First line TKI + something in EGFR mutated Lung Cancer

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Points of discussion

Rationale

Evidence

Guidelines

My thoughts

Rationale

It’s a strategy to prevent emergence of resistance

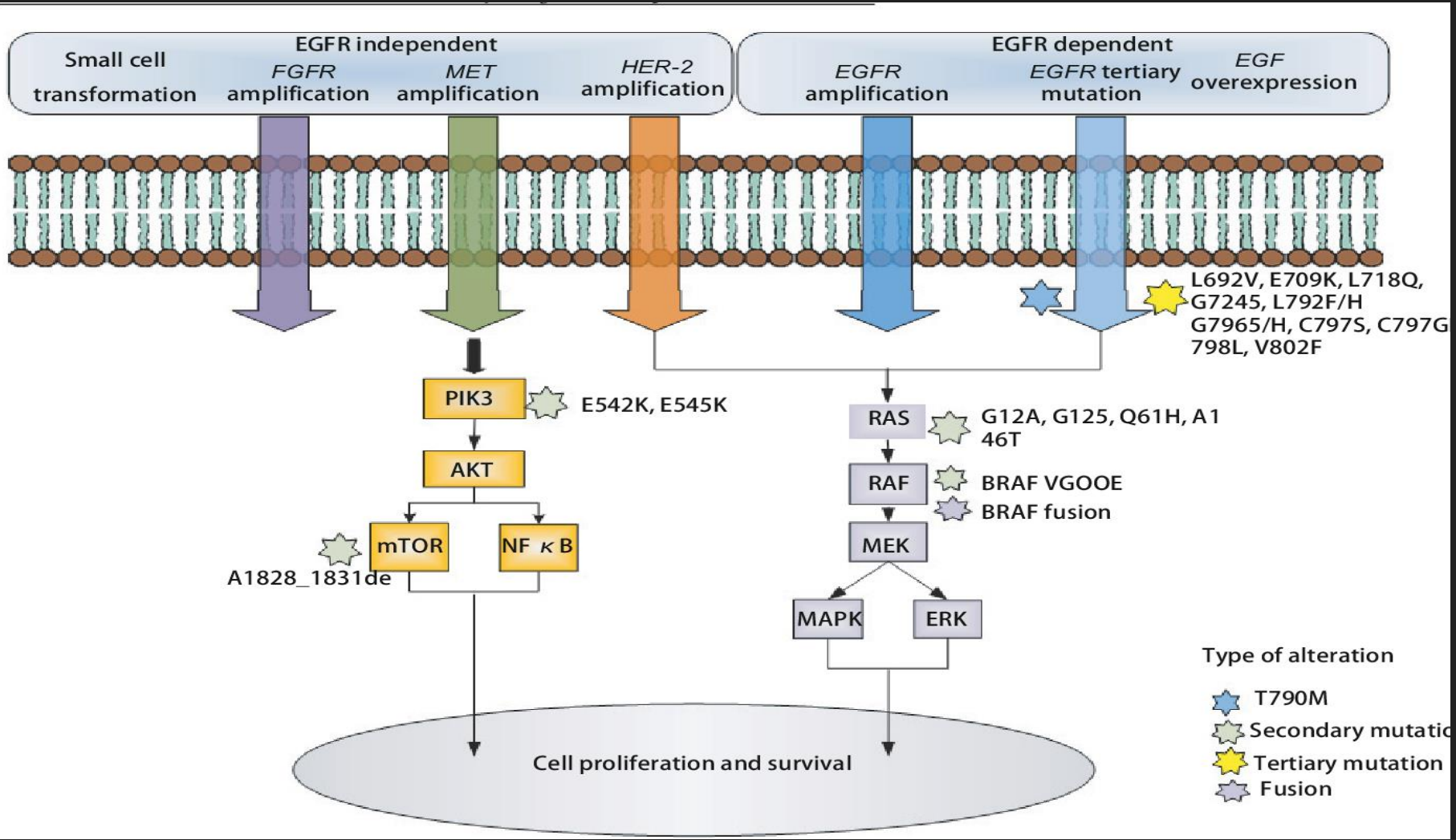
Expectation from “Something”

- To prevent or delay the development of resistance - tumour is heterogenous, so prevent the development of resistant subclones by treating non overlapping pathways

- 20-30 % patients do not receive second line therapy, HIT HARD first time

- Few treatment options for resistant mutations, so to reserve the drugs for second line → better sequence

- Affordable options


Small cell transformation
EGFR independent
FGFR amplification
MET amplification
HER-2 amplification
EGFR dependent
EGFR amplification
EGFR tertiary mutation
EGF overexpression
L692V, E709K, L718Q,
G7245, L792F/H
G7965/H, C797S, C797G
798L, V802F
PIK3
E542K, E545K
AKT
mTOR
A1828_1831de
NF κ B
RAS
G12A, G125, Q61H, A1
46T
RAF
BRAF VGOOE
BRAF fusion
MEK
MAPK
ERK
Cell proliferation and survival
Type of alteration
T790M
Secondary mutatic
Tertiary mutation
Fusion

EGFR and VEGF

- EGFR mutant mNSCLC → higher VEGF expression and mediated signaling

- EGFR and VEGFR-2 signaling both can trigger activation of the PI3K/AKT and RAS/RAF/ERK pathways

- EGFR activation leads to HIF-1α upregulation, which may lead to VEGF gene expression and a positive feedback loop

- VEGF signaling in turn contributes to the emergence of resistance to EGFR TKIs

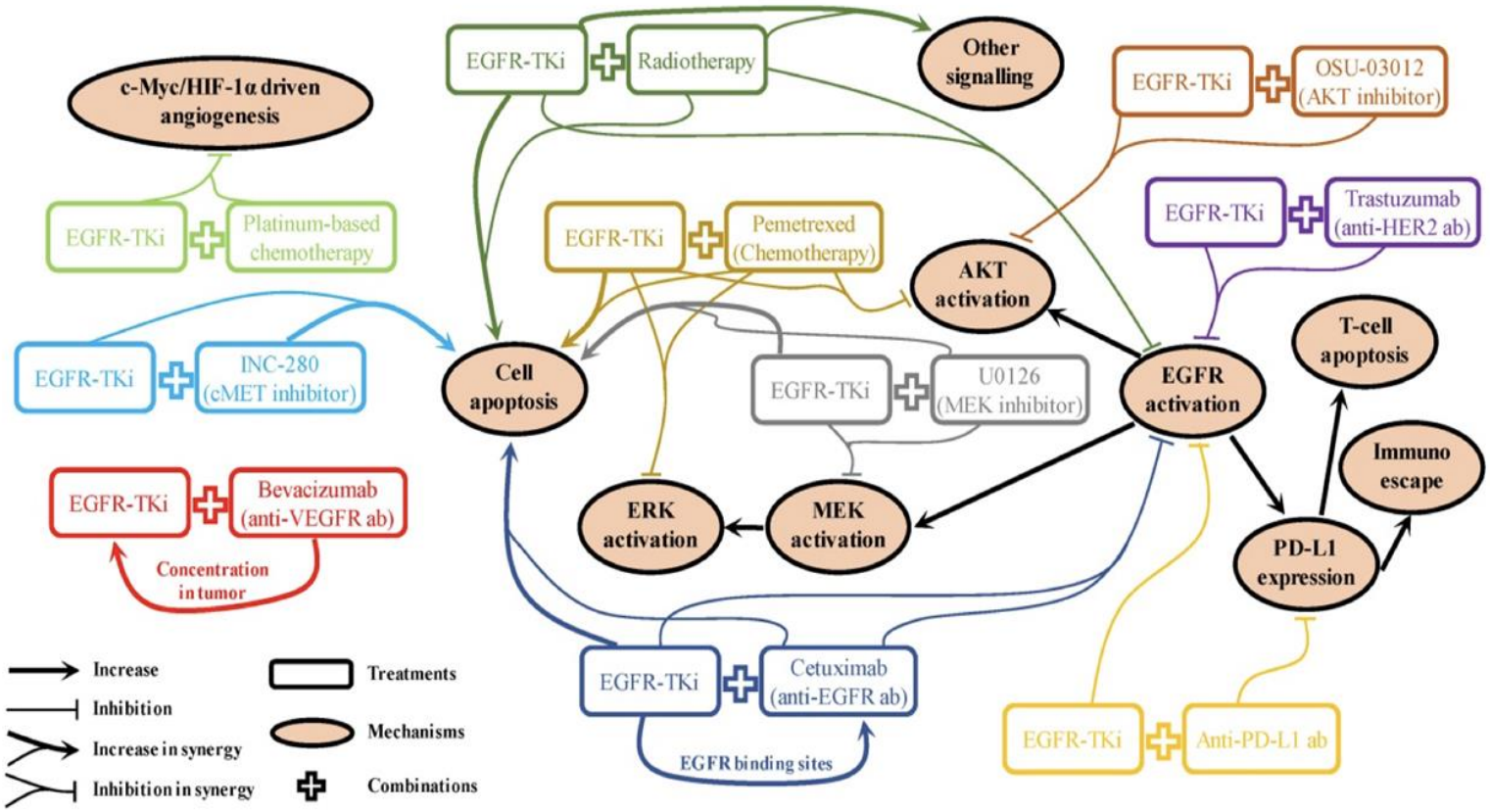


Figure. 2 Mechanism of drug actions for EGFR-TKi involved combination strategies reported in pre-clinical results

