SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

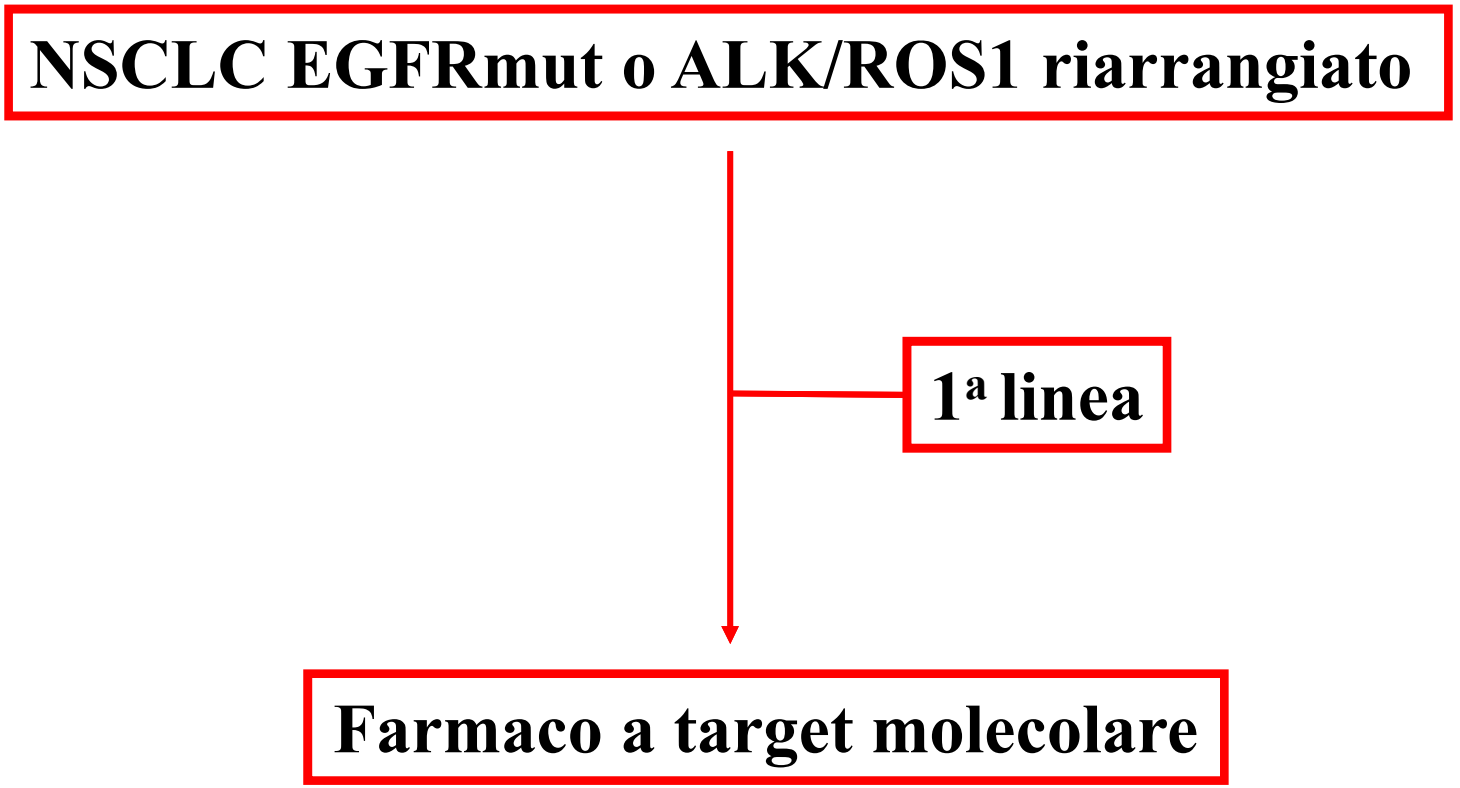
Policlinico S. Orsola-Malpighi

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

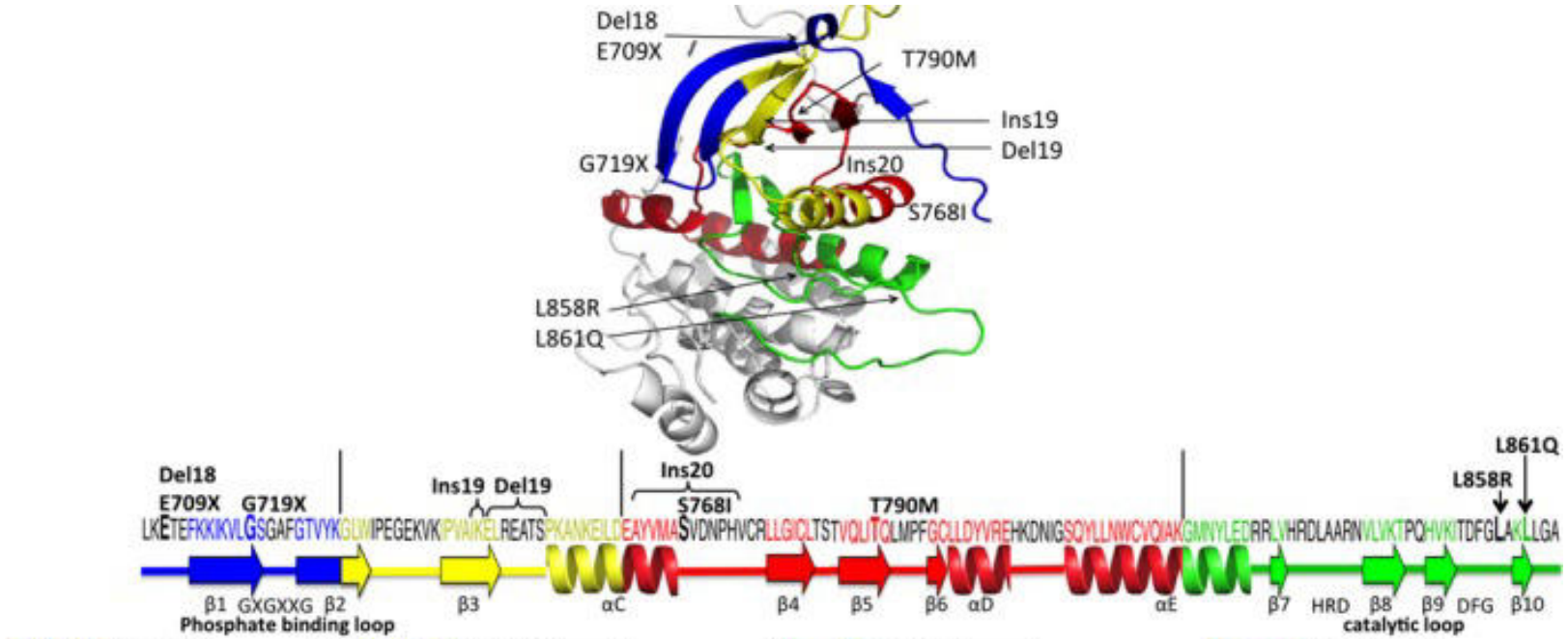
New option for oncogene-addicted NSCLCs: potential improvement in 1st line

Andrea Ardizzoni
UOC Oncologia Medica

Strategia terapeutica nel NSCLC con «actionable molecular alterations»



EGFR Mutations



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%)

