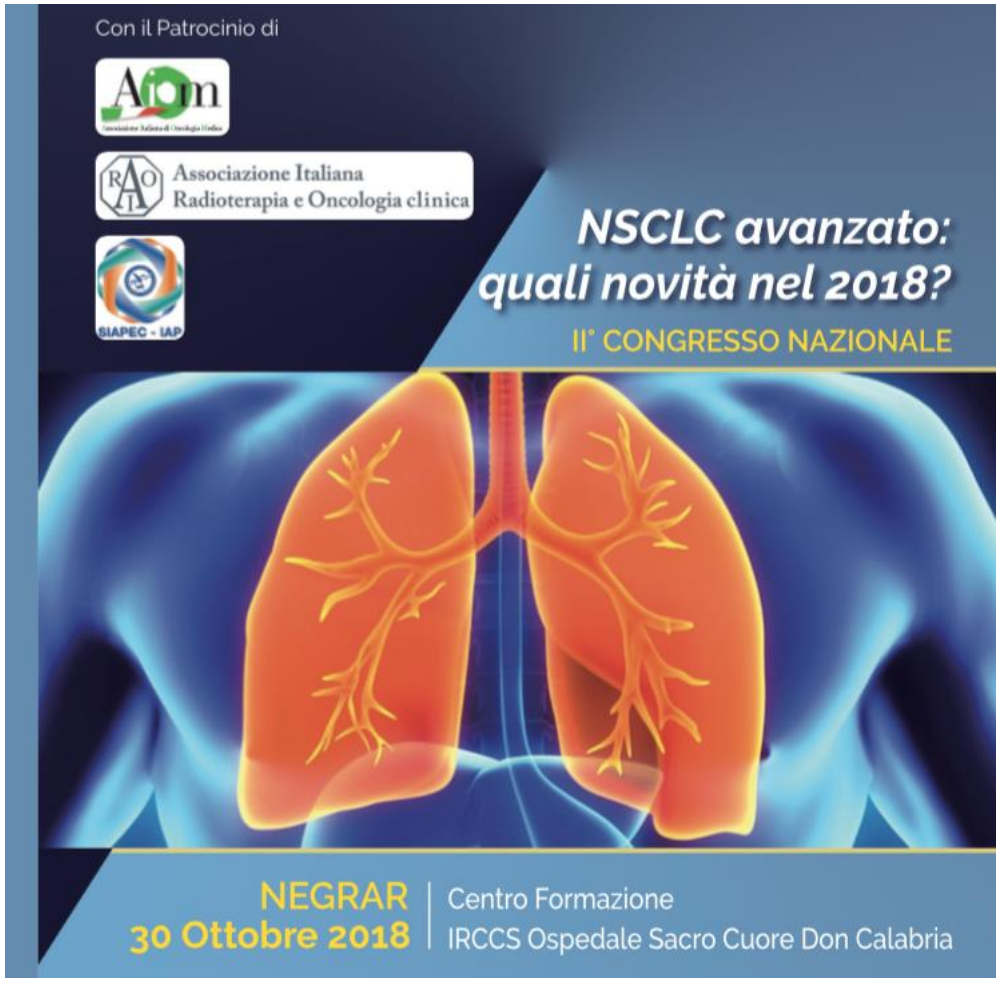
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna



Trattamento della malattia avanzata oncogene-addicted

Quale sequenza terapeutica nella malattia EGFR+

Chiara Bennati
AUSL della Romagna
Ravenna, Italy

A matter of fact

- ✓ *EGFR* TKIs are better than chemotherapy (10 randomized studies)
- ✓ Ist gen TKIs are equal in efficacy
- ✓ Expected mPFS ranges from 10 to 14 mo (no OS advantage due to crossover)
- ✓ Treatment beyond RECIST progression (ASPIRATION: extension of 4 mo)
- ✓ ~ 50% are T790M mut + at progression and should be treated with osimertinib
- ✓ For T790M mut - the standard of care is platinum chemotherapy (without continuation of TKI)

Outline

- ✓ Can we improve PFS/OS with 2 nd/ 3 rd generation *EGFR* TKIs?
- ARCHER 1050
- FLAURA

- ✓ What is the impact of the “optimal” sequence on resistance mechanisms?
- After Osimertinib in I st line
- Activation of different pathways/SCLC transition

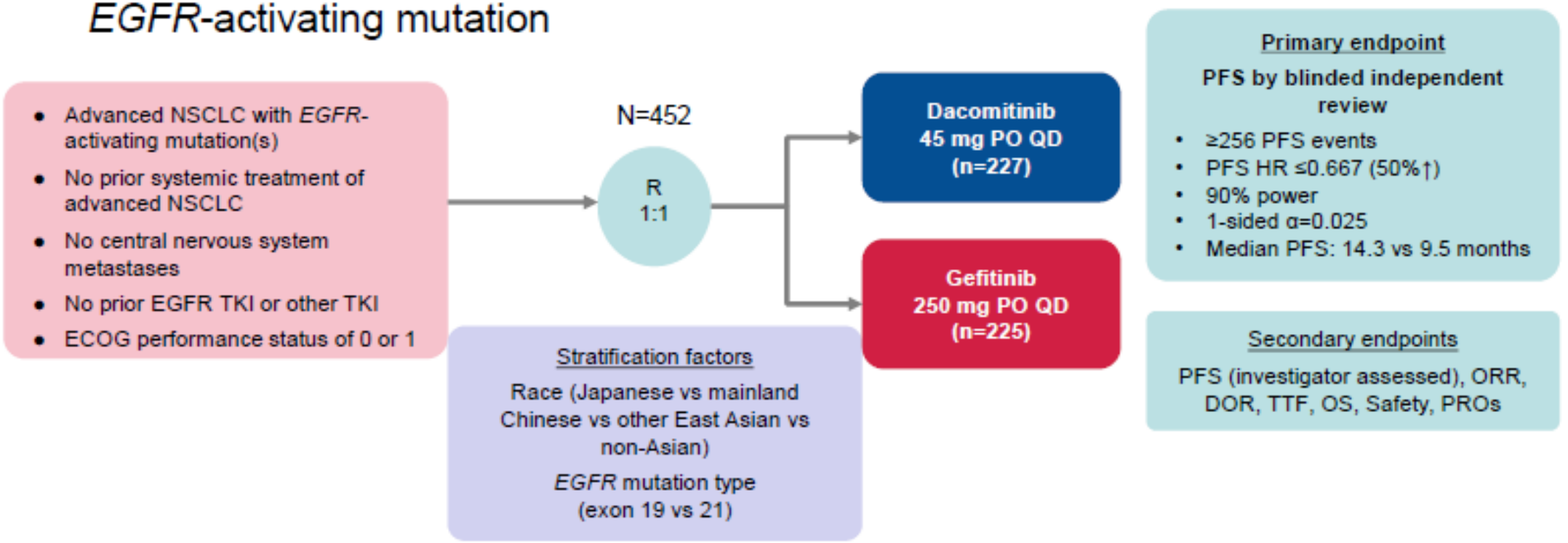
- ✓ Can we improve treatment outcome with combination therapy?
- Dealing with angiogenesis

- ✓ What is the role of immunotherapy?
- See ESMO guidelines

New options for first-line NSCLC

ARCHER 1050: Study Design

- Randomized, open-label, phase 3 study to evaluate dacomitinib as an alternative first-line treatment for patients with advanced NSCLC with an *EGFR*-activating mutation



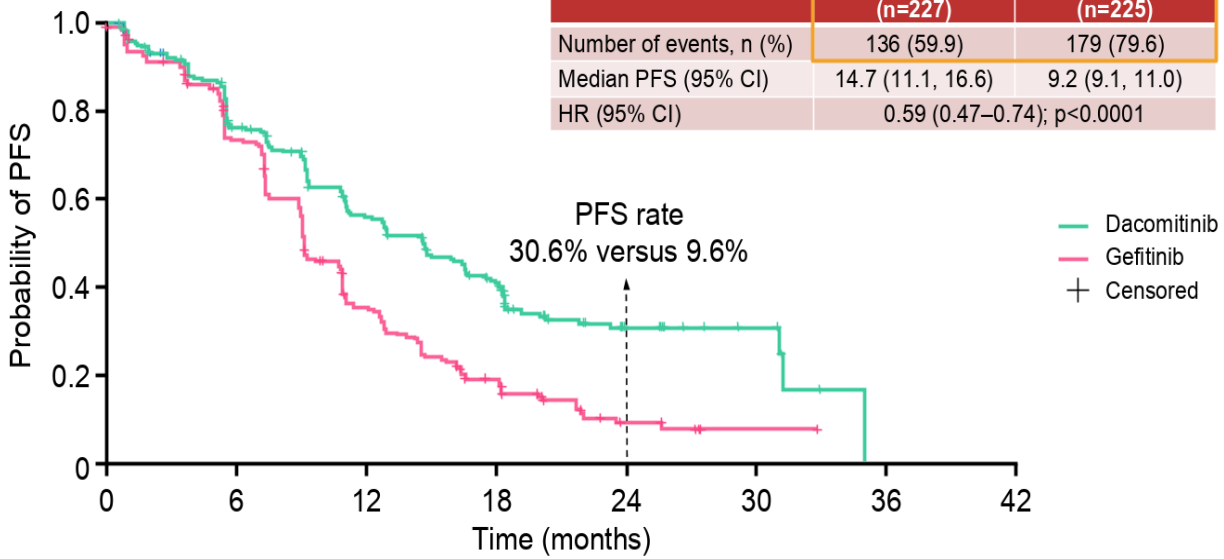
Wu YL, et al. Lancet Oncol 2017

ARCHER 1050
dacomitinib versus gefitinib

PFS by BIRC

14.7 vs 9.2 mo

	Dacomitinib (n=227)	Gefitinib (n=225)
Number of events, n (%)	136 (59.9)	179 (79.6)
Median PFS (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	

