Tumori del polmone

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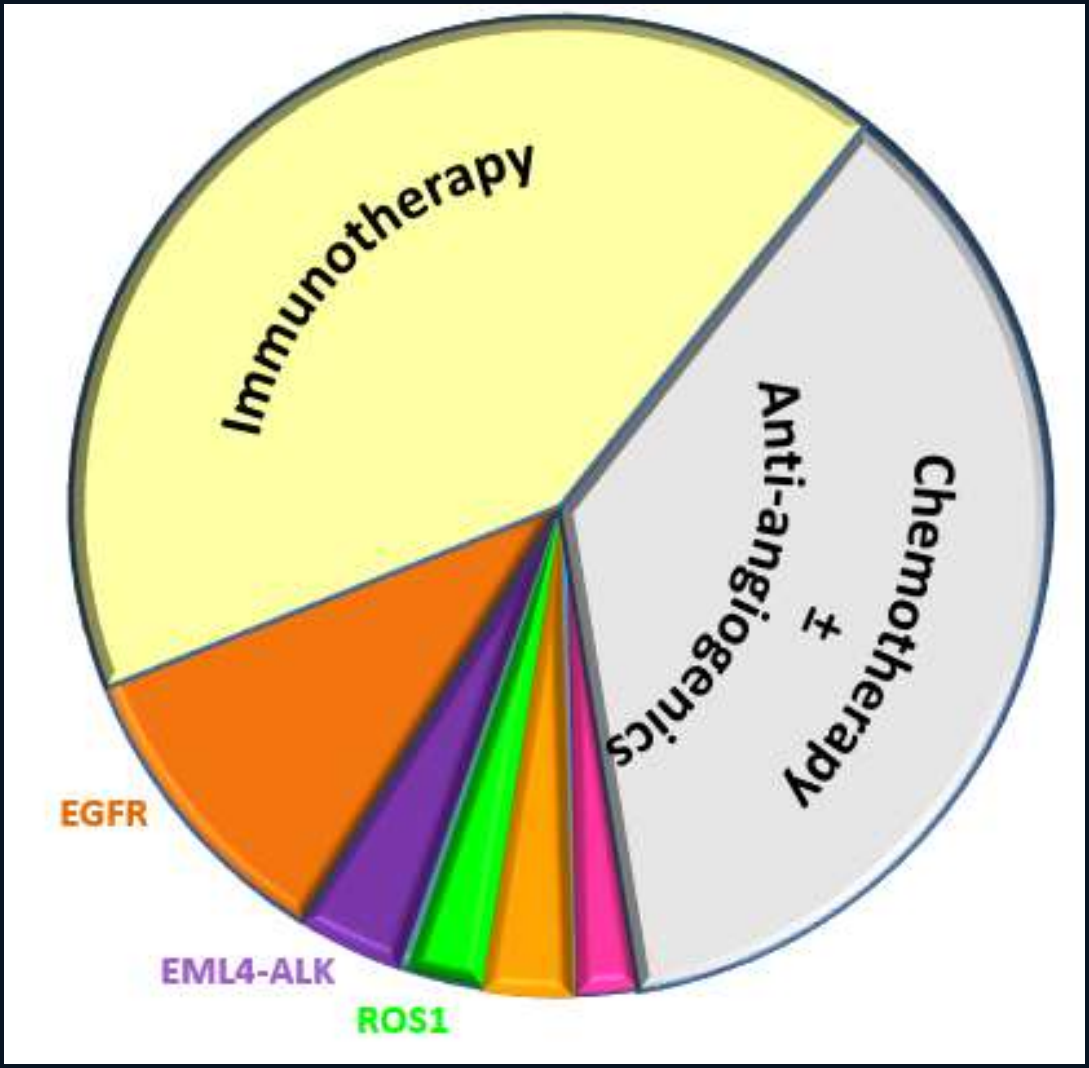
Milano

NSCLC - Clinical practice



Trattamento del NSCLC

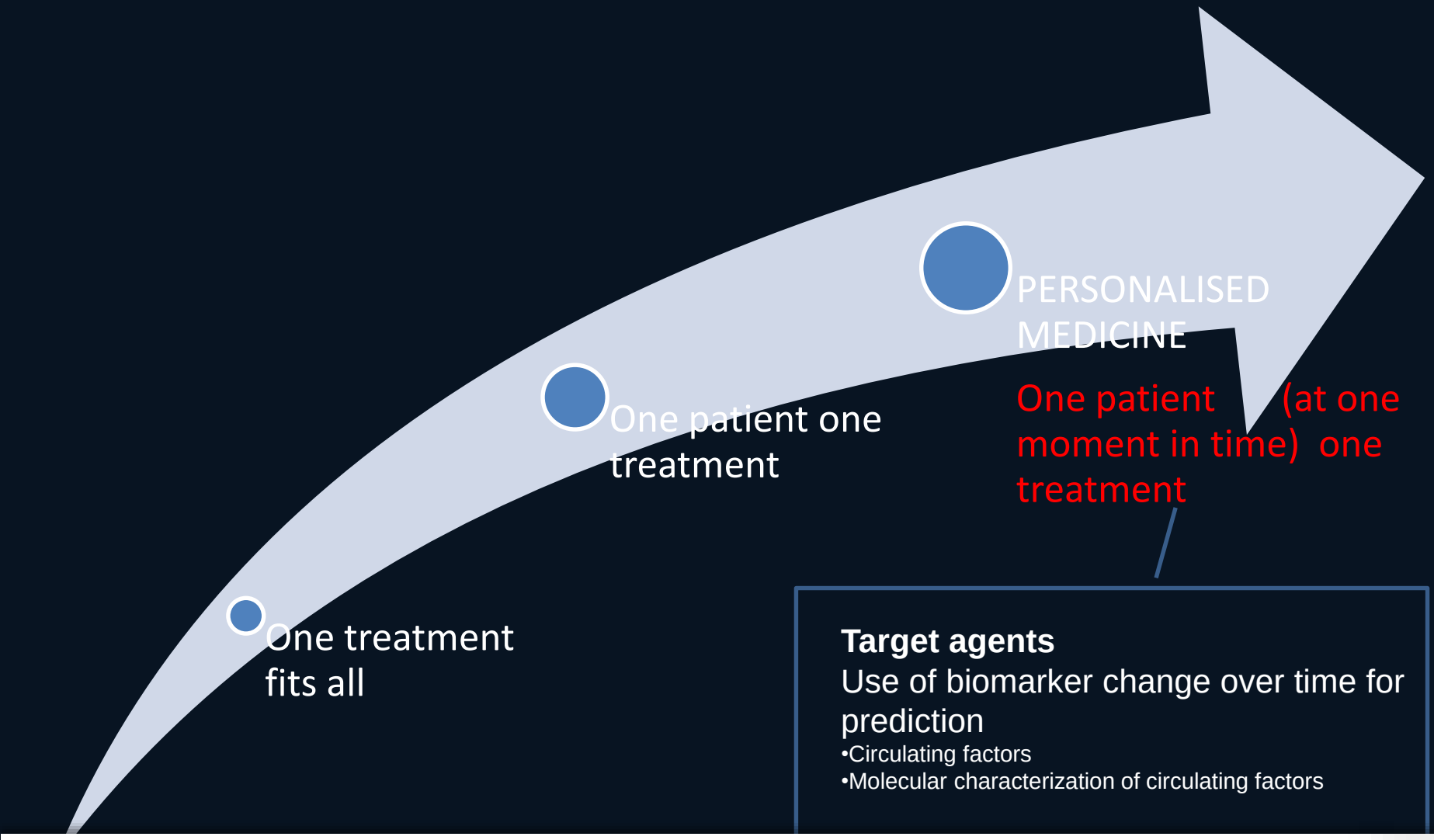
Fattori relativi alla malattia

1. Precisa definizione dello stadio
2. Precisa definizione anatomopatologica del sottotipo istologico
3. Adeguata caratterizzazione molecolare e valutazione di PDL1

4. Fattori relativi al paziente

5. Performance status
6. Presenza di comorbidità
7. Età anagrafica
8. *Specifiche preferenze*

Evolution of concepts for use of biomarkers



- *Incoraggiare la cessazione del fumo*

  può modificare la biodisponibilità dei farmaci e condiziona l'andamento della malattia ->

  la cessazione del fumo è parte ***integrante del programma di cura***

- *Mantenere il paziente all'interno di percorsi multidisciplinari* (possibile impiego di procedure loco-regionali nell'ambito della malattia avanzata)

Qualità globaledell'evidenza	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	La sottotipizzazione del NSCLC con l'utilizzo almeno di un minimo pannello immunoistochimico comprendente un marcatore di differenziazione adenocarcinoma (TTF-1) ed uno di differenziazione squamocellulare (p40 o p63) dovrebbe essere considerata come opzione di prima intenzione. Così facendo, la quota di NSCLC non altrimenti specificati (N.A.S.) deve risultare inferiore al 10%.	**Positiva forte**
Moderata	La determinazione dello stato mutazionale di *EGFR* dovrebbe essere considerata come opzione di prima intenzione per scegliere la migliore strategia terapeutica in pazienti con NSCLC in stadio avanzato, con istotipo adenocarcinoma, carcinoma a grandi cellule, NSCLC misto con adenocarcinoma, e NSCLC N.A.S., i quali presentano la più alta probabilità di riscontro di mutazioni.	**Positiva forte**
	l'esame di *ALK* dovrebbe essere preso in considerazione come opzione di prima intenzione.	

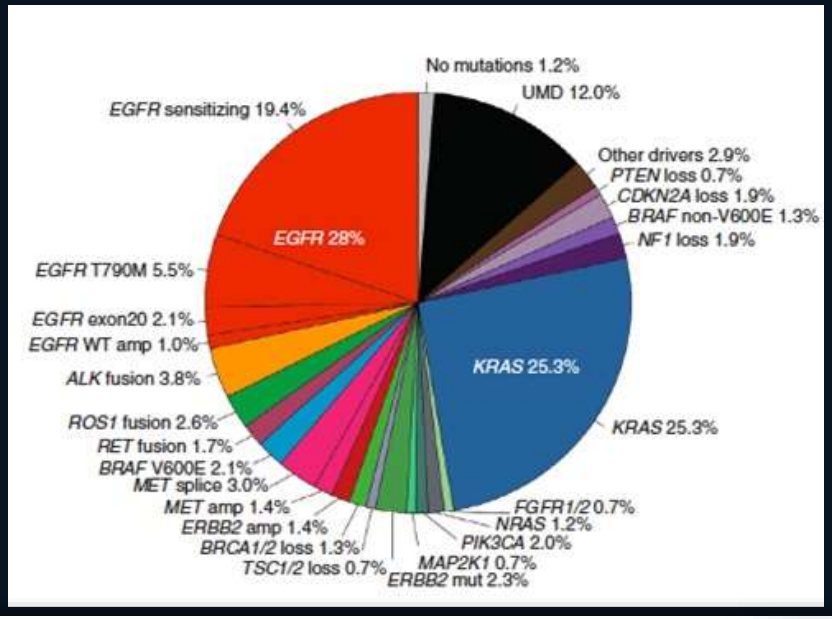
Due mondi diversi

What would we like to know?

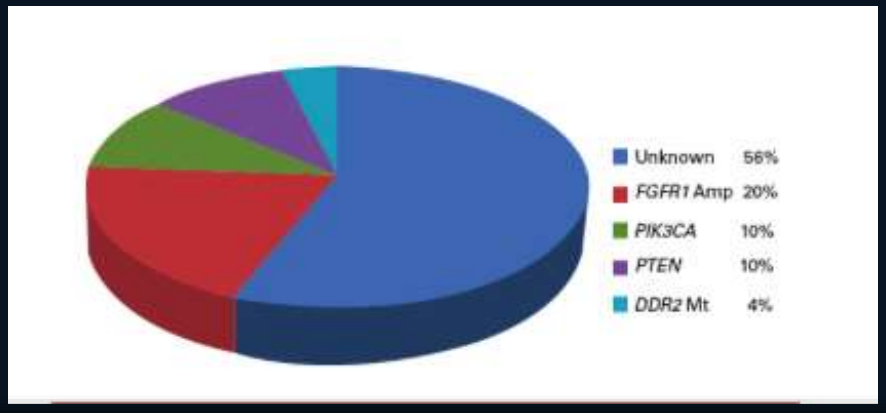
PD-L1 Status

Single nucleotide variations (SNVs)	EGFR, BRAF, HER2, TMB
Insertions and deletions (indels)	EGFR
Copy number variations (CNVs)	MET,HER2
Rearrangements	ALK, ROS1, RET
Splice variants	MET

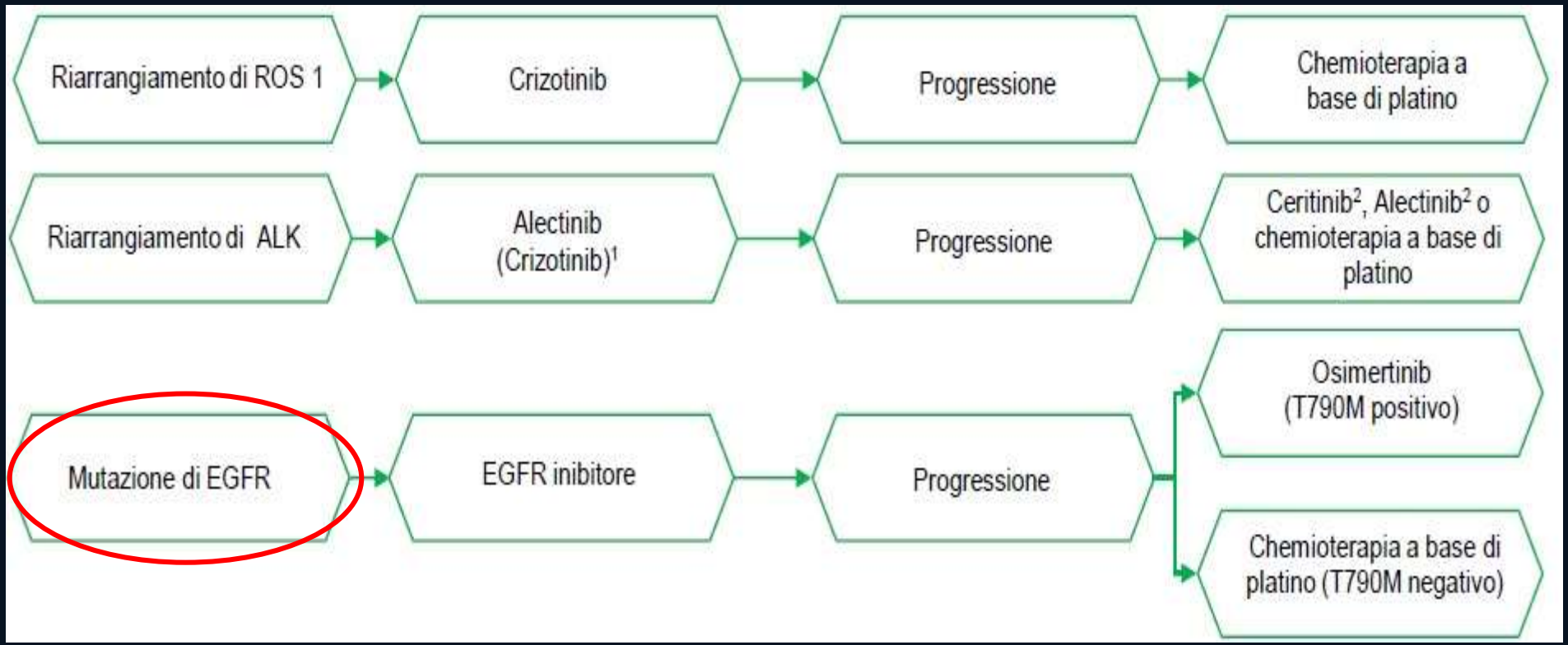
Adenocarcinoma



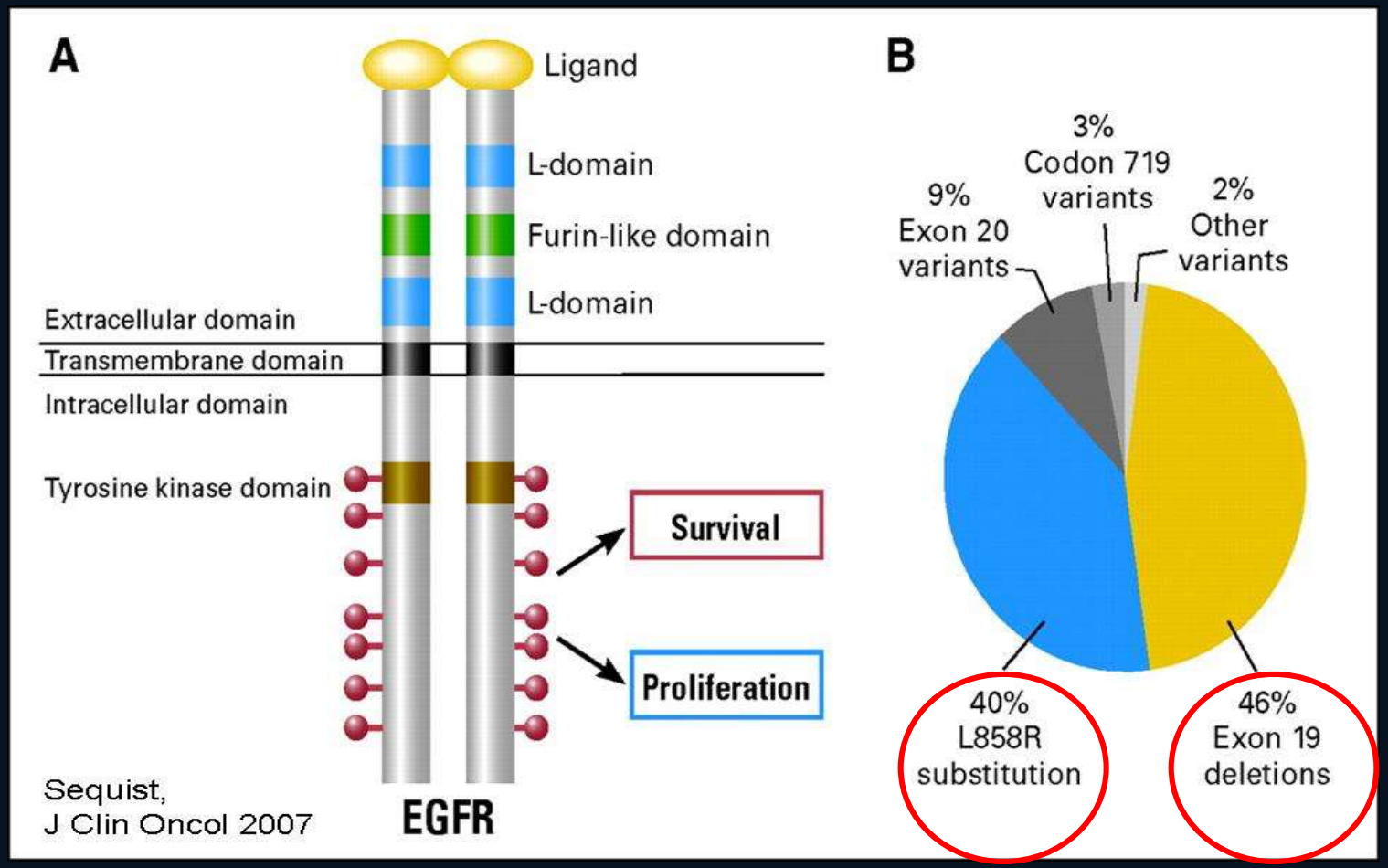
Squamous cell carcinoma



Malattia oncogene-addicted

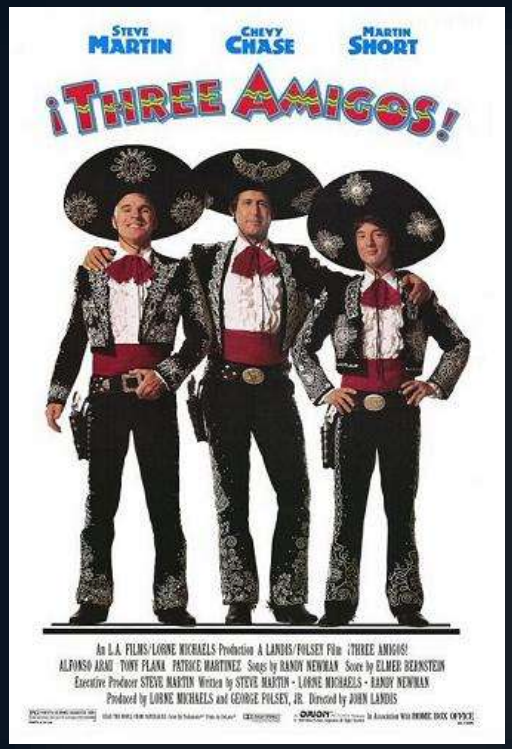


EGFR mutations



Qualità globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Molto bassa	Nei pazienti affetti da NSCLC in stadio localmente avanzato o metastatico con mutazione di *EGFR* classica (Ex19del, L858R), un trattamento di prima linea con un inibitore tirosino-chinasico di EGFR come gefitinib, erlotinib o afatinib deve essere preso in considerazione come opzione terapeutica di prima scelta [139-146].	**Positiva forte**
Molto bassa	Nei pazienti con NSCLC localmente avanzato o metastatico con mutazioni non comuni di *EGFR* (mutazioni/duplicazioni degli esoni 18-21), il trattamento con inibitore tirosino-chinasico di EGFR (gefitinib, erlotinib o afatinib) può essere preso in considerazione come opzione terapeutica di prima scelta [158-164].	**Positiva debole**
Molto bassa	Nei pazienti con NSCLC localmente avanzato o metastatico con inserzione dell'esone 20 o mutazione T790M *de novo* di *EGFR* il trattamento con inibitore tirosino-chinasico di EGFR (gefitinib, erlotinib o afatinib) non deve essere preso in considerazione come opzione terapeutica [158-164].	**Negativa forte**

Quale EGFR-TKI in EGFR mutati? Indicazioni AIFA



Gefitinib

Indicato in qualunque linea in EGFR mutati

Erlotinib

Indicato in I linea negli EGFR mutati; II-III linea indipendentemente da EGFR

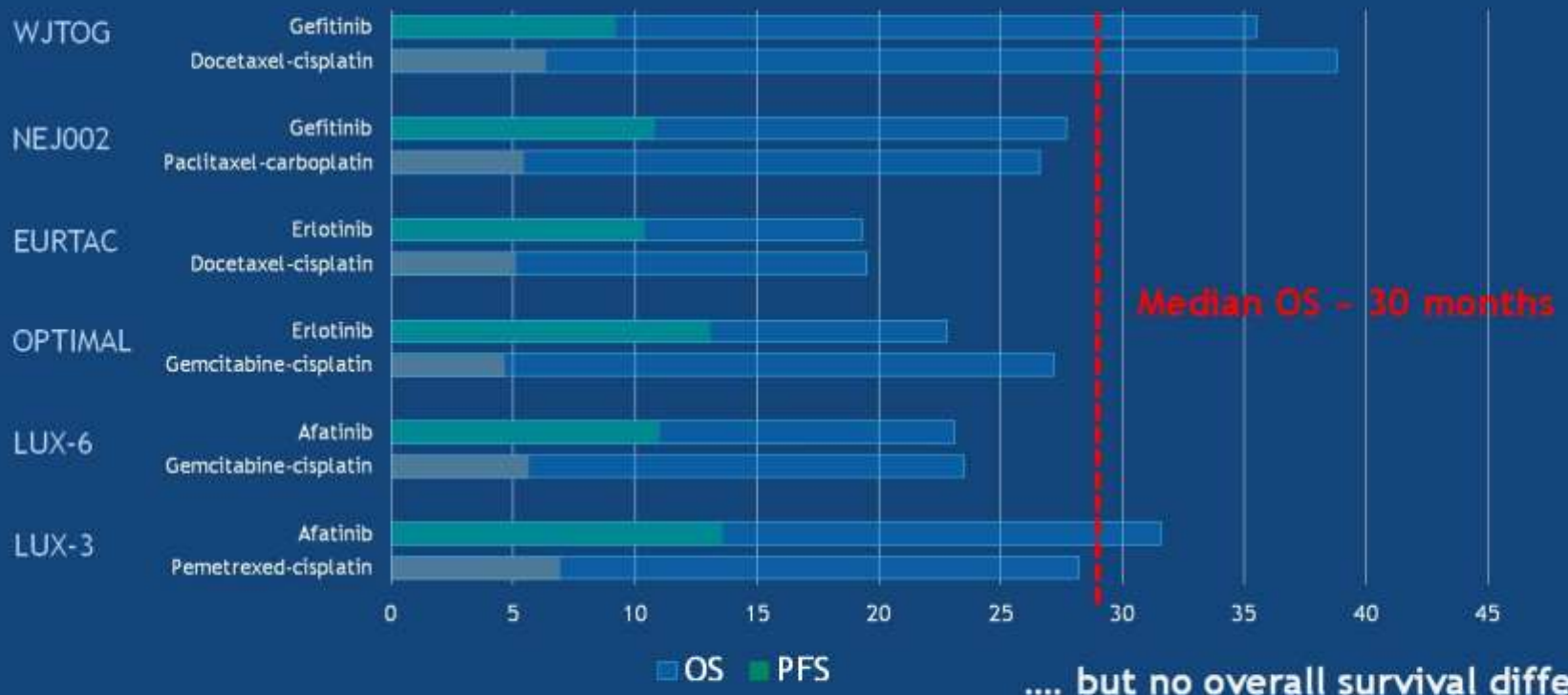
Afatinib

Indicato in I linea negli EGFR mutati

EGFR TKIs in First Line (PFS)