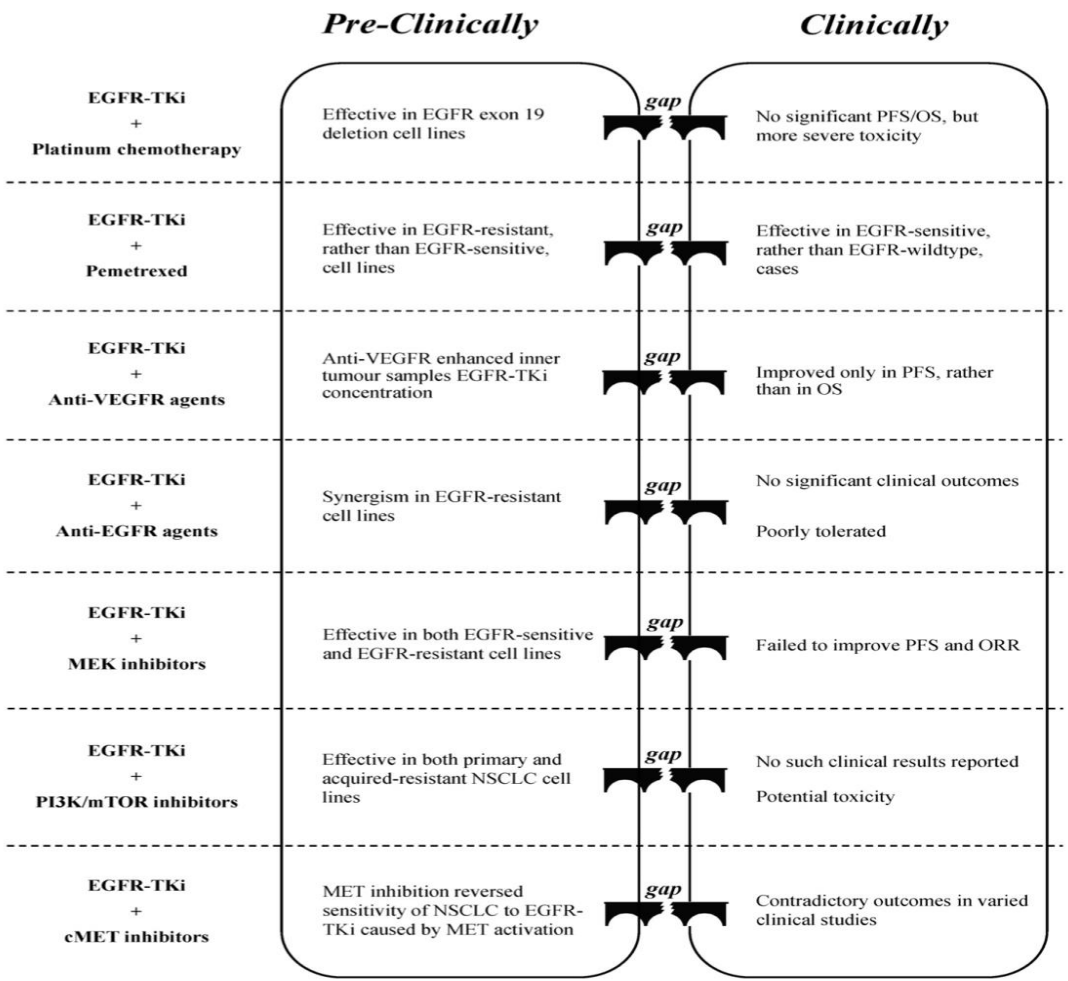


Figure. 1 Gaps between pre-clinical evaluation and clinical outcome when EGFR-TKi combined with chemotherapy/targeted therapy

TKI

(I Generation)

(III Generation)

Something

(Anti VEGF agent)

(Chemotherapy)

(Other TKI including **I + III**)

Evidence

I gen	Erlotinib with Anti VEGF	BEVERLY NEJ026
I gen	Erlotinib with Anti VEGFR2	RELAY
I gen	Gefitinib with Chemotherapy	NEJ009 TMH Study
I gen	III gen	NCT03122717

III gen	Osimertinib with Chemotherapy	FLAURA 2
III gen	I gen	NCT03122717
III gen (Lazertinib)	Amivantamab	MARIPOSA
III gen Osimertinib	Bevacizumab	BOOSTER WJOG9717L
III gen Osimertinib	Ramucirumab	RAMOSE

Combinations With the First-Generation EGFR TKI

Bevacizumab plus erlotinib versus erlotinib alone in Japanese patients with advanced, metastatic, *EGFR*-mutant non-small-cell lung cancer (NEJ026): overall survival analysis of an open-label, randomised, multicentre, phase 3 trial

Yosuke Kawashima, Tatsuro Fukuhara, Haruhiro Saito, Naoki Furuya, Kana Watanabe, Shunichi Sugawara, Shunichiro Iwasawa, Yoshio Tsunezuka, Ou Yamaguchi, Morihito Okada, Kozo Yoshimori, Ichiro Nakachi, Masahiro Seike, Koichi Azuma, Futoshi Kurimoto, Yukari Tsubata, Yuka Fujita, Hiromi Nagashima, Gyo Asai, Satoshi Watanabe, Masaki Miyazaki, Koichi Hagiwara, Toshihiro Nukiwa, Satoshi Morita, Kunihiko Kobayashi, Makoto Maemondo

Summary

Background Bevacizumab is a promising candidate for combination treatment with epidermal growth factor receptor tyrosine-kinase inhibitors (eg, erlotinib), which could improve outcomes for patients with metastatic *EGFR*-mutant non-small-cell lung cancer (NSCLC). We have previously shown in NEJ026, a phase 3 trial, that the combination of bevacizumab plus erlotinib significantly prolonged progression-free survival compared with erlotinib alone in these patients. In further analyses, we aimed to examine the effects of bevacizumab–erlotinib on overall survival, time from enrolment to progressive disease during second-line treatment or death, and quality of life.

Methods This open-label, randomised, multicentre, phase 3 trial (NEJ026) was done in 69 hospitals and medical, community-based centres across Japan. Eligible patients had stage IIIB, stage IV, or postoperative recurrent, *EGFR*-mutant (exon 19 deletion or exon 21 Leu858Arg point mutation) NSCLC, had not previously received systemic chemotherapy, and were randomly assigned (1:1) by a computer-generated randomisation sequence and minimisation to receive either 150 mg oral erlotinib once daily plus 15 mg/kg intravenous bevacizumab once every 21 days, or 150 mg oral erlotinib once daily, until disease progression or intolerable toxicity. Randomisation was stratified according to sex, smoking status, *EGFR* mutation subtype, and clinical disease stage. All participants, investigators, and study personnel (including those assessing outcomes) were unmasked to treatment allocation. We report the secondary outcomes of overall survival and quality of life (the period from enrolment to confirmation of a minimally important difference on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ]-C30), and the exploratory outcome of time from enrolment to progressive disease during second-line treatment or death.

