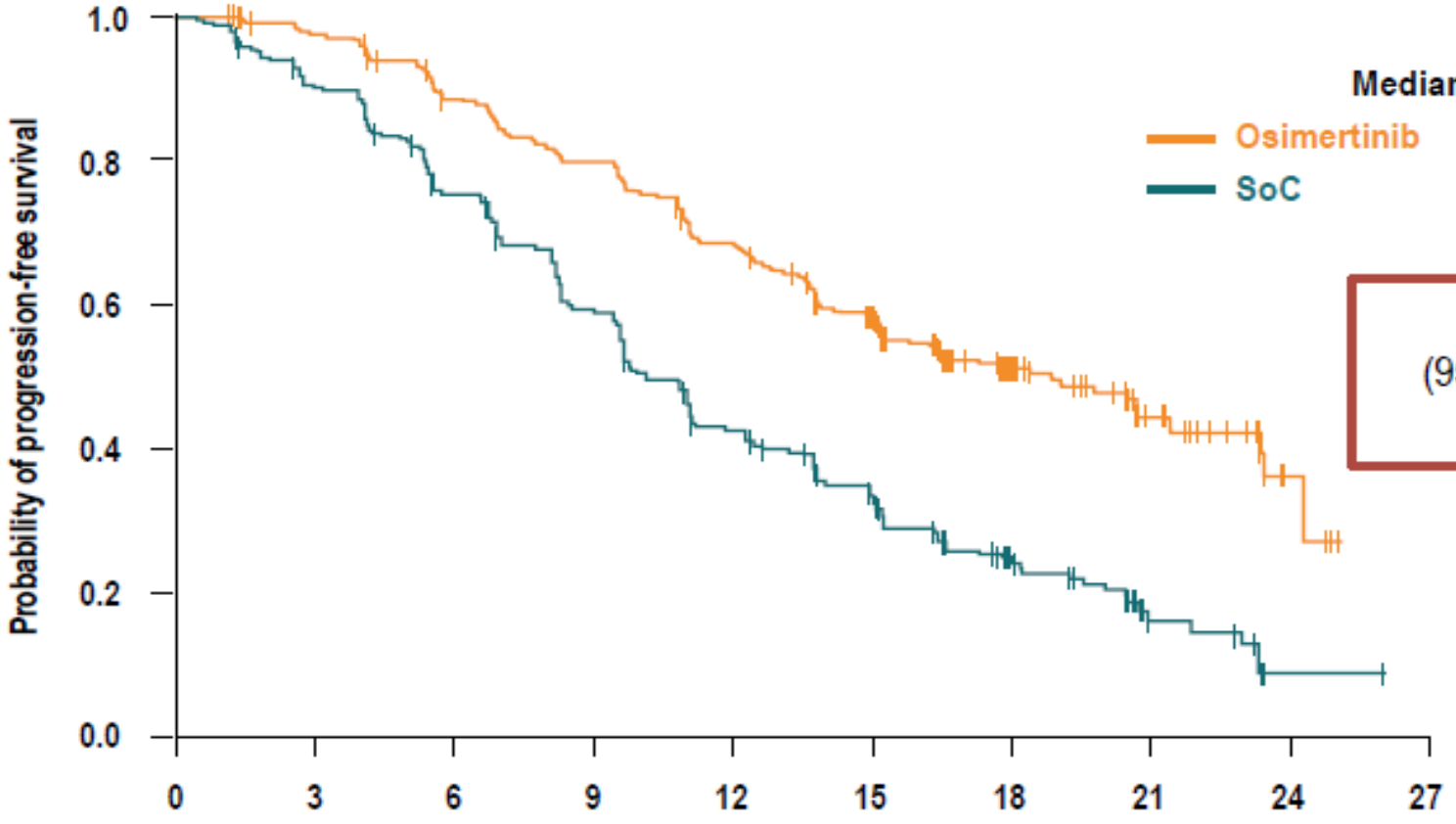
*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months

CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; qd, once daily; SoC, standard-of-care; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

MADRID 2017 ESMO congress

PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)

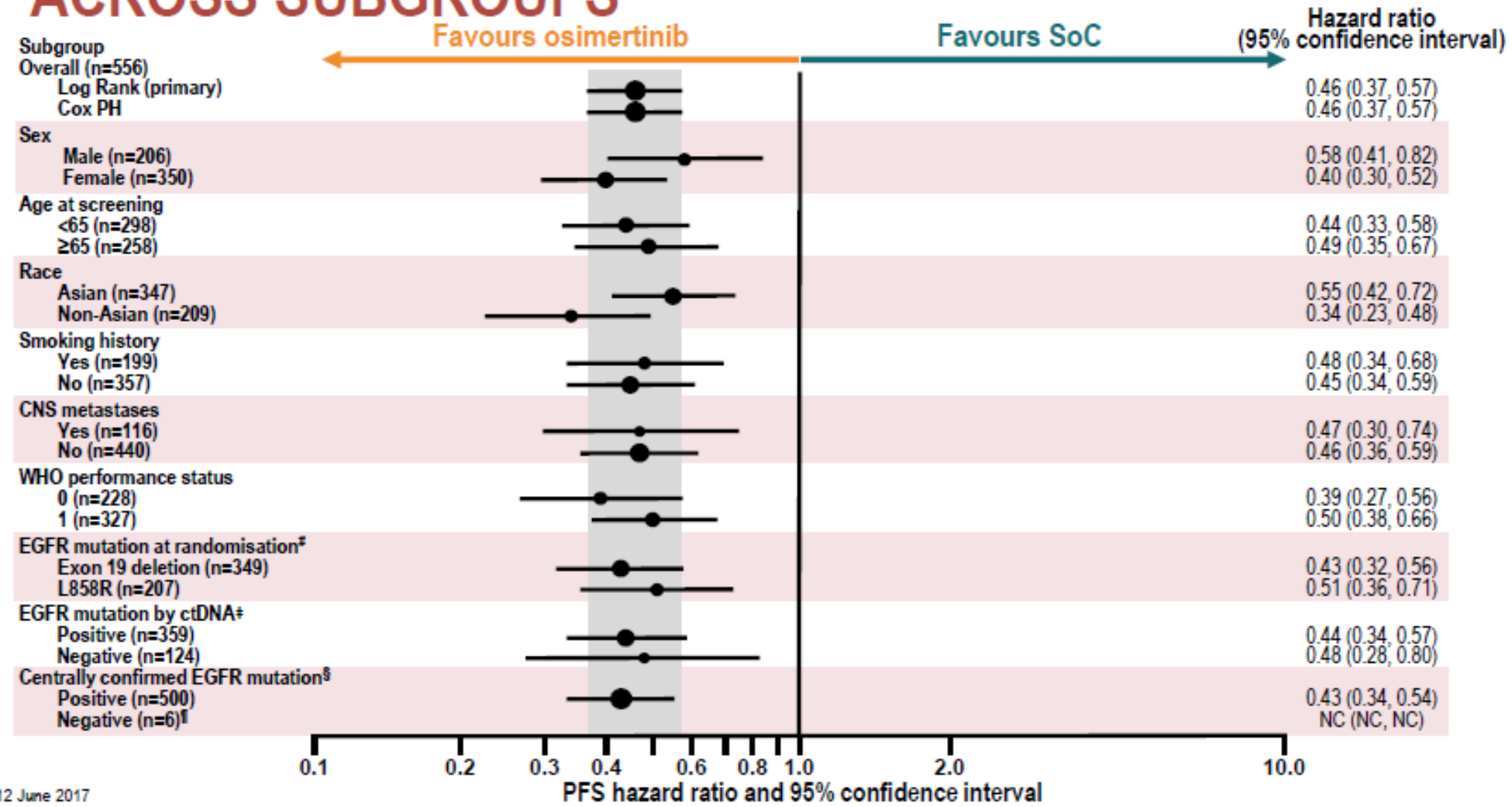


No. at risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
SoC	277	239	197	152	107	78	37	10	2	0

FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data;
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; SoC, standard-of-care; PFS, progression-free survival

MADRID 2017 ESMO congress

PFS* ACROSS SUBGROUPS



FLAURA data cut-off: 12 June 2017

Hazard ratio <1 implies a lower risk of progression on osimertinib 80 mg. Size of circle is proportional to the number of events

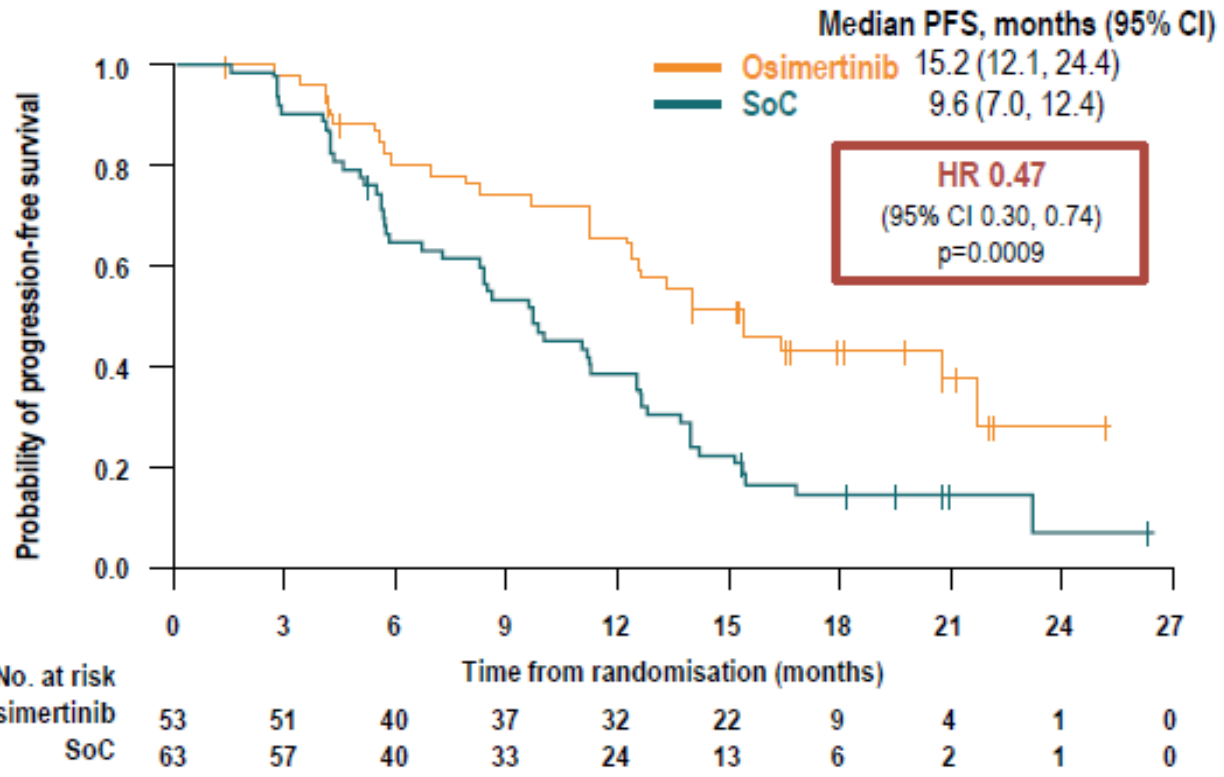
*By Investigator assessment; ‡Local or central test; †Result missing for 36 patients in the osimertinib arm and 37 patients in the SoC arm; §Result missing for 21 patients in the osimertinib arm and 29 patients in the SoC arm; ¶Subgroup categories with less than 20 events were excluded from the analysis

CNS, central nervous system; ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; PFS, progression-free survival; SoC, standard-of-care; WHO, World Health Organization

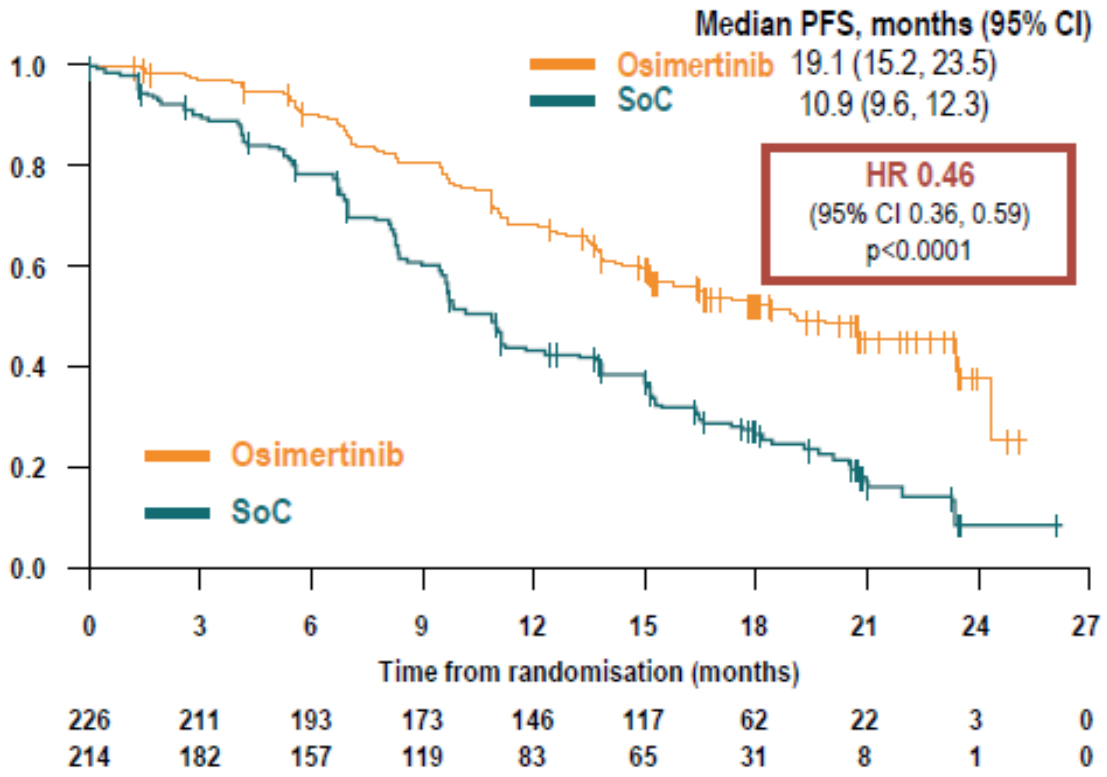
MADRID 2017 ESMO congress

PFS* IN PATIENTS WITH AND WITHOUT CNS METASTASES AT STUDY ENTRY

With CNS metastases (n=116)