	EGFR TKIs	Chemio	N° mutati	HR-PFS	95%CI
IPASS	gefitinib	Carbo/taxol	261	0.48	0.36-0.64
First-SIGNAL	gefitinib	Cis/gem	309	0.54	0.26-1.10
CALGB 30406	erlotinib	Carbo/taxol	181	0.81	0.68-0.85
WJTOG	gefitinib	Cis/doc	177	0.48	0.33-0.71
NEJSG	gefitinib	Carbo/taxol	230	0.30	0.22-0.41
OPTIMAL	erlotinib	Carbo/gem	164	0.16	0.10-0.26
EURTAC	erlotinib	Every platinum	174	0.37	0.25-0.54
TORCH	erlotinib	Cis/gem	39	0.86	n.a-1.40
LUX-LUNG3	afatinib	Cis/pem	308	0.47	0.34-0.65
LUX-LUNG 6	afatinib	Cis/gem	364	0.28	0.20-0.39

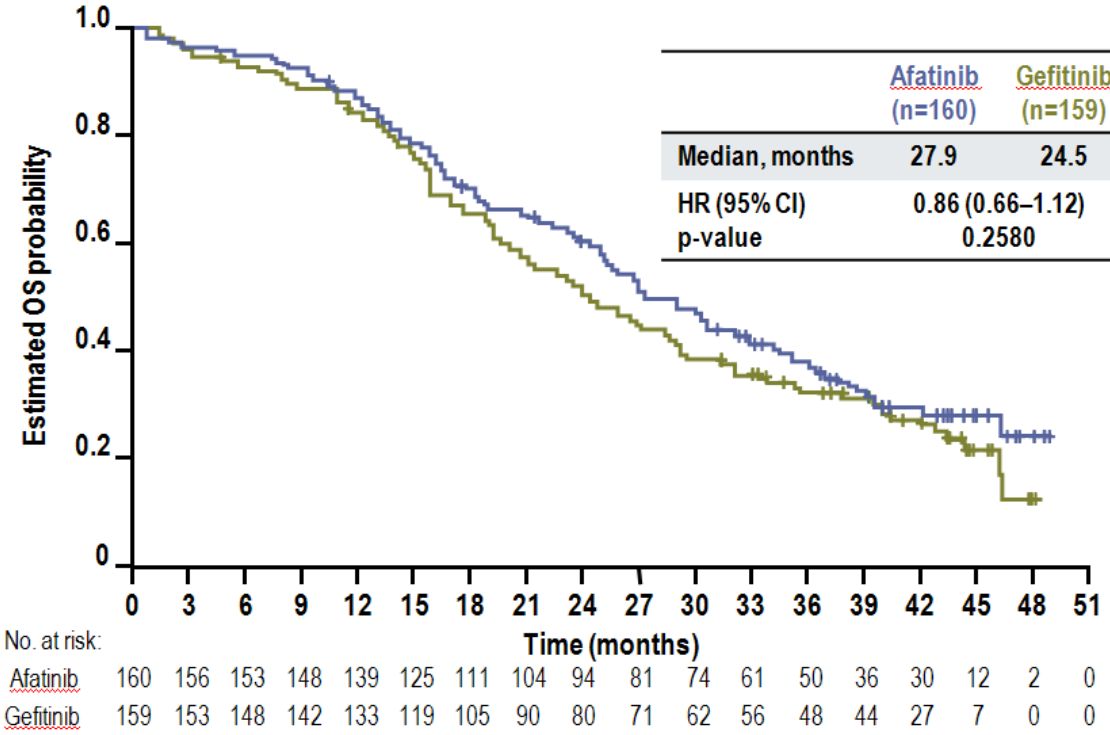
EGFR TKIs approved in 1L: PFS benefit



.... but no overall survival difference

LUX-Lung7: Sopravvivenza globale

OS (OVERALL POPULATION)



	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

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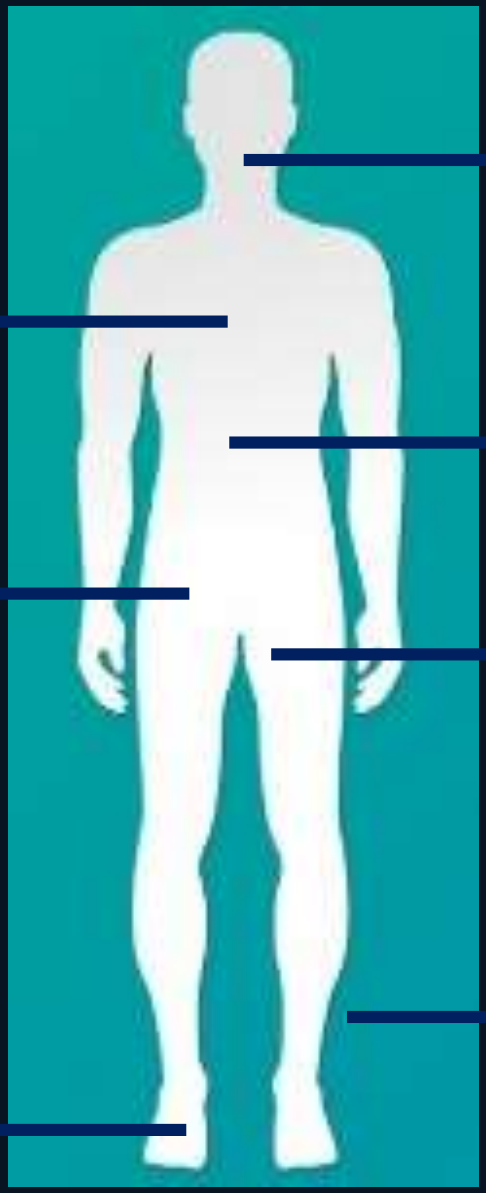
Fatigue:
Afatinib: 10-17%
Gefitinib: 10-39%
Erlotinib: 5-57%

Anorexia:
Afatinib: 10-20%
Gefitinib: 14-44%
Erlotinib: 31%

Transaminitis:
Erlotinib: 6%
Afatinib: 11%
Gefitinib: 40-60%

Paronichia:
Erlonib: 4%
Gefitinib: 13-32%
Afatinib: 32-56%



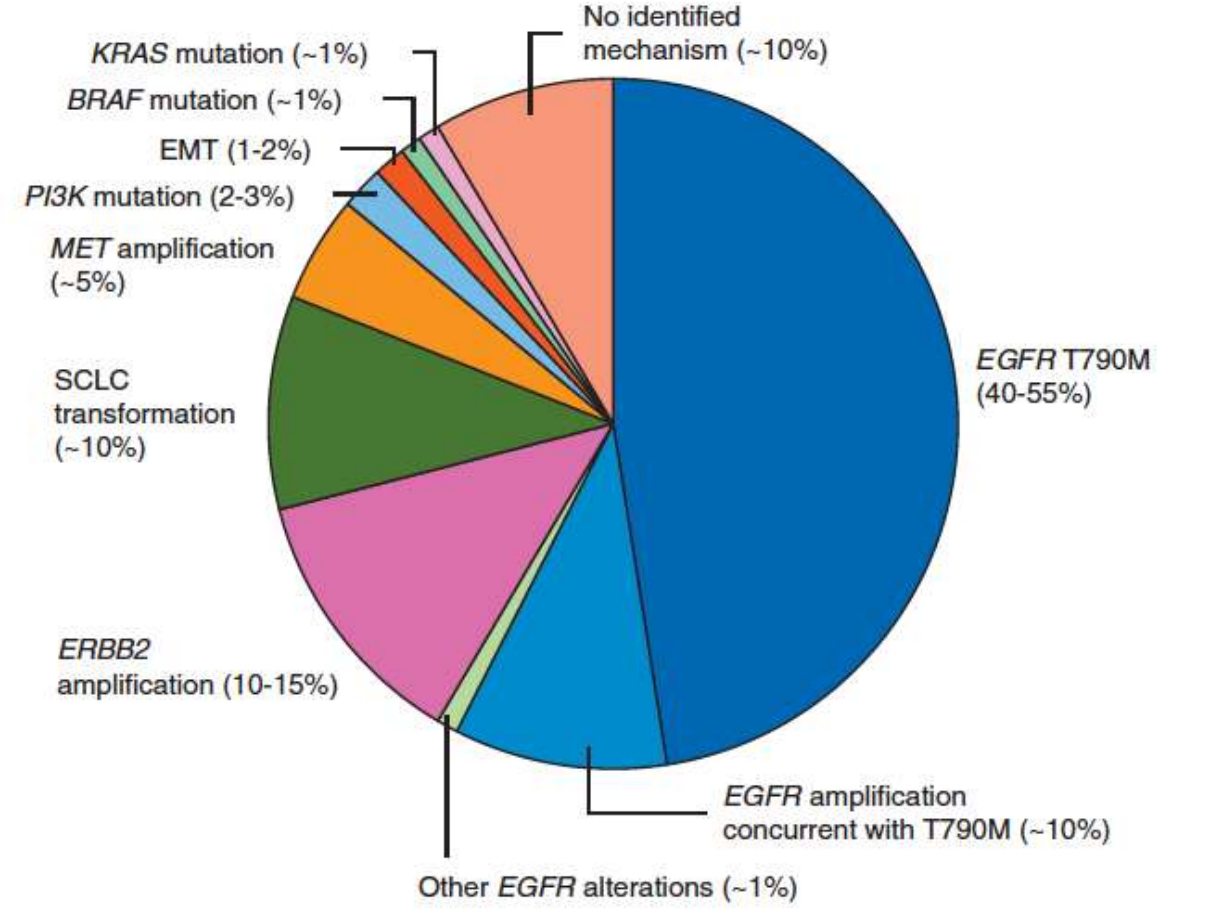
Stomatitis:
Erlonib: 13%
Gefitinib: 9-40%
Afatinib: 50-72%

Vomiting:
Erlonib: 1%
Afatinib: 9-17%
Gefitinib: 12-19%

Diarrhoea:
Erlonib: 25-57%
Gefitinib: 34-54%
Afatinib: 88-95%

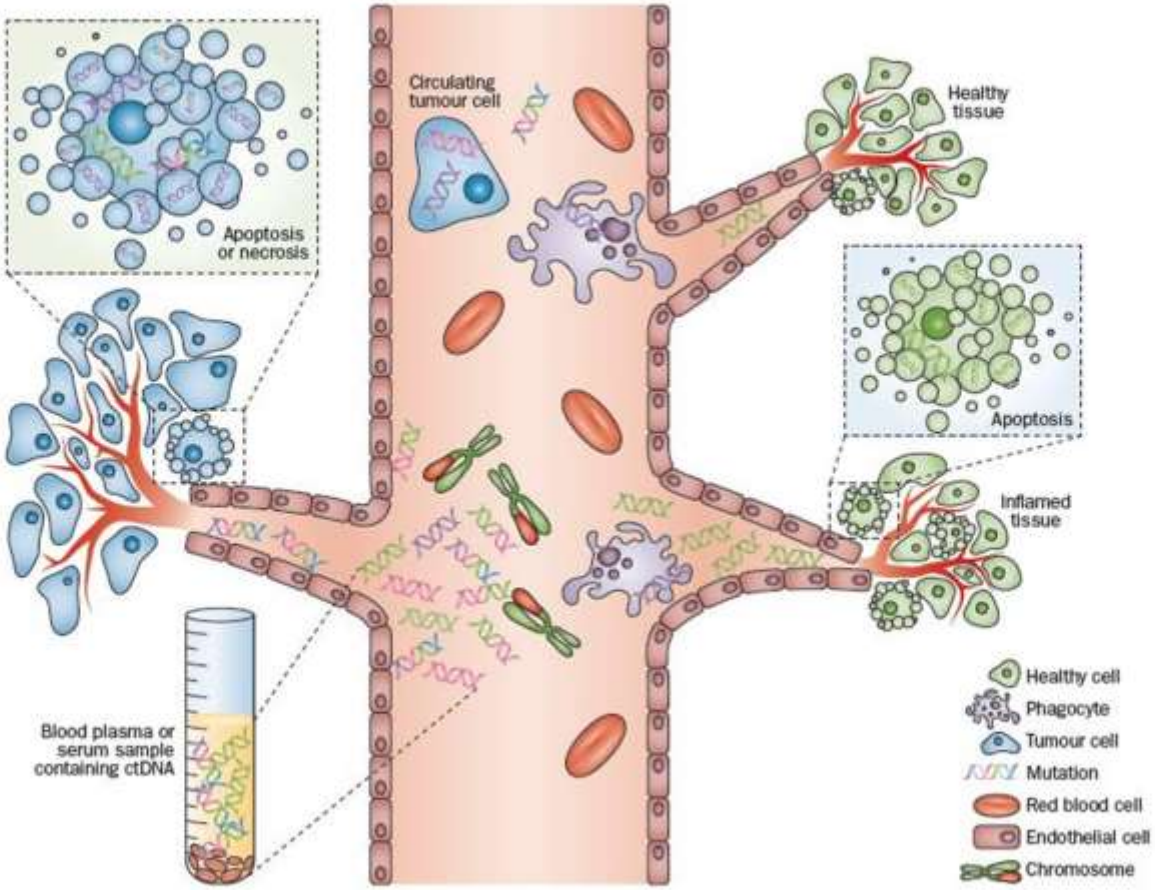
Skin Rash:
Gefitinib: 49-85%
Erlotinib: 73-79%
Afatinib: 80-89%

EGFR mutati
meccanismi di resistenza a TKI di I-II gen



Westover et al, Ann Oncol 2018

Can we find EGFR T790M from the blood ?

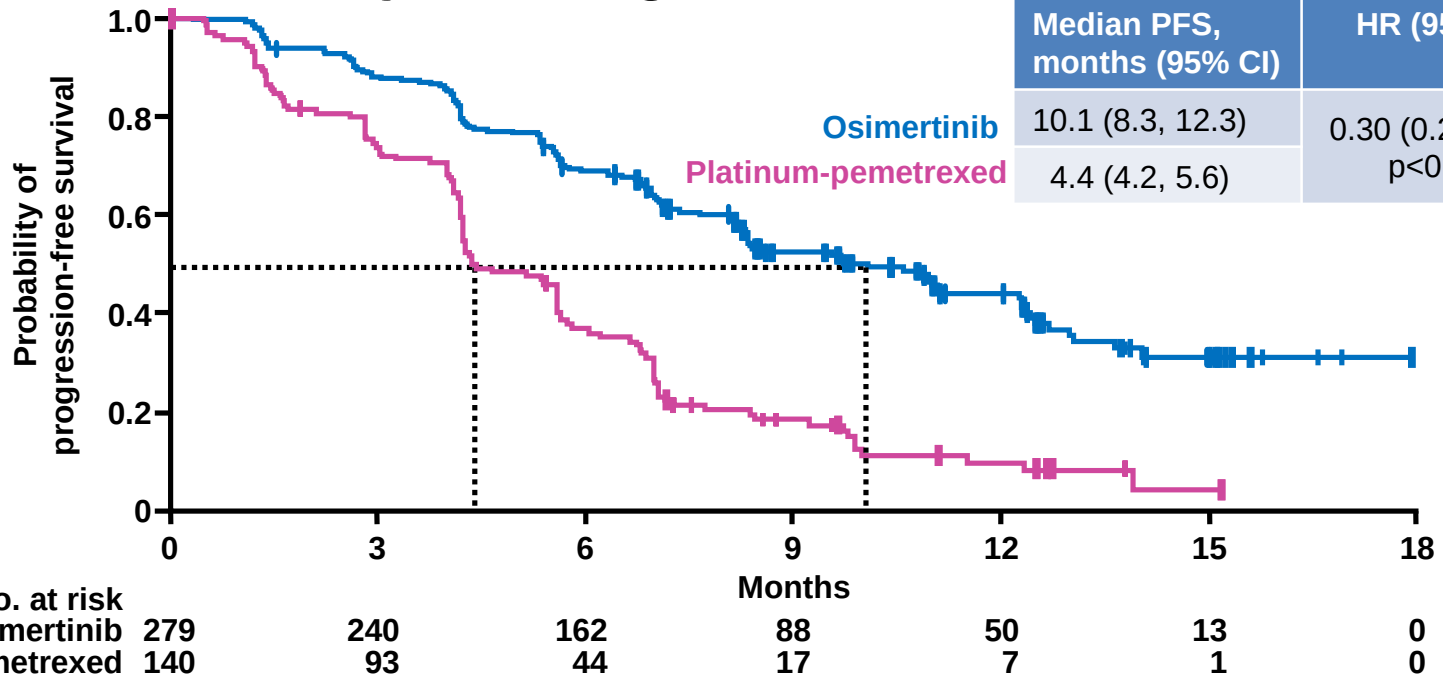


Crowley E et al. Nat Rev Clin Oncol. 2013;10(8):472-84.

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione clinica
Molto bassa	Nei pazienti affetti da NSCLC in stadio avanzato con mutazione attivante l'*EGFR* classica (Ex19del, L858R) e con mutazione T790M dimostrata (mediante biopsia liquida o solida) al momento della progressione a gefitinib, erlotinib o afatinib, un trattamento con osimertinib deve essere preso in considerazione come opzione terapeutica di prima scelta [168].	**Positiva forte**

AURA3 primary endpoint: PFS by investigator assessment

	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	10.1 (8.3, 12.3)	0.30 (0.23, 0.41) p<0.001
Platinum-pemetrexed	4.4 (4.2, 5.6)	

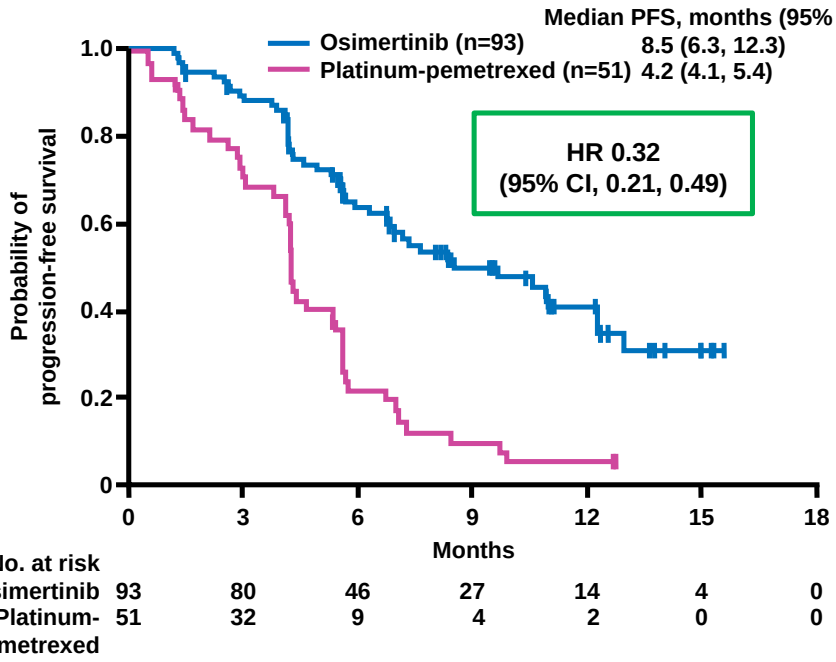


- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

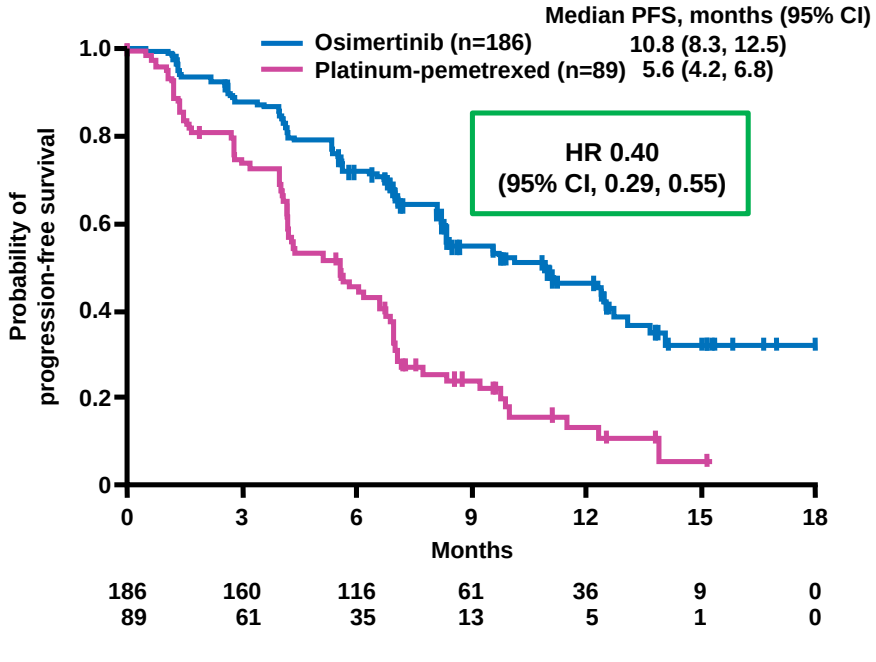
Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death; calculated using the Kaplan-Meier approach. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data; CI, confidence interval

PFS benefit in AURA3 patients with CNS metastases at baseline

With CNS metastases



Without CNS metastases



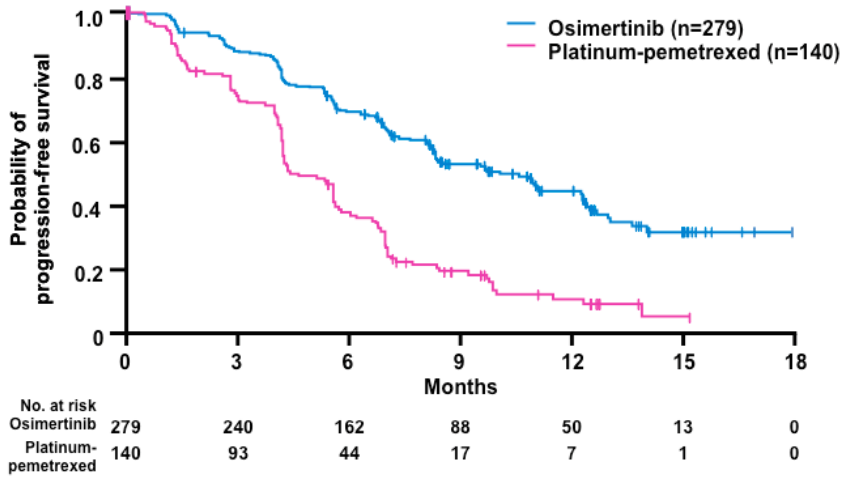
Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death; calculated using the Kaplan-Meier approach. Progression included deaths in the absence of RECIST progression. Tick marks indicate censored data. CNS metastases determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy.