Terapia anti-EGFR nel NSCLC EGFR-mut+: Stato dell'arte

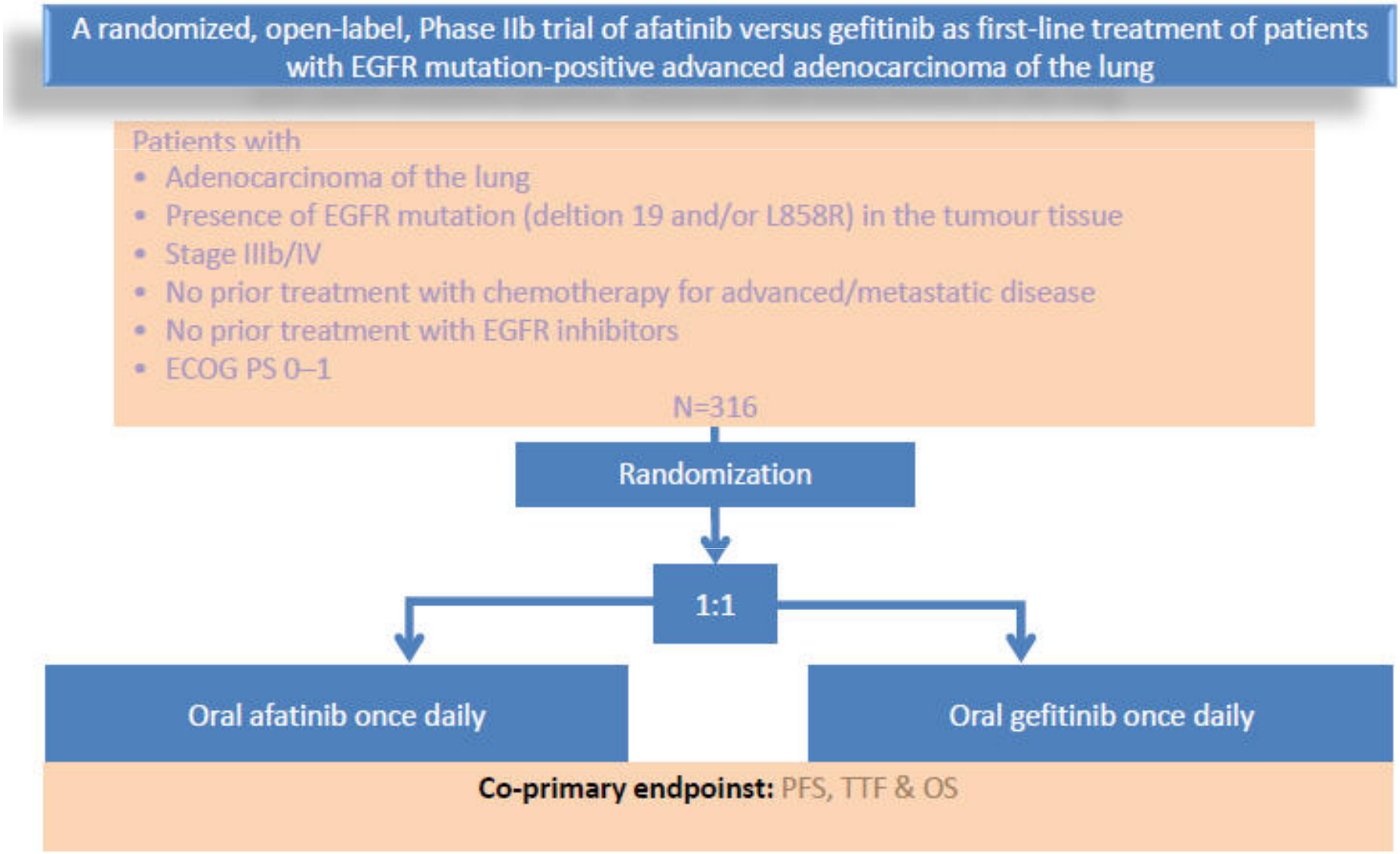
- **3 farmaci registrati (gefitinib, erlotinib, afatinib)**
- **10 studi randomizzati hanno dimostrato la superiorità rispetto a polichemioterapia in prima linea (RR 20-40% -> 60-80%; PFS 5-6 -> 9-13 mesi, OS 20-28 mesi)**
- **Migliore controllo dei sintomi e QoL**
- **Farmaci ben tollerati (dermatite, diarrea) ed utilizzabili anche in pz anziani ed in scadenti condizioni generali**
- **Effetto anti-neoplastico rapido (pochi giorni) ed in tutte le sedi di malattia (incluso encefalo)**
- **Efficacia maggiore nelle Ex19Del vs Ex21Mut (L858R)**

Terapia di 1ª linea nel NSCLC con «actionable molecular alterations»

NSCLC EGFR+ (mutazioni comuni esoni 19, 21)

EGFR-TKI di 1ª e 2ª generazione (erlotinib, gefitinib, afatinib)

LUX-Lung 7: study design



LUX-LUNG 7: Afatinib vs Gefitinib in 1st-line therapy of EGFRmut+ A-NSCLC

End-Point	Afatinib	Gefitinib	P value
mPFS (months)	11	10.9	0.017
mTTF (months)	13.7	11.5	0.013
mOS (months)	27.9	24.5	0.25
RR%	72.5	56	0.002
Toxicity (worse)	Skin Stomatitis Diarrea	GOT/GPT	

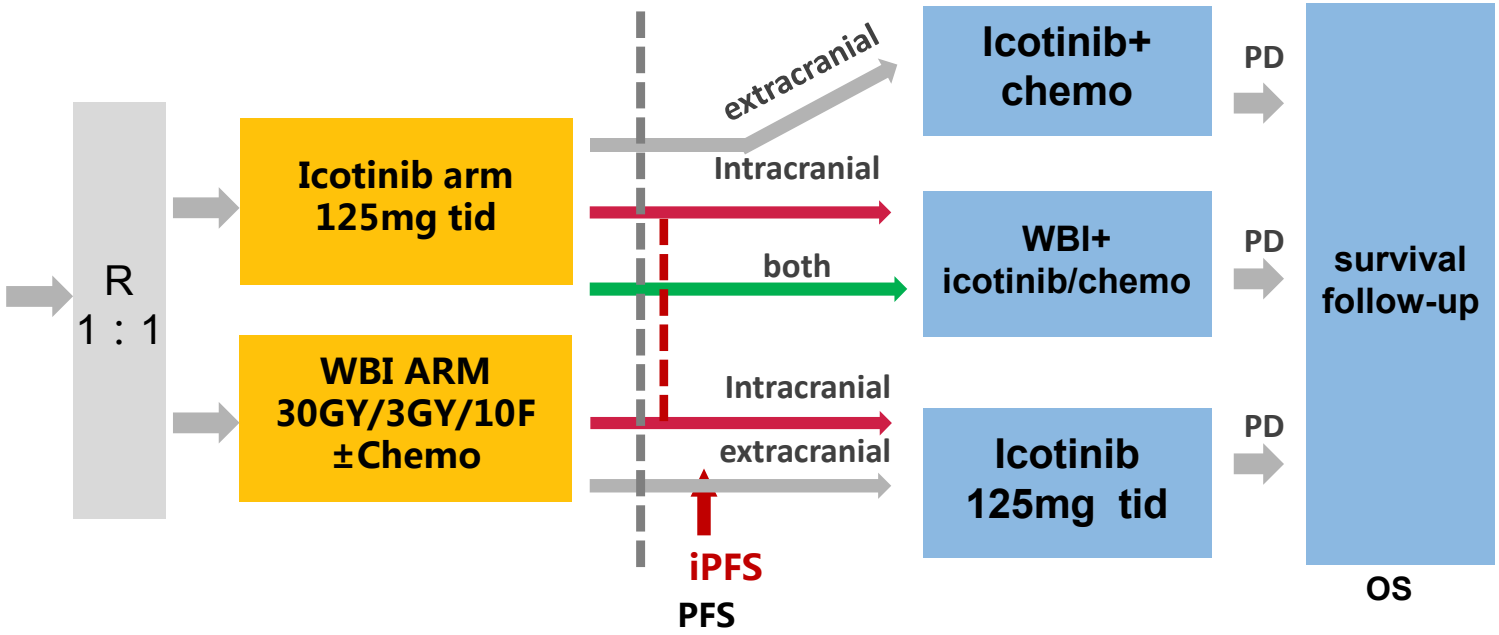
Paz-Ares L et al, AO'17

Quale EGFR-TKI in 1ªlinea? Conclusioni

- **Efficacia in termini di impatto sulla sopravvivenza sostanzialmente sovrapponibile**
- **Afatinib > Gefitinib in termini di RR e PFS**
- **Afatinib > Gefitinib in termini di tossicità (diarrea, rash cutaneo, mucosite)**
- **La scelta dell'EGFR-TKI in 1° linea deve essere basata sulla valutazione del rapporto rischio/beneficio in ogni singolo paziente e sulle differenze in termini di costi**

Study Design (NCT01724801)

- Advanced NSCLC with BM
- *EGFR* mutation & EGFR TKIs naive
- Brain metastatic sites≧3
- 18-75 years
- Life expectancy ≧12 weeks
- ECOG PS score 0-1

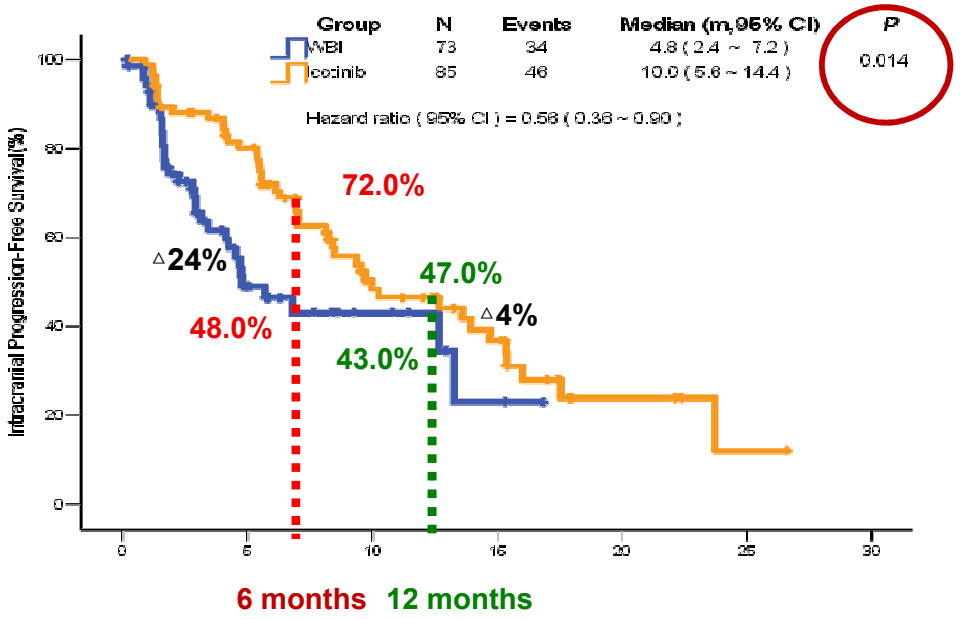


Primary endpoint:
Intracranial progression-free survival (iPFS)

