Oncology Latin American Association

OLA

NEW ORLEANS SUMMER CANCER MEETING

EGFR: Common and Uncommon Mutations & What Is Next For This Patient Population?

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July 21, 2018

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EGFR: Common and Uncommon Mutations & What Is Next For This Patient Population?

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The Medical Educator Consortium

13th Annual NEW ORLEANS SUMMER CANCER MEETING

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

How did we get here?

Since 2015,
there have been ~13 studies that have transformed the management of NSCLC
with targeted therapies or immunotherapies

Osimertinib in previously treated EGFRm

Dabrafenib/trametinib for BRAF

FDA approves broad genomic testing in solid tumors

Alectinib in ROS1 positive NSCLC

First anti-PD-1/PD-L1 in previously treated advanced NSCLC
CheckMate 017
CheckMate 057

Pembrolizumab monotherapy in 1L PD-L1 high NSCLC
KEYNOTE-024

Pembrolizumab + platinum doublet chemotherapy in 1L NSCLC
KEYNOTE-021G

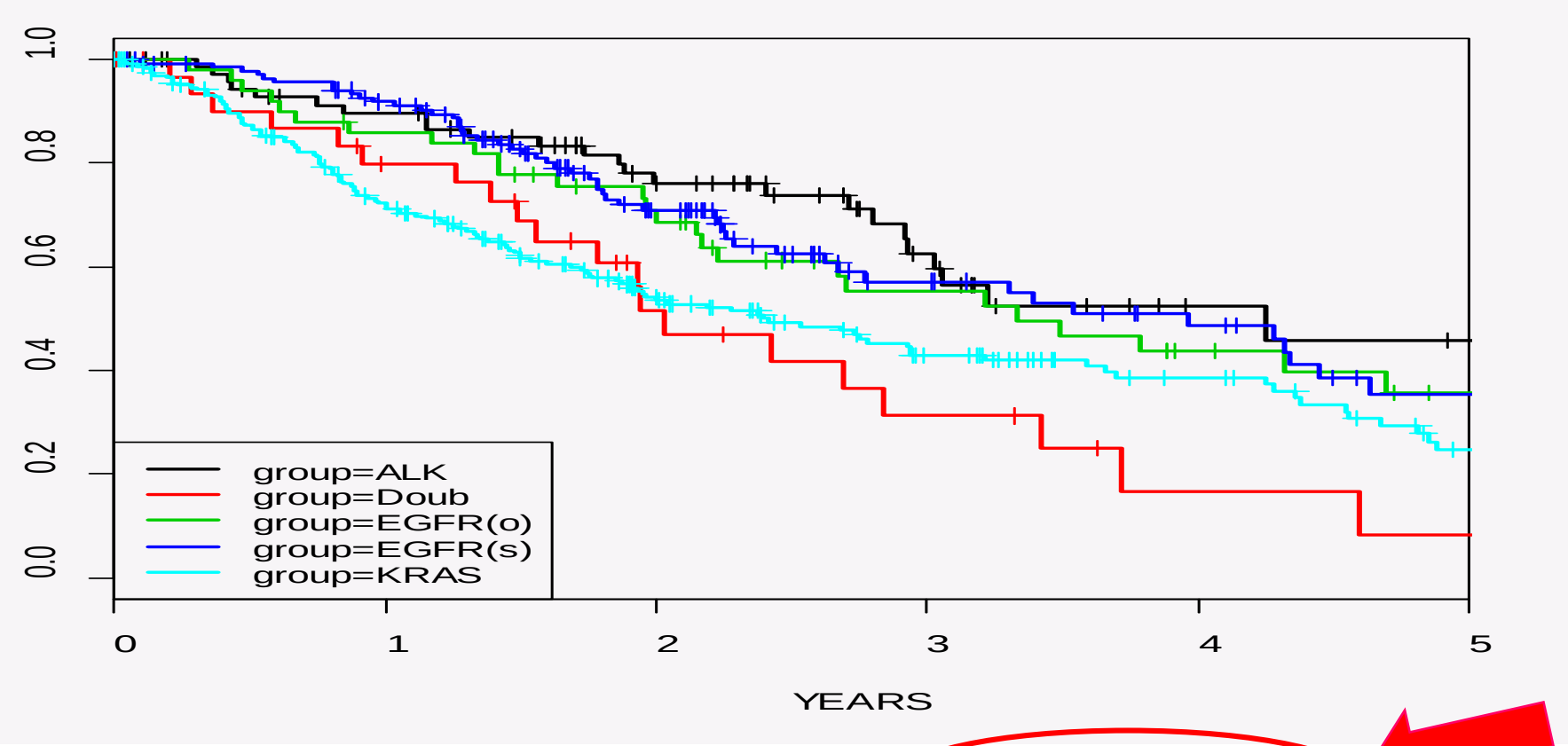
2018

KEYNOTE-189: Carbo/Pem/Pem For NSq-NSCLC

KEYNOTE-407: Carbo/Paclit or nab-Paclit/Pem For Sq-NSCLC

IMPOWER 150: Carbo/Paclit/Bev/Atezo For NSq-NSCLC (EGFR+/ALK+)

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)

It is key

LUNG CANCER MUTATION CONSORTIUM
Matching Patients with the Best Possible Therapies

Kris and Johnson; JAMA 2014

IASLC 2017

EGFR MUTANT TUMORS

EGFR Sequencing vs Non-Sequencing

WHERE ARE WE RIGHT NOW? For sure… more tx options for patients

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

2) Afatinib vs Osimertinib? (no data)

3) Dacomitinib vs Osimertinib (no data)

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

5) Dacomitinib > Gefitinib (ARCHER 1050; phase III trial)

6) Gefitinib/Carbo/Pem > Gefitinib (NEJ 009; phase III trial)

THIS IS NOW!!! JULY 21, 2018

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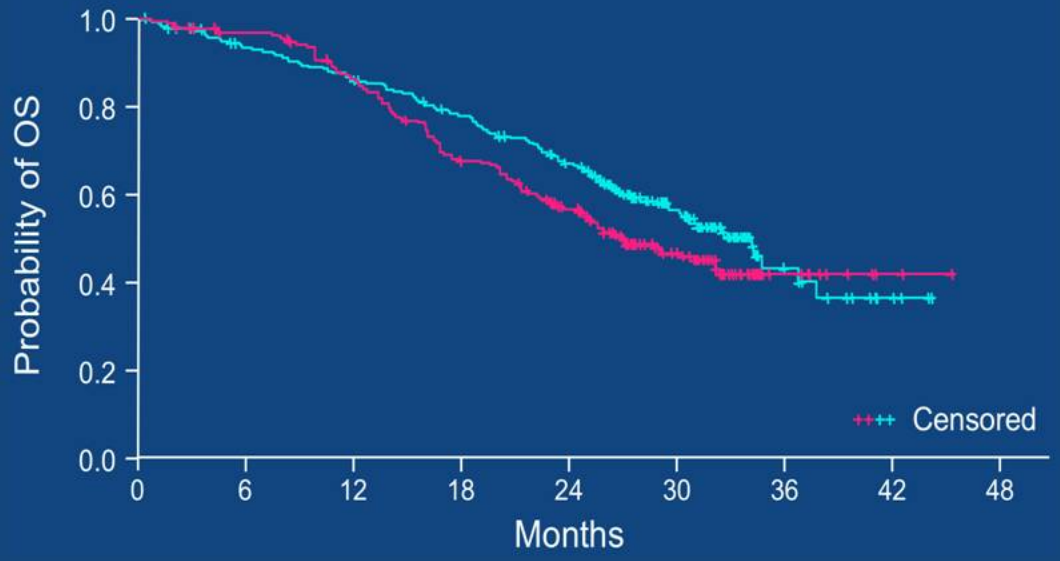
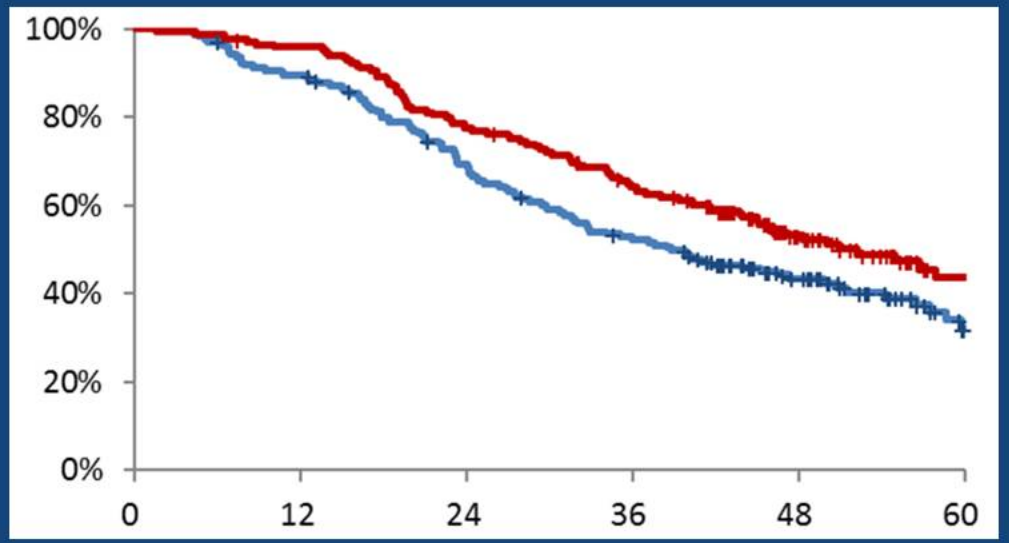
First phase III trials demonstrating OS benefit in EGFR M+ NSCLC
with an EGFR TKI control

ARCHER 1050 (n=452)
Median f/u 31.3 m



	Median OS	95% CI
Gefitinib	26.8 m	23.7 - 32.1
Dacomitinib	34.1 m	29.5 - 37.7
	HR 0.76 (95%CI 0.582 - 0.993) p=0.0219	

NEJ009 (n=345)
Median f/u minimum 42 m



	Median OS	95% CI
Gefitinib	38.8 m	31.1 - 50.8
Gefitinib + PemCb	52.2 m	44.0 - NR
	HR 0.695 (95%CI 0.520 - 0.927) p=0.013	

Is overall survival benefit still a relevant endpoint?

- Has traditionally been the gold standard endpoint... together with quality of life

- Some commonly cited limitations:
  - Crossover effect
    - Chemotherapy → TKI
  - Long duration of follow up required

- RR & PFS have been an acceptable surrogate endpoint in targeted therapies in NSCLC
  - Threshold of surrogacy is highly context dependent e.g. type of intervention

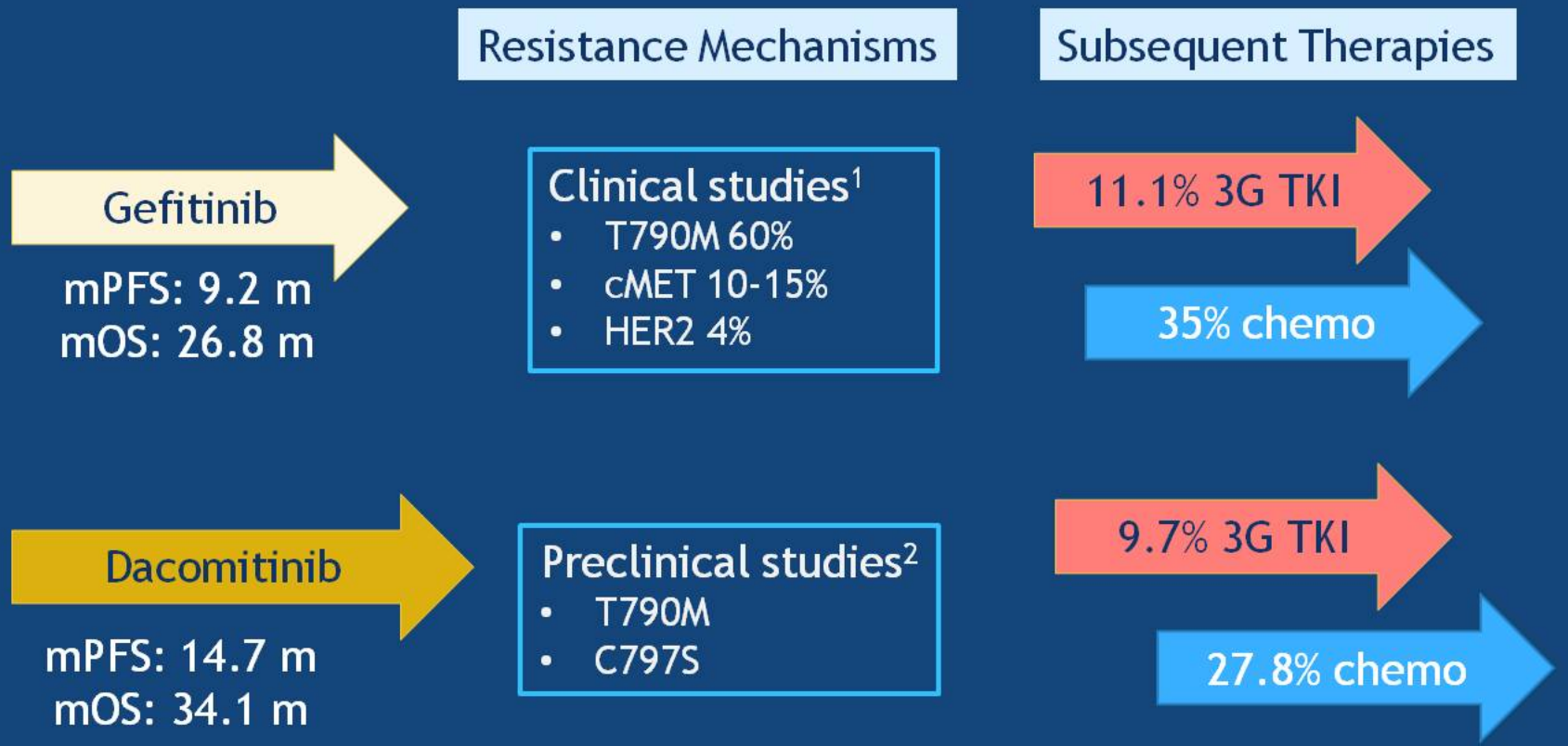
How does ARCHER 1050 compare with other 1L trials of 2nd & 3rd Gen EGFR TKI

	LUX-Lung 7[1]	ARCHER 1050[2]	FLAURA[3]
Median OS	27.9 m v 24.5 m	34.1 m v 26.8 m	Immature
Phase	IIb (n=319)	III (n=452)	III (n=556)
Arms	Afatinib vs gefitinib	Dacomitinib vs gefitinib	Osimertinib vs gefitinib/erlotinib
RR	70% v 56%	75% v 71.2%	80% v 76%
PFS (all comers)	11 m v 10.9 m (BIRC) HR 0.73 (0.57 - 0.95) p=0.017	14.7 m v 9.2 m (BIRC) [No BM] HR 0.59 (0.47-0.74) p<0.0001	17.7 m v 9.7 m (BIRC) HR 0.45 (0.36 - 0.57) p<0.001
PFS (no brain mets)		16.6 m v 11.0 (INV) HR 0.62 (0.50-0.78) p<0.0001	19.1 m v 10.9 m (INV) HR 0.46 (0.36-0.59) p<0.001

Will sequencing a 3G TKI after failure of dacomitinib > upfront 3G TKI?