Osimertinib – plasma AURA 3

AURA3: osimertinib benefit in patients with plasma T790M-positive status is similar to patients with tumour tissue T790M-positive status

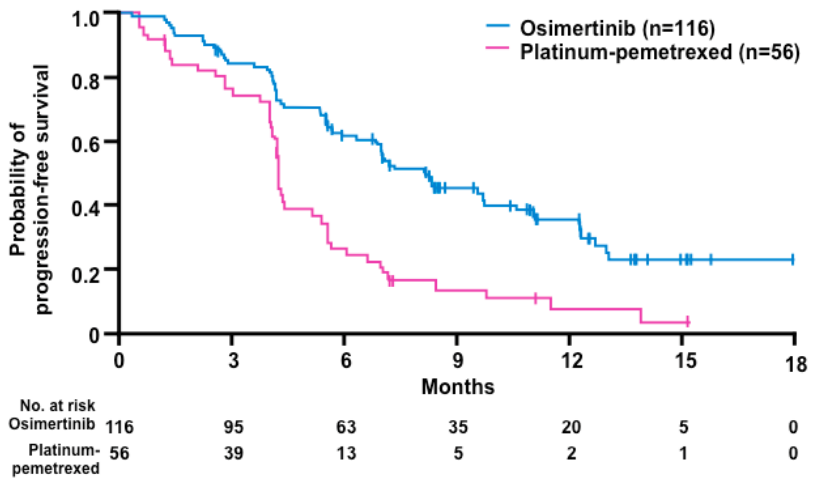
Tumour T790M-positive (intent-to-treat)*

	Osimertinib	Platinum-pemetrexed
PFS HR (95% CI)	0.30 (0.23, 0.41)*, p<0.001	
Median PFS, months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
ORR†, % (95% CI)	71 (65, 76)	31 (24, 40)



Plasma T790M-positive status

	Osimertinib	Platinum-pemetrexed
PFS HR (95% CI)	0.42 (0.29, 0.61)	
Median PFS, months (95% CI)	8.2 (6.8, 9.7)	4.2 (4.1, 5.1)
ORR†, % (95% CI)	77 (68, 84)	39 (27, 53)



Tick marks indicate censored data. PFS is defined as time from randomisation until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression. Osimertinib administered 80 mg orally once daily. Platinum-pemetrexed group treatment consisted of pemetrexed 500 mg/m^2 + carboplatin AUC 5 or cisplatin 75 mg/m^2 Q3W for up to 6 cycles + optional maintenance pemetrexed for patients whose disease had not progressed after 4 cycles of platinum-pemetrexed. RECIST v1.1 assessments performed every 6 weeks until objective disease progression.
*PFS adjusted for ethnicity. All patients were selected using a tumour tissue test for *EGFR* T790M (by **cobas**® EGFR Mutation Test) from a biopsy after disease progression prior to study entry; †Response did not require confirmation per RECIST v1.1; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

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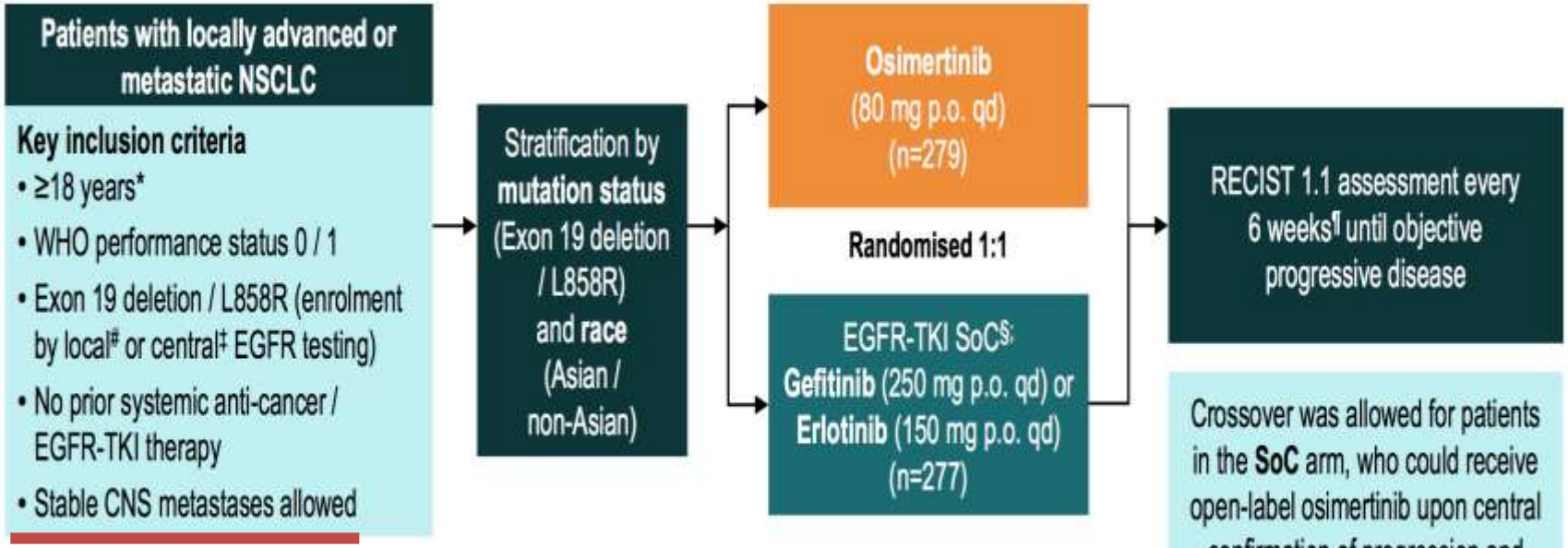
FLAURA DOUBLE-BLIND STUDY DESIGN

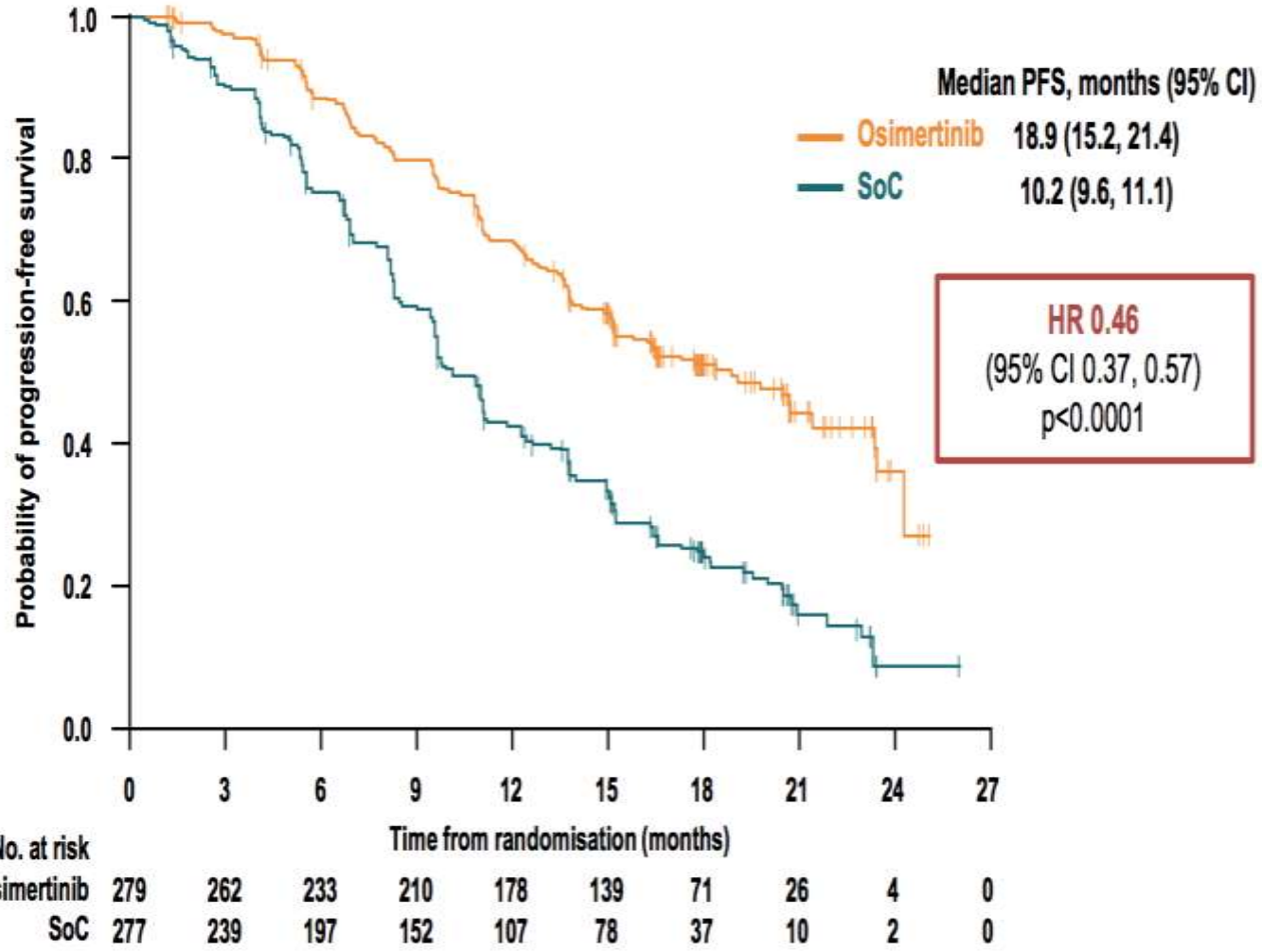


Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

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

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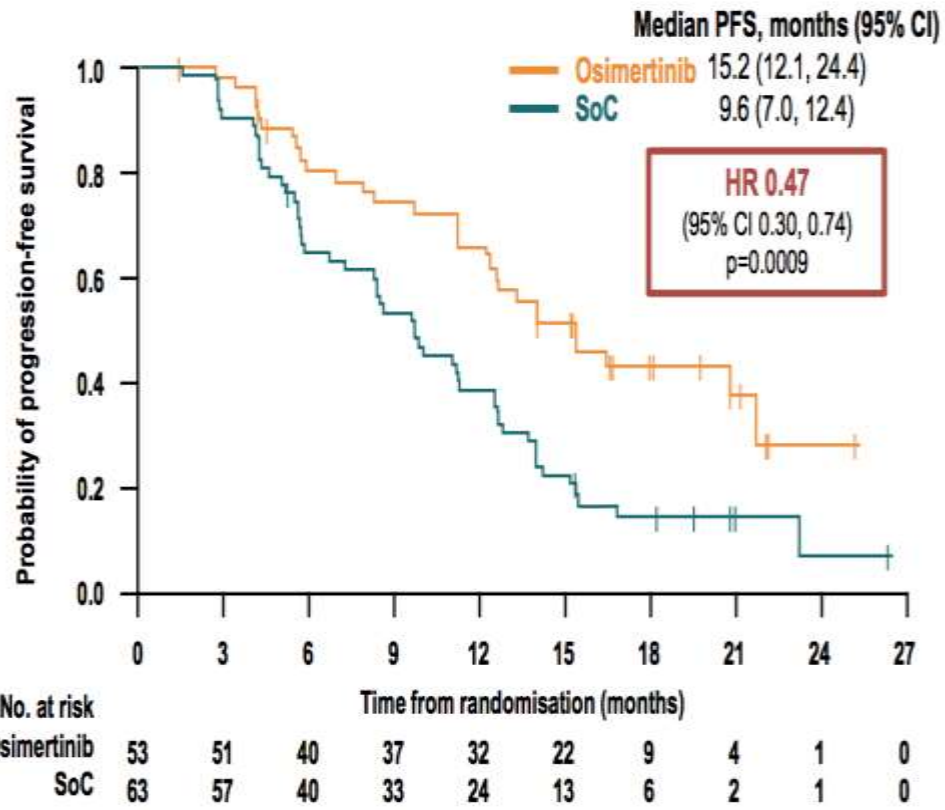
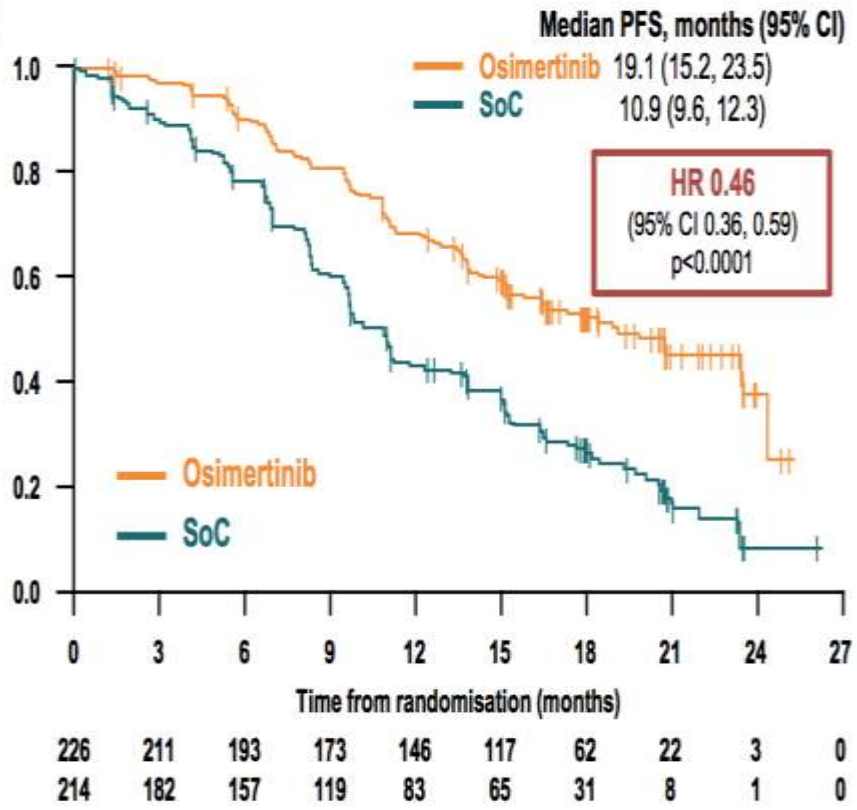
PFS* IN PATIENTS WITH AND WITHOUT CNS METASTASES AT STUDY ENTRY

With CNS metastases (n=116)



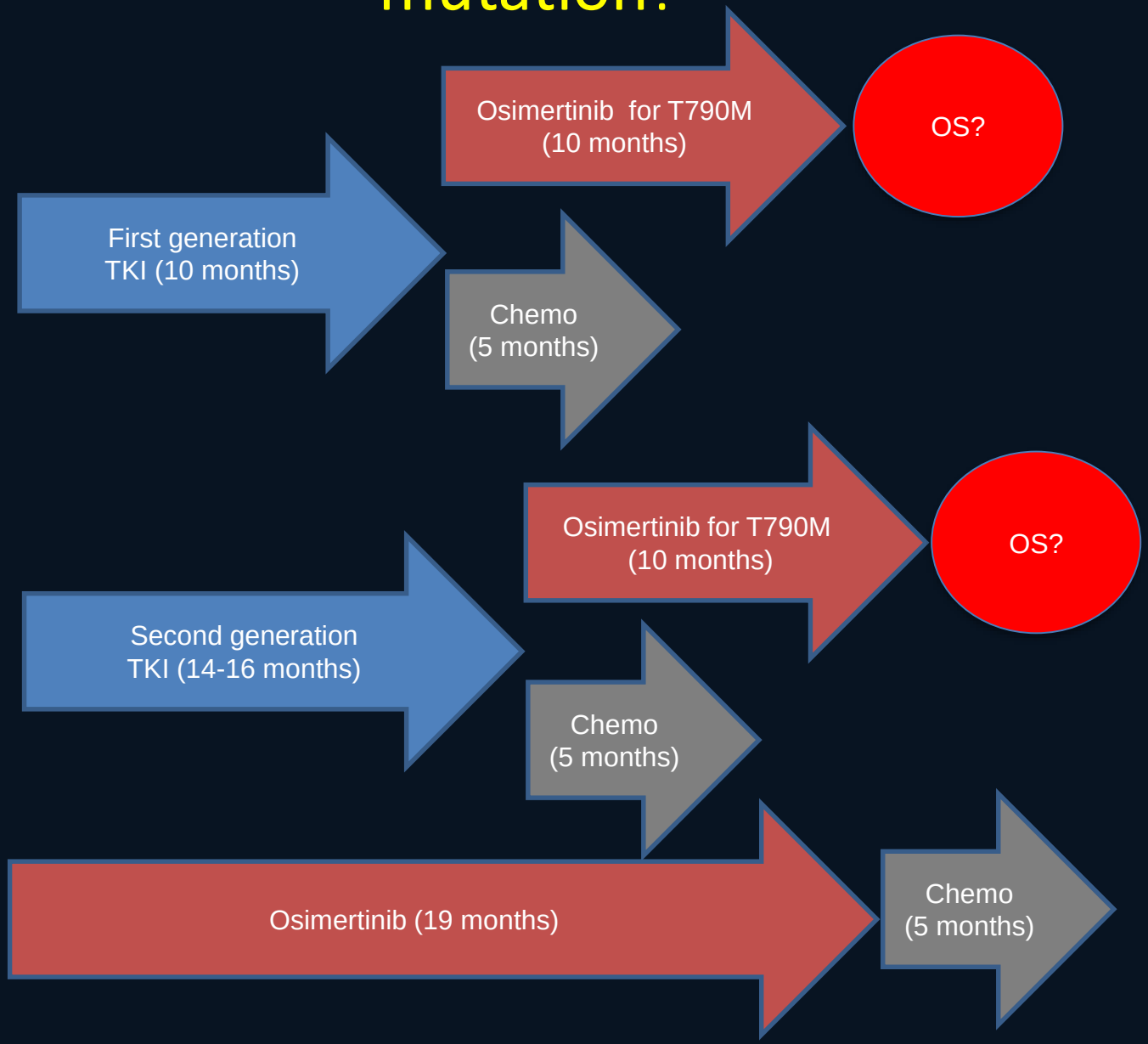
Without CNS metastases (n=440)



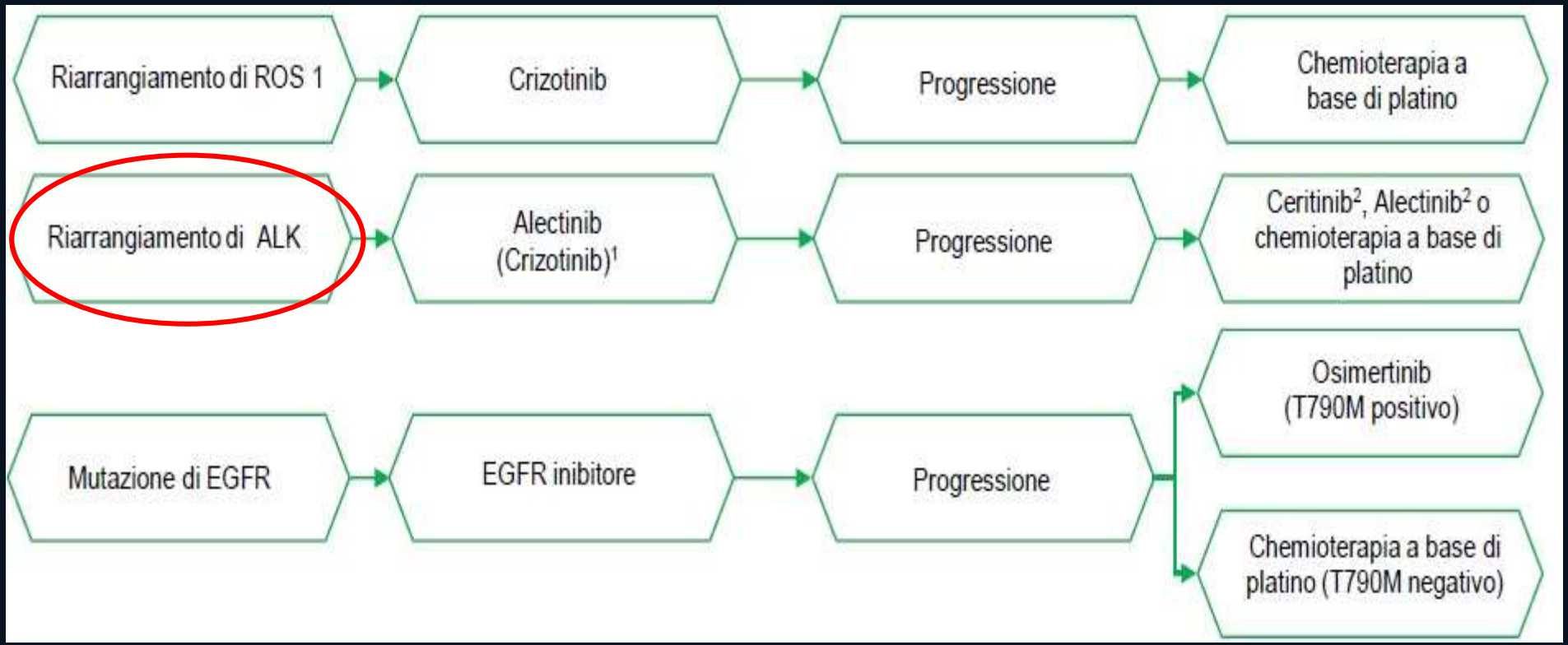
CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data; *By Investigator assessment
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PFS, progression-free survival; SoC, standard-of-care

Optimal sequence for EGFR mutation?