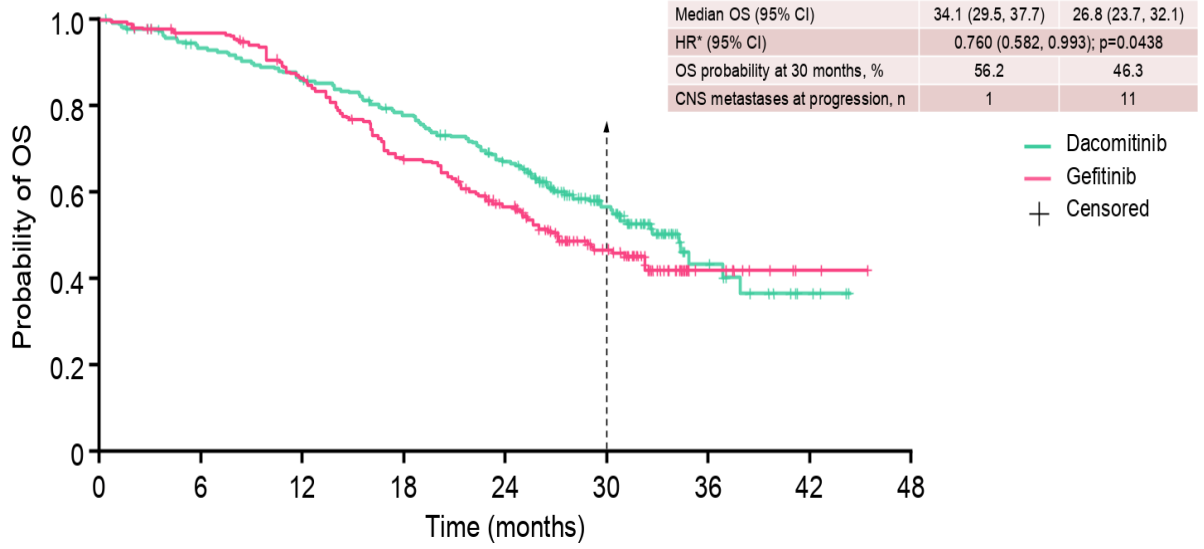


Wu YL, et al. Lancet Oncol 2017

OS

34.1 vs 26.8 mo

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



Mok T, et al. JCO 2018

Impact of dacomitinib on other EGFR-TKIs usage

More adverse events in daco arm

Adverse event	Dacomitinib (N = 227)						Gefitinib (N = 224)					
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Number of patients (percent)											
Diarrhea	198 (87.2)	113(49.8)	65 (28.6)	19 (8.4)	0	1 (0.4)	125 (55.8)	103 (46.0)	20 (8.9)	2 (0.9)	0	0
Paronychia	140 (61.7)	46 (20.3)	77 (33.9)	17 (7.5)	0	0	45 (20.1)	30 (13.4)	12 (5.4)	3 (1.3)	0	0
Dermatitis acneiform	111 (48.9)	37 (16.3)	43 (18.9)	31 (13.7)	0	0	64 (28.6)	43 (19.2)	21 (9.4)	0	0	0
Stomatitis	99 (43.6)	51 (22.5)	40 (17.6)	8 (3.5)	0	0	40 (17.9)	33 (14.7)	6 (2.7)	1 (0.4)	0	0
Decreased appetite	70 (30.8)	40 (17.6)	23 (10.1)	7 (3.1)	0	0	55 (24.6)	48 (21.4)	6 (2.7)	1 (0.4)	0	0
Dry skin	63 (27.8)	42 (18.5)	18 (7.9)	3 (1.3)	0	0	38 (17.0)	35 (15.6)	3 (1.3)	0	0	0
Weight decreased	58 (25.6)	31 (13.7)	22 (9.7)	5 (2.2)	0	0	37 (16.5)	22 (9.8)	14 (6.3)	1 (0.4)	0	0
Alopecia	53 (23.3)	41 (18.1)	11 (4.8)	1 (0.4)	0	0	28 (12.5)	26 (11.6)	2 (0.9)	0	0	0
Cough	48 (21.1)	39 (17.2)	9 (4.0)	0	0	0	42 (18.8)	36 (16.1)	5 (2.2)	1 (0.4)	0	0
Pruritus	45 (19.8)	27 (11.9)	17 (7.5)	1 (0.4)	0	0	31 (13.8)	24 (10.7)	4 (1.8)	3 (1.3)	0	0
ALT increased	44 (19.4)	37 (16.3)	5 (2.2)	2 (0.9)	0	0	88 (39.3)	45 (20.1)	24 (10.7)	19 (8.5)	0	0

Dose Modification higher in daco arm

Dacomitinib
- First dose reduction: 30 mg/day
- Second reduction: 15 mg/day

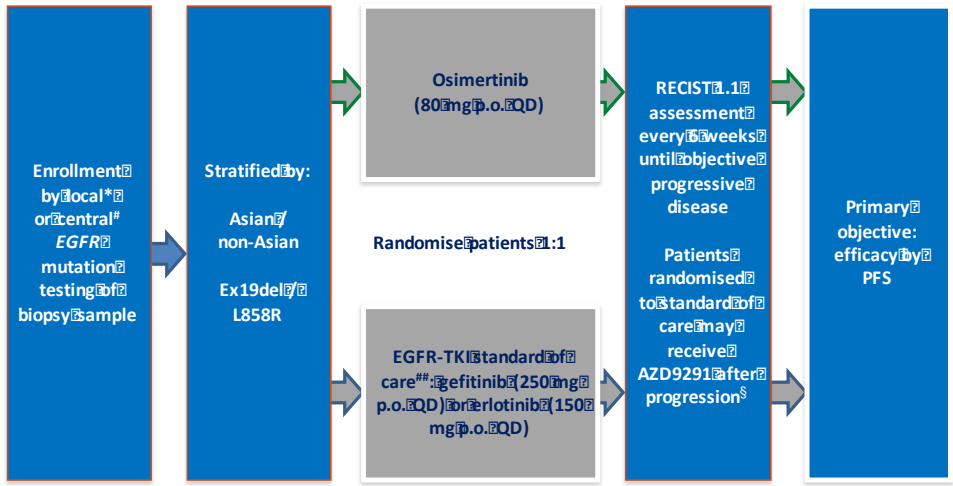
Gefitinib
- 250 mg every two days

	Median time to dose reduction	Median duration of dose reduction	Reduction to 30 mg daily	Reduction to 15 mg daily	Total number of patients with dose modification
Dacomitinib (n=227)	2.8 months (range, 0.3 to 20.3)	11.3 months (range, 0.1 to 33.6)	87 (38.3%)	63 (27.8%)	150 (66.1%)
Gefitinib (n=224)	3.3 months (1.2 to 25.7)	5.2 months (0.3 to 17.8)	NA	NA	18 (8.0%)

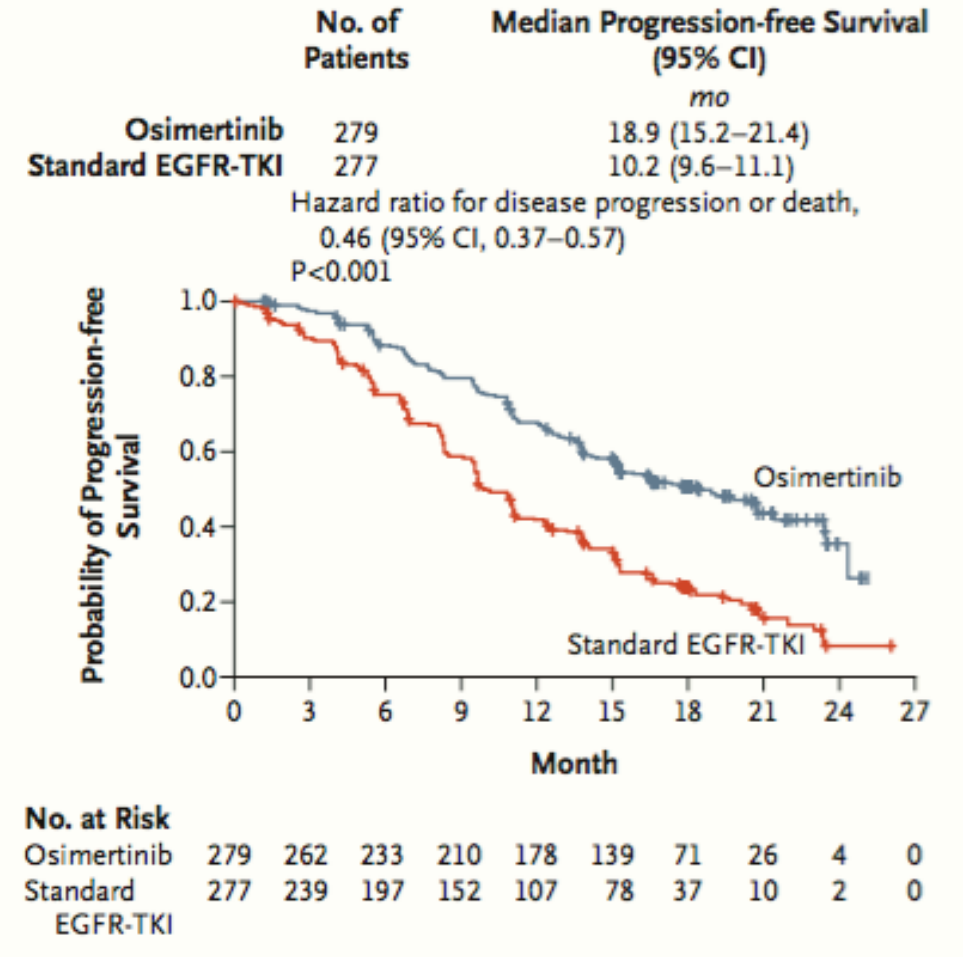
In vitro sensitivity of Ba/F3 cells expressing *EGFR* mutations to various TKIs

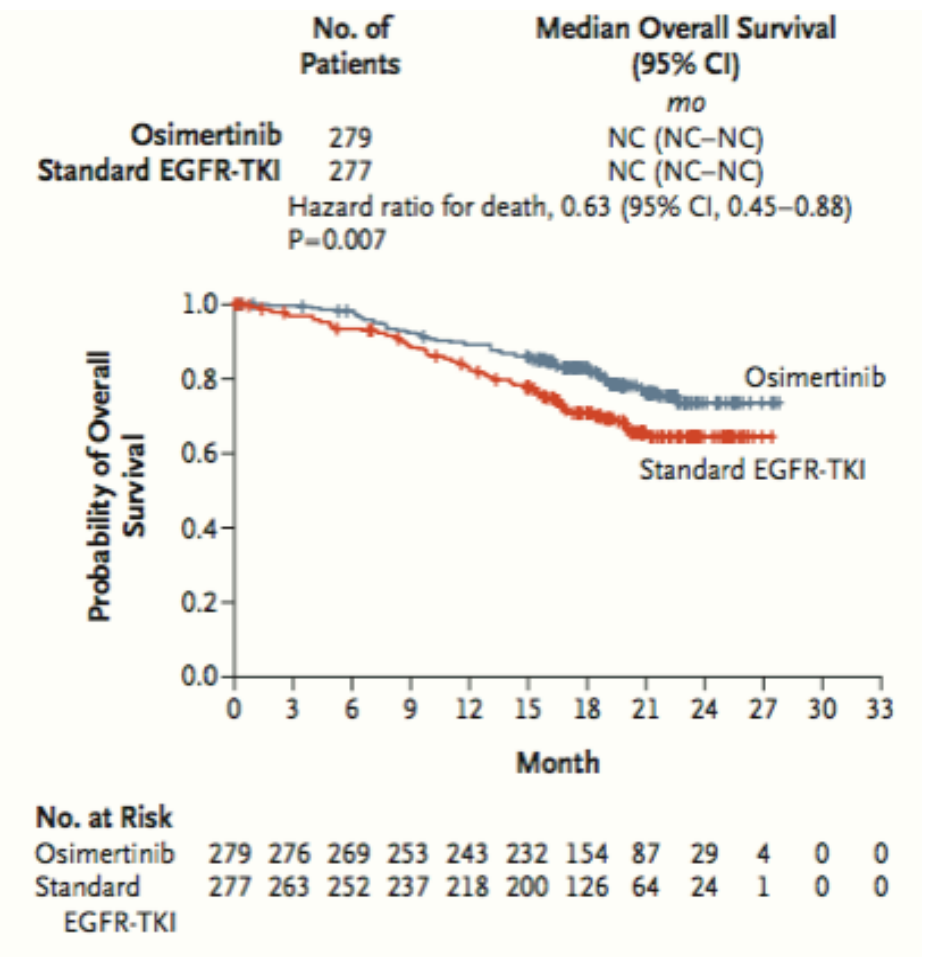
Exon	Category	Mutations	First generation		Second generation			Third generation	
			Gefitinib	Erlotinib	Afatinib	Dacomitinib	Neratinib	Osimertinib	Rociletinib
18	Del18	delE709_T710insD	882	884	1.7	29	27	93	999
	E709X	E709K	187	215	0.7	16	6	62	706
	G719X	G719A	213	167	0.9	6	1.1	53	214
19	Del19	delE746_A750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

