NSCLC overview

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INTRODUCTION

- The leading cause of cancer death around the world
- The most common cancer worldwide since 1985, both in terms of incidence and mortality
- Sugery (+CT ≥IB) is curative therapy in about 50% of early stagies (I-III)

however…

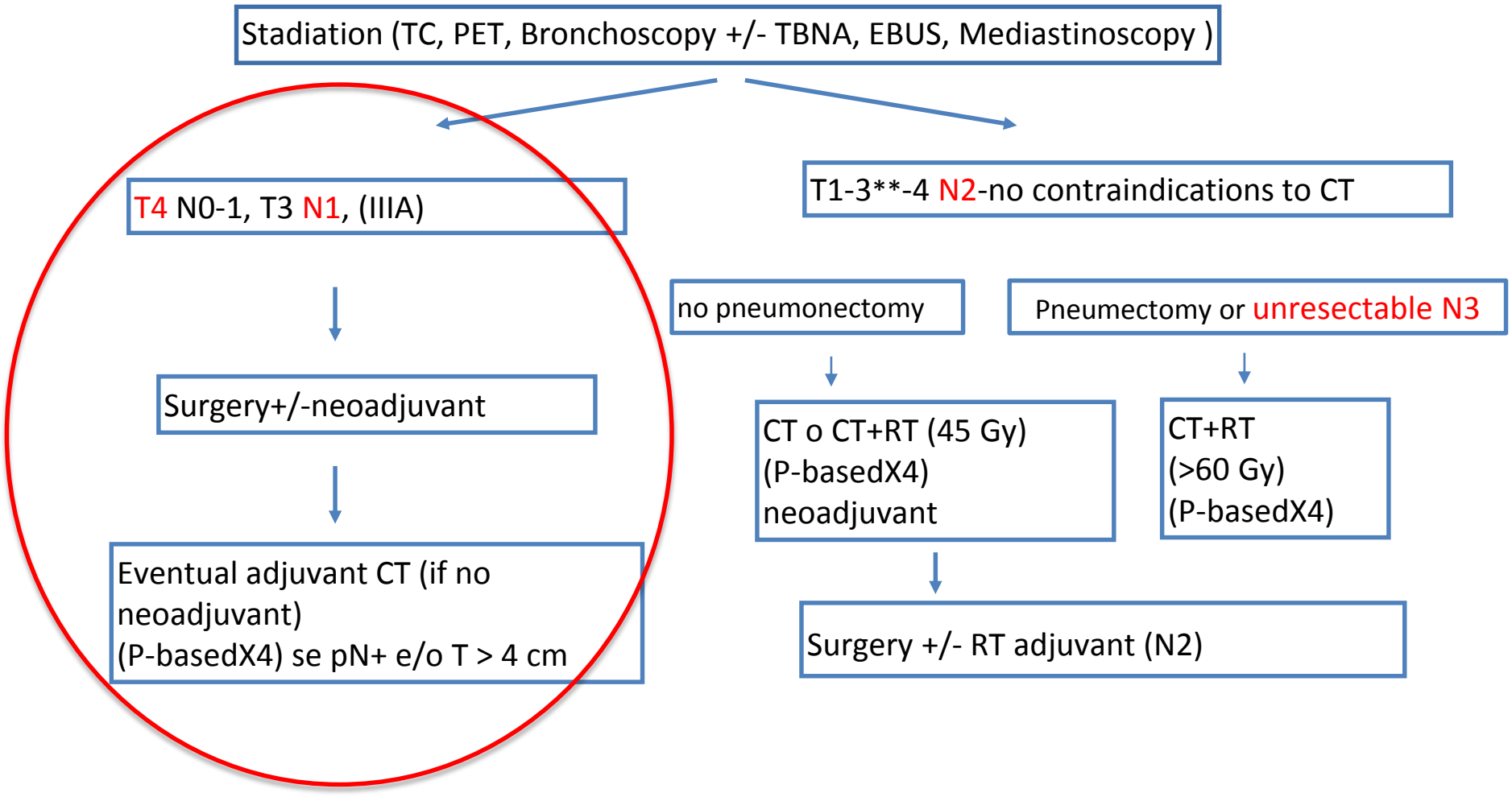
- 70 % advanced stage: mOS 12-13 mo

(until 1995 no treatment was available, OS 4 m)

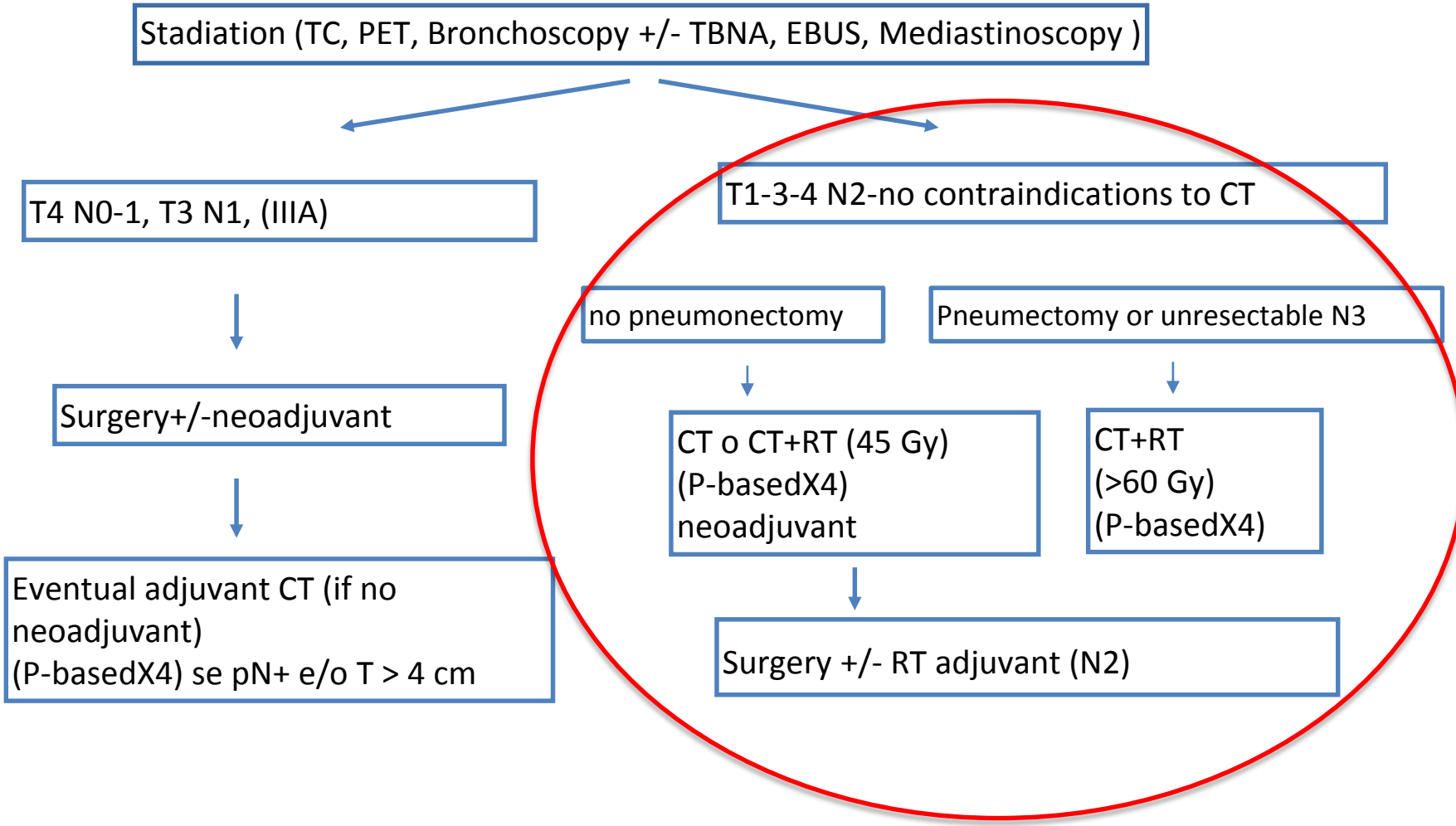
but…

  - 1/4 of lung cancer patients are non smokers; 50% of them are oncogene addicted: mOS 2y, RR 60-80%
  - 1/4 are PDL >50% and have different patient history if they receive immunotherapy

Stage III NSCLC therapeutic algorithm



Stage III NSCLC therapeutic algorithm

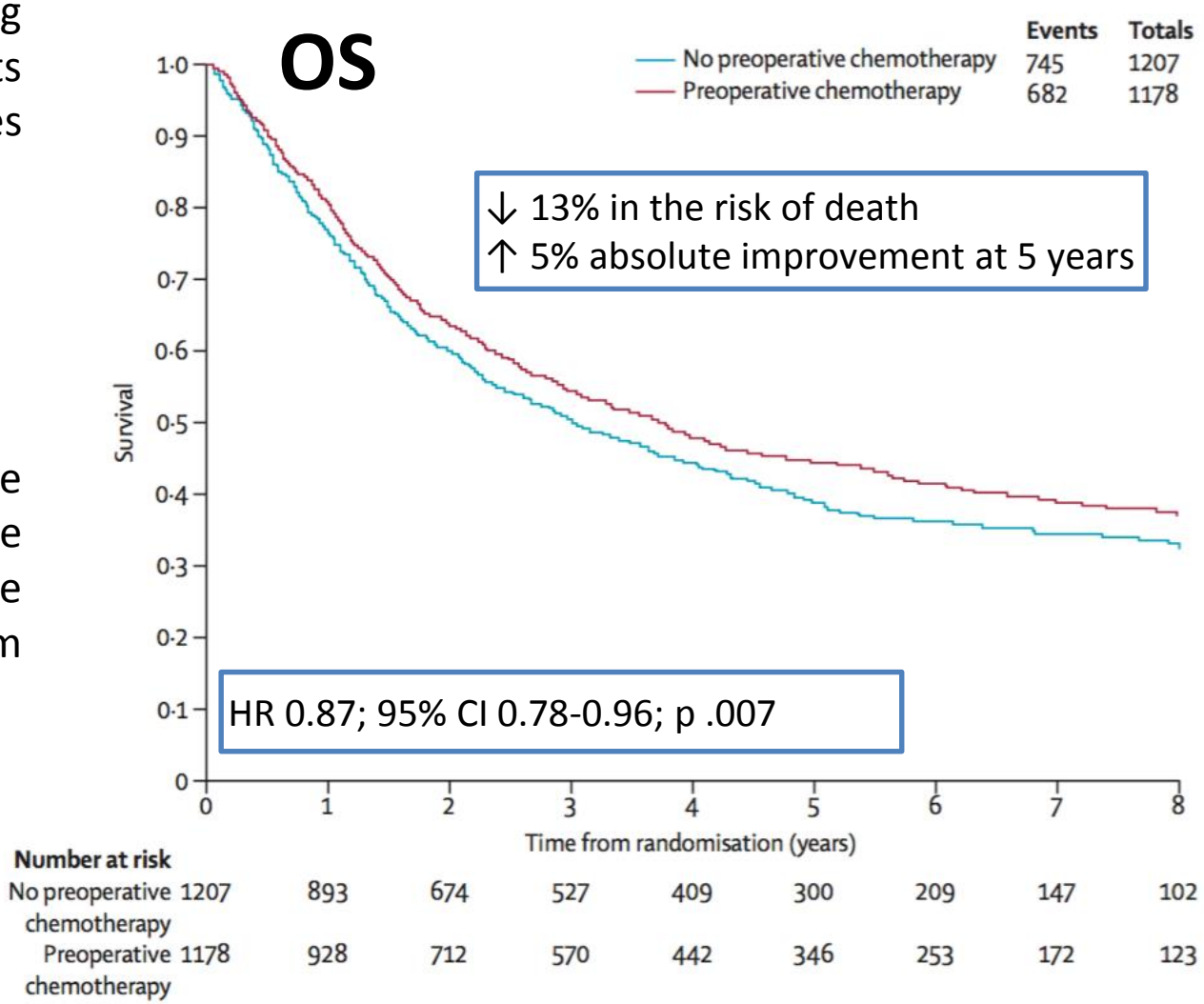


Neoadjuvant chemotherapy

- 15 randomized trials, including 2385 unresected patients without distant metastases (IIIA/IIIB)

- 10 trials evaluated preoperative chemotherapy only, 5 pre operative and post operative chemotherapy, 14 platinum based chemotherapy

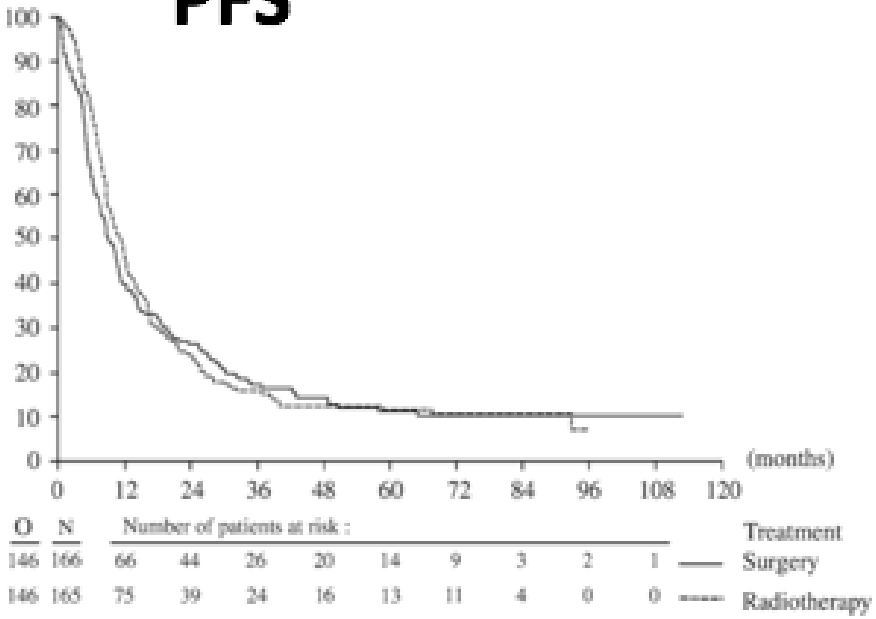
- Median 3 cycles



NSCLC Meta-analysis collaborative group ; Lancet; 2014

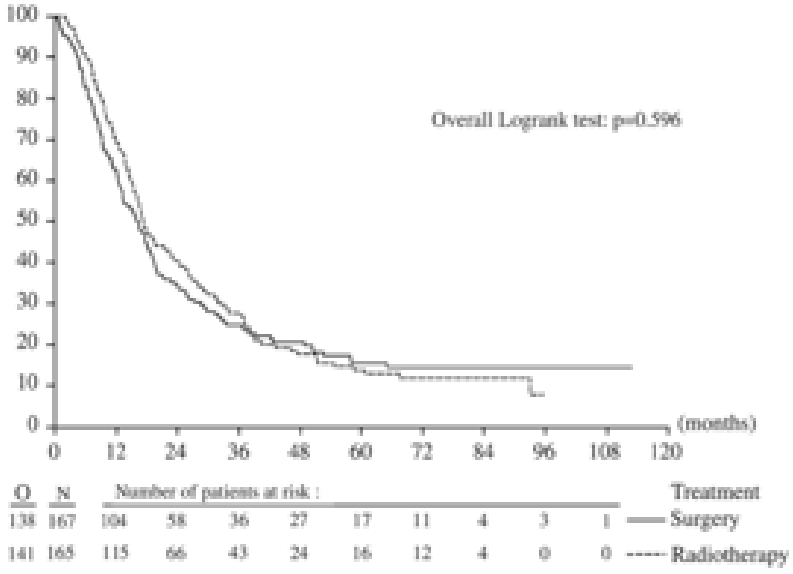
Surgery does not improve survival after a radiologic response to induction chemotherapy