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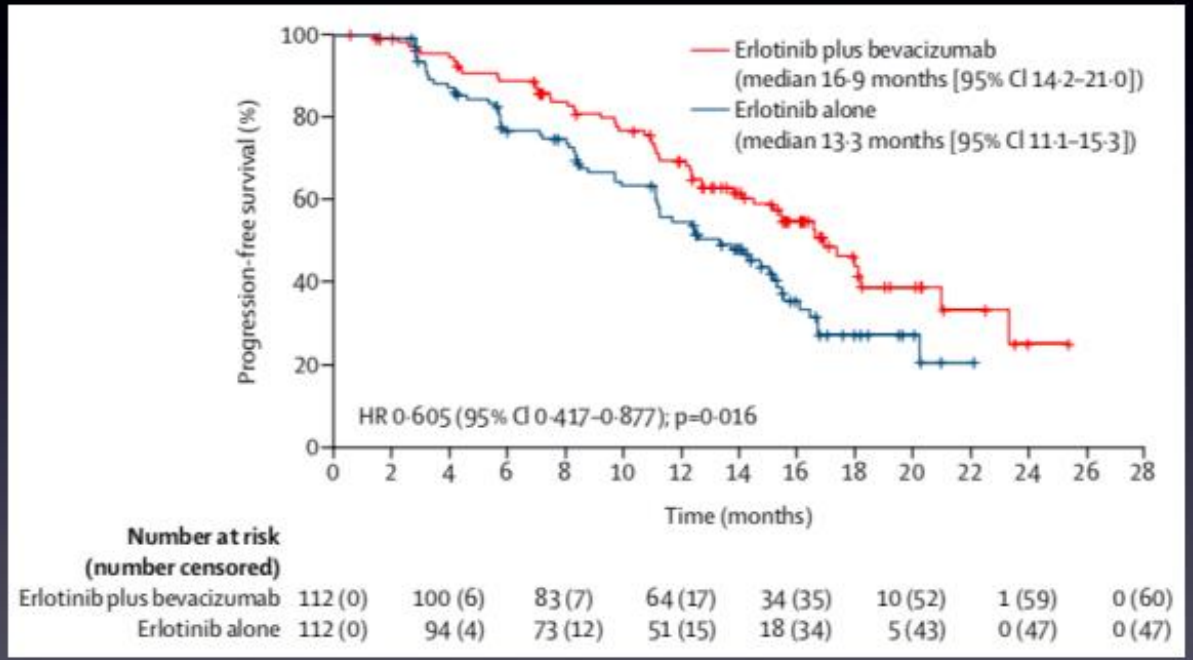
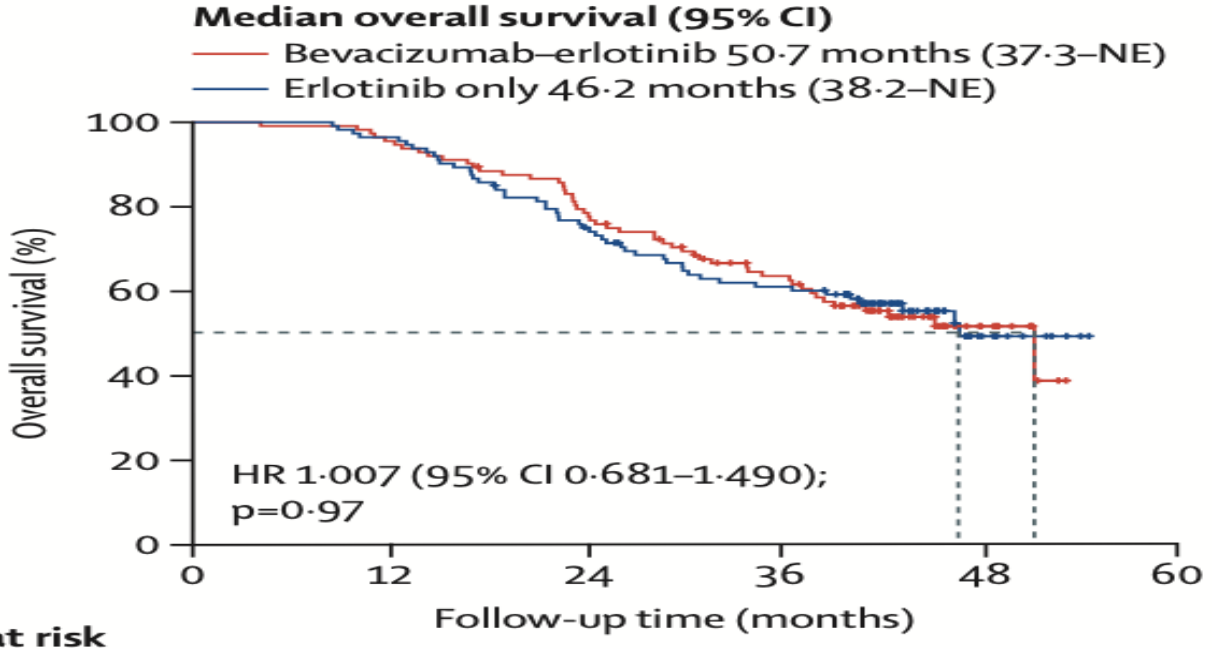
NEJ026 – PFS



Number at risk (number censored)								
Erlotinib plus bevacizumab	112 (0)	100 (6)	83 (7)	64 (17)	34 (35)	10 (52)	1 (59)	0 (60)
Erlotinib alone	112 (0)	94 (4)	73 (12)	51 (15)	18 (34)	5 (43)	0 (47)	0 (47)

Saito et al, Lancet Oncology 2019; Maemondo et al, ASCO 2020

OS numerically more than FLAURA and ARCHER



Number at risk (number censored)						
Bevacizumab–erlotinib	112 (0)	107 (0)	85 (1)	62 (9)	12 (50)	0 (61)
Erlotinib only	112 (0)	108 (0)	81 (2)	65 (4)	10 (52)	0 (62)

Figure 2: **Kaplan–Meier curves for overall survival in the modified intention-to-treat population**

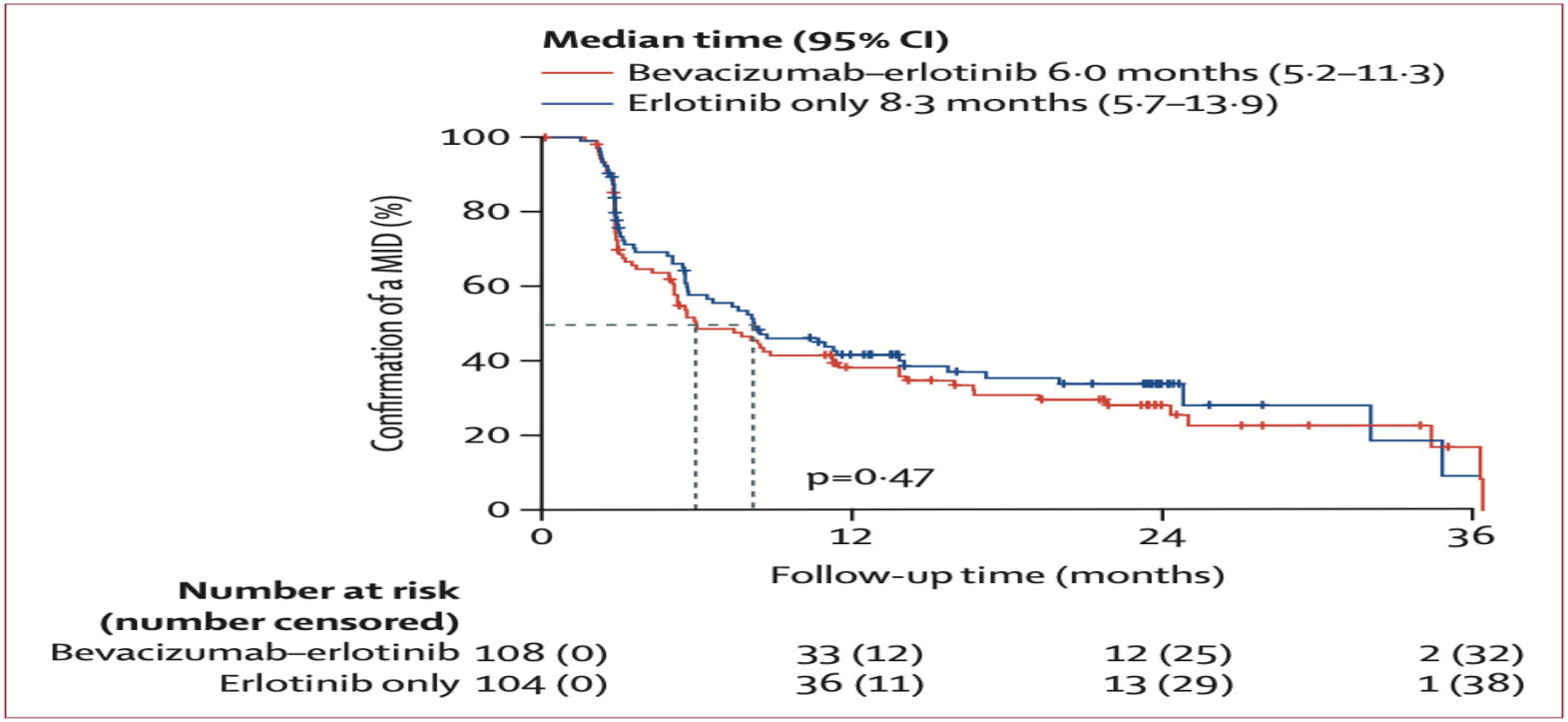


Figure 3: **Kaplan–Meier curves for quality of life in the modified intention-to-treat population with completed questionnaires**

The tick marks indicate censored observations. The MID was defined as a decline of 1 or more from the total combined score of items 29 and 30 of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30, version 3.0. The two-sided p value was calculated by use of a log-rank test. MID=minimally important difference.