Park TLO 2016; Mok ASCO 2018; Soria NEJM 2018

Resistance mechanisms to dacomitinib and subsequent therapy on ARCHER 1050



KEY TAKEAWAY

- T790M can emerge as a resistance mechanism to dacomitinib
- Subsequent therapies were balanced and not likely to drive OS

Are there potential specific patient subsets that might benefit most from a 2nd Gen TKI?

Yu et al. CCR 2013; Kobayashi JTO 2018

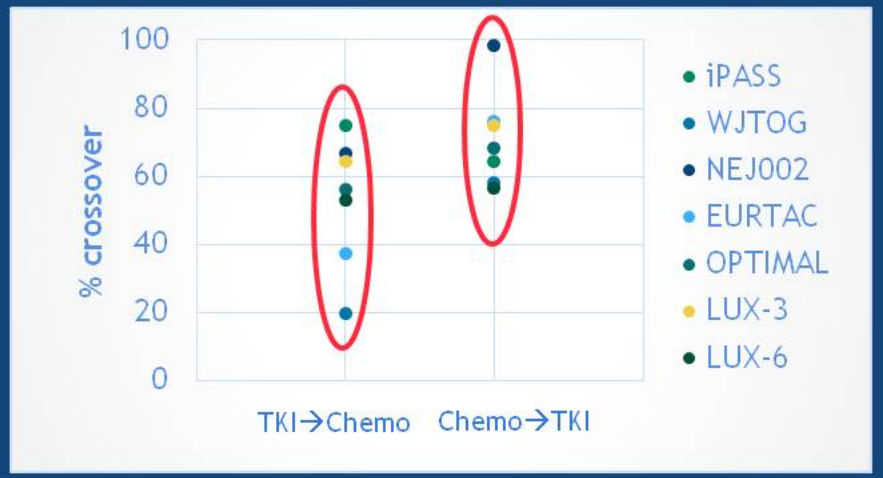
The case for chemotherapy in EGFR M+ NSCLC

1. Variable proportion of patients crossover from TKI → chemotherapy
   - 28% on TKI arm did not receive subsequent therapy (NEJ002)[1]

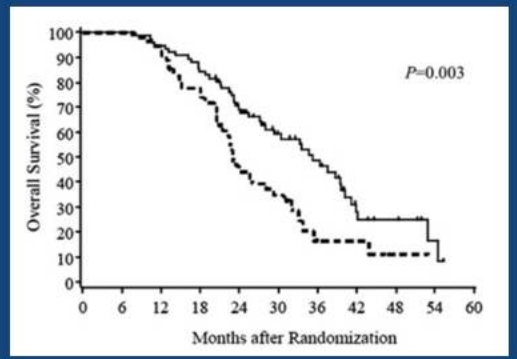
2. EGFR TKI have comparable efficacy regardless in 1st or 2nd line

3. Impact of chemotherapy on survival?

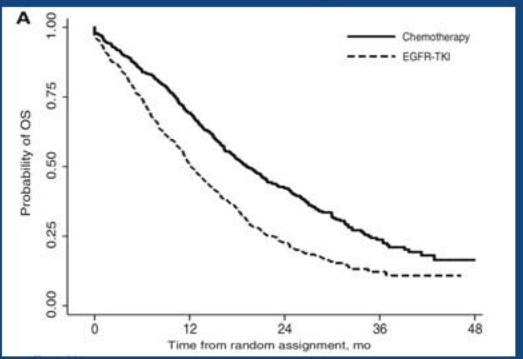
Crossover in EGFR M+ phase III trials



As subsequent lines[1]



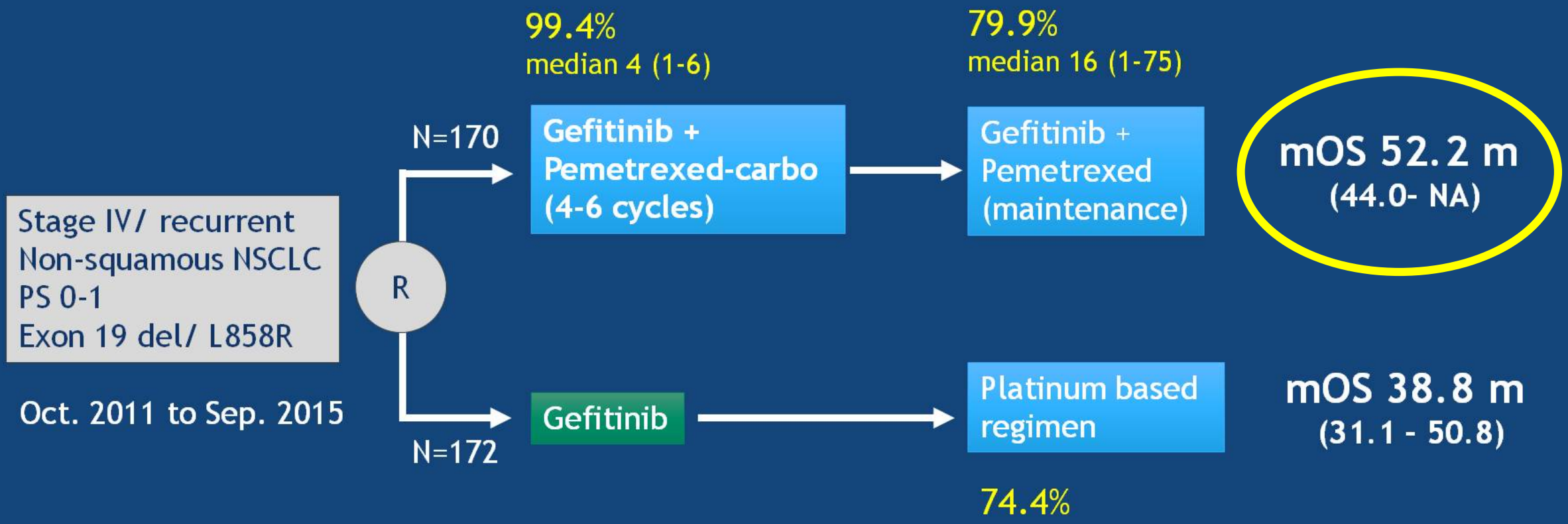
Randomized upfront[2]



[1]Inoue et al. Ann Onc 2012; [2]Lee CK JNCI 2017

Would upfront chemotherapy be a solution?

NEJ009



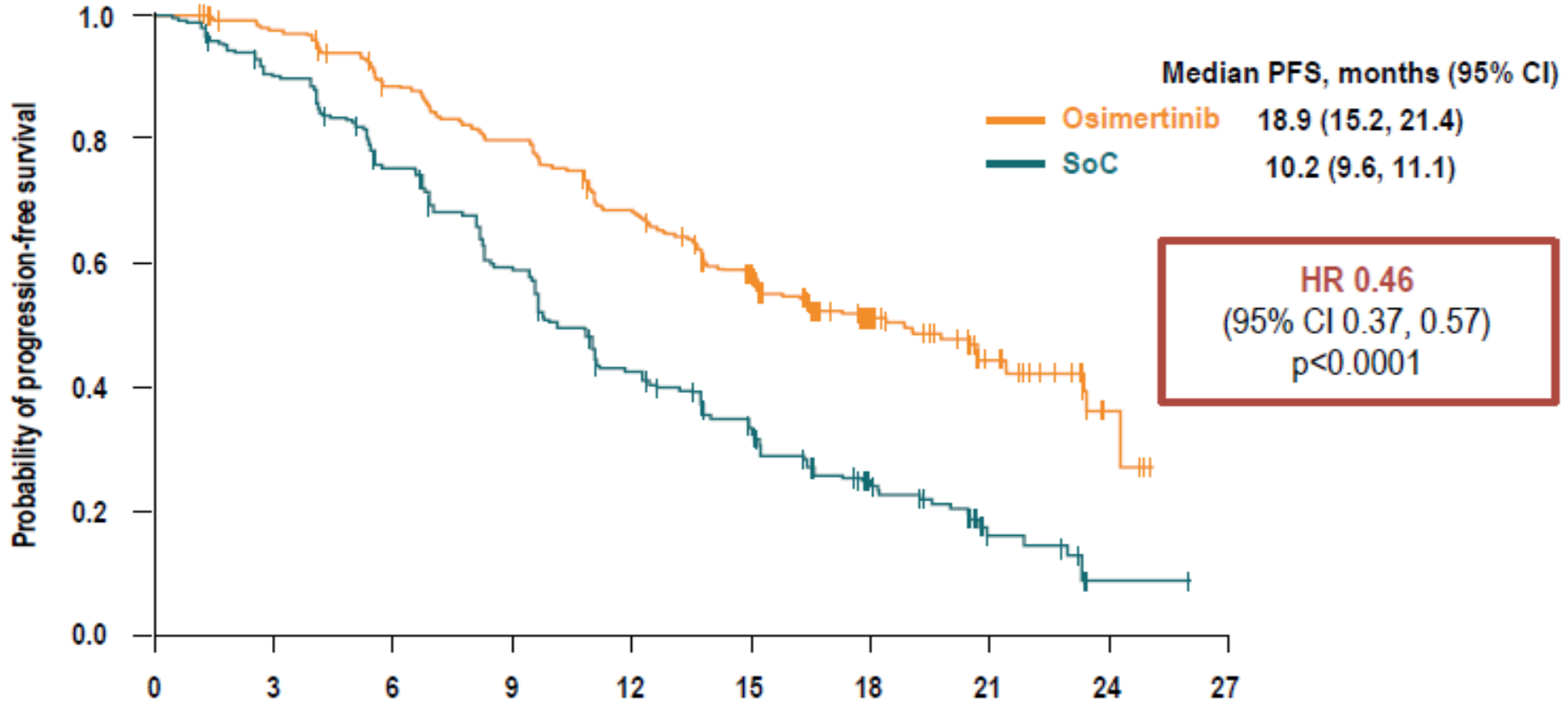
80% power to show OS in HR=0.70 at two-sided α=0.05
Hierarchical sequential testing PFS → PFS2 → OS

So, based on the FLAURA study…..

Should the winner take it all?

PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT

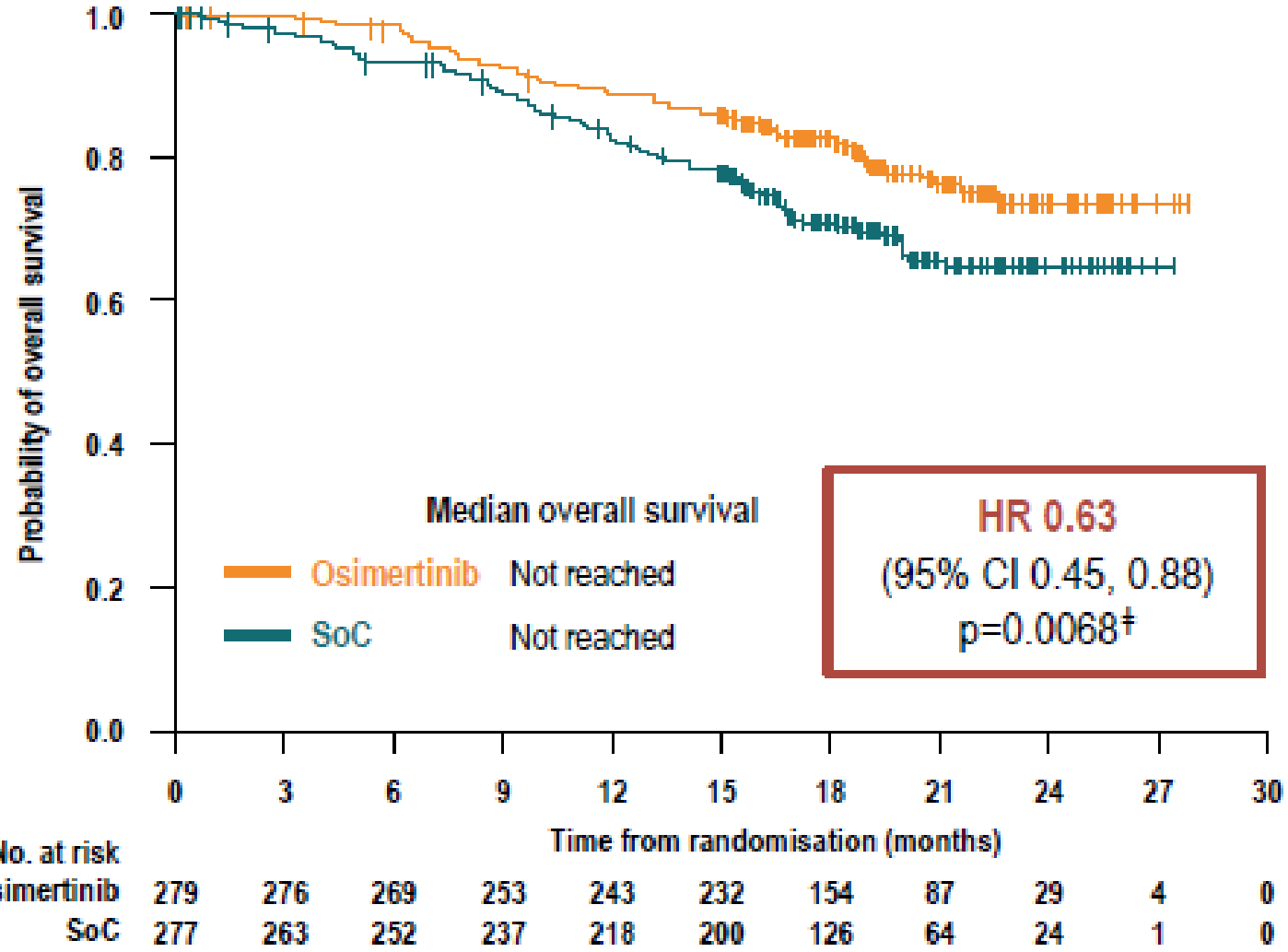
342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)



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

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

Osimertinib is best first line treatment

NO 2nd line treatment (35%)

* Symptomatic CNS progression (3x higher, 15% vs 6%)

Erlotinib/Afatinib/Gefitinib mPFS 11 mo → Osimertinib mPFS 9 mo

NO EGFR T790M (40%)

Diagnosis

Osimertinib mPFS 19 mo

Progression → Chemo +/- IO Clinical Trial

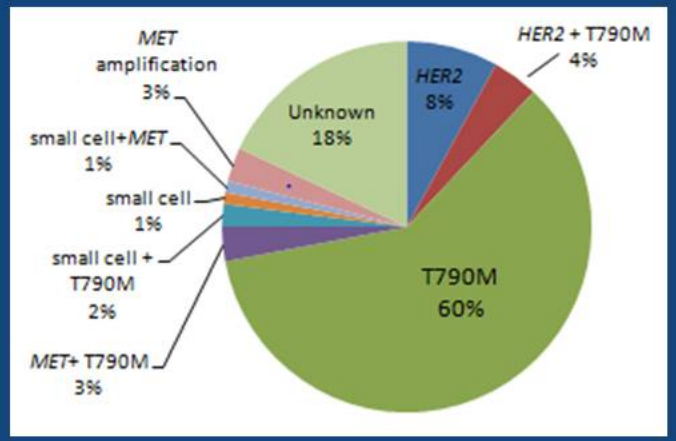
Always give your best treatments first. Not everyone gets second line treatment