PFS



Radiotherapy vs Surgery
11.3 vs 9 months
HR 1.06 (95% CI 0.85-1.33) p 0.6

OS

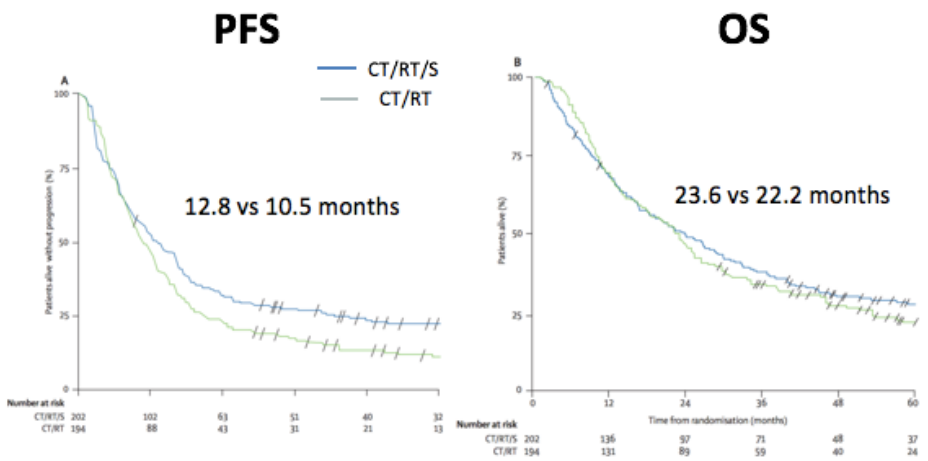


Radiotherapy vs Surgery
17.5 vs 16.4 months
HR 1.06 (95% CI 0.84-1.35) p 0.6

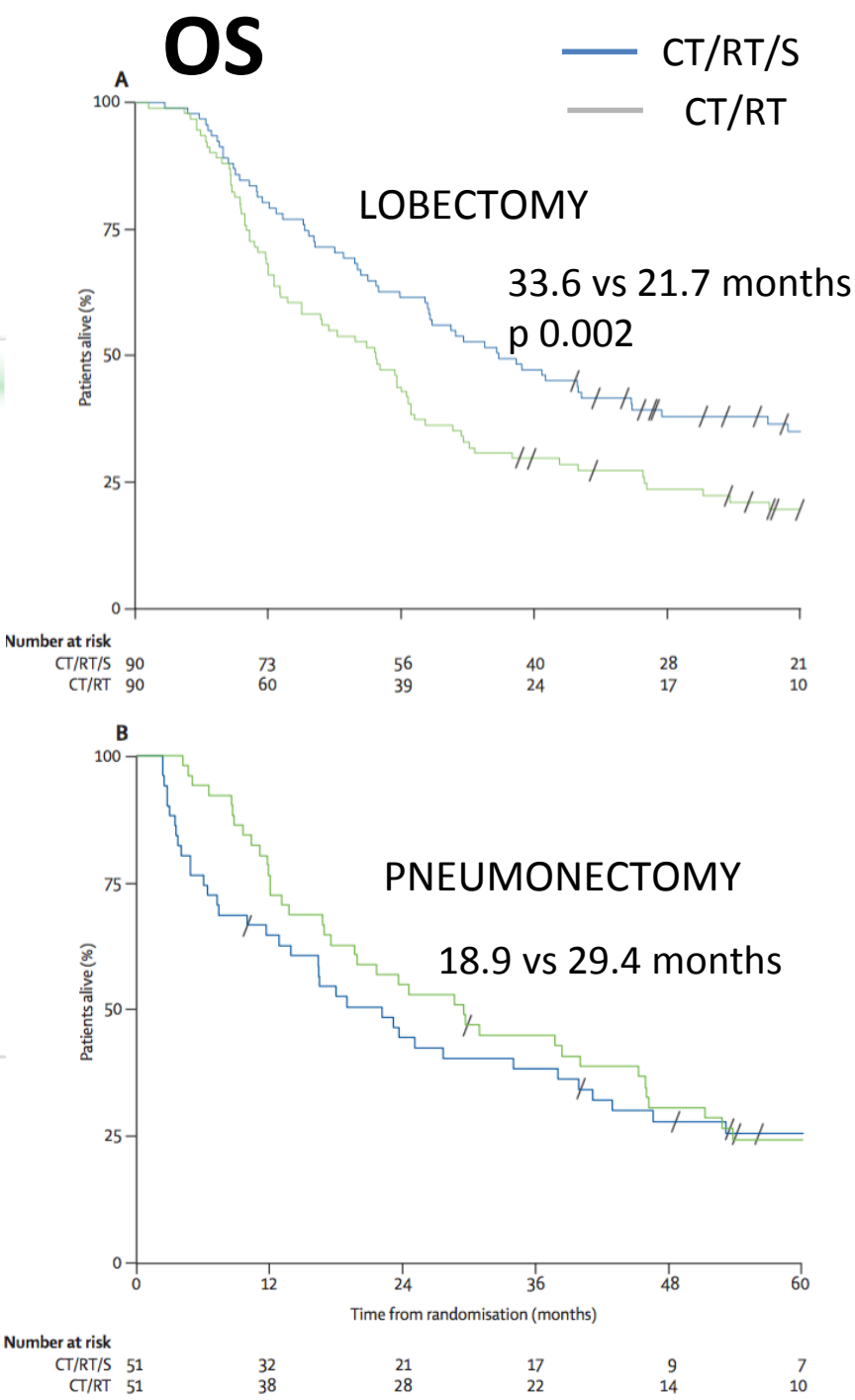
van Meerbeek et al; JNCI; 2007

Surgery after CT-RT if lobectomy only!

Improved PFS, no difference in OS



Albain et al; Lancet; 2009

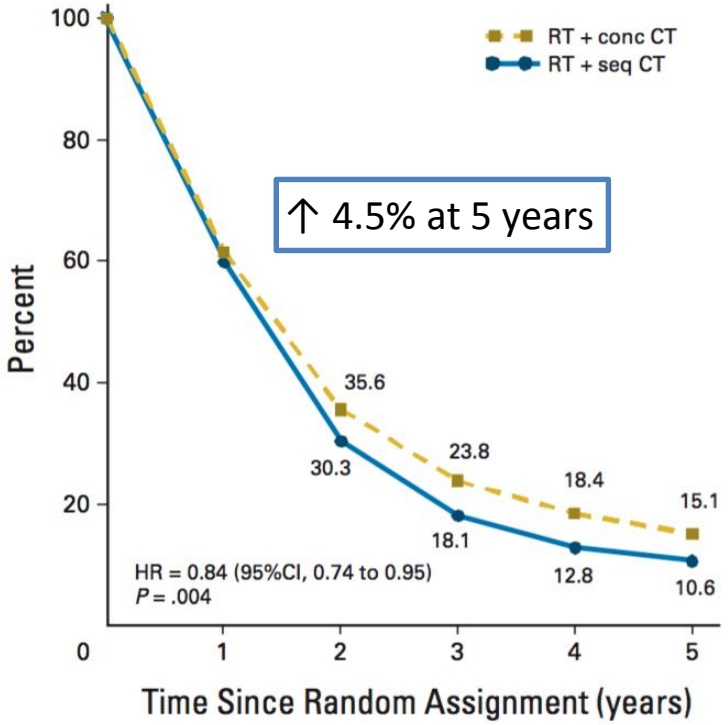


Concurrent chemo-radioterapy is the standard of care for locally advanced unresectable NSCLC

6 randomized trials, including 1205 unresected patients without distant metastases (IIIA/IIIB)

Enrollment period: 1990-2003

OS

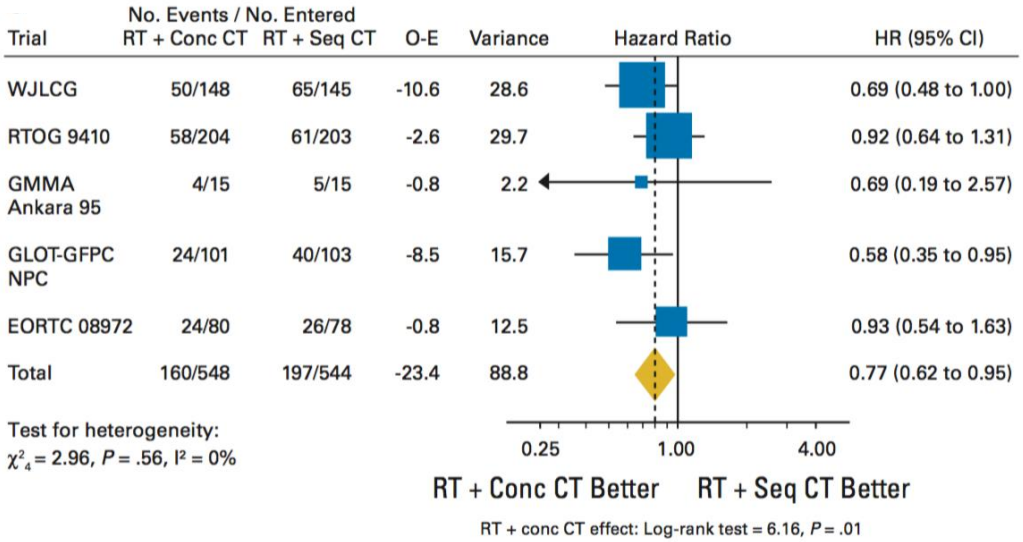


↑ 4.5% at 5 years

Deaths/Person-Years by Period

	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 603)	240/498	147/276	67/171	30/116	37/186
RT+ seq CT (n = 602)	253/491	171/242	70/129	30/ 83	23/126

Local recurrence



HR 0.77; 95% CI 0.62-0.95; p 0.01

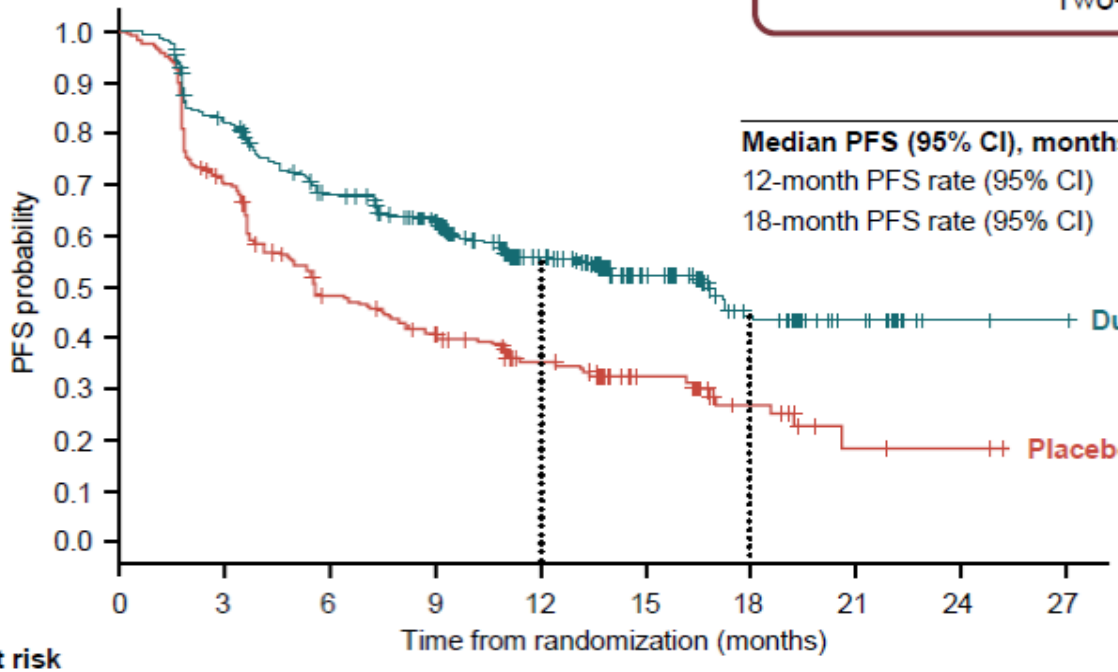
Auperin et al; JCO; 2010

Immune checkpoint inhibitors after concurrent chemoradiotherapy: PACIFIC

PFS

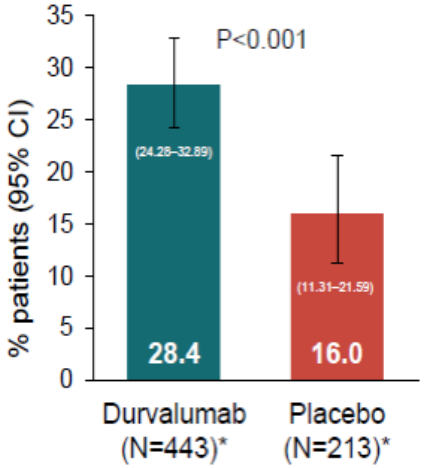
Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65)
Two-sided P<0.0001

	Durvalumab (N=476)	Placebo (N=237)
Median PFS (95% CI), months	**16.8 (13.0–18.1)**	**5.6 (4.6–7.8)**
12-month PFS rate (95% CI)	55.9% (51.0–60.4)	35.3% (29.0–41.7)
18-month PFS rate (95% CI)	44.2% (37.7–50.5)	27.0% (19.9–34.5)



No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

Objective Response



Treatment effect (RR [95% CI])¶:
1.78 (1.27–2.51)

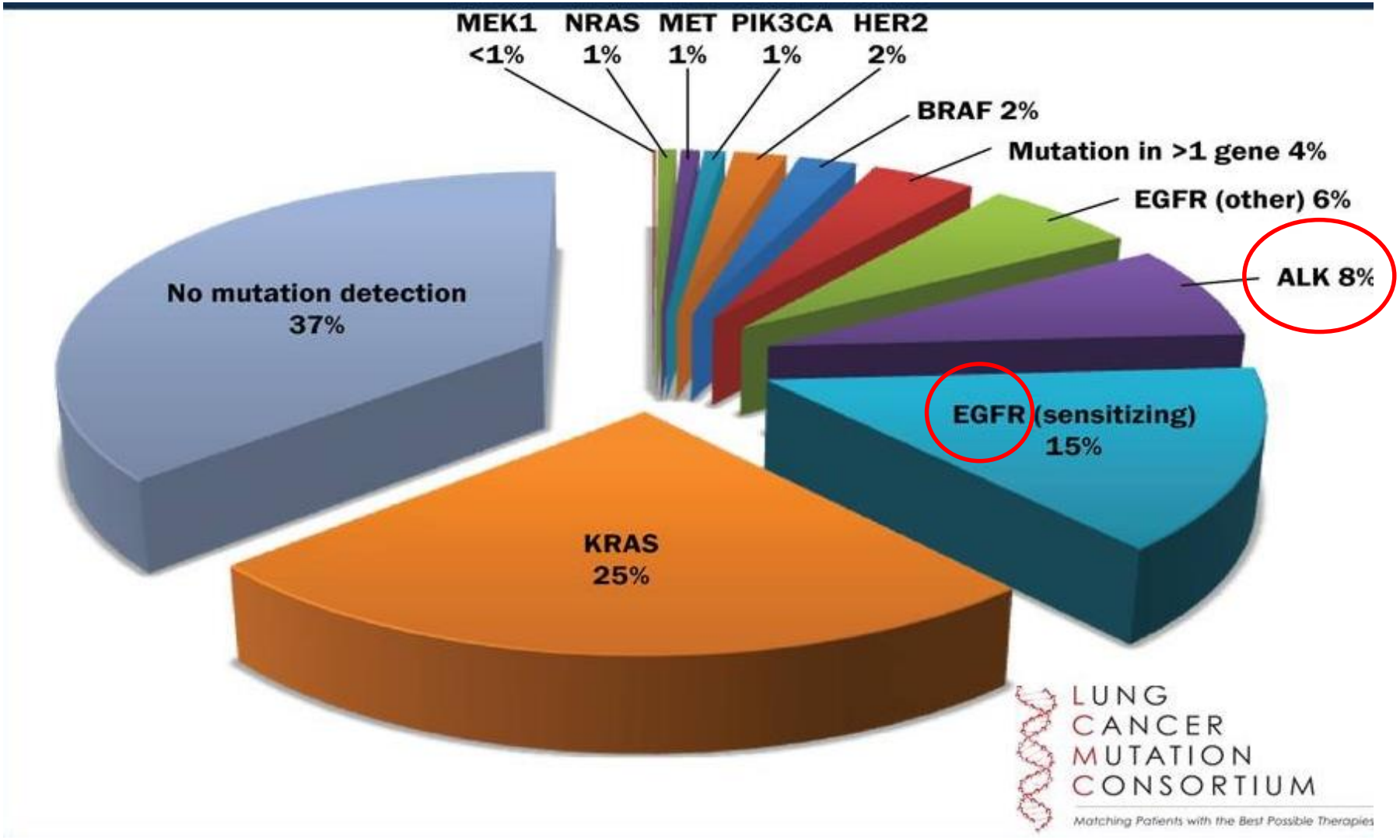
Paz Ares et al; ESMO; 2017

Original Investigation

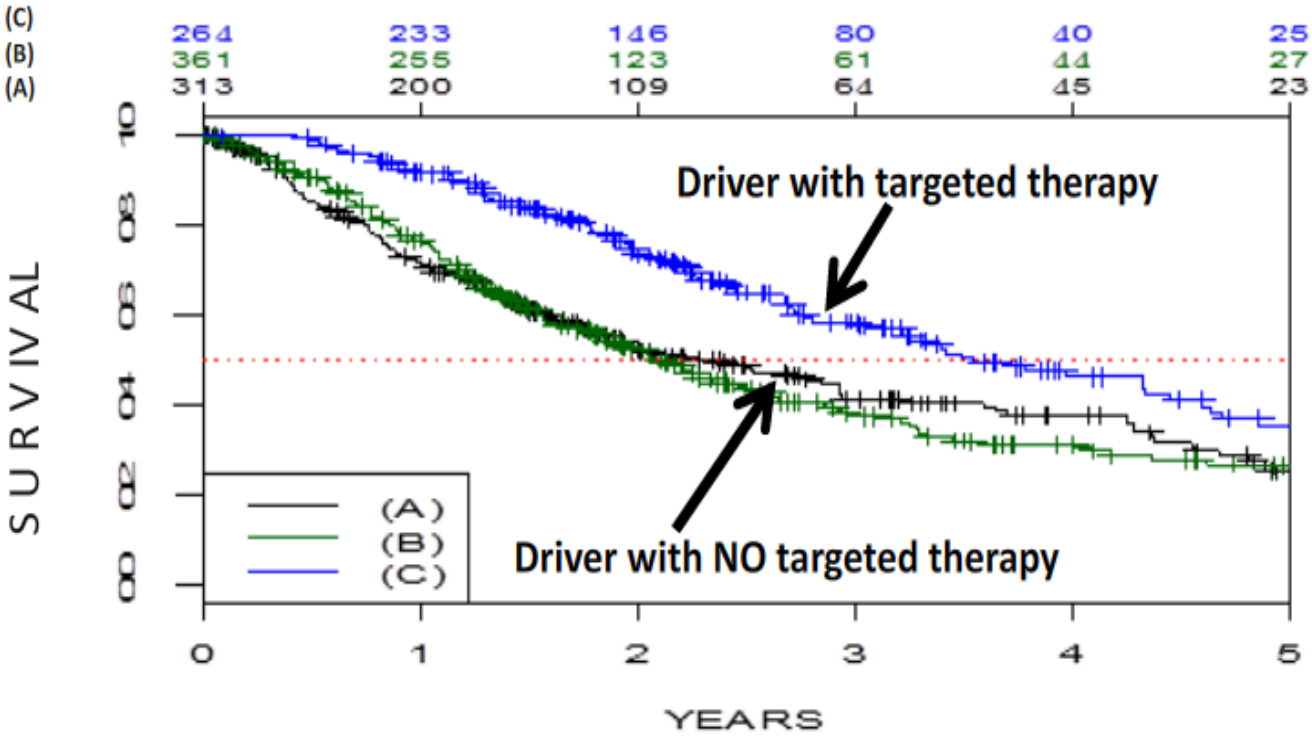
Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

JAMA. 2014;311(19):1998-2006.