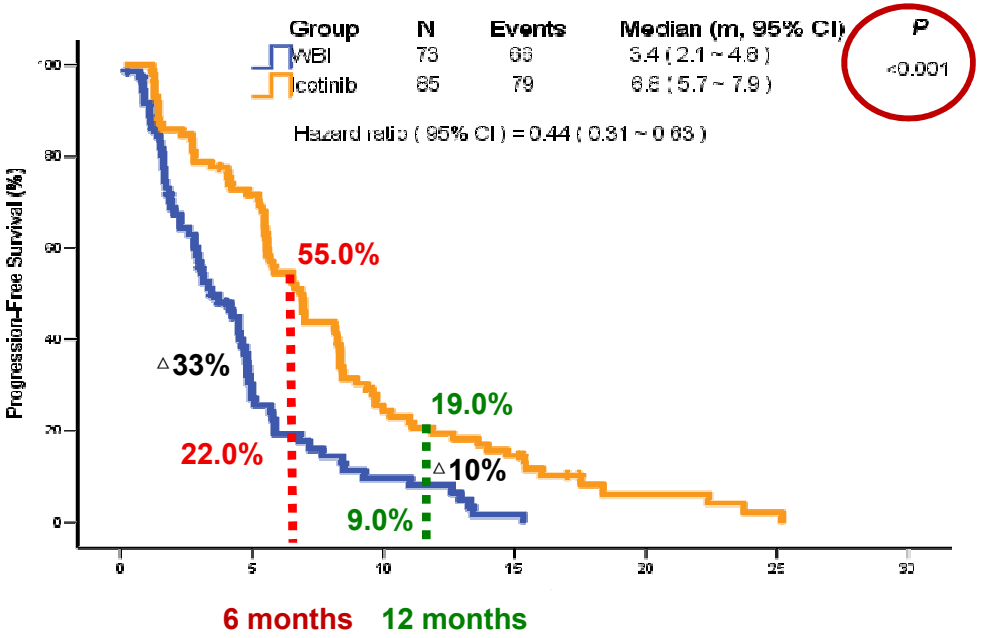
Secondary endpoints:
Progression –free survival(PFS)
Intracranial Objective response rate (iORR) ; Overall survival(OS)
Safety and tolerability