Acquired Resistance to Osimertinib

EGFR TKI
Erlotinib
Afatinib
Gefitinib

→ **Acquired Resistance** →

EGFR TKI
Osimertinib



↓

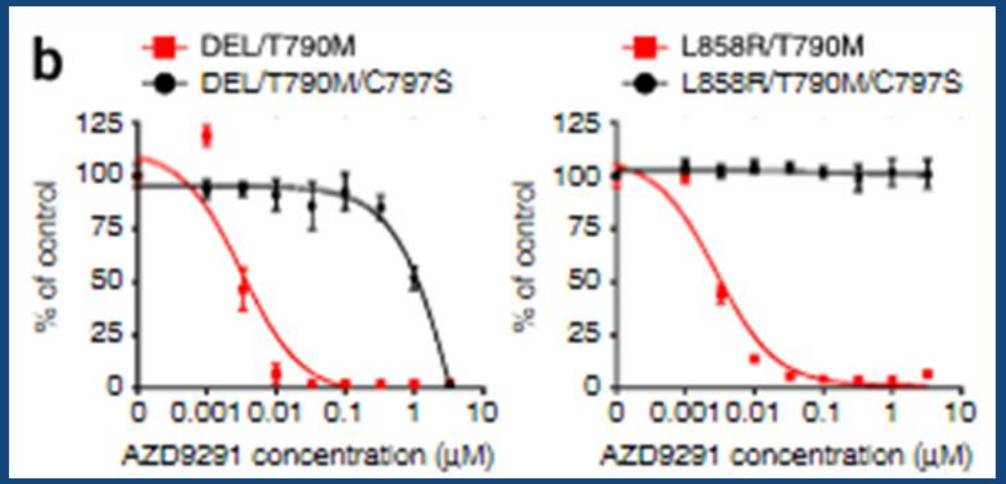
Acquired Resistance #2

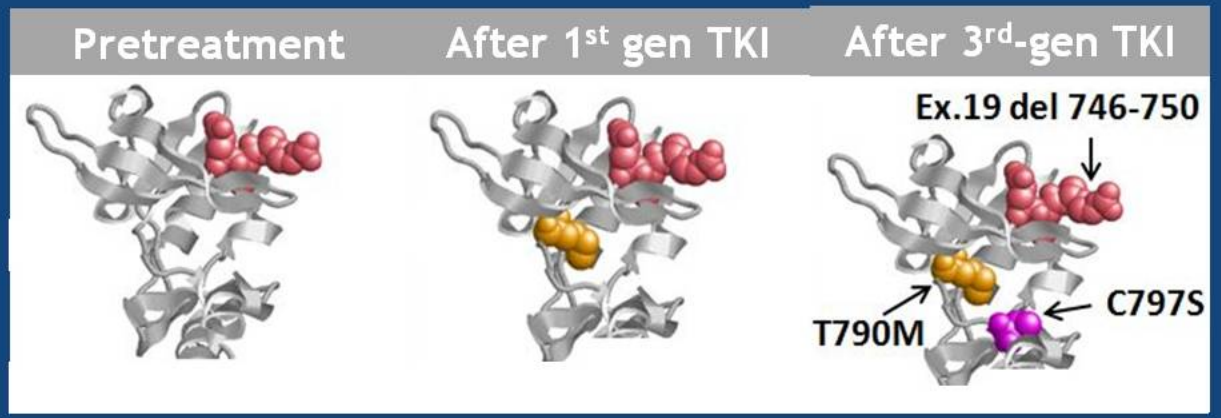
EGFR TKI
Osimertinib

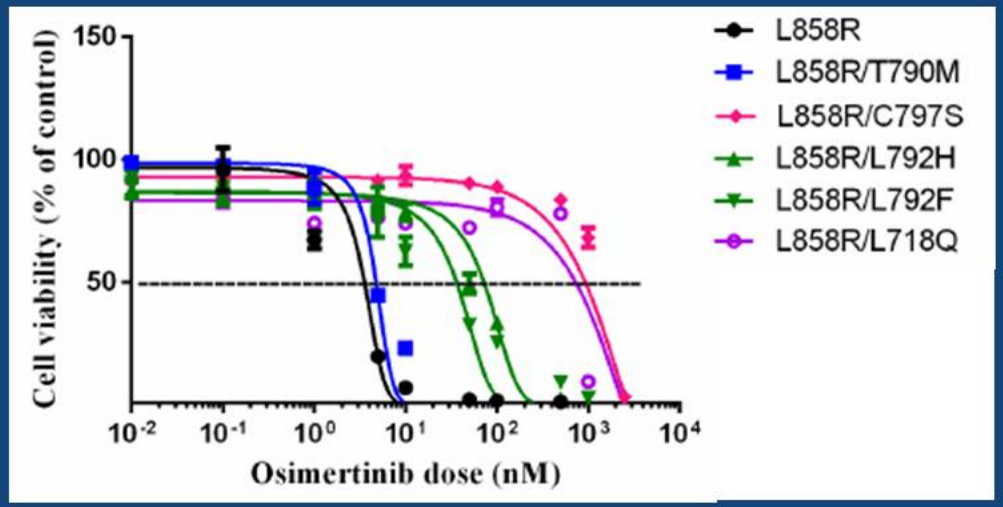
→ **??**

Acquired *EGFR* mutations
Acquired alterations
Tumor heterogeneity
Histologic transformation

EGFR C797S and other acquired EGFR mutations



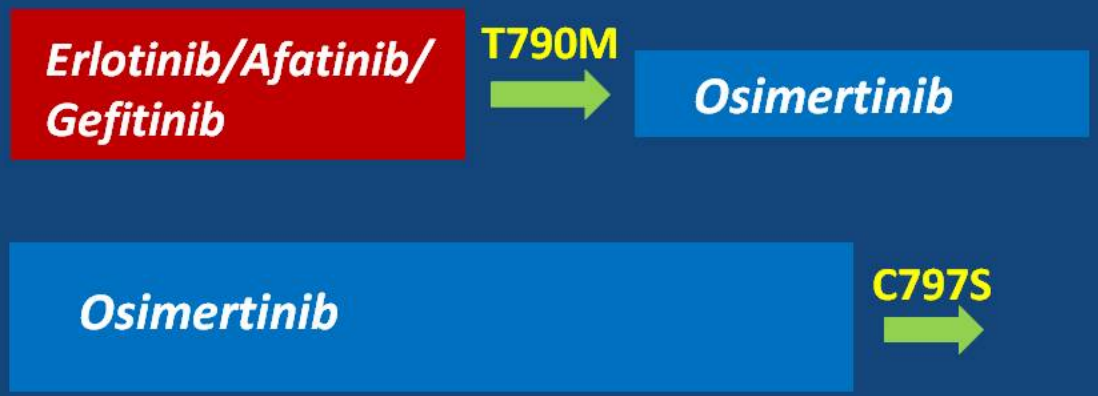




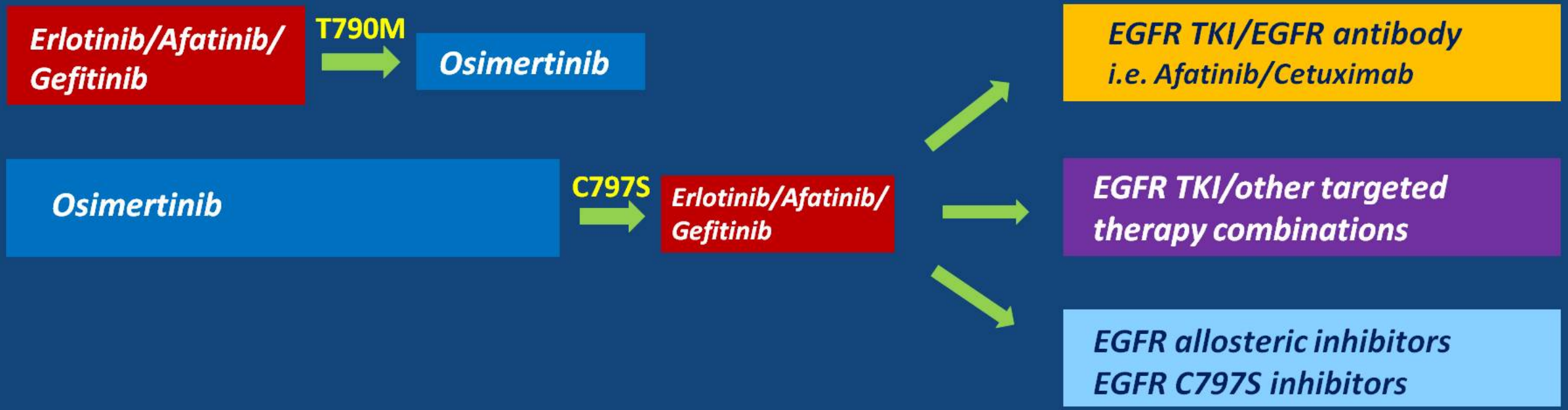
- 3rd-generation EGFR TKIs bind at *EGFR* C797. Acquired EGFR C797S induces resistance to osimertinib.
- Small series report prevalence of C797S to be 10-40%
- Other acquired EGFR mutations: G796, L792 (12%, 11/93) , L718 (8%, 9/93) seen with osimertinib resistance.

Thress Nat Med 2015, Yu JAMA Onc 2015, Ercan CCR 2015, Bersanelli JTO 2016, Yang CCR 2018, Ou Lung Cancer 2017

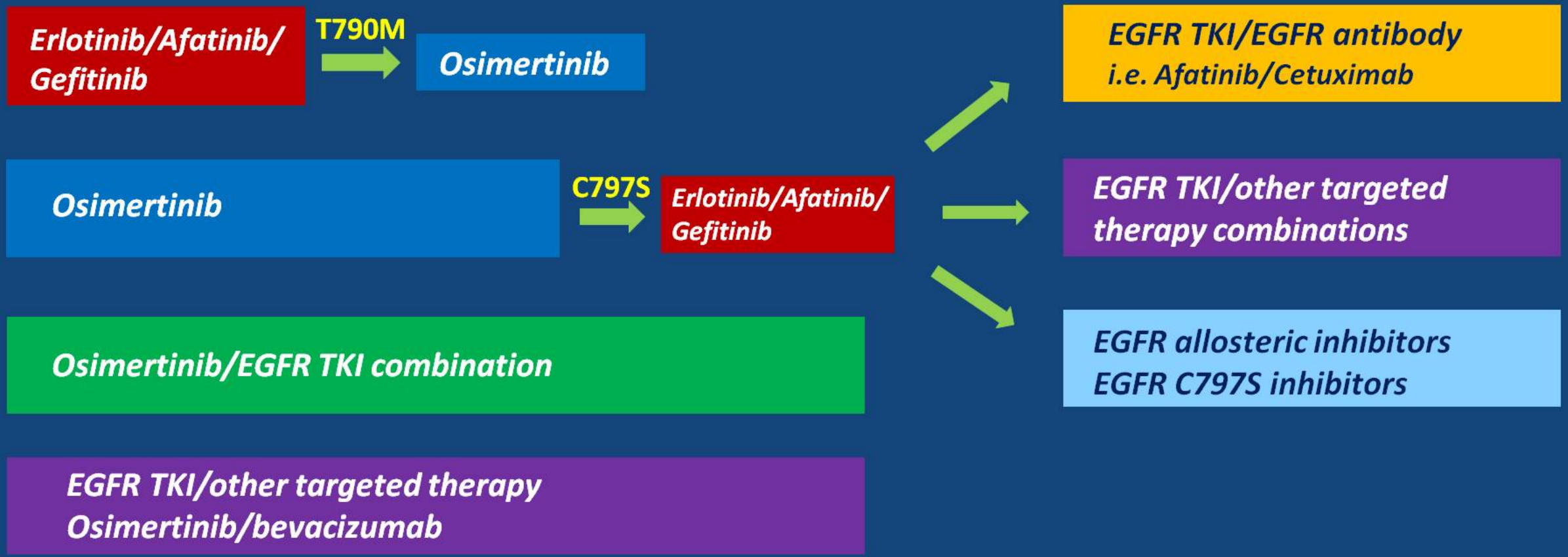
Sequencing of EGFR TKIs



Sequencing of EGFR TKIs

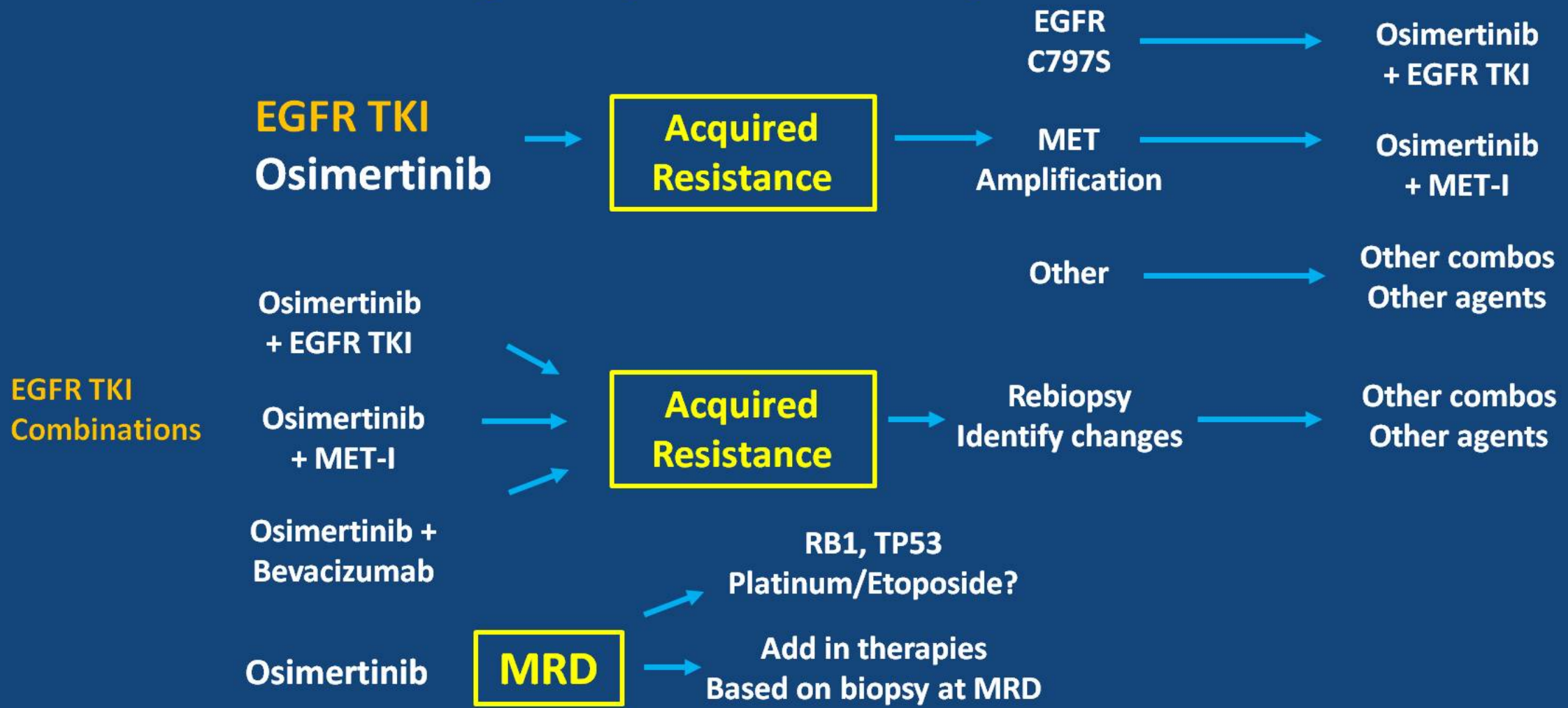


Sequencing of EGFR TKIs



Combination treatment – which combos and when?