Malattia oncogene-addicted



Pazienti ALK riarrangiati

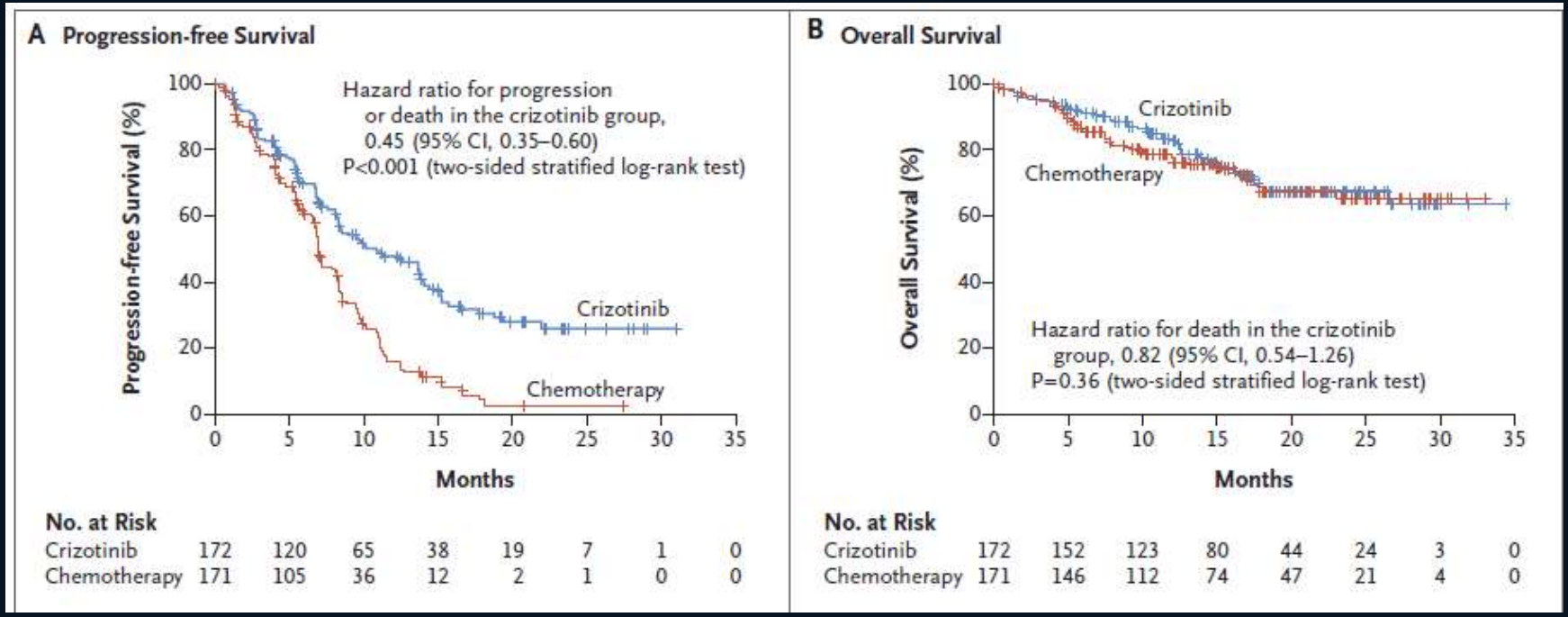
Qualità globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Molto bassa	Nei pazienti affetti da NSCLC in stadio localmente avanzato o metastatico con riarrangiamento di *ALK*, un trattamento di di prima linea con crizotinib deve essere preso in considerazione come opzione terapeutica di prima scelta rispetto alla chemioterapia [170].	**Positiva forte**

Molto bassa	Nei pazienti affetti da NSCLC in stadio localmente avanzato o metastatico con riarrangiamento di *ALK*, un trattamento di prima linea con alectinib deve essere preso in considerazione come opzione terapeutica di prima scelta rispetto al crizotinib [171,172].	**Positiva forte**

ORIGINAL ARTICLE

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

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D.,



Solomon BJ, et al. N Engl J Med 2014

Antitumor Activity – PFS and ORR[a]

	ITT population		Brain metastases present[b]		Brain metastases absent[b]	
	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (n=39)	Chemotherapy (n=40)	Crizotinib (n=132)	Chemotherapy (n=131)
Median PFS, mo (95% CI)	10.9 (8.3–13.9)	7.0 (6.8–8.2)	9.0 (6.8–15.0)	4.0 (1.5–6.8)	11.1 (8.3–14.0)	7.2 (6.9–8.3)
HR (95% CI)	0.45 (0.35–0.60)		0.40 (0.23–0.69)		0.51 (0.38–0.69)	
P[c]	<0.001		<0.001		<0.001	
ORR, % (95% exact CI)	74 (67–81)	45 (37–53)	77 (61–89)	28 (15–44)	74 (66–82)	50 (42–59)
Difference[d] (95% exact CI)	29 (20–39)		49 (30–69)		24 (13–35)	
P[e]	<0.001		<0.001		<0.001	

•[a]By IRR; [b]at baseline; [c]two-sided log-rank test (ITT population: stratified; patient subgroups with/without baseline brain metastases: unstratified); [d]crizotinib vs. chemotherapy; [e]two-sided Pearson χ^2 test

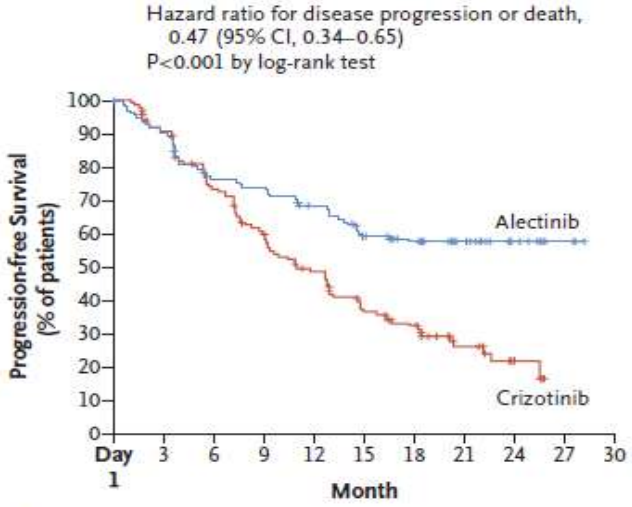
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D.,

A Progression-free Survival

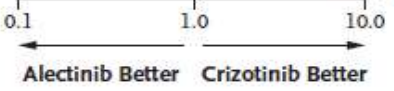


No. at Risk

Alectinib	152	135	113	109	97	81	67	35	15	3
Crizotinib	151	132	104	84	65	46	35	16	5	

B Subgroup Analysis

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	164/303	0.48 (0.35–0.66)
Age		
<65 yr	125/233	0.48 (0.34–0.70)
≥65 yr	39/70	0.45 (0.24–0.87)
Sex		
Female	91/171	0.39 (0.25–0.60)
Male	73/132	0.61 (0.38–0.98)
Race		
Asian	72/138	0.46 (0.28–0.75)
Non-Asian	92/165	0.49 (0.32–0.75)
Smoking status		
Active smoker	12/17	1.16 (0.35–3.90)
Nonsmoker	103/190	0.44 (0.29–0.66)
Former smoker	49/96	0.42 (0.23–0.77)
ECOG performance status		
0	44/97	0.40 (0.21–0.77)
1	105/186	0.48 (0.32–0.71)
2	15/20	0.74 (0.25–2.15)
CNS metastases at baseline		
Yes	78/122	0.40 (0.25–0.64)
No	86/181	0.51 (0.33–0.80)
Previous brain radiation		
Yes	26/47	0.33 (0.14–0.74)
No	138/256	0.52 (0.36–0.73)

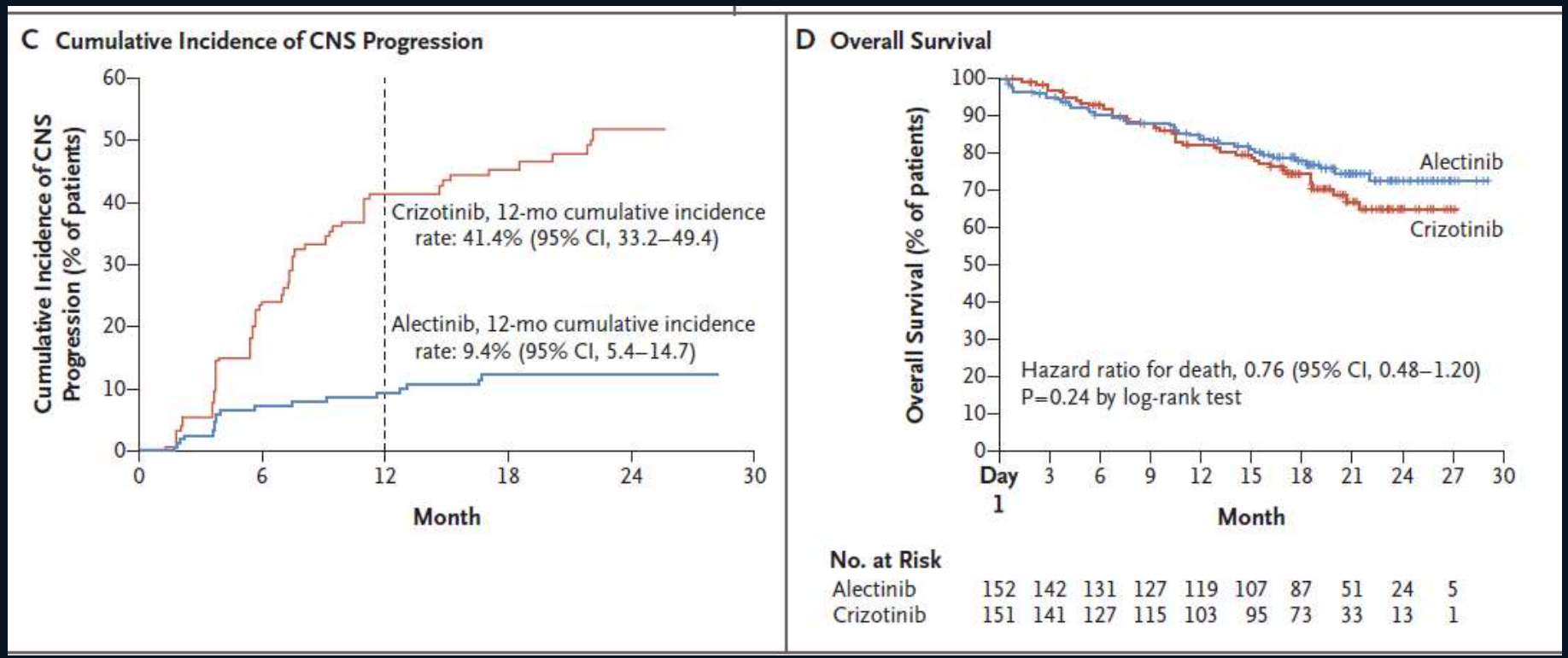


The NEW ENGLAND JOURNAL of MEDICINE

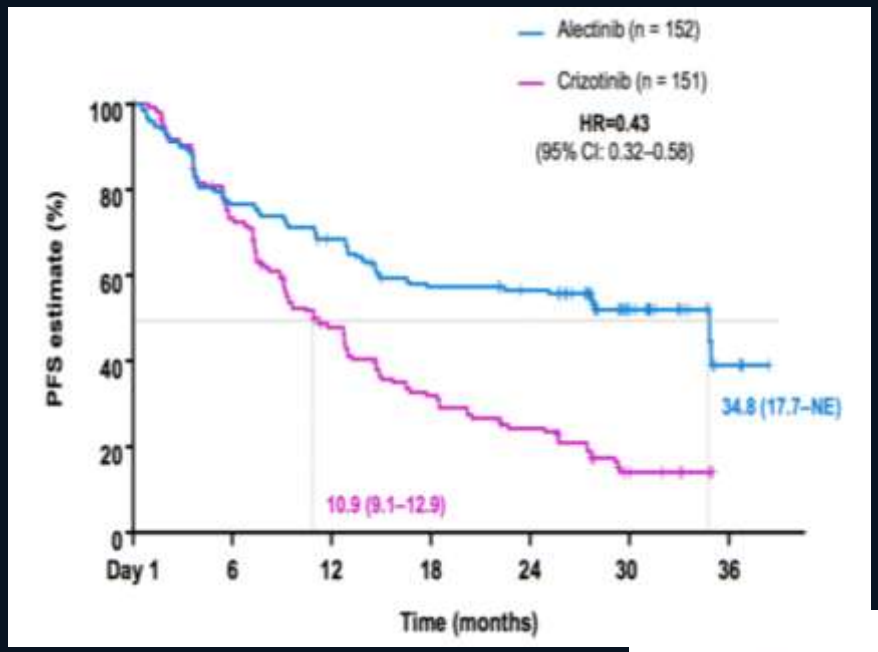
ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D.,



ALEX: Investigator-assessed PFS (primary endpoint)



Camidge DR, et al. ASCO 2018

Patients with CNS metastases at baseline

	Alectinib (n = 64)	Crizotinib (n = 58)
Median PFS	27.7	7.4
(95% CI)	(9.2–NE)	(6.6–9.6)
HR	0.35	
(95% CI)	(0.22–0.56)	

Patients without CNS metastases at baseline

	Alectinib (n = 88)	Crizotinib (n = 93)
Median PFS	34.8	14.7
(95% CI)	(22.4–NE)	(10.8–20.3)
HR	0.47	
(95% CI)	(0.32–0.71)	

Qualità globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Molto bassa	Nei pazienti affetti da NSCLC in stadio avanzato con riarrangiamento di ALK in progressione a una terapia con crizotinib, un trattamento con ceritinib o alectinib deve essere preso in considerazione come opzione terapeutica di prima scelta [177,180].	**Positiva forte**

ALK TKi		Approved	First-line setting	mPFS (mo)	After crizotinib setting	mPFS (mo)
1° Generation	*Crizotinib 250mg bd	First-line (FDA/EMA/PMDA)	PROFILE 1014	10.9	--	--
2° Generation	*Alectinib 600mg bd	First-line and after crizotinib (FDA/EMA/PMDA)	JALEX	25.9	ALUR	9.6
			ALEX	34.8		
	*Ceritinib 750mg/die	First-line and after crizotinib (FDA/EMA/PMDA)	ASCEND 4	16.6	ASCEND 5	5.4
	Brigatinib 90mg x 7 days → 180 mg/die	After crizotinib (FDA)	ALTA 1L (ongoing)	NA	ALTA	15.6
3° Generation	Lorlatinib 150mg/die	Pending approval after crizotinib (FDA)	NCT03052628 (ongoing)	NA	NCT01970865	13.5

* Approved drugs in Italy

Solomon BJ. NEJM, 2014 - Peters S. NEJM, 2017 - Novello S. Annals of Oncol, 2018 - Soria JC. Lancet, 2017 - Shaw AT. Lancet, 2017 - Kim DW. J Clin Oncol, 2017 - Solomon B. JTO, 2017

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 31), pp: 22137-22146

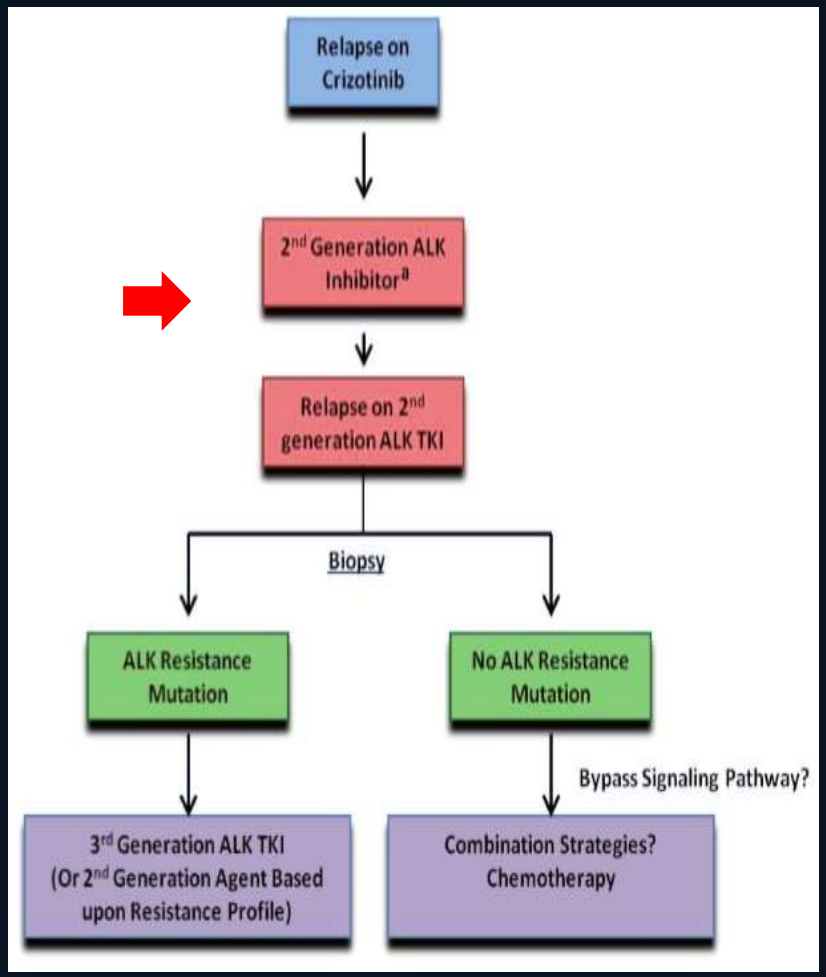
Meta-Analysis

Systematic review and meta-analysis of selected toxicities of approved *ALK* inhibitors in metastatic non-small cell lung cancer

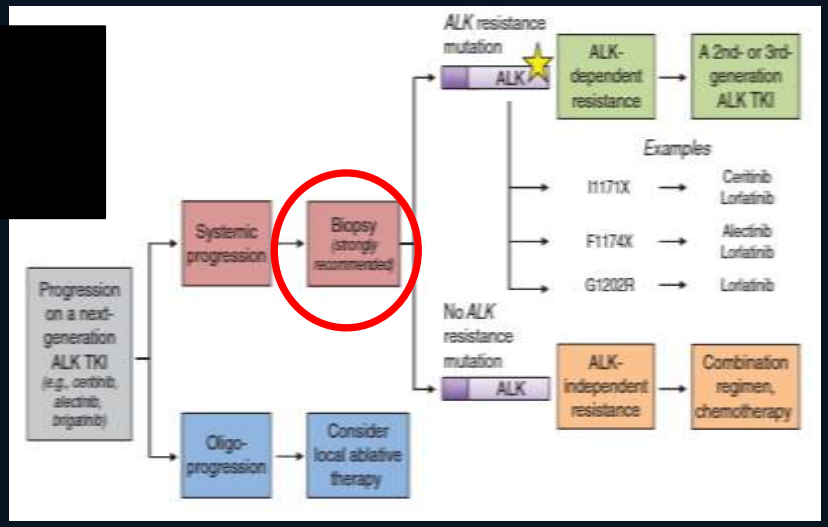
AE	Alectinib	Brigatinib	Ceritinib	Crizotinib	*p*-value*
Any AE (%)	96.7	ND	99.6	97.7	0.022
Any Serious AE (%)	21.6	ND	44.9	31.1	< 0.001
Any Grade 3/4 AE (%)	ND	ND	75.3	43.4	0.009
Diarrhea (%)	13.7	38.2	81.2	56.0	< 0.001
Diarrhea 3/4 (%)	0.6	0.5	5.6	1.7	< 0.001
Nausea (%)	15.3	40.0	73.9	55.3	< 0.001
Nausea 3/4 (%)	0.5	0.9	5.7	1.8	< 0.001
Vomiting (%)	9.8	22.7	60.4	43.9	< 0.001
Vomiting 3/4 (%)	0.6	0.5	5.2	2.0	< 0.001
Constipation (%)	34.1	15.5	24.3	37.1	< 0.001
Constipation 3/4 (%)	0.4	0.5	0.8	1.5	0.37
Fatigue (%)	25.7	27.3	34.5	21.7	0.039
Fatigue 3/4 (%)	1.0	0.5	6.0	2.1	< 0.001
ALT (%)	14.3	ND	46.9	21.8	< 0.001
ALT 3/4 (%)	4.0	ND	22.8	9.1	< 0.001
AST (%)	15.0	14.5	38.8	21.0	< 0.001
AST 3/4 (%)	3.9	0.5	11.4	5.7	0.007
QT (%)	1.2	ND	9.0	14.4	0.025
QT 3/4 (%)	0.8	ND	0.9	3.9	0.003
ILD (%)	0.6	ND	2.4	2.4	0.610
ILD 3/4 (%)	0.4	ND	2.1	2.0	0.310

Progression on frontline ALK inhibitor: To biopsy or not biopsy?

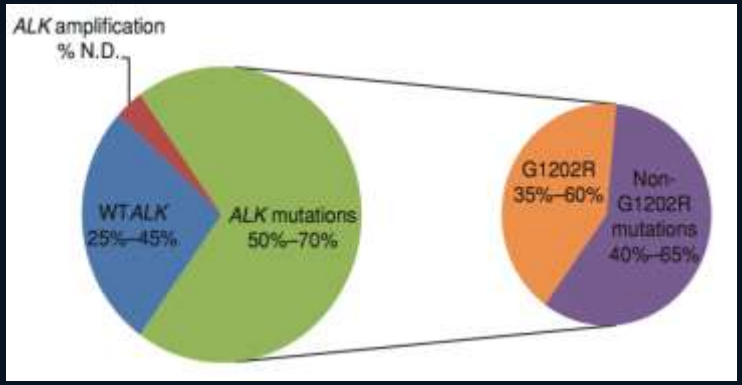
Not Mandatory at frontline Crizotinib Failure



Strongly recommended at a II-gen ALK TKI Failure



Second-generation ALK TKI–resistant cases



Lin J, et al. Cancer Discov 2017

Efficacy of 3rd generation ALKIs in heavily ALKIs-pretreated NSCLC

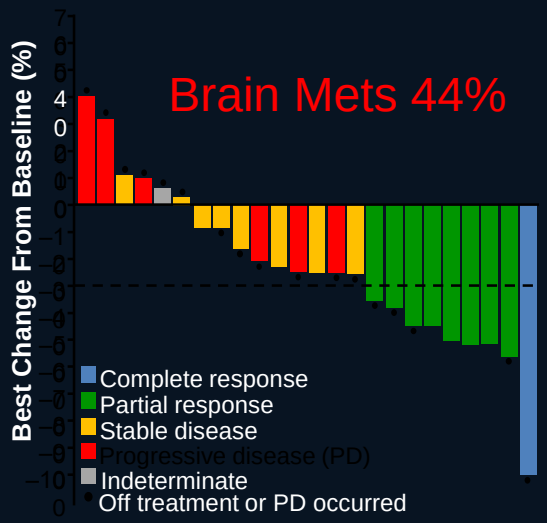
Lorlatinib is a Potent, Selective, CNS-Penetrant ALK/ROS1 TKI

	Cellular ALK Phosphorylation Mean IC_{50} (nM)				
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
EML4-ALK	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0[a]	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0

IC_{50} ≤50 nM IC_{50} >50–<200 nM IC_{50} ≥200 nM

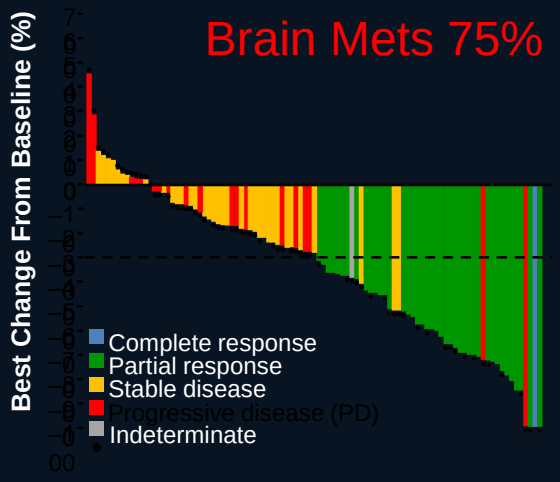
Gainor JF, et al. Cancer Discov. 2016
Johnson TW, et al. J Med Chem. 2014

Overall[a,b]



EXP3B: 1 non-crizotinib TKI ± chemo (n=27)	
ORR, n/N (%) (95% CI)	9/27 (33) (16, 54)
IC ORR, n/N (%) (95% CI)	5/12 (42) (15, 72)
Median PFS, mo (95% CI)	5.5 (2.9, 9.0)

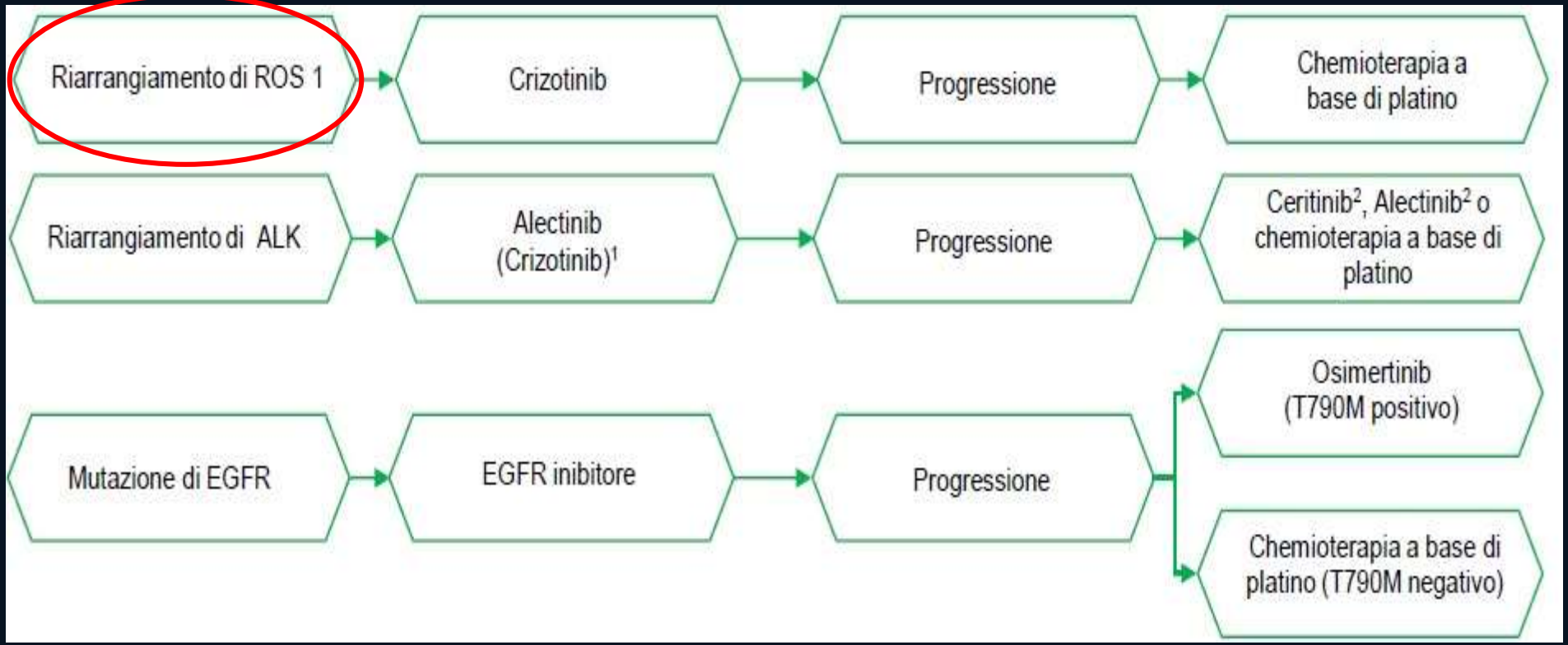
Overall[a,b]