Why no benefit ?

Skewed due to subsequent therapies

Shorter follow up and small sample size

BEVERLY trial-Italian JTO Sept 2022

ORIGINAL ARTICLE

IASLC

Addition of Bevacizumab to Erlotinib as First-Line Treatment of Patients With *EGFR*-Mutated Advanced Nonsquamous NSCLC: The BEVERLY Multicenter Randomized Phase 3 Trial

Maria Carmela Piccirillo, MD,[a] Laura Bonanno, MD,[b] Marina Chiara Garassino, MD,[c] Giovanna Esposito, MD,[d] Claudio Dazzi, MD,[e] Luigi Cavanna, MD,[f] Marco Angelo Burgio, MD,[g] Francesco Rosetti, MD,[h] Simona Rizzato, MD,[i] Floriana Morgillo, PhD,[j] Saverio Cinieri, MD,[k] Antonello Veccia, MD,[l] Maximilan Papi, MD,[m] Giuseppe Tonini, PhD,[n] Vittorio Gebbia, PhD,[o] Serena Ricciardi, MD,[p] Daniele Pozzessere, MD,[q] Alessandra Ferro, MD,[b] Claudia Proto, MD,[c] Raffaele Costanzo, MD,[d] Manolo D'Arcangelo, MD,[e] Manuela Proietto, MD,[f] Piera Gargiulo, MD,[a] Raimondo Di Liello, MD,[a] Laura Arenare, MSc,[a] Filippo De Marinis, MD,[r] Lucio Crinò, MD,[s] Fortunato Ciardiello, PhD,[j] Nicola Normanno, MD,[t] Ciro Gallo, MD,[u] Francesco Perrone, PhD,[a,*] Cesare Gridelli, MD,[v] Alessandro Morabito, MD[d]

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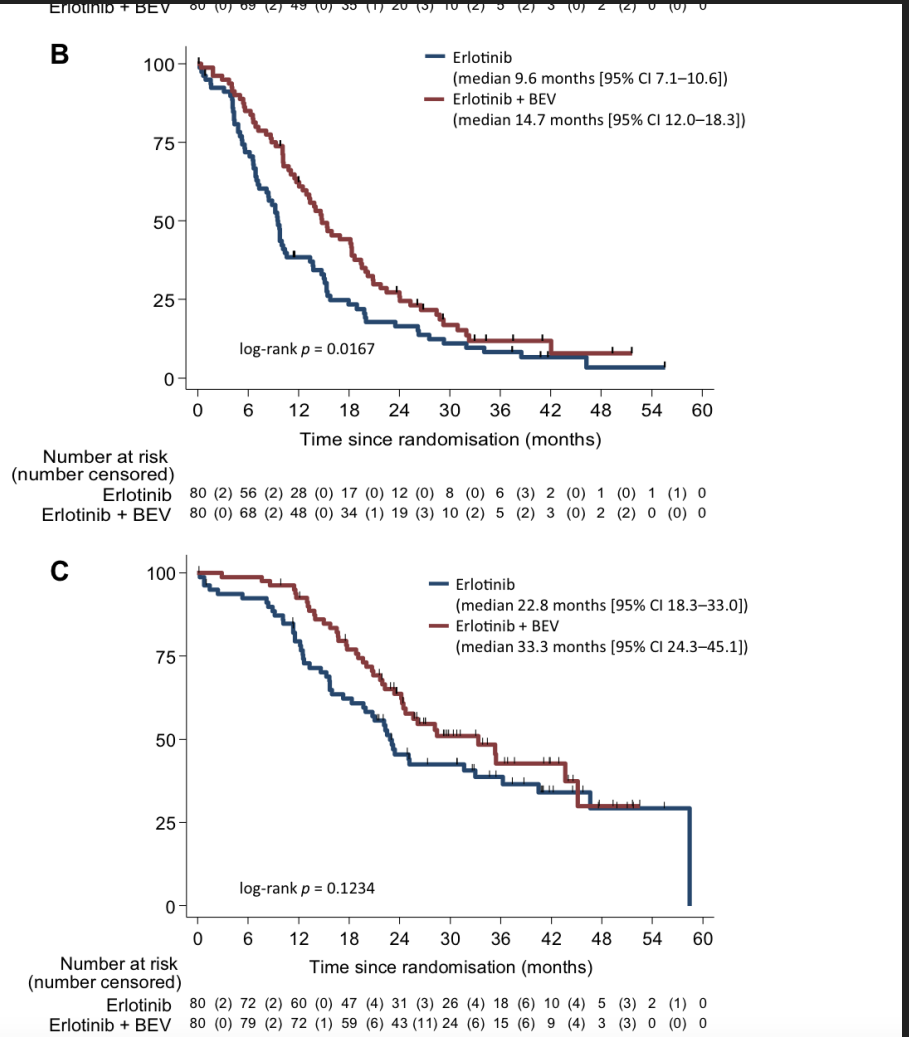
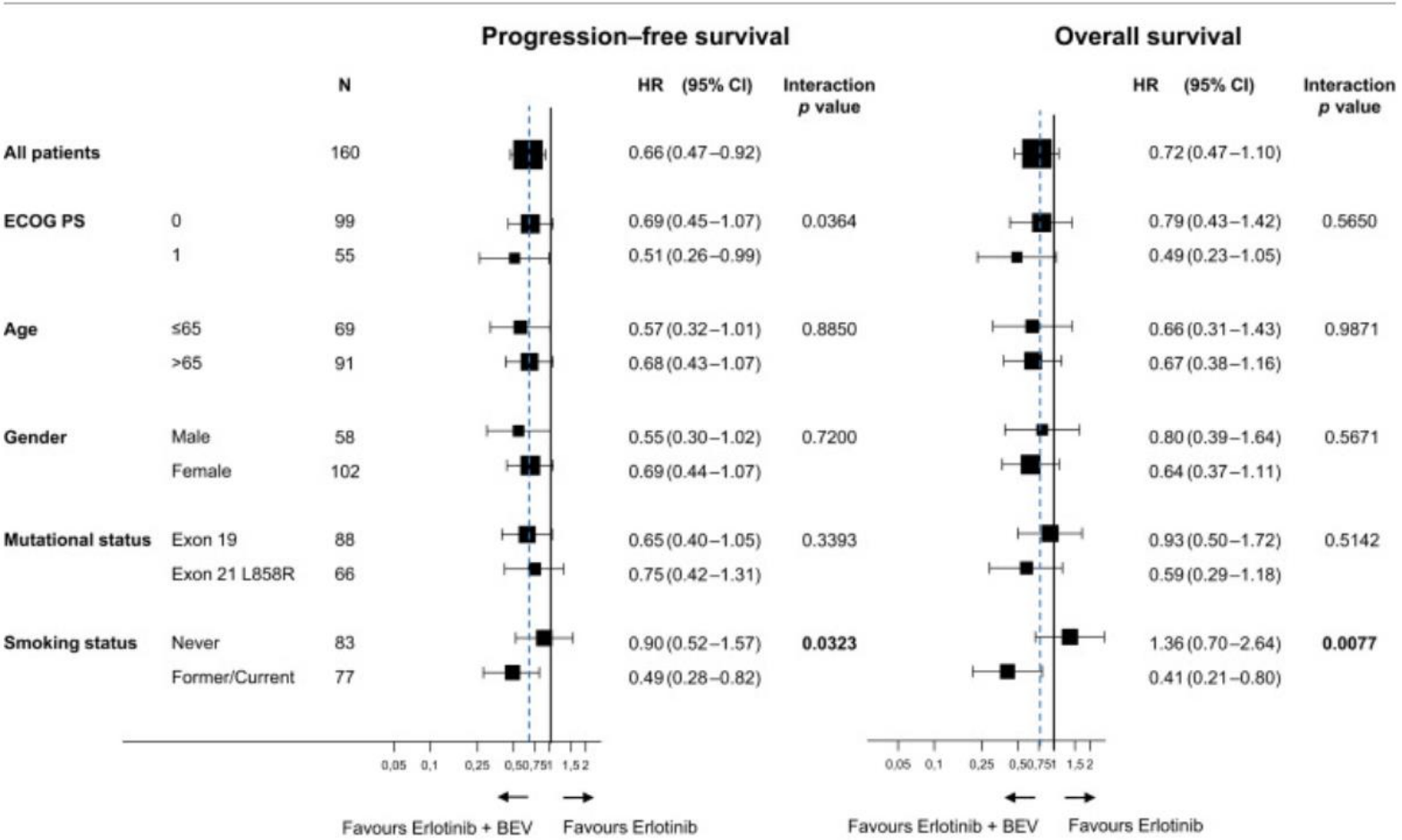