Without CNS metastases (n=440)



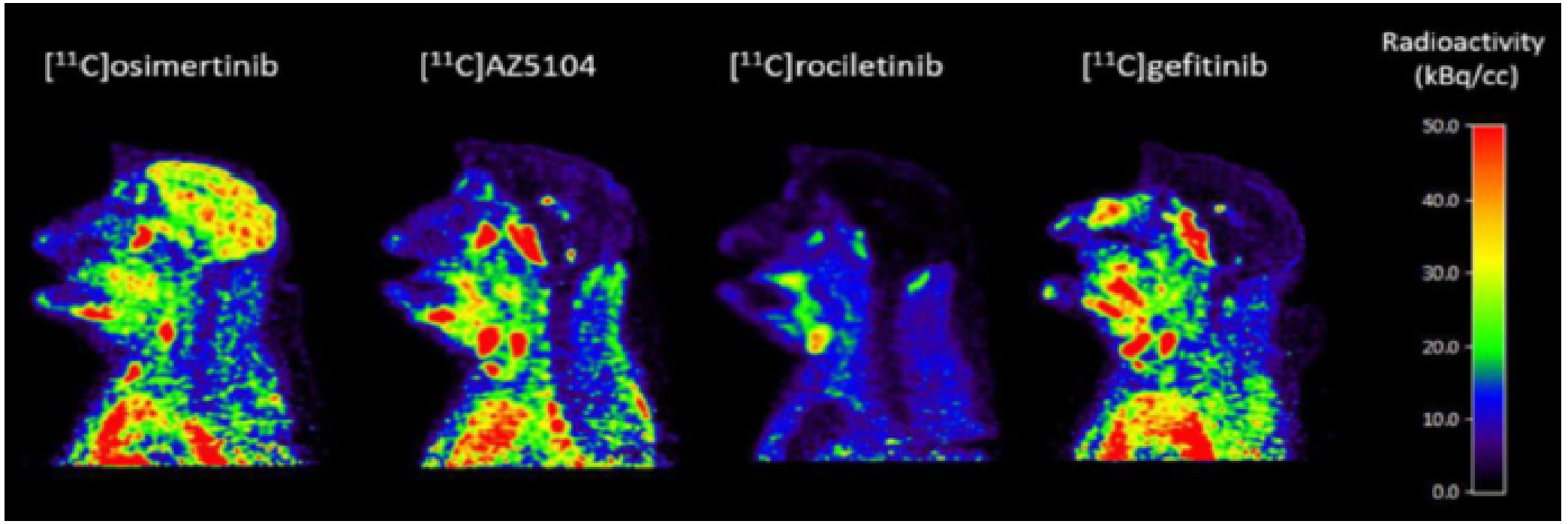
CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data; *By Investigator assessment
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PFS, progression-free survival; SoC, standard-of-care

Drug Exposure in the Brain

	Osimertinib	Gefitinib	Rociletinib	Afatinib
Dose (mg/kg)	25	6.25	100	7.5
Plasma C_{max} (μmol/L)	0.82	0.82	3.32	0.14
Brain C_{max} (μmol/L)	2.78	0.17	BLQ	BLQ
Brain/plasma C_{max} ratio	3.41	0.21	<0.08	<0.36

NOTE: Doses equivalent to clinical doses or reported previously.
Abbreviation: BLQ, below limit of quantification (rociletinib 0.25 μmol/L, afatinib 0.05 μmol/L); C_{max}, maximum plasma concentration.

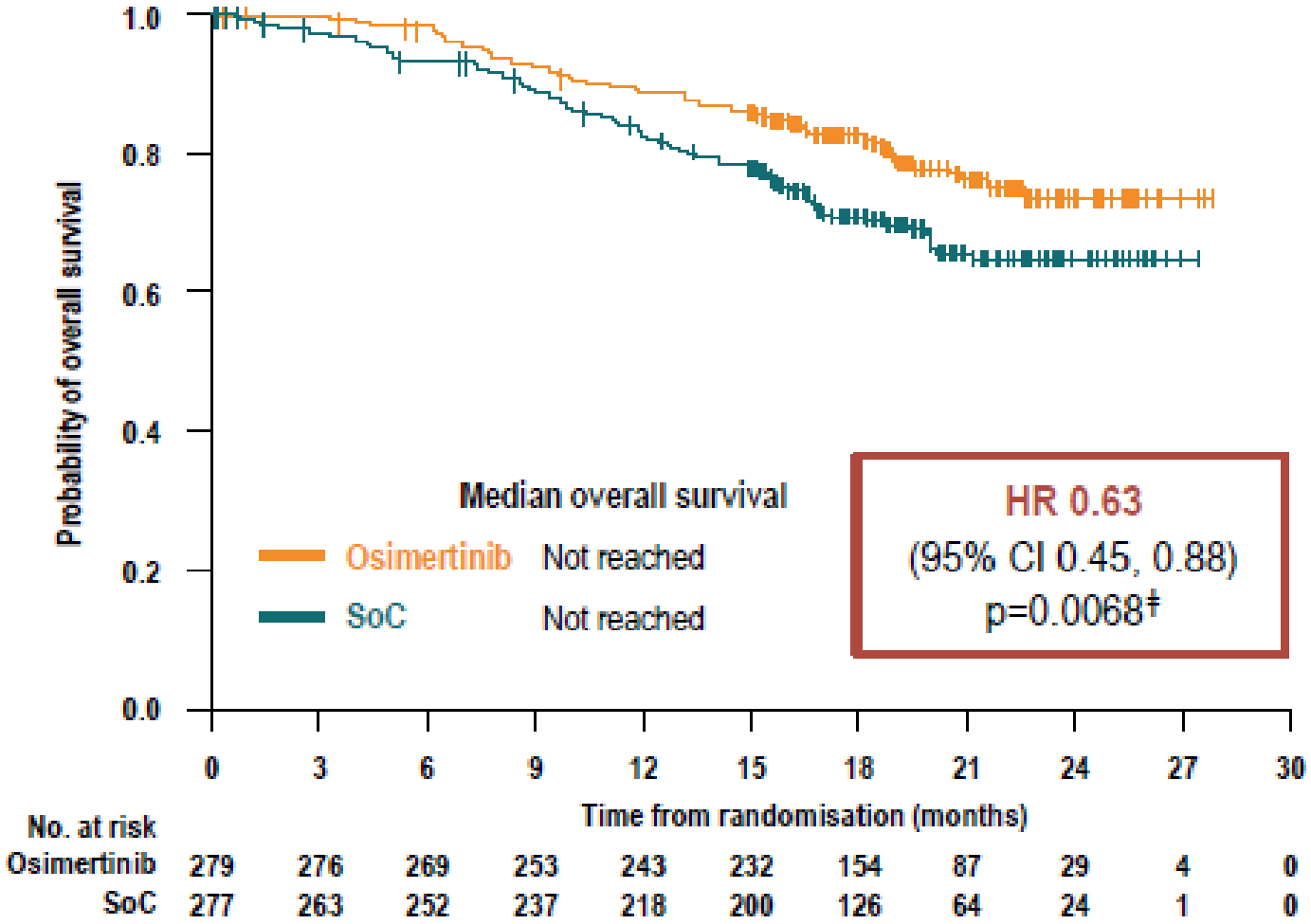


Ballard et al, Clin Cancer Res, 2016

MADRID 2017 ESMO congress

OVERALL SURVIVAL INTERIM ANALYSIS

141 deaths in 556 patients at DCO: 25% maturity; osimertinib: 58 deaths (21%), SoC: 83 deaths (30%)



‡A p-value of <0.0015 was required for statistical significance at current maturity

FLAURA data cut-off: 12 June 2017; Tick marks indicate censored data
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; SoC, standard-of-care

So, based on the FLAURA study…..

Should the winner take it all?

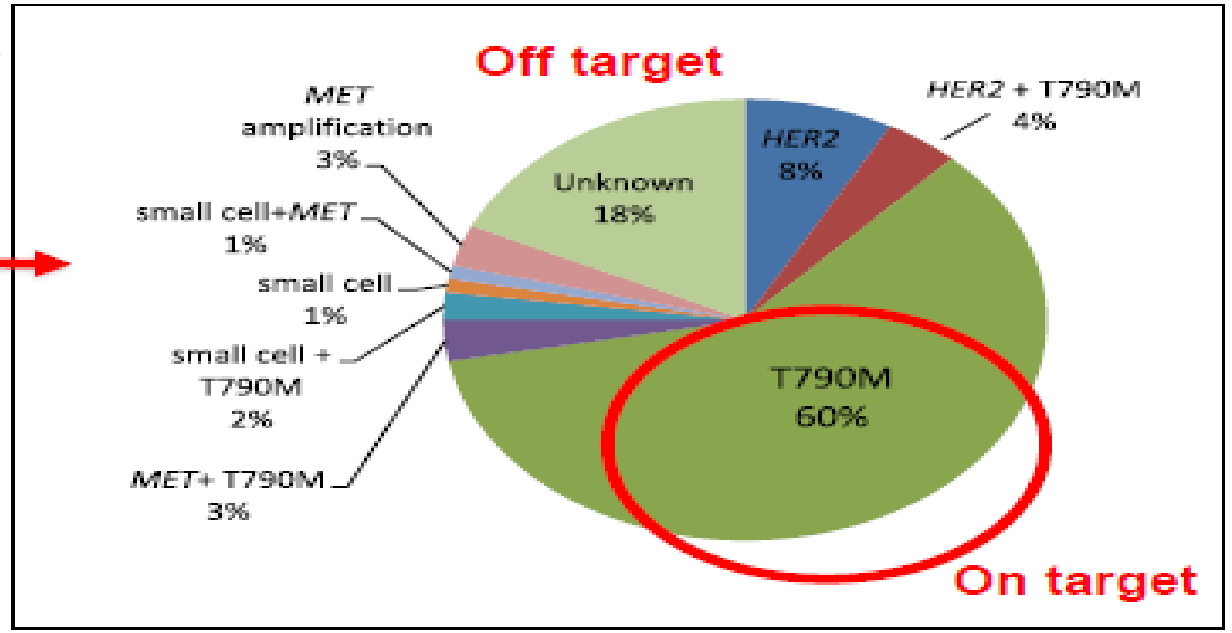
Molecular mechanisms of acquired resistance to 1st and 2nd gen. TKIs: in about 60% of cases EGFR T790M resistance mutation