Major outcomes

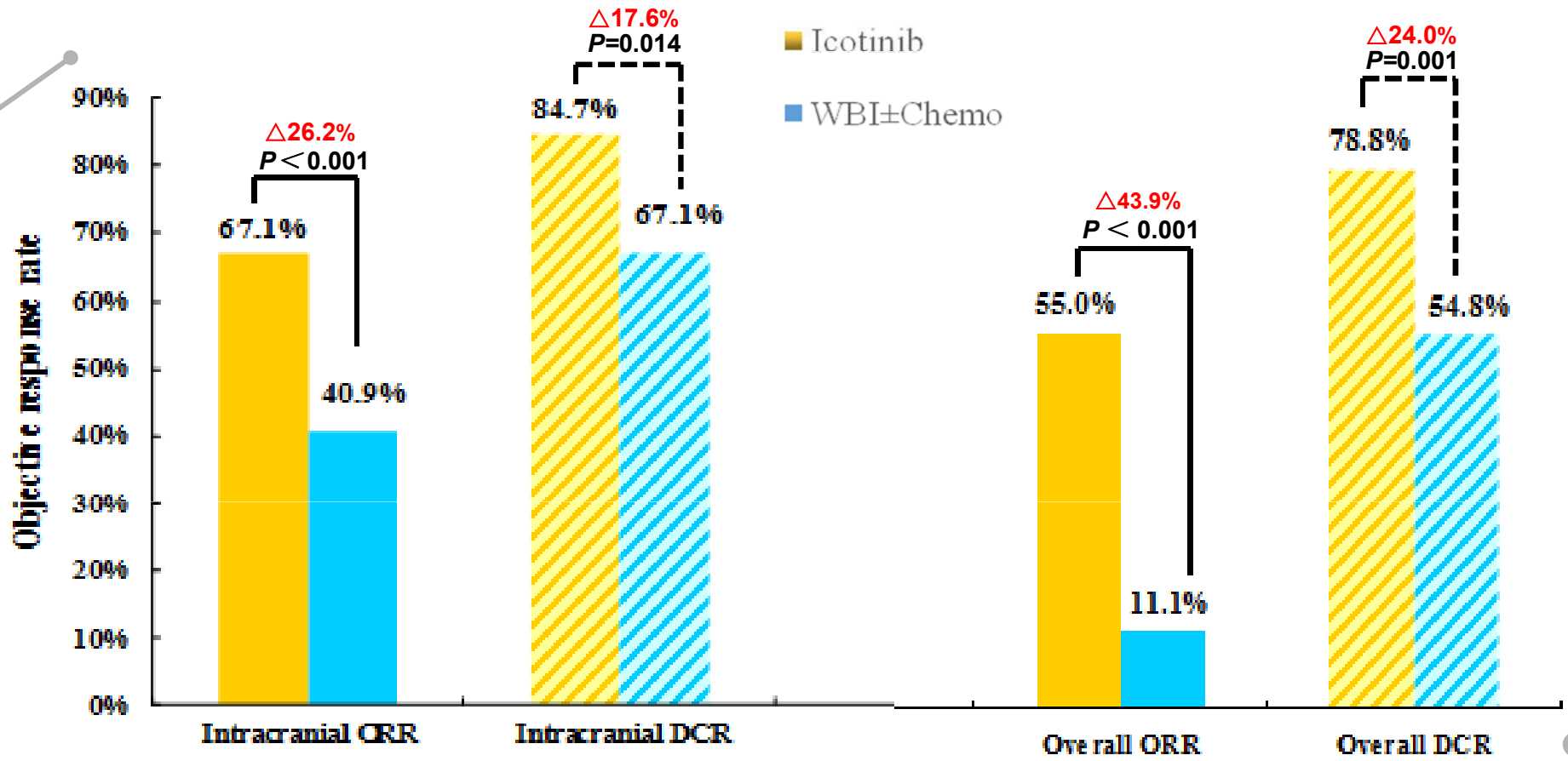
Intracranial PFS



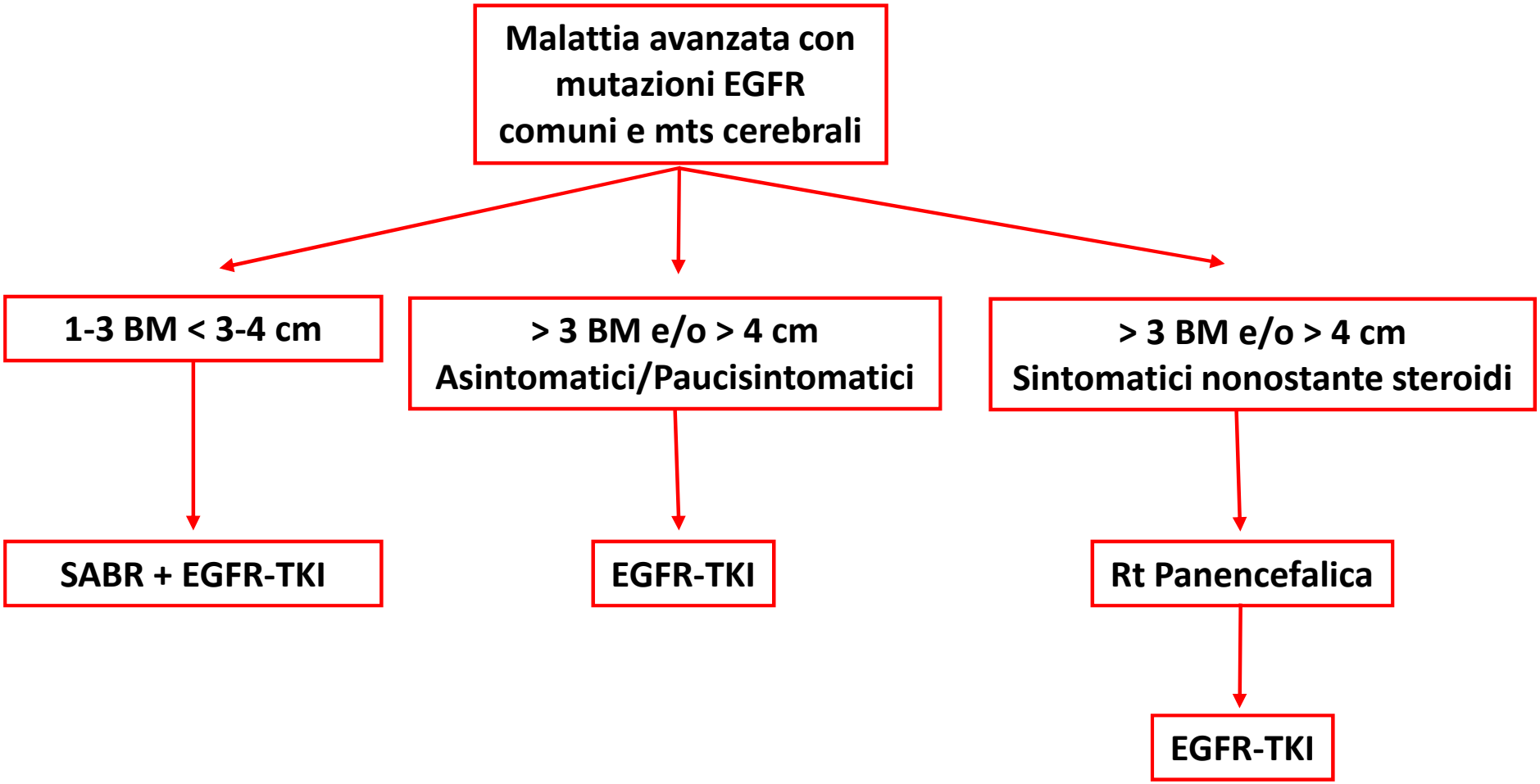
Systemic PFS



Intracranial RR and overall RR



EGFR-mut NSCLC with brain mts: Treatment strategy

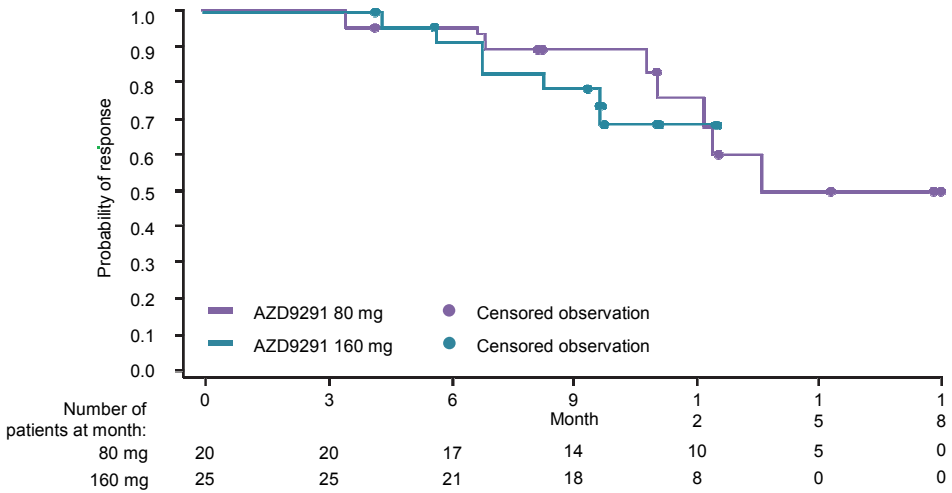


Come migliorare i risultati del trattamento di 1ª linea del NSCLC EGFR-mut+

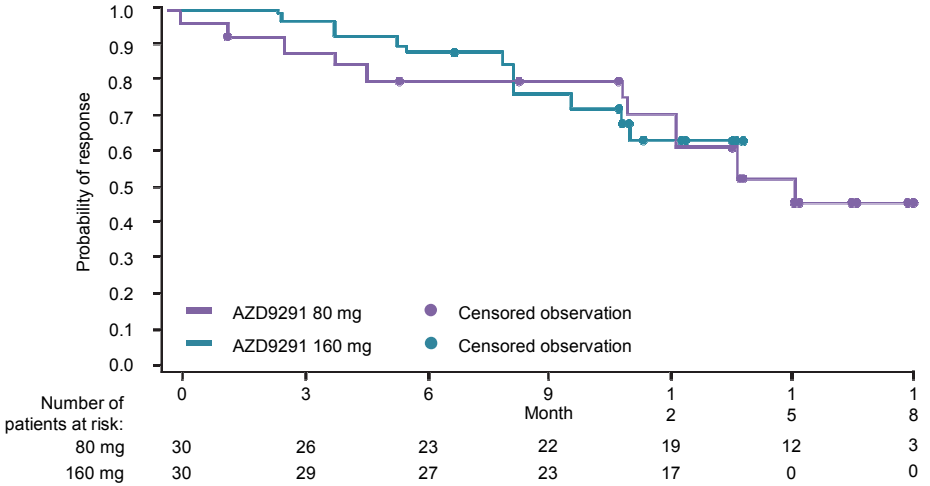
- **TKI di 3ª generazione in prima linea**
- **Combinazione con**
  - Anti-angiogenici
  - Chemioterapia
  - Anti-MET
  - Anti-PD1/PDL1

DoR and PFS in AZD9291 first-line cohorts (investigator assessed)

Duration of response



Progression-free survival



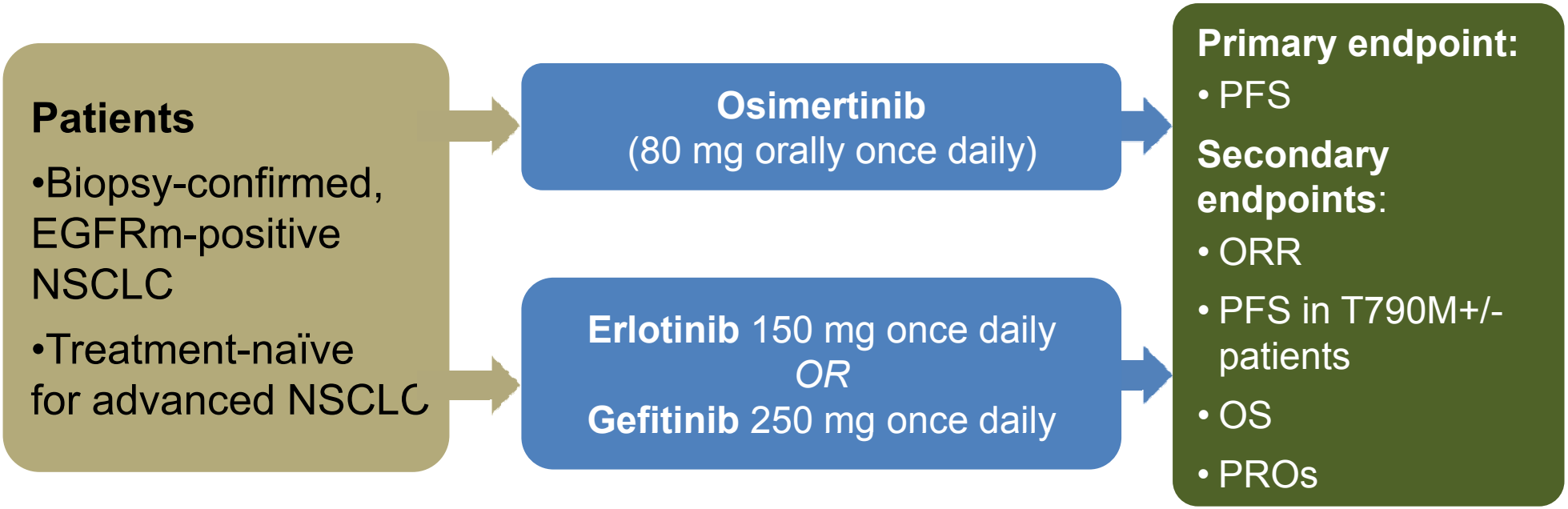
	80 mg N=20	160 mg N=25	Total N=45
Median DoR,* months (95% CI)	13.6 (11.1, NC) Maturity: 35%	NC (9.7, NC) Maturity: 28%	NC (12.3, NC) Maturity: 31%
Maximum DoR, months	18.0+	12.6+	18.0+
Remaining in response,† % (95% CI)			
9 months	89 (64, 97)	78 (56, 90)	83 (68, 92)
12 months	76 (46, 90)	69 (45, 84)	71 (53, 83)

	80 mg N=30	160 mg N=30	Total N=60
Median PFS,‡ months (95% CI)	NC (12.3, NC) Maturity: 40%	NC (11.1, NC) Maturity: 30%	NC (13.7, NC) Maturity: 35%
Maximum PFS, months	19.2+	13.8+	19.2+
Remaining alive and progression-free,† % (95% CI)			
9 months	83 (64, 93)	80 (60, 90)	81 (69, 89)
12 months	75 (55, 87)	69 (48, 82)	72 (58, 82)

ECIST assessment for patients who do not progress;
†Calculated using the Kaplan-Meier technique; ‡Progression-free survival is the time from date of first dosing until the date of objective disease progression or death
DoR, duration of response; NC, not calculable; PFS, progression-free survival

Ramalingam et al, WCLC 2015

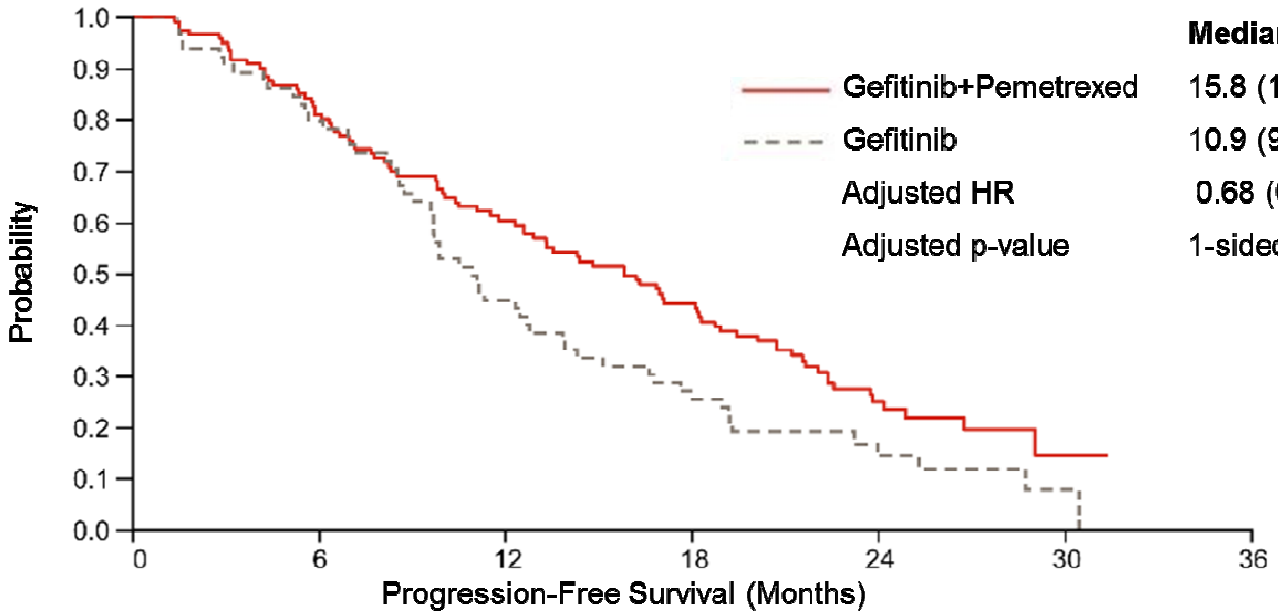
FLAURA: Phase III, Double-Blind, Randomized Trial of Osimertinib as First-Line Therapy



- EGFRm = epidermal growth factor receptor mutation; ORR=objective response rate; OS = overall survival; PFS = progression-free survival; PROs = patient-reported outcomes.
- NCT02296125, www.clinicaltrials.gov.

