NSCLC: Terapia medica nella fase avanzata

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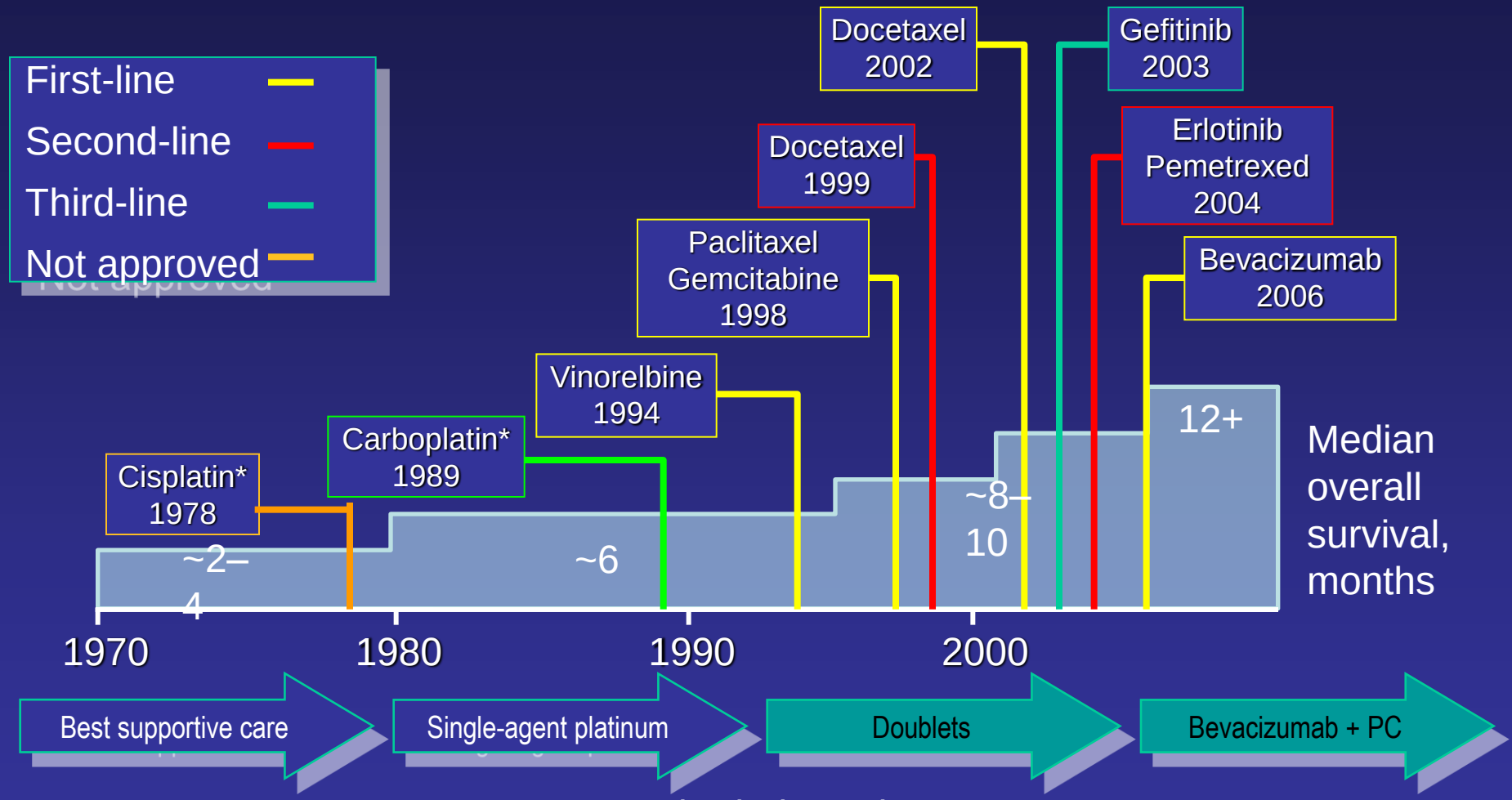
MONZA SC ONCOLOGIA MEDICA

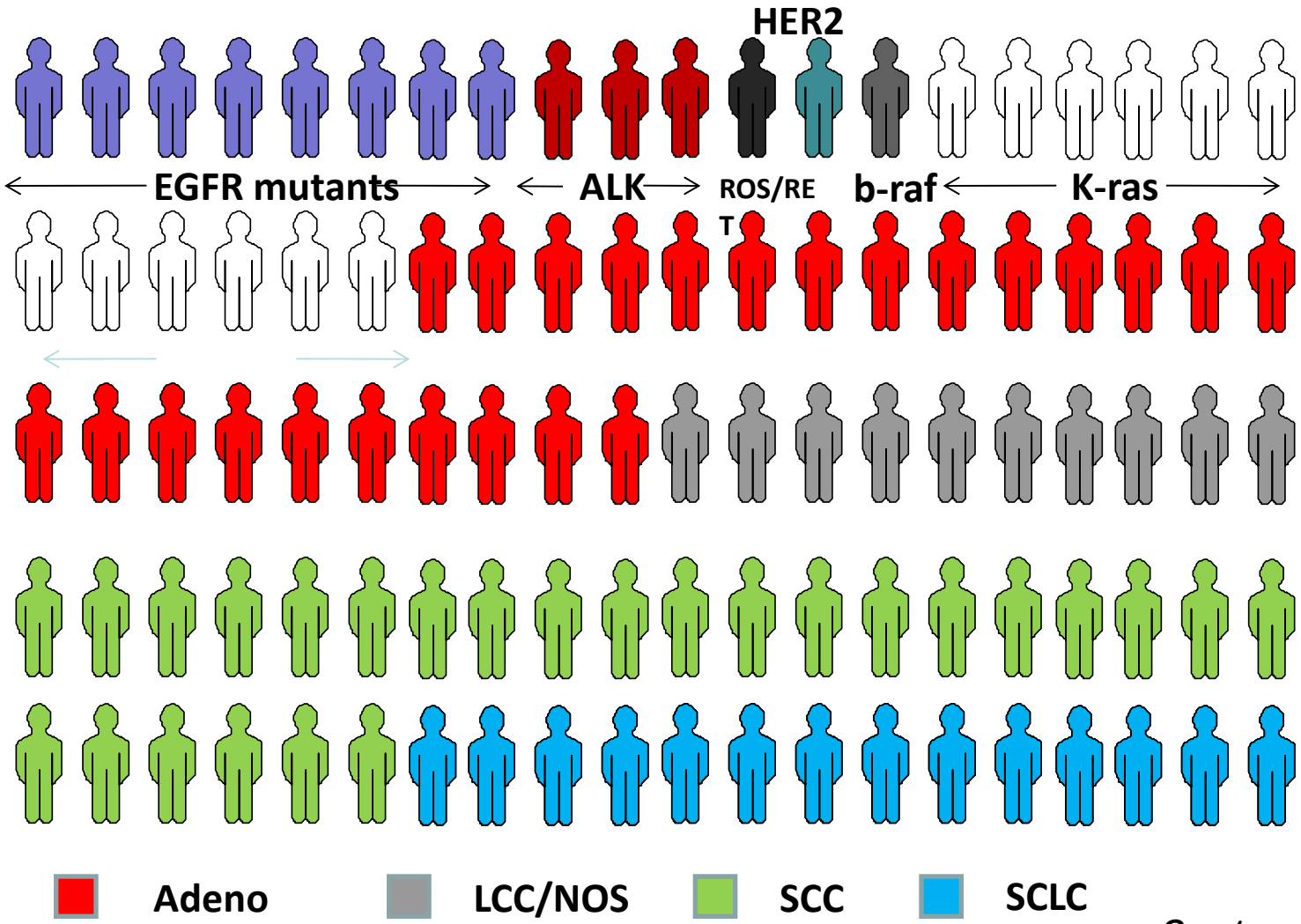
CT AND SILENT APPROVAL



*Label does not include NSCLC-specific indication

Food and Drug Administration. At http://www.fda.gov/cder/cancer/druglistframe.htm. Accessed August 28, 2006.; National Comprehensive Cancer Network (NCCN). Practice Guidelines in Oncology. Non-small cell lung cancer v2.2006. Accessed August 28, 2006. Schrump et al. Non-small cell lung cancer. In: Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