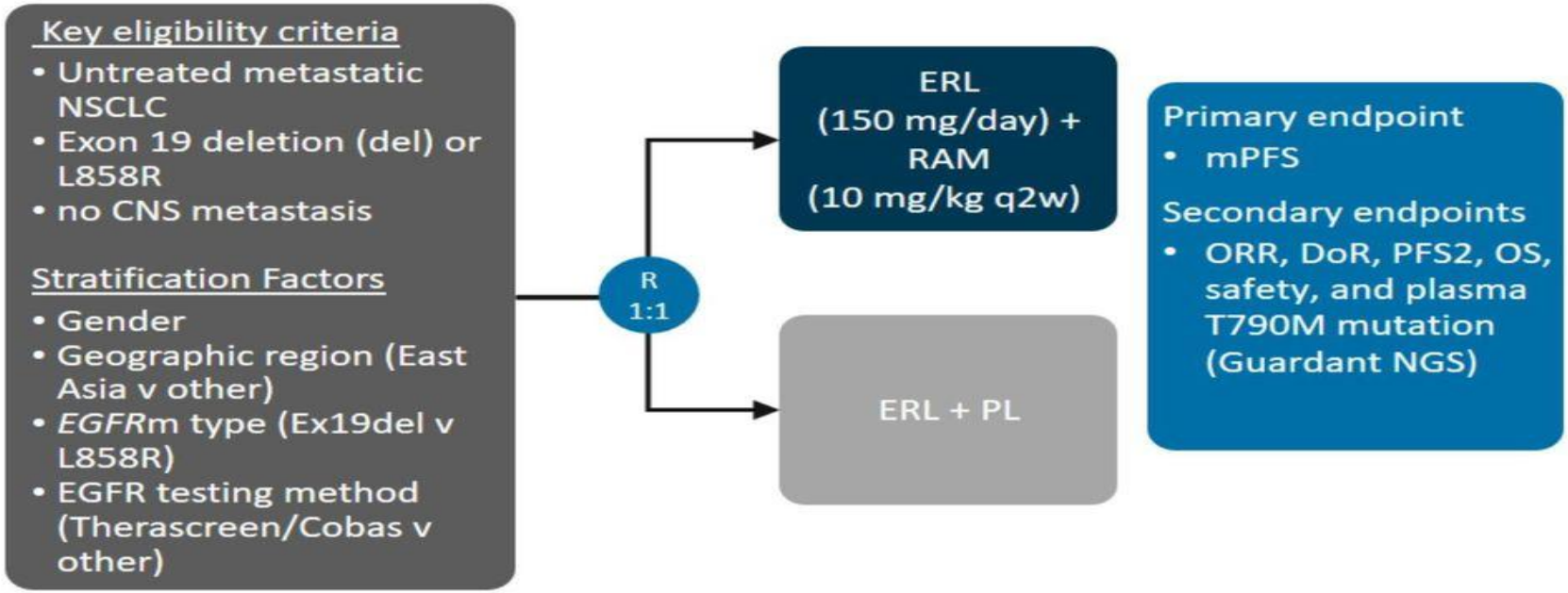
PFS benefit only

No OS benefit !


Progression–free survival
Overall survival
N
HR (95% CI)
Interaction p value
All patients
160
0.66 (0.47–0.92)
0.72 (0.47–1.10)
ECOG PS
0
99
0.69 (0.45–1.07)
0.0364
0.79 (0.43–1.42)
0.5650
1
55
0.51 (0.26–0.99)
0.49 (0.23–1.05)
Age
≤65
69
0.57 (0.32–1.01)
0.8850
0.66 (0.31–1.43)
0.9871
>65
91
0.68 (0.43–1.07)
0.67 (0.38–1.16)
Gender
Male
58
0.55 (0.30–1.02)
0.7200
0.80 (0.39–1.64)
0.5671
Female
102
0.69 (0.44–1.07)
0.64 (0.37–1.11)
Mutational status
Exon 19
88
0.65 (0.40–1.05)
0.3393
0.93 (0.50–1.72)
0.5142
Exon 21 L858R
66
0.75 (0.42–1.31)
0.59 (0.29–1.18)
Smoking status
Never
83
0.90 (0.52–1.57)
0.0323
1.36 (0.70–2.64)
0.0077
Former/Current
77
0.49 (0.28–0.82)
0.41 (0.21–0.80)
0,05 0,1 0,25 0,5 0,75 1 1,5 2
Favours Erlotinib + BEV
Favours Erlotinib

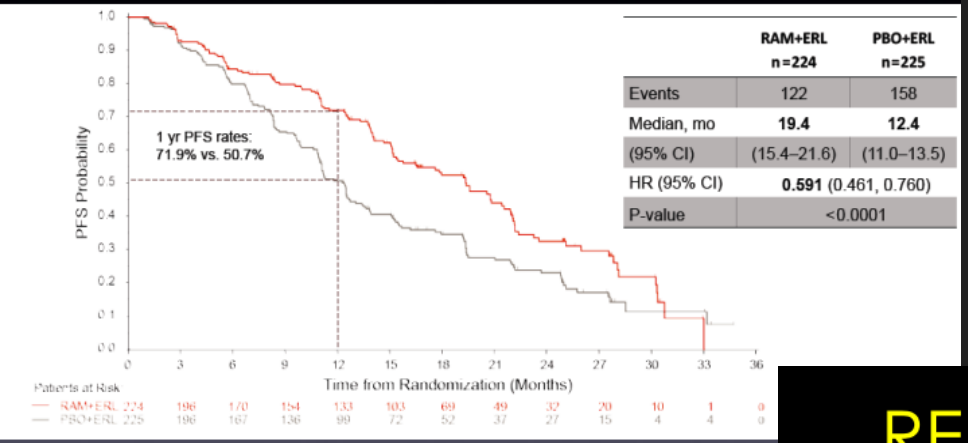
TKI + VEGF Inhibition
RELAY Trial: Erlotinib +/- Ramucirumab

(N = 449)



Nakagawa K, et al. *J Clin Oncol.* 2019;37(suppl; abstr 9000).

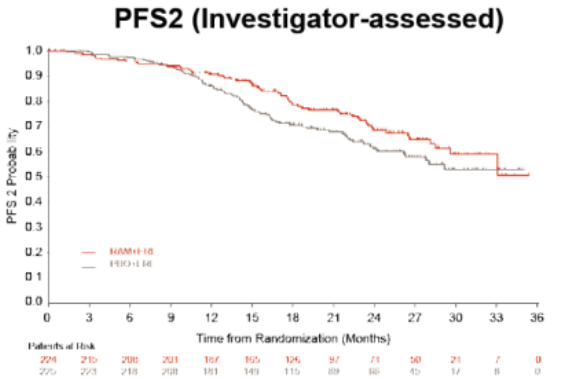
RELAY - PFS



	RAM+ERL n=224	PBO+ERL n=225
Events	122	158
Median, mo	**19.4**	**12.4**
(95% CI)	(15.4–21.6)	(11.0–13.5)
HR (95% CI)	**0.591** (0.461, 0.760)	
P-value	<0.0001	

RELAY– PFS2 and interim OS

		RAM+ERL N=224	PBO+ERL N=225
PFS2	Events,	61	79
	Censoring rate	73%	65%
	Median, mo	NR	NR
	HR (95% CI)	0.690 (0.490, 0.972)	
Interim OS	Events	37	42
	Censoring rate	83%	81%
	Median, mo	NR	NR
	HR (95% CI)	0.832 (0.532, 1.303)	



RELAY - AEs of special interest

	RAM+ERL N=221		PBO+ERL N=225	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Bleeding/Hemorrhage Events	121 (55)	4 (2)	59 (26)	4 (2)
Epistaxis	74 (34)	0	27 (12)	0
GI Hemorrhage Events[a]	23 (10)	3 (1)	6 (3)	1 (<1)
Pulmonary Hemorrhage Events	15 (7)	1 (<1)	4 (2)	1 (<1)
Hypertension	100 (45)	52 (24)*	27 (12)	12 (5)
Proteinuria[b]	76 (34)	6 (3)	19 (8)	0
Liver Failure/Liver Injury	140 (63)	31 (14)	120 (53)	28 (12)
Increased ALT	94 (43)	19 (9)	70 (31)	17 (8)
Increased blood bilirubin	68 (31)	3 (1)	70 (31)	2 (1)
Infusion-related reactions	6 (3)	0	4 (2)	0
Other TEAE of interest:				
ILD events[c]	4 (2)	1 (<1)	7 (3)	3 (1)

[a]The 2 most common GI hemorrhage events were anal hemorrhage (3% vs. <1%) and hemorrhoidal hemorrhage (2% vs. 2%)
[b]No events of nephrotic syndrome; [c]ILD events included pneumonitis