No data on BM and osimertinib data



FLAURA: PFS and OS
Undoubtedly a positive study

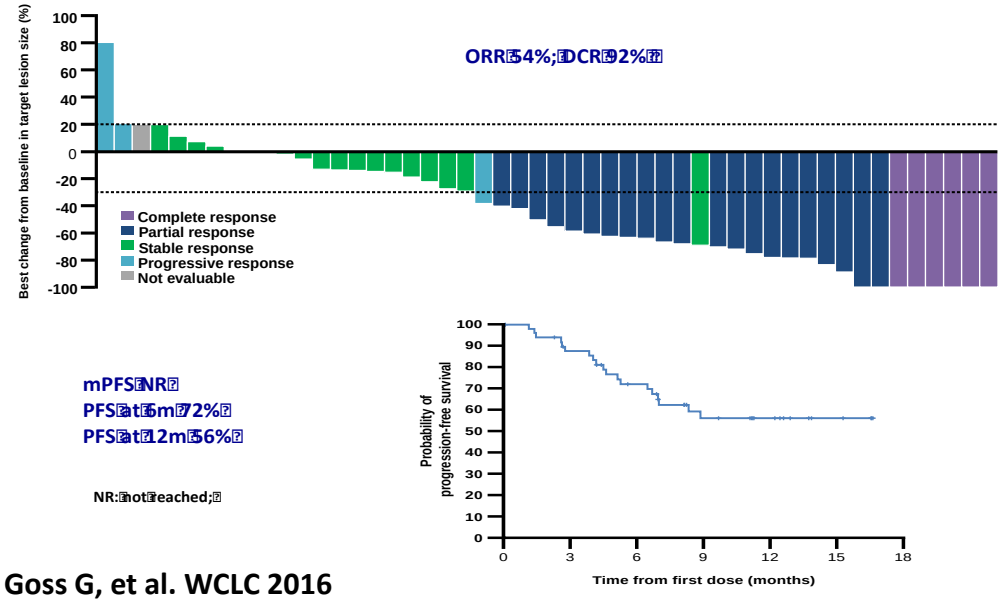




Soria JC et al., NEJM 2017

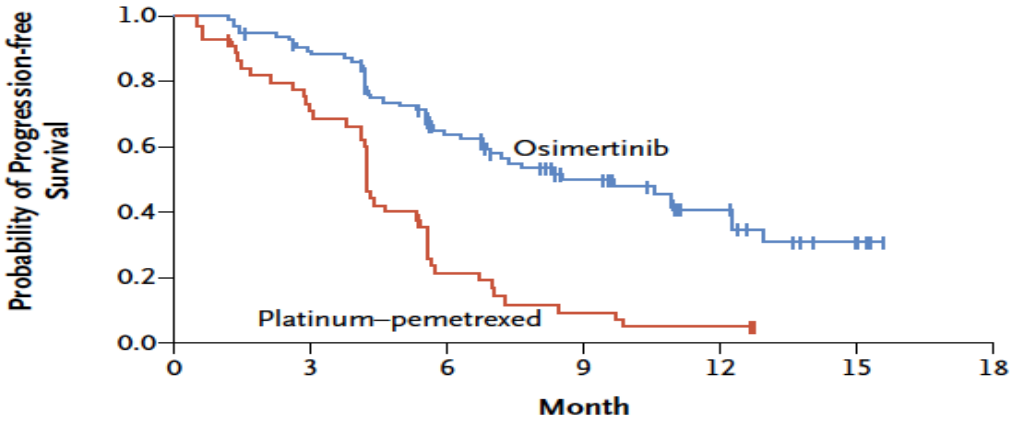
Osimertinib CNS activity

Pooled analysis AURA I/II



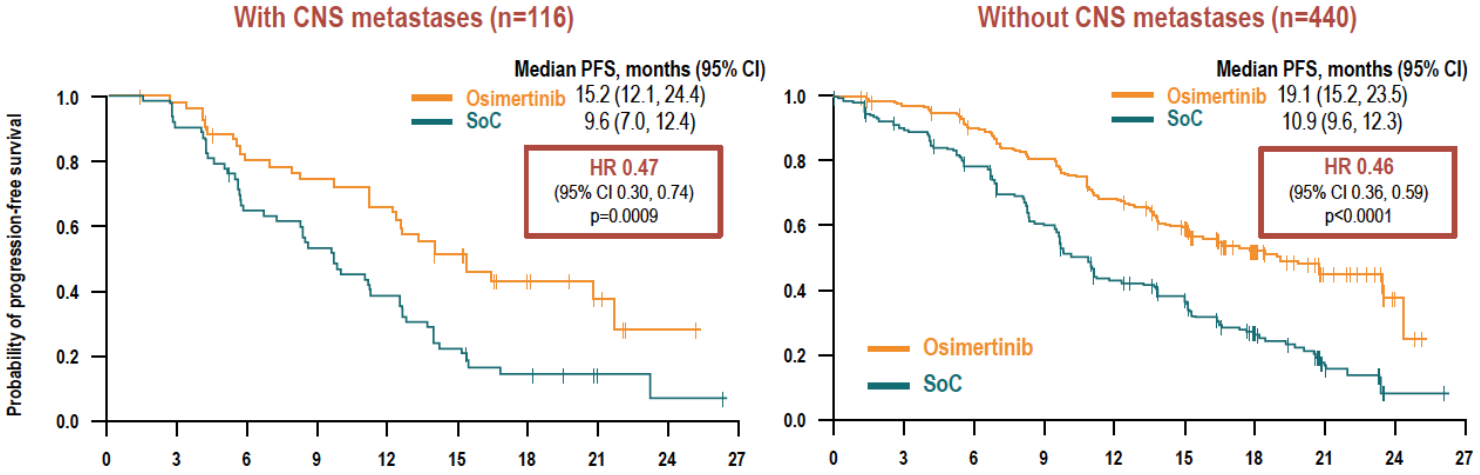
Goss G, et al. WCLC 2016

AURA 3



Mok T, et al. NEJM 2016

FLAURA



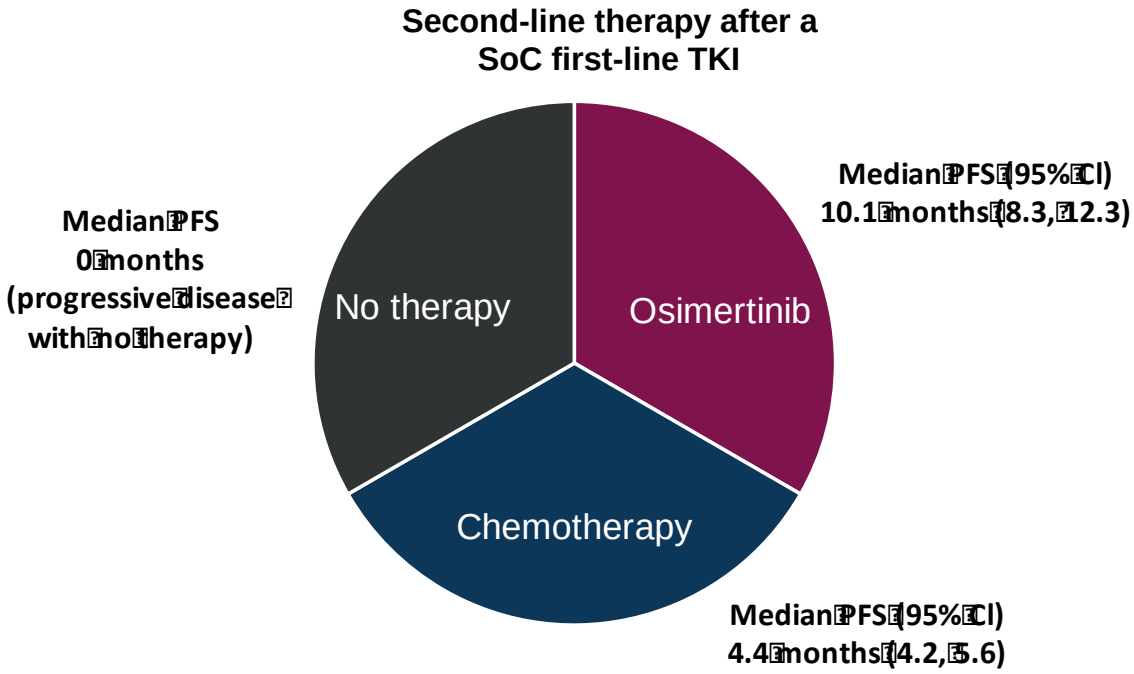
Ramalingam S, et al. ESMO 2017

Sequence matters

Key factors that may impact OS/QoL:

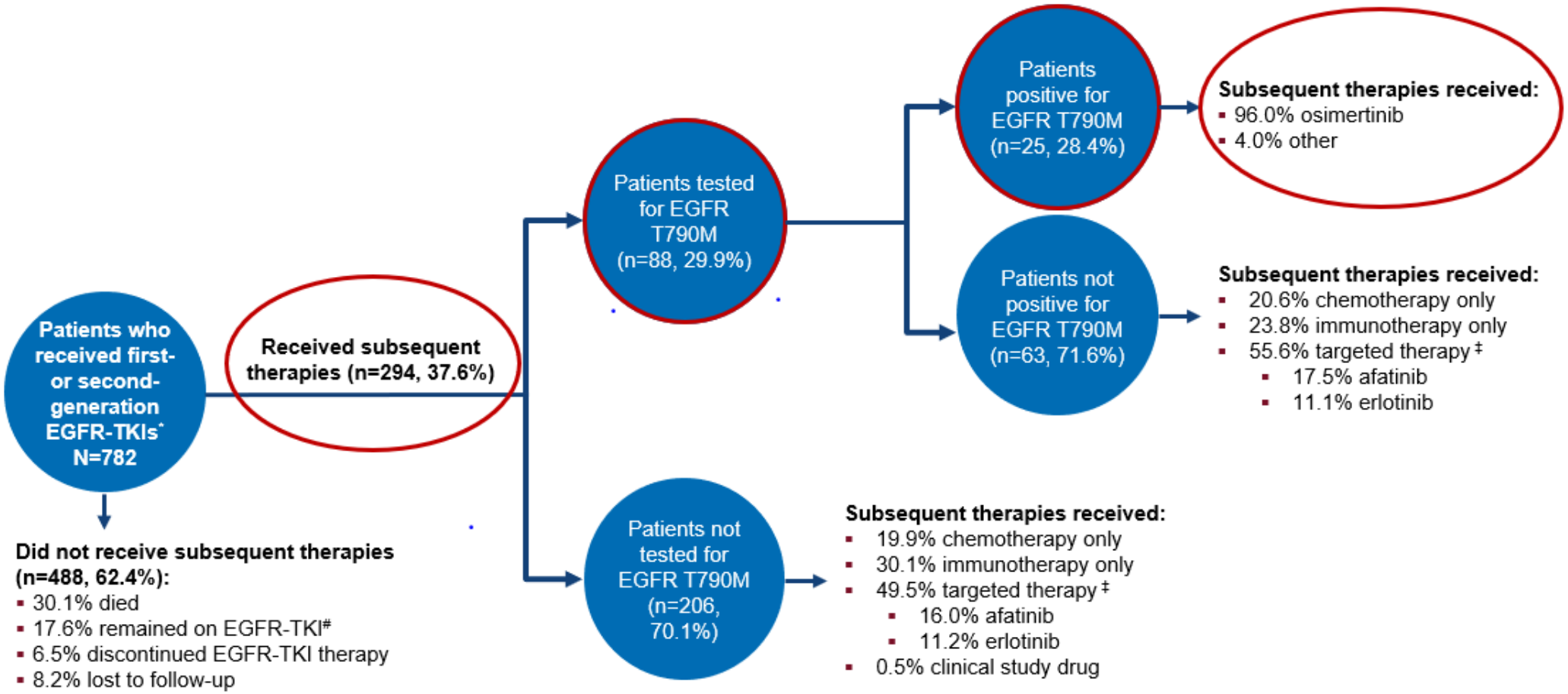
1. CNS efficacy
2. Impact on subsequent therapies
3. Mechanism of resistance
4. Patients willing