2002-2015 – Changes in the therapeutic landscape of stage IV lung cancer



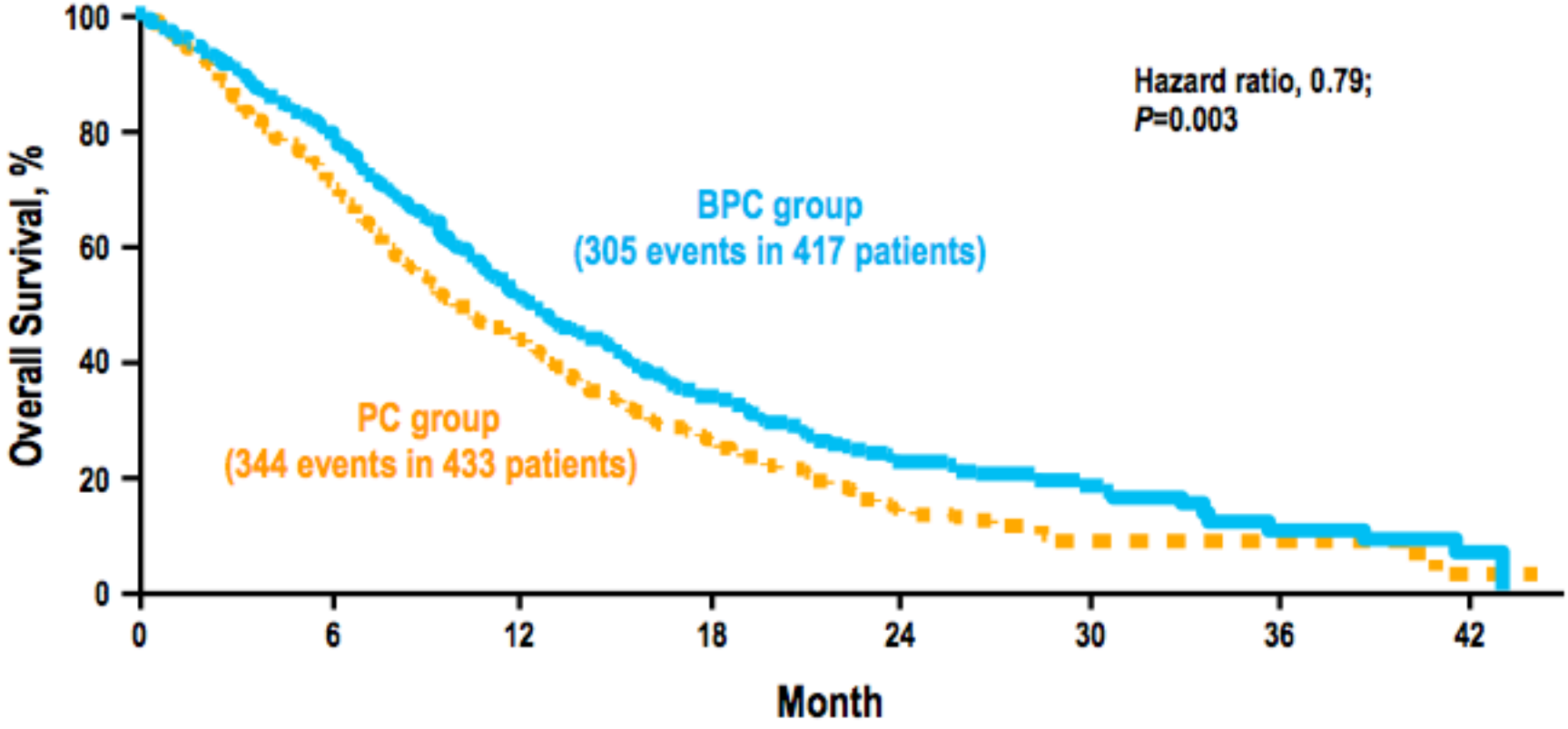
Courtesy G Scagliotti

THE FIRST HIT ON HISTOLOGY

The NEW ENGLAND JOURNAL of MEDICINE

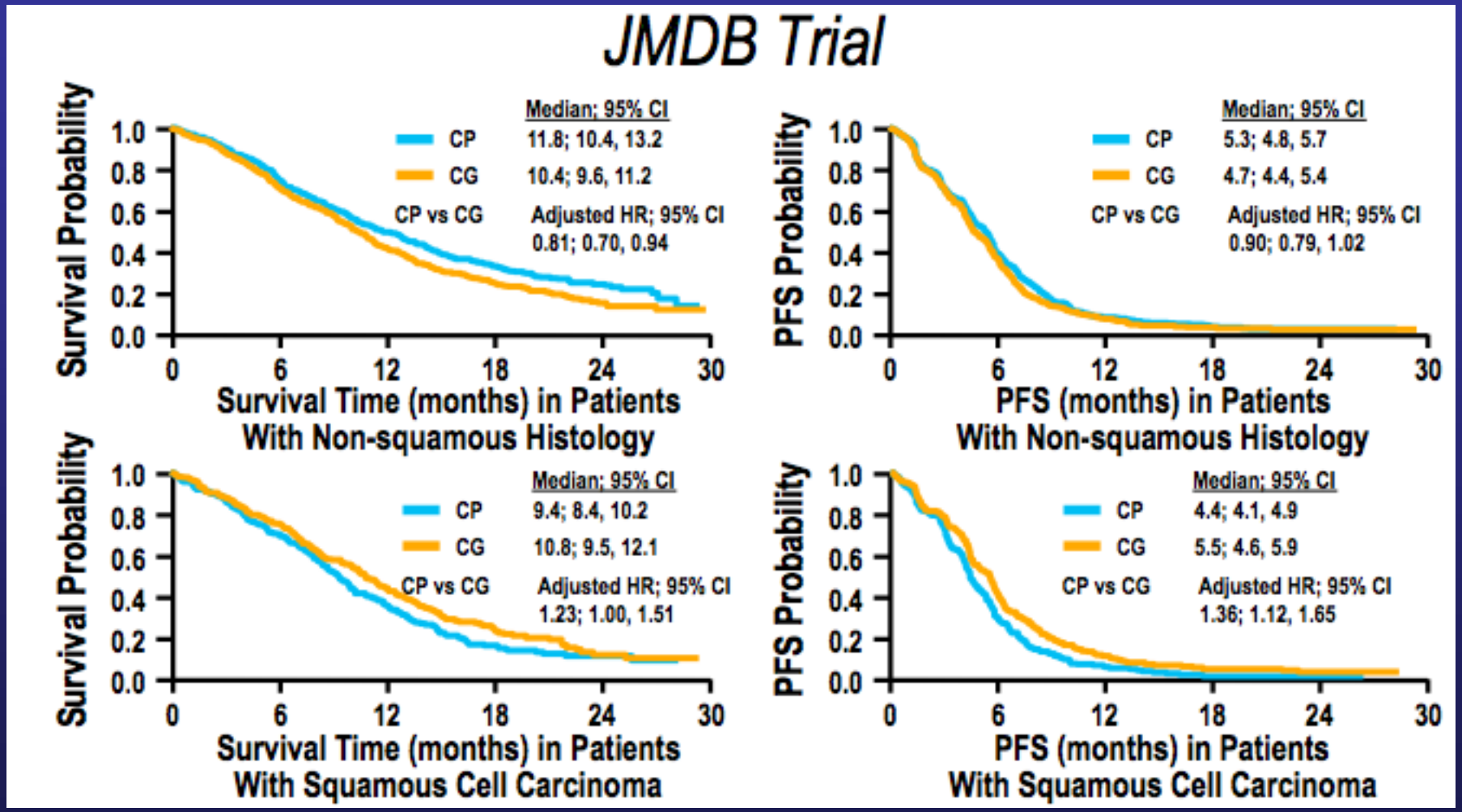
Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer

Alan Sandler, M.D., Robert Gray, Ph.D., Michael C. Perry, M.D., Julie Brahmer, M.D., Joan H. Schiller, M.D., Afshin Dowlati, M.D., Rogerio Lilenbaum, M.D., and David H. Johnson, M.D.