Primary Endpoint: PFS – ITT Population

- **Significantly prolonged median PFS in the gefitinib+pemetrexed arm (15.8 months) vs. the gefitinib arm (10.9 months)**



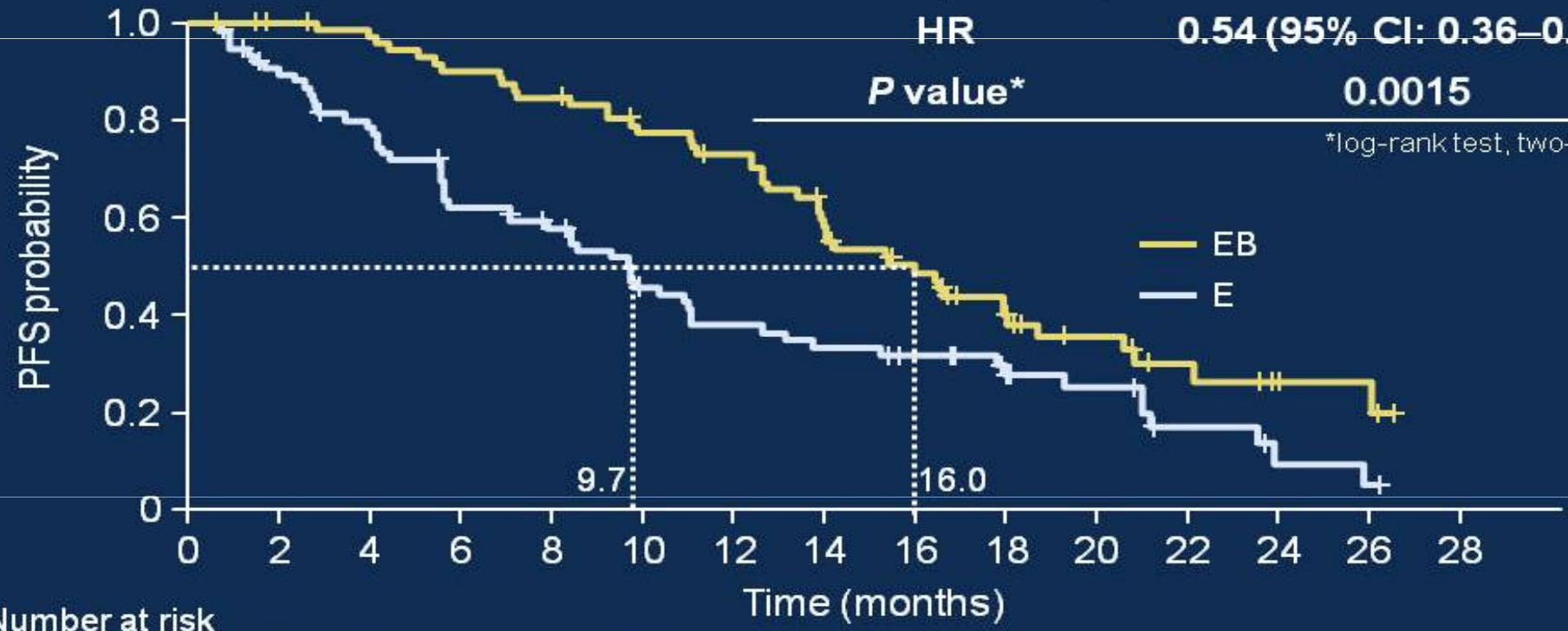
Patients at Risk							
Gefitinib+Pemetrexed	126	97	69	49	18	1	0
Gefitinib	65	51	28	17	6	1	0

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; PFS=progression-free survival

Primary endpoint: PFS by independent review

	EB	E
Median (months)	16.0	9.7
HR	0.54 (95% CI: 0.36–0.79)	
P value*	0.0015	

*log-rank test, two-sided



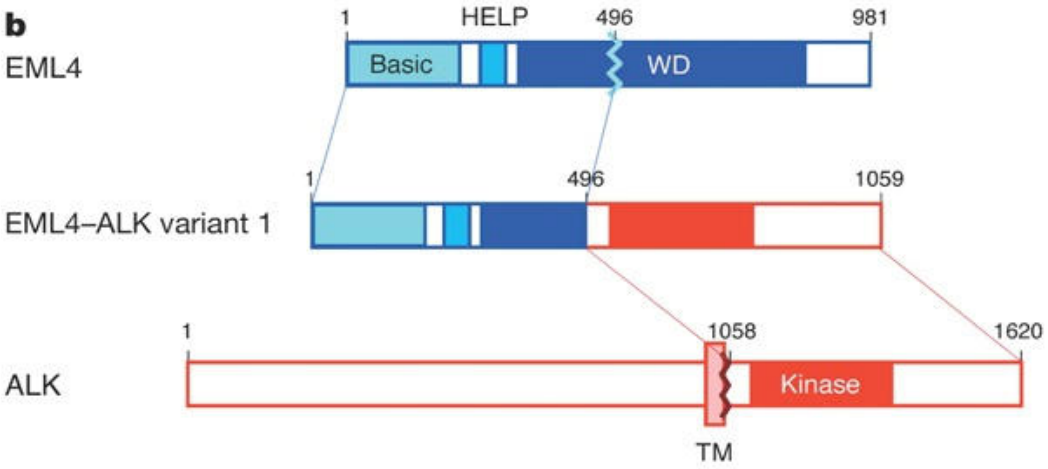
Number at risk															
EB	75	72	69	64	60	53	49	38	30	20	13	8	4	4	0
E	77	66	57	44	39	29	24	21	18	12	10	5	2	1	0

Presented by: Terufumi Kato

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



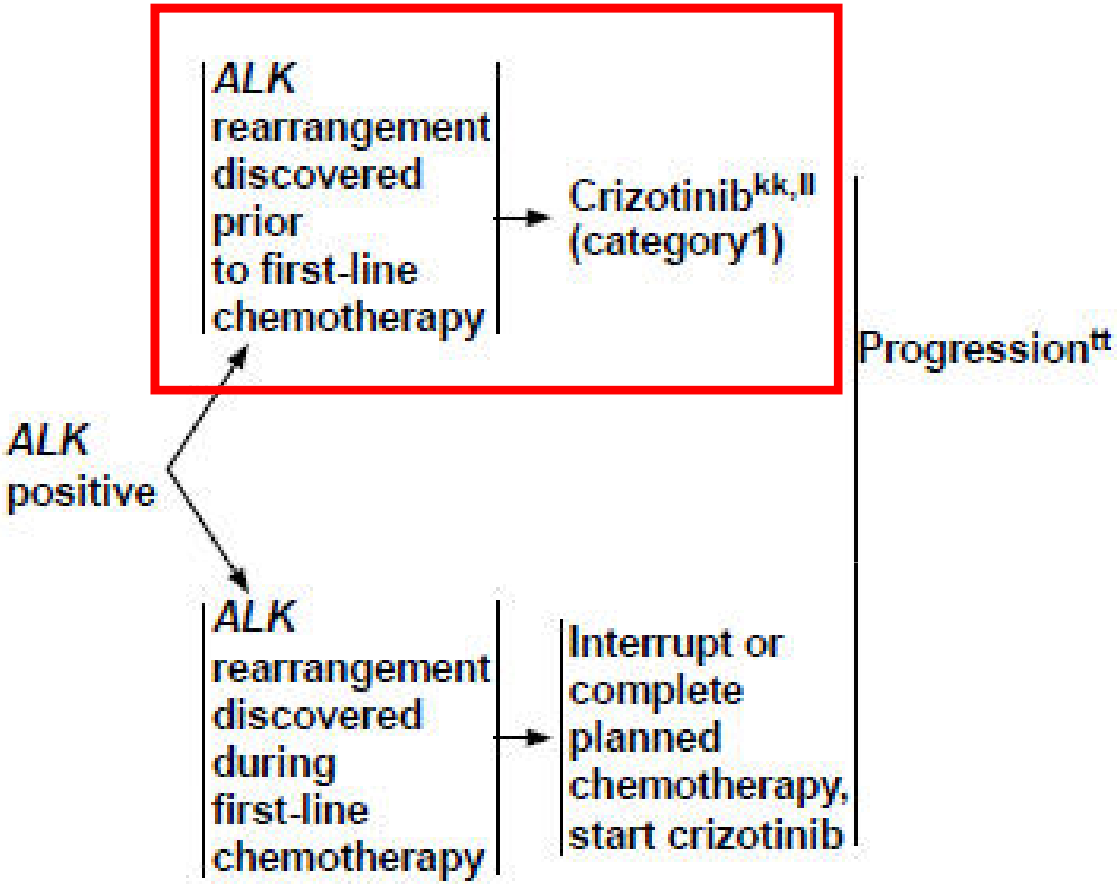
First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

	Platinum-Pemetrexed	Crizotinib	P-value
RR%	**45**	**74**	**<0.001**
mPFS (months)	**7**	**10.9**	**<0.001**
1-Year OS%	**79**	**84**	**NS**
QLQ-LC13	**-**	+	**<0.001**

Solomon et al, NEJM'14

ALK POSITIVE[a]