In clinical trials 2/3 receive post-TKI therapy and 1/3 osimertinib



	IPASS[1] n=132	IFUM[2] N=106	NEJ002[3] N=114	WJTOG[4] 3405 N=86	EURTAC[5] N=86	OPTIMAL[6] N=82	ENSURE[6] N=110	CTONG0901[8] N=128 N=128		LL3[9] N=230	LL6[9] N=242	LL7[9] N=160 N=159	
TKI	Gefitinib	Gefitinib	Gefitinib	Gefitinib	Erlotinib	Erlotinib	Erlotinib	Gefitinib	Erlotinib	Afatinib	Afatinib	Afatinib	Gefitinib
OS, months	21.6	19.2	27.7	34.8	19.3	22.8	26.3	20.1	22.9	28.2	23.1	27.9	24.5
Post-TKI treatment*	76%	49%	72%	88%	68%	63%	66%	55%	51%	71%	57%	73%	77%

Subsequent therapies received among patients tested for EGFR T790M

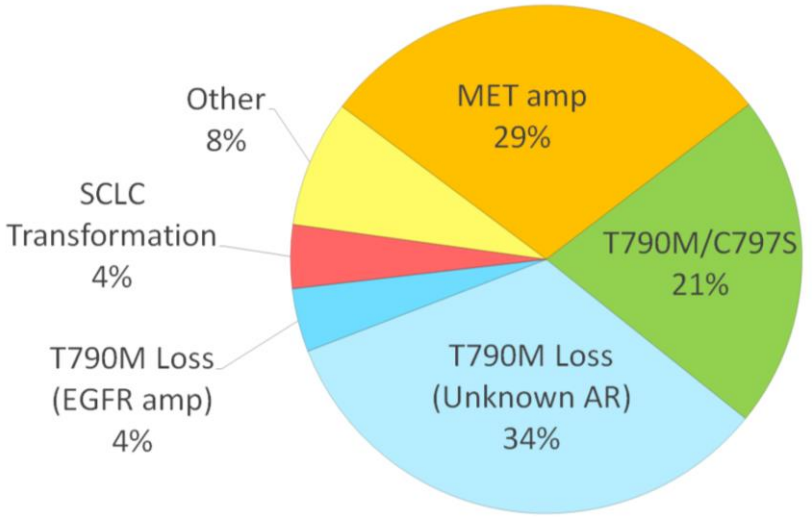


Chiang AC, WCLC 2018

Resistance mechanisms post ≥second-line osimertinib

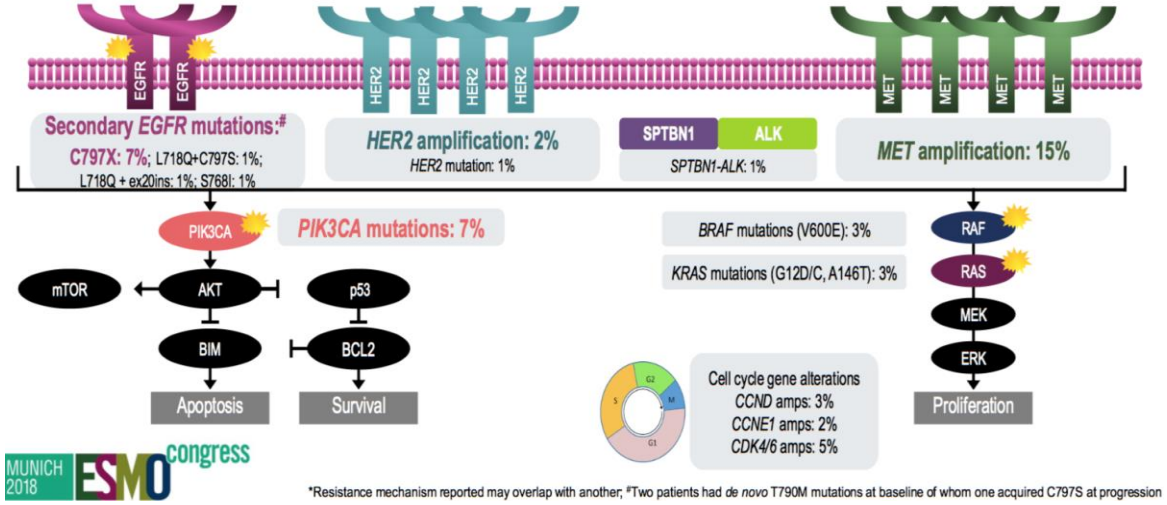
Pt	EGFR mutation	# Prior Therapies	Prior 3rd gen TKI	TISSUE (NGS, FISH)	PLASMA ctDNA (NGS)
1	L858R	1		*MET* amp, T790 wt	*MET* amp, T790 wt
2	Del19	1		-	T790 wt
3	Del19	2	Y	-	T790 wt
4	L858R (de novo T790M)	2	Y	*MET* amp, *EGFR* amp T790M (germline)	-
5	L858R	3	Y	T790wt, *EGFR* amp	T790 wt
6	L858R	4	Y	T790 wt	T790 wt
7	Del19	3	Y	-	T790 wt
8*	Del19	3		T790M/C797S	T790M/C797S
9	L858R	4	Y	T790 wt	-
10	Del19	3	Y	-	*PIK3CA* E545K, *PIK3CA* amp, T790 wt
11	Del19	2	Y	*MET* amp, *EGFR* amp, T790 wt	T790 wt
12	Del19	2	Y	-	T790M/C797S
13	Del19	9		T790 wt	-
14	Del19	2	Y	T790 wt	T790 wt
15	Del19	1		T790 wt	*FGFR1* D60N, *FGFR1* amp, T790 wt
16	L858R	2		*MET* amp, T790 wt	*MET, EGFR* amp, T790 wt
17	L858R	3	Y	T790 wt	T790 wt
18	Del19 (de novo T790M)	3		SCLC, T790 wt	T790 wt, *EGFR* amp
19	Del19	3	Y	T790 wt	T790M/C797S, *MET* amp, *EGFR* amp
20	L858R	2		*MET* amp, *EGFR* amp, T790 wt	-
21	L858R	3		-	T790M/C797S, *EGFR* amp
22*	L858R	1		MET amp, T790M wt	-
23	Del19	4	Y	-	T790M/C797S

- **Loss of T790M (42-68%) frequently occurs with a range of competing resistance mechanisms**
- **Most common resistance mechanisms are EGFR C797S and *MET* amplification**
- **Other mechanisms including, but not limited to:**
  - ✓ **Rare acquired *EGFR* mutations other than C797S**
  - ✓ **Amplifications in *EGFR, HER2, KRAS, PIK3CA***



Le et al. Clin Cancer Res 2018 [ePub]
Lin, et al. Lancet Respir Med 2018
Oxnard et al. JAMA Oncol 2018 [ePub]
Piotrowska et al. J Clin Oncol 2017;35:(Suppl) abs 9020
Yang et al. Clin Cancer Res 2018;24:3097–107

Resistance mechanisms to Osimertininb in *EGFR* + NSCLC from the FLAURA study [91 patients]



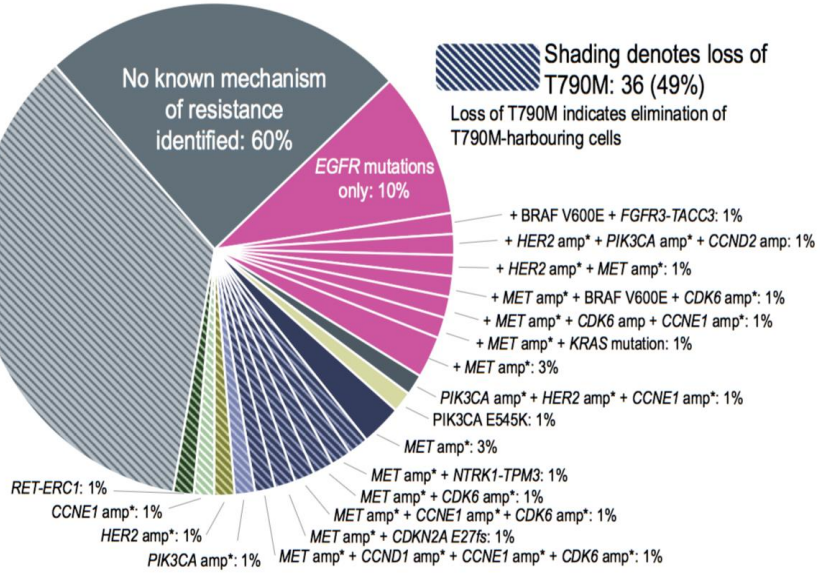
*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

Ramalingam S S et al, ESMO 2018

Resistance mechanisms to Osimertininb in *EGFR* T790M + NSCLC from the AURA 3 study [73 patients]

Summary

- Acquired *EGFR* mutations: 21%
- *MET* amp*: 19%
- Cell cycle gene alterations: 12%
- *HER2* amp*: 5%
- *PIK3CA* amp* / mutation: 5%
- Oncogenic fusion: 4%
- BRAF V600E: 3%



Papadimitrakopoulou V et al, ESMO 2018

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were MET ampl (15%) and EGFR C797S mut (7%)
- Other mechanisms included HER2 amplification, PIK3CA and RAS mutations

C797X 15% [always in cis position when co-occurring with T790M]

Loss of T790M was associated with a slightly shorter median PFS

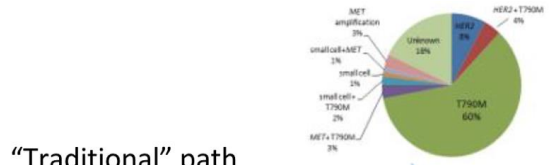
- ✓ T790M lost: 5.54 mo (95% CI 4.14, 9.69)
- ✓ T790M retained: 7.06 mo (95% CI 5.62, 10.97)

Overlapping targetable alterations in 19% of patients, which may influence subsequent treatments

Paths to acquired resistance: convergent or divergent?