EXP4–5: ≥2 prior ALK TKIs ± chemo (n=111)	
ORR, n/N (%) (95% CI)	43/111 (39) (30, 49)
IC ORR, n/N (%) (95% CI)	40/83 (48) (37, 59)
Median PFS, mo (95% CI)	6.9 (5.4, 9.5)

Solomon BJ, et al. J Thorac Oncol:2017

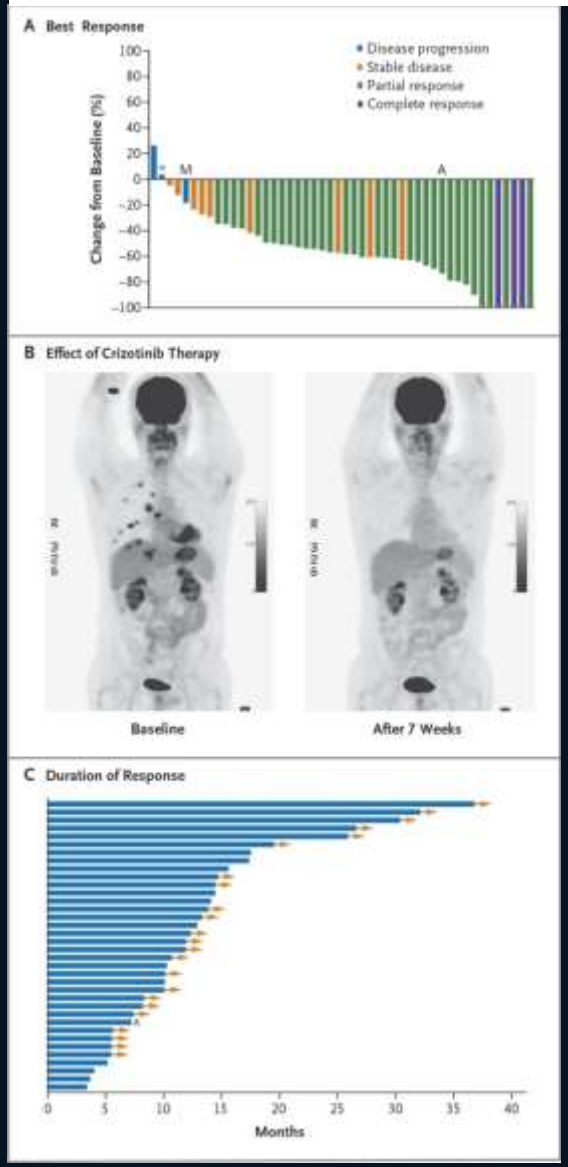
Malattia oncogene-addicted



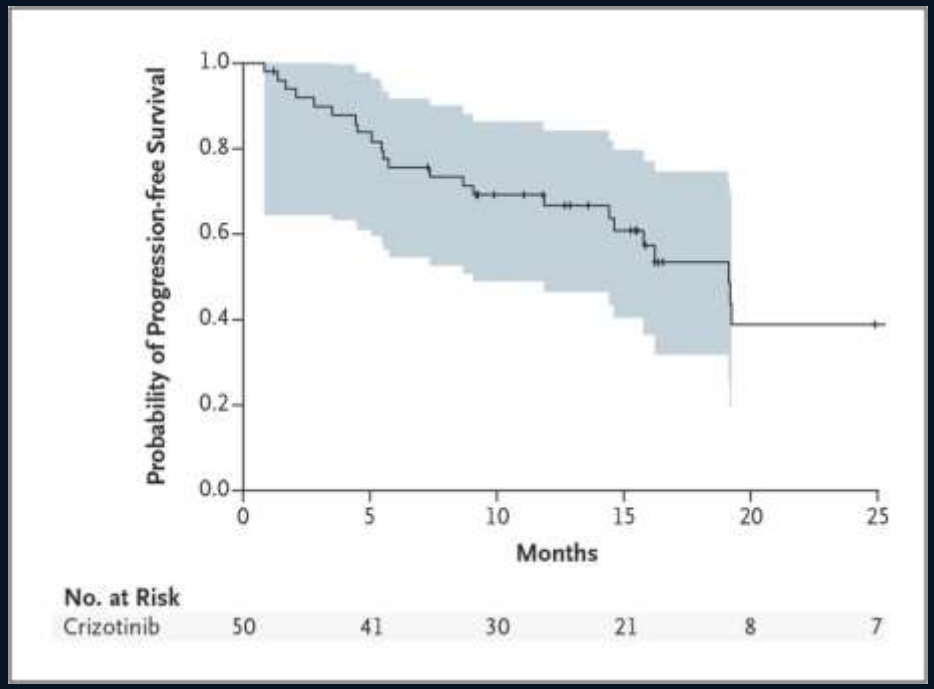
Qualità globale delle evidenze	Raccomandazione	Forza della raccomandazione clinica
Molto bassa	Nei pazienti affetti da NSCLC in stadio localmente avanzato o metastatico con riarrangiamento di *ROS1*, un trattamento di prima linea con crizotinib deve essere preso in considerazione come opzione terapeutica di prima scelta [184,185].	**Positiva forte**

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

Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D.



ORR 72% (3 RC)
Durata mediana di risposta 17.6 mesi



PFS mediana 19.2 mesi
OS a 12 mesi 85%
Buona tollerabilità

N Engl J Med 2014

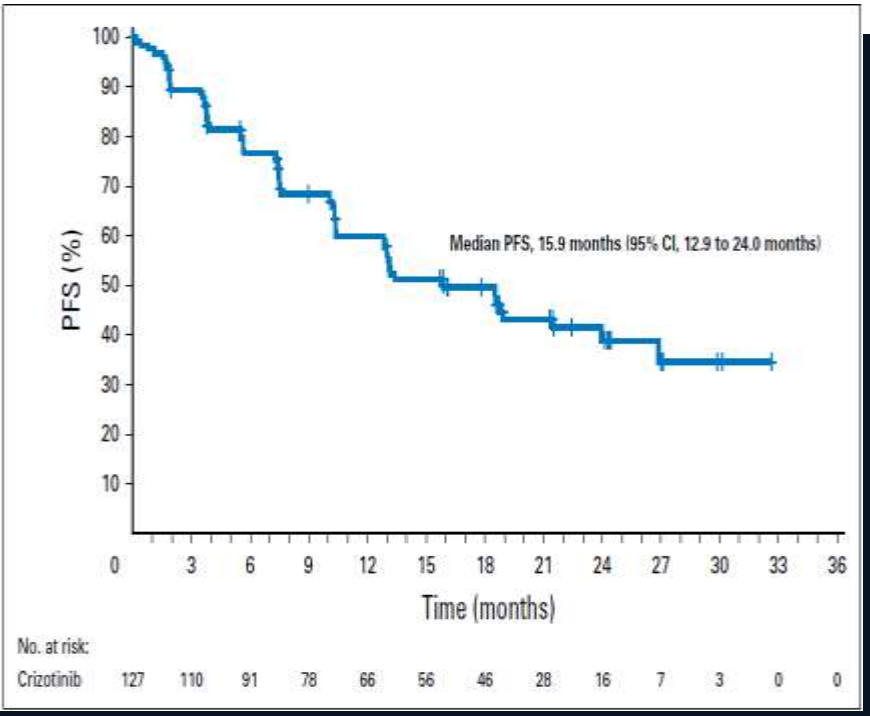
VOLUME 36 · NUMBER 14 · MAY 10, 2018

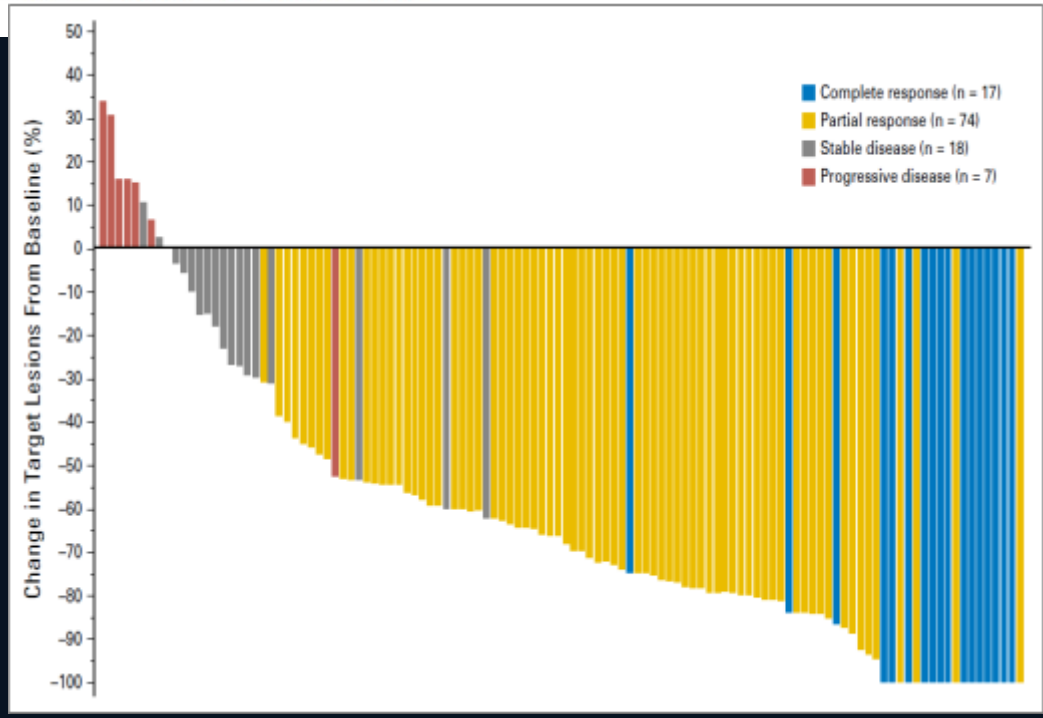
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

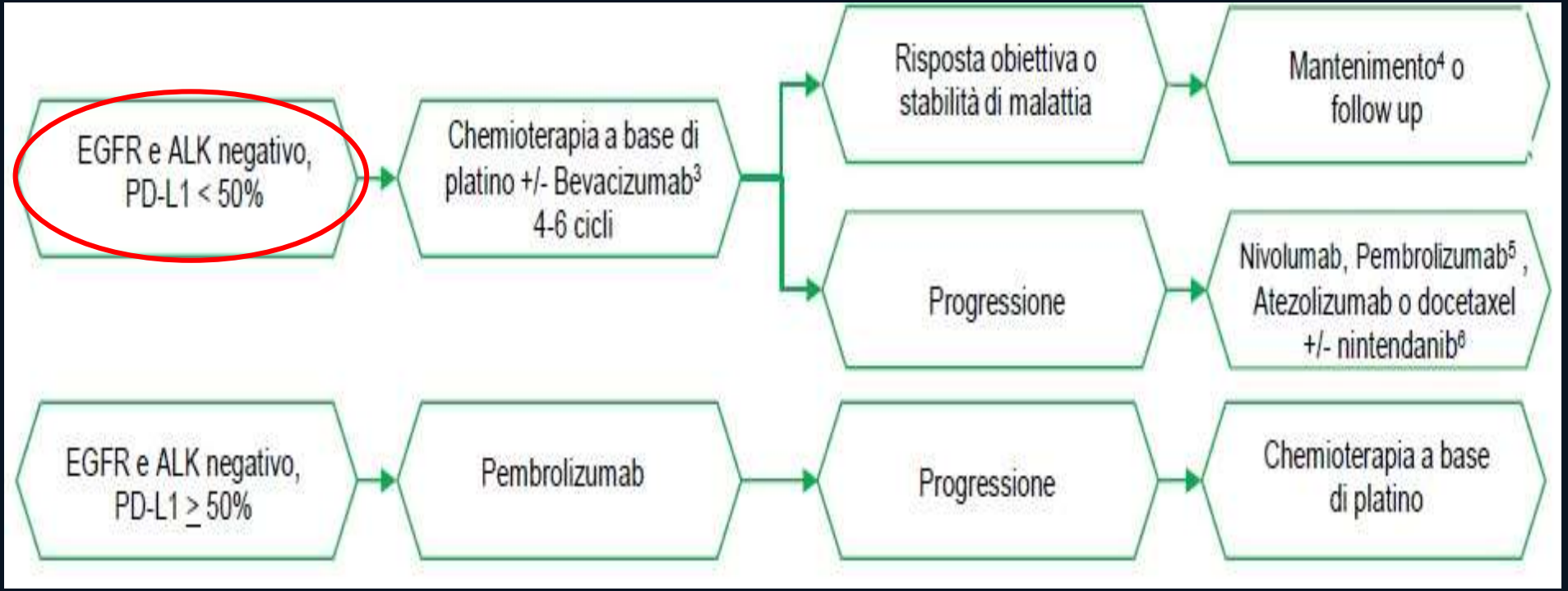
Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non–Small-Cell Lung Cancer

Yi-Long Wu, James Chih-Hsin Yang, Dong-Wan Kim, Shun Lu, Jianying Zhou, Takashi Seto, Jin-Ji Yang, Noboru Yamamoto, Myung-Ju Ahn, Toshiaki Takahashi, Takeharu Yamanaka, Allison Kemner, Debasish Roychowdhury, Jolanda Paolini, Tiziana Usari, Keith D. Wilner, and Koichi Goto





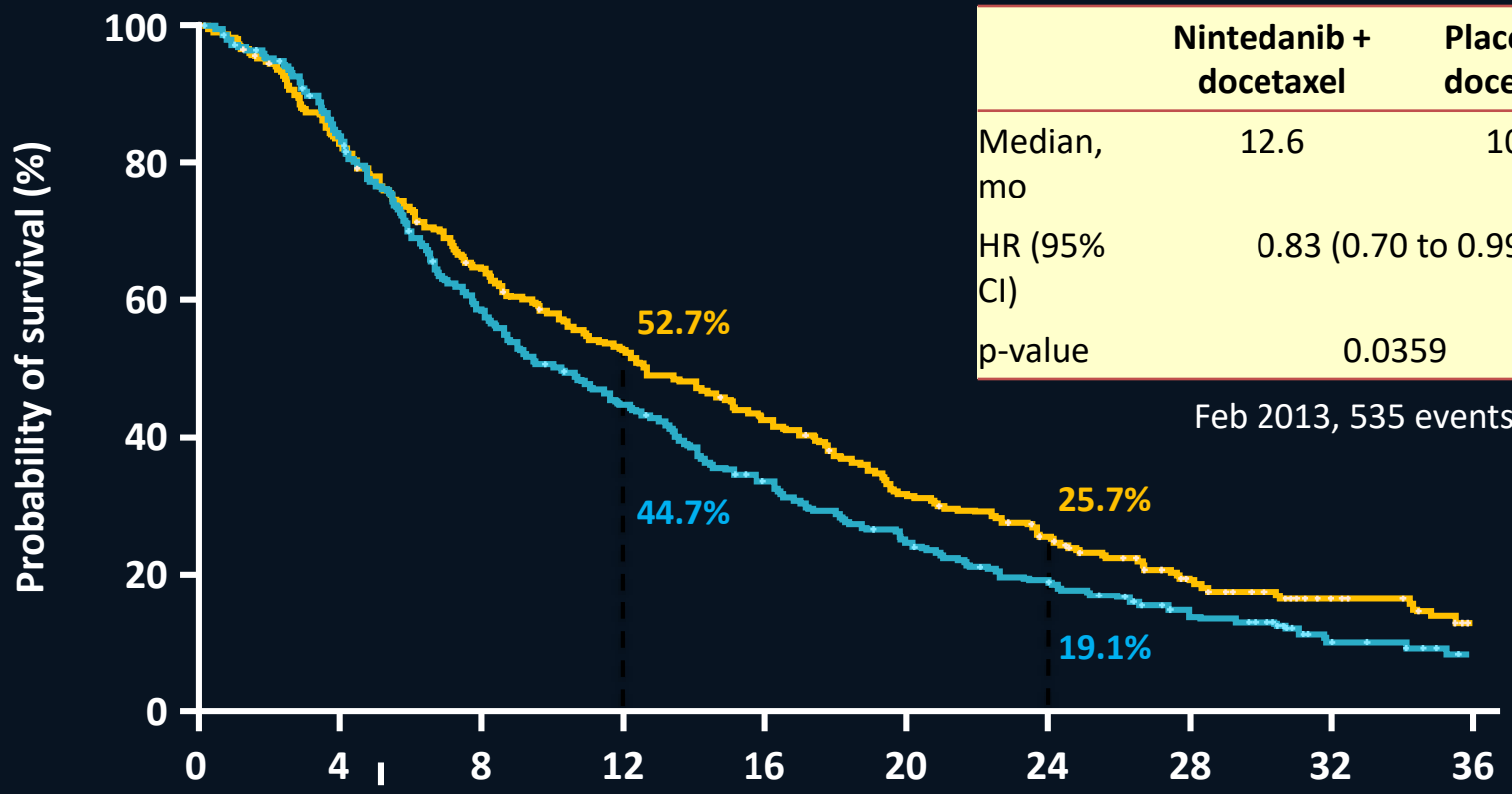
Malattia non oncogene-addicted



Qualità globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Molto bassa	Nei pazienti affetti da NSCLC ad istologia adenocarcinoma, localmente avanzato o metastatico, l'aggiunta di nintedanib a docetaxel può essere considerata, soprattutto per i pazienti con malattia in progressione entro i 9 mesi dall'inizio della terapia di prima linea [235].	Positiva debole

LUME-Lung 1: OS

Adenocarcinoma Histology



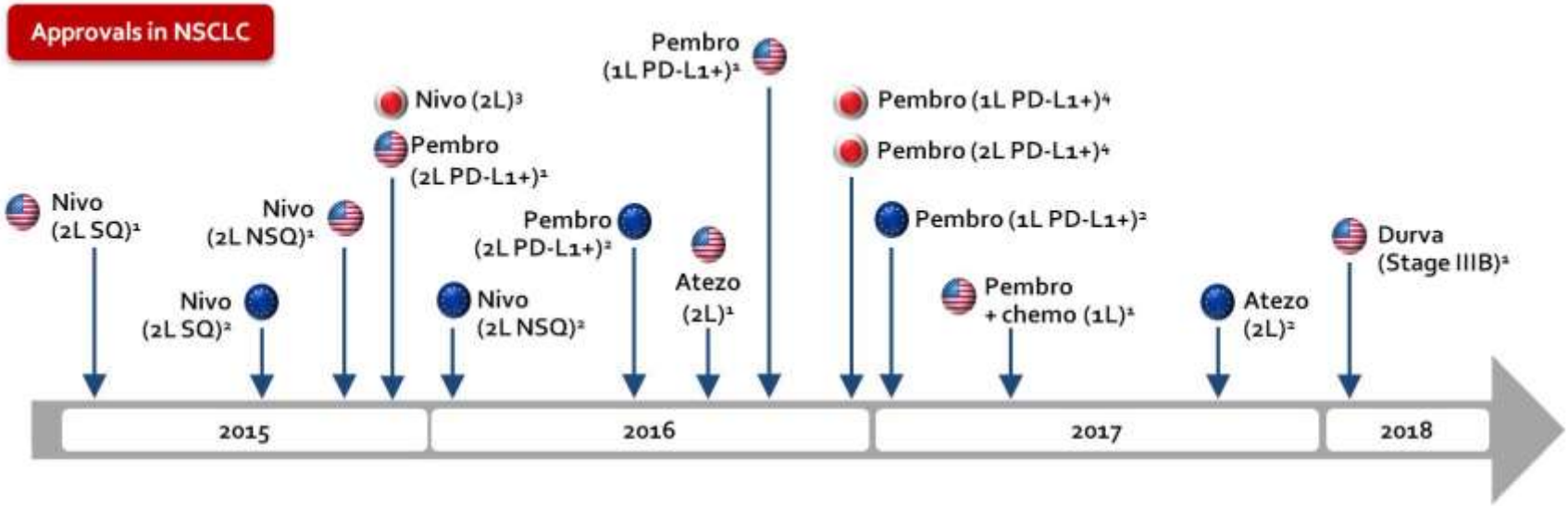
	Nintedanib + docetaxel	Placebo + docetaxel
Median, mo	12.6	10.3
HR (95% CI)	0.83 (0.70 to 0.99)	
p-value	0.0359	

Feb 2013, 535 events

Qualità globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Molto bassa	Nei pazienti affetti da NSCLC in stadio avanzato in progressione a una prima linea di chemioterapia, una immunoterapia con nivolumab, atezolizumab o pembrolizumab (quest'ultimo solo in caso di PD-L1 $\geq$ 1%) può essere presa in considerazione [231-234].	**Positiva debole**

NSCLC - Clinical practice

Checkpoint inhibitors in NSCLC
Key milestones

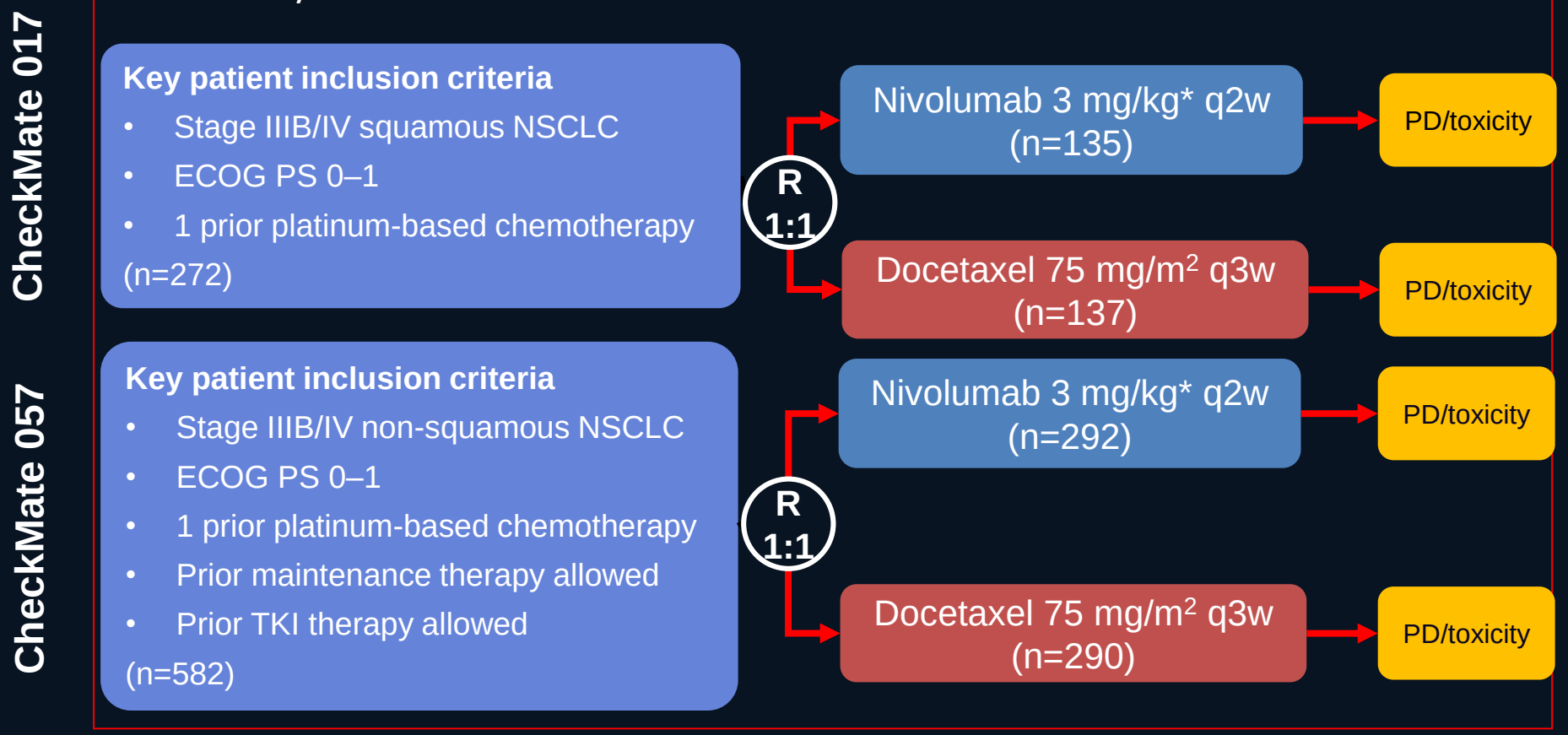


Many ongoing trials in early stage NSCLC

1. U.S. Food and Drug Administration. 2. European Medicines Agency. 3. ONO Pharmaceutical Co., Ltd. 4. Merck [press release]. December 19, 2016.