Sandler NEJM 2006

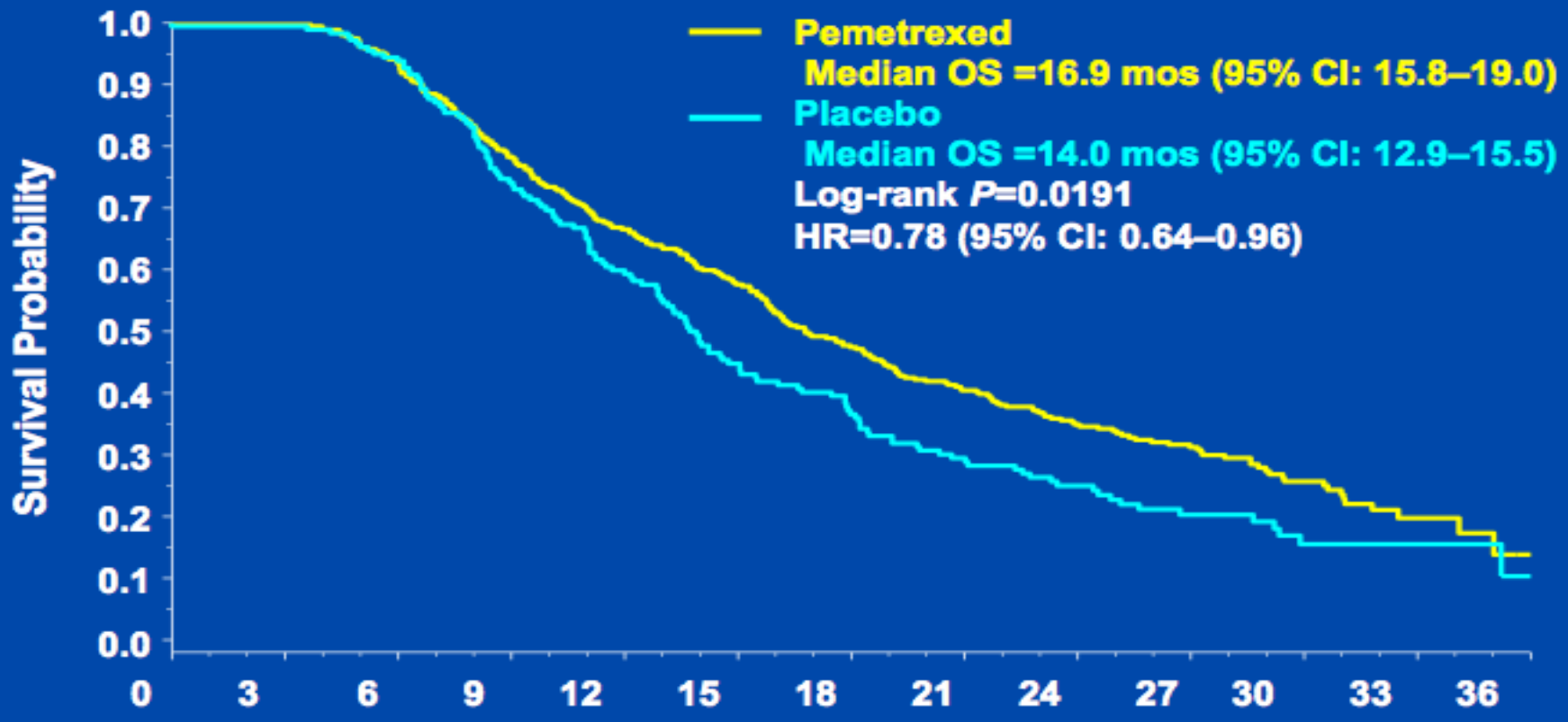
THE SECOND HIT ON HISTOLOGY



Scagliotti JCO 2008

MAINTENANCE TREATMENT

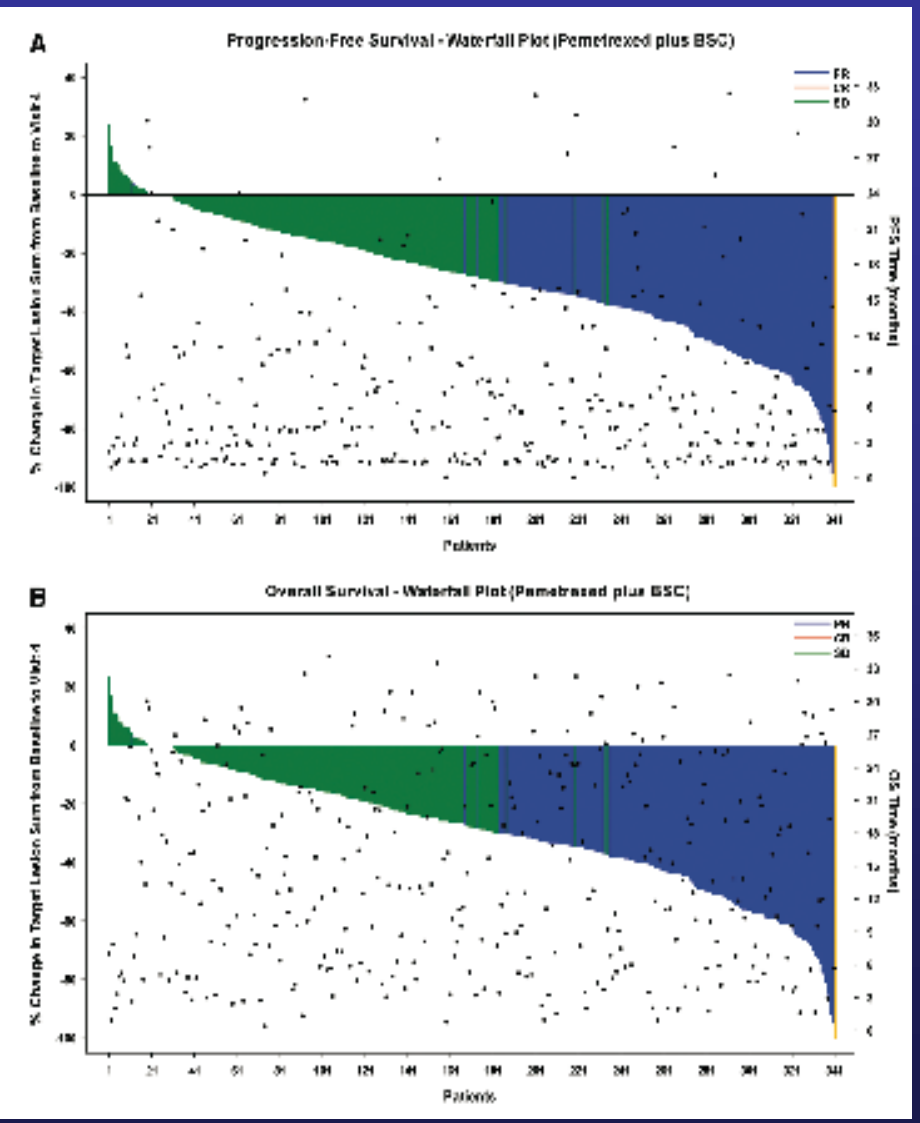
PARAMOUNT: Final OS from Induction

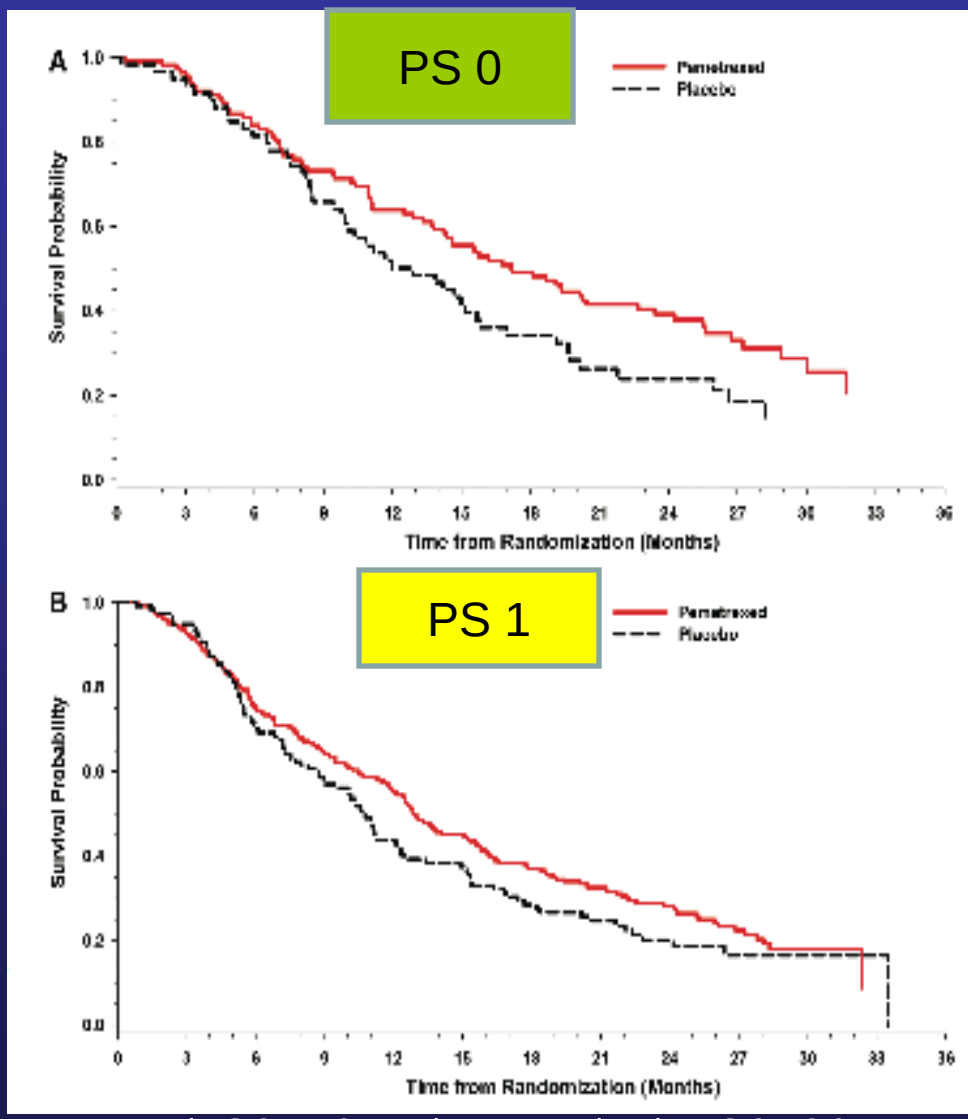


Patients at Risk										
Pem + BSC	359	335	276	234	200	164	138	106	77	42
	15	2	0							
Placebo + BSC	180	168	132	103	78	63	49	35	23	
	12	8	3	0						

Paz Ares JCO 2013

THE DRIVERS OF CHOICE





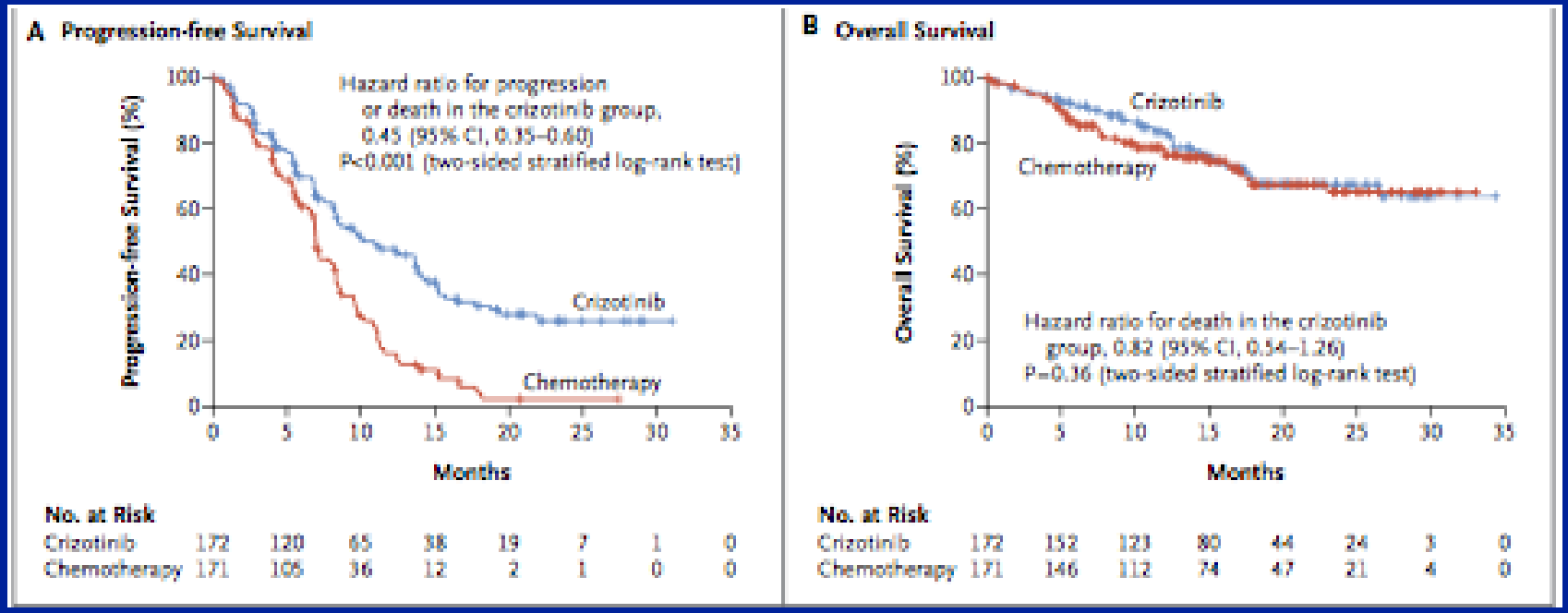
pemetrexed PS 0: 17.2 months versus placebo PS 0: 12.9, p = 0.059; pemetrexed PS 1: 12.9 months versus placebo PS 1: 10.7, p = 0.121

Reck JTO JCO 2014

Benefit of first-line EGFR TKIs: 9 randomized phase III studies

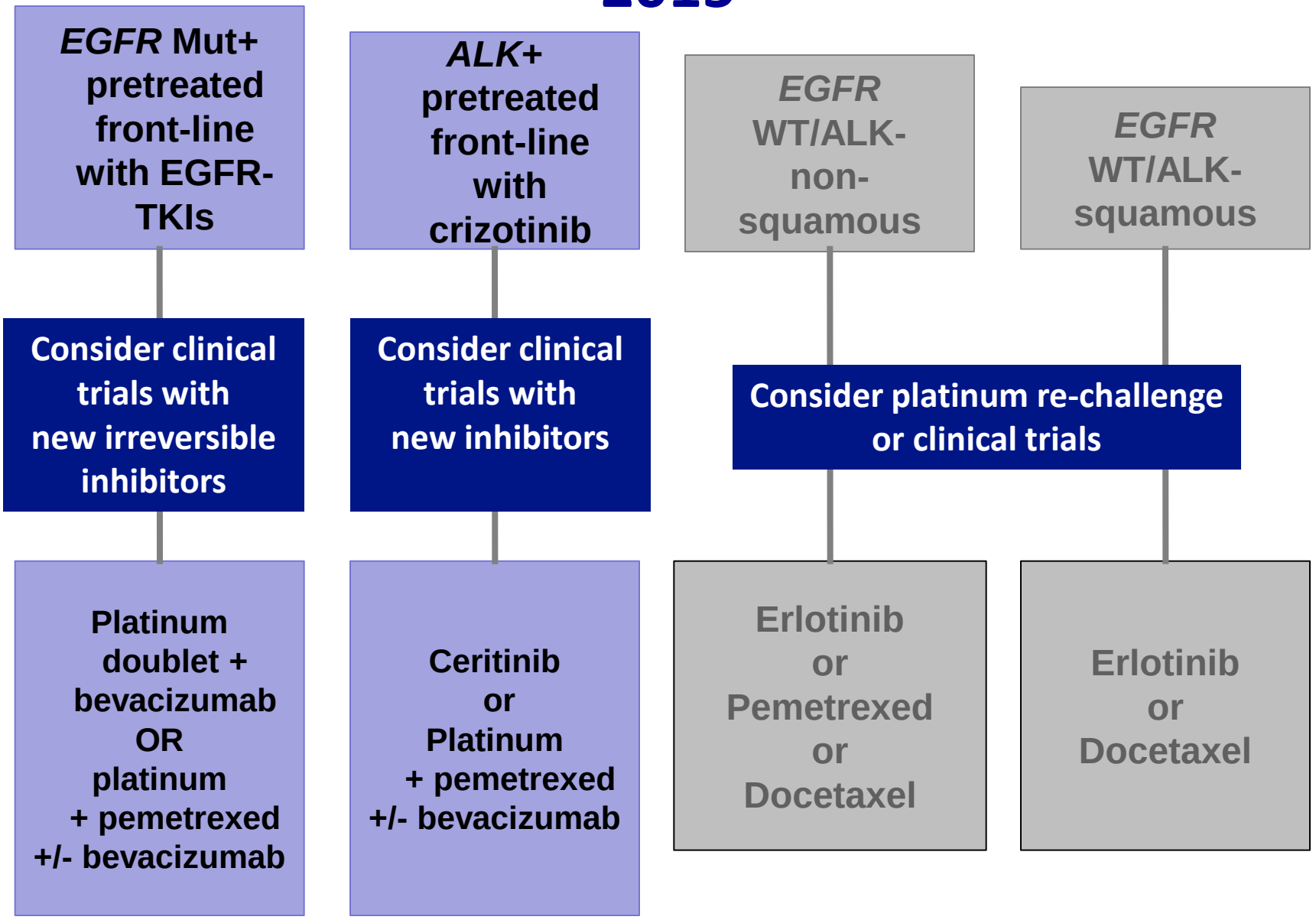
Study	Ref.	TKI	CTx	N #	PFS mos	HR 95% CI	OS mos