Osimertinib resistance

	FLAURA	AURA3	Le *et al.*	Piotrowska *et al.*
N	91	83	42	41
% T790M loss	(N/A)	49	50	63
Acquired changes (%)				
EGFR mut	9	17	26	24
MET amp	15	19	15	19
HER2 amp	2	5	2	5
PIK3CA mut	7	1	5	12
BRAF mut	3	3		
KRAS mut	3		2	
Fusions	1	3	5	10
SCLC/SqCC			5	7
Other	60	52	40	23



"Traditional" path

1st/2nd gen EGFR TKI → Osimertinib

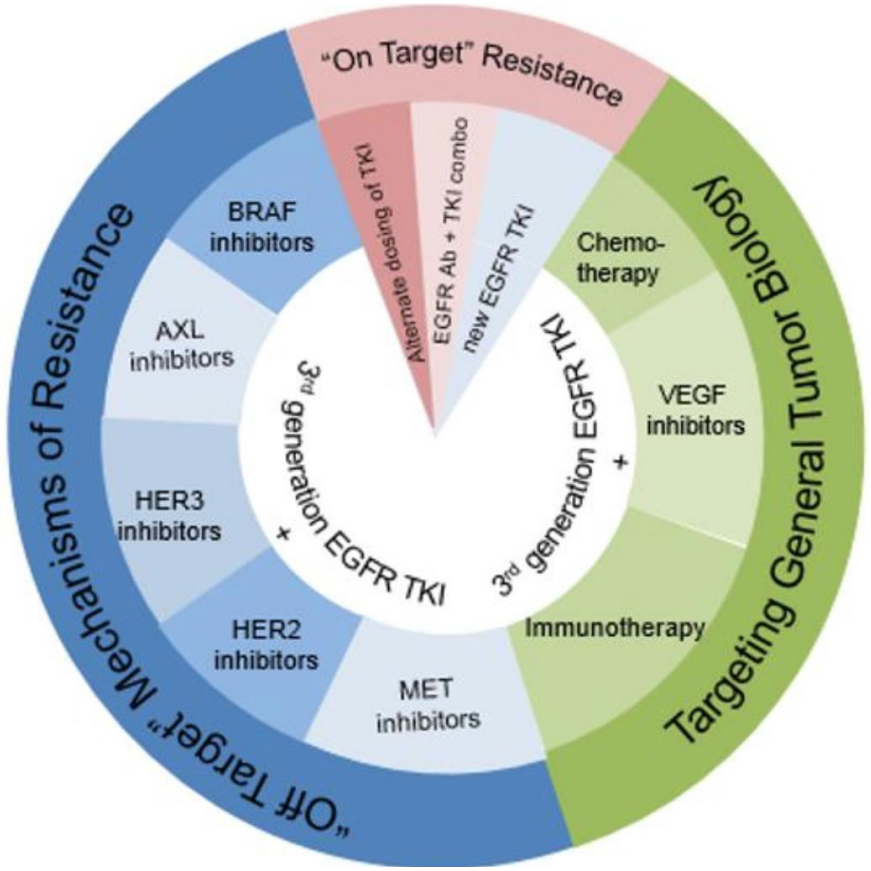
New path

Osimertinib

Do we end up in the same place?

Le et al, Clin Cancer Res 2018

How to avoid or treat acquired resistance?

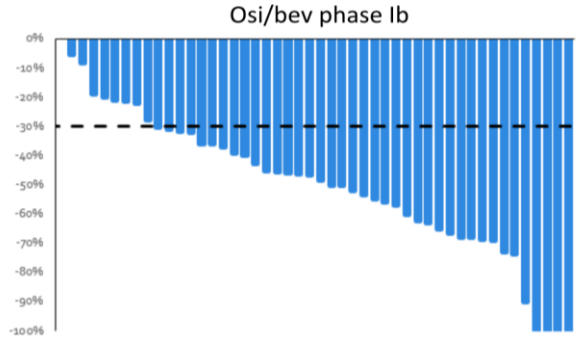


Arbour and Riely, Cancer 2018

Rudin CM, ESMO Munich 2018

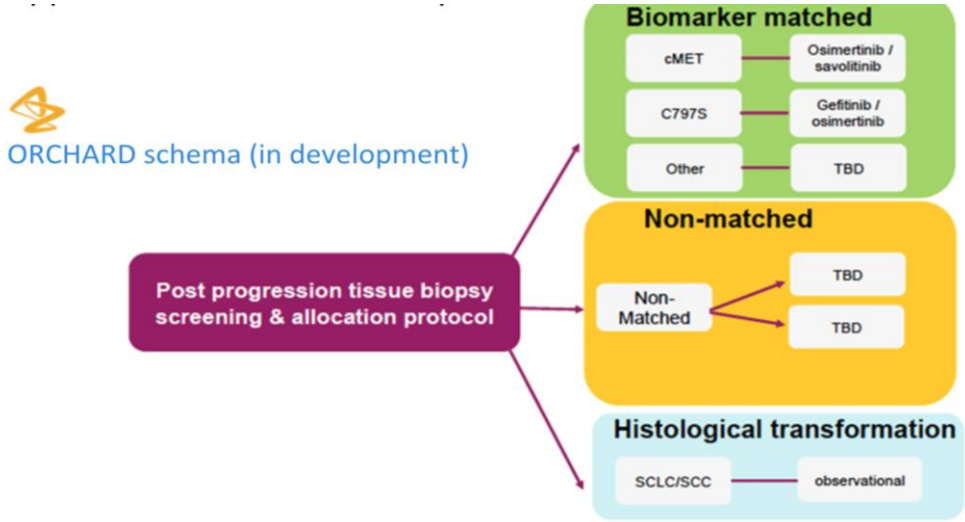
1. Combination Upfront

- with gefitinib
- with dacomitinib
- with bevacizumab
- with dasatinib
- with selumetinib
- with…



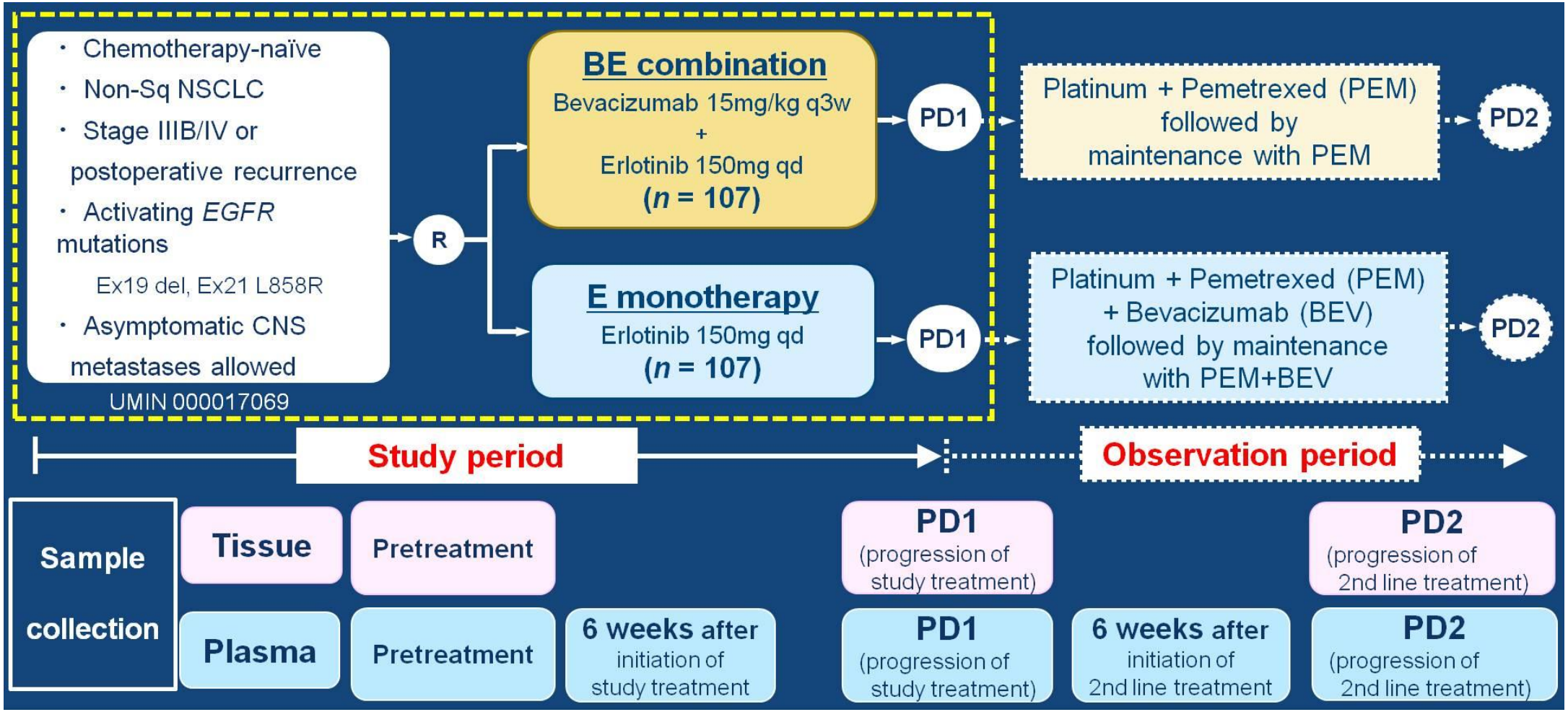
31 ongoing on treatment
Reasonable toxicity profile
No CNS progression (mandated interval MRIs)
Pre/post treatment biopsies, serial plasma
Primary endpoint not yet evaluable (April 2019)

2. Divide and hit at PD



NEJ 026 study design

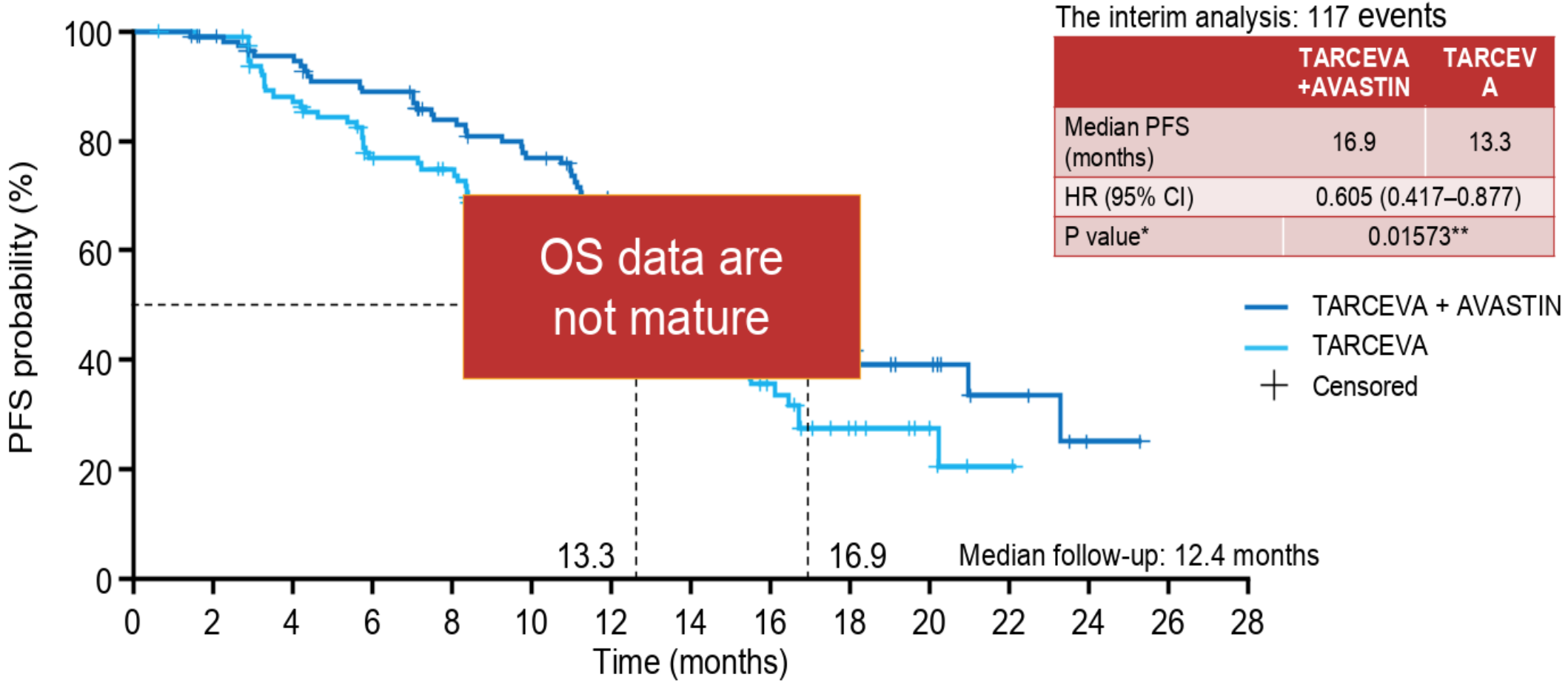
Phase III study comparing erlotinib+bevacizumab versus erlotinib in *EGFR*$^{mut+}$