Initial biopsy

EGFR del 19 L858R

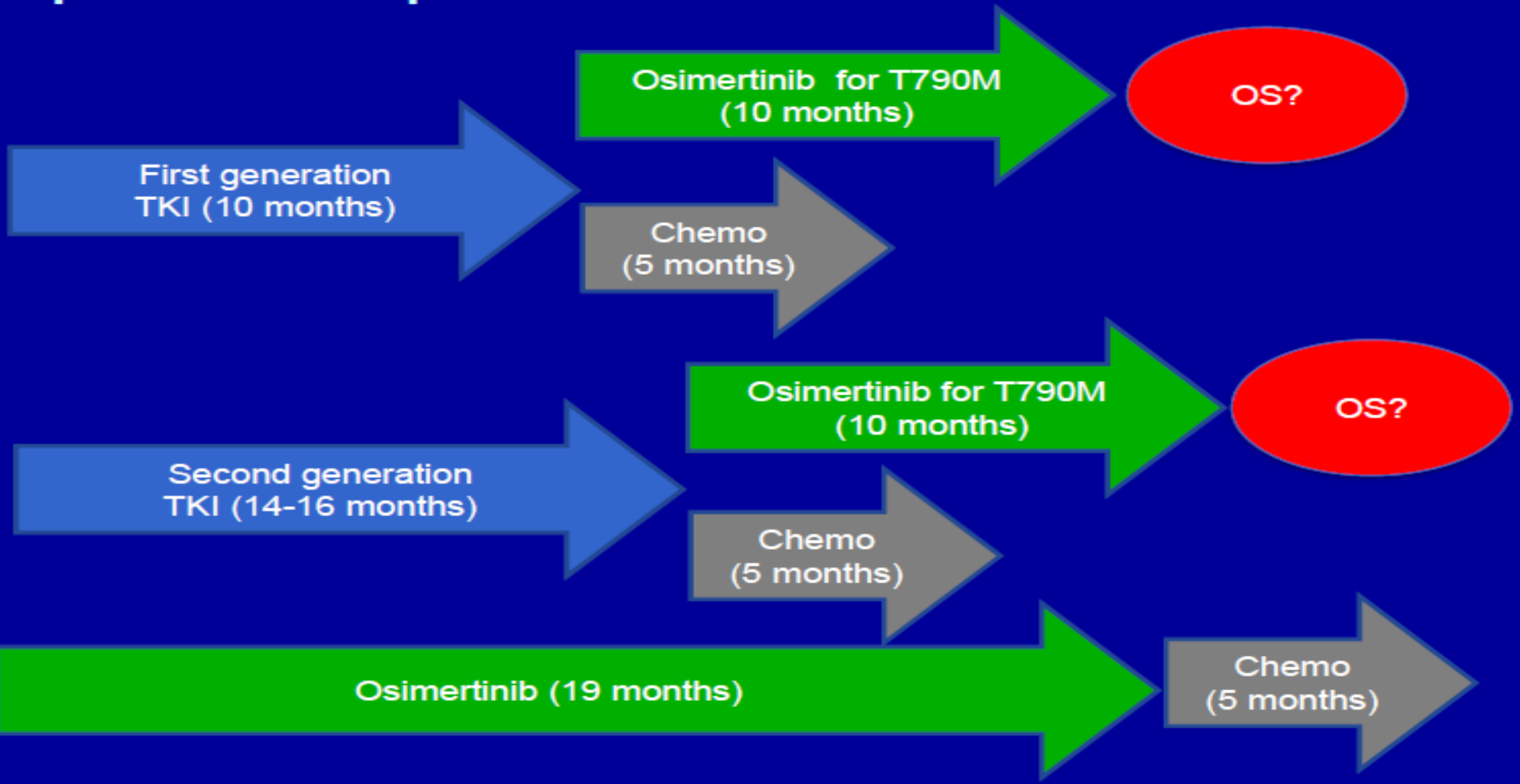
1st and 2nd gen. EGFR-TKI

PD: rebiopsy

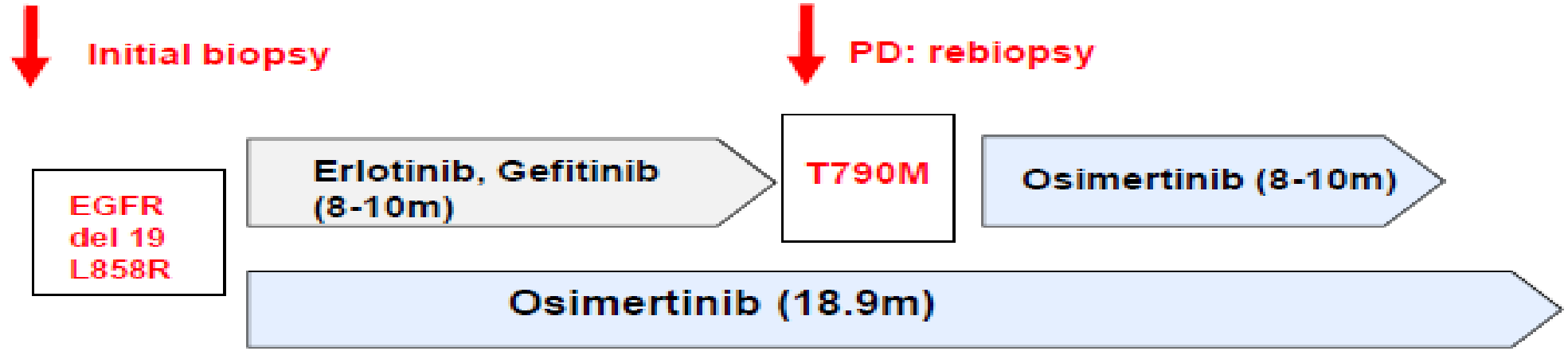


Yu et al., Clin Cancer Res 2013

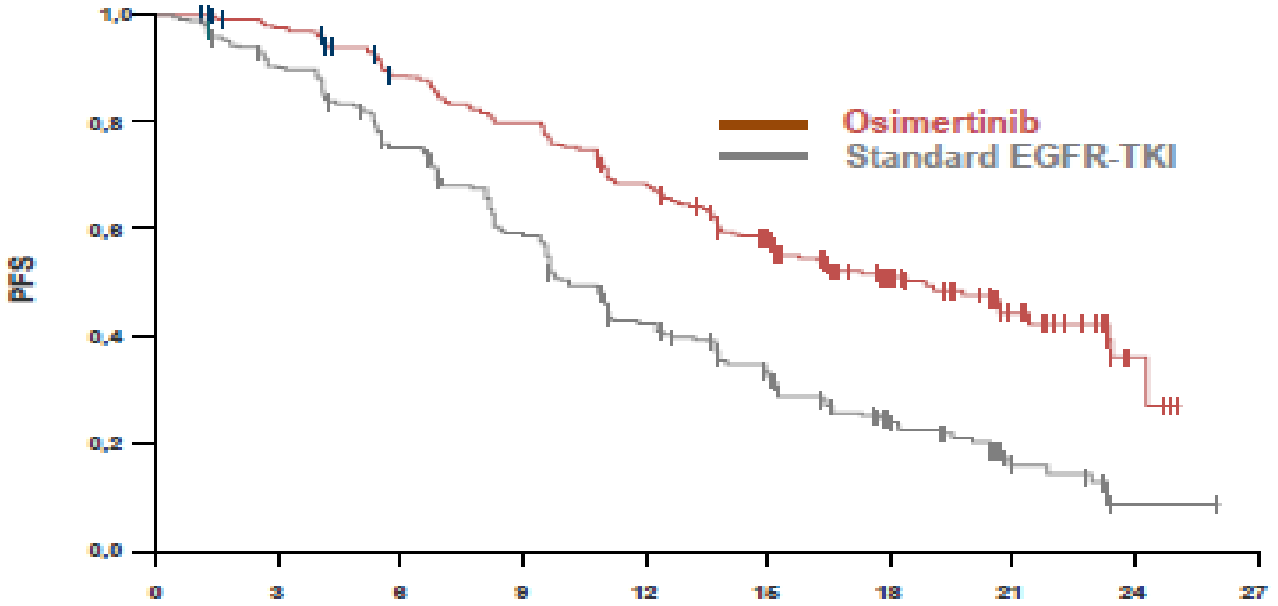
Optimal sequence for EGFR mutation?



3rd gen. EGFR-TKI as 1st line therapy are superior to 1st gen. inhibitors



FLAURA
Phase III
Osimertinib
vs. Standard
EGFR-TKI

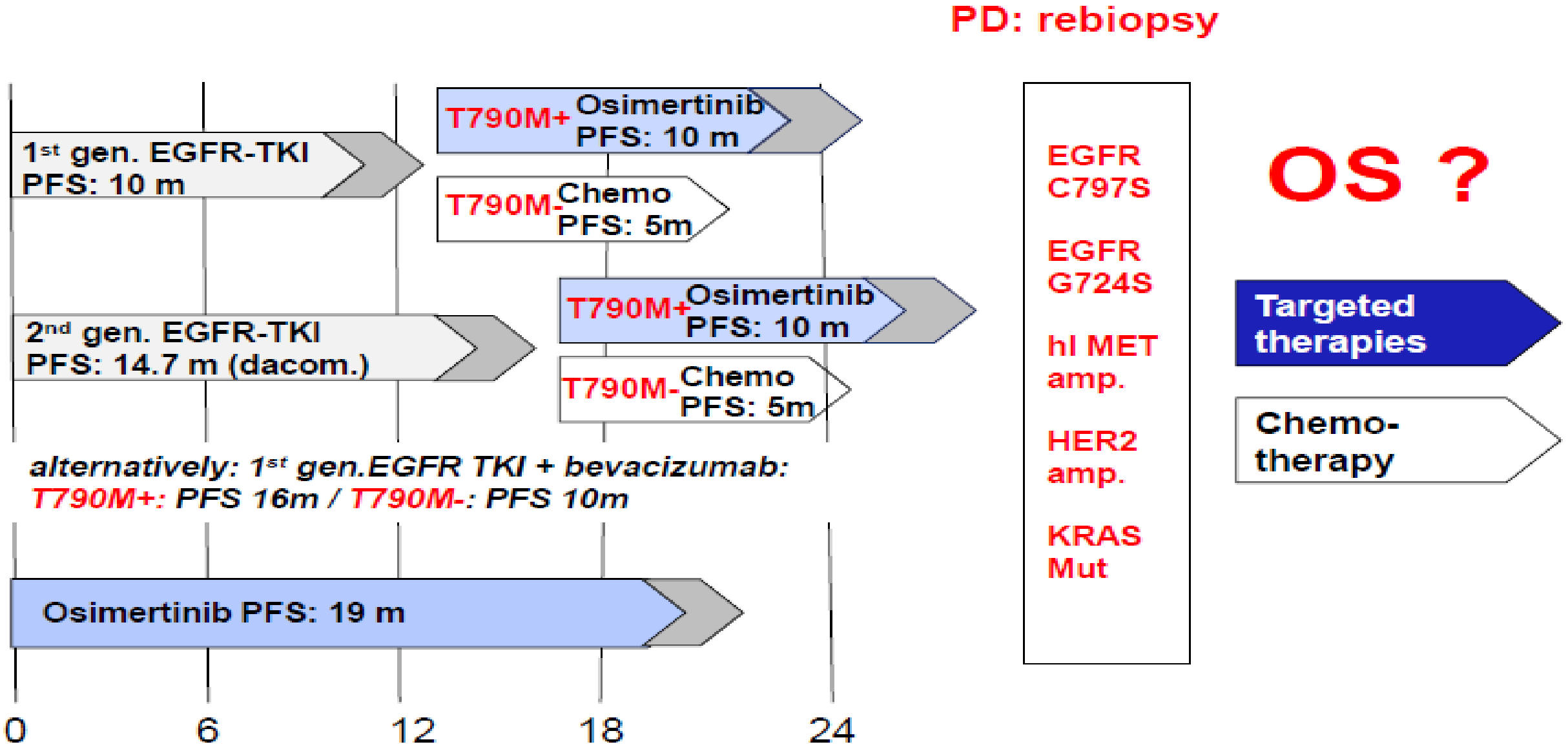


Median PFS, months (95%KI)
18,9 (15,2; 21,4)
10,2 (9,6; 11,1)

HR 0,46
(95%KI 0,37; 0,57)
p<0,0001

Soria et al, NEJM 2018

Sequential therapy in EGFRmut NSCLC: increasingly molecularly guided



Genetic alterations associated with Acquired Resistance to Osimertinib

Target-dependent

- *C797S*
- *G724S*
- *L718Q*
- *G796S/R/D*
- *L792F/H/Y*

Target-independent

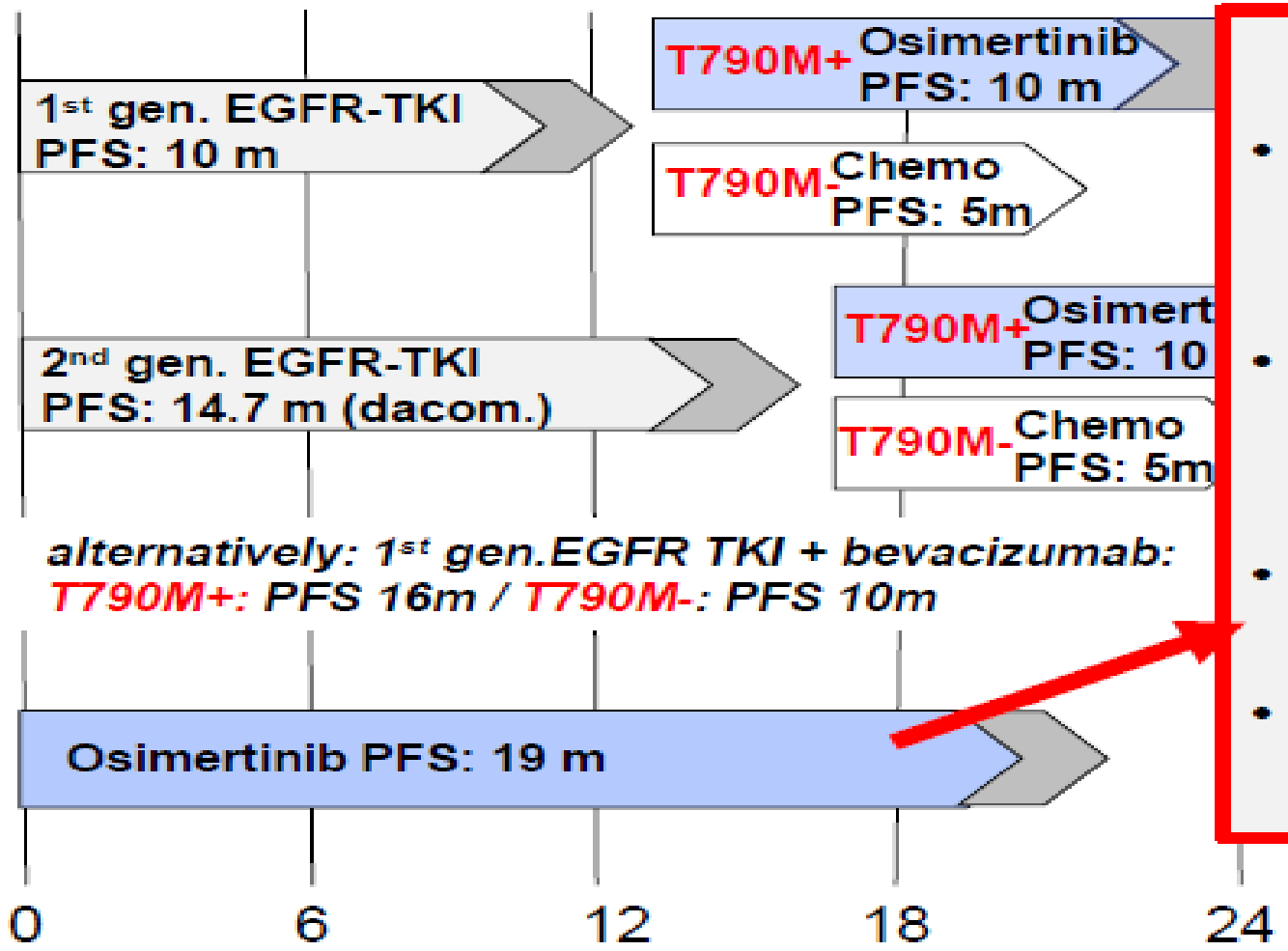
- *MET* amplification
- *HER2* amplification
- *EGFR* amplification
- *KRAS* amplification
- $KRAS^{G12S}$
- $BRAF^{V600E}$
- $MEK1^{G128V}$
- $JAK2^{V617F}$
- *ERBB2* exon 20 insertion
- *FGFR3-TACC3* fusions
- small cell transformation

Oncology Latin American Association
OLA

IASLC 2017

Arguments for 3rd gen. inhibitor 1st line

PD: rebiopsy



- PFS superior to 1st and 2nd gen. TKI
- Treatment option for all pts. (not only in T790M +)
- Toxicity profile better
- Evidence also for brain mets