IPASS	Mok NEJM 2009	GEFITINIB	Cb/Pac	261	9.5 vs. 6.3	**0.48** 0.36 – 0.64	21.6 vs. 21.9
First-signal	Han JCO 2012	GEFITINIB	Cis/Gem	42	8.0 vs. 6.3	**0.54** 0.26-1.10	27.2 vs. 25.6
NEJ002	Maemondo NEJM 2010	GEFITINIB	Cb/Pac	194	10.8 vs. 5.4	**0.35** 0.22-0.41	30.5 vs. 23.6
WJTOG 3405	Mitsudomi Lancet 2010	GEFITINIB	Cis/Doc	172	9.2 vs. 6.3	**0.49** 0.33-0.71	30.9 vs NR
OPTIMAL	Zhou Lancet Oncol 2011	ERLOTINIB	Cis/Gem	164	13.1 vs. 4.6	**0.16** 0.10-0.26	Not mature
EURTAC	Rosell Lancet Oncol 2012	ERLOTINIB	P/Doc or Gem	174	10.4 vs 5.1	**0.34** 0.23-0.29	19.3 vs 19.5
ENSURE	Wu P WCLC 2013	ERLOTINIB	P/ Gem	217	11.0 vs. 5.6	**0.42** 0.27-0.66	Not mature
LUX-LUNG 3	Sequist JCO 2014	AFATINIB	Cis/Pem	308	13.6 vs. 6.9	**0.47** 0.34-0.65	31.5 vs 28.3
LUX-LUNG 6	Wu Lancet Oncol 2014	AFATINIB	Cis/Gem	364	11.0 vs. 5.6	**0.28** 0.20-0.39	23.6 vs. 23.5