Mark G. Kris, MD; Bruce E. Johnson, MD; Lynne D. Berry, PhD; David J. Kwiatkowski, MD; A. John Iafrate, MD; Ignacio I. Wistuba, MD; Marileila Varella-Garcia, PhD; Wilbur A. Franklin, MD; Samuel L. Aronson, ALM, MA; Pei-Fang Su, PhD; Yu Shyr, PhD; D. Ross Camidge, MD, PhD; Lecia V. Sequist, MD; Bonnie S. Glisson, MD; Fadlo R. Khuri, MD; Edward B. Garon, MD; William Pao, MD, PhD; Charles Rudin, MD, PhD; Joan Schiller, MD; Eric B. Haura, MD; Mark Socinski, MD; Keisuke Shirai, MD; Heidi Chen, PhD; Giuseppe Giaccone, MD; Marc Ladanyi, MD; Kelly Kugler, BA; John D. Minna, MD; Paul A. Bunn, MD



Drivers with targeted therapies: impact on OS



Group	N	Median Survival (95% CI)
Driver, no targeted therapy (A)	313	2.4 years (1.8 to 2.9)
No driver (B)	361	2.1 years (1.8 to 2.5)
Driver, targeted therapy (C)	264	3.5 years (3.2 to 4.6)

EGFR-TKIs
AIFA approvals

Gefitinib

All EGFR mutated

Erlotinib

I line in EGFR mutated

II-III line EGFR mutated or wt

Afatinib

I line in EGFR mutated

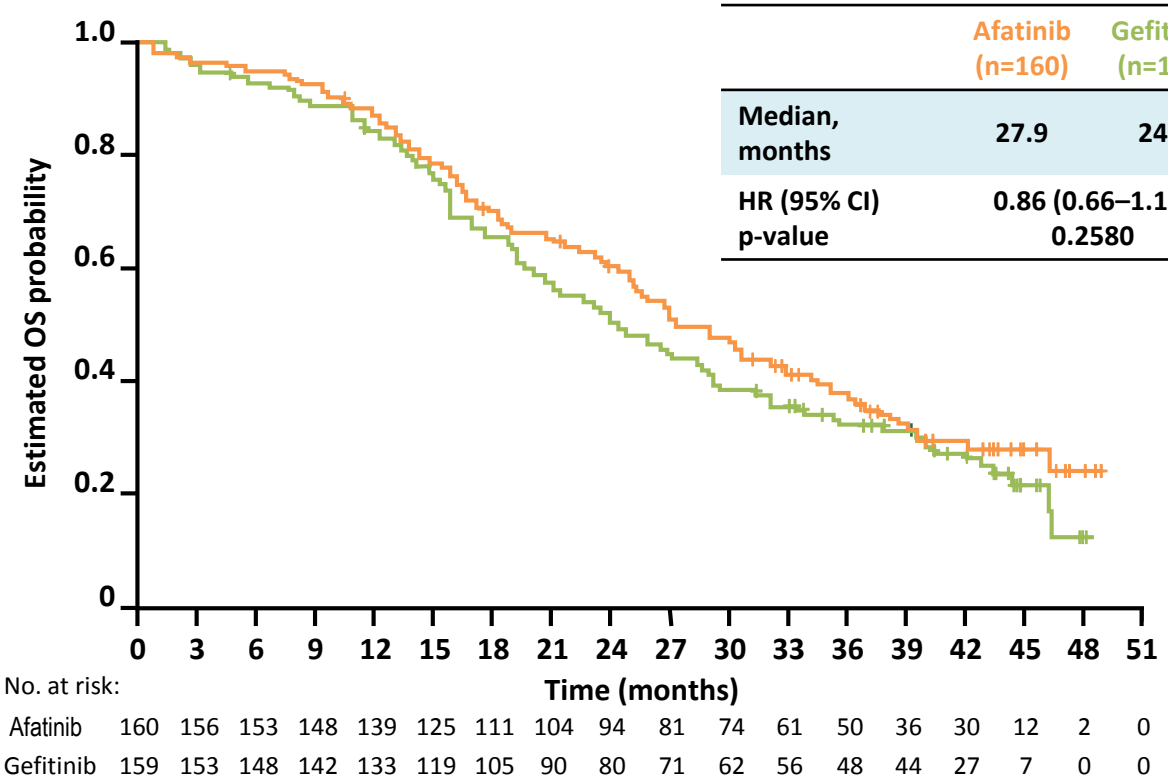
EGFR-TKIs
I line treatment of EGFR mutated NSCLC patients

RR 54-80%

PFS >8-13 mesi

STUDIO	TERAPIA	PZ	0RR (%)	PFS (m)
IPASS	Gefitinib vs CBDCA+Tax	261	71.2 vs 47.3	9.8 vs 6.4
First-Signal	Gefitinib vs CDDP+GEM	42	84.6 vs 37.5	8.4 vs 6.7
WJTOG3405	Gefitinib vs CDDP+TXT	174	62.1 vs 32.2	9.2 vs 6.3
NEJM2010	Gefitinib vs CBDCA+Tax	230	73.7 vs 30.7	10.8 vs 5.4
Optimal	Erlotinib vs CBDCA+GEM	154	83 vs 36	13.1 vs 4.6
EURTAC	Erlotinib vs CDDP based CHT	174	54.5 vs 10.5	9.7 vs 5.2
Lux Lung 3	Afatinib vs CDDP-PEM	345	56 vs 23	11.1 vs 6.9
Lux Lung 6	Afatinib vs CDDP-GEM	364	66.9 vs 23	11.1 vs 5.6

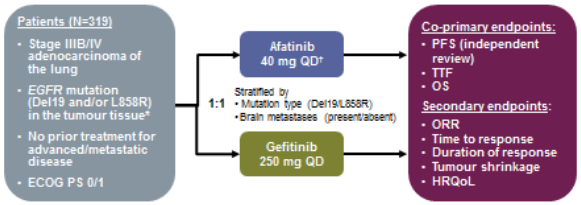
GEFITINIB VS AFATINIB
I line EGFR mutated NSCLC patients



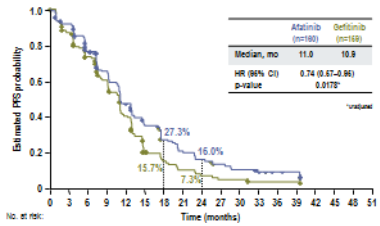
	Afatinib (n=160)	Gefitinib (n=159)
Median, months	27.9	24.5
HR (95% CI)	0.86 (0.66–1.12)	
p-value	0.2580	

- Median follow-up: 42.6 months (as of 08 April 2016)
- Median treatment duration (afatinib vs gefitinib): 13.7 vs 11.5 months

LUX-LUNG 7 STUDY DESIGN

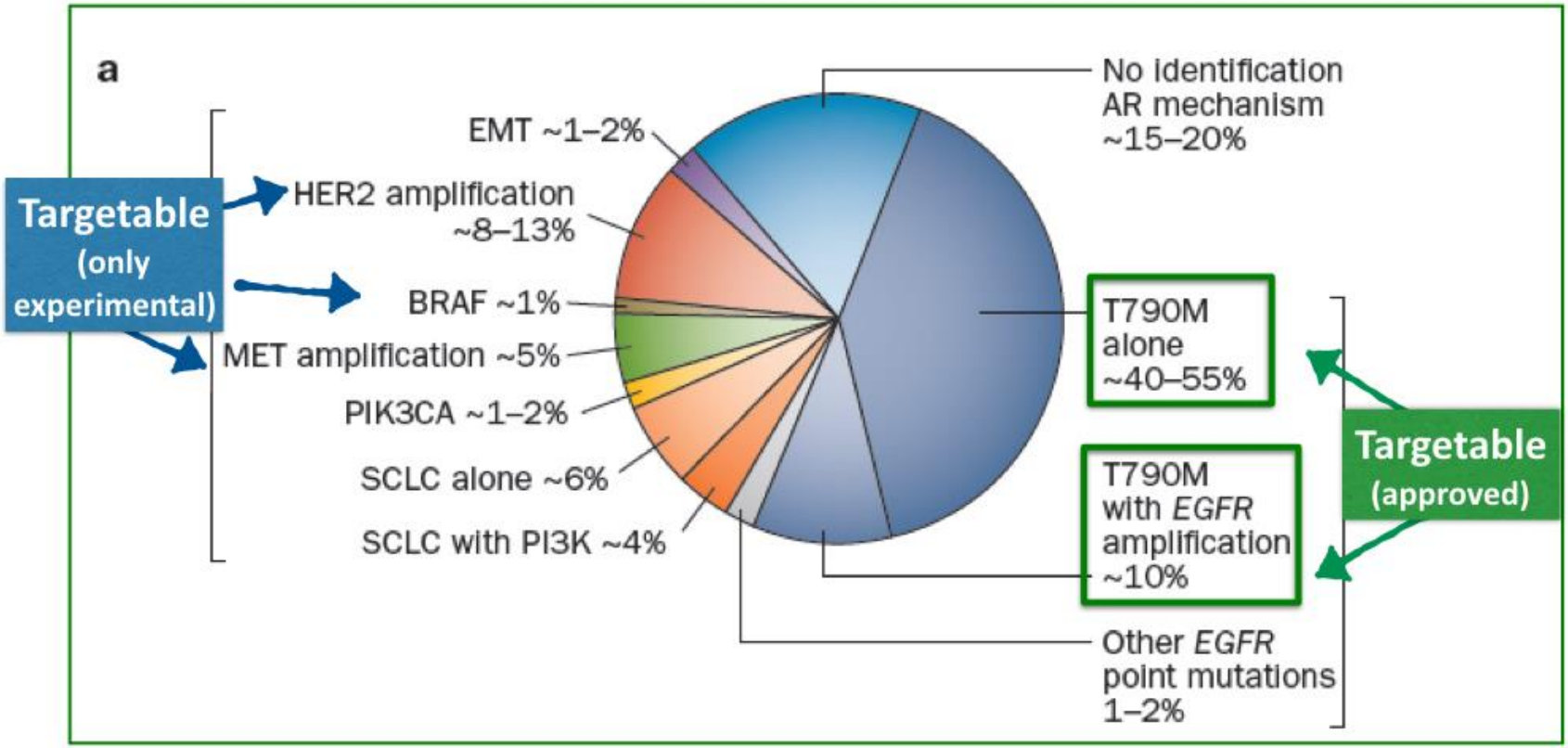


UPDATED PFS (INDEPENDENT REVIEW)



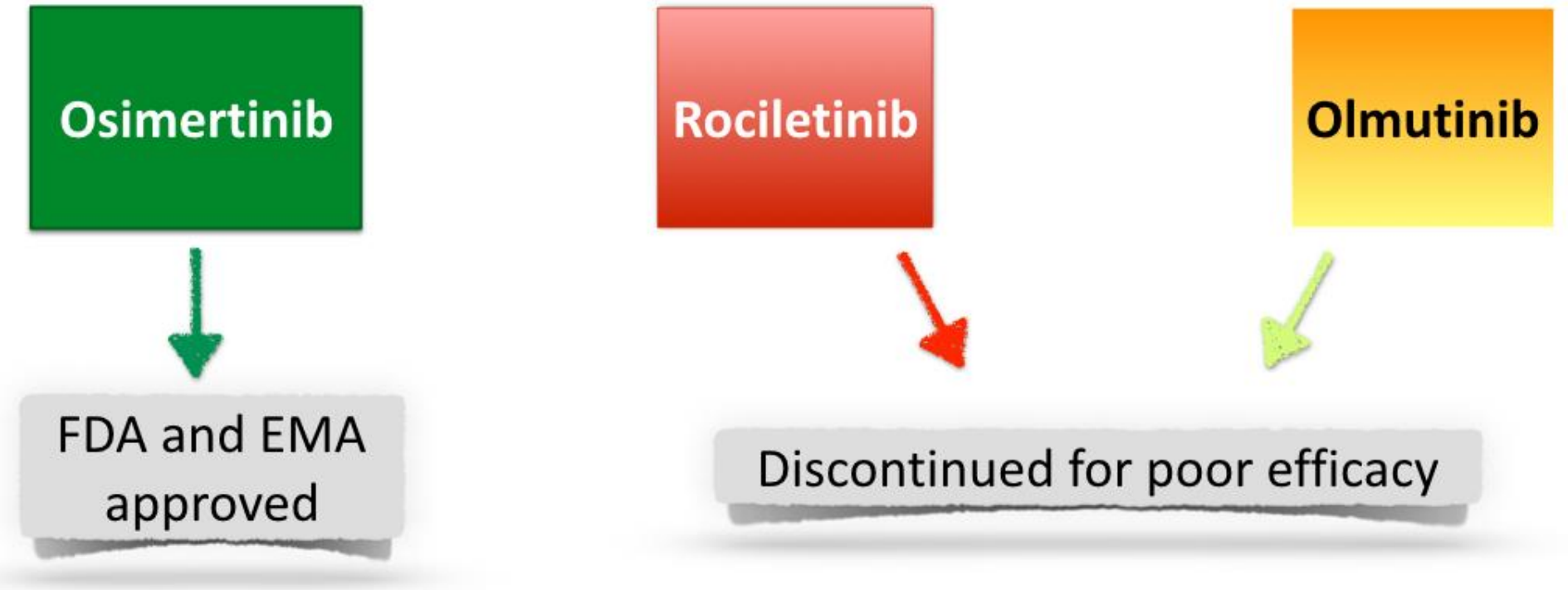
Park K et al. *Lancet Oncol*. 2016
Paz-Ares L et al. *Ann Oncol*, 2017

Mechanisms responsible for acquired resistance to EGFR-TKIs



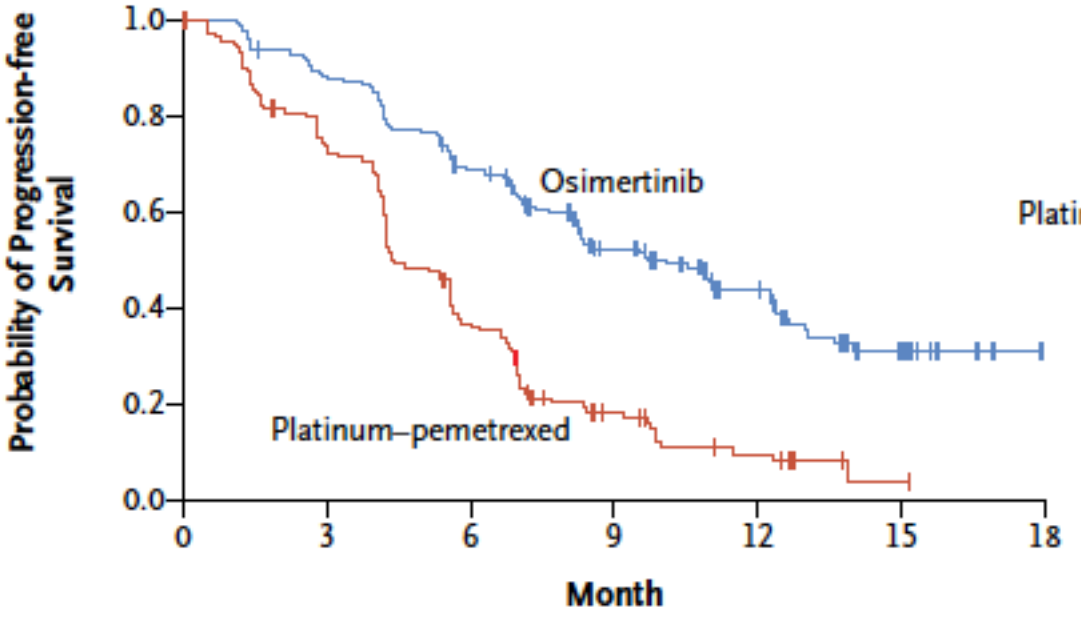
Camidge et al, Nat Rev Clin Oncol 2014

Treatment strategies for patients developing EGFR T790M mutation



Osimertinib is a recommended targeted therapy for EGFR T790M+ NSCLC - Phase III AURA3 trial

A Patients in Intention-to-Treat Population



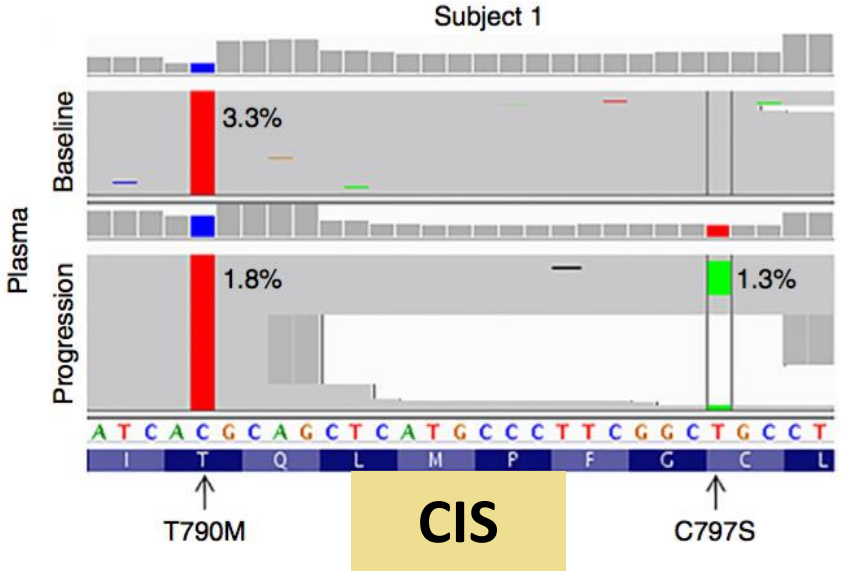
No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

	No. of Patients	Median Progression-free Survival *mo (95% CI)*
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