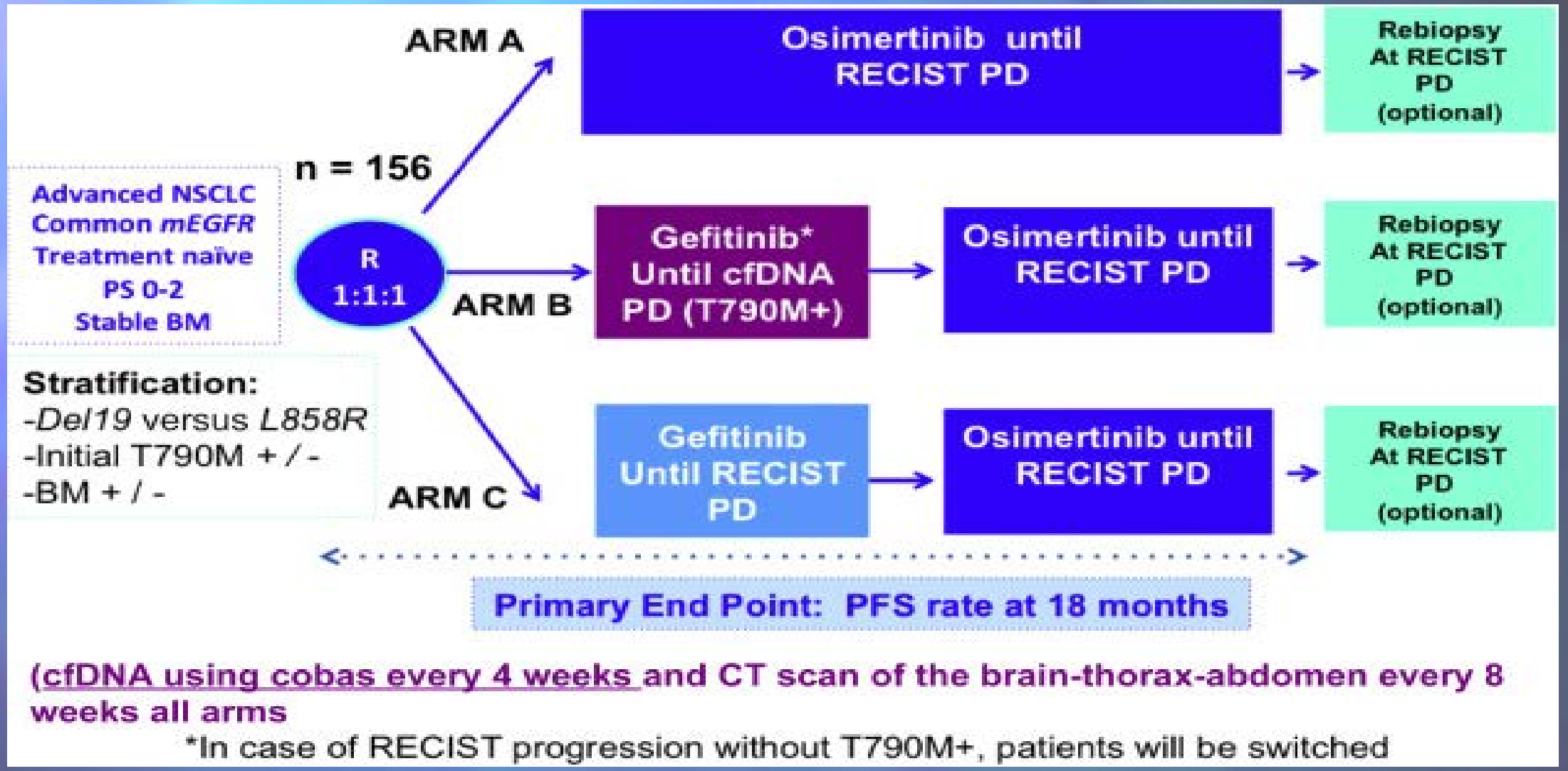
> final OS analysis of FLAURA might underline these arguments

The Case for Using Osimertinib as 1st Line T_x

- Superior PFS
- Favorable OS trend (cross-over allowed)
- CNS activity
- Better tolerance
- Overcome key resistance mechanisms

Suresh Ramalingam. Is PFS Still a Relevant Endpoint for 1st Line TKI? European Lung Cancer Congress, April 11-14, 2018

APPLE Trial under EORTC



Randomized, open-label, multicenter, 3-arms, phase II study in advanced, *G*-mutant and EGFR TKI naïve NSCLC patients, to evaluate the best strategy of sequencing gefitinib and osimertinib treatment.

What about uncommon EGFR mutations and EGFR exon 20 insertion mutations ?

EGFR mutation	Approximate frequency (%)	EGFR TKI [*in vitro* sensitivity and expected overall response rate (ORR)]		
EGFR TKI sensitivity type		1st generation	2nd generation	3rd generation
		Gefitinib 250 mg Erlotinib 150 mg	Afatinib 40 mg	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.

?

Costa et al, TLCR 2016

Uncommon EGFR mutations: afatinib 1st line indication extended (Jan 2018)

EGFR Mutation	Number of Afatinib Treated Patients (N = 32)	Number of Confirmed Responses (N=21)	Duration of Response (months) (N=21)
S768I	1	1	37.3
S768I and G719X	5	4	4.1, 13.2, 15.2, 29.5+
S768I and L858R	2	1	34.5+
G719X	8	6	5.7+, 8.1, 9.6, 23.5+, 25.2, 31.8+
G719X and L861Q	3	2	2.8+, 6.8
L861Q	12	7	2.8, 4.0, 4.1, 8.3+, 12.9, 15.2, 20.6
L861Q and Del 19	1	0	NA

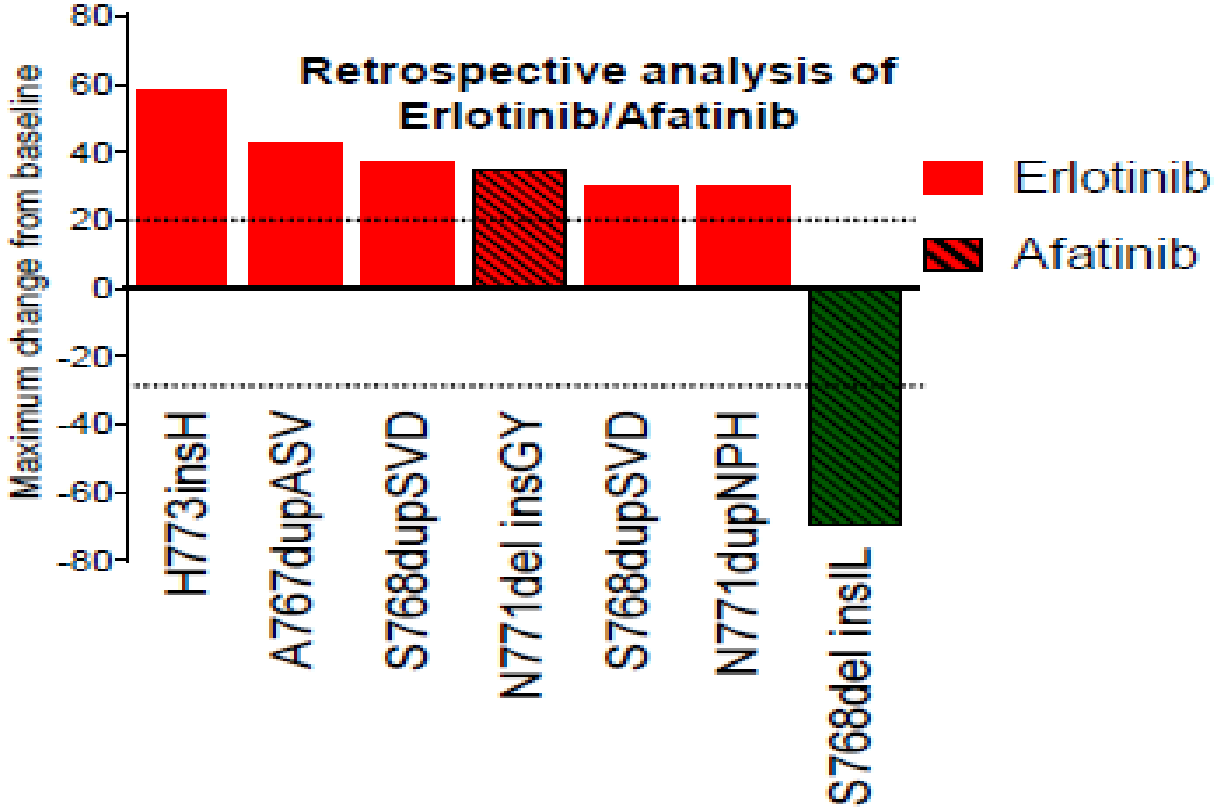
+ response ongoing at time of censoring

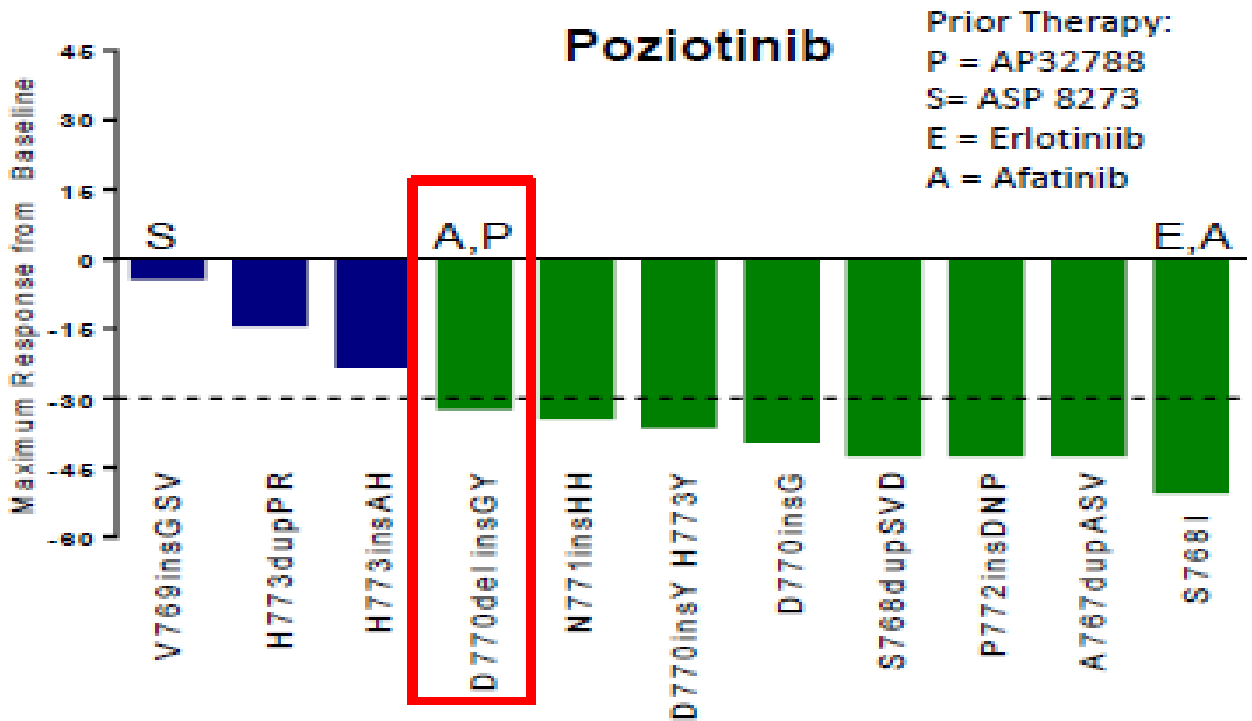
Subset analysis LUX lung 2,3,6 (32pts):

ORR: 66%

DOR > 12m: 52%

EGFR exon 20 insertion mutations: no therapeutic efficacy of 1st and 2nd gen. EGFR-TKIs > poziotinib induces partial response in 73% (8/11)





Elamin et al. , WCLC 2017 abstract ID 10369

ALK Translocation Present

Controversy

SHOULD ALECTINIB BE THE UNDISPUTABLE FIRST LINE THERAPY IN ALK MUTANT LUNG CANCERS?

Crizotinib vs Alectinib (ALEX study)

Resurrection of Ceritinib

Brigatinib given unprecedented results in crizotinib-naïve pts

The question here *IS NOT* Sequence vs No Sequence….

……. *IT IS*: WHAT SHOULD BE THE SEQUENCE?

THIS IS NOW!!! APRIL 28, 2018

Alectinib vs crizotinib in treatment-naïve advanced *ALK*+ NSCLC: primary results of the global phase III ALEX study (LBA9008)

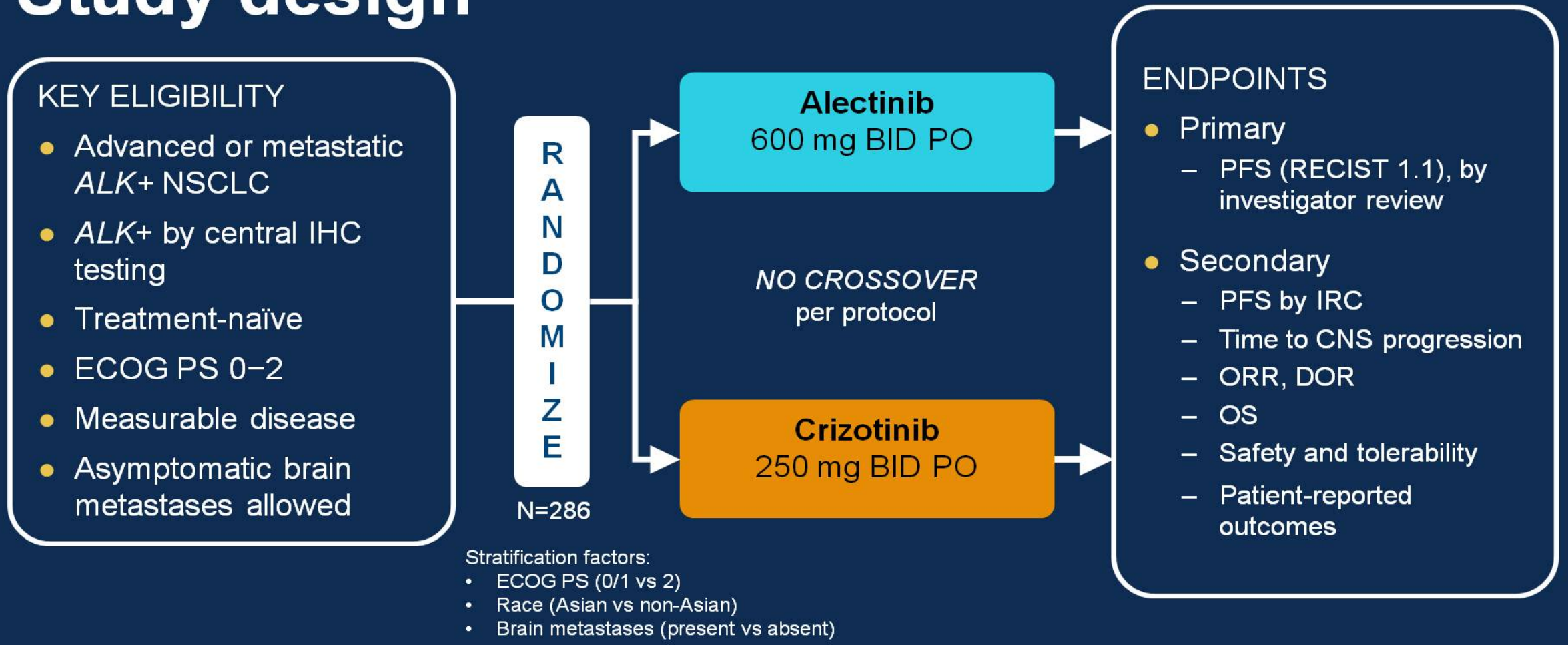
Alice Shaw[1], Solange Peters[2], Tony Mok[3], Shirish M. Gadgeel[4], Jin Seok Ahn[5], Sai-Hong Ignatius Ou[6], Maurice Perol[7], Rafal Dziadziuszko[8], Dong-Wan Kim[9], Rafael Rosell[10], Ali Zeaiter[11], Ting Liu[11], Sophie Golding[11], Bogdana Balas[11], Johannes Noe[11], Peter N. Morcos[12], and D. Ross Camidge[13] on behalf of the ALEX investigators