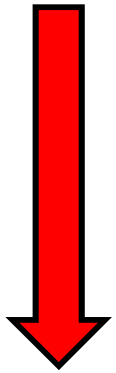
FIRST-LINE THERAPY[ee]



Potential loss of efficacy with sequential ALK TKIs

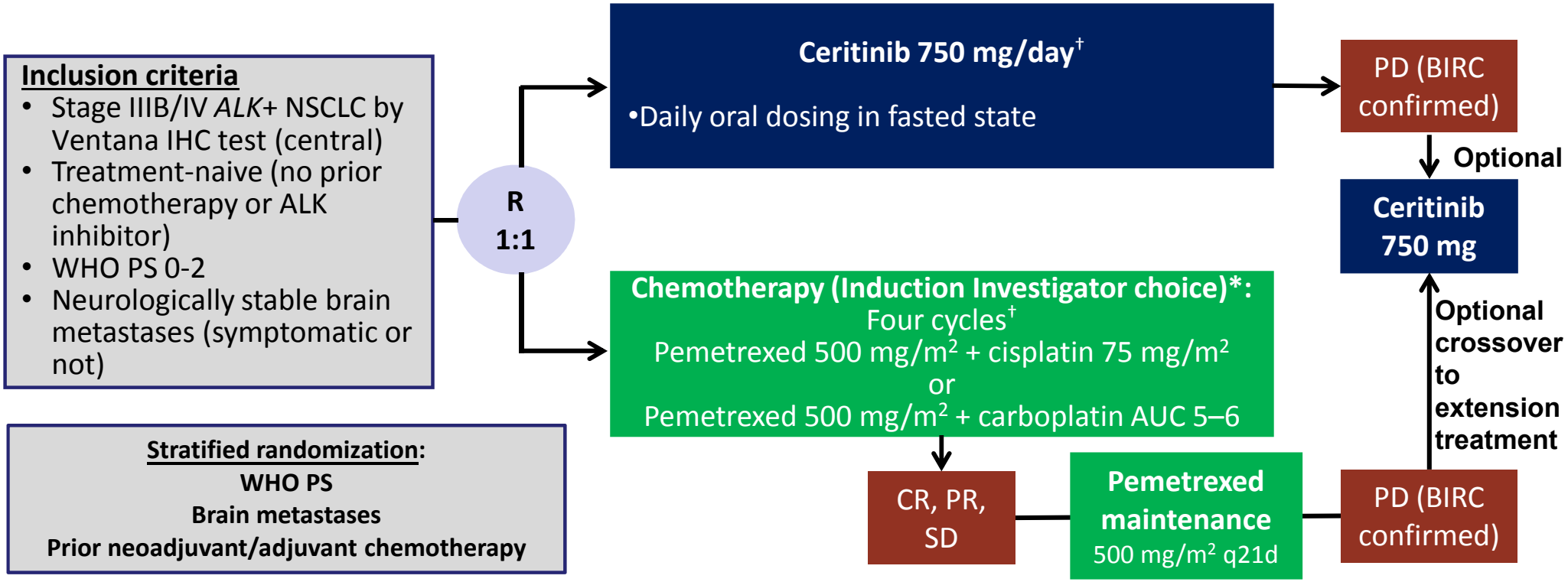
ALK TKI	Ceritinib	Alectinib	Brigatinib	Lorlatinib[7]	Ensartinib[8]
1st line	79%[1]	94%[3]	100%[5]	NA	71%
2nd line	50%[2]	50%[4]	59%[6]	57%	64%
3rd line	NA	NA	NA	42%	23%

Decreasiing ORR



[1]Felip E, et al. ESMO. 2016; abstr 12080
[2] Mok T, et al. ASCO. 2015 abstr 8059
[3]Nokihara H, et al., ASCO 2016
[4] Ou I, et al. ASCO. 2015 (abstr 8008)
[5]Bazhenova et al, ESMO 2016
[6]Kim D-W et al. J Clin Oncol. 2016;34:abstr 9007
[7]Solomon B et al., ASCO 206
[8] Horn L, et al., ESMO 2016

ASCEND 4 - Phase 3, Randomized, Global, Open-label Study (NCT01828099)



***At the time when ASCEND-4 was designed and initiated, pemetrexed-platinum chemotherapy followed by pemetrexed maintenance was the standard of care in patients with non-squamous advanced NSCLC**

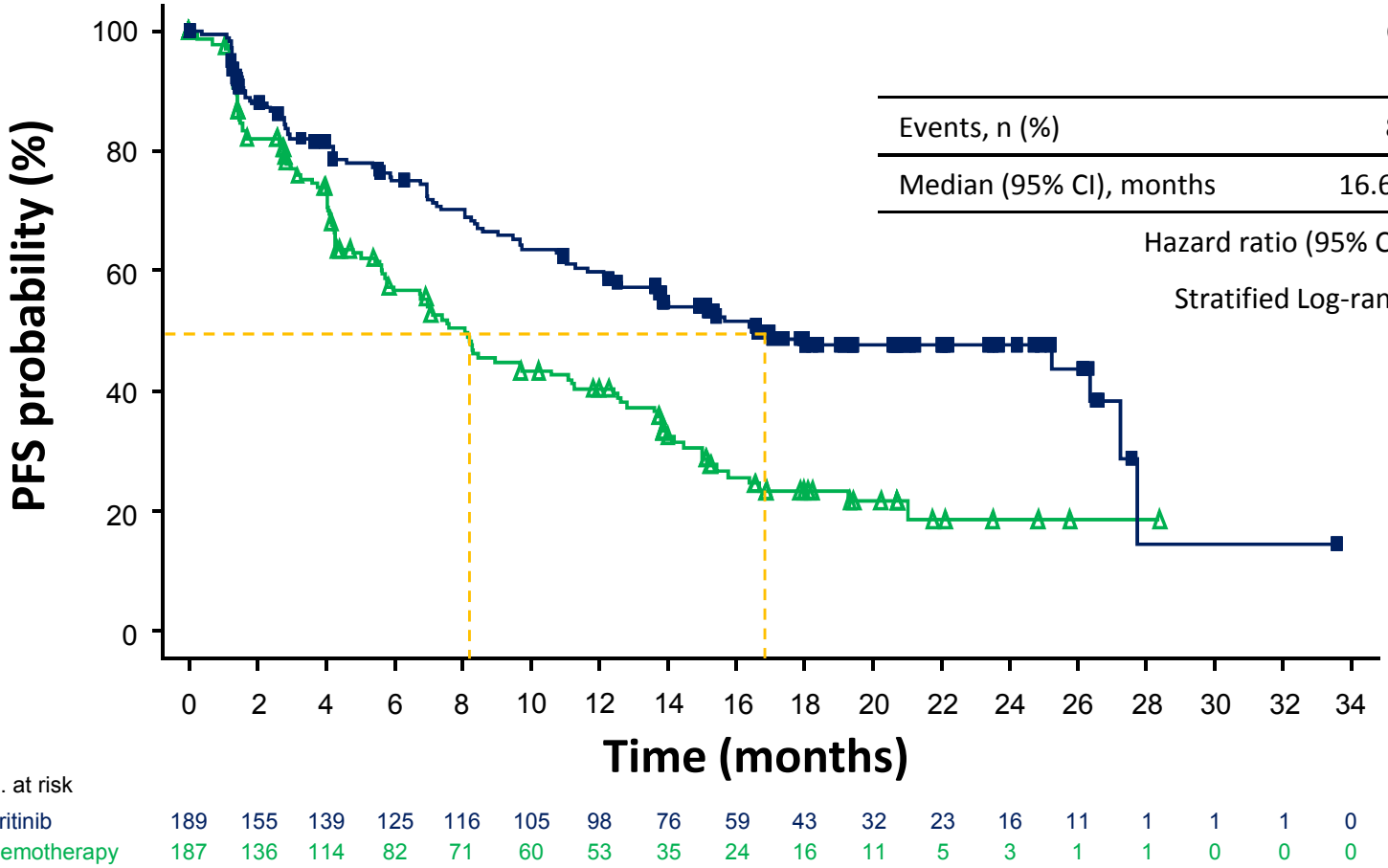
†One cycle = 21 days

BIRC, Blinded Independent Review Committee; CR, complete response; IHC, immunohistochemistry; PD, progressive disease; PR; partial response; PS, performance status; SD, stable disease; WHO, World Health Organization;

De Castro et al, IASLC 2016

Primary Endpoint: PFS by BIRC

Ceritinib Demonstrated an Estimated 45% Risk Reduction Vs Chemotherapy



	Ceritinib (N=189)	Chemotherapy (N=187)
Events, n (%)	89 (47.1)	113 (60.4)
Median (95% CI), months	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)

Hazard ratio (95% CI) = 0.55 (0.42, 0.73)

Stratified Log-rank p-value < 0.001

No. at risk

Ceritinib	189	155	139	125	116	105	98	76	59	43	32	23	16	11	1	1	1	0
Chemotherapy	187	136	114	82	71	60	53	35	24	16	11	5	3	1	1	0	0	0

De Castro et al, IASLC 2016

Comparing Efficacy

STUDY (n)	ASCEND-4 (n=376) De Castro et al WCLC 2016		PROFILE 1014 (n=343) Solomon et al JCO 2016	
	Ceritinib	ChemoT	Crizotinib	ChemoT
PFS (mths) overall population	16.6	8.1	10.9	7.0
Brain metastases (BM) present	N=61	N=60	N=39	N=40
Prior brain radiotherapy number (%)	24 (40%)	24 (40%)	Treated*	Treated*
PFS in BM subgroup (mths) [95%CI] PFS in no BM subgroup (mths) [95% CI]	10.7 [8.1,16.4] 26.3 [15.4,27.7]	6.7 [4.1,10.6] 8.3 [6.0,13.7]	9 [6.8,15] 11.1 [8.3,14]	4 [1.5,6.8] 7.2 [6.9,8.3]
Intracranial response rate	73% (22)	27.3% (22)	NE	NE
Intracranial DCR at 24 weeks	86%	50%	56%	25%
Intracranial Progression number (%)	NR	NR	25 (15%)	26 (15%)