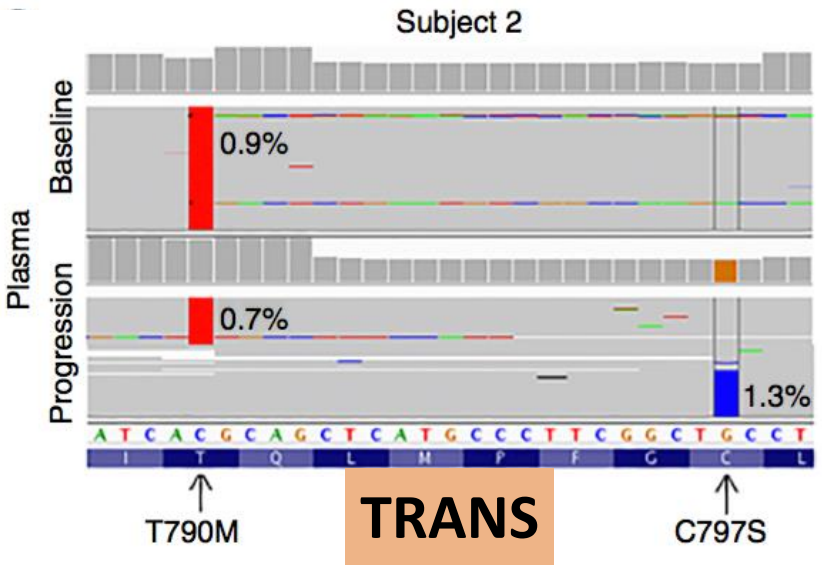
Mok et al, NEJM; 2017

Acquired resistance mechanisms to third generation EGFR-TKIs - C797S



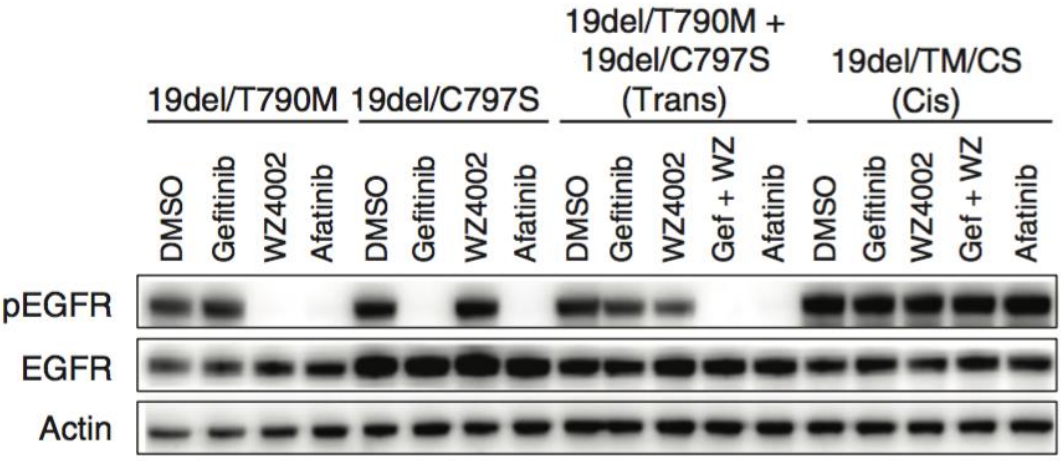
C797S coexists with T790M on the same alleles

Resistance to all 3 generations EGFR-TKIs



C797S and T790M are on different alleles

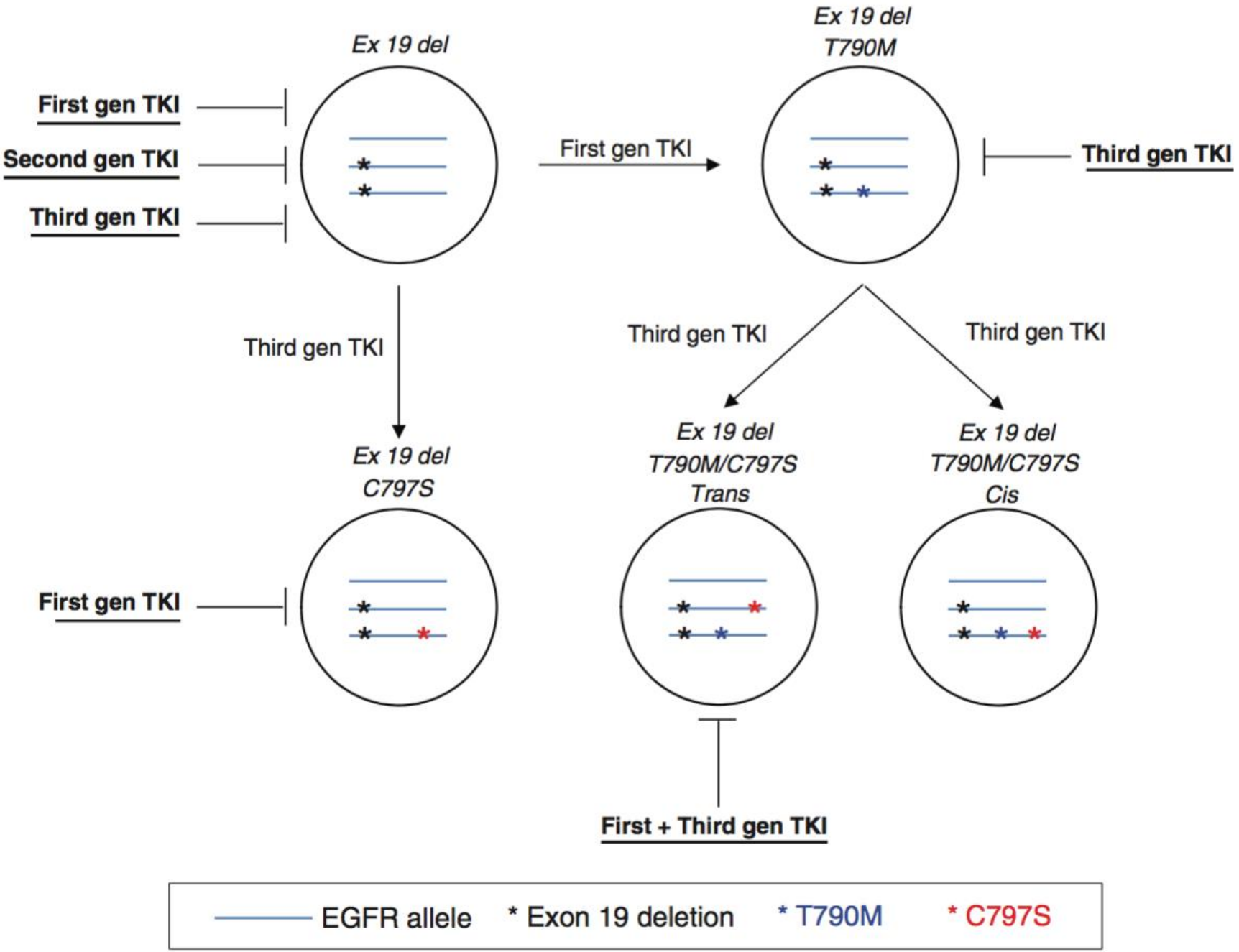
Sensitive to 1st/2nd generations EGFR-TKIs



Third generation require cyst for binding

First and second generation do not bind cyst

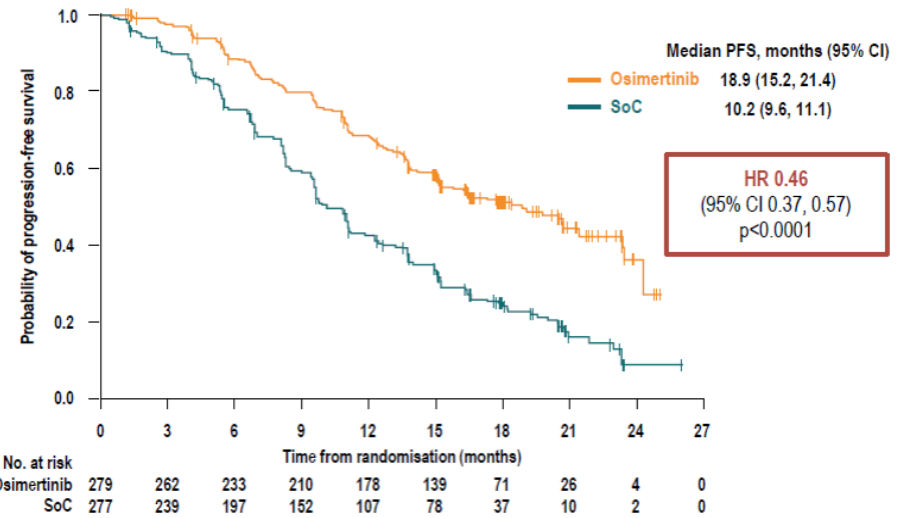
Niederst et al; Clin Canc Res 2015



Niederst et al; Clin Canc Res 2015

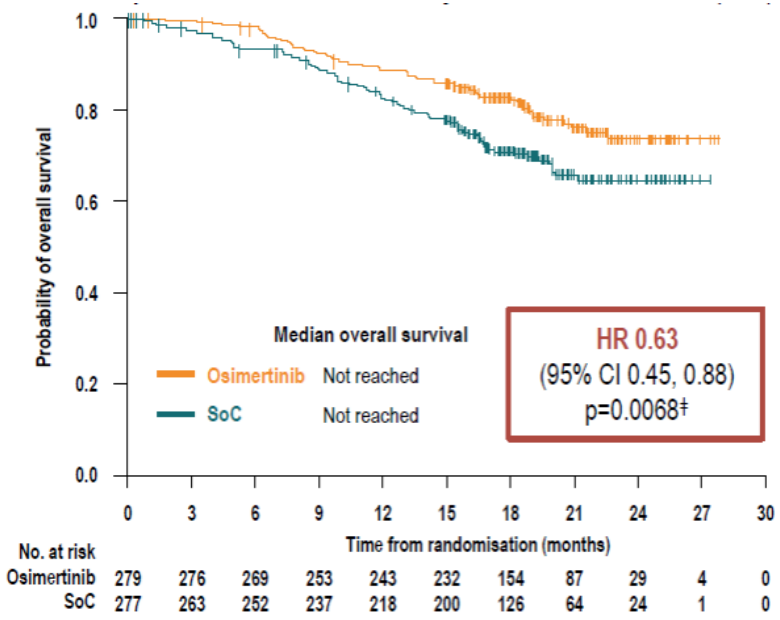
Osimertinib in the first line setting - FLAURA

PFS



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

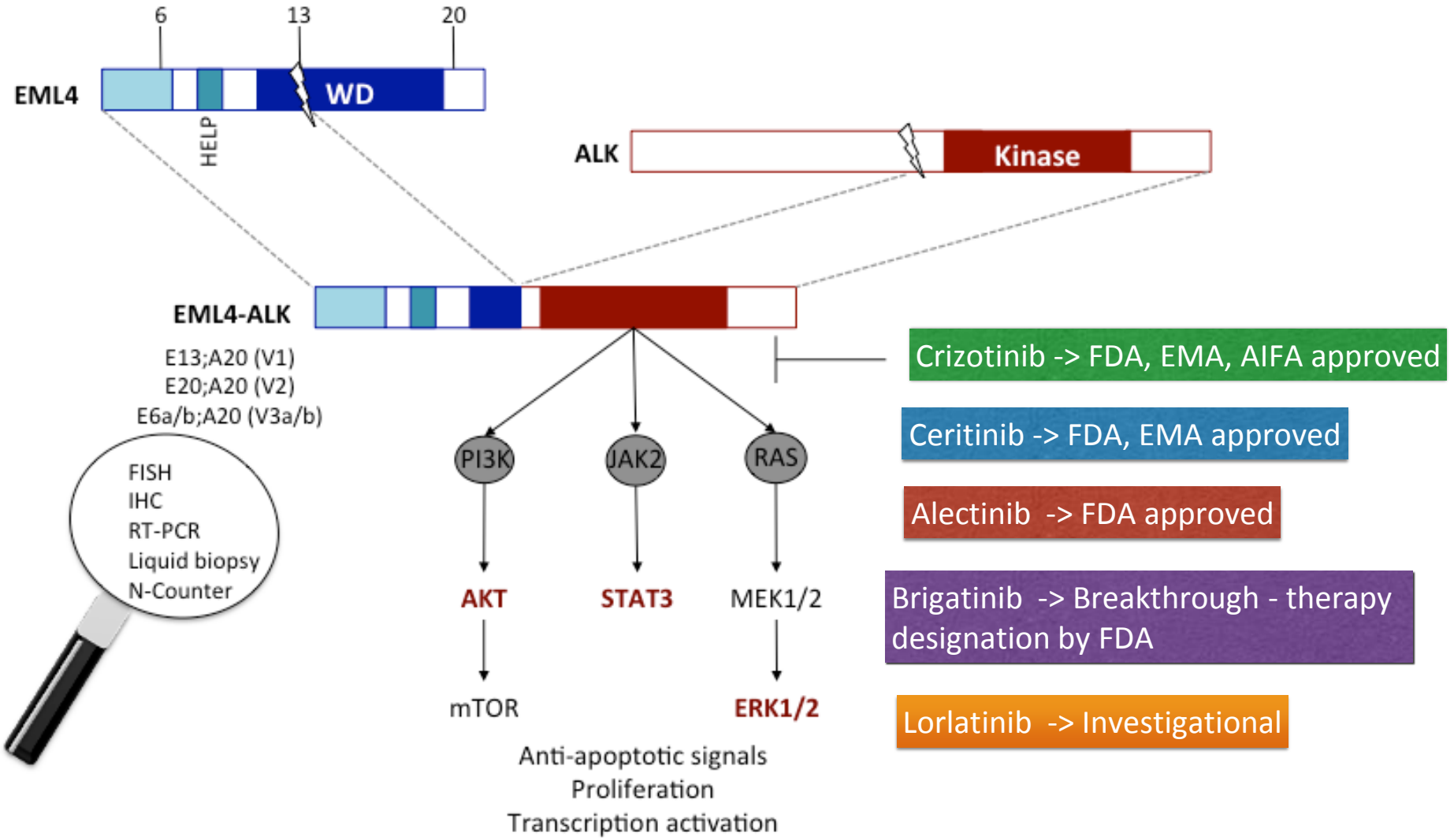
OS



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

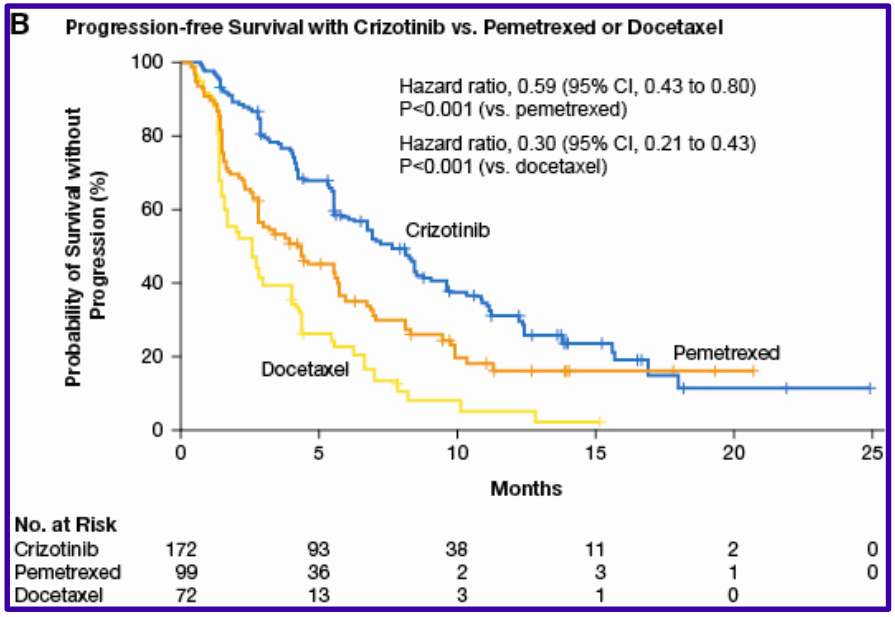
Ramalingam et al; ESMO; 2017

EML4-ALK traslocated NSCLC



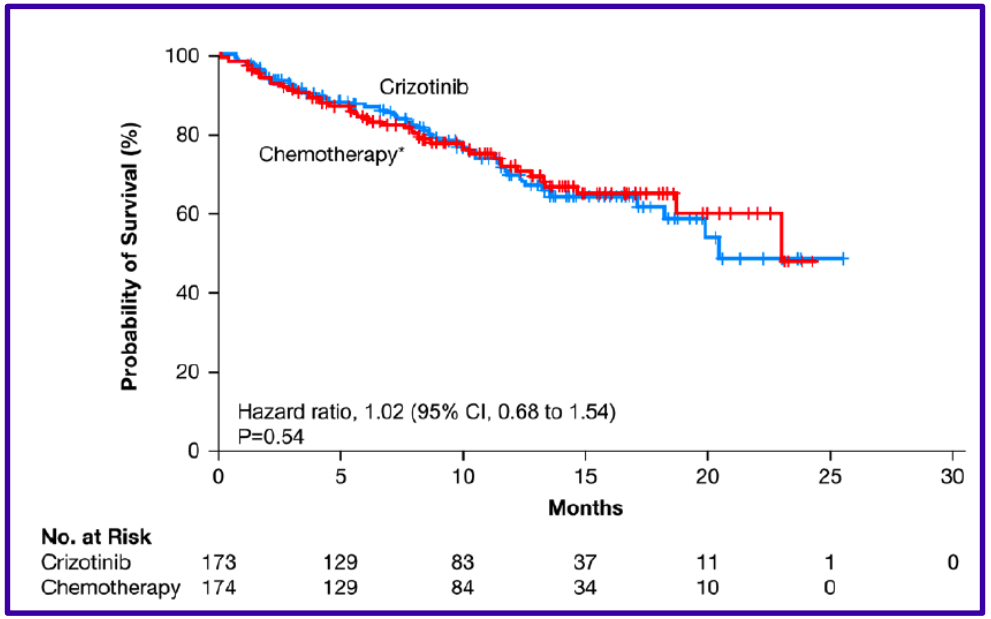
PF1007: Crizotinib over second line CT

PFS



Median PFS: 7.7 m vs 3.0 m
(4.2 m with pemetrexed and 2.6 m with docetaxel)