1. Massachusetts General Hospital, Boston, MA, USA; 2. Lausanne University Hospital, Switzerland; 3. Chinese University of Hong Kong, Hong Kong; 4. Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; 5. Sungkyunkwan University School of Medicine, Seoul, South Korea; 6.Chao Family Comprehensive Cancer Center, University of California, Irvine School of Medicine, Orange, CA, USA; 7. Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France; 8. Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; 9. Seoul National University Hospital, Seoul, South Korea; 10. Catalan Institute of Oncology, Barcelona, Spain; 11. F. Hoffmann-La Roche Ltd, Basel, Switzerland; 12. Roche Innovation Center, New York, USA; 13. University of Colorado, Denver, CO, USA

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

http://tago.ca/Lfq

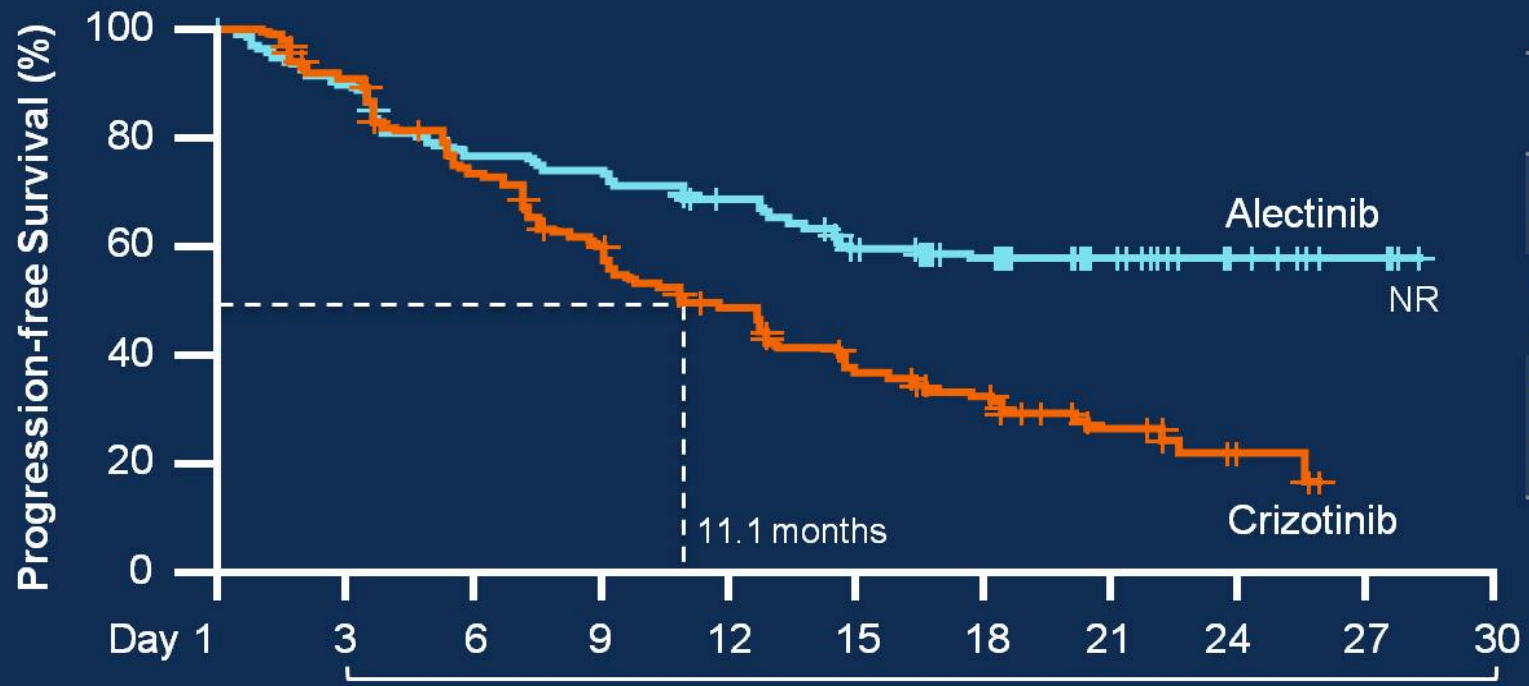
Study design



Stratification factors:
- ECOG PS (0/1 vs 2)
- Race (Asian vs non-Asian)
- Brain metastases (present vs absent)

ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PO, by mouth; PFS, progression-free survival; IRC, independent review committee; CNS, central nervous system; ORR, objective response rate; DOR, duration of response; OS, overall survival

Primary endpoint: PFS, investigator-assessed

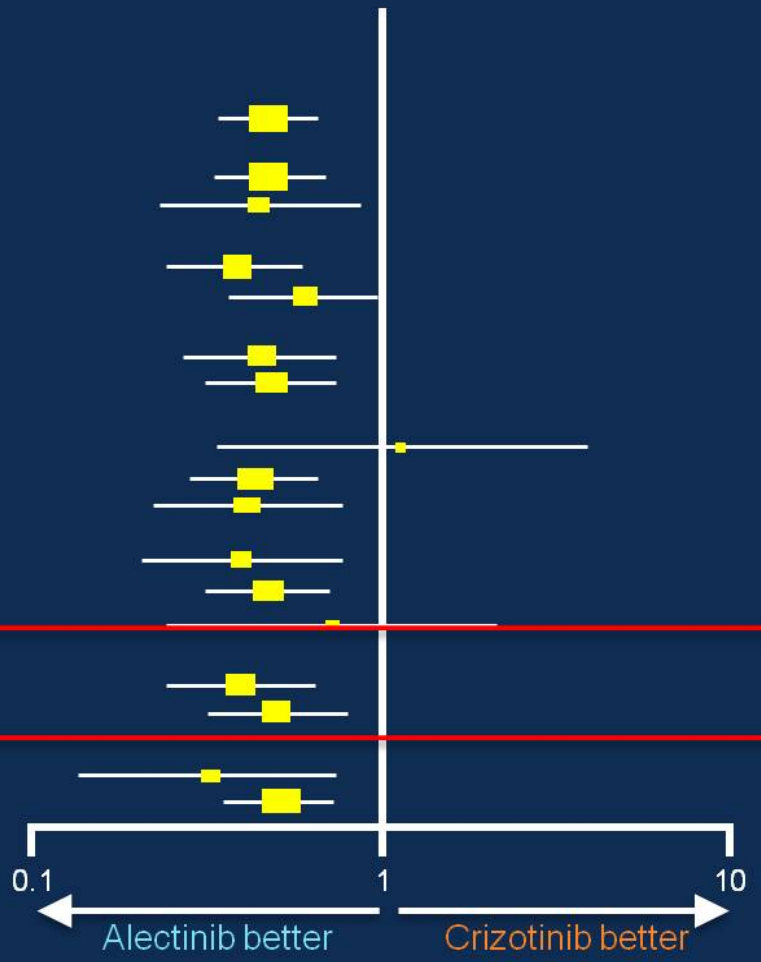


No. at Risk										
Crizotinib	151	132	104	84	65	46	35	16	5	
Alectinib	152	135	113	109	97	81	67	35	15	3

	Crizotinib (N=151)	Alectinib (N=152)
Patients with events, n (%)	102 (68)	62 (41)
Median PFS, months (95% CI)	**11.1** (9.1–13.1)	**NR** (17.7–NR)
HR (95% CI) P-value (log-rank test)	**0.47** (0.34–0.65) P<0.0001	

PFS: analysis by subgroups*

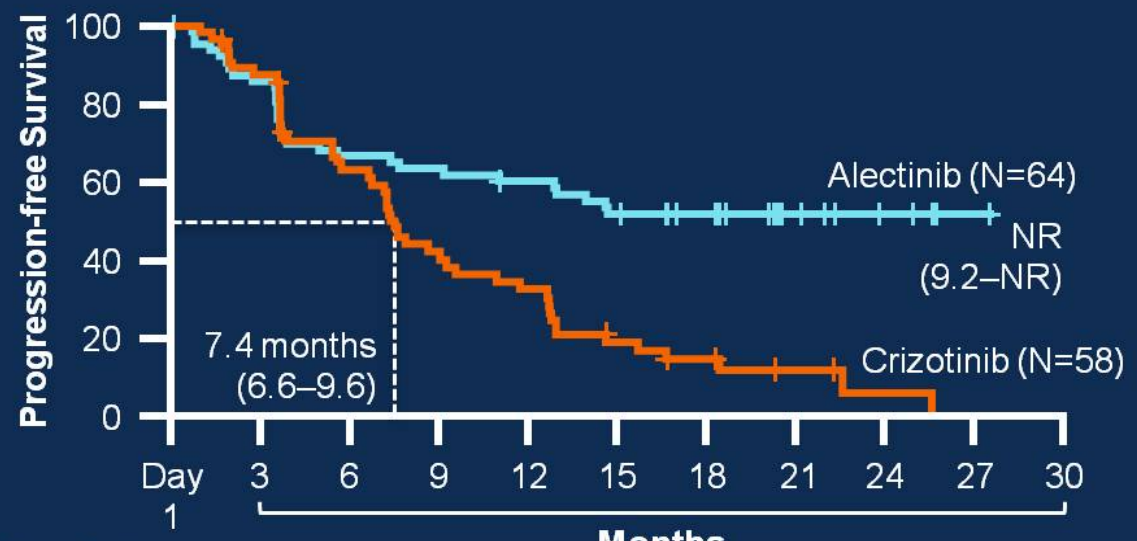
Subgroup	No. of events/ No. of patients	Hazard ratio (95% CI)
Overall	164/303	0.48 (0.35–0.66)
Age		
<65	125/233	0.48 (0.34–0.70)
≥65	39/70	0.45 (0.24–0.87)
Sex		
Female	91/171	0.39 (0.25–0.60)
Male	73/132	0.61 (0.38–0.98)
Ethnicity		
Asian	72/138	0.46 (0.28–0.75)
Non-Asian	92/165	0.49 (0.32–0.75)
Smoking status		
Active smoker	12/17	1.16 (0.35–3.90)
Non-smoker	103/190	0.44 (0.29–0.66)
Past smoker	49/96	0.42 (0.23–0.77)
ECOG PS		
0	44/97	0.40 (0.21–0.77)
1	105/186	0.48 (0.32–0.71)
2	15/20	0.74 (0.25–2.15)
CNS Mets at baseline		
Yes	78/122	0.40 (0.25–0.64)
No	86/181	0.51 (0.33–0.80)
Prior brain radiation		
Yes	26/47	0.33 (0.14–0.74)
No	138/256	0.52 (0.36–0.73)



*Investigator assessment

PFS by baseline CNS metastases status*

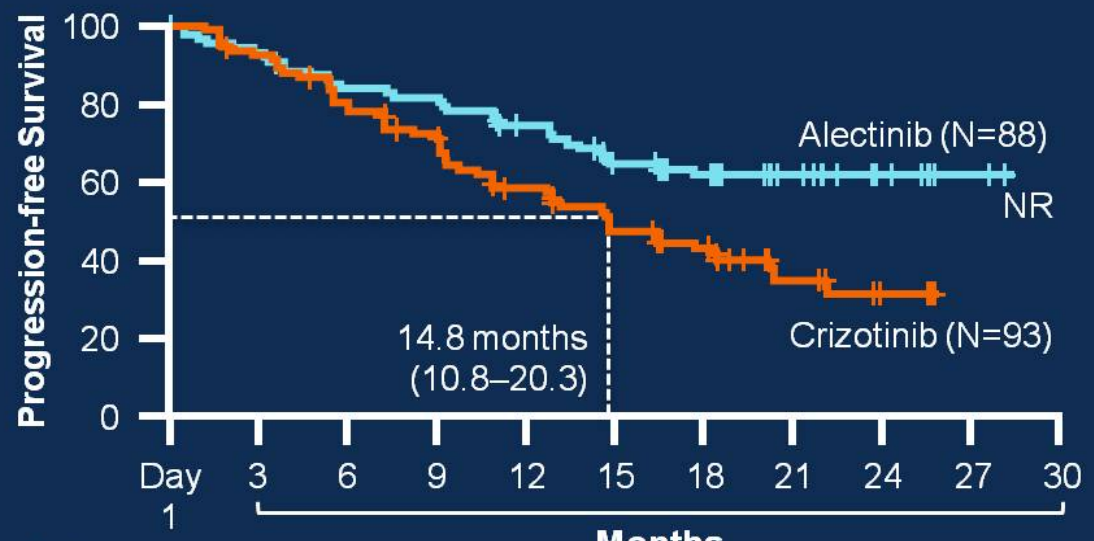
Patients with CNS metastases at baseline



No. at Risk										
Crizotinib	58	48	33	22	17	9	6	3	1	
Alectinib	64	54	41	39	36	31	24	10	4	1

HR 0.40
(95% CI 0.25–0.64)