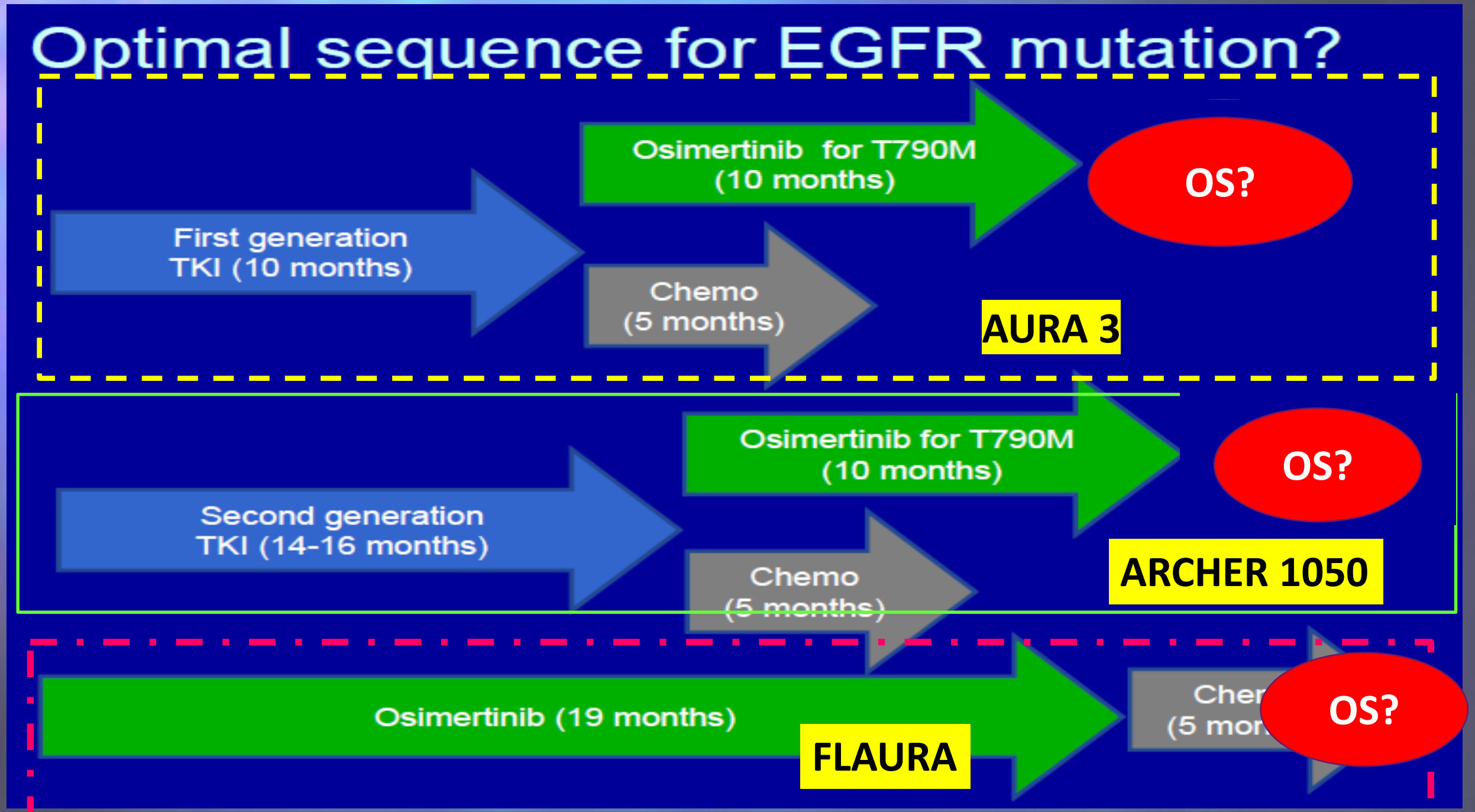
Osimertinib +/- other drugs is the first-line treatment of choice



At the European Lung Cancer Congress ELCC 2018

May 2018

Optimal sequence for EGFR mutation?



Parenthesis……. FINAL RESULTS OF ARCHER 1050 Clinical Trial

ASCO Meeting

June 1-5, 2018

Improvement in Overall Survival in a Randomized Study Comparing Dacomitinib With Gefitinib in Patients With Advanced Non-Small Cell Lung Cancer Harboring *EGFR*-Activating Mutations

Tony S. Mok,[1] Ying Cheng,[2] Xiandong Zhou,[3] Ki Hyeong Lee,[4] Kazuhiko Nakagawa,[5] Seiji Niho,[6] Min Young Lee,[7] Rolf Linke,[8] Rafael Rosell,[9] Jesus Corral,[10] Maria Rita Migliorino,[11] Adam Pluzanski,[12] Eric I. Sbar,[13] Tao Wang,[14] Jane Liang White,[14] Yi-Long Wu[15]

[1]State Key Laboratory of South China, Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong, China; [2]Jilin Provincial Cancer Hospital, Changchun, China; [3]First Affiliated Hospital of Third Military Medical University, Chongqing, China; [4]Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea; [5]Kindai University Hospital, Osaka, Japan; [6]National Cancer Center Hospital East, Kashiwa, Japan; [7]SFJ Asia Pacific, Singapore; [8]SFJ Pharmaceuticals Group, Pleasanton, CA, USA; [9]Catalan Institute of Oncology, Barcelona, Spain; [10]Hospital Universitario Virgen del Rocio, Seville, Spain; [11]Pulmonary Oncology Unit, San Camillo-Forlanini Hospital, Rome, Italy; [12]The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; [13]Pfizer Inc., Collegeville, PA, USA; [14]Pfizer Inc., Groton, CT, USA; [15]Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Tony S. Mok, MD

ARCHER 1050: Study Design

- Phase 3 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 metastases
- No prior EGFR TKI or other TKI
- ECOG PS of 0 or 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)

- Target HR ≤0.667 (50%↑)
- 90% power
- 1-sided α = 0.025
- Assumed median PFS: 14.3 vs 9.5 months

Stratification factors

Race (including Asian vs non-Asian)

EGFR mutation type (exon 19 vs 21)

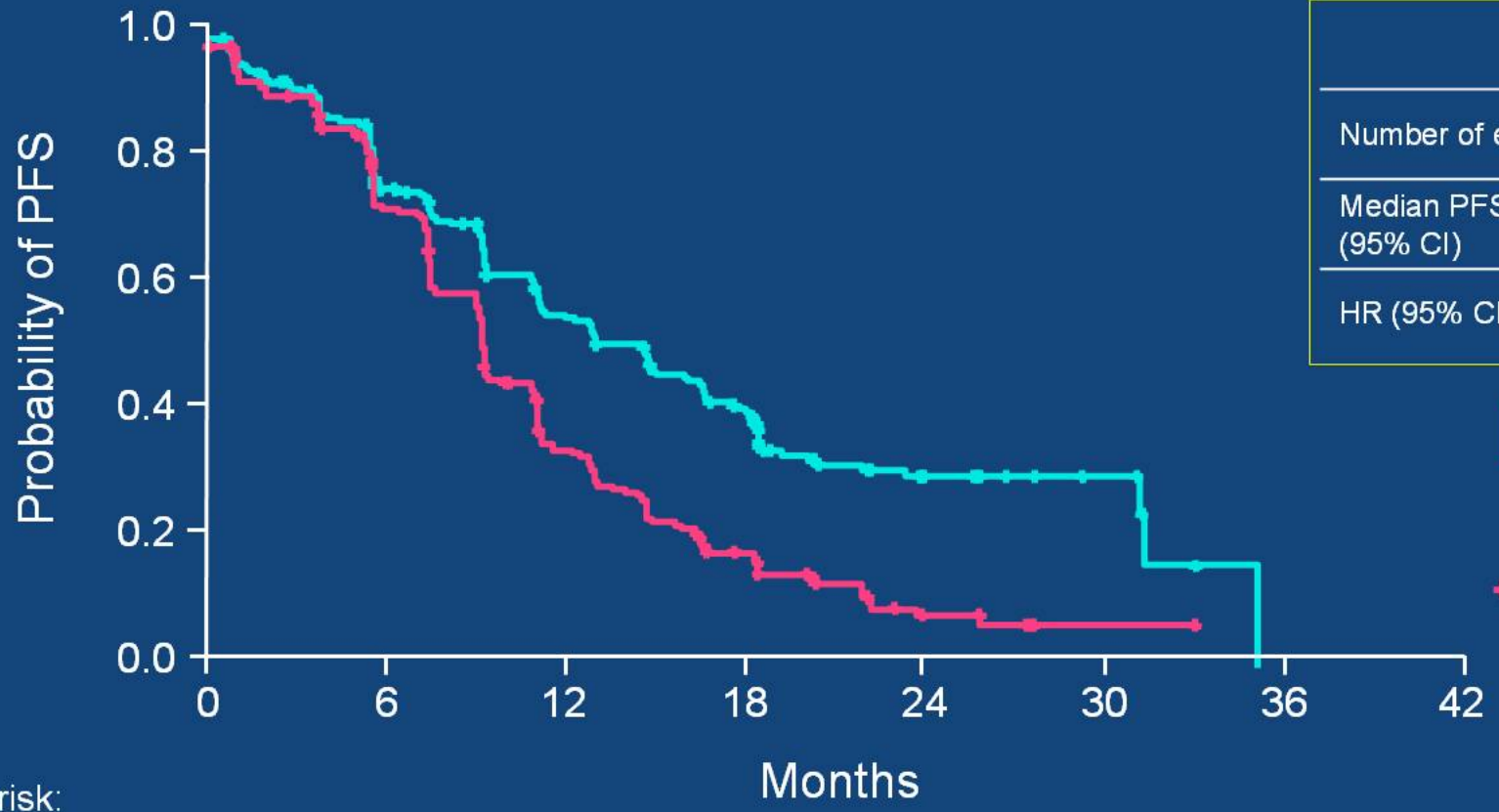
Secondary endpoints

OS

PFS (investigator assessed), ORR, DOR, TTF, Safety, PROs

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01774721.
CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PO, orally; PROs, patient-reported outcomes; PS, performance status; QD, once daily; R, randomized; TTF, time to treatment failure.

PFS: Blinded Independent Review
(Intention-to-Treat Population)



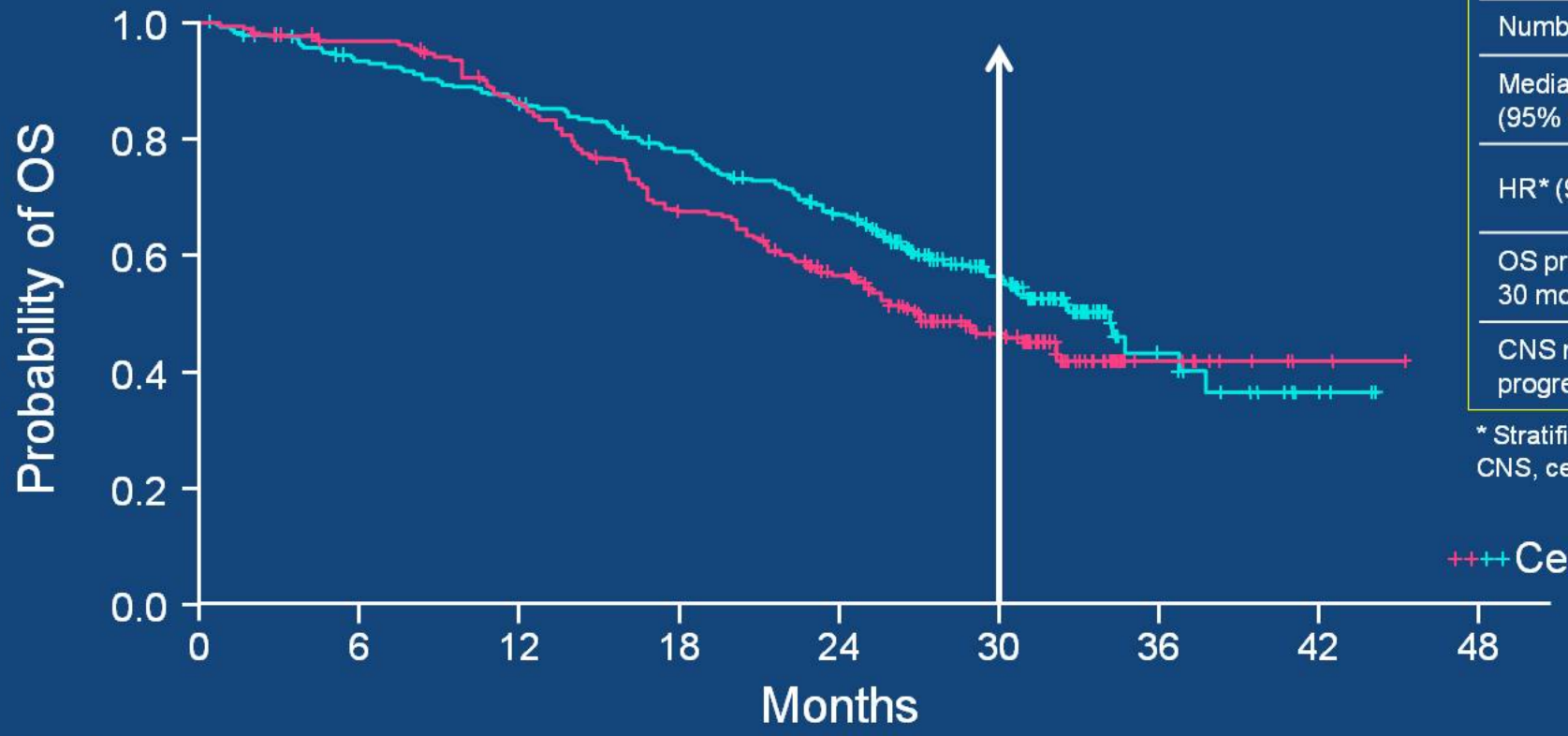
	Dacomitinib (n = 227)	Gefitinib (n = 225)
Number of events, n (%)	136 (59.9)	179 (79.6)
Median PFS, months (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI)	0.59 (0.47, 0.74) *P* < 0.0001	

Data cutoff date: July 29, 2016

No. at risk:								
Dacomitinib	227	154	106	73	20	6	0	0
Gefitinib	225	155	69	34	7	1	0	0

Wu YL, et al. *Lancet Oncol* 2017;18(11):1454–1466

Final OS (Primary Analysis)



	Dacomitinib (n = 227)	Gefitinib (n = 225)
Number of deaths, n (%)	103 (45.4)	117 (52.0)
Median OS, months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR* (95% CI)	0.760 (0.582, 0.993) 2-sided *P** = 0.0438	
OS probability at 30 months, %	56.2	46.3
CNS metastases at progression, n	1	11

* Stratified analysis.
CNS, central nervous system.