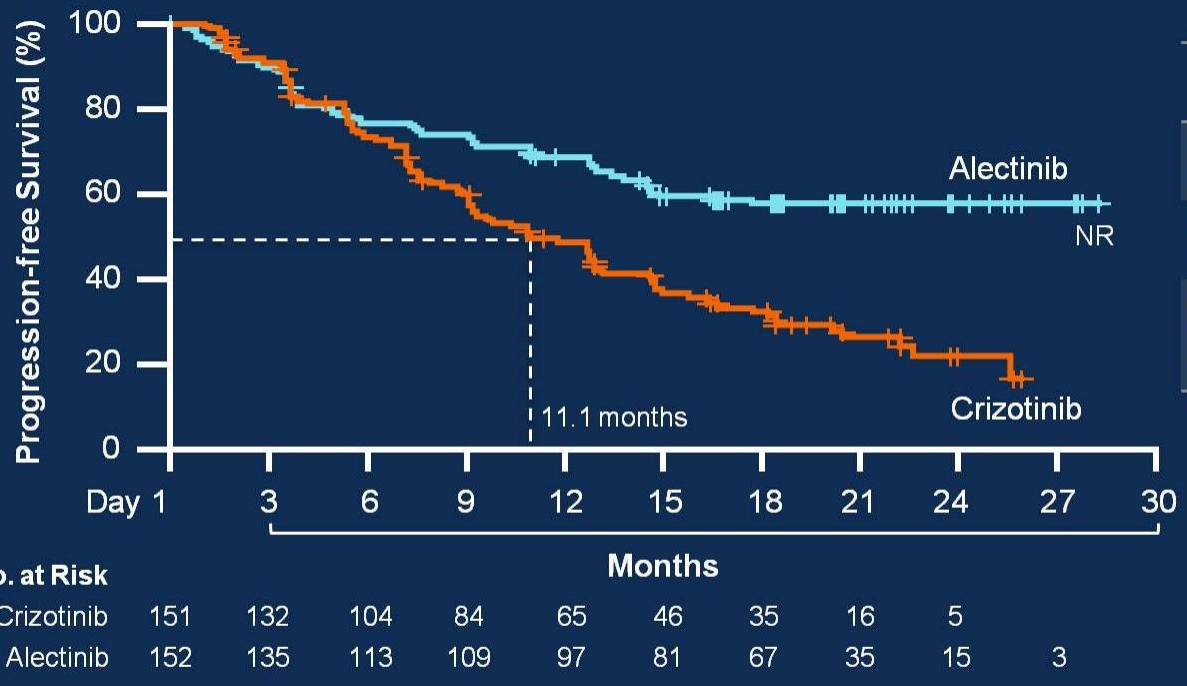
OS



Median OS: 20.3 m vs 22.8 m
(40% of the total number of events required for the final analysis)

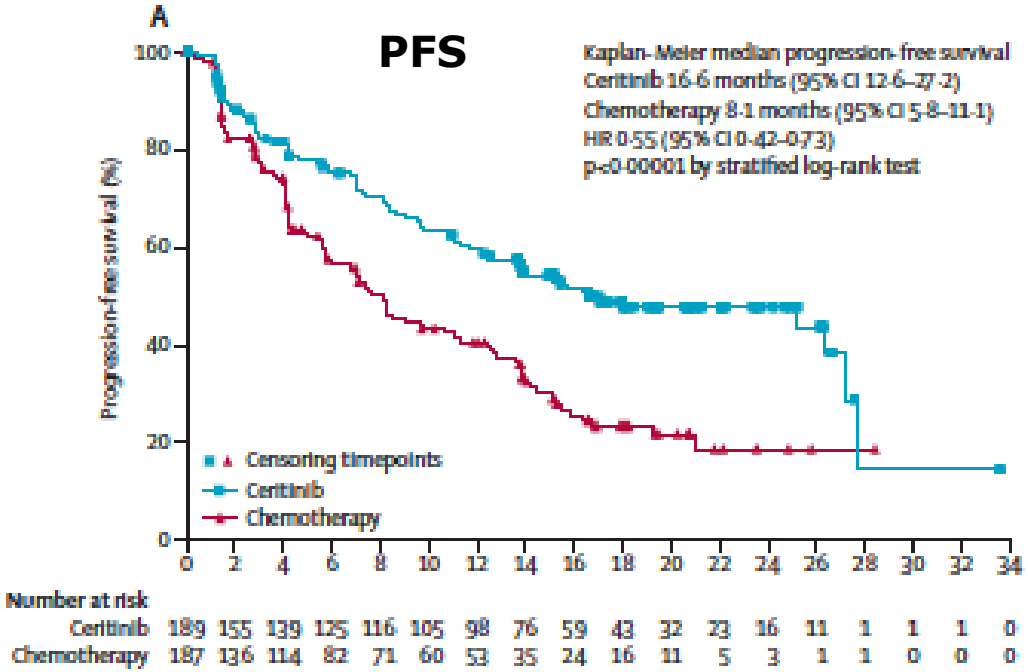
RR: 65% for crizotinib and 20% for chemotherapy (7% for docetaxel, 30% for pemetrexed), p<0.001

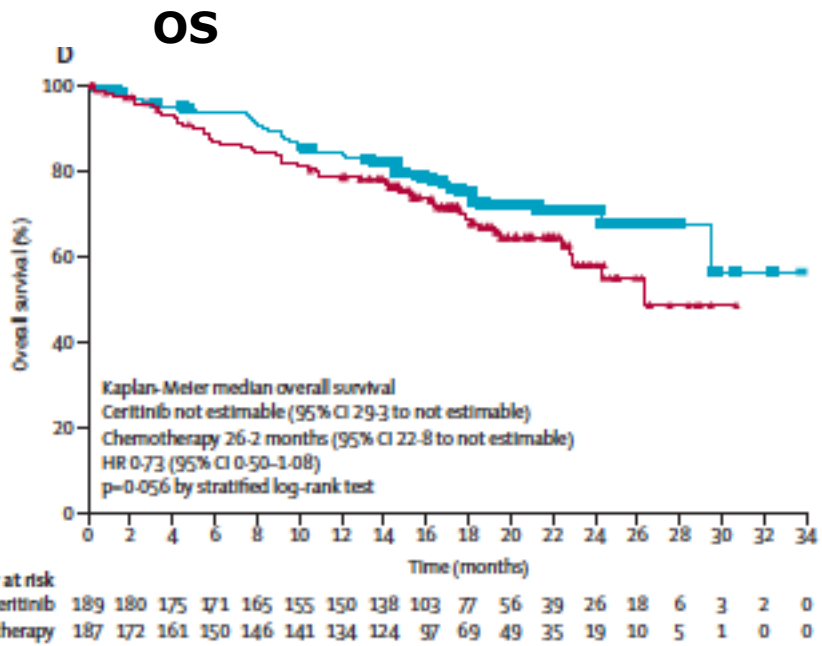
ALEX: superiority of alectinib over crizotinib



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

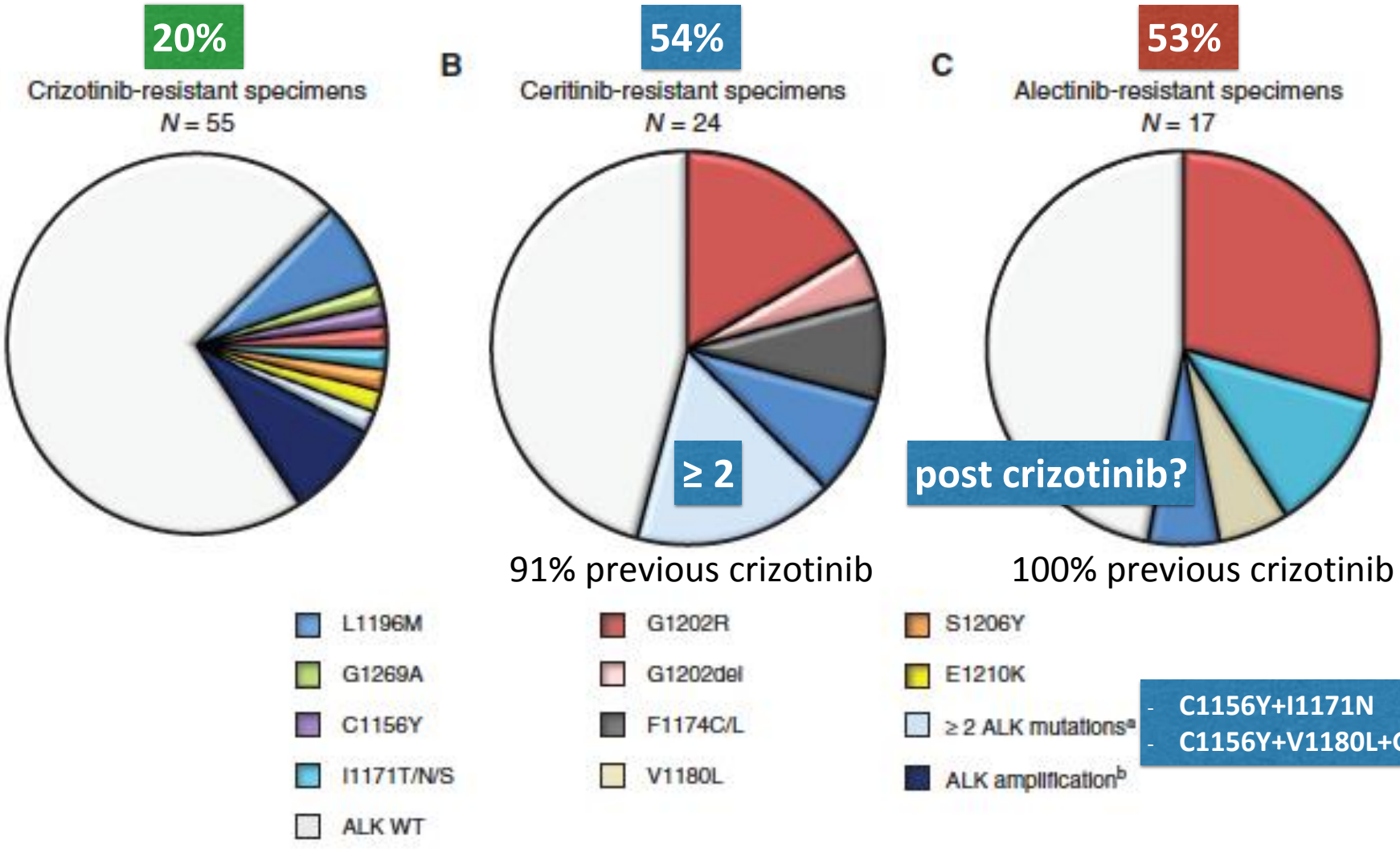
ASCEND-4: superiority of ceritinib over platinum based CT





Soria et al; Lancet; 2017

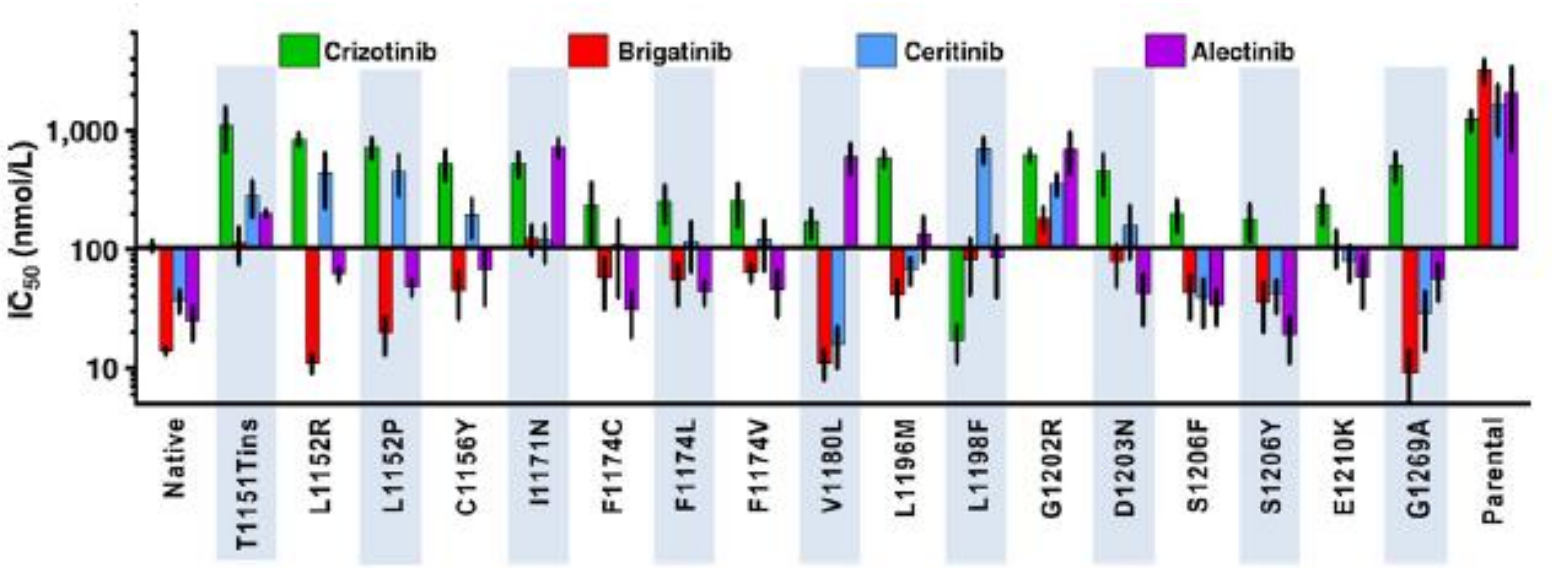
Acquired resistance mechanisms to ALK inhibitors - ALK secondary mutations



Gainor et al; Cancer Discovery; 2016

Up-front or sequential strategy?

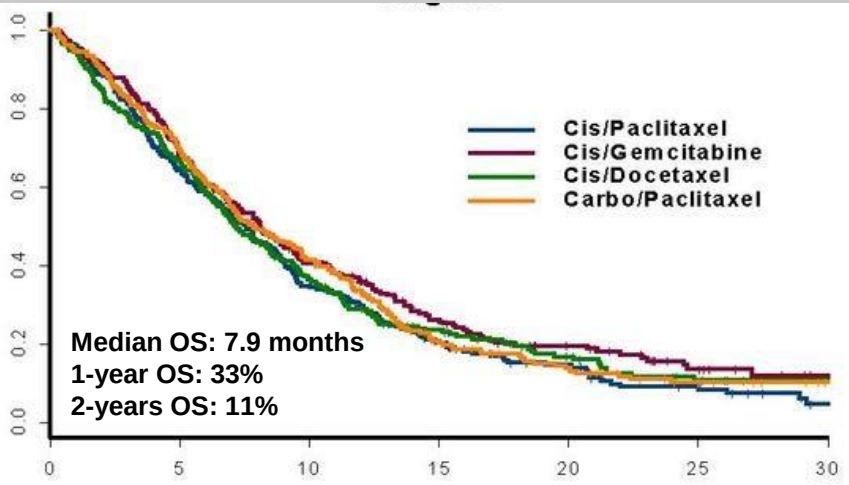
	Ceritinib		Alectinib		Brigatinib	
	Crizotinib naive	**Crizotinib pretreated**	**Crizotinib naive**	**Crizotinib pretreated**	**Crizotinib naive**	**Crizotinib pretreated**
ORR	**79%** (ASCEND-4)	**56%** (ASCEND-1) **38.6%** (ASCEND-2)	**94%** (AF-001JP)	**52%** (NP28761)	**100%** (Phase I/II)	**74%** (Phase I/II)
PFS	**16.6 months** (12.6-27.2)	**6.9 months** **5.7 months** (5.4 - 7.6).	**NR at 3 years**	**8·1 months** (6·2–12·6)	**NR**	**11.2 months** (7·6–29·7)



Zhang et al; Clin Canc Res; 2016

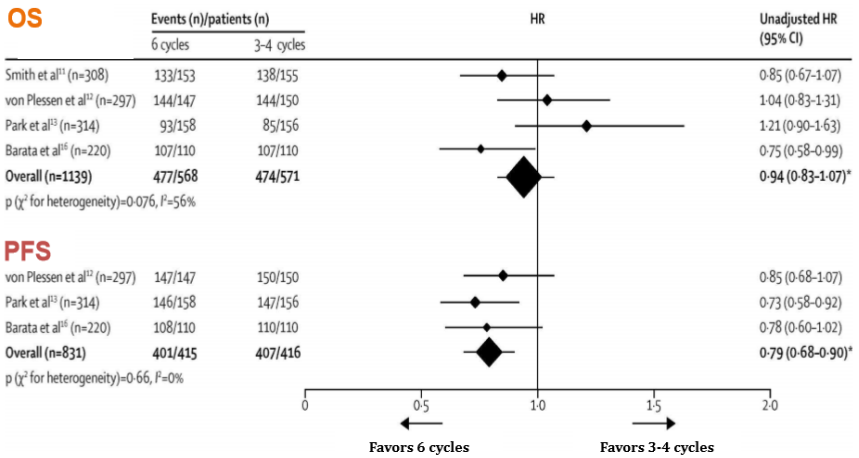
First line CT

Comparison of 4 CT regimens



Schiller et al, N Engl J Med. 2002

6 vs 3-4 CT cycles in 1st line

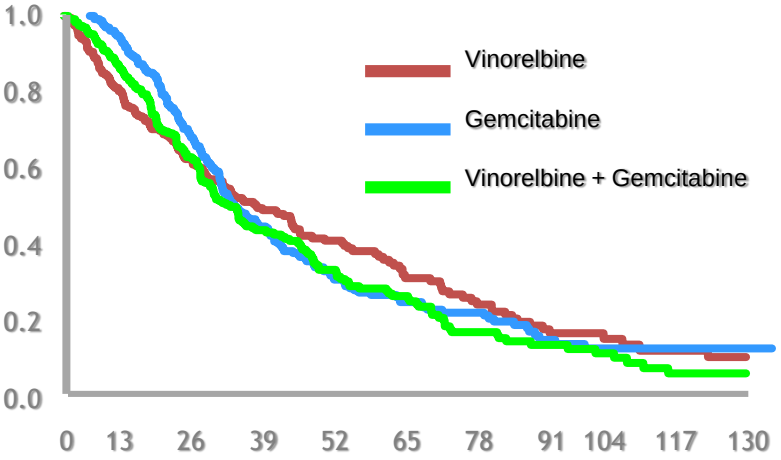


OS; HR = 0.94 (95% CI, 0.83 to 1.07; *P* = .33 (stratified by trial)

PFS; HR 0.79 (95% CI 0.68–0.90), *P* = .0007 (stratified by trial)

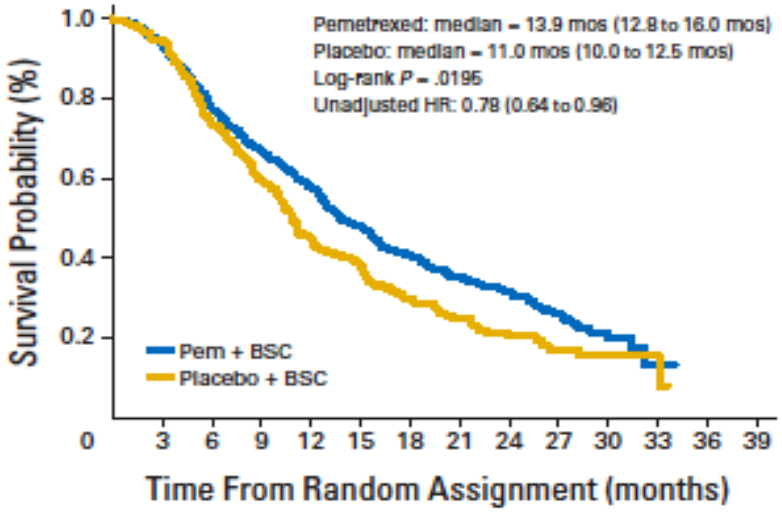
Rossi A, et al. *Lancet Oncol.* 2014;15(11):1254-1262.