Three-year follow-up from CheckMate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer (NSCLC) – Felip E

- **Study objective**
  - To assess the efficacy and safety of nivolumab in patients with NSCLC after >3 years



Primary endpoint
- OS

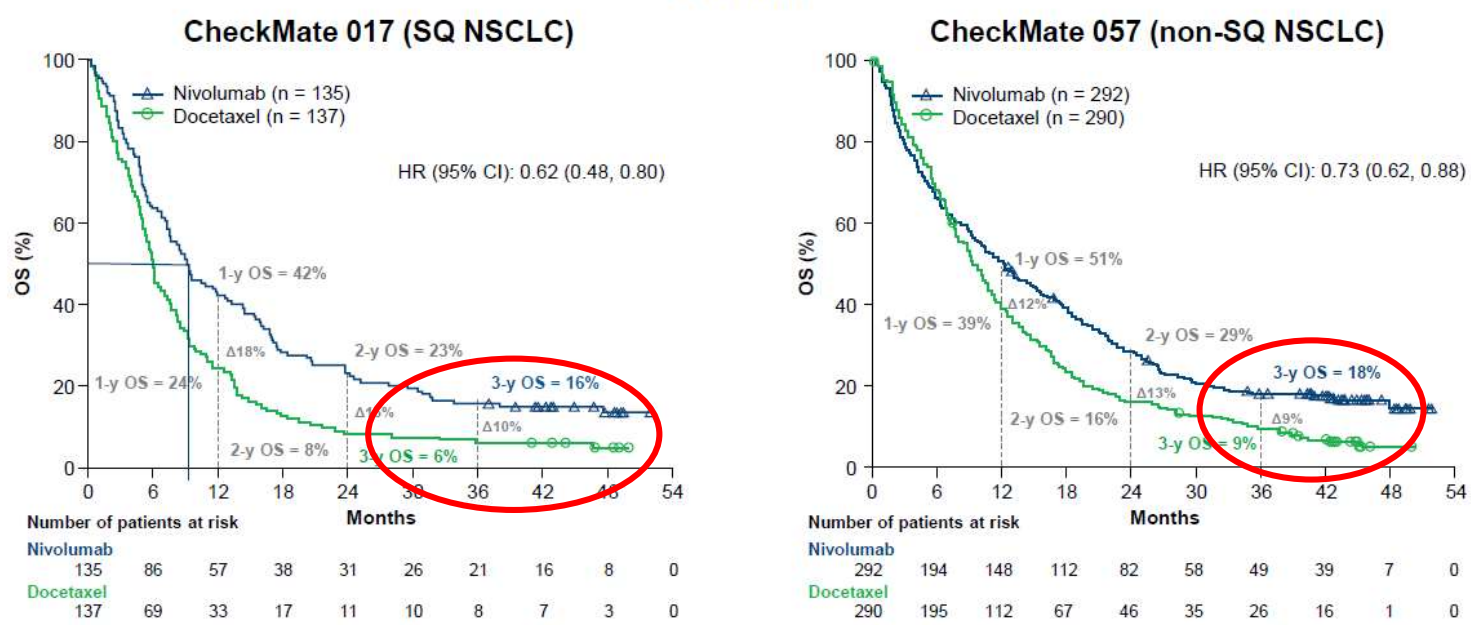
Secondary endpoints
- PFS, ORR, efficacy by PD-L1 expression, safety, QoL

Felip E et al. Ann Oncol 2017;28(suppl 5

Three-year follow-up from CheckMate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer (NSCLC) – Felip E

What are the long term outcomes?

OS Data



- 3-year OS rates were 16% versus 6% in CheckMate 017 and 18% versus 9% in CheckMate 057 with nivolumab and docetaxel, respectively
- Of the 3-year survivors treated with docetaxel, the majority received subsequent immunotherapy, either during crossover to nivolumab or as post-study treatment (CheckMate 017: 75% [6/8 patients]; CheckMate 057: 73% [19/26 patients])

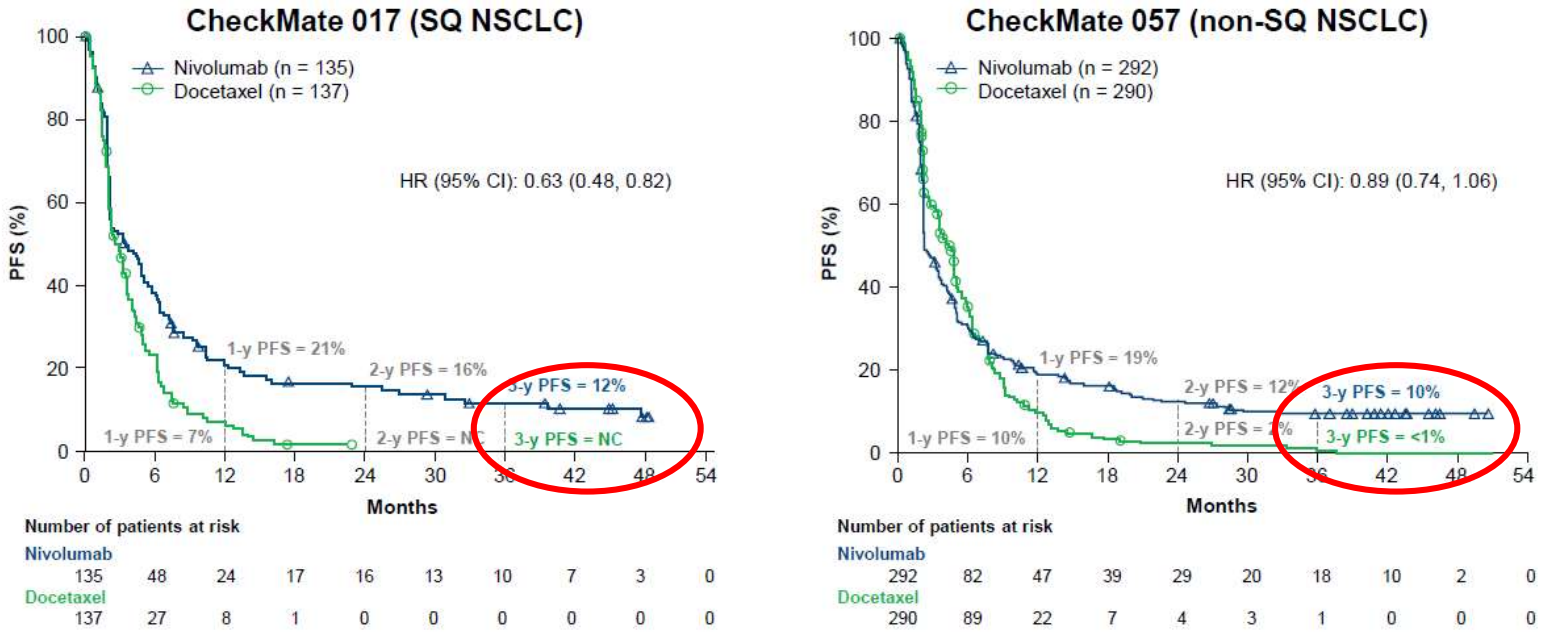
MADRID 2017 ESMO congress

CI = confidence interval; HR = hazard ratio

14

What are the long term outcomes?

PFS Data



- 3-year PFS rates were 12% versus not calculable in CheckMate 017 and 10% versus <1% in CheckMate 057 with nivolumab and docetaxel, respectively

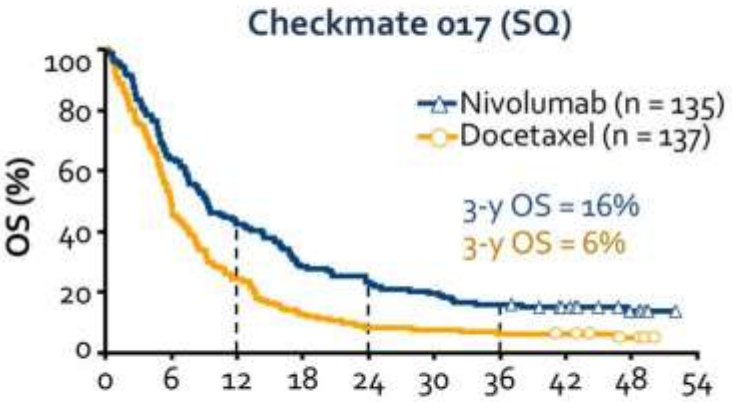
MADRID 2017 ESMO congress

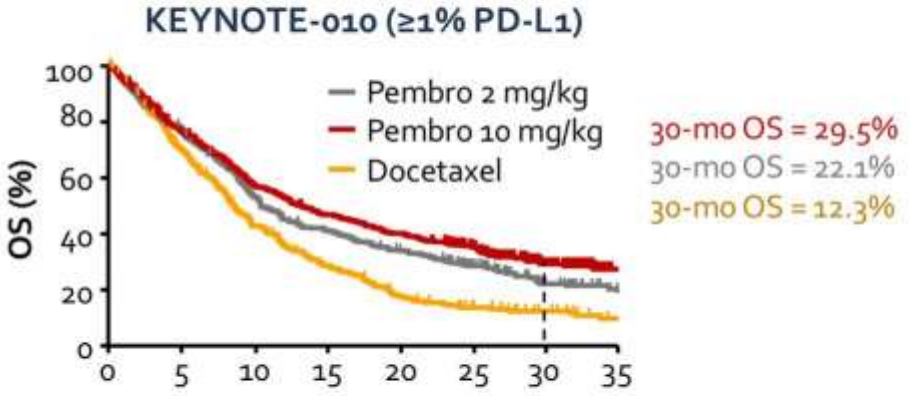
[a]Investigator-assessed

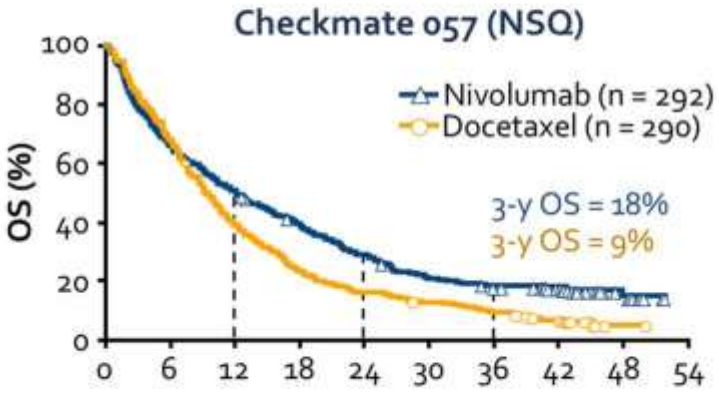
NC = not calculable

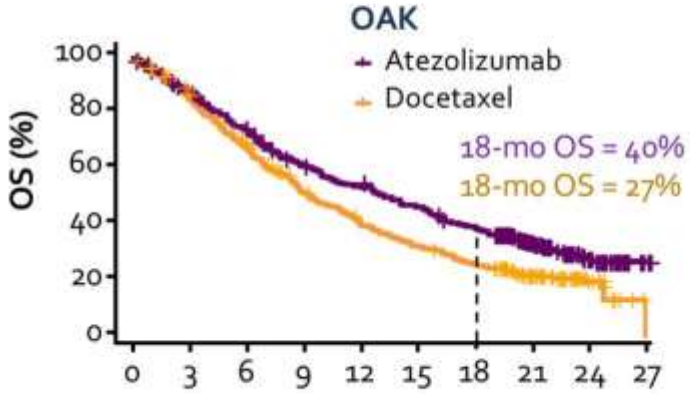
2° line anti PD1/PD-L1 for A-NSCLC

A consistent but limited OS benefit in 2nd line





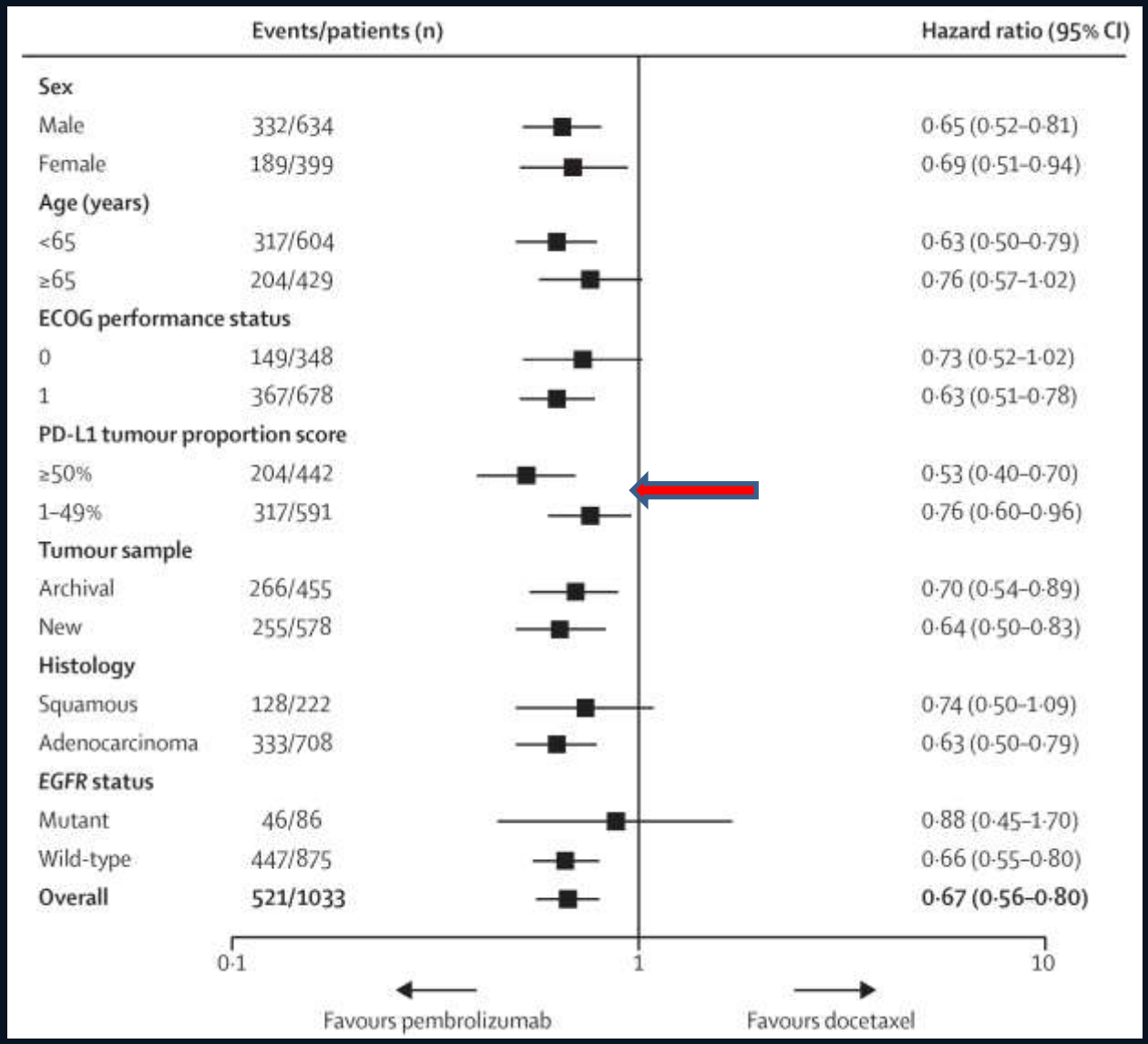




Felip, ESMO 2017; Herbst, ASCO 2017; Rittmeyer, Lancet 2017

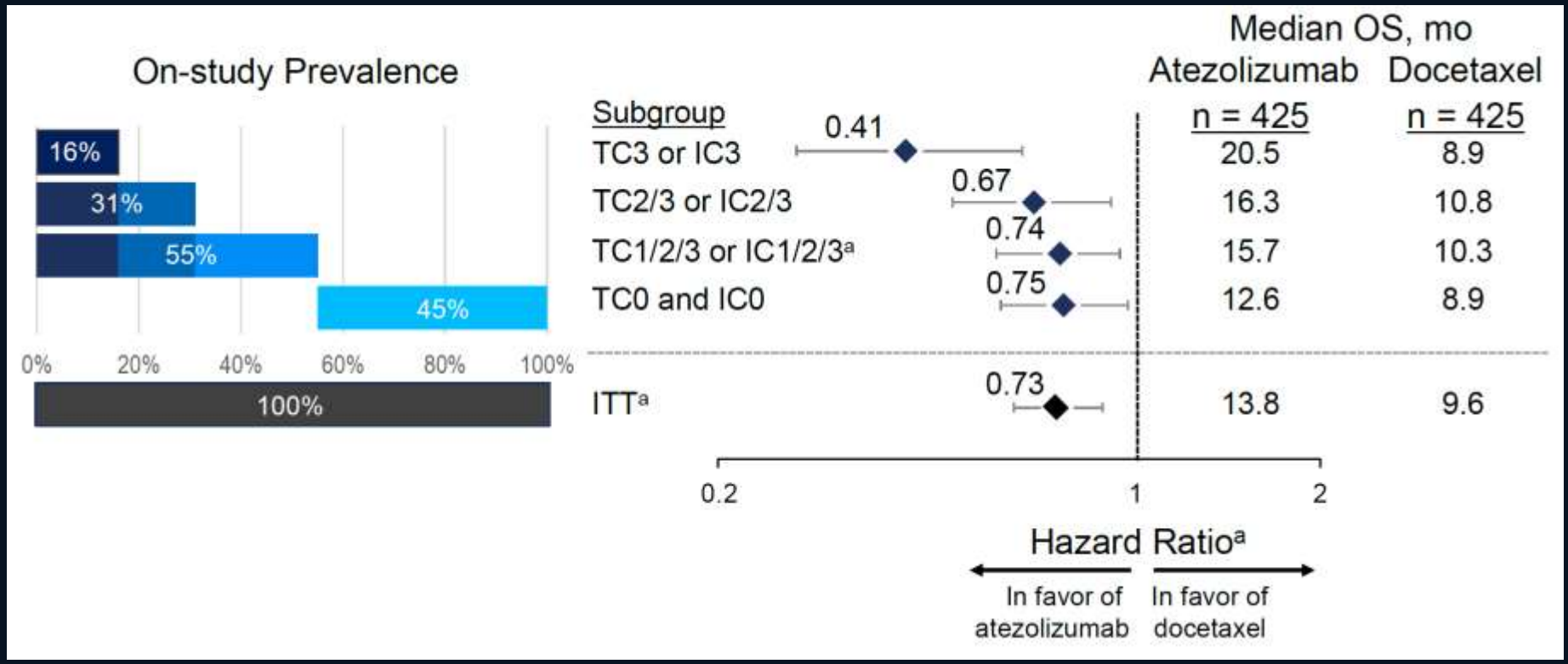
Presented By Solange Peters at 2018 ASCO Annual Meeting

KEYNOTE-010: OS by PD-L1 expression



Rittmeyer A, et al. Lancet 2017;389(10066):255-265.

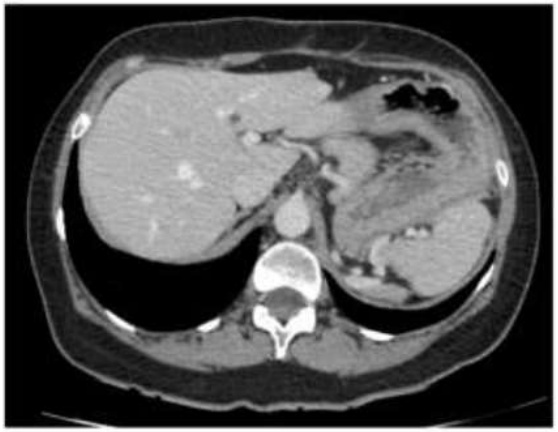
OAK: OS by PD-L1 expression



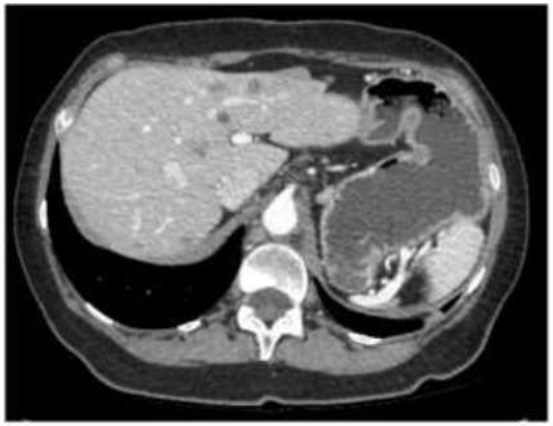
[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

Rittmeyer A, et al. Lancet 2017;389(10066):255-265

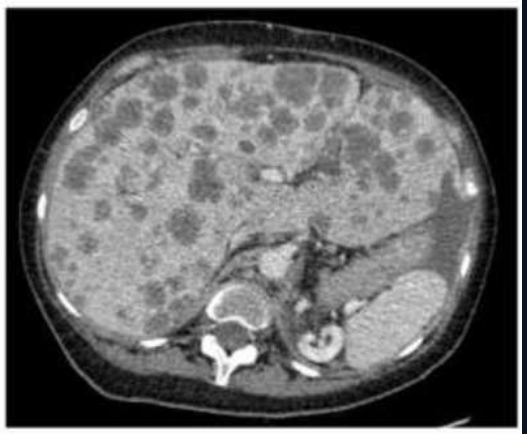
but...ATTENTION TO HPD!!!