Crizotinib in first line

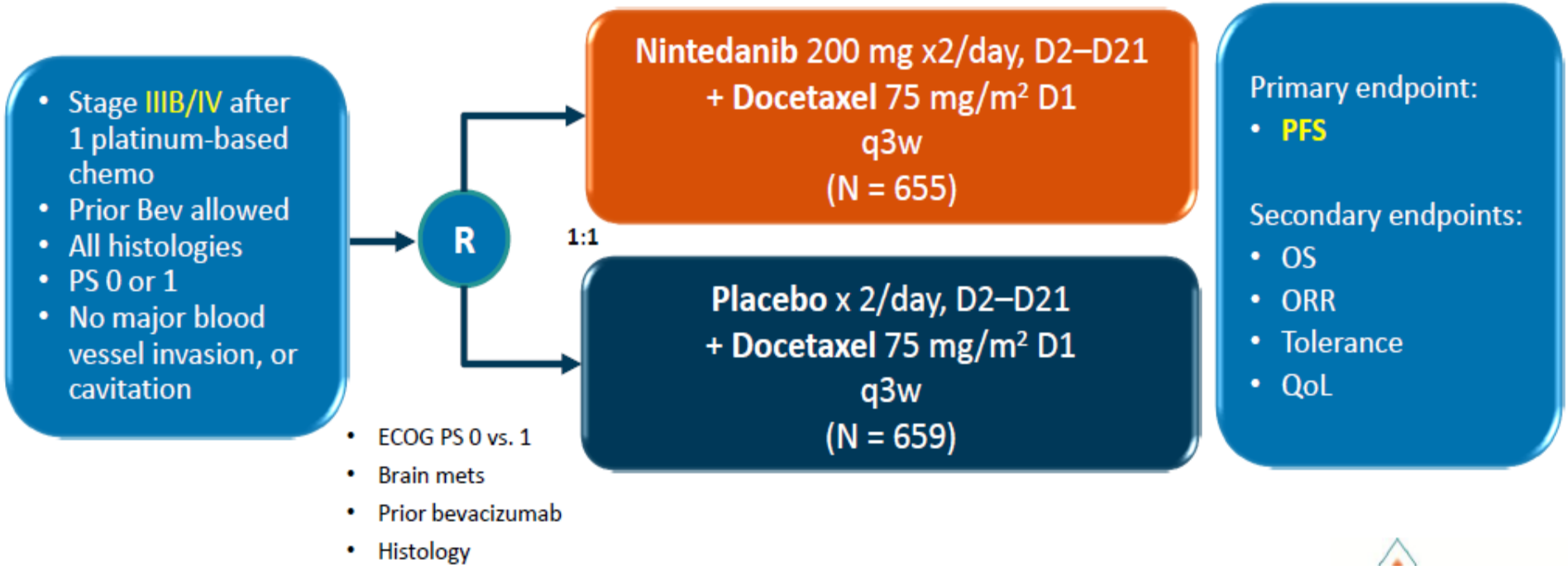


Solomon BJ 2014

Second-line options for metastatic NSCLC in 2015



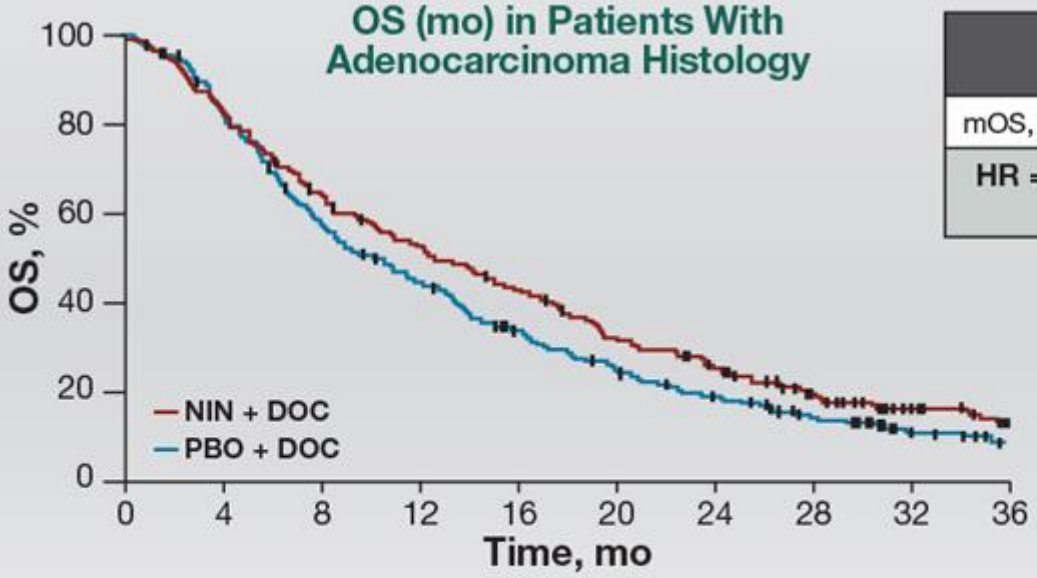
- None of the studies assessing addition of VEGFR TKI to chemotherapy demonstrated a survival benefit over chemotherapy alone in 1st or 2nd line treatment
- Nintedanib (BIBF1120)
  - Anti-angiogenic multitarget TKI active against VEGFR 1–3, FGFR 1–3, PDFGR α/β and RET



Reck M, et al. Lancet Oncol 2014;15:143–55.