MILES: VNR vs GEM vs VNR+GEM-ELDERLY



Gridelli C et al. J Natl Cancer Inst, 2003

Pemetrexed: continuation maintenance

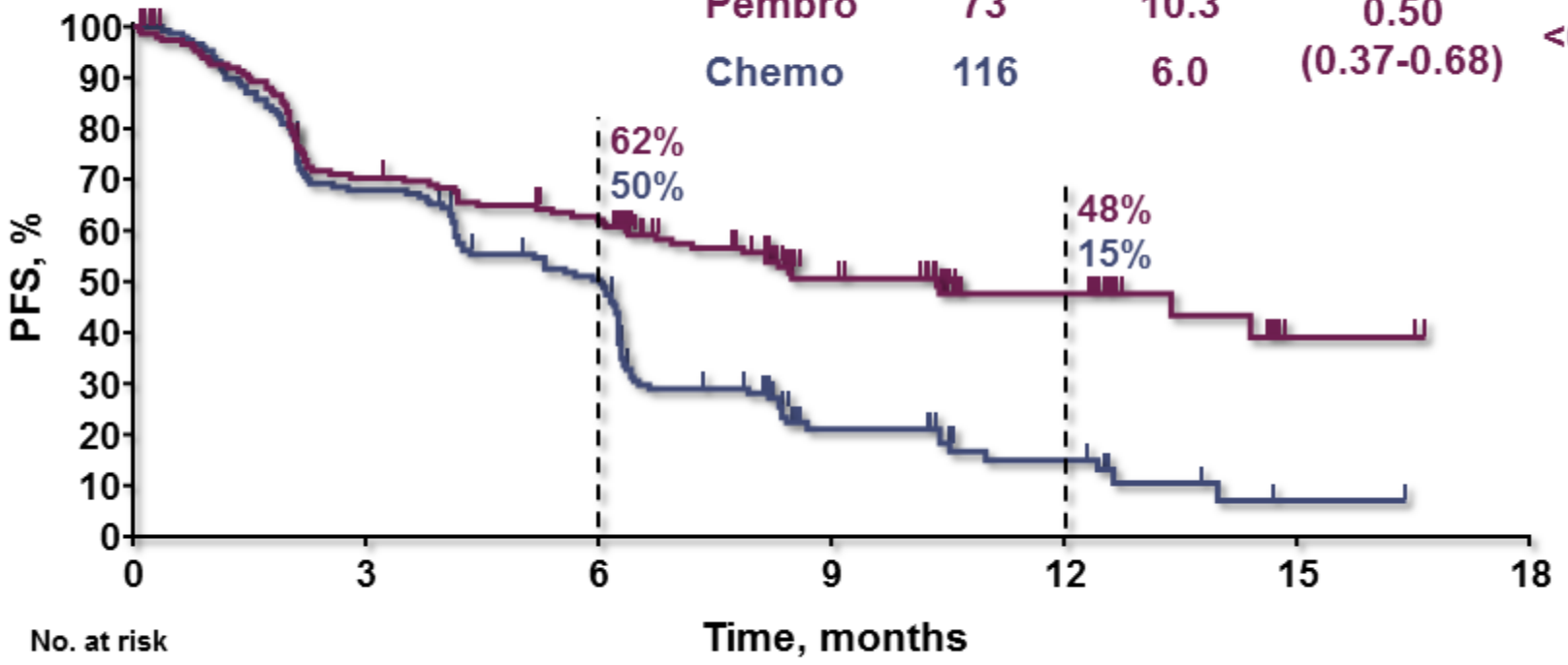


KEYNOTE-024: superiority of pembrolizumab over platinum based CT

M Reck. ESMO 2016.

Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



No. at risk

154	104	89	44	22	3	1
151	99	70	18	9	1	0

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

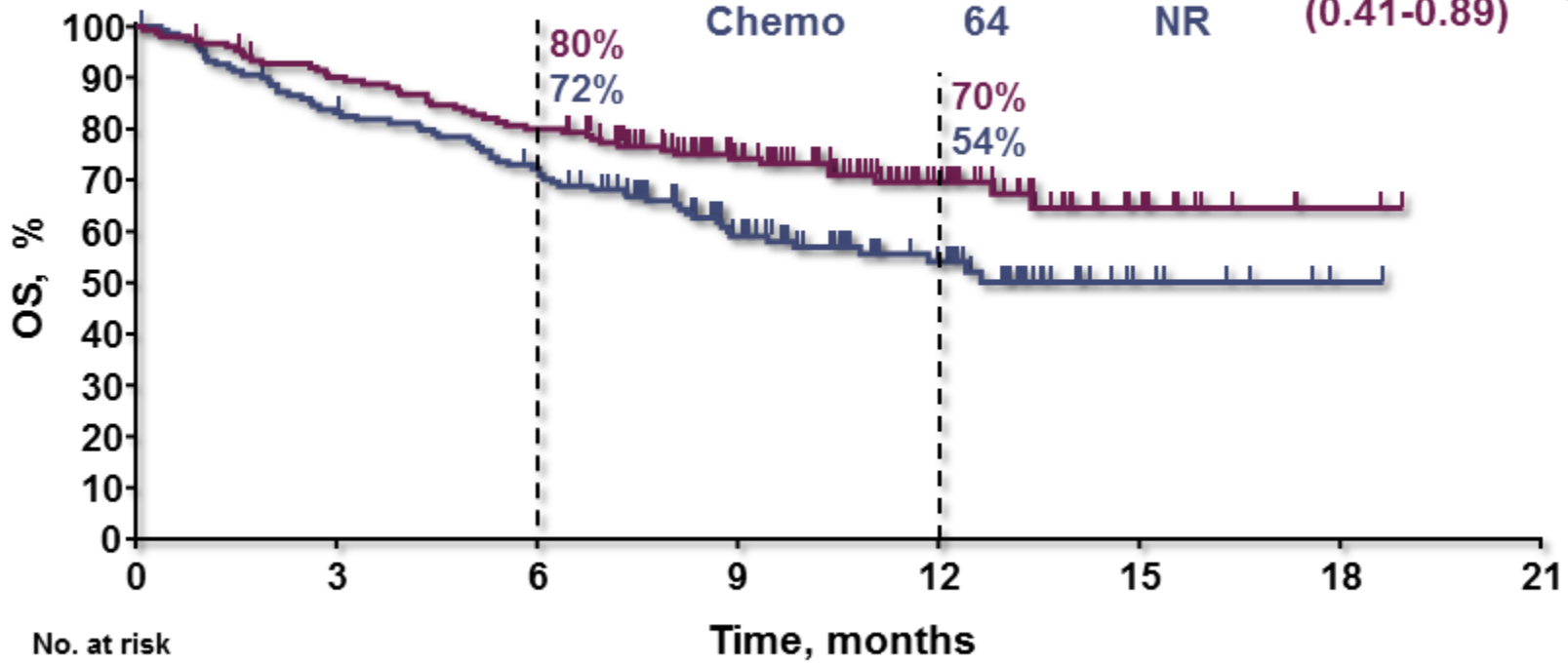
COPENHAGEN 2016 ESMO congress

KEYNOTE-024: superiority of pembrolizumab over platinum based CT

M Reck. ESMO 2016.

Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab

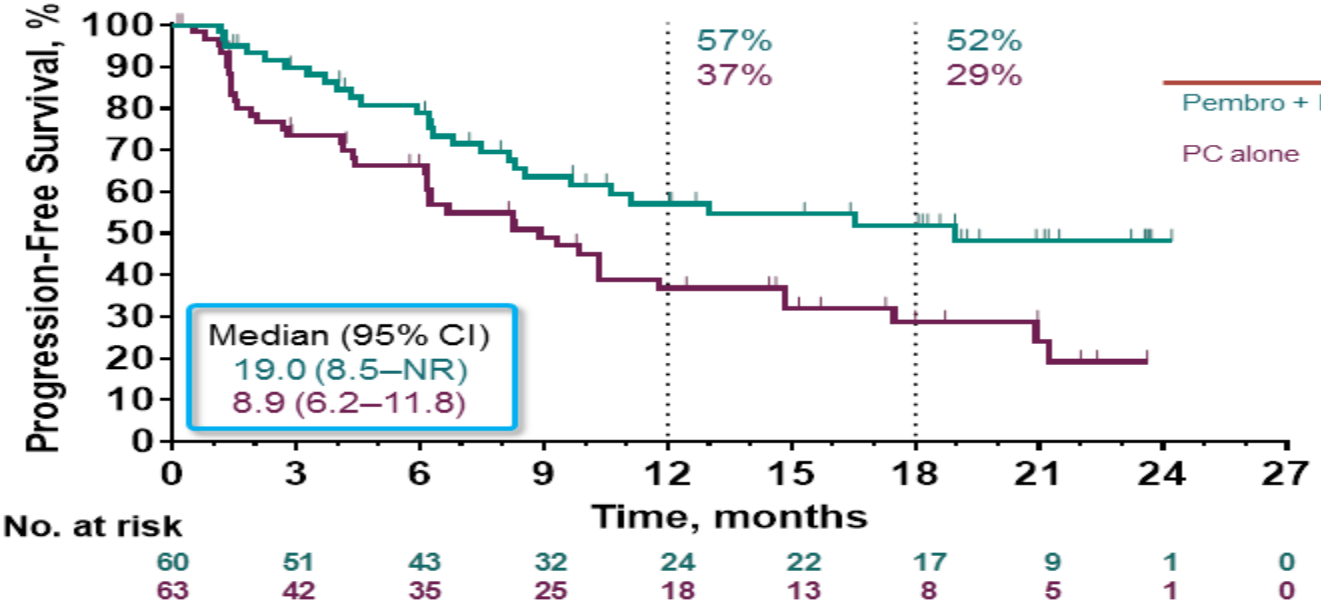
Data cut-off: May 9, 2016.

COPENHAGEN 2016 ESMO congress

KEYNOTE-021: combination of pembrolizumab + platinum based CT

Progression-Free Survival (RECIST v1.1 by Blinded, Independent Central Review)

Borghaei ESMO 2017



	Events, n/N	HR (95% CI)
Pembro + PC	26/60	0.54 (0.33–0.88)
PC alone	40/63	$P = 0.0067$[a]

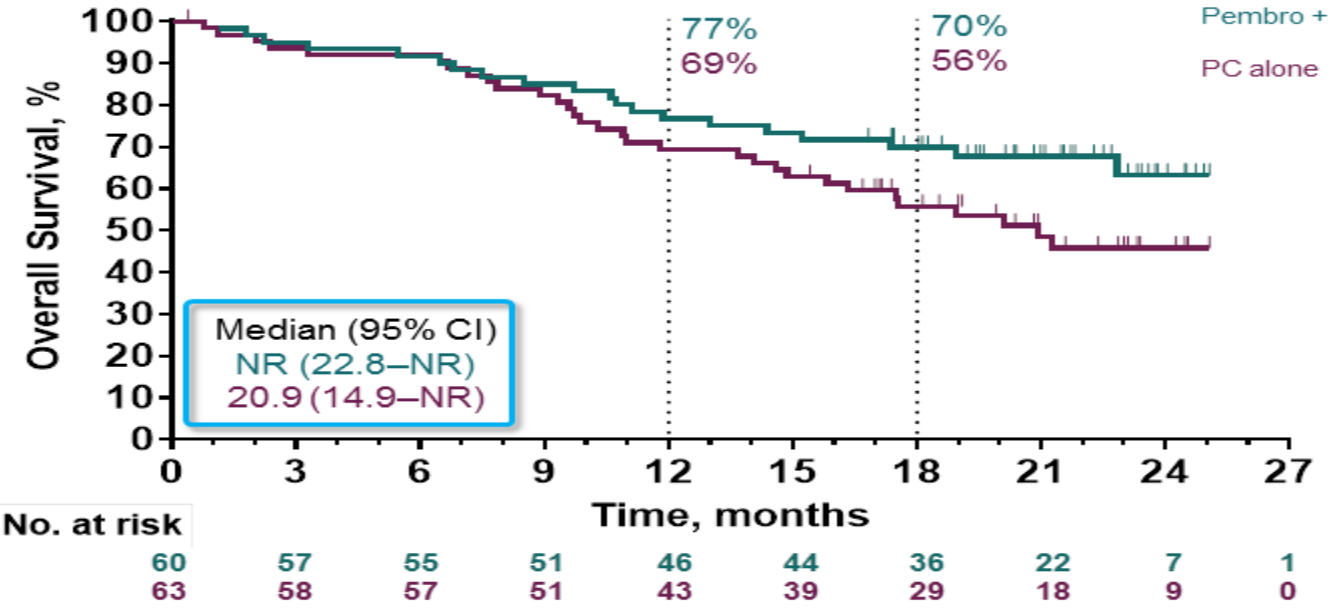
[a]*P* value is descriptive (one-sided $P < 0.025$).
Data cut-off: May 31, 2017.

MADRID 2017 ESMO congress

KEYNOTE-021: combination of pembrolizumab + platinum based CT

Borghaei ESMO 2017

Overall Survival

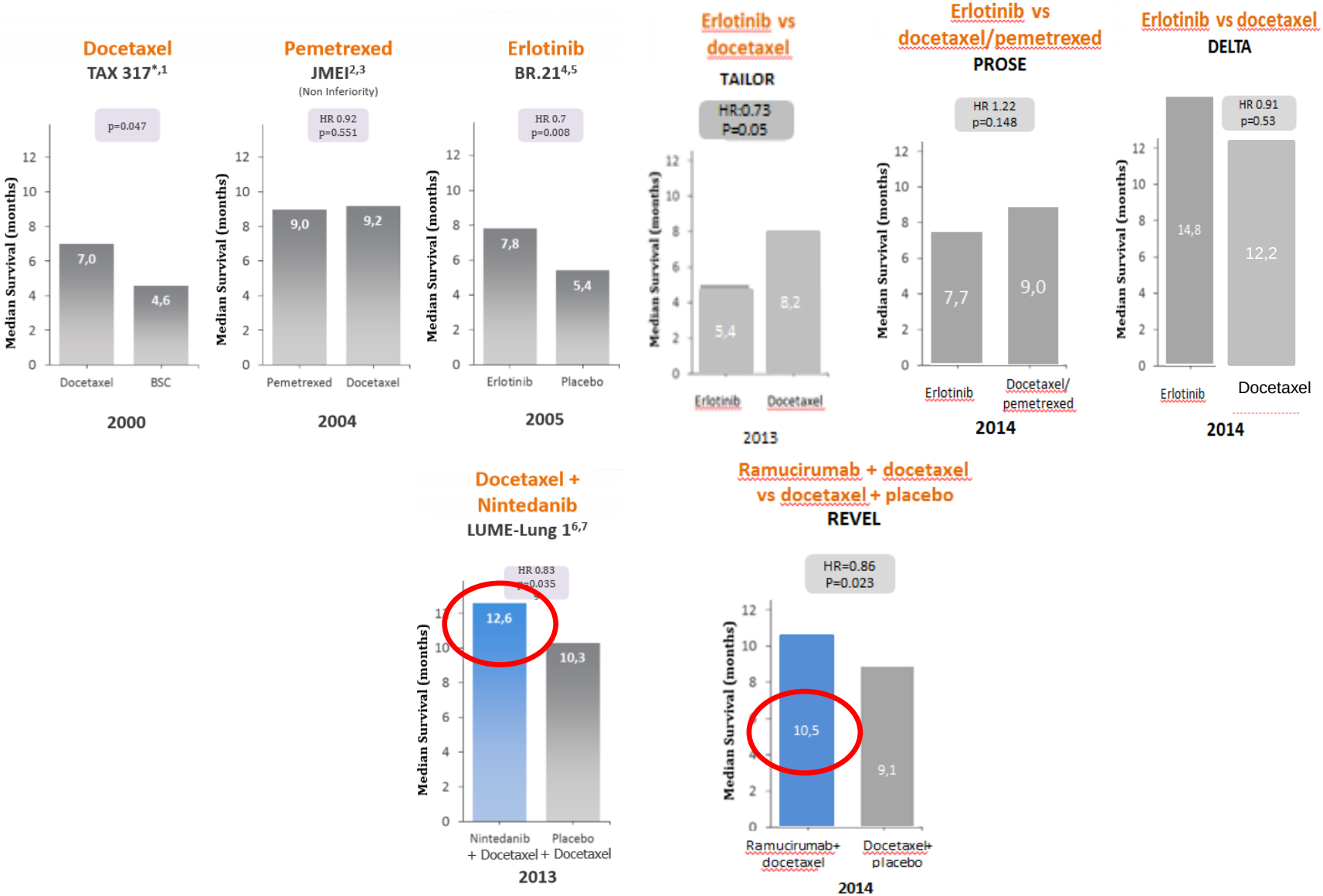


	Events, n/N	HR (95% CI)
Pembro + PC	20/60[a]	0.59 (0.34–1.05)
PC alone	31/63[a]	$P = 0.03$[b]