No. at risk:

Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Impact of Subsequent Treatment Analysis[a]

Subsequent Treatment[b]	Dacomitinib (n = 227)	Gefitinib (n = 225)
Chemotherapy[c]		
Patients, n (%)	63 (27.8)	80 (35.6)
Deaths, n (%)	35/63 (55.6)	47/80 (58.8)
Median OS, months (95% CI)	29.5 (25.1, 37.7)	24.6 (21.3, 29.1)
Third-generation EGFR TKI[d]		
Patients, n (%)	22 (9.7)	25 (11.1)
Deaths, n (%)	8/22 (36.4)	)
Median OS, months (95% CI)	36.7 (30.1, NR)	R)
Other EGFR TKI[e]		
Patients, n (%)	20 (8.8)	19 (8.4)
Deaths, n (%)	10/20 (50.0)	10/19 (52.6)
Median OS, months (95% CI)	34.7 (15.6, NR)	32.1 (20.5, NR)

[a] These are not predefined and randomized subgroups.
[b] Patients were censored at first subsequent therapy.
[c] Includes pemetrexed, cisplatin, carboplatin, paclitaxel, bevacizumab (given with chemotherapy), nedaplatin, tegafur/gimeracil/oteracil, vinorelbine, bleomycin, carboplatin/pemetrexed, carboplatin/gemcitabine, capecitabine, cisplatin/paclitaxel, cisplatin/pemetrexed, cis-DDP, custirsen (antisense molecule given with chemotherapy), etoposide, lobaplatin, paclitaxel/carboplatin, temozolomide, thalidomide, methotrexate, "chemotherapeutics," cisplatin/gemcitabine, docetaxel, gemcitabine, TAS-102 (oral thymidine-based nucleic acid analog and a thymidine phosphorylase inhibitor) and irinotecan hydrochloride hydrate.
[d] Includes osimertinib (AZD9291), olmutinib (HM61713), rociletinib (CO-1686), avitinib (AC0010), TAS-121 and unspecified "EGFR TKI inhibitor.
[e] Includes gefitinib, erlotinib, icotinib, afatinib and unspecified "EGFR TKI."
NR, not reported.

Conclusions

- ARCHER 1050 is the first randomized phase 3 study comparing two EGFR TKIs as first-line therapy for *EGFR* mutation-positive NSCLC that has demonstrated improvement in OS
- Dacomitinib was superior to gefitinib in both PFS and OS
  - PFS: 41% lower risk of progressive disease or death (HR, 0.59; $P < 0.0001$), with an improvement of 5.5 months in median PFS (14.7 vs 9.2 months, respectively)
  - OS: 24% lower risk of death (HR, 0.76; $P = 0.0438$), with an improvement of 7.3 months in median OS (34.1 vs 26.8 months, respectively)
- Evidence of improvement in all prespecified subgroups
- Median OS of patients with dacomitinib followed by a third-generation EGFR TKI was 36.7 months !!!!
- **Dacomitinib should be considered as a new treatment option for first-line management of patients with *EGFR* mutation-positive advanced NSCLC**

To Make Things More Complex in the EGFR arena

at ASCO…. the resurrection of anti-angiogenesis

ASCO Meeting
June 1-5, 2018

North East Japan Study Group

Phase III study comparing bevacizumab plus erlotinib to erlotinib in patients with untreated NSCLC harboring activating *EGFR*-mutations: NEJ 026

Naoki Furuya[1], Tatsuro Fukuhara[2], Haruhiro Saito[3], Kana Watanabe[2], Shunichi Sugawara[4], Shunichiro Iwasawa[5], Yoshio Tsunezuka[6], Ou Yamaguchi[7], Morihito Okada[8], Kouzou Yoshimori[9], Ichiro Nakachi[10], Akihiko Gemma[11], Koichi Azuma[12], Koichi Hagiwara[13], Toshihiro Nukiwa[14], Satoshi Morita[15], Kunihiko Kobayashi[7], and Makoto Maemondo[16],

North East Japan Study Group

[1]St. Marianna University School of Medicine, [2]Miyagi Cancer Center, [3]Kanagawa Cancer Center, [4]Sendai Kousei Hospital, [5]Chiba University Hospital, [6]Ishikawa Prefectural Central Hospital, [7]Saitama Medical University International Medical Center, [8]Hiroshima University, [9]Fukujuji Hospital, JATA, [10]Saiseikai Utsunomiya Hospital, [11]Nippon Medical School, [12]Kurume University School of Medicine, [13]Jichi Medical University, [14]Tohoku University, [15]Kyoto University Graduate School of Medicine, [16]Iwate Medical University.

Bevacizumab plus Erlotinib combination (2nd line)

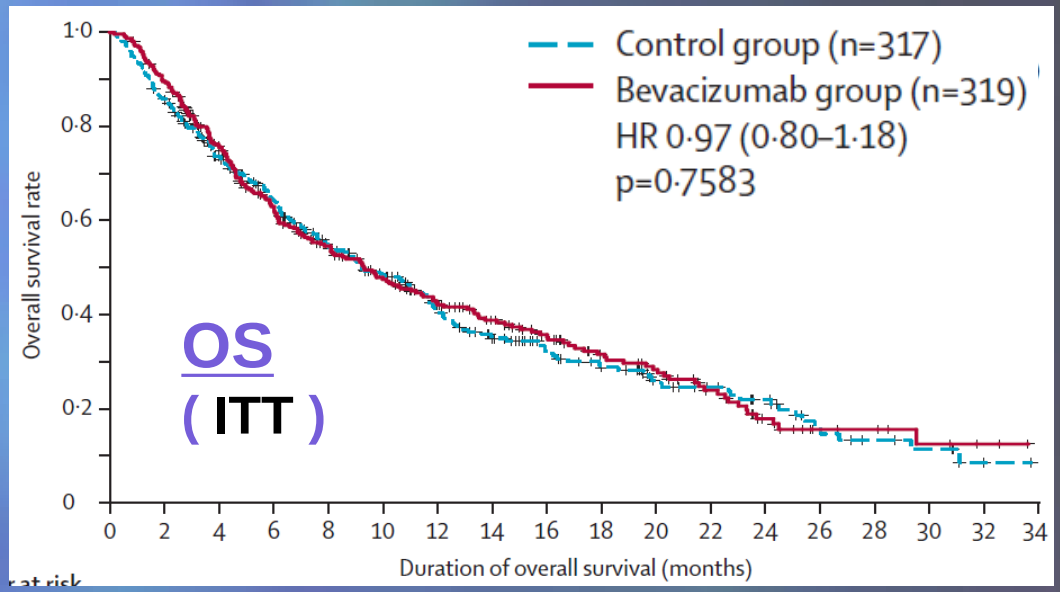
BeTa Lung（Phase III study）

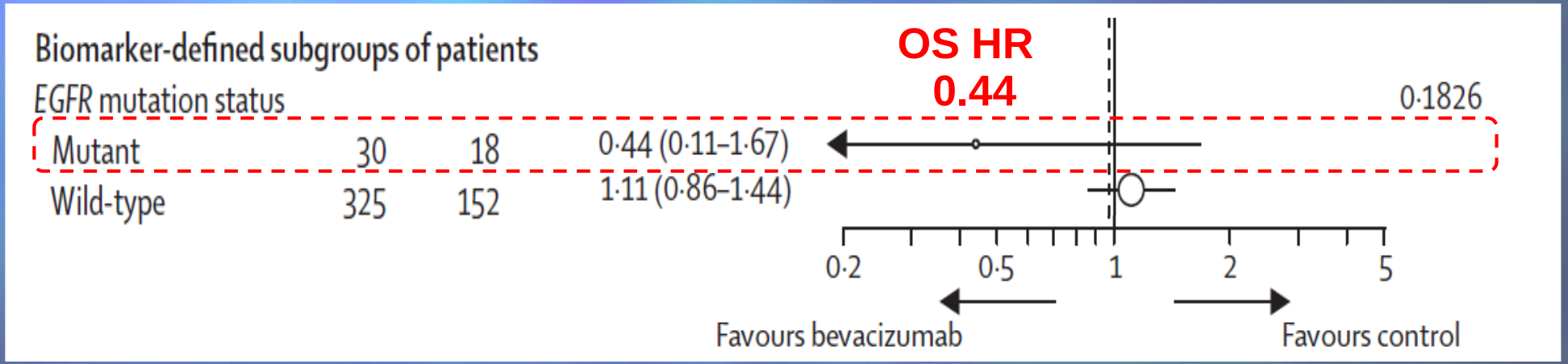
2nd line setting
Advanced stage
NSCLC
All-comers
Age ≥18 years
PS 0–2

R
1:1

Bevacizumab group
Erlotinib 150mg qd
+
Bevacizumab 15mg/kg q3w
(*n* = 319)

Control group
Erlotinib 150mg qd
+
Placebo q3w
(*n* = 317)





Herbst RS, et al. Lancet 2011; 377(9780): 1846-1854.

Bevacizumab plus Erlotinib combination (1st line)

JO25567（Randomized phase II study）

Chemotherapy-naïve

PS 0–1

Non-squamous

Stage IIIB/IV or

postoperative recurrence

Activating *EGFR* mutations*

Exon 19 deletion

Exon 21 L858R

No brain metastasis

***T790M excluded**

R

1:1

BE combination

Bevacizumab 15mg/kg q3w

+

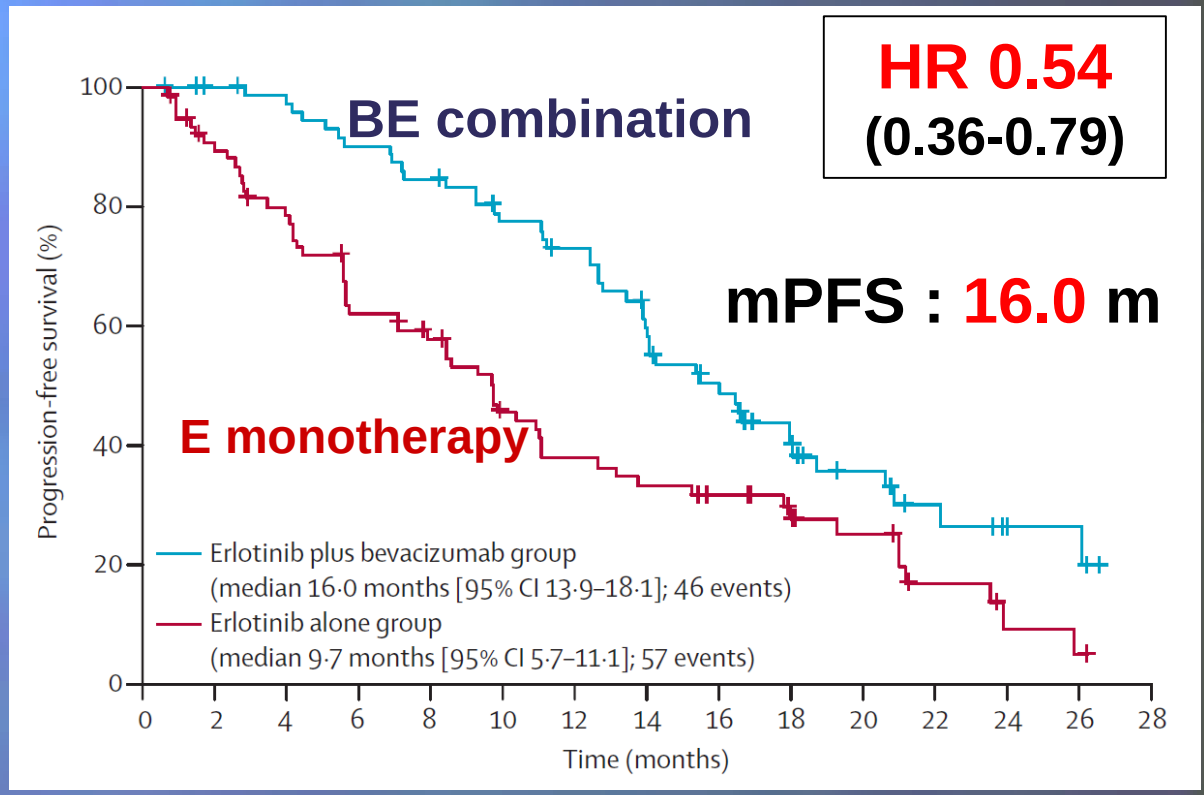
Erlotinib 150mg qd

(*n* = 75)

E monotherapy

Erlotinib 150mg qd

(*n* = 75)

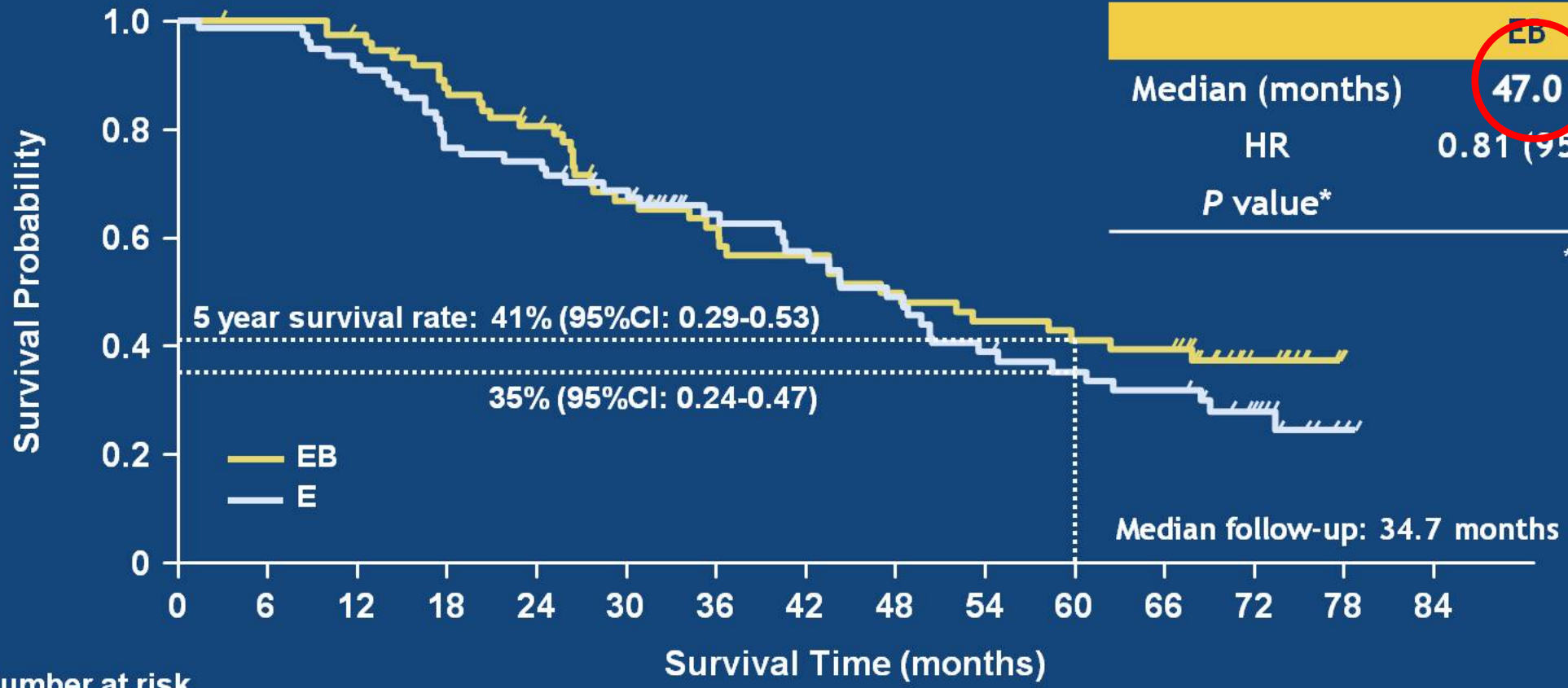


Kato T, et al. ASCO Annual Meeting 2014; Oral session #8005.
Seto T, et al. Lancet Oncol 2014; 15(11): 1235-1244.