Patients without CNS metastases at baseline

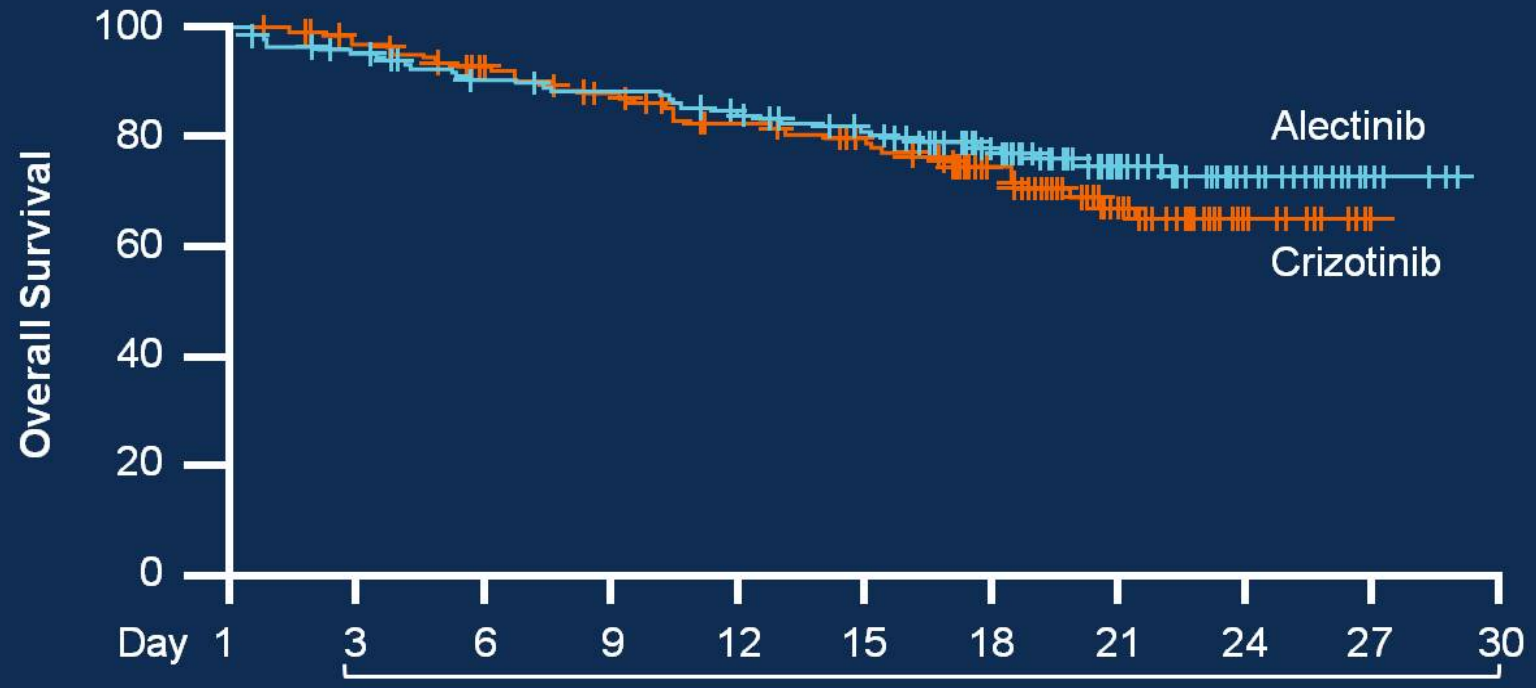


No. at Risk										
Crizotinib	93	84	71	62	48	37	29	13	4	
Alectinib	88	81	72	70	61	50	43	25	11	2

HR 0.51
(95% CI 0.33–0.80)

*Investigator assessment

Secondary endpoint: OS



No. at Risk

Crizotinib	151	141	127	115	103	95	73	33	13	1
Alectinib	152	142	131	127	119	107	87	51	24	5

	Crizotinib (N=151)	Alectinib (N=152)
Patients with events, n (%)	40 (27)	35 (23)
Median OS, months (95% CI)	NR (NR)	NR (NR)
HR (95% CI) P-value (log-rank test)	0.76 (0.48–1.20) P=0.24	

Summary

- This is the first global randomized phase III study to compare next- versus first-generation ALK inhibitors in previously untreated, advanced *ALK*+ NSCLC
- Compared to crizotinib, alectinib:
  - significantly prolonged PFS
    - HR 0.47, 95% CI 0.34-0.65; p<0.0001
  - significantly delayed time to CNS progression
  - significantly improved intracranial ORR and DOR
  - had a more favorable AE profile

Despite these impressive results….

There are other Marvel Avengers……

Brigatinib

Lorlatinib

Ceritinib

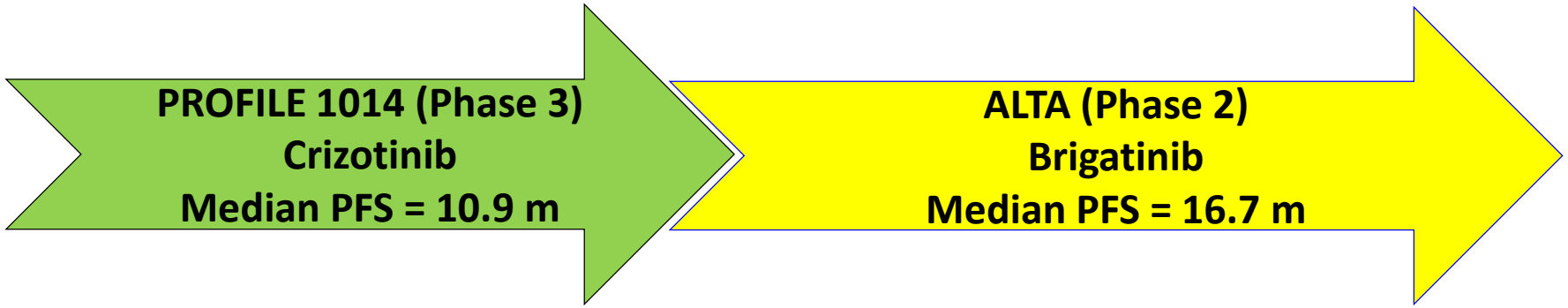
Different Potential Sequence Scenarios of ALK Inhibitors Treatment:

PFS1 + PFS2 (PROFILE 1014 + ALTA)

(CRIZOTINIB) (BRIGATINIB)

Total PFS = 27.6 months!! (> 25.7 months)

(ALECTINIB)



Oncology Latin American Association
OLA

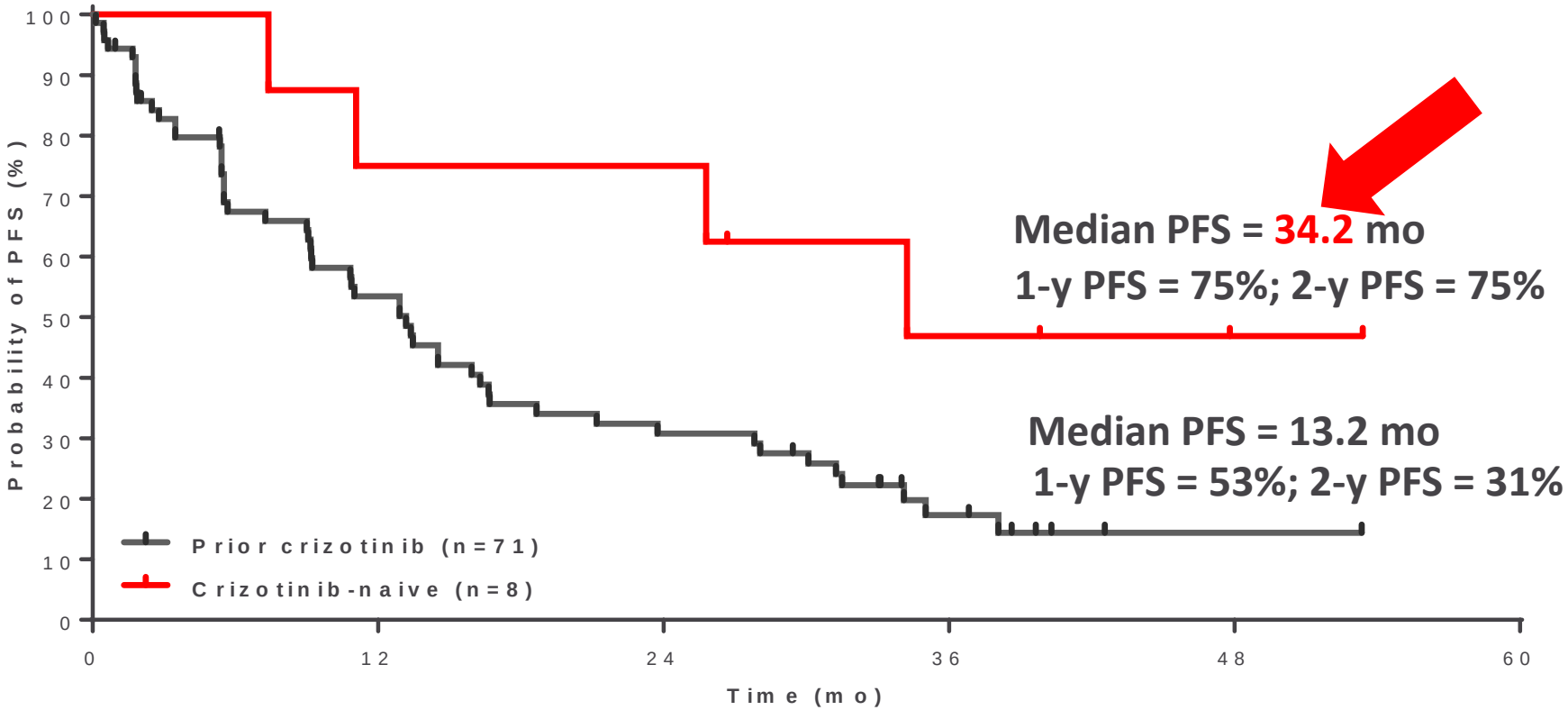
SCENARIO # 1

Caution! Post-Crizotinib PFS drop-off from Ph2 to Ph3

ALK TKI	Ceritinib	Alectinib	Brigatinib
Phase 1	6.9 months[1]	NA	NA
Phase 2	7.2 months[2]	8.4 months[4]	16.7 months[6]
Phase 3	5.4 months[3]	7.1 months[5]	??? No trial

1. Kim et al, Lancet Oncol 2016;17:452-463
2. Crino et al, JCO 2016; 34: 2866-2873
3. Shaw et al, Lancet Oncol 2017;18: 874-886
4. Yang et al, J Thorac Oncol 2017; 12: 1552-1560
5. Novello et al, ESMO 2017

Phase 1/2 Trial of Brigatinib PFS in *ALK+* NSCLC Patients



- For patients with prior crizotinib who received 90 mg → 180 mg qd (n=25):
  - Median PFS was 16.3 months (95% CI, 9.2–28.1 months)
  - Kaplan-Meier (KM) probability of PFS was 62% at 1 year and 38% at 2 years

Lyudmila A Bazhenova et al: ESMO 2017 Madrid Poster 1344

PFS1 + PFS2 (PROFILE 1014 + ALTA)

Total PFS = 27.6 months!!

PROFILE 1014 (Phase 3)
Crizotinib
Median PFS = 10.9 m

ALTA (Phase 2)
Brigatinib
Median PFS = 16.7 m

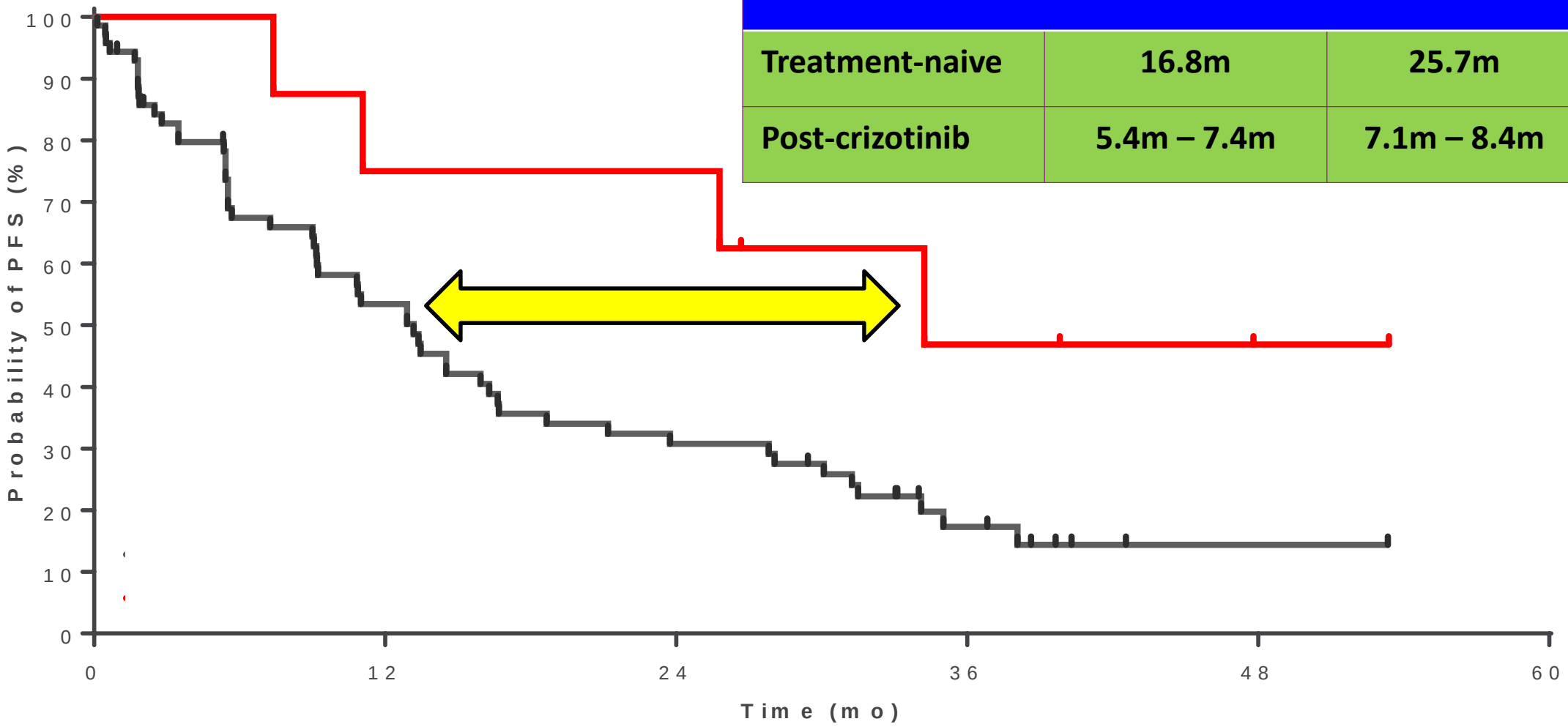
Total PFS = 34.2 months??????