*Grade 3 only

ILD, Interstitial Lung Disease

Importance of RELAY

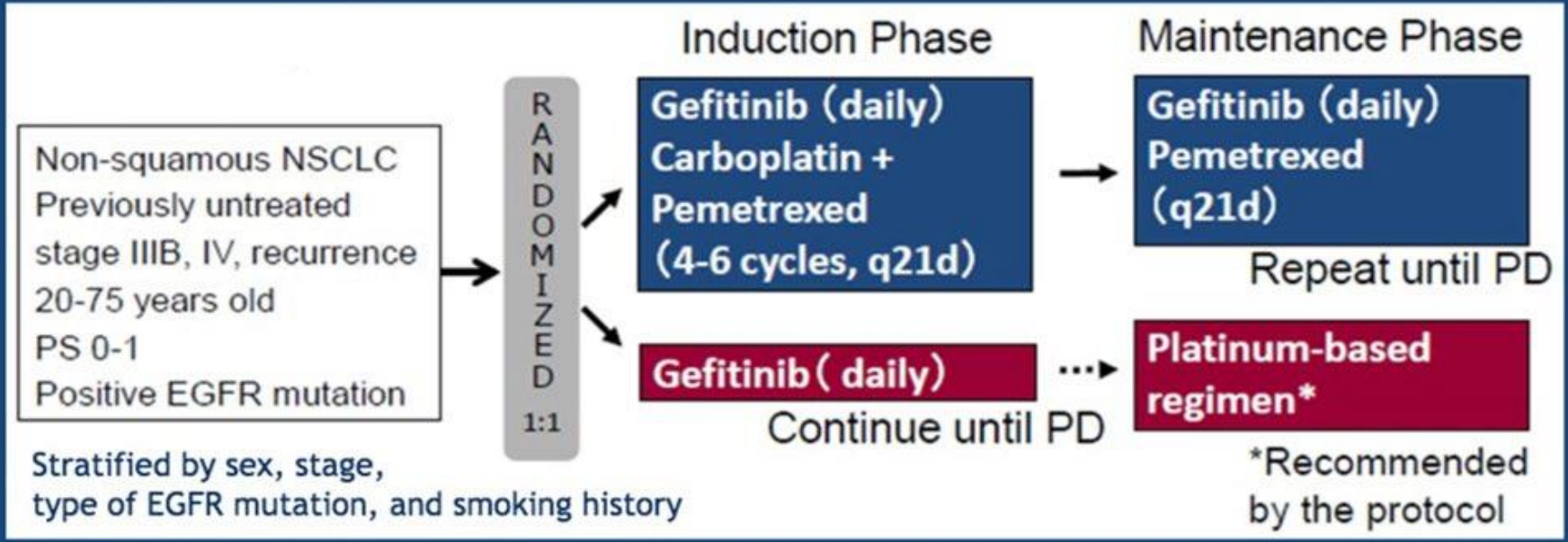
Broader spectrum of activity, higher response rates

Evidence to suggest a viable option

All subgroups benefited, no change in incidence of T790M

Await OS data !!

Study Design of NEJ009



- From Oct. 2011 to Sep. 2014, 345 patients were enrolled from 47 institutions across Japan. In Oct.2017, a number of pre-planned events for primary endpoint analysis were observed.

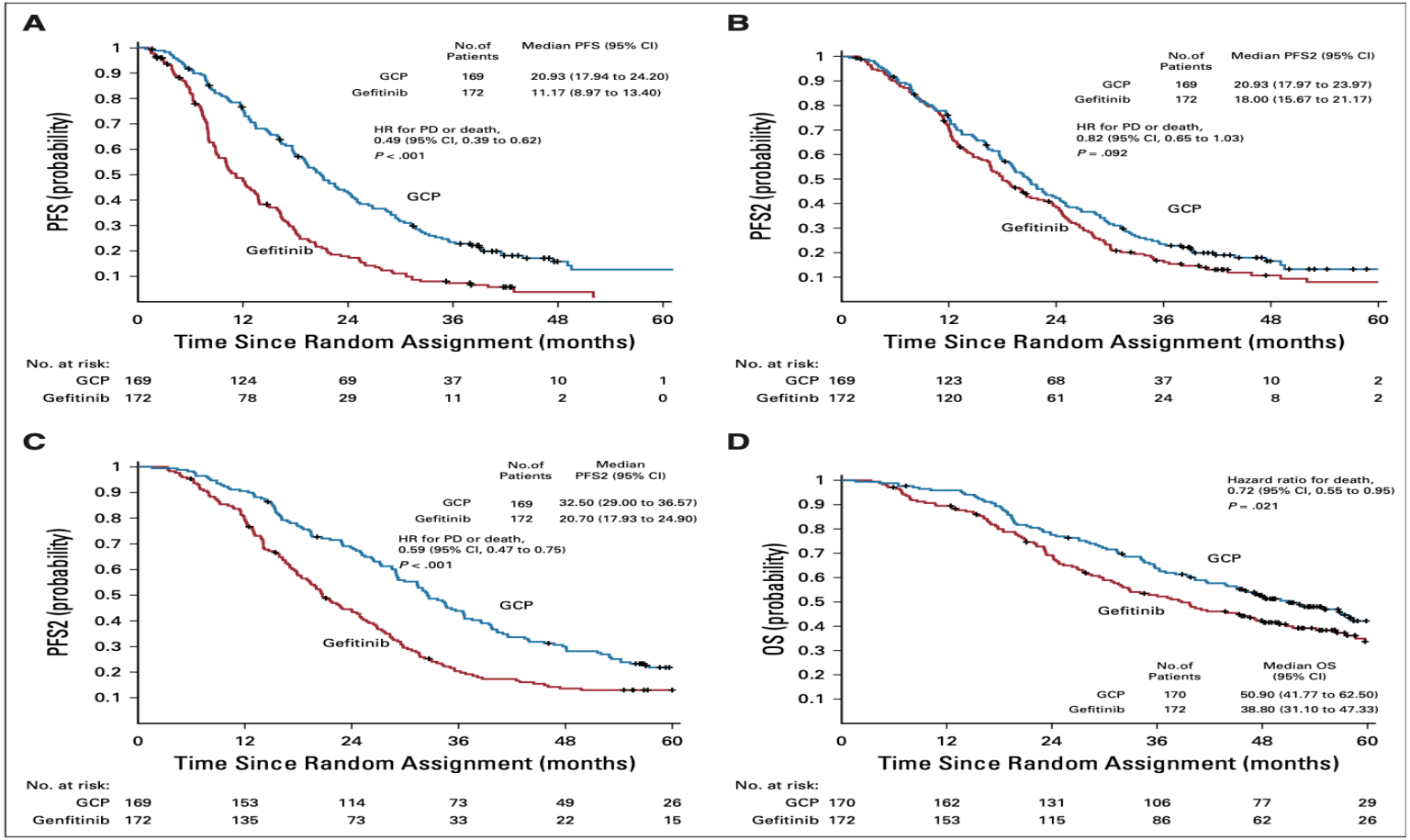


FIG 1. Progression-free survival (PFS) and overall survival (OS). Kaplan-Meier curves for (A) PFS, (B) PFS2, (C) PFS2 with a same definition, and (D) OS of patients treated with gefitinib and carboplatin plus pemetrexed (GCP) and those treated with gefitinib alone are shown. Bars indicate censored patients at the data cutoff point. HR, hazard ratio; PD, progressive disease.