Before
(-8 weeks)

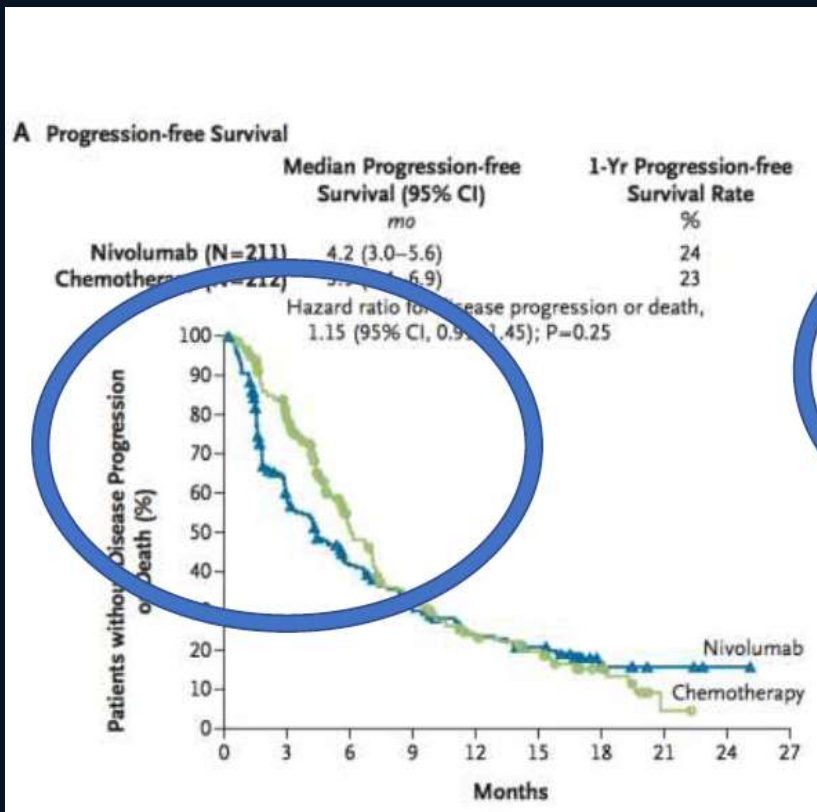


Baseline

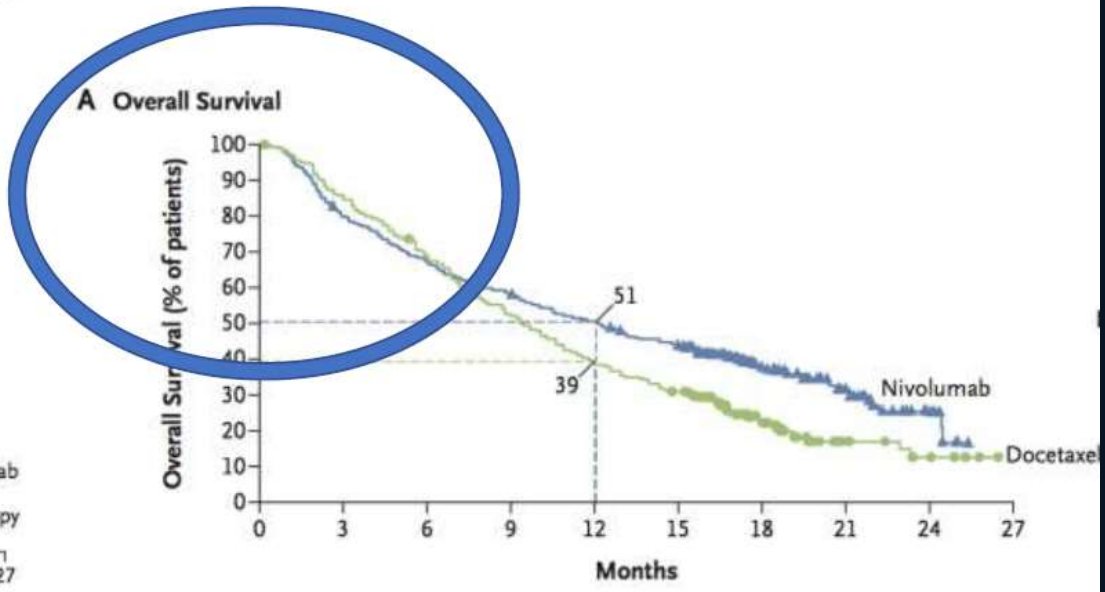


1st Evaluation
(+8 weeks)

Champiat et al, CCR 2016

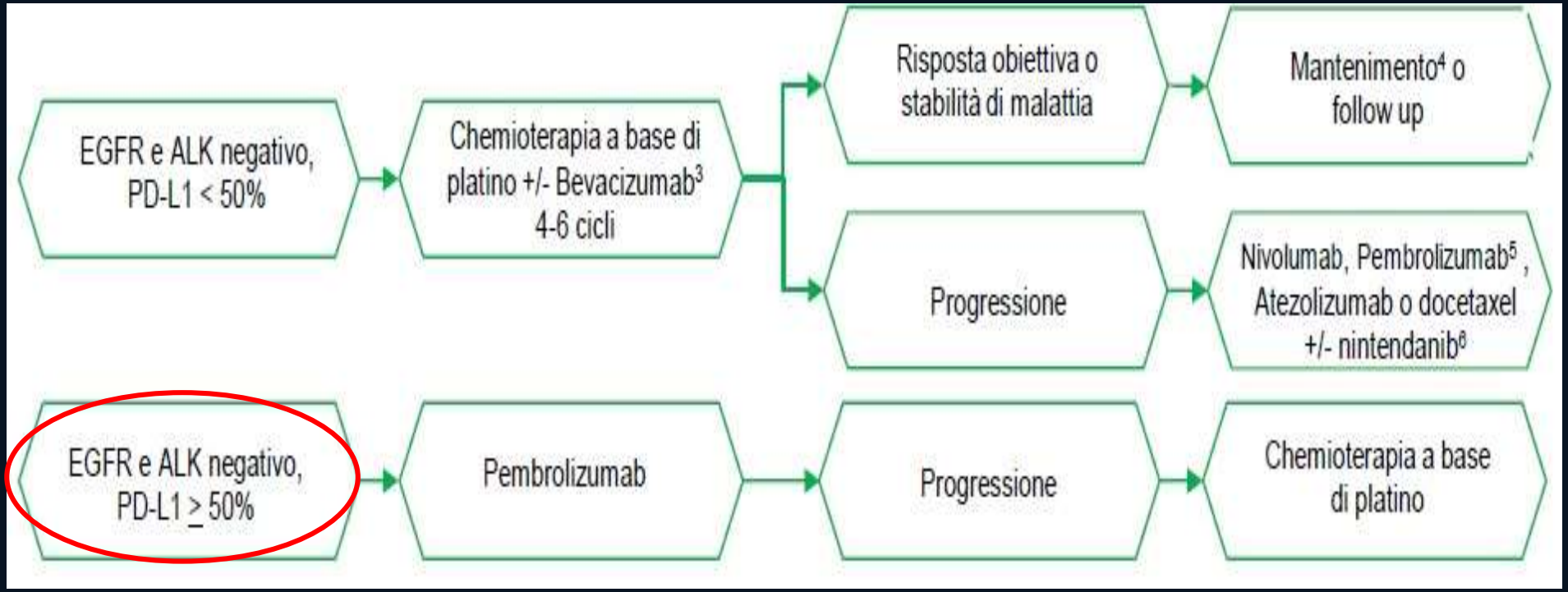


Checkmate 026



Checkmate 057

Malattia non oncogene-addicted



Qualità globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Bassa	Nei pazienti con NSCLC metastatico, senza mutazione di *EGFR* o riarrangiamento di *ALK*, con espressione di PD-L1 ≥ 50%, il trattamento di prima linea con pembrolizumab dovrebbe essere preso in considerazione come opzione terapeutica di prima scelta [187].	Positiva forte

KEYNOTE-024: study design

Key Eligibility Criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1)
N = 305

Pembrolizumab
200 mg IV Q3W
(2 years)

Platinum-Doublet Chemotherapy
(4-6 cycles)

PD[a]

Pembrolizumab
200 mg Q3W
for 2 years

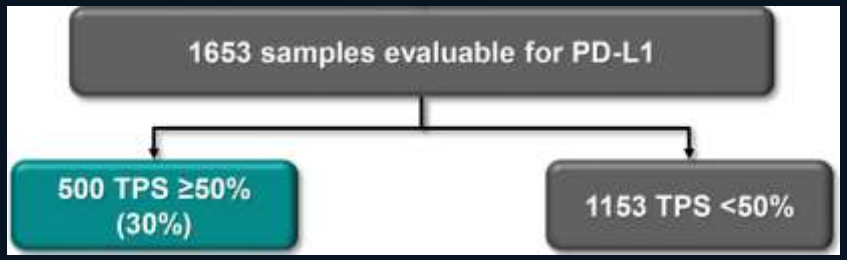
Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

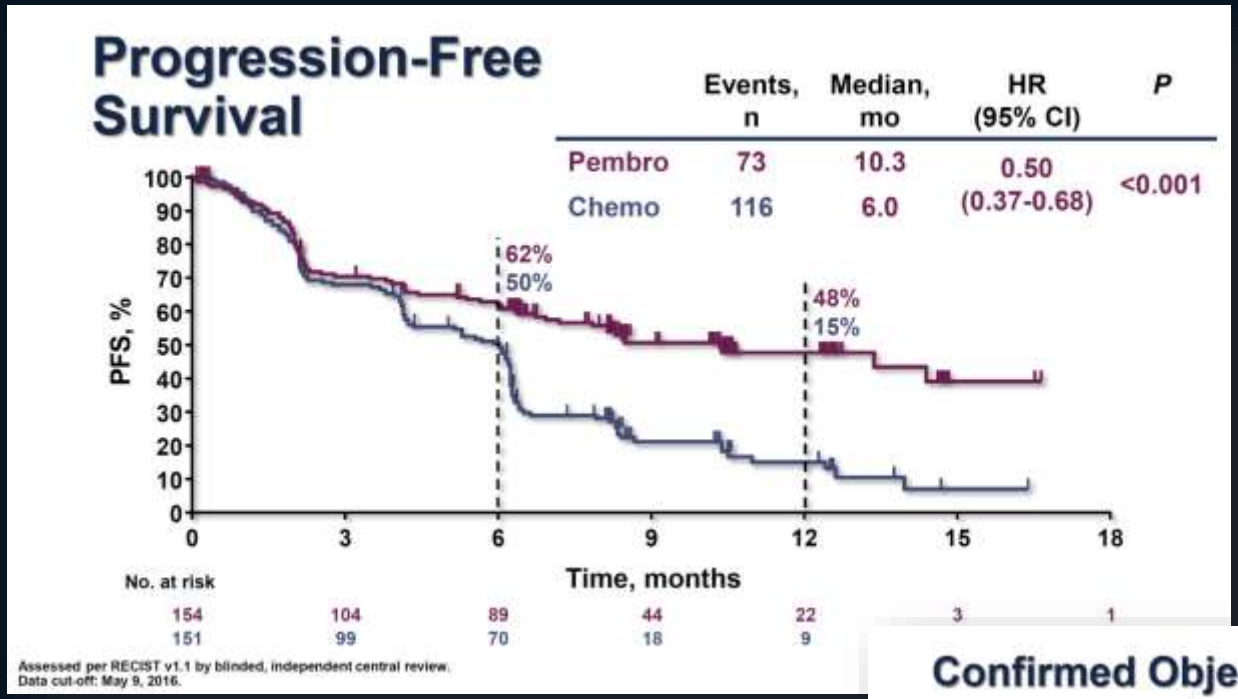
Exploratory: DOR

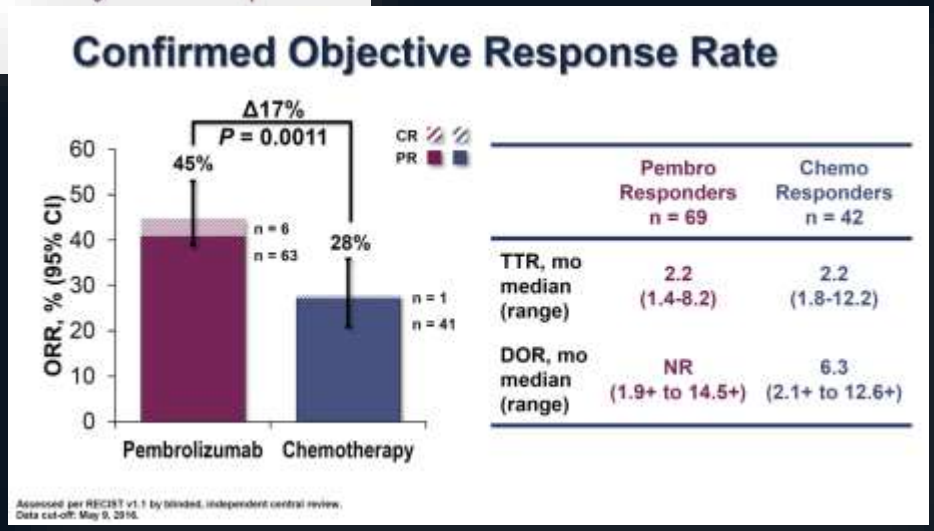
[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.



Reck M, et al. N Engl J Med 2016;375(19):1823-1833.

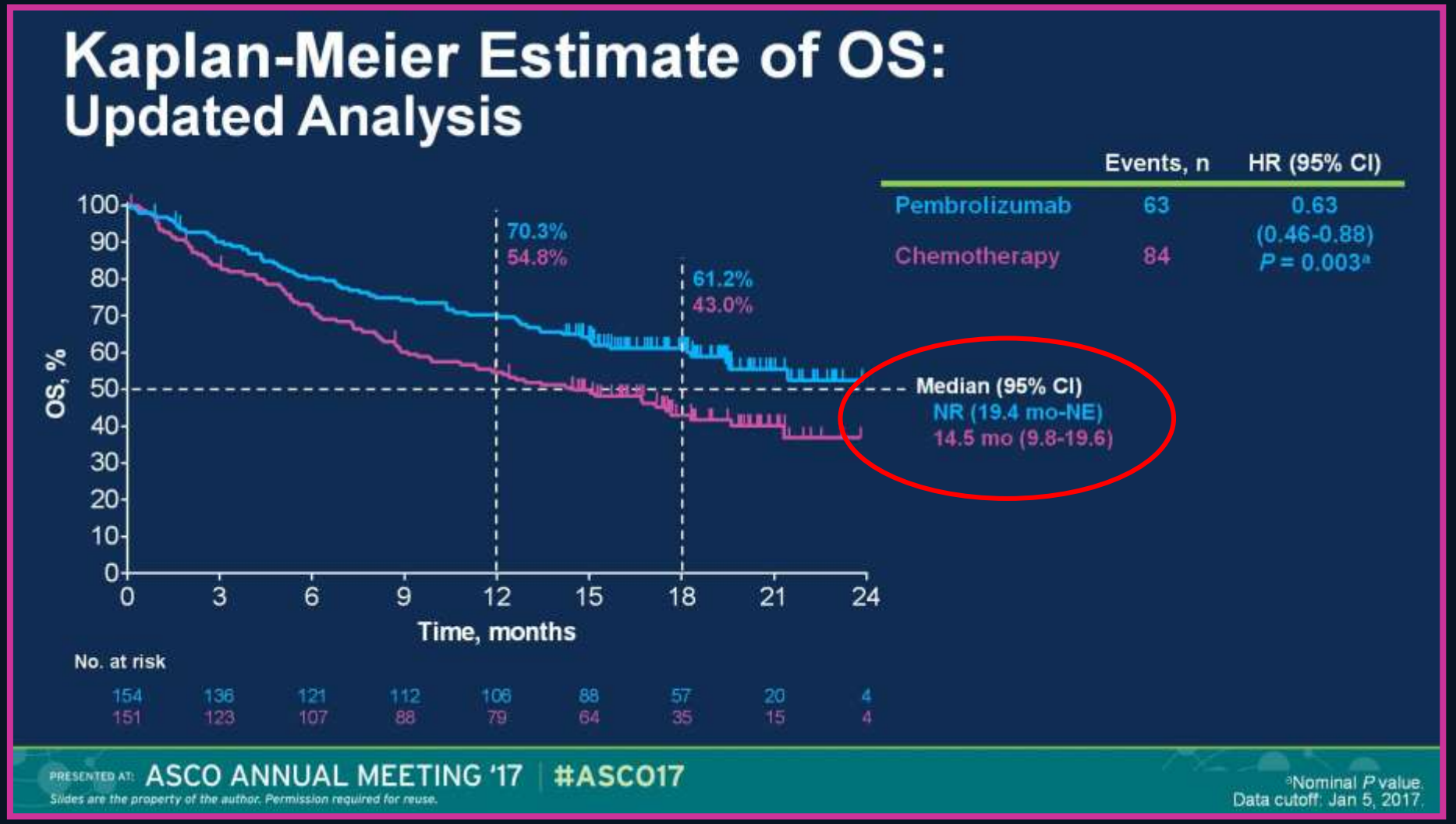
KEYNOTE-024: PFS and RR





Reck M, et al. N Engl J Med 2016;375(19):1823-1833.

KEYNOTE-024: Updated OS results



Presented By Julie Brahmer at 2017 ASCO Annual Meeting

KEYNOTE-024: safety

Exposure and AE Summary

	Pembrolizumab N = 154	Chemotherapy N = 150
Exposure, median (range)	7.0 mo (1 d-18.7 mo)	3.5 mo (1 d-16.8 mo)
Treatment-related AEs, n (%)	113 (73)	135 (90)
Grade 3-4	40 (26)	77 (51)
Serious	33 (21)	31 (21)
Led to discontinuation	11 (7)	16 (11)
Led to death	1 (<1)	3 (2)

Data cut-off: May 9, 2016.

Reck M, et al. N Engl J Med 2016;375(19):1823-1833.

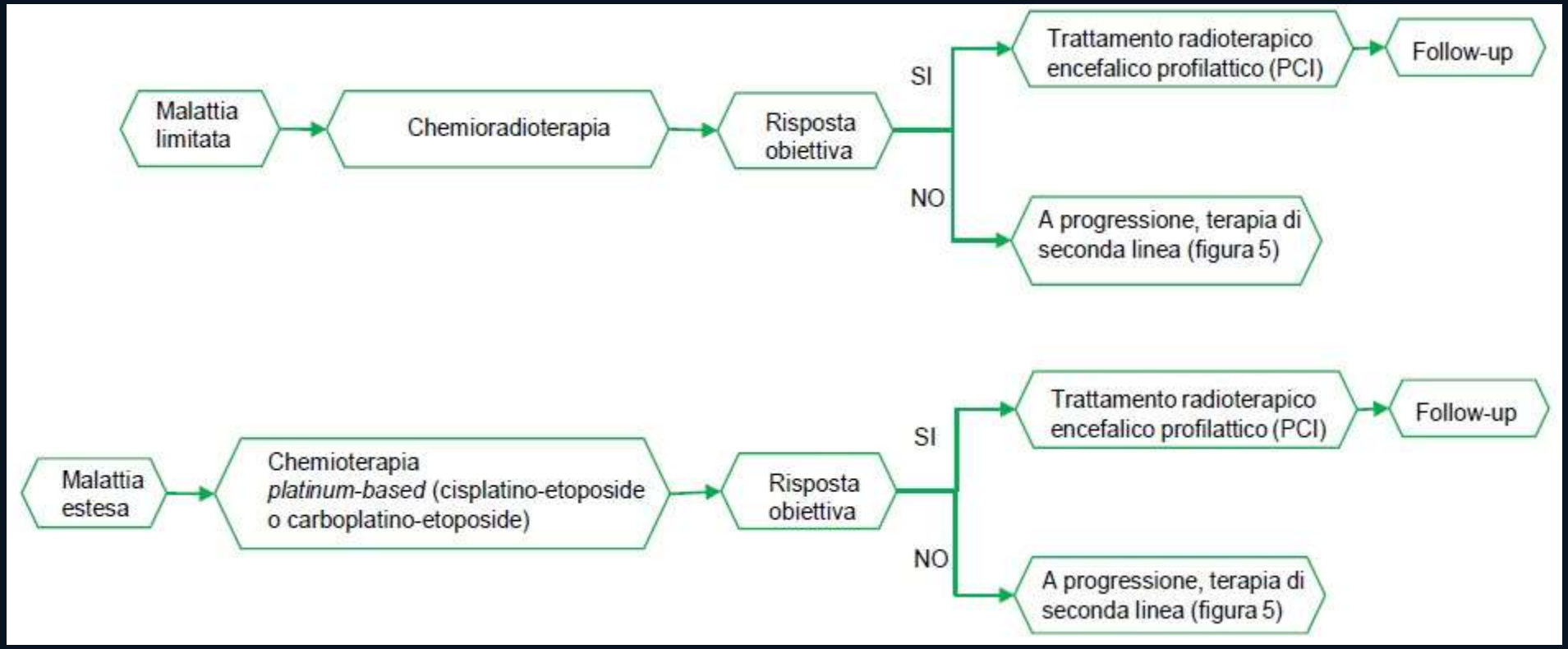
1st line Checkpoint inhibitors for NSCLC: summary of evidence

Phase 3 trials of first-line immunotherapy

Comparison	Selection	ORR	PFS	OS
Pembrolizumab vs. platinum doublet	PD-L1 ≥ 50%	44.8% vs 27.8%	HR=0.50 p<0.01	HR=0.60 p<0.01
Carboplatin/pemetrexed +/- pembrolizumab or placebo	PD-L1:unselected Nonsquamous	47.6% vs.18.9% p<0.01	HR=0.52 p<0.01	HR=0.49 p<0.01
Pembrolizumab vs platinum doublet	PD-L1≥ 1%	27.3% vs. 26.5%	HR=1.07 NS	0.81 p<0.01
Carboplatin, paclitaxel, bevacizumab +/- atezolizumab	PD-L1:unselected Nonsquamous	64% vs 48%	HR=0.62 p<0.01	Positive
Carboplatin (nab-paclitaxel or paclitaxel) +/- pembrolizumab	PD-L1: unselected Squamous	58.4% vs 35.0% p<0.01	HR=0.56 p<0.01	HR=0.64 p<0.01
Nivolumab/ipilimumab vs. platinum doublet	TMB high ≥ 10 mutations/Mb	45.3% vs 26.9%	HR=0.58 p<0.01	Immature

Reck et al NEJM 2016, Gandhi et al NEJM 2018, Lopes et al ASCO 2018, Reck et al ESMO-Immuno-oncology 2017, Kowanetz et al AACR 2018 Paz-Ares et al ASCO 2018, Socinski et al ASCO 2018, Hellman et al NEJM 2018

SCLC

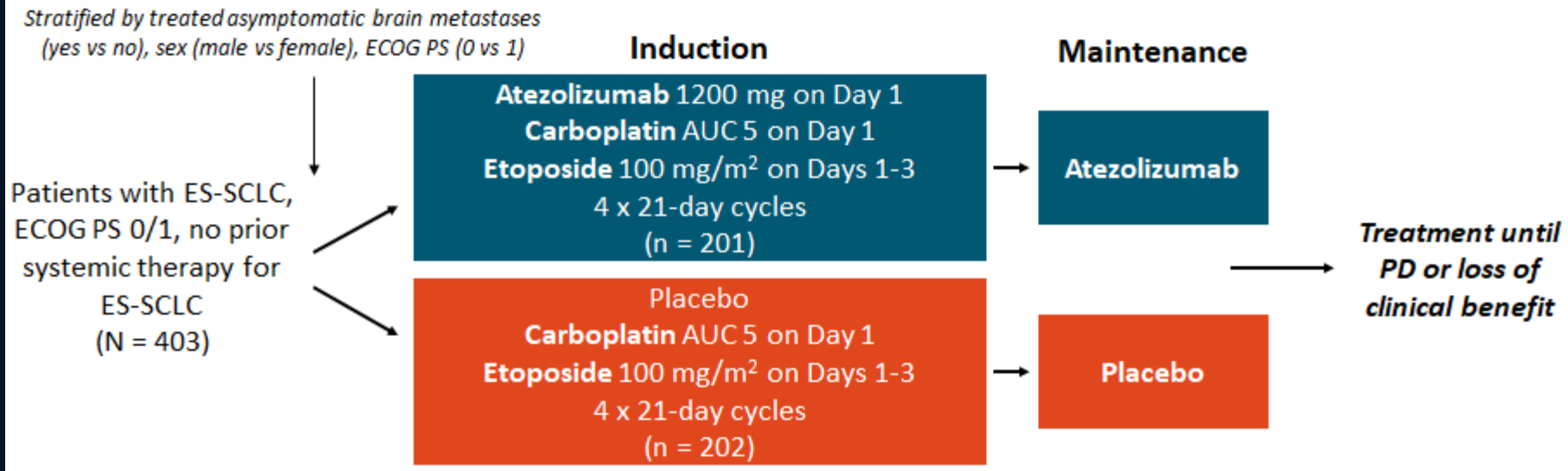

Malattia limitata
Chemioradioterapia
Risposta obiettiva
SI
Trattamento radioterapico encefalico profilattico (PCI)
Follow-up
NO
A progressione, terapia di seconda linea (figura 5)
Malattia estesa
Chemioterapia *platinum-based* (cisplatino-etoposide o carboplatino-etoposide)
Risposta obiettiva
SI
Trattamento radioterapico encefalico profilattico (PCI)
Follow-up
NO
A progressione, terapia di seconda linea (figura 5)

IMpower 133:

Atezolizumab plus chemotherapy as first line treatment in ED-SCLC

- Randomized, double-blind, placebo-controlled phase I/III trial

Stratified by treated asymptomatic brain metastases (yes vs no), sex (male vs female), ECOG PS (0 vs 1)