ALTA (Phase 1)
Brigatinib
Median PFS = 34.2 m

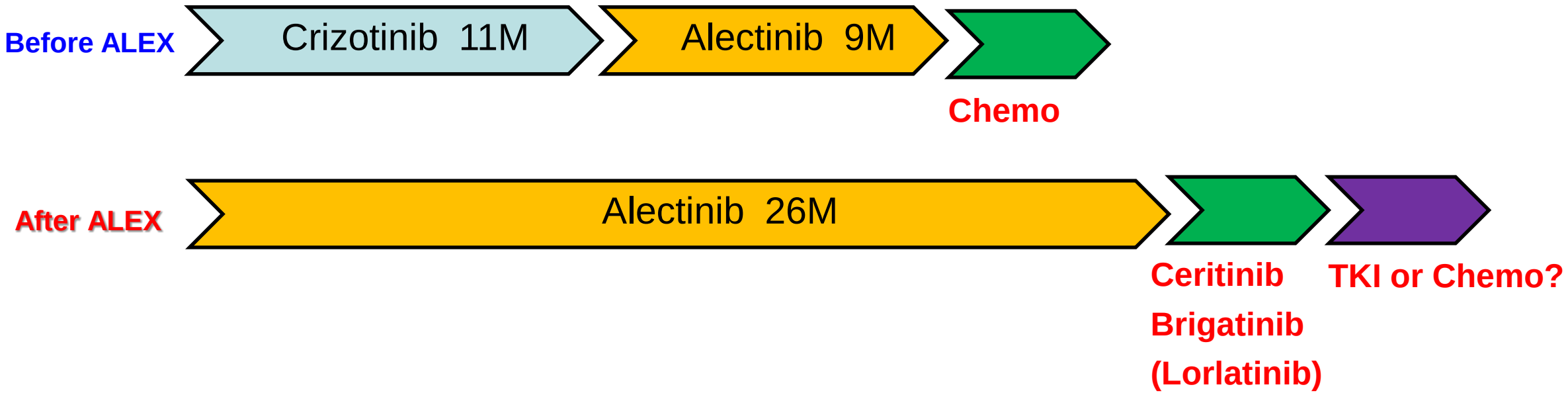
SCENARIO # 2

PFS model of 2G ALK TKI as first-line versus subsequent line of treatment

	Ceritinib	Alectinib	Brigatinib
Treatment-naive	16.8m	25.7m	(34.2m)
Post-crizotinib	5.4m – 7.4m	7.1m – 8.4m	16.7m



Current Sequence of ALK-TKI



Oncology Latin American Association
OLA

IASLC 2017

The Case for Using Alectinib as 1st Line T_x

- Superior PFS
- CNS activity
- Better tolerance
- Overcome key resistance mechanisms

Suresh Ramalingam. Is PFS Still a Relevant Endpoint for 1st Line TKI? European Lung Cancer Congress, April 11-14, 2018

Brigatinib: better PFS than that of Alectinib

Next generation ALK-TKI in crizotinib-refractory NSCLC			
Design/Assessment	Ceritinib Phase 1/2	Alectinib Phase 2	Brigatinib Phase 2
Median PFS	6.9M (5.6-8.7)	8.9M (5.6-11.3)	15.6M (11.1-NR)
ORR	56% (49-64)	50% (41-59)	55% (44-66)
IC ORR	36%	57%	67%
Duration of Response	8.3M	11.2M	14.8M

□ revised chart of Shirish M, et al. Curr. Treat Options in Oncol 2017 18:36□

IASLC 2017

Lorlatinib:TKI-naive

	EXP1 (n=30)
ORR, n/N (%) (95% CI)	27/30 (90) (74, 98)
IC ORR, n/N (%) (95% CI)	6/8 (75) (35, 97)
Median DOR, mo (95% CI)	NR (10.2, NR)
DOR ≥6 mo, n⁰/n (%)	16/27 (59)
Median PFS, mo (95% CI)	NR (11.4, NR)

Results of ALEX

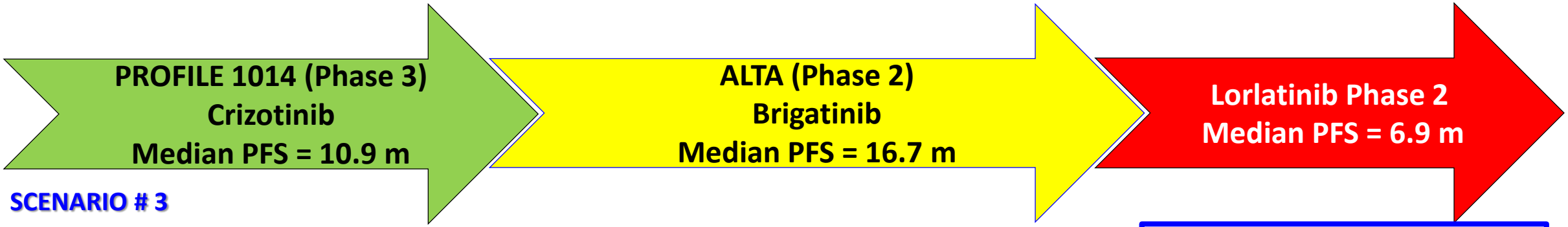
	Crizotinib	Alectinib
ORR	75.5%	83%
IC ORR	29%	53%
mPFS	10.4M	25.7M

(N Engl J Med 2017; 377:829-838)

IASLC 2017

PFS1 + PFS2 + PFS3 (PROFILE1014 + ALTA + Lorlatinib Phase 2) OR PFS1 + PFS2 (ALEX + Lorlatinib Phase 2)

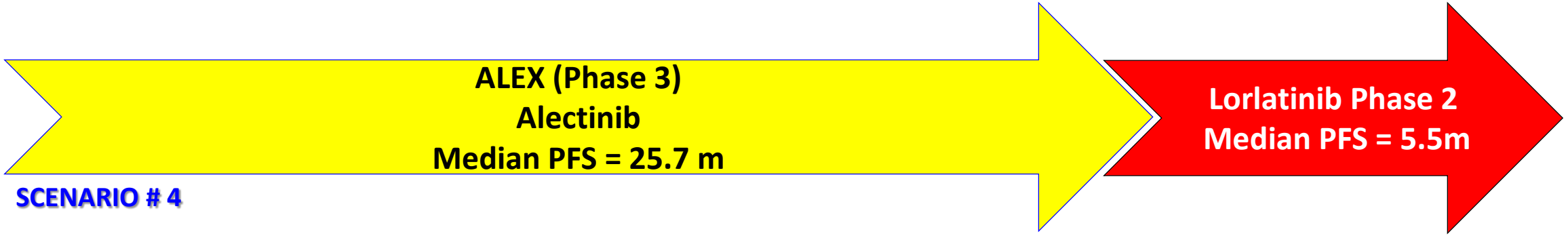
Total PFS = 34.5 months!!



SCENARIO # 3

3.3 months advantage in PFS when sequencing from crizotinib

Total PFS = 31.2 months!



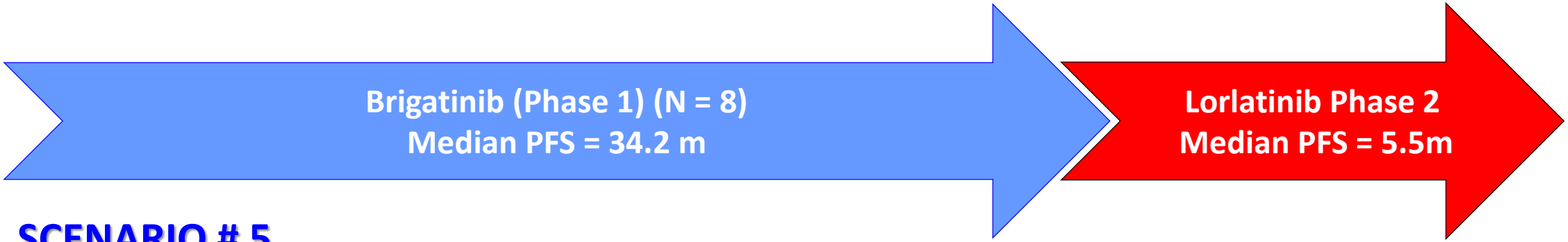
SCENARIO # 4

3.3

Coming Up Soon…. Challenges

A Future Paradigm or Wishful Thinking?
PFS1 + PFS2 (Brigatinib Phase 1 + Lorlatinib Phase 2)

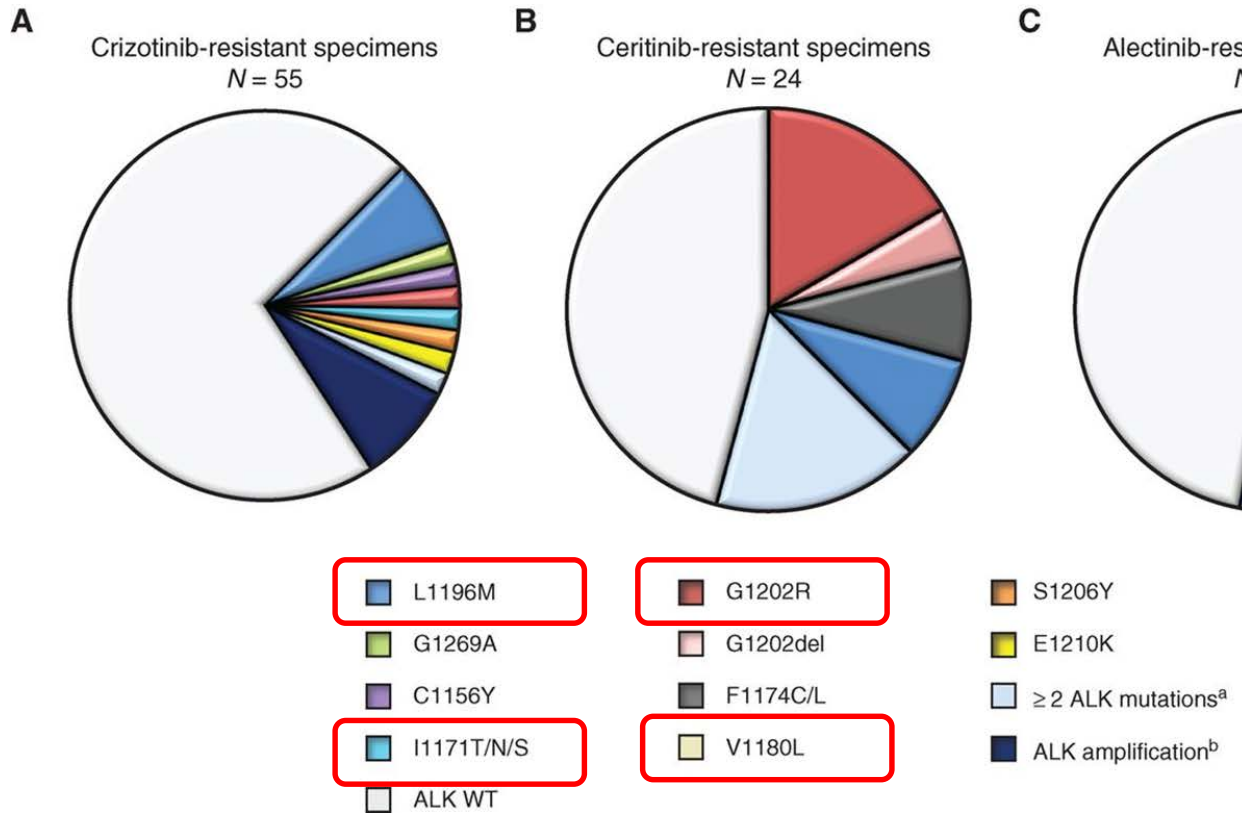
Total PFS = 39.7 months!!??



SCENARIO # 5

Coming Up Soon…. Challenges

Genetic diagnosis is needed!!!
Will the Choice of 1st Line ALKi TKI Impact on Patterns of Progression & Mechanism of Resistance?



G1202R → Lorlatinib

I1171T → Ceritinib/ Brigatinib/Lorlatinib

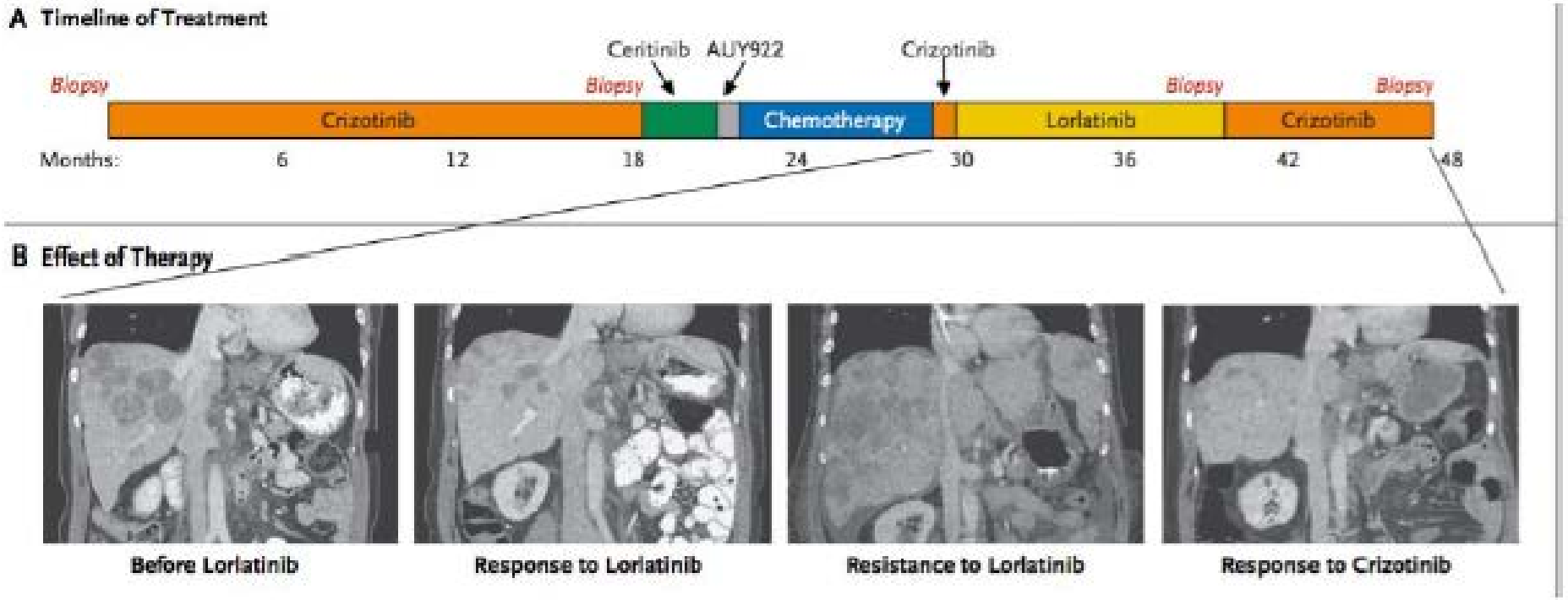
V1180L → Chemo? Other TKI?