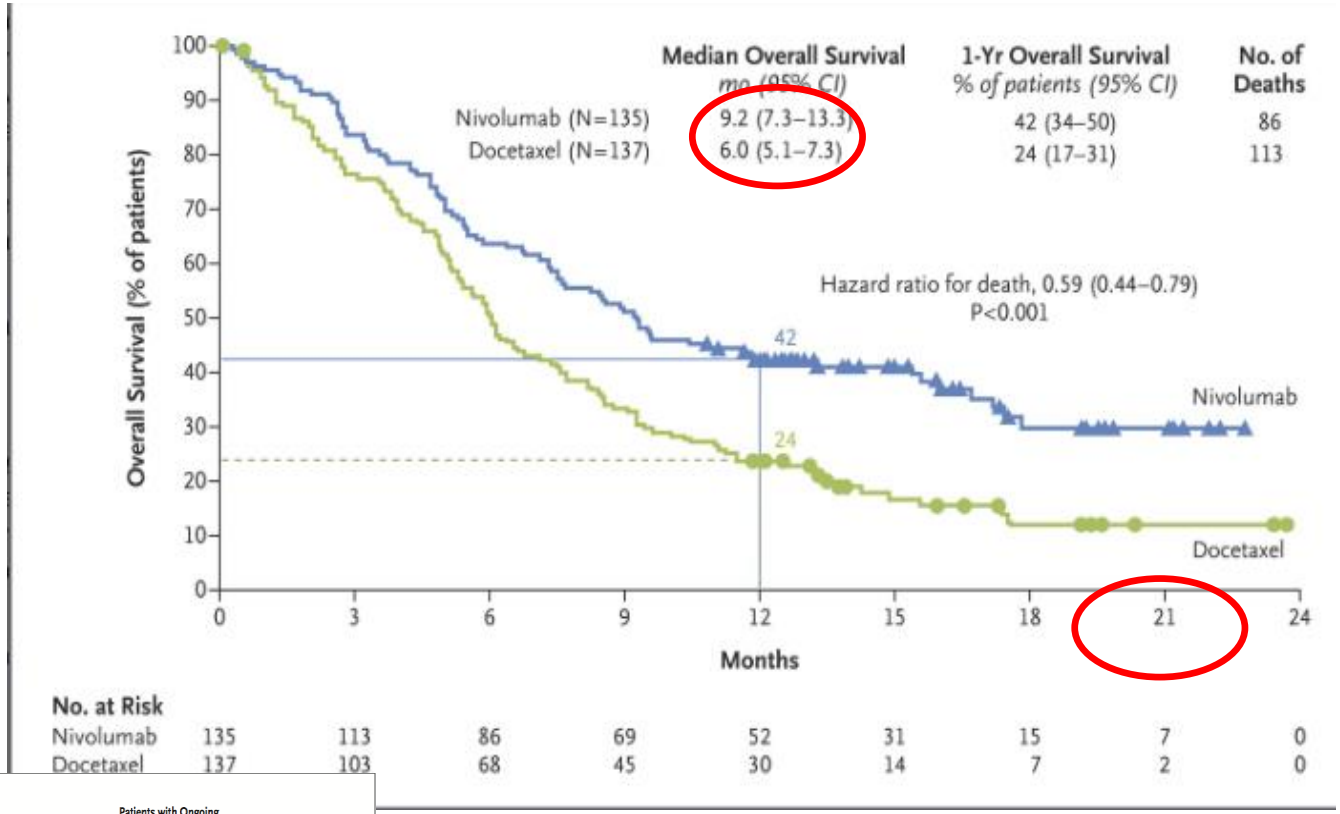
[a]24 additional deaths since primary analysis (pembro + PC, n = 7; PC alone, n = 17). [b]*P* value is descriptive (one-sided $P < 0.025$).
Data cut-off: May 31, 2017.

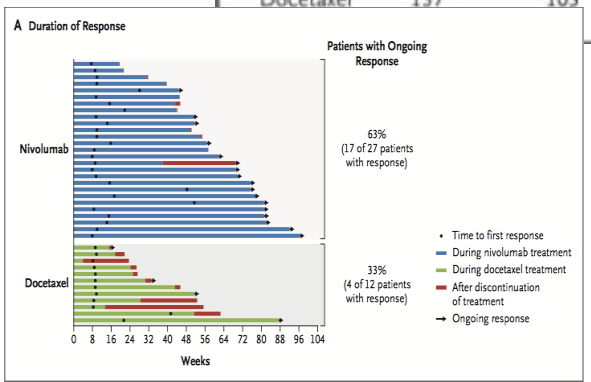
MADRID 2017 ESMO congress

Second-line therapeutic options in non-oncogene driven NSCLC-rising the bar

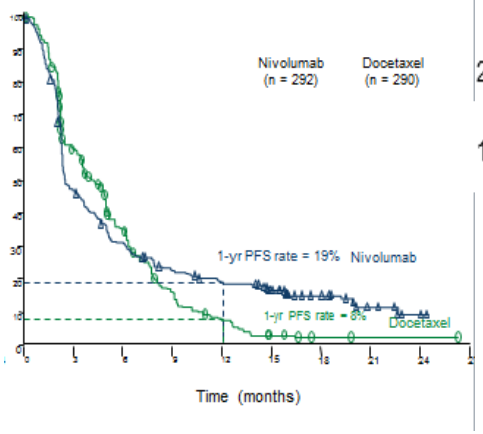


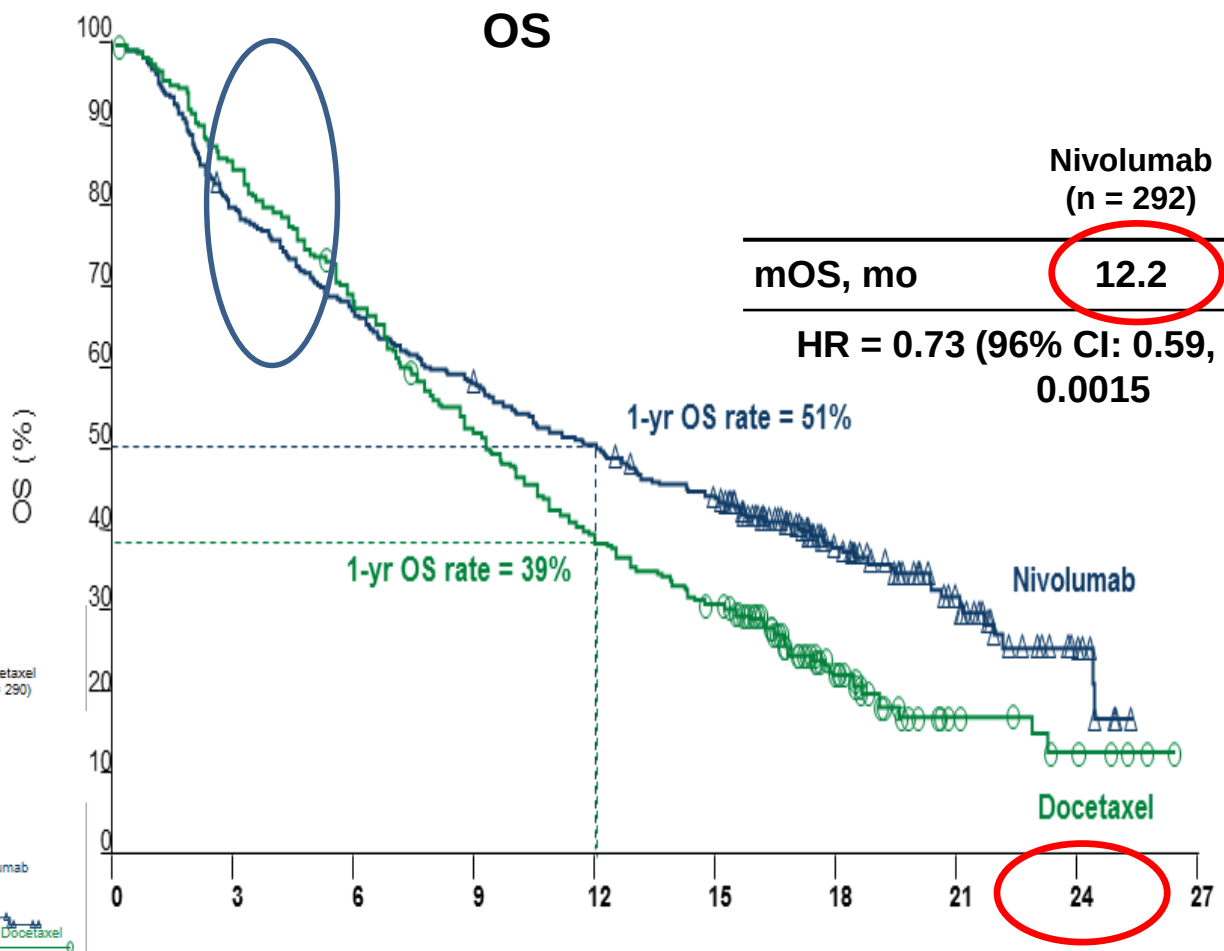
Second-line nivolumab vs docetaxel in squamous NSCLC





Check-Mate 057 second-line nivolumab vs docetaxel in non-squamous NSCLC





	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

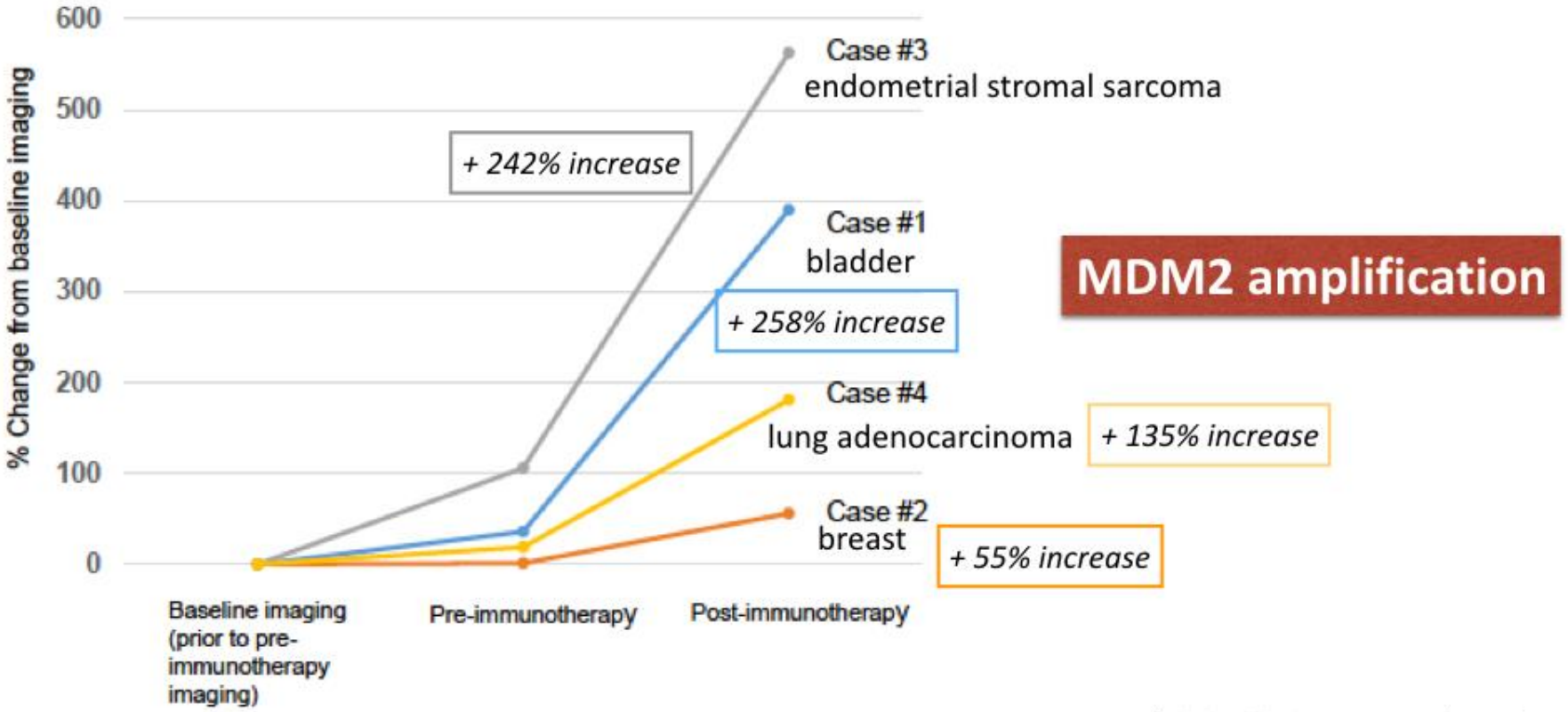
HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

Hyper progression under immunotherapy

- Time to treatment failure (TTF) < 2 months
- > 50% increase in tumor burden within 2 months
- > 2-fold increase in progression rate

→ 9% of patients

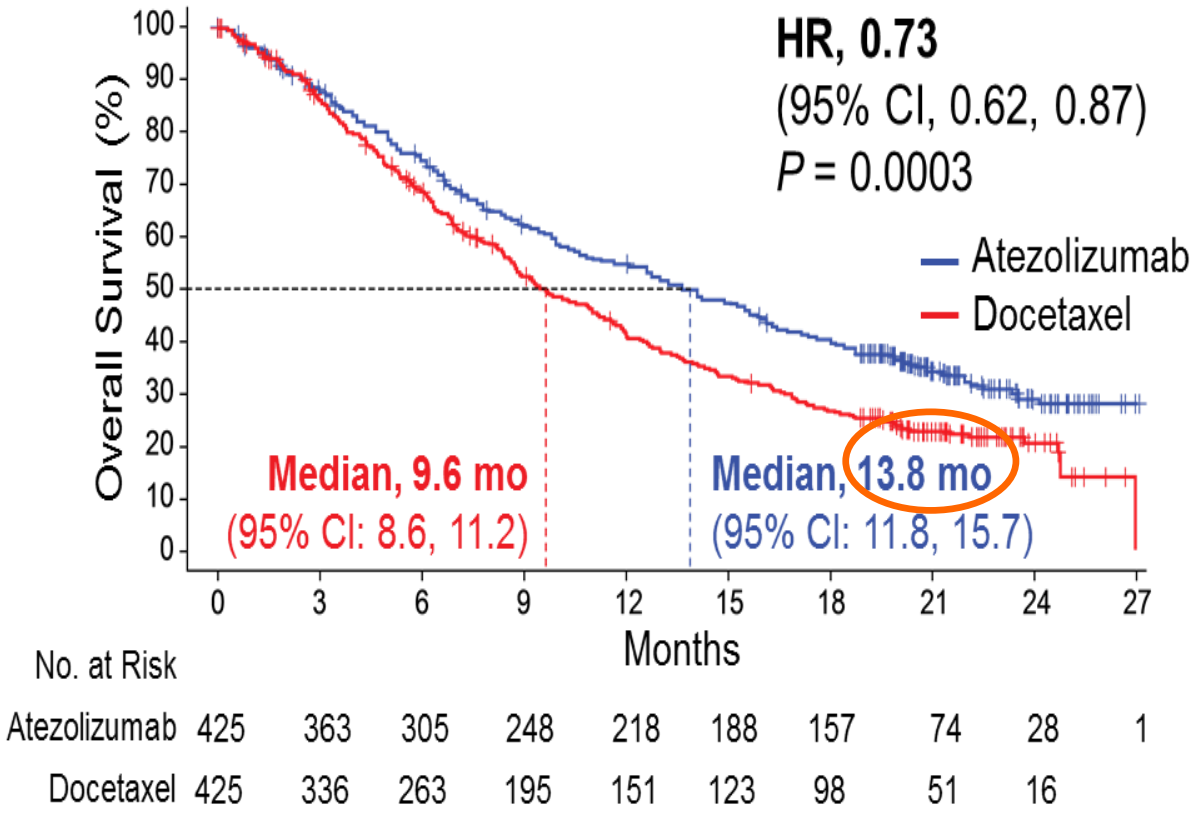
an oncogenic signaling?