Overall survival follow-up

- At the primary analysis of JO25567, OS data was immature.
- After primary completion in Mar 2014, we initiated this additional follow-up to evaluate OS with enough observation period.
- Seventy-five patients were enrolled into this follow-up between June and October 2014.
- The patients who could not provide written informed consent due to death or lost to follow-up were also included in this final OS analysis by using the data collected prior to the primary completion of JO25567.
- Sample size of JO25567 was not sufficiently powered to assess the OS benefit of erlotinib plus bevacizumab.

Final Overall survival



	EB	E
Median (months)	47.0	47.4
HR	0.81 (95% CI: 0.53-1.23)	
P value*	0.3267	

*log-rank test, two-sided

Number at risk

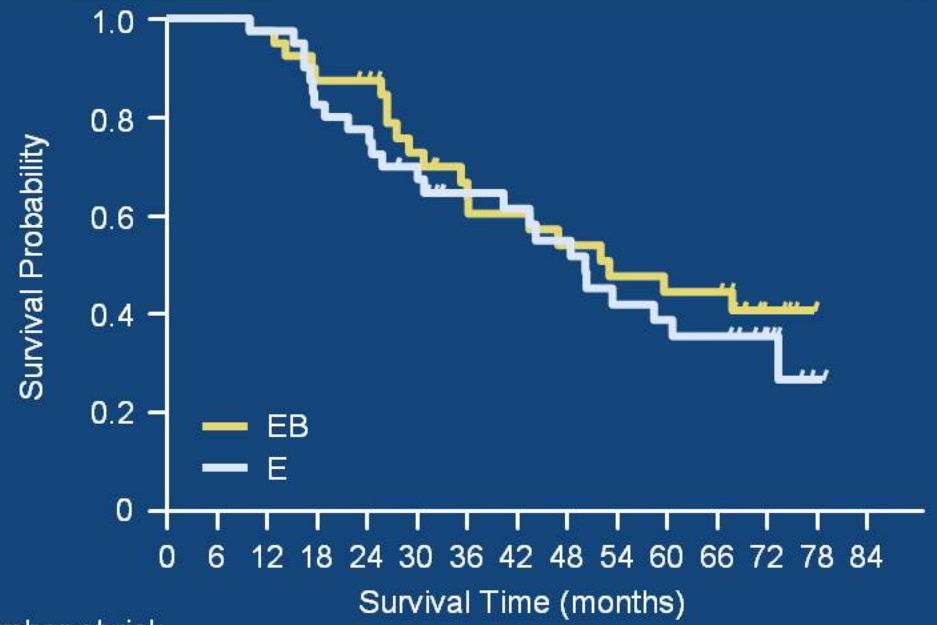
EB	75	74	71	63	55	43	36	33	29	26	24	23	9	0	0
E	77	76	71	59	57	50	38	34	29	23	20	18	11	1	0

Cut off date: October 31, 2017

Overall survival by *EGFR* mutation type

Exon 19 deletion

	EB	E
Median (months)	53.2	50.3
HR	0.79 (95% CI: 0.44-1.44)	

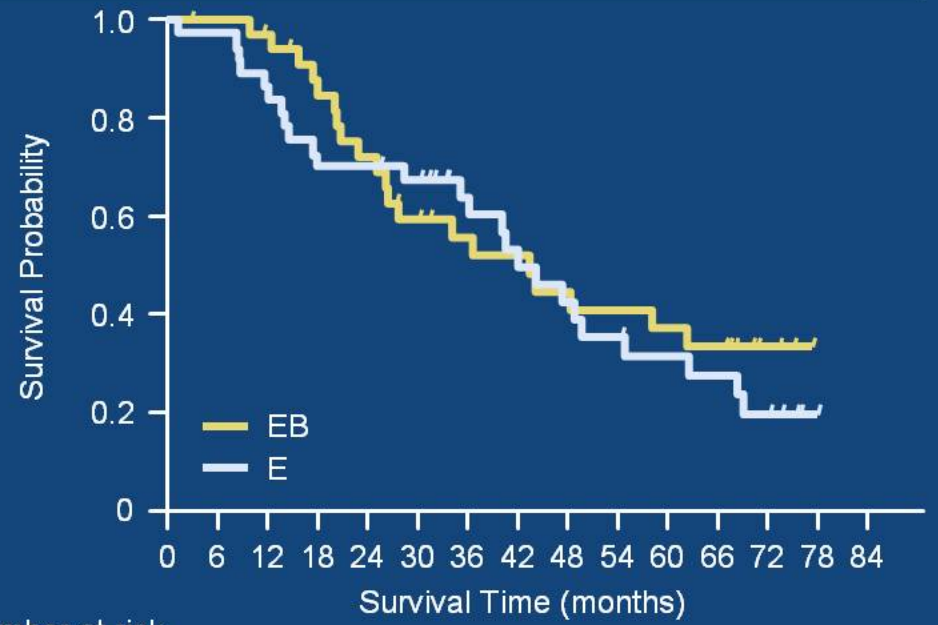


Number at risk

EB	40	40	39	35	32	25	21	19	17	15	14	14	6	0	0
E	40	40	39	33	31	26	20	19	17	13	12	11	6	1	0

Exon 21 L858R

	EB	E
Median (months)	43.6	42.1
HR	0.83 (95% CI: 0.46-1.49)	



Number at risk

EB	35	34	32	28	23	18	15	14	12	11	10	9	3	0	0
E	37	36	32	26	26	24	18	15	12	10	8	7	5	0	0

Study Period Design : NEJ 026 (Phase III study)

- Chemotherapy-naïve
- Non-Sq NSCLC
- PS 0-2
- Stage IIIB/IV
  or postoperative recurrence
- Activating *EGFR*-mutations*
  Ex19 del, Ex21 L858R
- Asymptomatic CNS metastases
  allowed

*T790M excluded

R

BE combination

Bevacizumab 15mg/kg q3w
+
Erlotinib 150mg qd

(*n* = 107)

E monotherapy

Erlotinib 150mg qd

(*n* = 107)

Stratification factors

Sex **Smoking status**
Clinical stage ***EGFR*-mutation subtypes**

Baseline characteristics

		BE (n=112)	E (n=112)
Pathology	Adenocarcinoma	110 (98.2%)	112 (100.0%)
	Large cell carcinoma	1 (0.9%)	0 (0%)
	Other	1 (0.9%)	0 (0%)
EGFR-mutation type	Ex19 deletion	56 (50.0%)	55 (49.1%)
	Ex21 L858R	56 (50.0%)	57 (50.9%)
Stage at screening	IIIB	8 (7.1%)	8 (7.1%)
	IV	82 (73.2%)	84 (75.0%)
	Postoperative recurrence	22 (19.6%)	20 (17.9%)
CNS metastases	(+)	**36 (32.1%)**	**36 (32.1%)**
	(-)	76 (67.9%)	76 (67.9%)

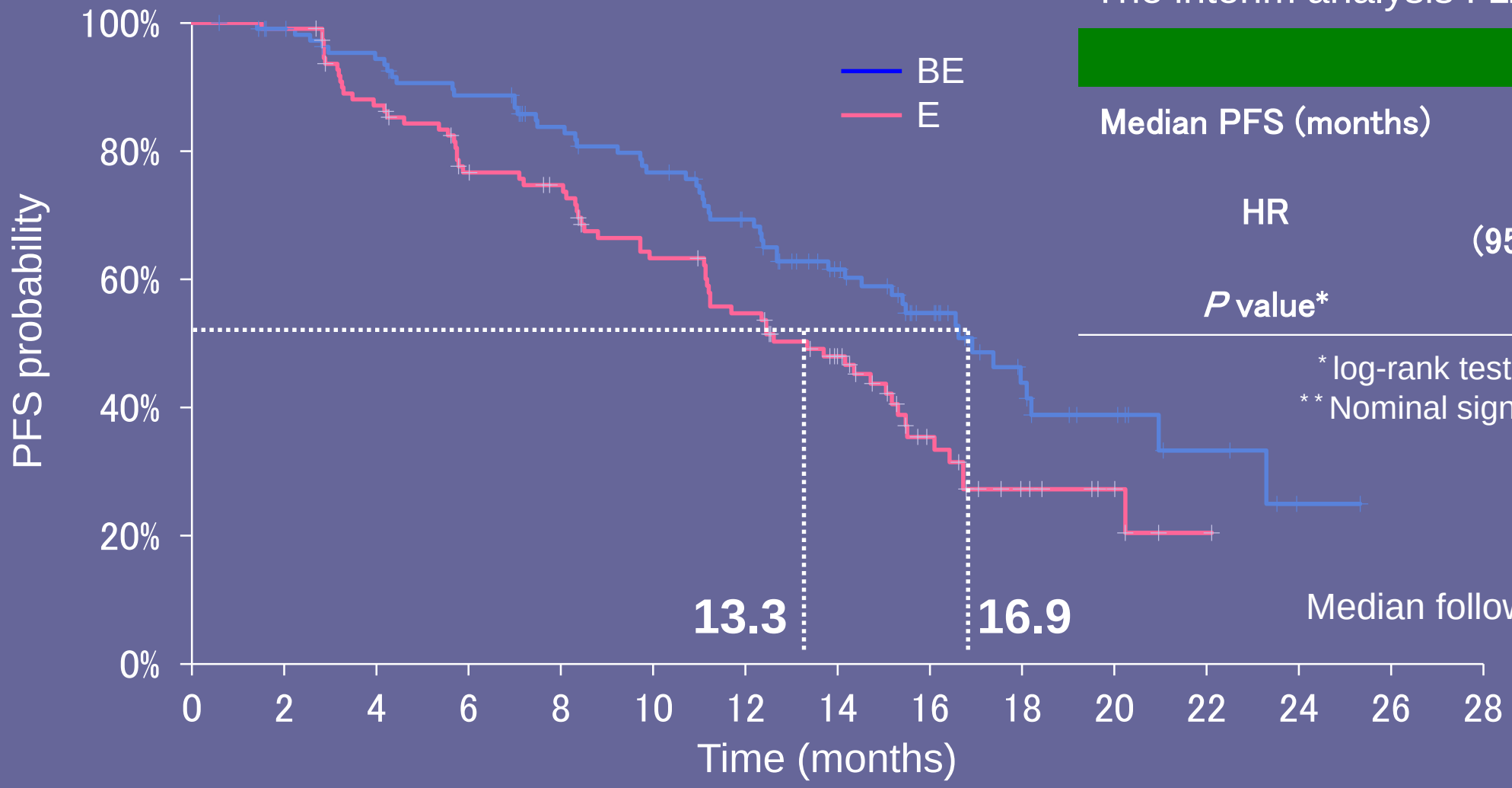
Primary endpoint：PFS by independent review

The interim analysis : 117 events

	BE	E
Median PFS (months)	16.9	13.3
HR	0.605 (95% CI : 0.417–0.877)	
P value*	0.01573**	

* log-rank test, two-sided

** Nominal significance level : 0.02398



Median follow up : 12.4 months

Naoki Furuya

Adverse events

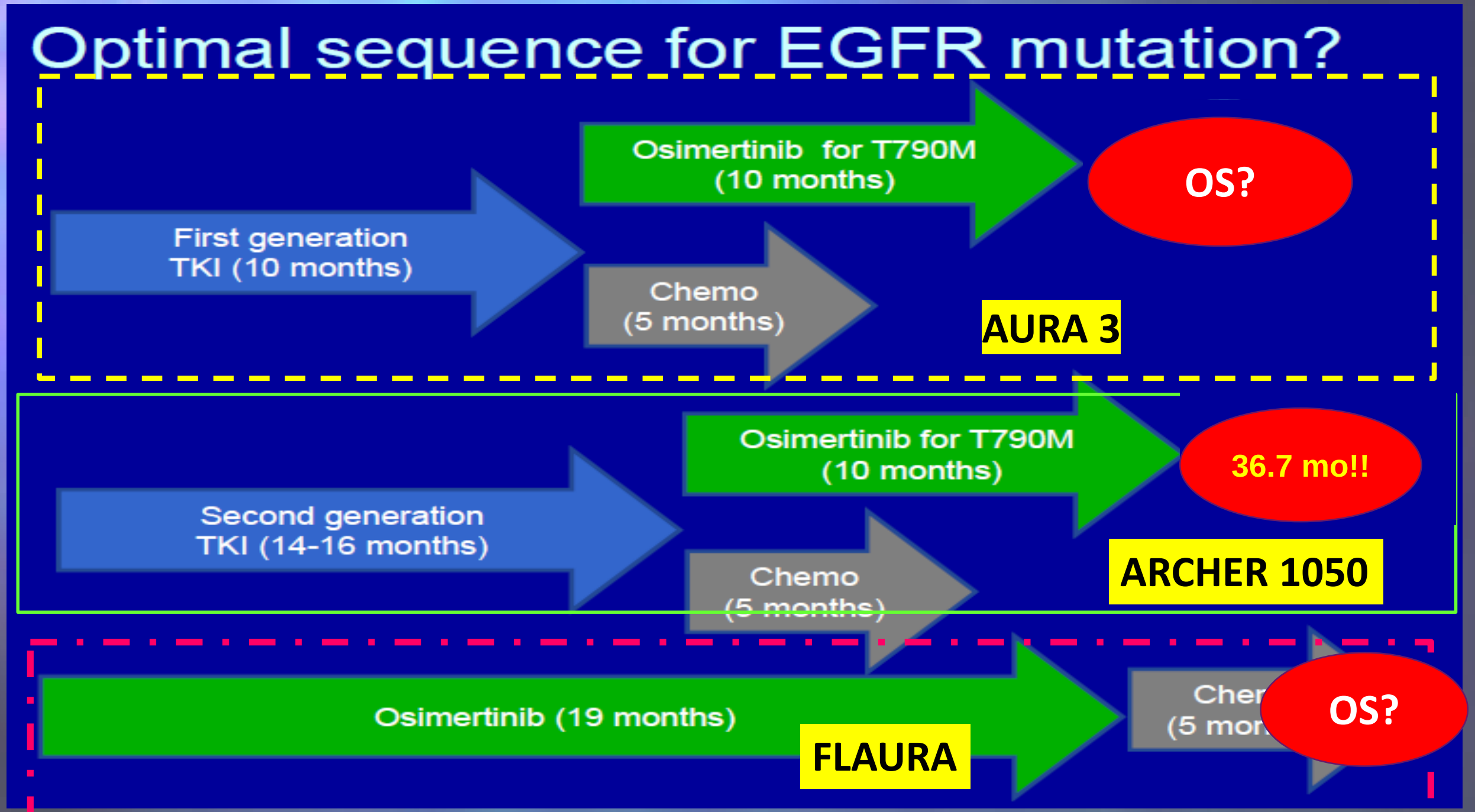
	All grades		Grade ≧3	
	BE (n=112)	E (n=114)	**BE (n=112)**	**E (n=114)**
Rash	99 (88.4%)	99 (86.8%)	23 (20.5%)	24 (21.1%)
Diarrhea	53 (47.3%)	47 (41.2%)	6 (5.4%)	2 (1.8%)
Hypertension	51 (45.5%)**	10 (8.8%)	**25 (22.3%)****	0 (0%)
Proteinuria	36 (32.1%)**	3 (2.6%)	**8 (7.1%)***	0 (0%)
Hepatic dysfunction	30 (26.8%)	34 (29.8%)	9 (8.0%)	6 (5.3%)
Pulmonary hemorrhage (PH)	3 (2.7%)	0 (0%)	0 (0%)	0 (0%)
Hemorrhage (PH excluded)	**29 (25.9%)****	3 (2.6%)	2 (1.8%)	1 (0.9%)
Thrombosis	2 (1.8%)	6 (5.3%)	1 (0.9%)	1 (0.9%)
Interstitial lung disease (ILD)	**0 (0%)**	5 (4.4%)	0 (0%)	0 (0%)