DCR : Disease control rate (CR,PR,SD), NE : Not evaluated, NR : Not reported *details of prior radiotherapy not known

WCLC 2016 PL03.08: Discussant F Blackhall First-line ceritinib vs chemotherapy – G de Castro et al

Toxicity% : All Grades (G3/4)

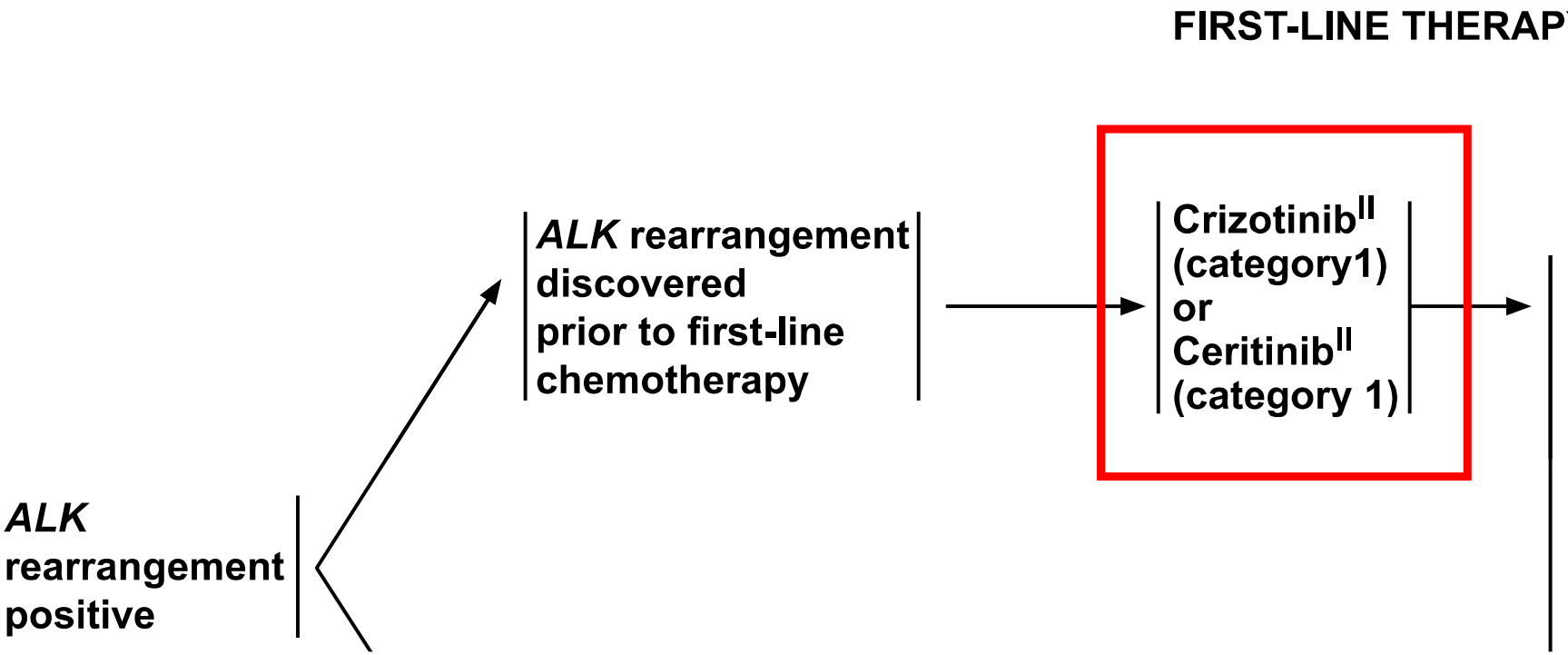
	ASCEND-4 De Castro et al WCLC 2016		PROFILE 1014 Solomon et al NEJM 2014	
	Ceritinib	Chemo	Crizotinib	Chemo
Vision Disorder	-	-	71 (1)	9 (0)
Diarrhea	84.7 (**5.3**)	10.9 (1.1)	61 (2)	13 (1)
Edema	-	-	49 (1)	12 (1)
Vomiting	66.1 (5.3)	36 (5.7)	46 (2)	36 (3)
Nausea	68.8 (2.6)	55.4 (5.1)	56 (1)	59 (2)
Fatigue	29.1 (4.2)	29.7 (2.9)	29 (3)	38 (2)
Elevated transaminases [ALT for ASCEND-4]	60.3 (**30.7**)	21.7 (2.9)	36 (14)	13 (2)
Discontinuation due to AEs (study drug) %	11.1 (5.3)	16.6 (11.4)	12 (5)	14 (8)

WCLC 2016 PL03.08: Discussant F Blackhall First-line ceritinib vs chemotherapy – G de Castro et al

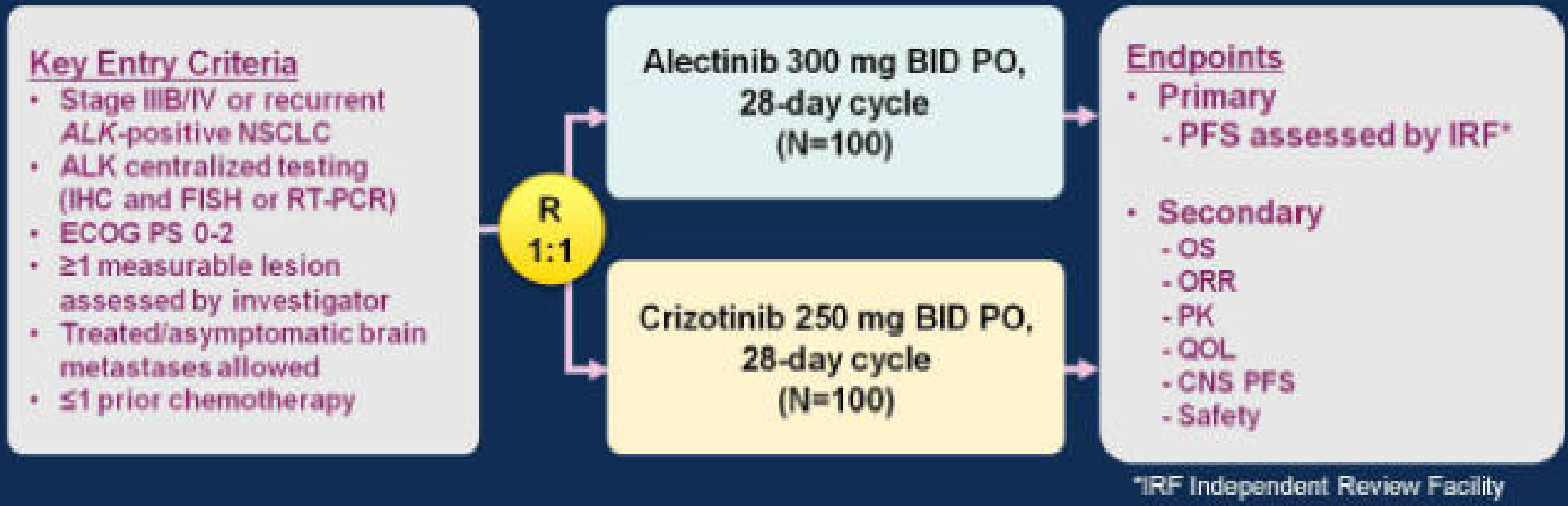
National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2017
Non-Small Cell Lung Cancer

ALK REARRANGEMENT POSITIVE[a]