L1196M → Ceritinib/ Brigatinib/Lorlatinib

Justin F. Gainor et al. Cancer Discov 2016;6:1118-1133

IASLC 2017

The Art of Precision Medicine

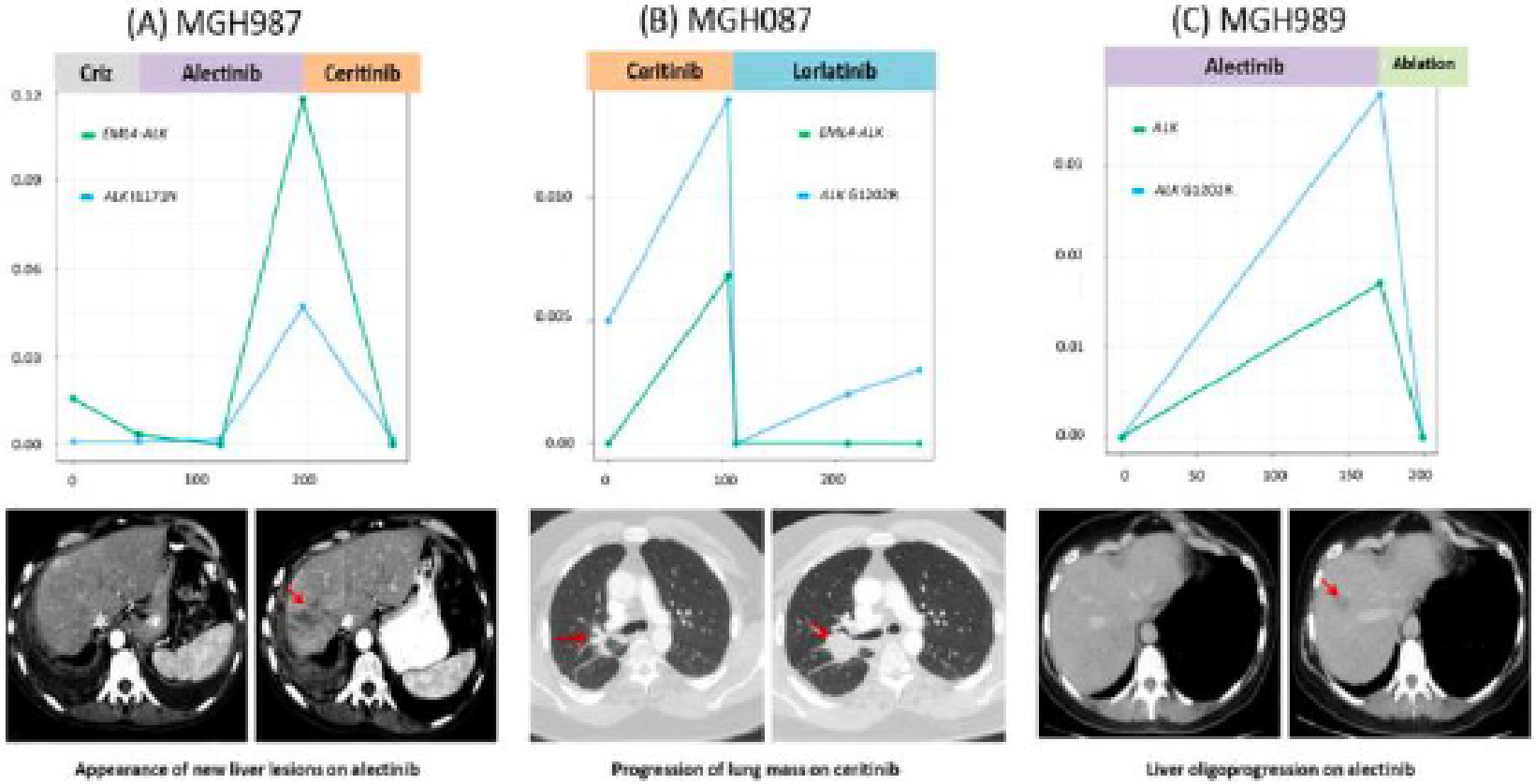


Resensitization to Crizotinib by the Lorlatinib *ALK* Resistance Mutation L1198F

Shaw et al.
NEJM 2016

Tracking the Evolution of Resistance to ALK Tyrosine Kinase Inhibitors through Longitudinal Analysis of Circulating Tumor DNA

Ibiayi Dagogo-Jack et al. JCO Precis Oncol 2018



Plasma *ALK* mutation kinetics during treatment. The figure illustrates the change in allelic fraction of *EML4-ALK* and *ALK* mutations during sequential treatment with next-generation ALK inhibitors for A) MGH987 and C) MGH087; B) ALK fusion and mutation kinetics prior to and after ablation of an oligometastasis. The x axis depicts days from initial plasma collection, whereas the y axis reports allelic fraction. Criz, crizotinib; Chemo/A, chemotherapy + alectinib; lorlat, lorlatinib.

Currently recruiting

- crizotinib vs brigatinib
- crizotinib vs lorlatinib
- crizotinib vs ensartanib

Will translational research from these studies help to define the future algorithm for selection and sequencing of ALK TKIs ?

- ALK Master Protocol is due to open 2018 in US

Focus on ALK positive patients who have progressed on a next generation ALKi; on PD will have biopsy and ALK mutation status (tissue or liquid biopsy) will be used for ALK TKI selection

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

Efficacy and Updated Safety of Ceritinib (450 mg or 600 mg) With Low-Fat Meal vs 750 mg Fasted in *ALK*+ Metastatic NSCLC

Authors: Cho BC,[1] Obermannova R,[2] Bearz A,[3] Kim DW,[4] Orlov S,[5] Borra G,[6] Kim SW,[7] Postmus P,[8] Laurie S,[9] Park K,[10] Geater SL,[11] Bettini A,[12] Osborne K,[13] Passos VQ,[14] Chen Z,[14] Dziadziuszko R[15]

Affiliations: [1]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Masaryk Memorial Cancer Institute, Czech Republic; [3]Centro di Riferimento Oncologico-IRCC, Aviano, Italy; [4]Seoul National University Hospital, Seoul, Republic of Korea; [5]State Pavlov Medical University, St Petersburg, Russia; [6]Az. Osp. Univ.Maggiore della Carità, Italy; [7]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]The Clatterbridge Centre NHS Foundation Trust, Liverpool, United Kingdom; [9]Ottawa Hospital Cancer Centre, Ottawa, Canada; [10]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [11]Songklanagarind Hospital, Prince of Songkla University, Songkhla, Thailand; [12]A.S.S.T. Papa Giovanni XXIII, Italy; [13]Novartis Pharma AG, Basel, Switzerland; [14]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [15]Medical University of Gdansk, Poland

OA 05.07

ASCEND-8: Phase 1, Randomized, Global, Open-label, Parallel Design Study (NCT02299505)

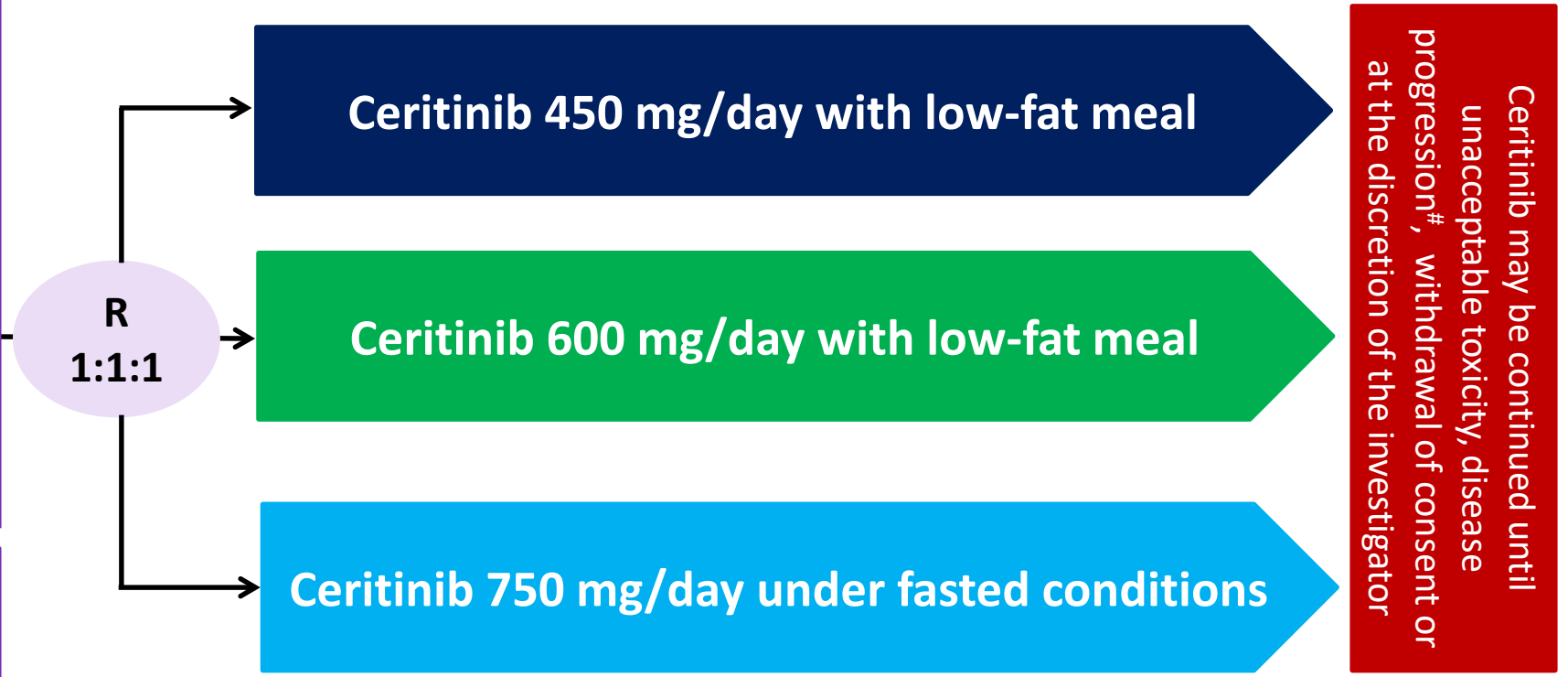
Inclusion criteria

- Stage IIIB/IV *ALK*+ NSCLC
- Treatment-naive* (efficacy analysis) or previously treated with ≥ 1 systemic therapy (PK analysis included both)
- *ALK*+ status was assessed by Ventana IHC (treatment-naive) or FDA approved FISH (previously treated)
- WHO PS 0-2
- Neurologically stable brain metastases (symptomatic or not)

Randomization is stratified by:

-Brain metastases – presence/absence

-Prior treatment (applicable only for PK analysis part) – prior crizotinib/ crizotinib naive but treated with other systemic therapy/treatment-naive with ALK+ by IHC



*Prior adjuvant or neo adjuvant therapy allowed if relapse occurred >12 months after chemotherapy

#Patients may continue to receive treatment with ceritinib following disease progression, including cases of isolated brain progression if, in the opinion of the investigator, continued treatment provides clinical benefit

FISH, florescence in-situ hybridization; IHC, immunohistochemistry; PK, pharmacokinetics; PS, performance status; WHO, World Health Organization

DOR and PFS by BIRC Assessment[Δ]

DOR	Ceritinib 450 mg fed (N = 32)	Ceritinib 600 mg fed (N = 30)	Ceritinib 750 mg fasted (N = 28)
Events, n (%)	6 (18.8)	6 (20.0)	11 (39.3)
Patients censored, n (%) Ongoing without event or death	**26 (81.2)** 23 (71.9)	**24 (80)** 22 (73.3)	**17 (60.7)** 17 (60.7)
Median duration of response, months (95% CI) Estimated 12-month DOR rate, % (95% CI)	**16.4** (7.1-16.4) 74.6 (48.4-88.8)	**NE** (6.9-NE) 72.5 (47.6-87.0)	**10.4** (7.1-NE) 42.5 (18.1-65.2)

PFS	Ceritinib 450 mg fed (N = 41)	Ceritinib 600 mg fed (N = 40)	Ceritinib 750 mg fasted (N = 40)
Events, n (%)	12 (29.3)	13 (32.5)	17 (42.5)
Patients censored, n (%) Ongoing without event or death	**29 (70.7)** 26 (63.4)	**27 (67.5)** 23 (57.5)	**23 (57.5)** 21 (52.5)
Median progression-free survival, months (95% CI) Estimated 15-month PFS rate, % (95% CI)	**17.6** (8.5-NE) 66.4 (46.5-80.4)	**NE** (8.3-NE) 58.0 (35.9-74.8)	**10.9** (6.3-NE) 41.0 (19.6-61.5)

better

better

[Δ]Efficacy-analysis set

Take home message….

- Osimertinib met its primary endpoint PFS over Gefitinib/Erlotinib; OS is immature, but ***promising***.
- Osimertinib is approved for 1st Line Therapy for sensitive EGFR mutations.
- Osimertinib: very active on CNS metastases & favorable toxicity profile.
- ALEX places Alectinib as the optimal first line ALK TKI choice
  - With CNS metastases
  - Without CNS metastases; relatively “neuroprotective”; delays emergence resistance mutation relative to crizotinib
  - OS is immature
  - PD on crizotinib is salvagable

Take home message….

- Mutational analysis ***will be necessary*** for TKI ALK inhibitor selection after PFS1.
- Best TKI ALKi sequence is not yet determined.
- ASCEND-8 data suggest that ceritinib at dose of 450 mg with food could be a potential new treatment regimen for managing GI AEs with similar efficacy as 750 mg fasted dose in treatment-naïve patients with *ALK*-rearranged advanced NSCLC.
- Brigatinib and Lorlatinib have shown ***promising*** PFS1 in crizotinib naive patients.
- How to treat EGFR and ALK mutant patients is a physician's decision based on his/her experience; today, there are not correct or wrong choices….

Just More Therapeutic Options for Our Lung Cancer Patients

13th Annual New Orleans Summer Cancer Meeting

"Immunotherapy - Targeted Therapy & Chemotherapy: Breaking the Enigma of Solid & Liquid Cancers"

July 20-22, 2018

The Roosevelt Hotel New Orleans
New Orleans, LA

For any question, email Dr. Santos: esantos@brrh.com

Or contact Teri Valls, Meeting Planner at: tvalls@meccinc.com