** $P < 0.001$ * $P < 0.01$

After ASCO 2018

June 1-5, 2018

Optimal sequence for EGFR mutation?



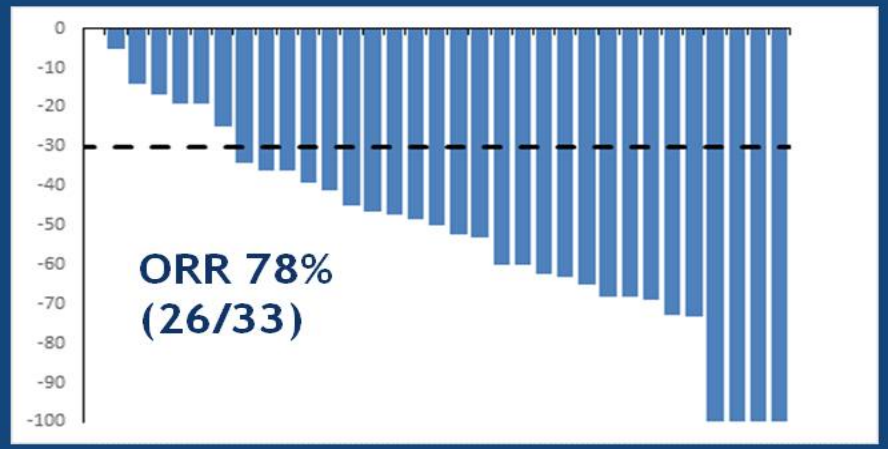
Other Anti-Angiogenic Combinations: *Ongoing trial.*

Osimertinib and bevacizumab

Patient population:
Untreated Metastatic EGFR+ LC
No prior EGFR TKI
No contraindications to Bev

Phase 1:
3+3 Dose de-escalation design
Dose level 1: Full doses both drugs

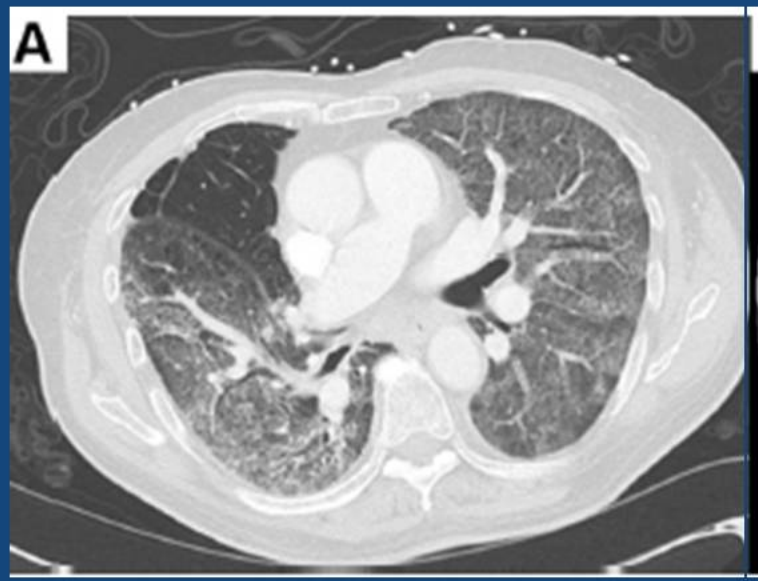
Phase 2:
MTD from Phase 1
Primary endpoint: PFS at 12 months
Accrual=49

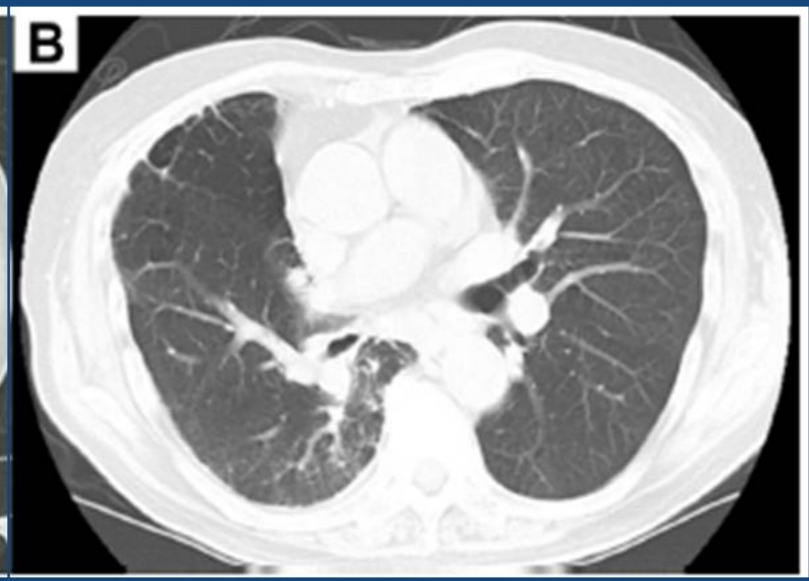


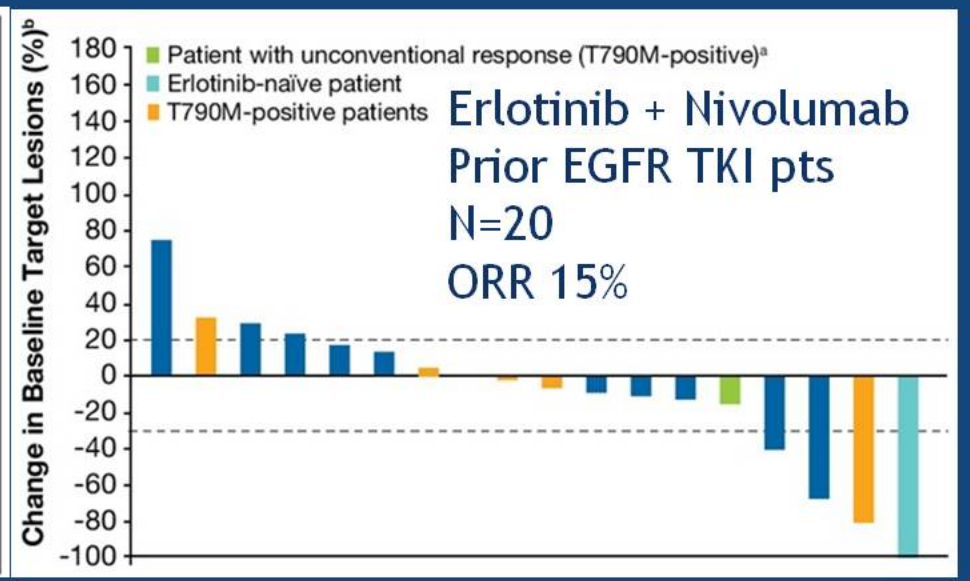
37 ongoing on treatment
Reasonable toxicity profile
No CNS progression (mandated interval MRIs)
Pre/post treatment biopsies, serial plasma
Primary endpoint not yet evaluable

Yu PASCO 2017

EGFR TKI and immunotherapy



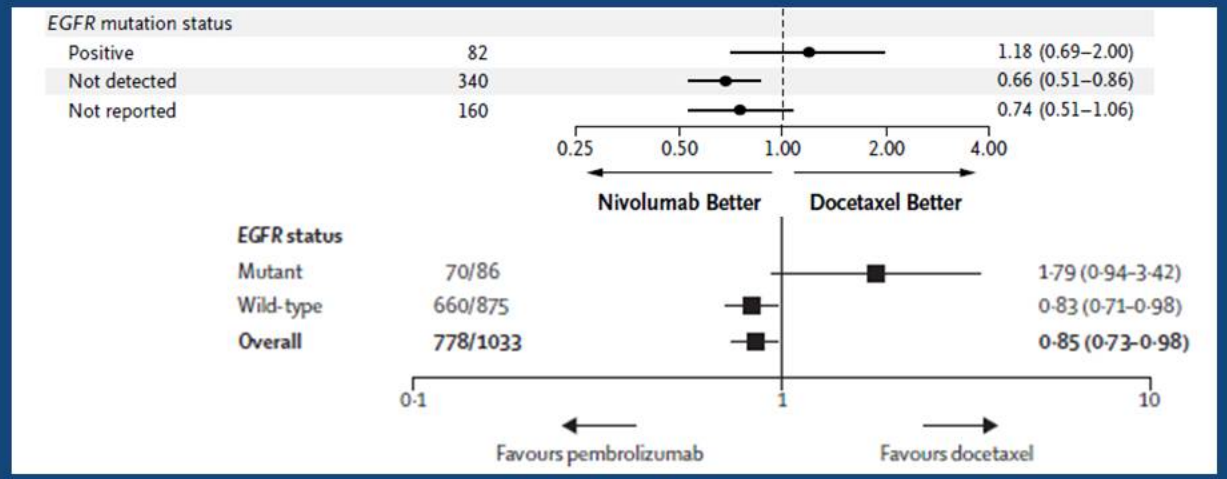




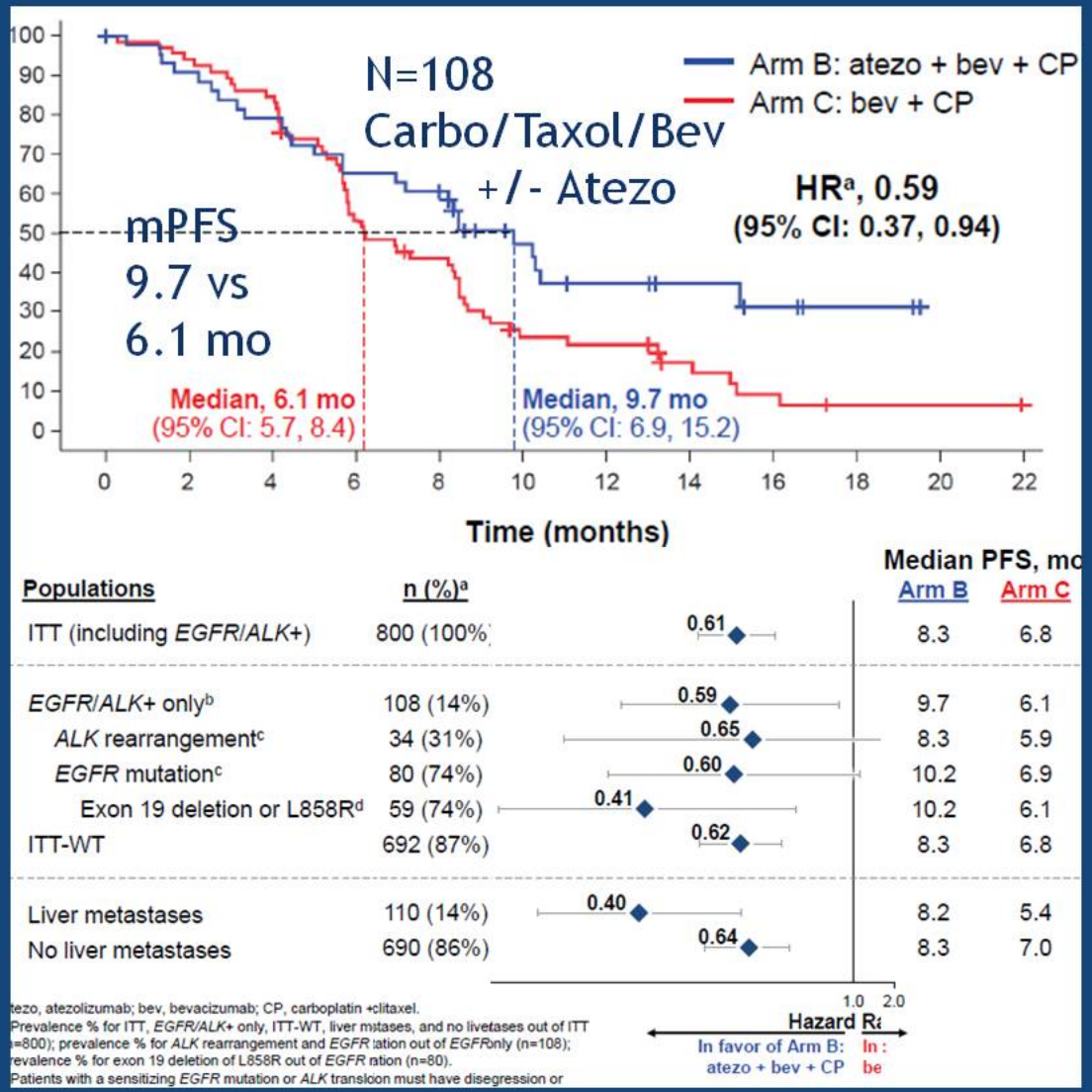
Osimertinib and durvalumab combination therapy with 38% incidence of pneumonitis

Rizvi PASCO 2014, Gettinger JTO in press, Ahn WCLC 2016, Nagasaka Clin Lung Cancer 2018

EGFR and Immunotherapy



- Lack of benefit with IO monotherapy as 2nd line treatment for pts with EGFR+ NSCLC
- Largely may be related to low PDL1 expression and low TMB
- IMpower150 first study to show benefit of addition of IO in EGFR+/ALK+ LCs
- Larger studies needed to define role of IO in this population