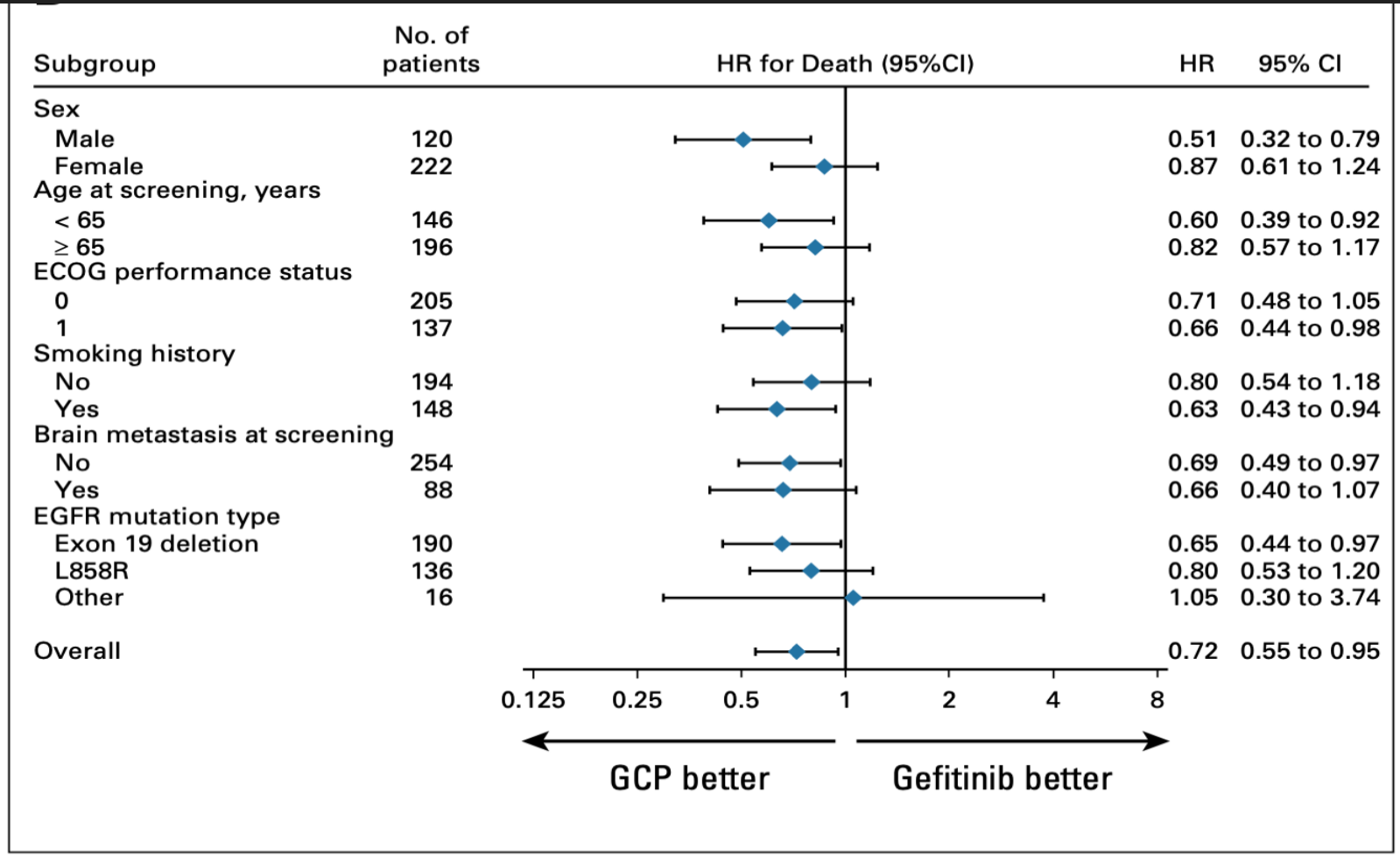

Subgroup
No. of patients
HR for Death (95%CI)
HR
95% CI
Sex
Male 120 0.51 0.32 to 0.79
Female 222 0.87 0.61 to 1.24
Age at screening, years
< 65 146 0.60 0.39 to 0.92
≥ 65 196 0.82 0.57 to 1.17
ECOG performance status
0 205 0.71 0.48 to 1.05
1 137 0.66 0.44 to 0.98
Smoking history
No 194 0.80 0.54 to 1.18
Yes 148 0.63 0.43 to 0.94
Brain metastasis at screening
No 254 0.69 0.49 to 0.97
Yes 88 0.66 0.40 to 1.07
EGFR mutation type
Exon 19 deletion 190 0.65 0.44 to 0.97
L858R 136 0.80 0.53 to 1.20
Other 16 1.05 0.30 to 3.74
Overall 0.72 0.55 to 0.95
0.125
0.25
0.5
1
2
4
8
GCP better
Gefitinib better

TABLE 2. Common Adverse Events

Adverse Event	Grade, No. (%)			
	Gefitinib (n = 171)		GCP (n = 170)	
	Any	≥ 3	Any	≥ 3
Treatment-related adverse events	168 (98.2)	53 (31.0)	163 (95.9)	111 (65.3)
Treatment-related adverse events with an incidence of > 10%				
Leukopenia	11 (6.4)	1 (0.6)	101 (59.4)	36 (21.2)
Neutropenia	7 (4.1)	1 (0.6)	101 (59.4)	53 (31.2)
Anemia	36 (21.2)	4 (2.3)	113 (65.5)	36 (21.2)
Thrombocytopenia	9 (5.3)	0 (0.0)	91 (53.5)	29 (17.1)
Liver dysfunction	102 (59.6)	38 (22.2)	103 (60.6)	21 (12.4)
Blood bilirubin increased	23 (13.5)	1 (0.6)	15 (8.8)	0 (0.0)
Creatinine elevation	11 (6.4)	0 (0.0)	43 (25.3)	0 (0.0)
Hyponatremia	6 (3.5)	1 (0.6)	34 (20.0)	5 (2.9)
Diarrhea	63 (36.8)	2 (1.2)	60 (35.3)	7 (4.1)
Vomiting	9 (5.3)	1 (0.6)	27 (15.9)	4 (2.4)
Stomatitis	29 (17)	0 (0.0)	52 (30.6)	1 (0.6)
Rash	138 (80.7)	5 (2.9)	110 (64.7)	7 (4.1)
Nail changes	57 (33.3)	2 (1.2)	44 (25.9)	5 (2.9)
Constipation	16 (9.4)	0 (0)	53 (31.2)	0 (0.0)
Anorexia	28 (16.4)	2 (1.2)	100 (58.8)	12 (7.1)
Edema limbs	7 (4.1)	0 (0.0)	29 (17.1)	3 (1.8)
Fatigue	20 (11.7)	0 (0.0)	67 (39.4)	7 (4.1)

Abbreviation: GCP, gefitinib and carboplatin plus pemetrexed.

Tata Memorial Centre study: Gefitinib vs gefitinib + chemotherapy

Key eligibility criteria
- Advanced chemotherapy-naïve NSCLC
- *EGFR* sensitising mutation (exon 19, 21 or 18)
- PS: 0 to 2
- Planned for palliative therapy

Stratification factors
- PS
- *EGFR* mutation

R 1:1

Gefitinib (550 mg/day) + **pemetrexed** (500 mg/m^2 IV) + **carboplatin AUC** 5 IV; 3 wks/4 cycles + **pemetrexed maintenance**

Geftinib 250 mg/day

- Primary endpoint: PFS
- Secondary endpoints: OS, safety, RR

TKI + chemotherapy

Results

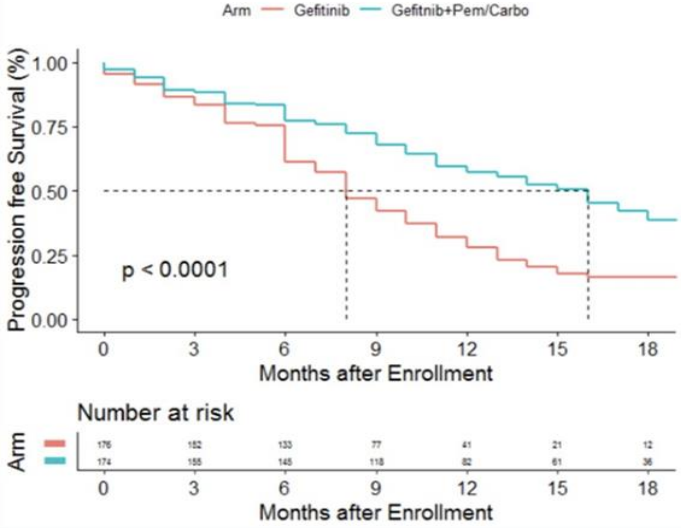
- Adding pemetrexed-carboplatin chemotherapy to gefitinib significantly prolonged PFS and OS
- Also increased toxicity

	Gefitinib + chemo (n=173)	Gefitinib (n=177)	HR	p value
mPFS, months	16	8	0.50	<0.001
mOS, months	NR	18	0.45	<0.001
Grade 3 + TRAEs, %	51	25	–	–

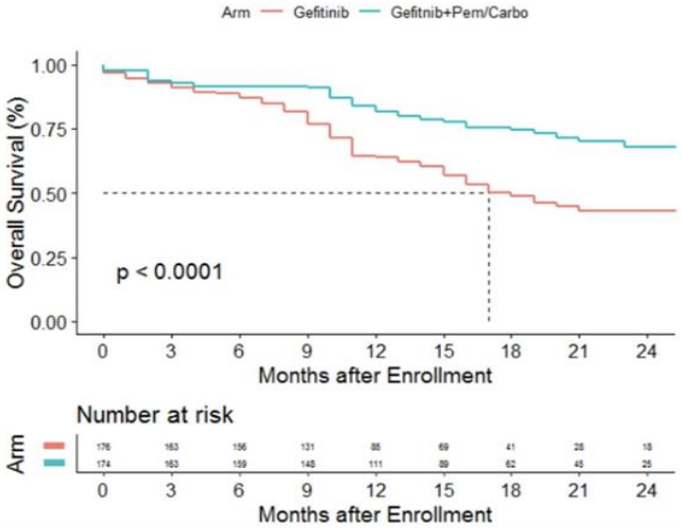
Pemetrexed-carboplatin+gefitinib may represent a new standard frontline therapy for *EGFR* mutant NSCLC; although treatment schedule is more rigorous for patient