Primary end point: PFS

Furuya N et al ASCO 2018

PFS by independent review



The interim analysis: 117 events

	TARCEVA +AVASTIN	TARCEVA
Median PFS (months)	16.9	13.3
HR (95% CI)	0.605 (0.417–0.877)	
P value*	0.01573**	

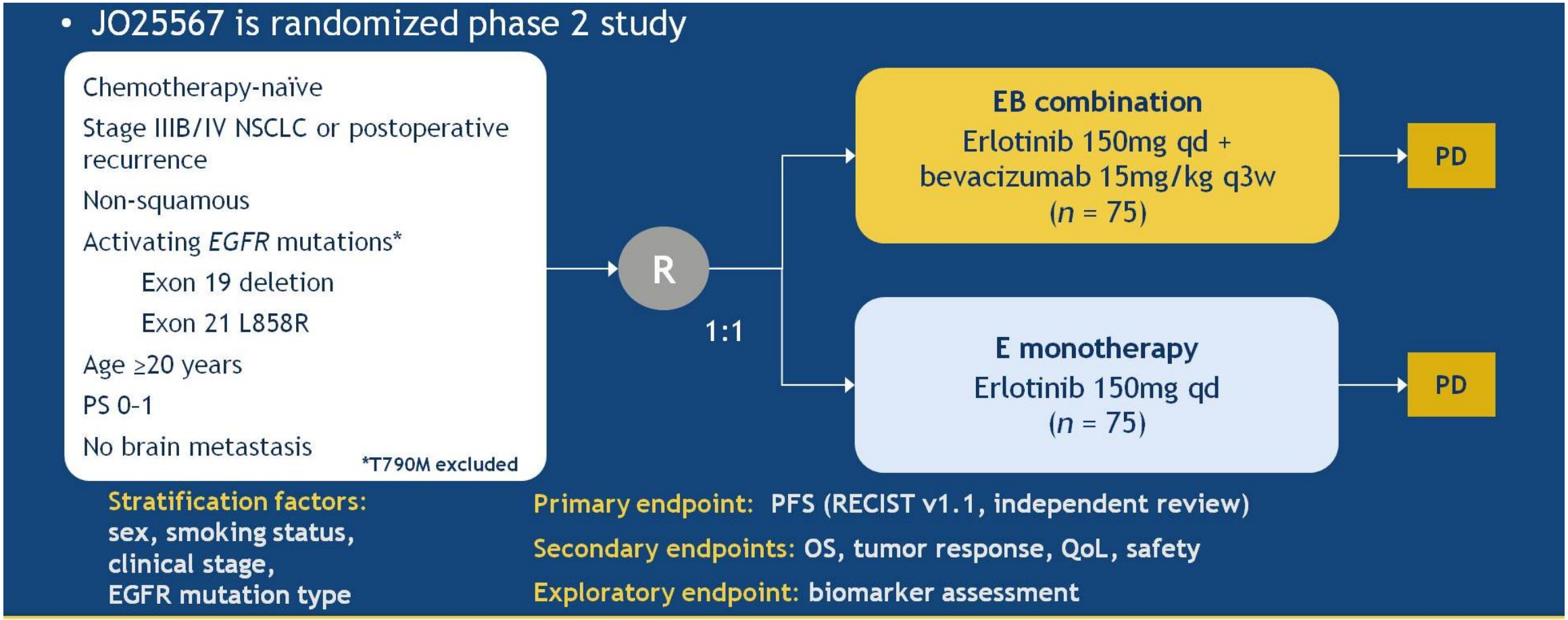
Furuya N et al ASCO 2018

Beva i.v infusion and toxicity as main limitation

	BE (n=112)	E (n=114)
Grade ≧ 3 AEs	63 (56.3%)	43 (37.7%)
Serious AEs	9 (8.0%)	5 (4.4%)
Death due to AE	0	0