J-ALEX Phase III Study Design



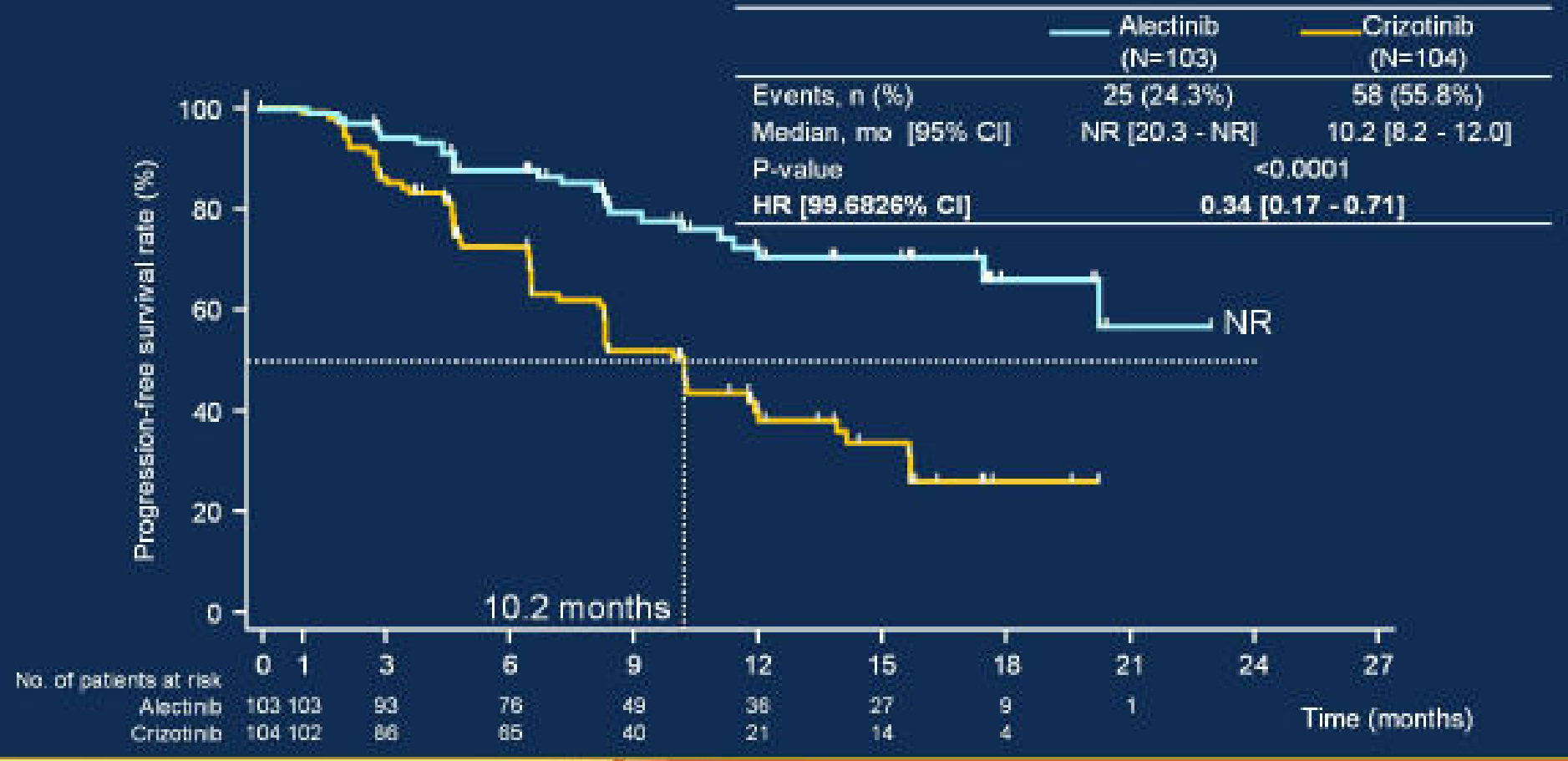
*IRF Independent Review Facility

Stratification factors: Clinical stage (IIIB/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)

JapicCTI-132316

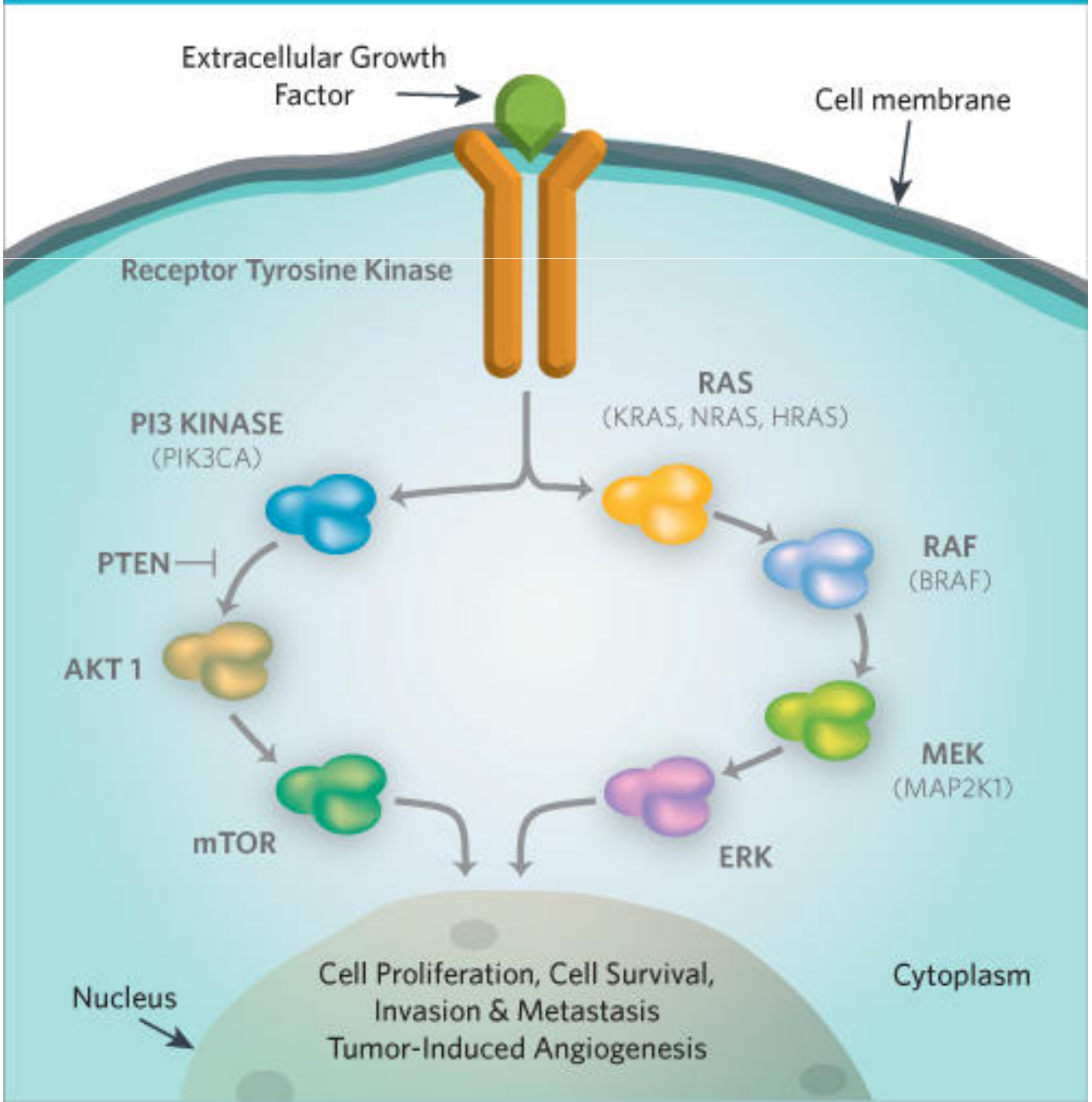
Presented By Hiroshi Nokihara at 2016 ASCO Annual Meeting

Primary Endpoint: PFS by IRF (ITT Population)



Presented By Hiroshi Nokihara at 2016 ASCO Annual Meeting

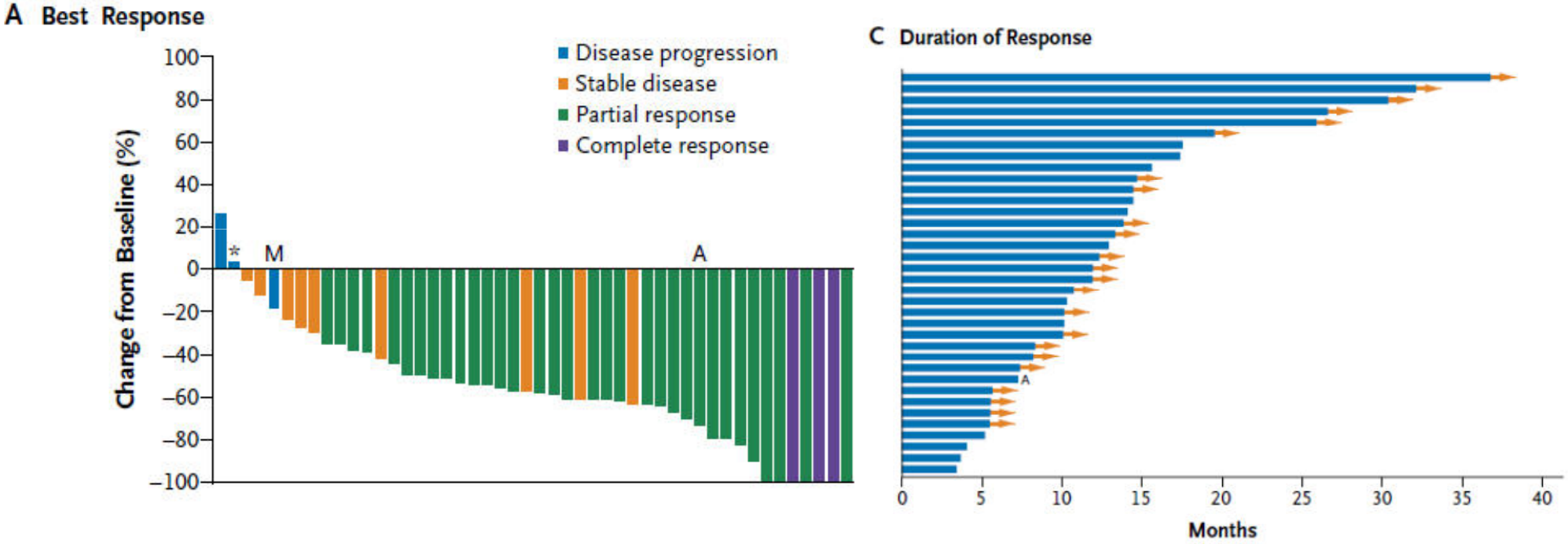
Cell Surface RTK Receptor Protein-ROS1



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2014 VOL. 371 NO. 21

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer



Shaw, NEJM’14

Novel TKIs for ROS1-rearranged NSCLC

Drug	N° Pts	RR
Ceritinib [1]	32	62%
Lorlatinib [2]	11	55%

1. Lim, ESMO'16; 2. Solomon, ASCO'16

ROS1 REARRANGEMENT POSITIVE[a]

FIRST-LINE THERAPY