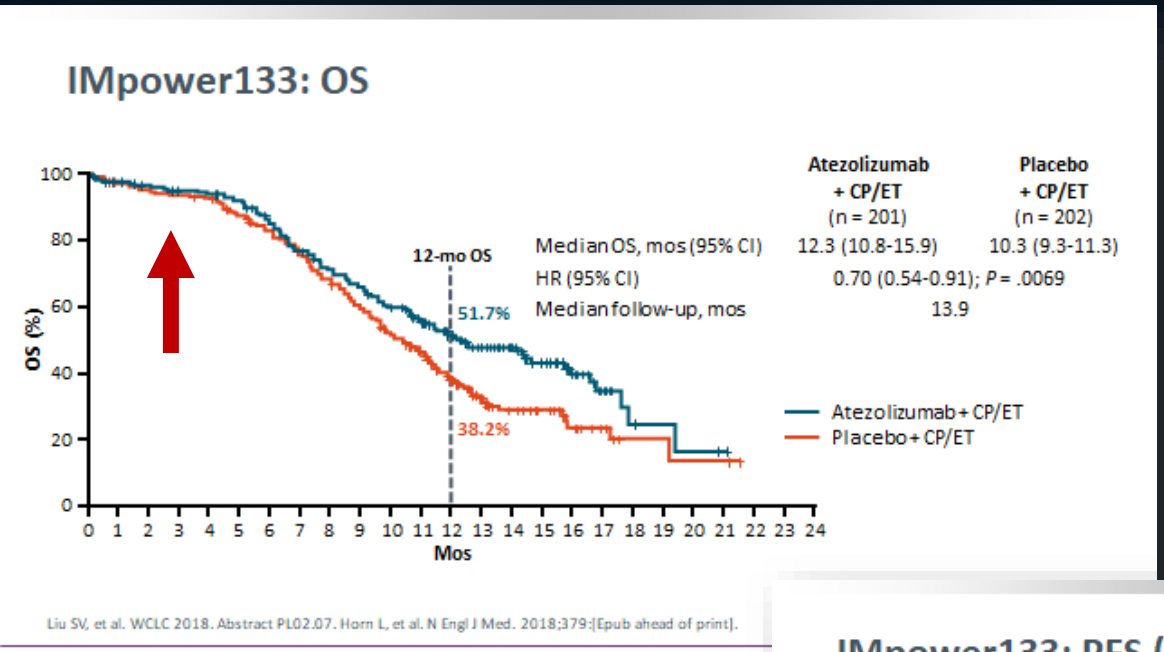


- Co-primary endpoints: investigator-assessed PFS, OS
- Secondary endpoints: ORR, DoR, safety

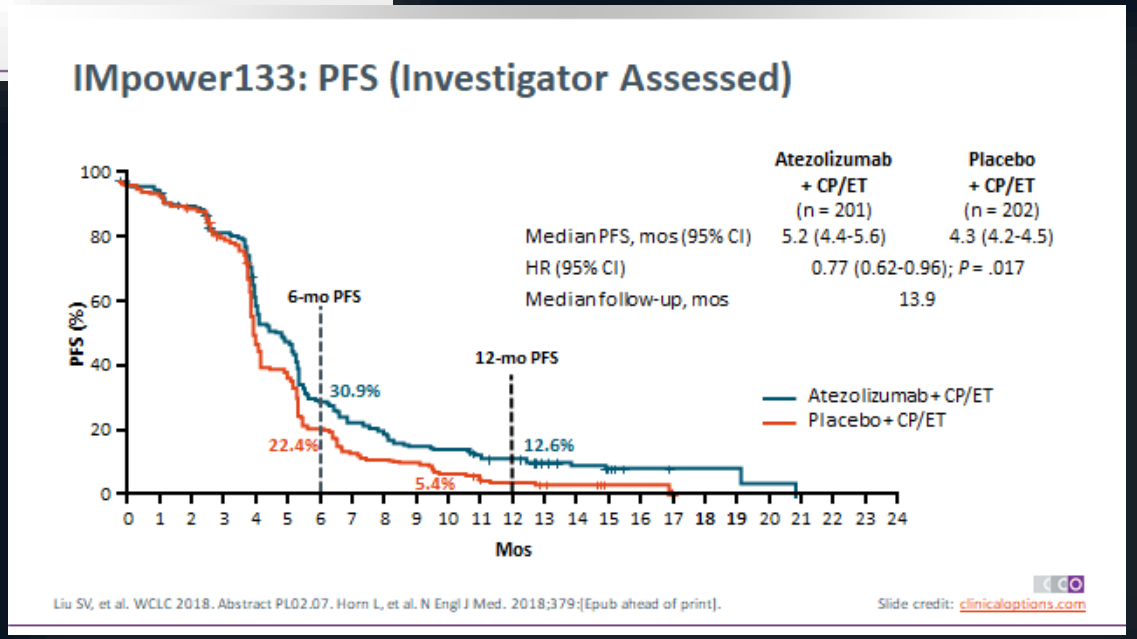
Liu SV, et al. WCLC 2018. Abstract PL02.07. Horn L, et al. N Engl J Med. 2018;379:[Epub ahead of print].

Slide credit: clinicaloptions.com

IMpower 133: OS and PFS

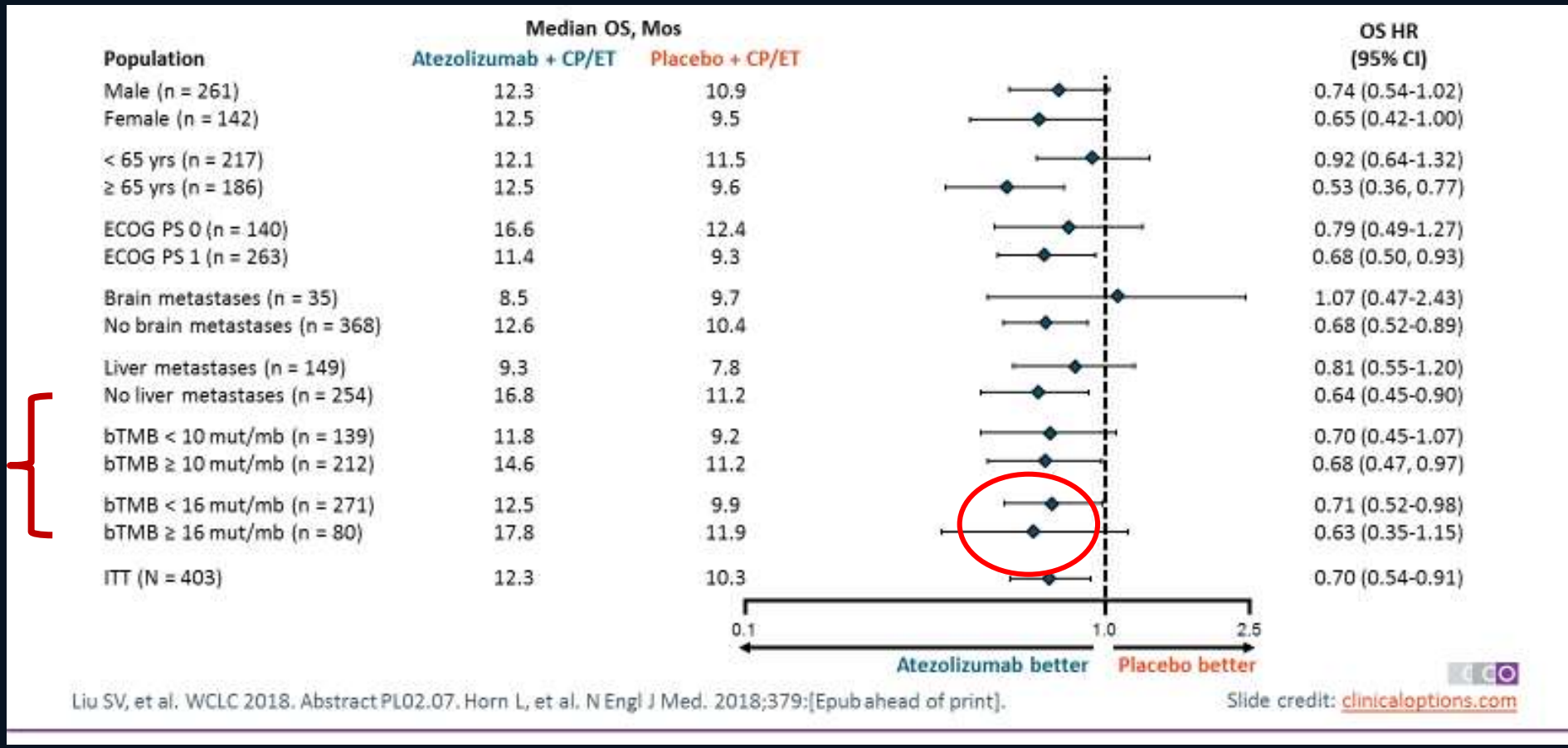


mOS benefit : 2 months



Horn NEJM 2018

IMpower 133: OS by subgroup

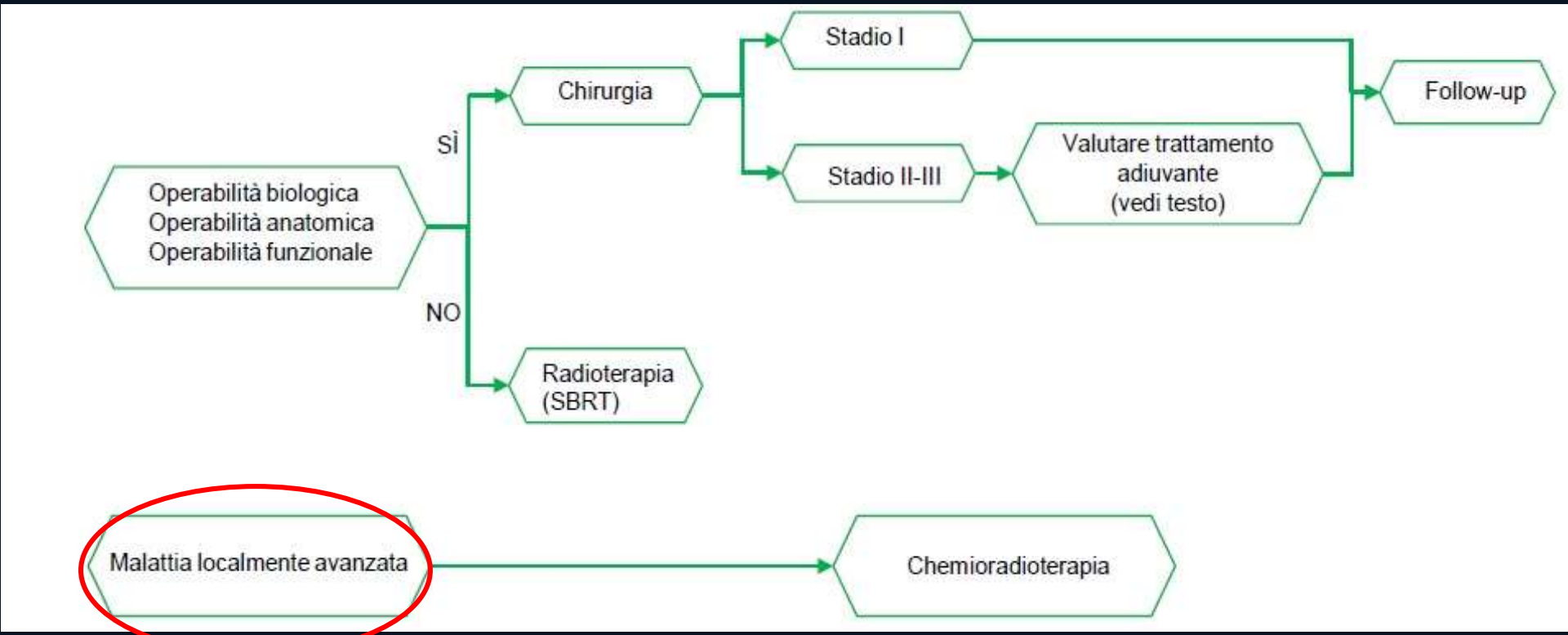


Liu SV, et al. WCLC 2018. Abstract PL02.07. Horn L, et al. N Engl J Med. 2018;379:[Epub ahead of print].

Slide credit: clinicaloptions.com

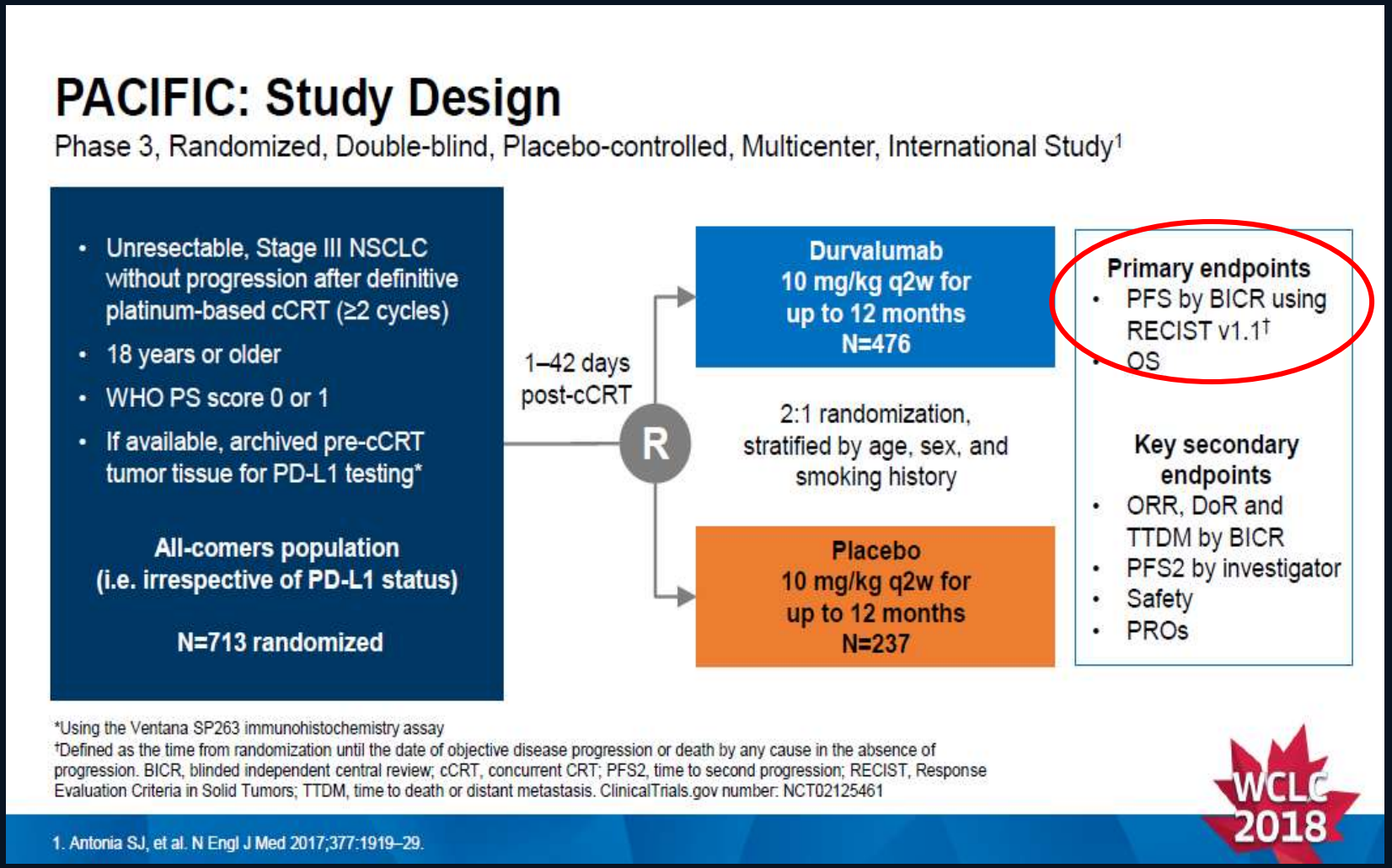
Horn NEJM 2018

Stadi iniziali e malattia localmente avanzata

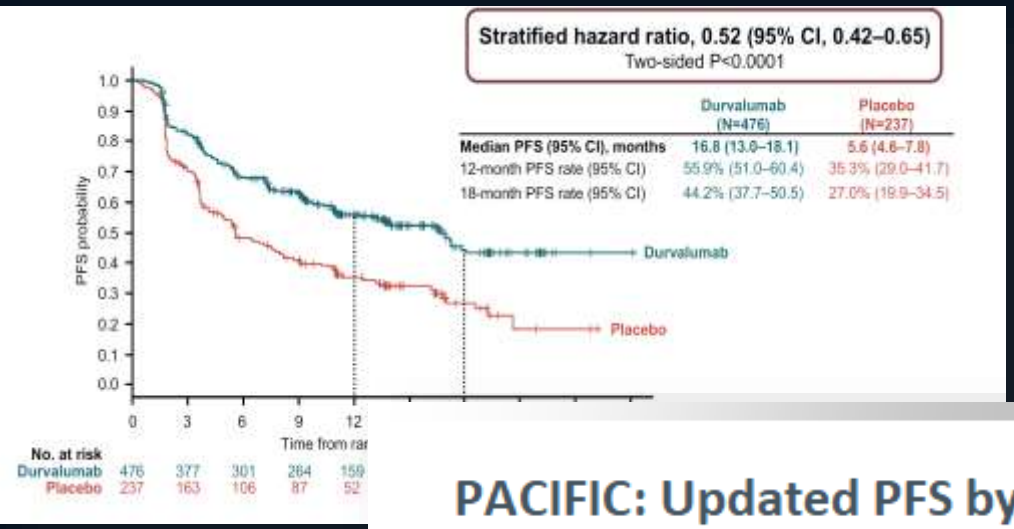


Qualità globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nei pazienti affetti da NSCLC stadio IIIA non resecabile (N2 bulky, e/o multipli livelli) o IIIB (con esclusione di N3 sovraclaveare), e clinicamente ben selezionati (buon *performance status*, assenza di calo ponderale alla diagnosi, assenza di patologie concomitanti maggiori) un trattamento combinato di chemio-radioterapia concomitante deve essere preso in considerazione come opzione terapeutica di prima intenzione [109-110].	**Positiva forte**

PACIFIC trial: Study Design

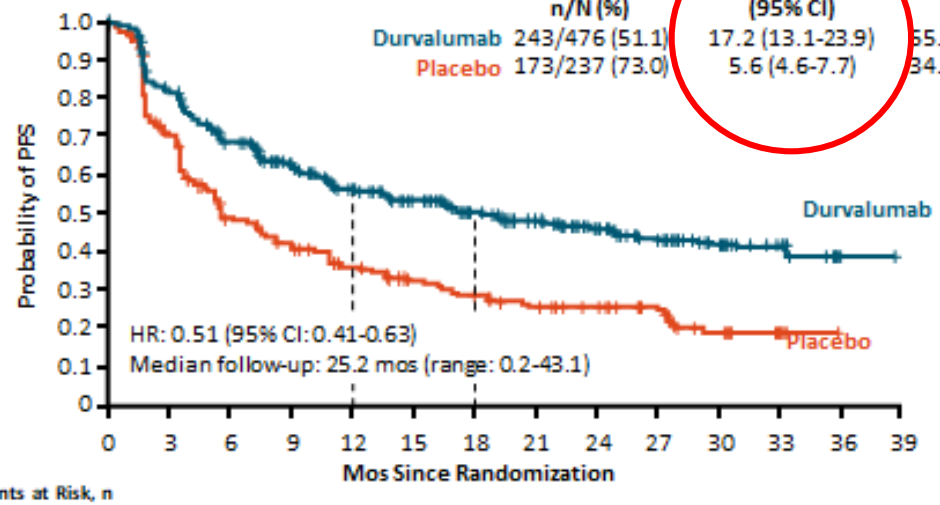


PACIFIC trial: PFS by BIRC



PACIFIC: Updated PFS by BICR (ITT)

	Events/Patients, n/N (%)	Median PFS, Mos (95% CI)	12-Mo PFS, % (95% CI)	18-Mo PFS, % (95% CI)
Durvalumab	243/476 (51.1)	17.2 (13.1-23.9)	55.7 (50.9-60.2)	49.5 (44.6-54.2)
Placebo	173/237 (73.0)	5.6 (4.6-7.7)	34.4 (28.2-40.7)	26.7 (20.9-32.9)



Patients at Risk, n

Durvalumab	476	377	302	268	213	188	163	143	116	83	43	23	1	0
Placebo	237	163	106	86	67	55	46	39	32	24	10	5	0	0

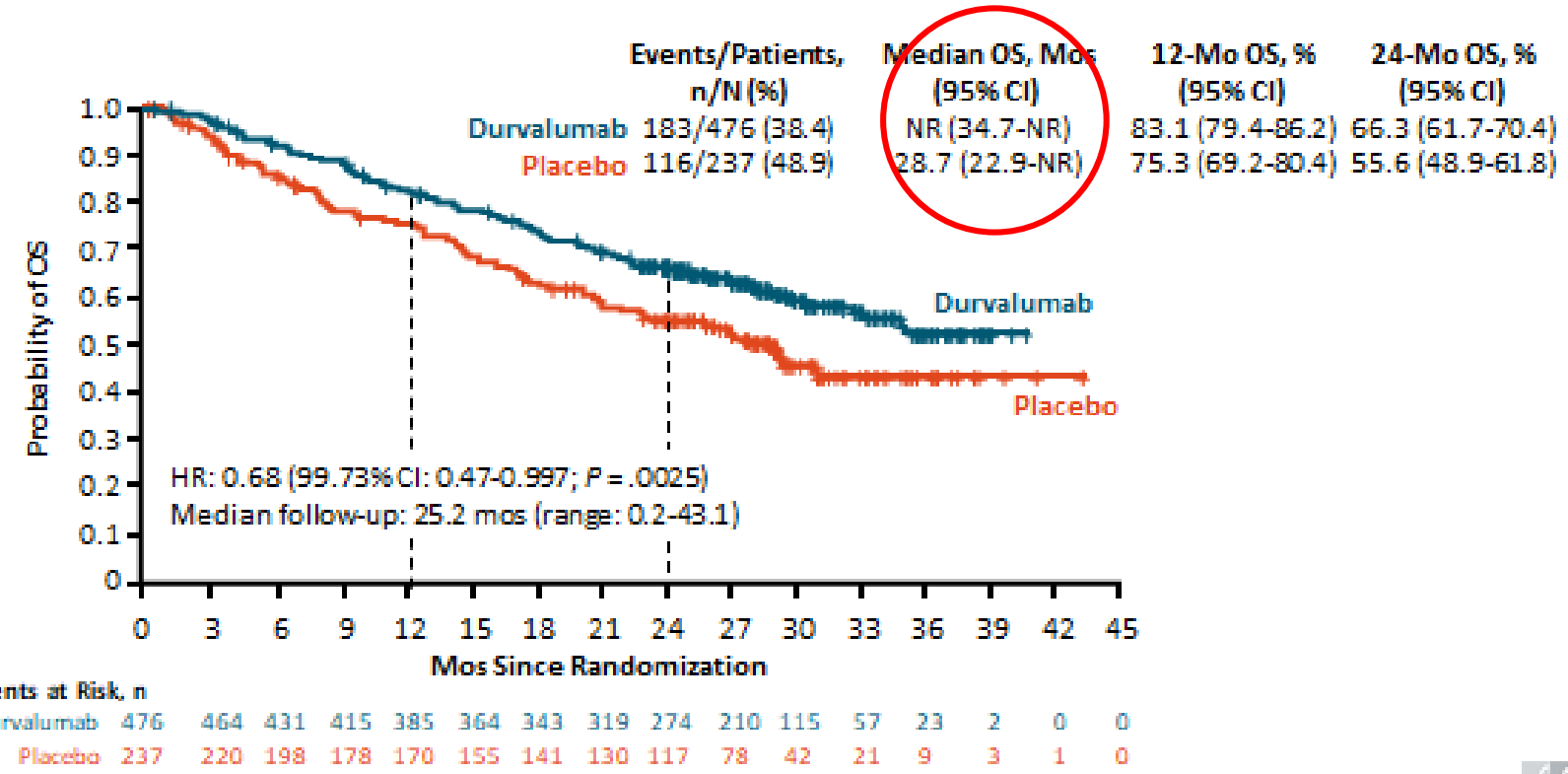
Antonia SJ, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

Antonia SJ, et al. N Engl J Med 2017;377(20):1919-1929.

PACIFIC trial: OS

PACIFIC: OS (ITT)



Antonia SJ, et al. N Engl J Med. 2018;[Epub ahead of print].

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Open questions

- What is the best therapeutic strategy?
  - Immuno + Immuno (and what type?)
  - Immuno + Chemo (and what type) +/- Anti-angio
  - For someone Immuno alone or No Immuno

- How can we better select patients?
  - Predictive biomarkers (PD-L1, TMB, others)
  - Steroids therapy, microbioma…
  - HPD

Grazie per la Vostra Attenzione !!!