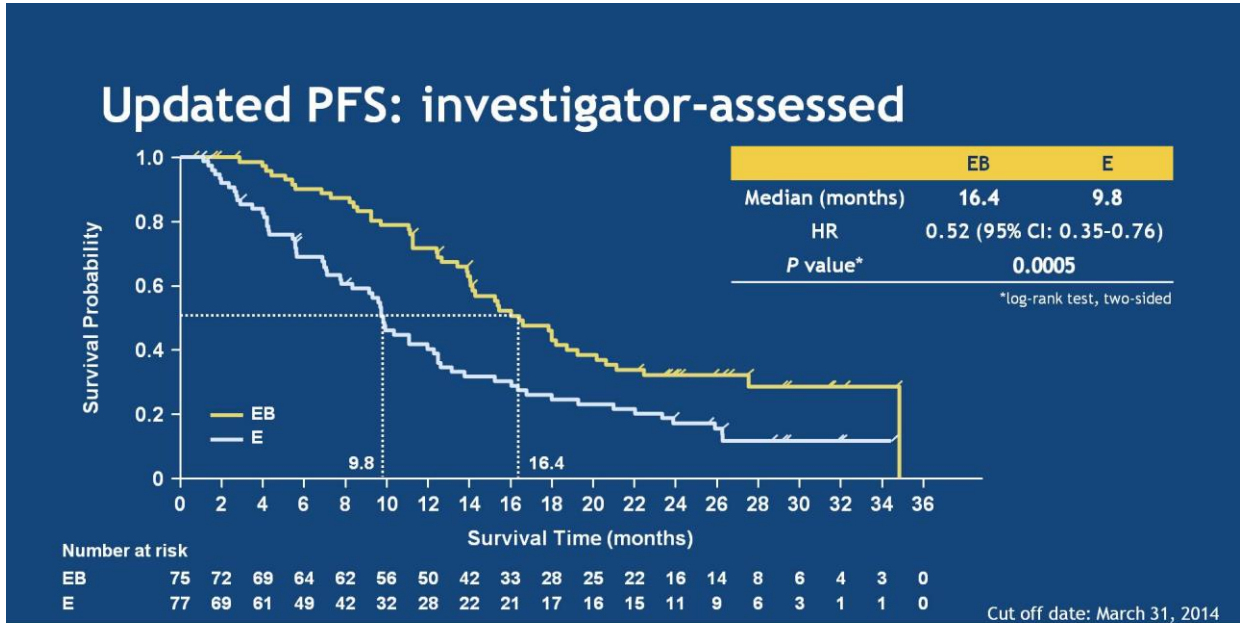
Furuya N et al ASCO 2018

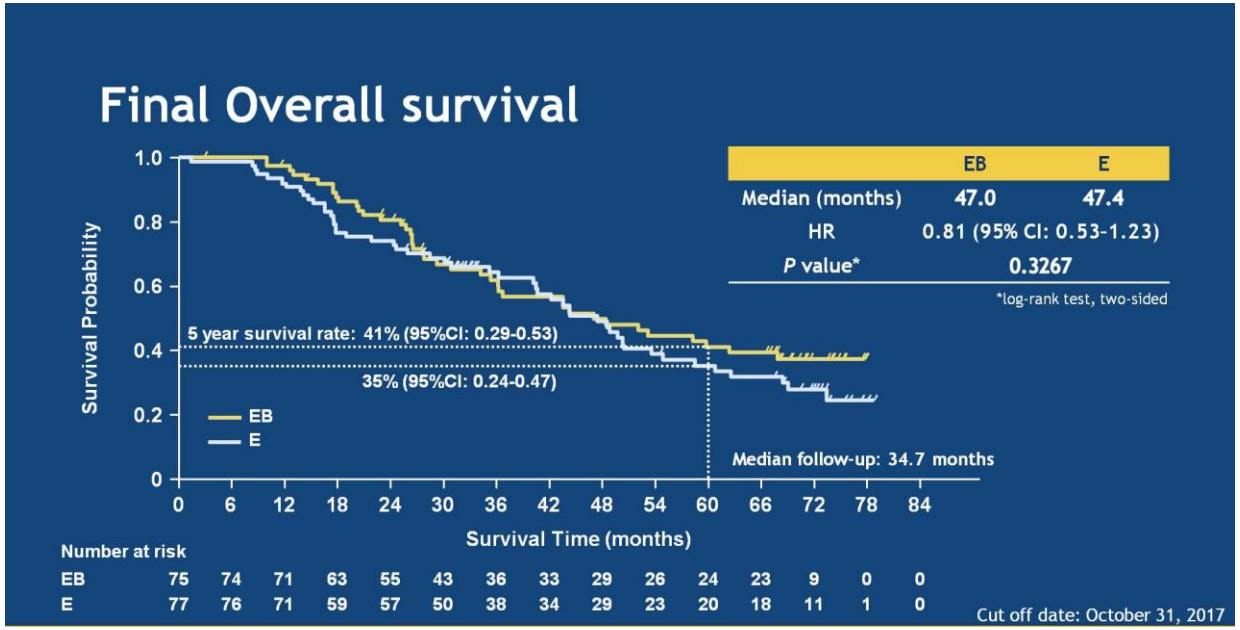
JO 25567 study design



Yamamoto N et al ASCO 2018

PFS and OS

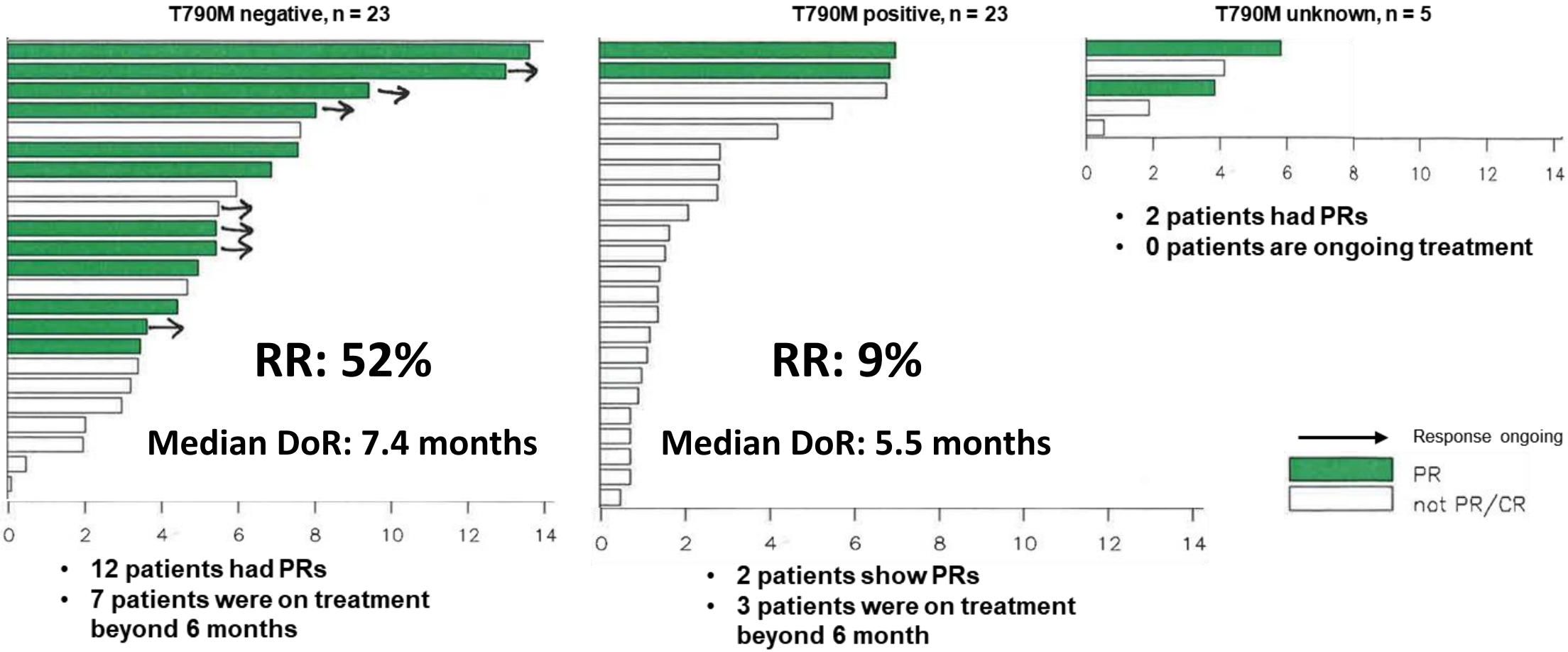




Yamamoto N et al ASCO 2018

Inhibiting MET in patients with acquired resistance to EGFR-TKIs

Results from a phase 1b study of savolitinib+gefitinib in NSCLC resistant to EGFR-TKIs with *MET* amplification



Data cut-off 21 August 2017; Data are preliminary and undergoing review
EGFRm, EGFR mutation

NCT02374645

Yang JJ, IASLC 2017

Sequence matters

Key factors that may impact OS/QoL:

1. CNS efficacy
2. Impact on subsequent therapies
3. Mechanism of resistance
4. Patients willing

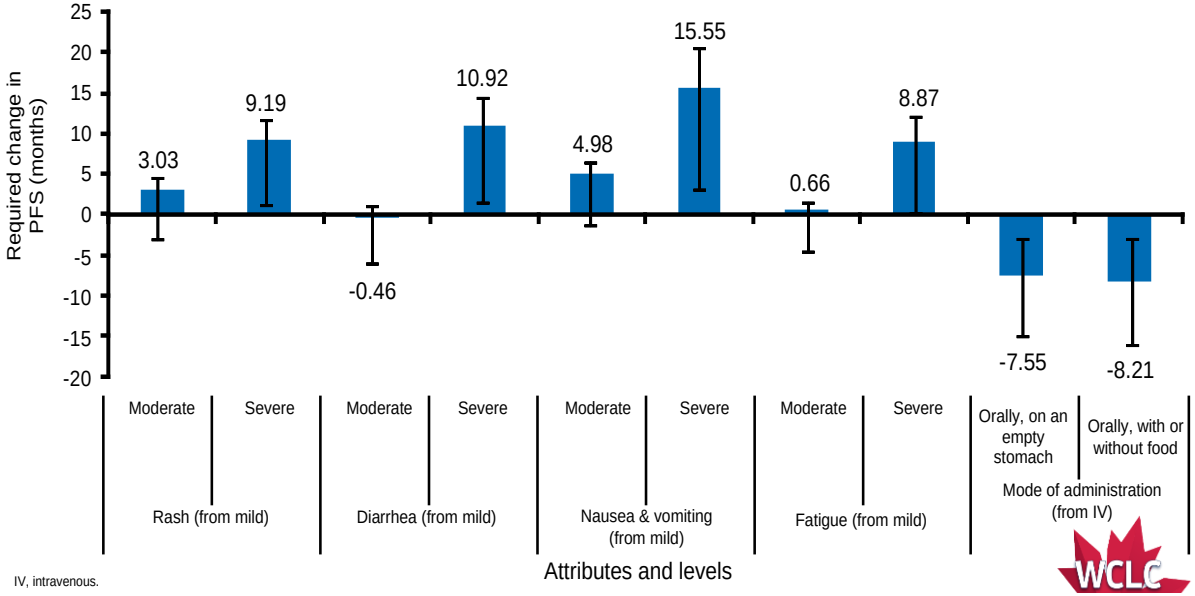
OA10.01 - Patient Preferences for TKI Treatments for EGFR + Metastatic NSCLC

Patients are split in terms of preferences between efficacy and side effects, but were generally less likely to take on significant side effects for smaller improvement in PFS.

Patient had a clear hierarchy for least desirable side effects:

1. Severe nausea/vomiting were least desirable (15.5mo)
2. Severe diarrhea (11mo)
3. Severe rash (9.2 mo)
4. Severe fatigue (8.9 mo)
5. Moderate N/V (5mo)
6. Moderate Rash (3mo)

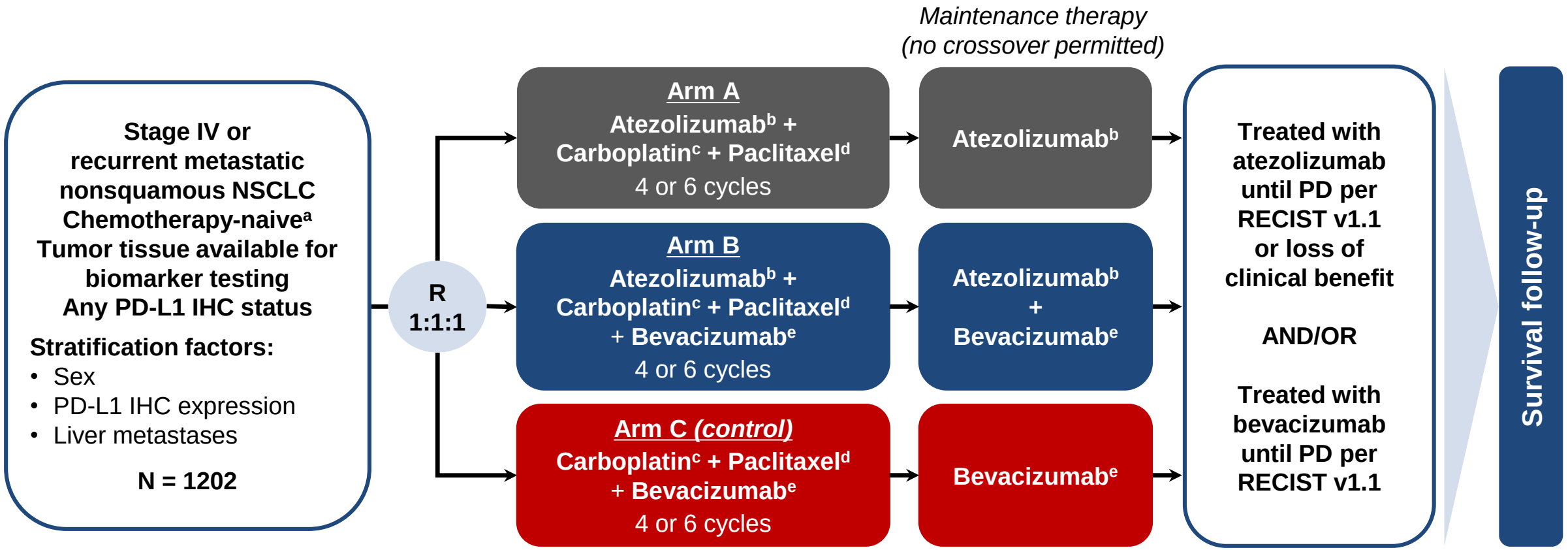
Results: discrete choice experiment



- **<u>Oncology is a team sport</u>**. Collaborations between patients, caregivers, clinicians, researchers, community and academic institutions, industry partners, patient advocacy groups and other stakeholders are essential to advancing oncology care and improving the lives of our patients.