LUME-Lung 1: Survival in Patients With Adenocarcinoma Histology

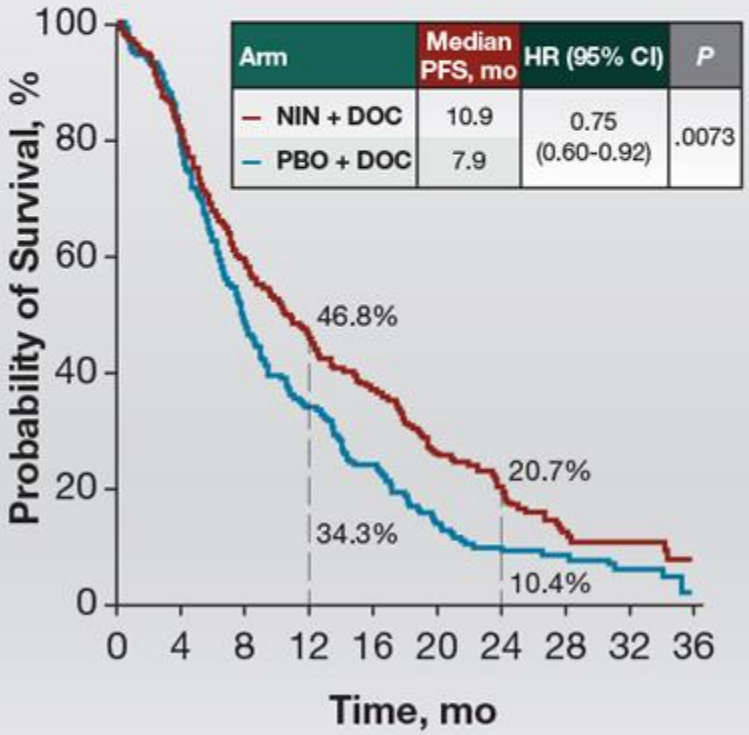
- Randomised, double-blind, phase 3 study of NIN + DOC vs PBO + DOC in patients with locally advanced or metastatic NSCLC after progression following first-line CT (N = 1,314)
  - Adenocarcinoma: 49% in NIN + DOC arm, 51% in PBO + DOC arm (n = 655)
- Primary objective: PFS by independent central review (ITT analysis)
- Key secondary objective: OS (ITT analysis)



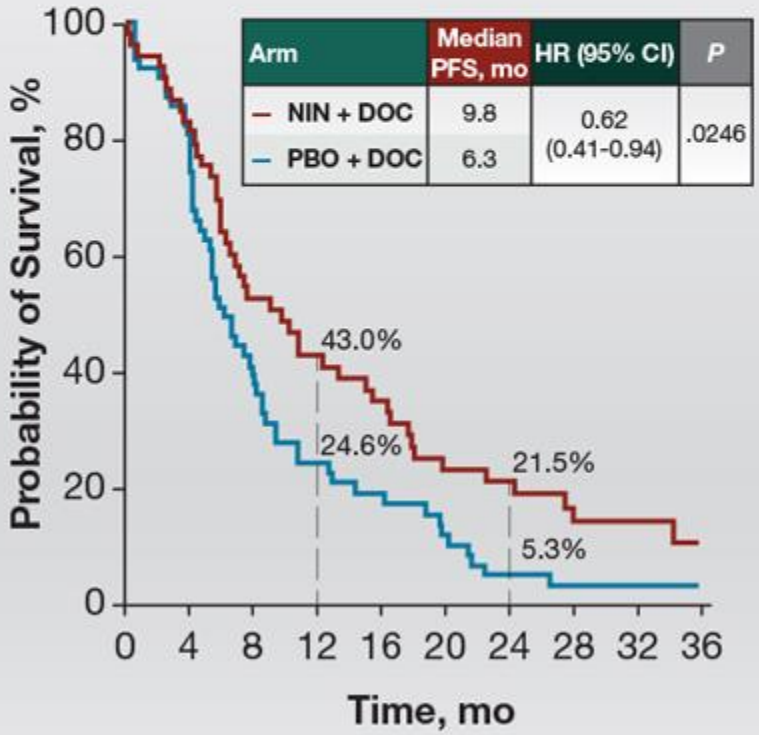
	NIN + DOC (n = 322)	PBO + DOC (n = 336)
mOS, mo	12.6	10.3
HR = 0.83 (95% CI, 0.70-0.99); *P* = .0359		

LUME-Lung 1: OS According to Response to First-Line Therapy in Patients With Adenocarcinoma

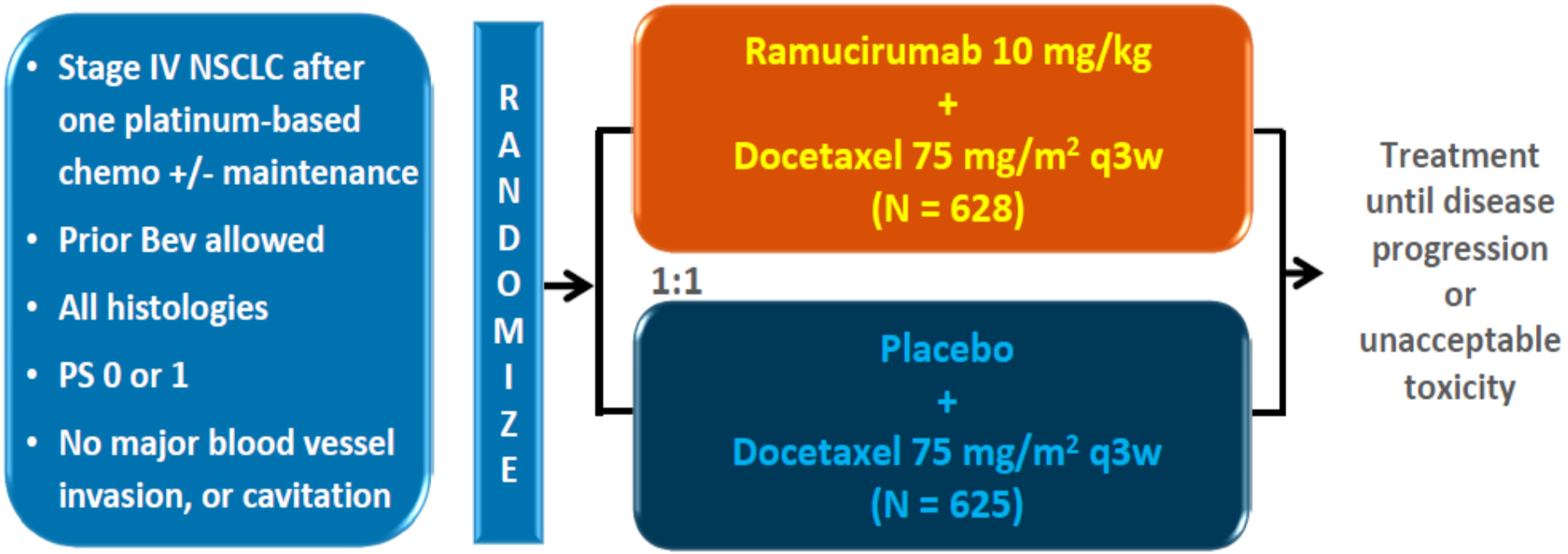
Response to First-Line Therapy <9 mo



Best Response of PD to First-Line Therapy



REVEL: Study Design



Stratification factors:

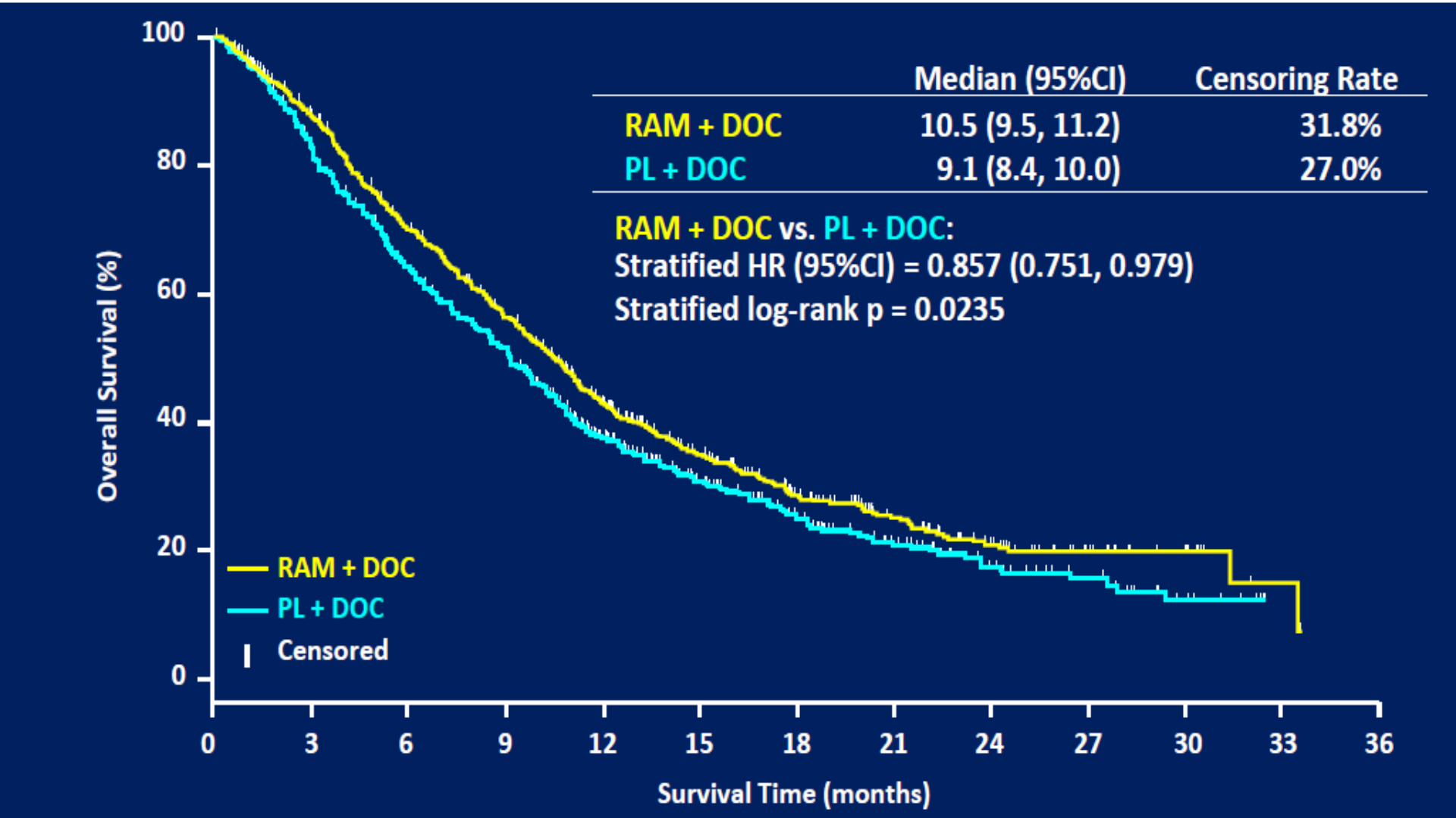
- ECOG PS 0 vs. 1
- Gender
- Prior maintenance
- East-Asia vs. ROW

Primary endpoint: **Overall Survival**

Secondary endpoints:
PFS, ORR, safety, patient-reported outcomes

Overall Survival

ITT Population



	Median (95%CI)	Censoring Rate
RAM + DOC	10.5 (9.5, 11.2)	31.8%
PL + DOC	9.1 (8.4, 10.0)	27.0%

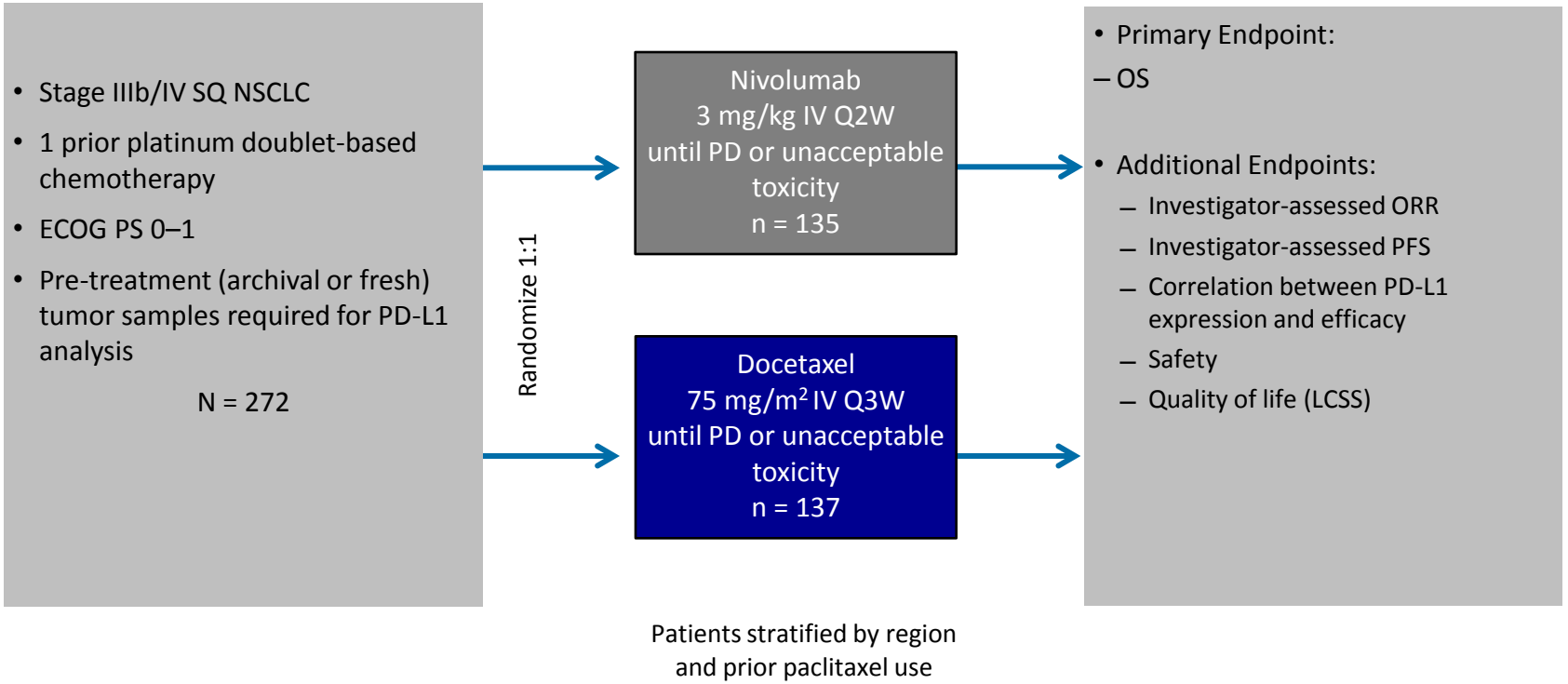
RAM + DOC vs. PL + DOC:
Stratified HR (95%CI) = 0.857 (0.751, 0.979)
Stratified log-rank p = 0.0235

Number at risk

RAM + DOC	628	527	415	329	231	156	103	70	45	23	11	2	0
PL + DOC	625	501	386	306	197	129	86	56	36	23	9	0	0

Pérol M, et al. J Clin Oncol 2014;32(suppl 5):abstr LBA8006^ [ASCO]; Garon EB, et al. Lancet 2014;384:665–73.