Noronha V, et al. *J Clin Oncol* 2019;37(suppl). Abs 9001

Arm	Number of patients	Number of events	Median PFS (95%CI)
Gefitinib	176	138	8 months (7.0 to 9.0)
Gefitinib + pemetrexed/carboplatin	174	99	16 months (13.5 to 18.5)
Hazard ratio for disease progression or death, 0.51; 95% CI, 0.39 to 0.66			



Arm	Number of patients	Number of events	Median OS (95%CI)
Gefitinib	176	80	17 months (13.5 to 20.5)
Gefitinib + pemetrexed/carboplatin	174	42	NC (NC to NC)
Hazard ratio for death, 0.45; 95% CI, 0.31 to 0.65			



OVERALL TOXICITIES	Gef + C arm (n=164)	Gef arm (n=170)	P-value
All ≥ grade 3 toxicities	123 (75%, 95% CI, 67.8 to 81)	84 (49.4%, 95% CI, 42 to 56.9)	<0.001
Clinically relevant ≥ gr 3 toxicities (excluding asympt lab abnormalities)	83 (50.6%, 95% CI, 43 to 58.2)	43 (25.3%, 95% CI, 19.4 to 32.4)	<0.001
Fatal toxicities	1 (0.6%)-FN	1 (0.6%)-ILD	1.0
Discontinuation due to toxicities • Pemetrexed • Gefitinib	 30 (16.7%) 0	 N/A 2 (1.1%)	

Combinations With the Third-Generation EGFR TKI

NCT03122717

Osimertinib is active against the acquired gefitinib-resistant mutation *EGFR* T790M, and gefitinib is active against the osimertinib-resistant mutation *EGFR* C797S

Combination of osimertinib plus gefitinib is being investigated in phase 1/2 trial (NCT03122717)

Findings from this single-arm trial showed that patients treated with the combination (n = 27) had an overall response rate (ORR) of 88.9% (95% CI, 71.9%-96.1%) with a disease-control rate of 100%

Other Combination Strategies

- MARIPOSA Trial

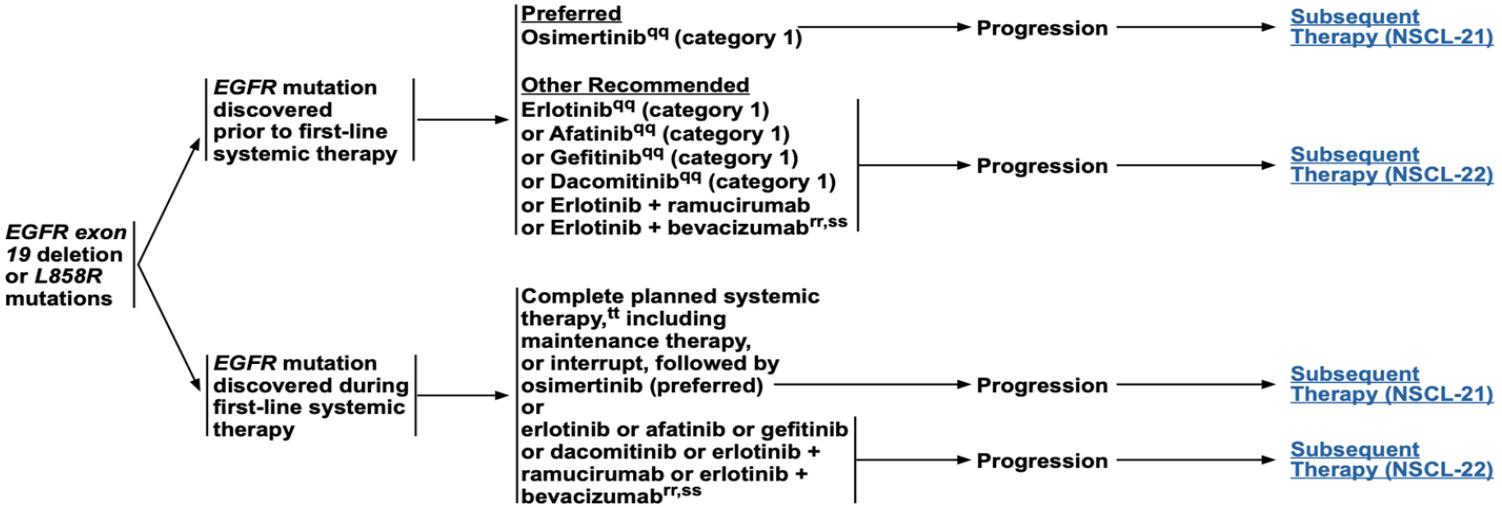
After the response in CHRYSALIS-2 trial (Amivantamab with Lazertinib), the combination is tested against Osimertinib in First line mNSCLC with EGFR mutation

- FLAURA 2 Trial

Osimertinib with chemotherapy

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

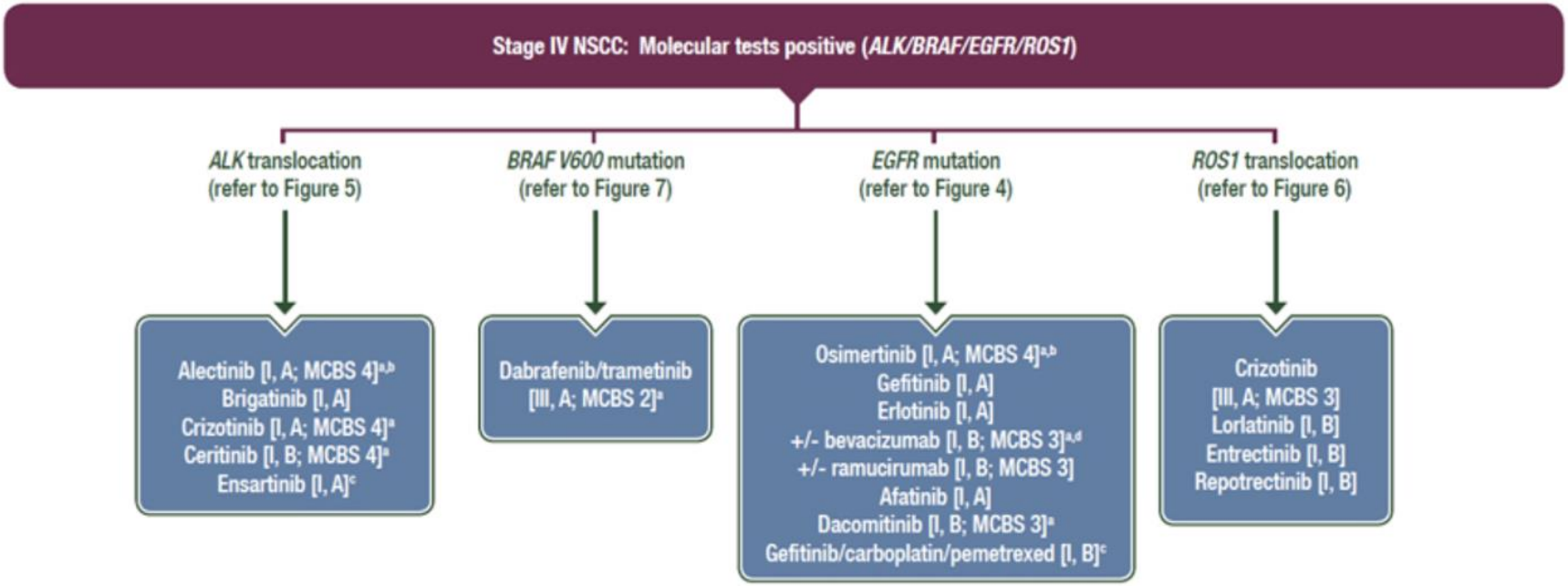
FIRST-LINE THERAPY[pp]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[rr] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis.
[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[tt] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ESMO guidelines



updated: 15 September 2020

My take

Brain metastasis : Osimertinib (RELAY did not include patients with brain mets)

Good PS or Low affordability: Gef with chemotherapy

Affordable and Good PS : Combination with Erlotinib and Ramucirumab

Food for thought

Gefitinib different from Erlotinib : Erlotinib inhibits absorption of cisplatin

Ramucirumab different from Bevacizumab:

Identification of sub groups more likely to benefit - smokers

THANKYOU :)