MDM2 amplification

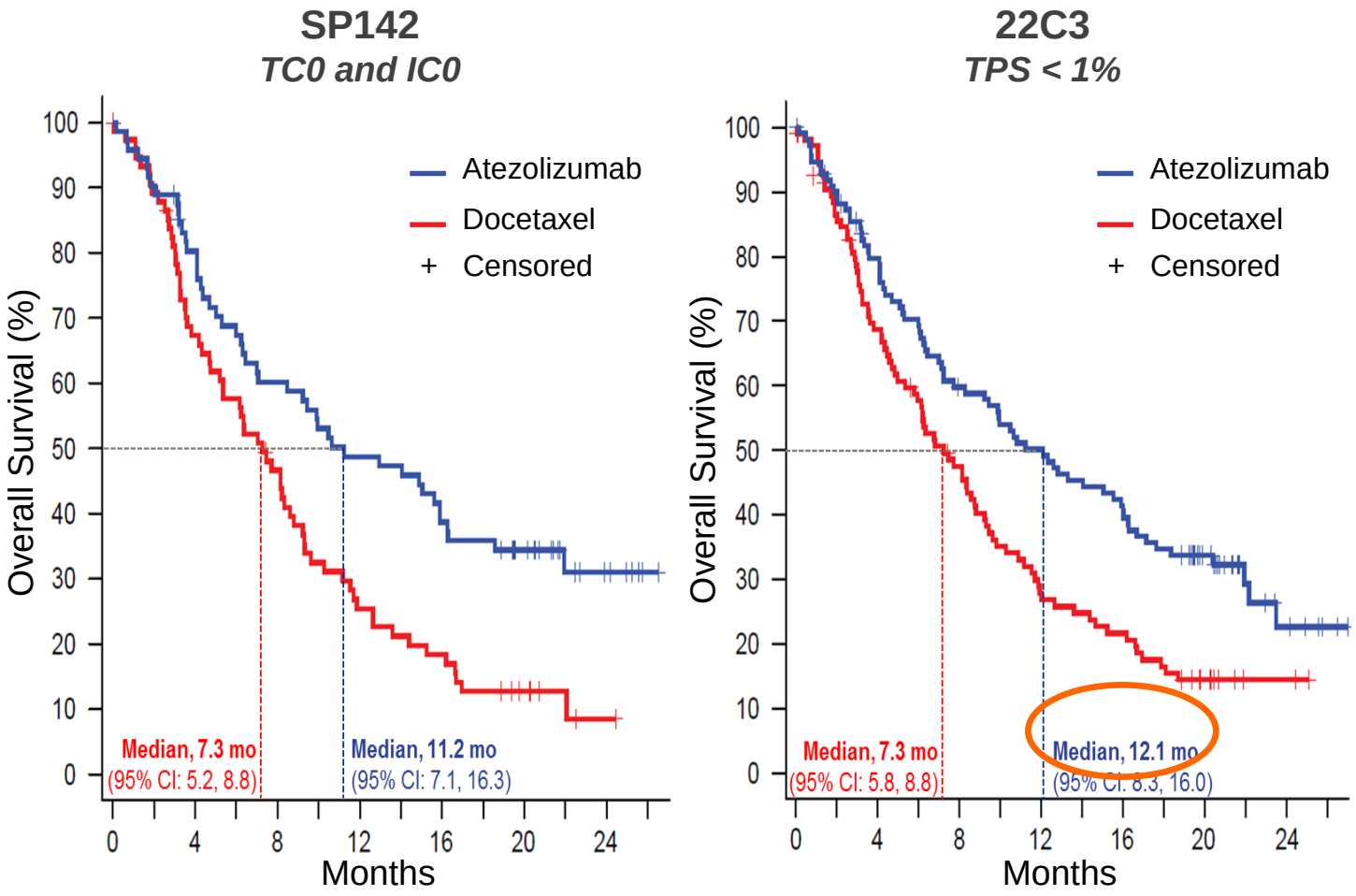
Kato et al; CCR; 2017

OAK Primary Analysis



Gadgeel S, et al. 22C3 vs SP142 in OAK ESMO 2017

Overall Survival in PD-L1 Negative Subgroups in OAK BEP



	OS HR (95% CI)
SP142 Dx- (N = 150)	0.55 (0.37, 0.80)
22C3 Dx- (N = 218)	0.61 (0.45, 0.84)

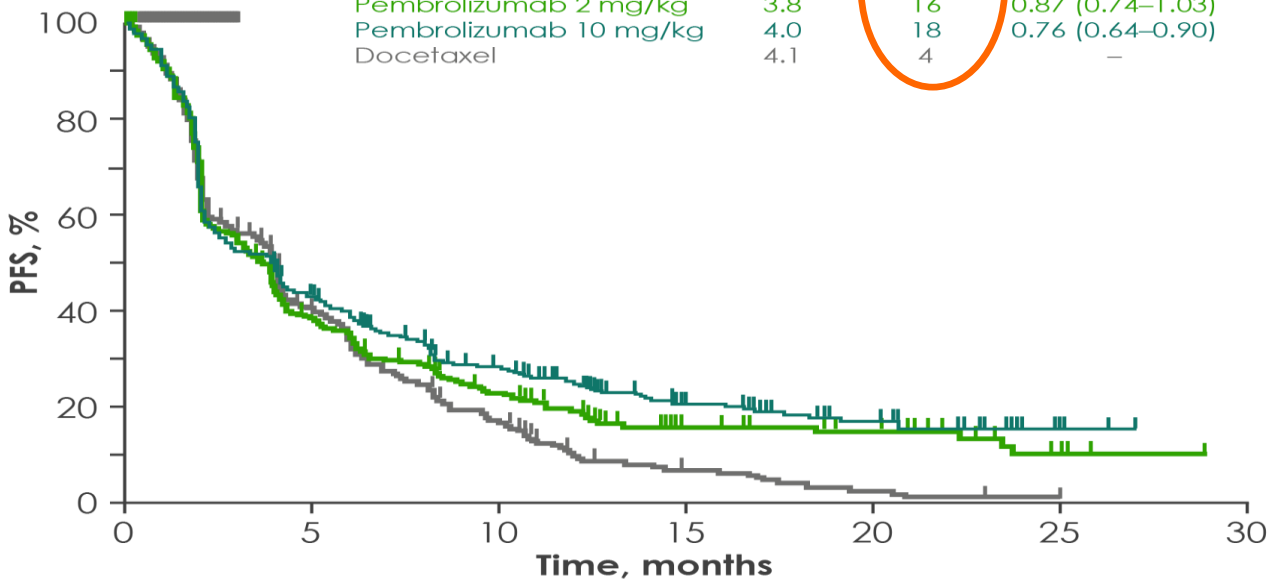
- OS benefit observed in PD-L1 negative populations as defined by either assay

SP142 assay: TC0 and IC0, PD-L1 expression on <1% TC and IC.
22C3 assay: TPS <1%, PD-L1 expression on <1% TC.
Dx-, no or low PD-L1 expression.

Gadgeel S, et al. 22C3 vs SP142 in OAK ESMO 2017

Updated progression-free survival Patients with PD-L1 TPS ≥1%

Treatment arm	Median months	PFS at 18 months	HR (95% CI)	p value[a]
Pembrolizumab 2 mg/kg	3.8	16	0.87 (0.74–1.03)	0.06
Pembrolizumab 10 mg/kg	4.0	18	0.76 (0.64–0.90)	0.0009
Docetaxel	4.1	4	–	–



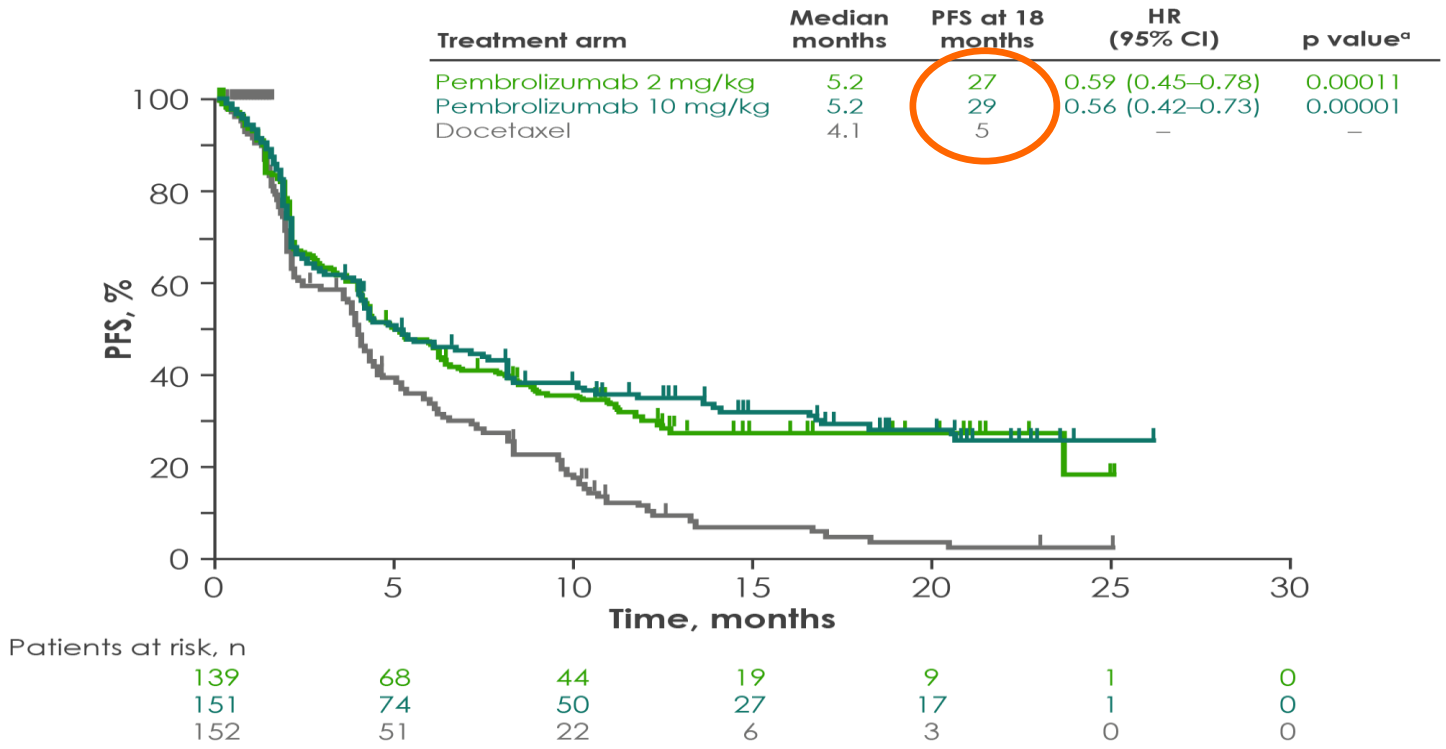
Patients at risk, n

344	128	70	30	17	3	0
346	142	85	40	24	2	0
343	115	45	11	4	0	0

Analysis cut-off date: 31 March 2016.

Herbst RS, et al. ESMO 2016 Poster presentation. Abstract LBA48.

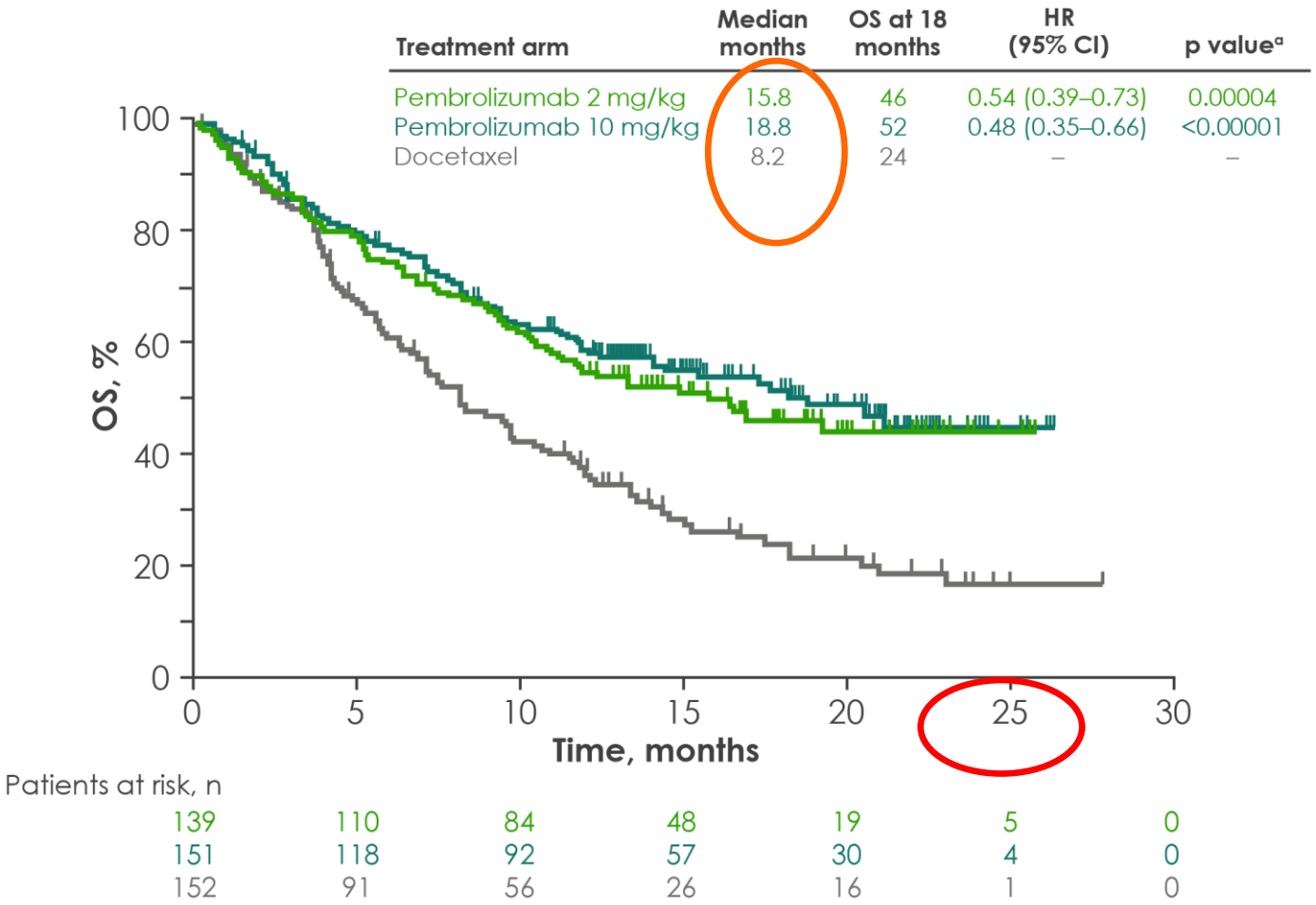
Updated progression-free survival Patients with PD-L1 TPS ≥50%



Analysis cut-off date: 31 March 2016.

Herbst RS, et al. ESMO 2016 Poster presentation. Abstract LBA48.

Updated overall survival
Patients with PD-L1 TPS ≥50%



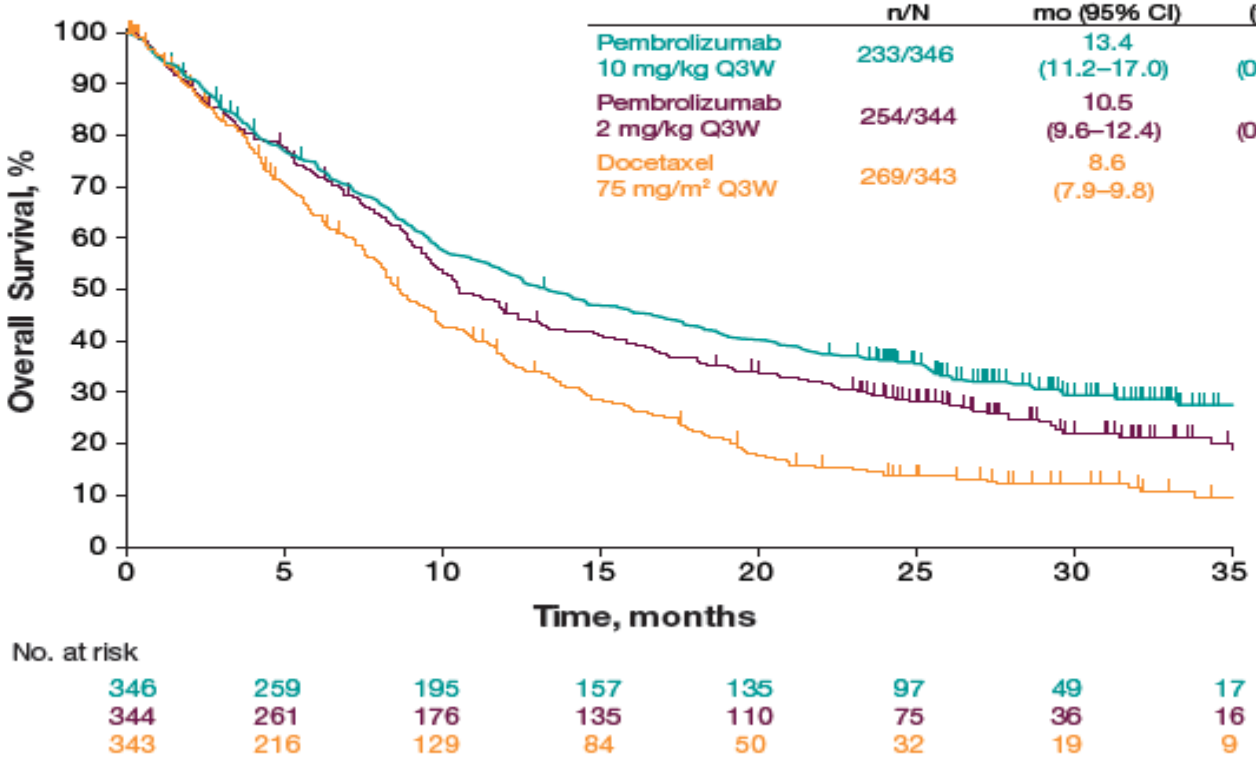
Analysis cut-off date: 31 March 2016.

Herbst RS, et al. ESMO 2016 Poster presentation. Abstract LBA48.

Updated overall survival at 30-mo!

Overall Survival

Figure 2. Kaplan-Meier Estimates of OS



	Events, n/N	Median, mo (95% CI)	Hazard Ratio (95% CI)[a]	*P* value[b]	30-mo rate, % (95% CI)
Pembrolizumab 10 mg/kg Q3W	233/346	13.4 (11.2–17.0)	0.59 (0.49–0.71)	< 0.00001	29.5 (24.4–34.8)
Pembrolizumab 2 mg/kg Q3W	254/344	10.5 (9.6–12.4)	0.73 (0.62–0.87)	0.00024	22.1 (17.4–27.1)
Docetaxel 75 mg/m² Q3W	269/343	8.6 (7.9–9.8)	—	—	12.3 (8.8–16.5)

[a]Hazard ratio for comparison with docetaxel.

[b]*P* value for comparison with docetaxel. No formal statistical comparison of the difference between treatment arms was performed; therefore, *P* values are nominal only.

Summary

Multimodality approach from stage Ib (CT+S; CT+S+RT)

In first line oncogene non addicted patients (70% of all NSCLC):

- Platinum based doublet chemotherapy is still a backbone for NSCLC therapy in PDL1<50%
- Maintenance therapy with Pemetrexed after front line chemotherapy improves overall survival in Non-squamous NSCLC
- In PDL-1 >50% immunotherapy with Pembrolizumab is the treatment of choice

In second line NSCLC setting:

- Immunotherapy with Nivolumab and Pembrolizumab (TPS >1%) is the option for squamous NSCLC and an option for Non-squamous NSCLC
- Nintedanib, multikinase inhibitor associated with docetaxel improves survival in non-squamous NSCLC

In oncogene addicted patients:

- In EGFRm single agent EGFR-Tkis in front line remain the best treatment option
- In ALK+ crizotinib in front line and at PD ceritinib and alectinib are the treatments of choice