John Bridges et al, ESMO Munich 2018

IMpower150 Study Design

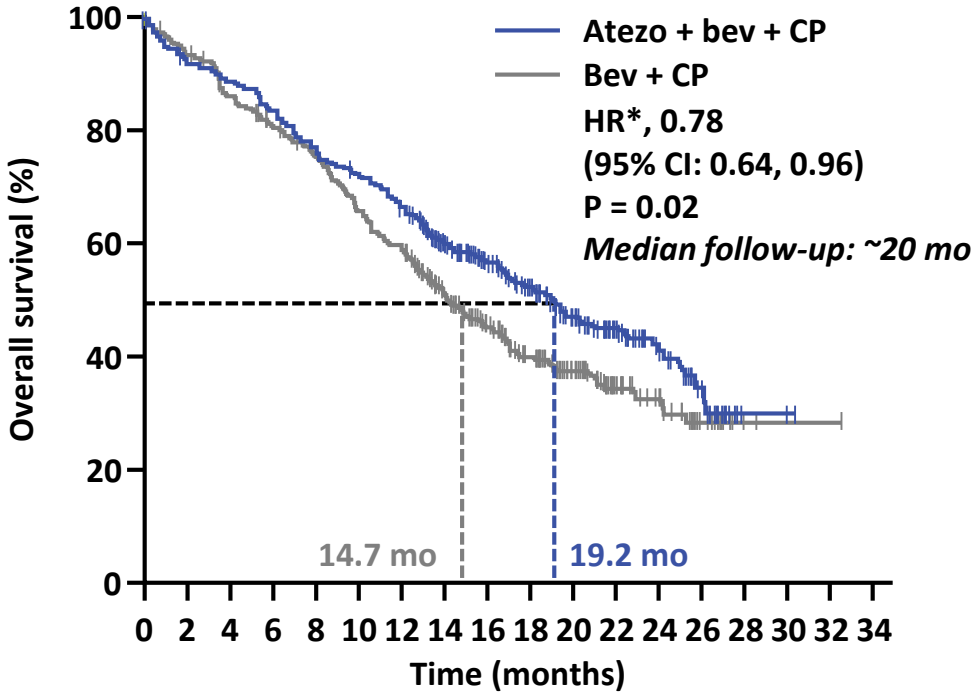


[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

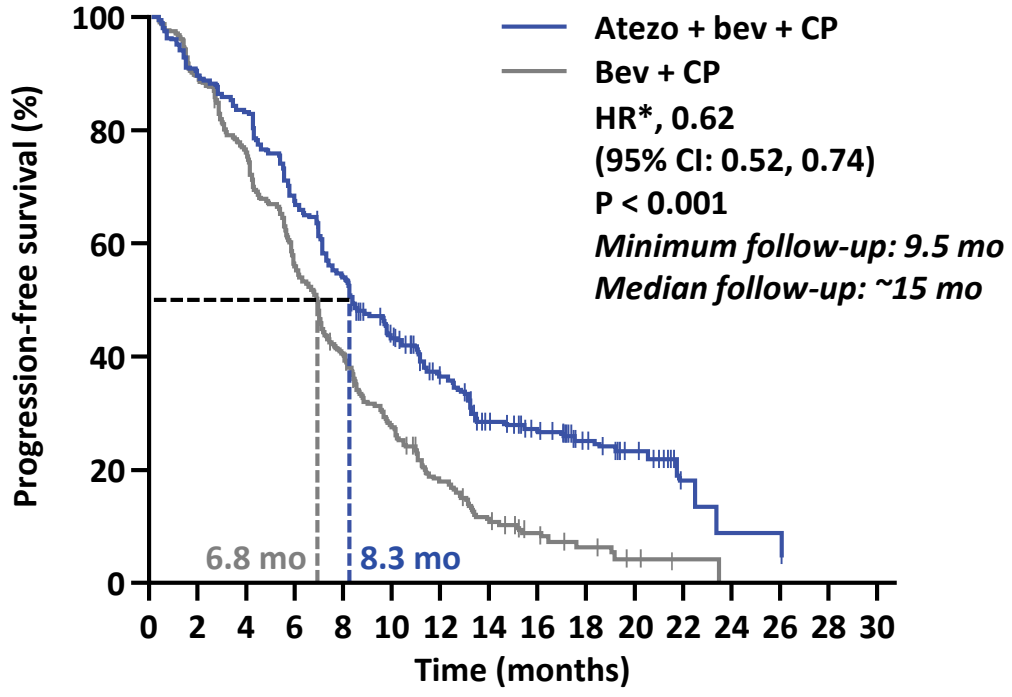
Socinski M et al. ASCO 2018

IMpower150 met its co-primary endpoints of OS and PFS in the ITT-WT population

OS



PFS



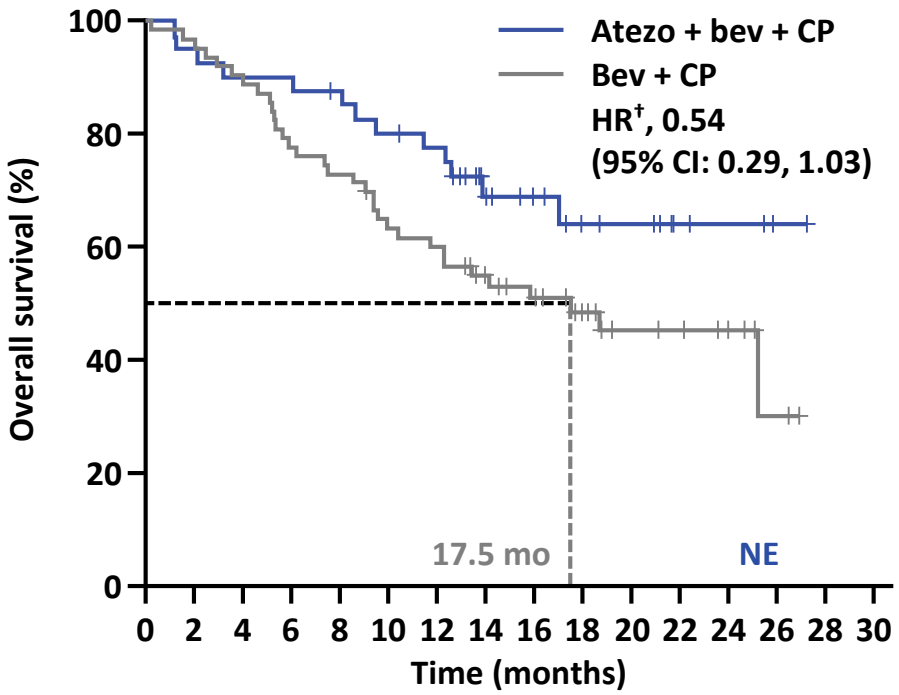
*Stratified HR

Data cut-off: 22 January 2018 (OS); 15 September 2017 (PFS)

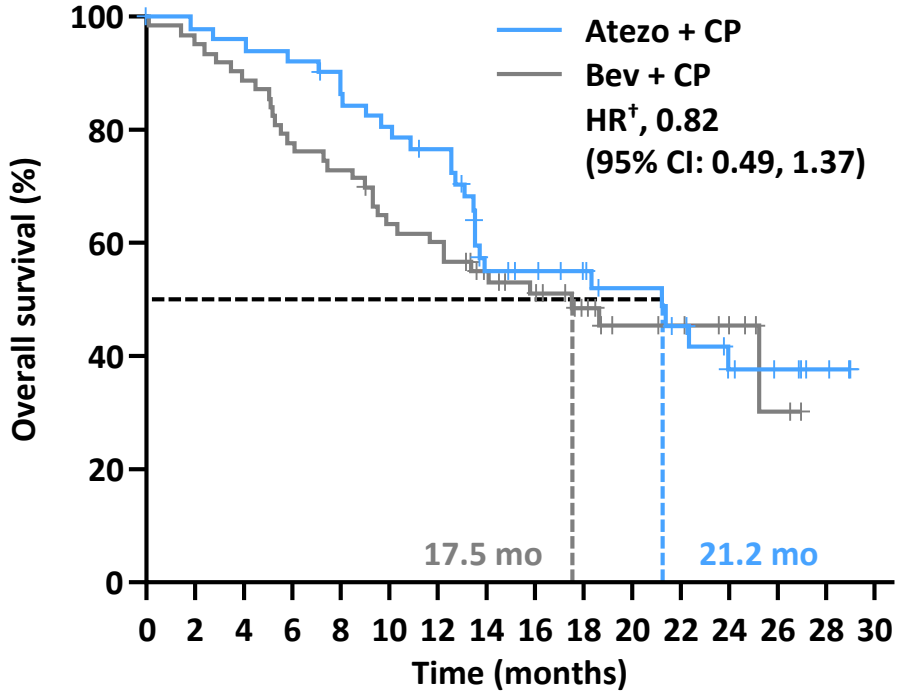
Socinski, et al. N Engl J Med 2018; Reck, et al. ESMO IO (Abs LBA1_PR)

Addition of bevacizumab to atezolizumab and chemotherapy prolongs survival of *EGFR/ALK*+ patients

Atezo + bev + CP* ***vs*** *Bev + CP*



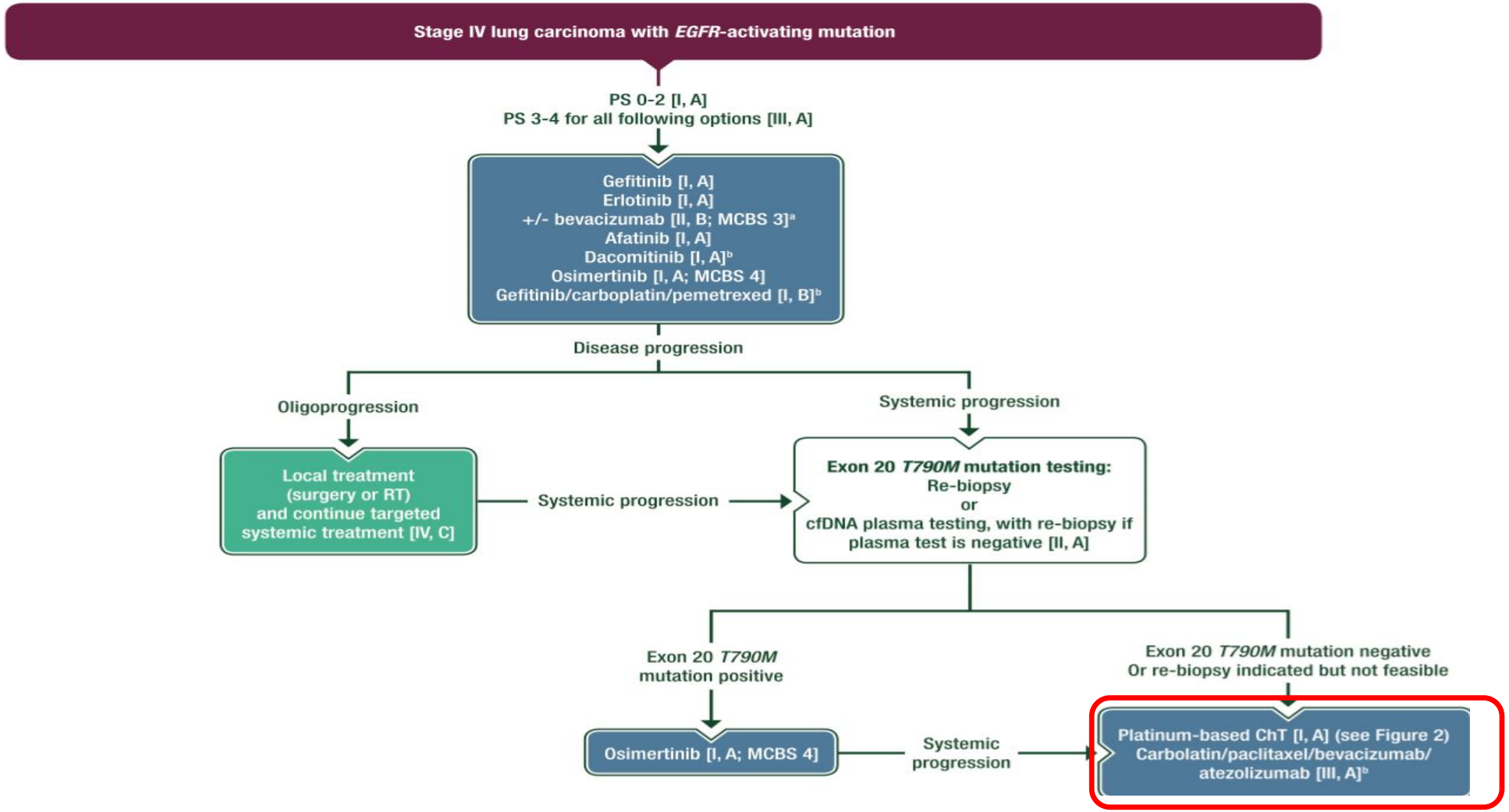
Atezo + CP ***vs*** *Bev + CP*



OS benefit in *EGFR/ALK*+ patients was observed despite lower PD-L1 expression in these patients

Socinski M et al. ASCO 2018

ESMO Guidelines 2018



Plachard D et al. Annals of Oncology 2018

My Visionary Oncology

Value of oncogene-driven patient groups

- They support patients and caregivers
- They increase awareness and education
- They accelerate research by
  - Grantmaking
  - Supporting clinical trial accrual
  - Creating more models of rare cancers for researchers

GROUP	FOCUS	STARTED	MBRS	CNTRY	EMAIL & WEBSITE
ROS1ders	ROS1+ cancer	May 2015	323	22+	ros1cancer.patient@gmail.com ros1cancer.com
ALK Positive	ALK+ NSCLC	Apr 2015	1210	41+	info@alkpositive.org www.alkpositive.org
Exon 20 Group	EGFR & HER2 Exon 20 insertions	Jun 2017	243	22	exon20@exon20group.org www.exon20group.org
EGFR Resisters	EGFR+ NSCLC plus cancers resistant to EGFR TKIs	Aug 2017	650	24	egfrresisters@gmail.com www.egfrcancer.org
RET Renegades	RET+ NSCLC	May 2018	43	2	retrenegades@gmail.com

Janet Freeman-Daily, The ROS1ders, USA, WCLC Toronto 2018