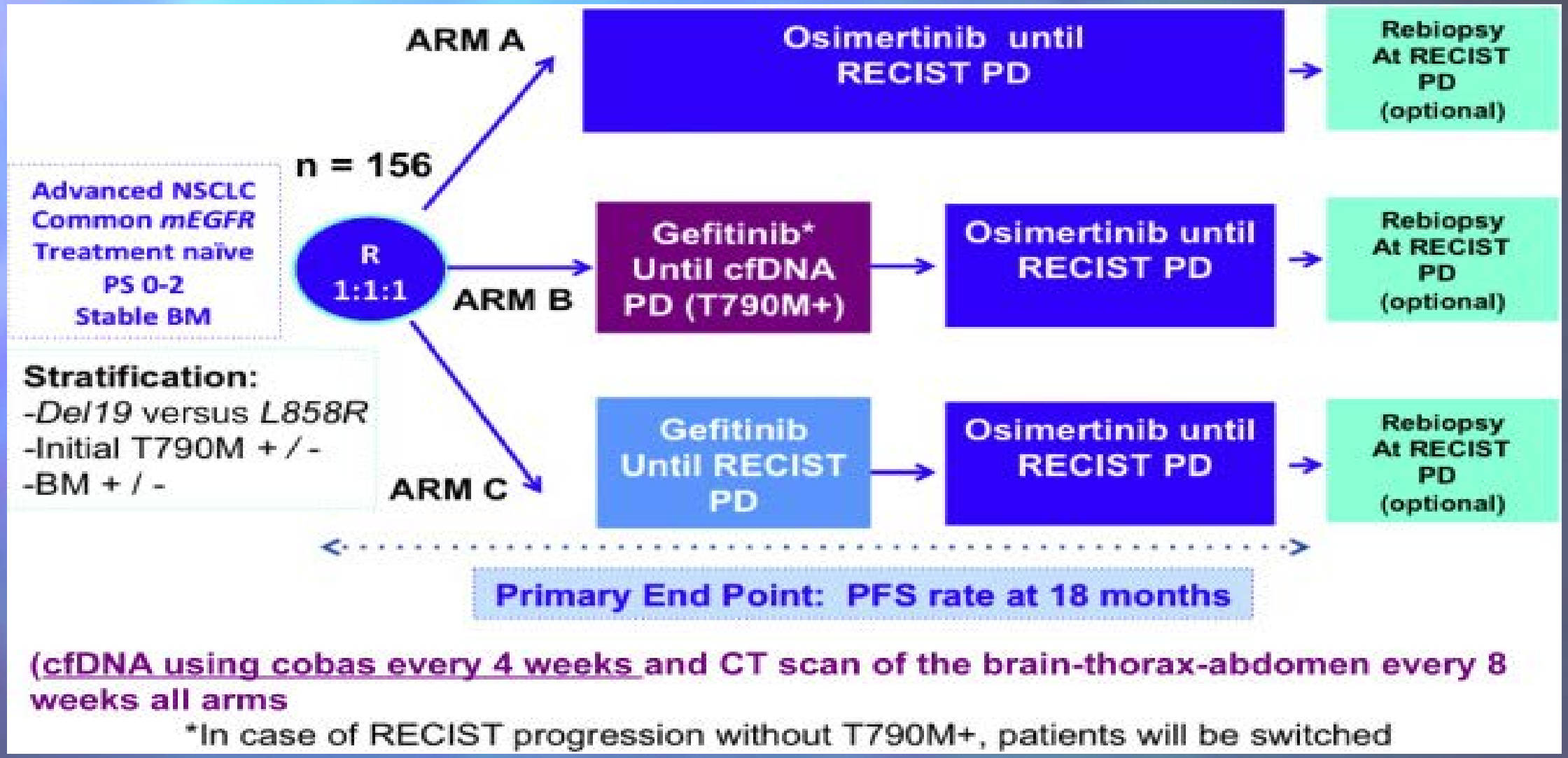


The Case for Using Osimertinib as 1st Line T_x

- 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



The APPLE Trial: Feasibility and Activity of AZD9291 (Osimertinib) Treatment on Positive Plasma T790M in EGFR - mutant NSCLC Patients. EORTC 1613: Randomized, open-label, multicenter, 3-arms, phase II study; to evaluate the best strategy of sequencing gefitinib and osimertinib treatment.

Uncommon EGFR Mutations

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 >80%)	++++ (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

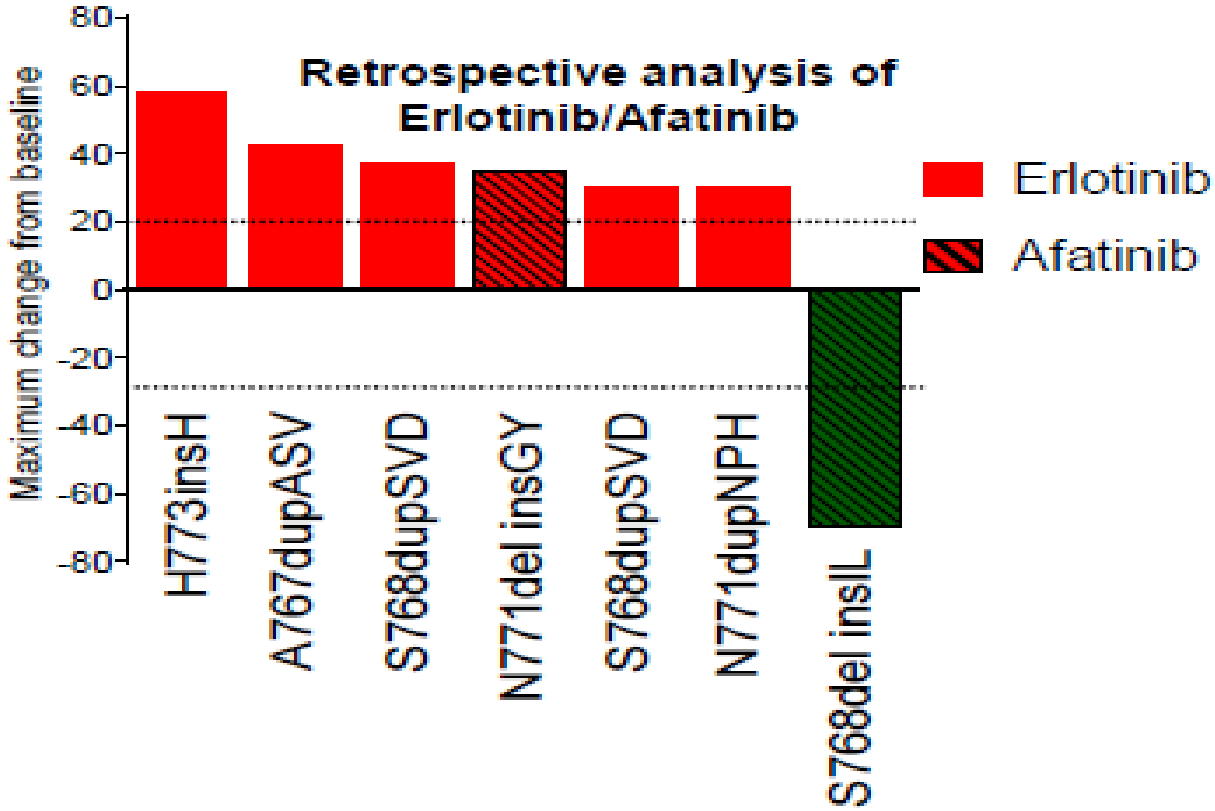
+ response ongoing at time of censoring

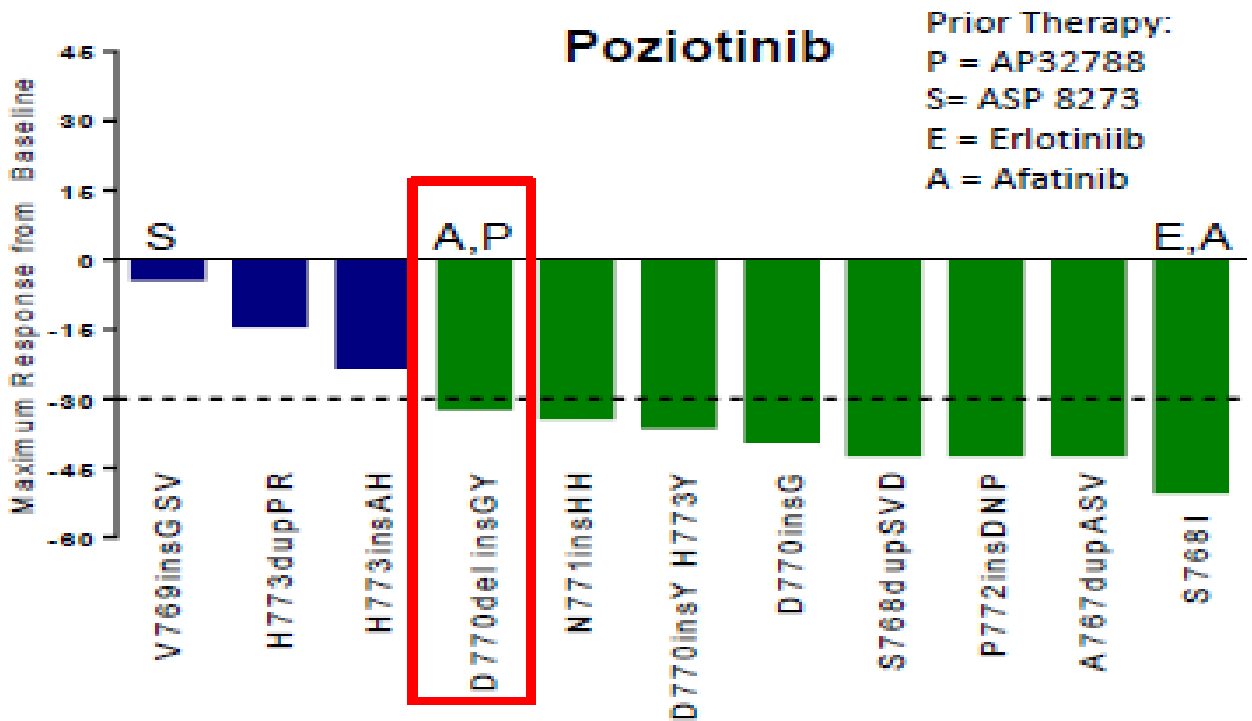
Subset analysis LUX lung 2,3,6 (32pts):

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

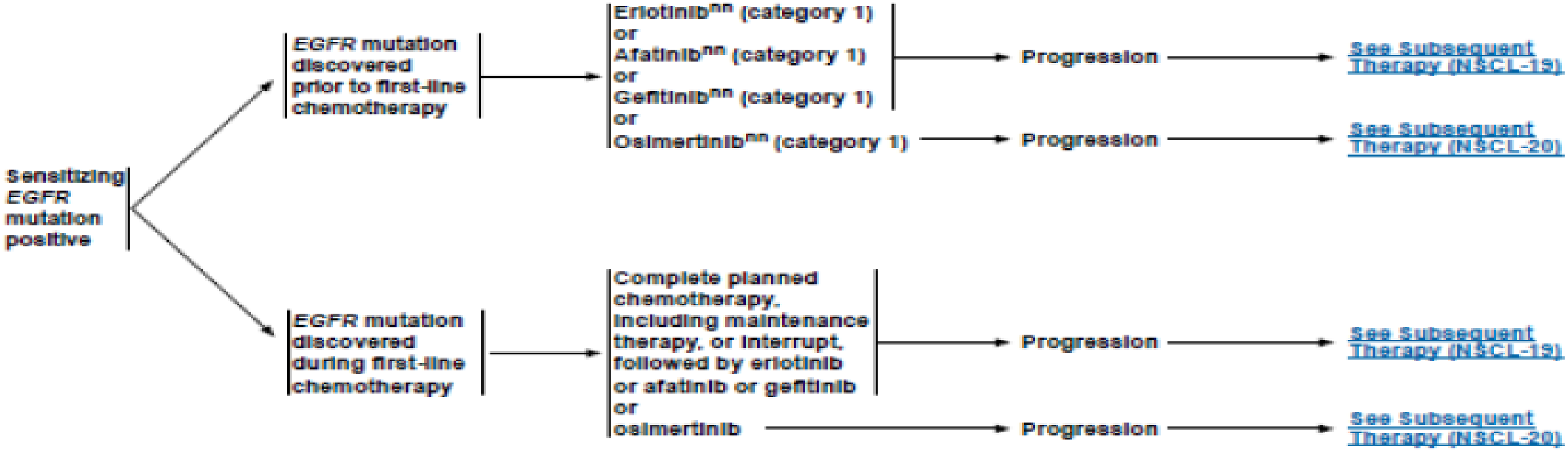
Take home message….

- Osimertinib met its primary endpoint PFS over Gefitinib/Erlotinib; OS is not mature yet, but ***promising***.

- Osimertinib is approved for 1st Line Therapy for sensitive EGFR mutations; category 1 by NCCN. To date, there are 4 category 1 as therapy (gefitinib, erlotinib, afatinib, osimertinib).

SENSITIZING EGFR MUTATION POSITIVE[hh]

FIRST-LINE THERAPY[mm]



[hh] See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn] For performance status 0-4.

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.

Take home message….

- Osimertinib met its primary endpoint PFS over Gefitinib/Erlotinib; OS is not mature yet, but ***promising***.
- Osimertinib is approved for 1st Line Therapy for sensitive EGFR mutations; category 1 by NCCN. To date, there are 4 category 1 as therapy (gefitinib, erlotinib, afatinib, osimertinib).
- Osimertinib: very active on CNS metastases & favorable toxicity profile.
- OS for exon 19 EGFR mutant (+) patient range 33-37 months based on LUX Lung 3 and ARCHER 1050. FLAURA and AURA 3 trials data is eagerly awaited. This trial raises the question of sequencing 2G → 3G.
- Gefitinib/Carbo/Pem… unprecendeted 52 months!! (upfront over gefitinib) [NEJ009]; this trial underscores the role of Carbo/Pem in EGFR + NSCLC.

Take home message….

- Combination of osimertinib plus Bev, MET inhibitors, and others are ongoing in different clinical settings.
- EGFR TKI and IO induces high rate of pneumonitis.
- Afatinib ***is the only*** EGFR TKI with FDA indication for uncommon EGFR mutations.
- Poziotinib seems to be promising for exon 20 insertion EGFR mutation.
- Erlotinib and Bev new standard of care in Asia, perhaps it is time to consider it in USA as another option; E/B > E alone. Phase II and III studies corroborate that (JO25567 and NEJ 026).
- In my opinion, exon 19 EGFR mutation patients have several therapeutic options (see NCCN guidelines; version 5.2018, June 27, 2018).

Take home message….

- The treatment for *EGFR* mutant patients has several choices after what we have learned in the last 10 months.
- Good for our patients, more work for us…. the clinicians.
- More questions than ever.

I need time to digest too much info.

Lynn Cancer Institute
Boca Raton Regional Hospital