CheckMate 017 (NCT01642004) - Study Design



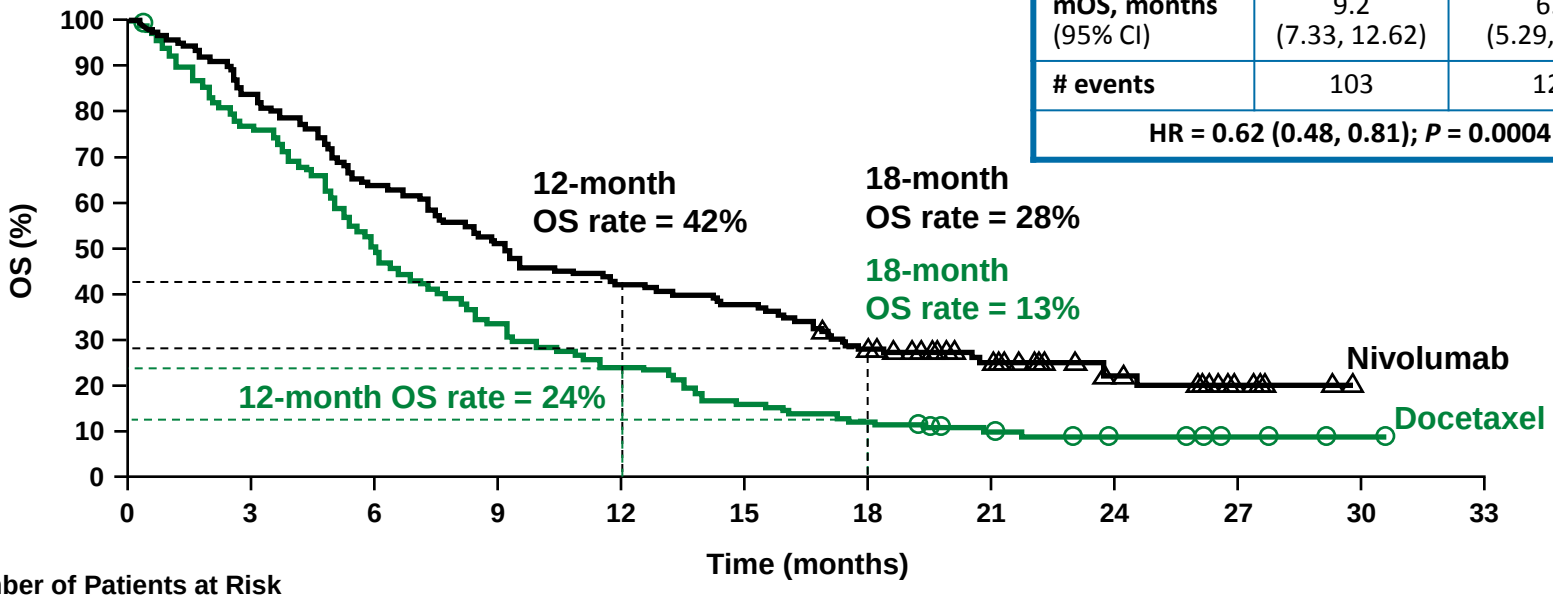
- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

LCSS = Lung cancer symptom scale

Brahmer J, et al. NEJM 2015

CheckMate 017: Overall Survival

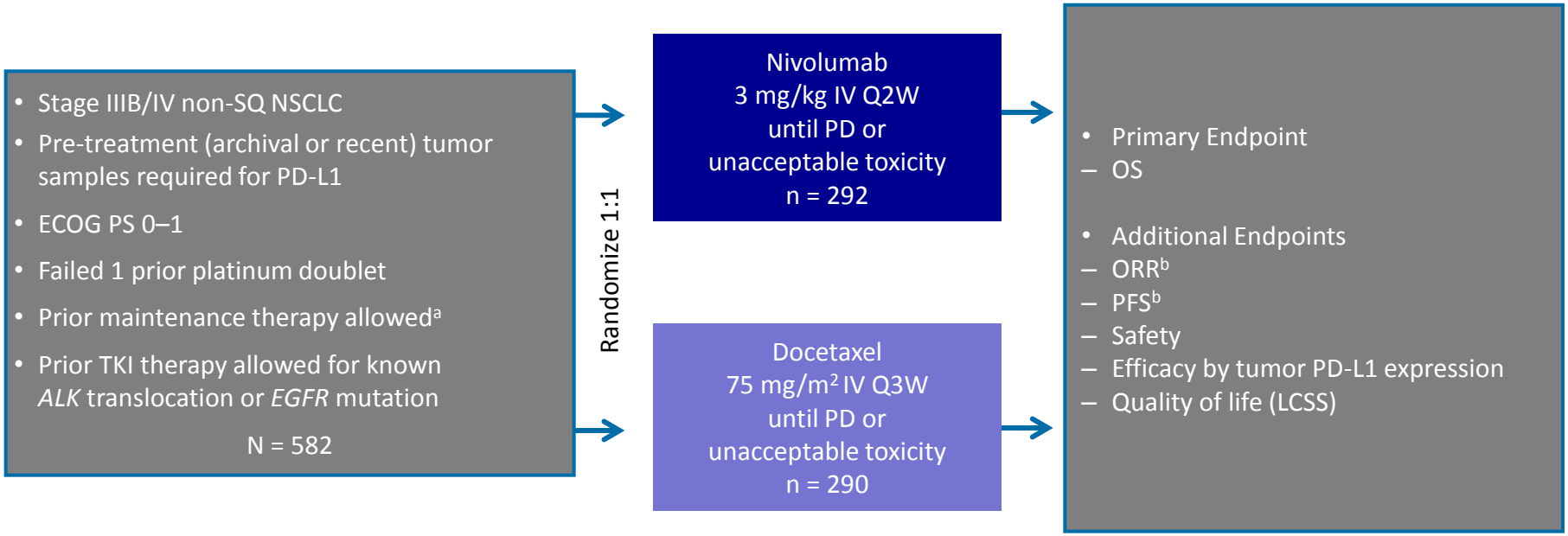
	Nivolumab n = 135	Docetaxel n = 137
mOS, months (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR = 0.62 (0.48, 0.81); *P* = 0.0004		



Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	15	11	7	3	1	0

CheckMate 057 (NCT01673867) Study Design



Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

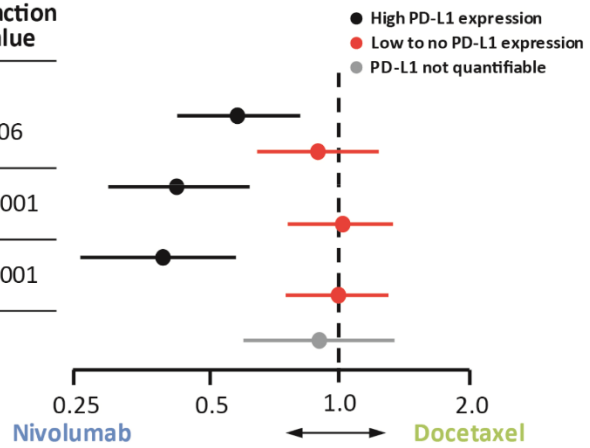
[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

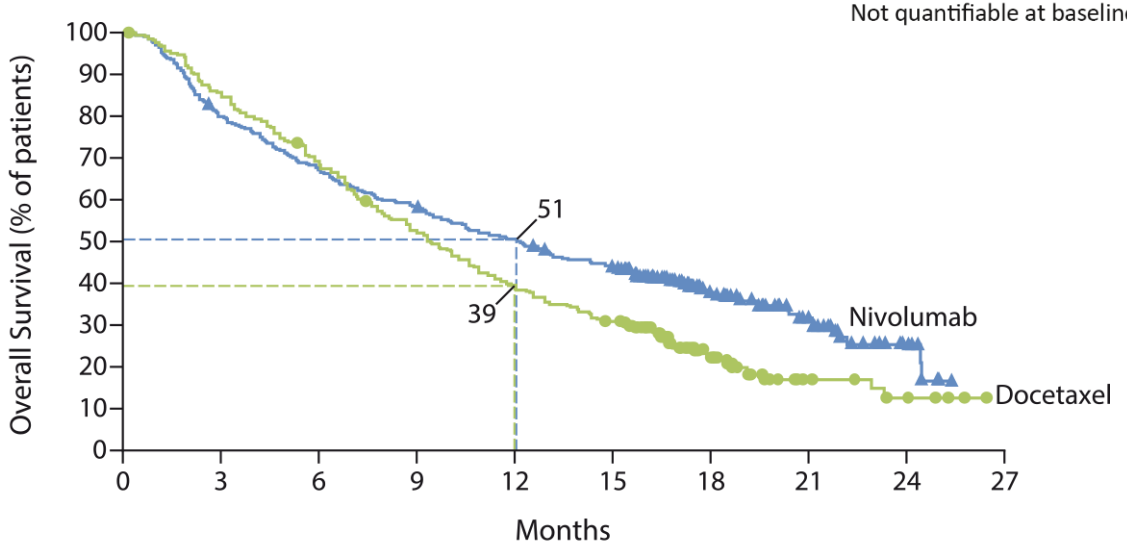
Paz-Ares L, et al. ASCO 2015

CheckMate 057 (NCT01673867)- OS

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4
HR = 0.73 (96% CI: 0.59, 0.89); P = 0.0015		

PD-L1expression level	Interaction *P*-value
OS	
≥1%	0.06
<1%	
≥5%	<0.001
<5%	
≥10%	<0.001
<10%	
Not quantifiable at baseline	





No. at Risk

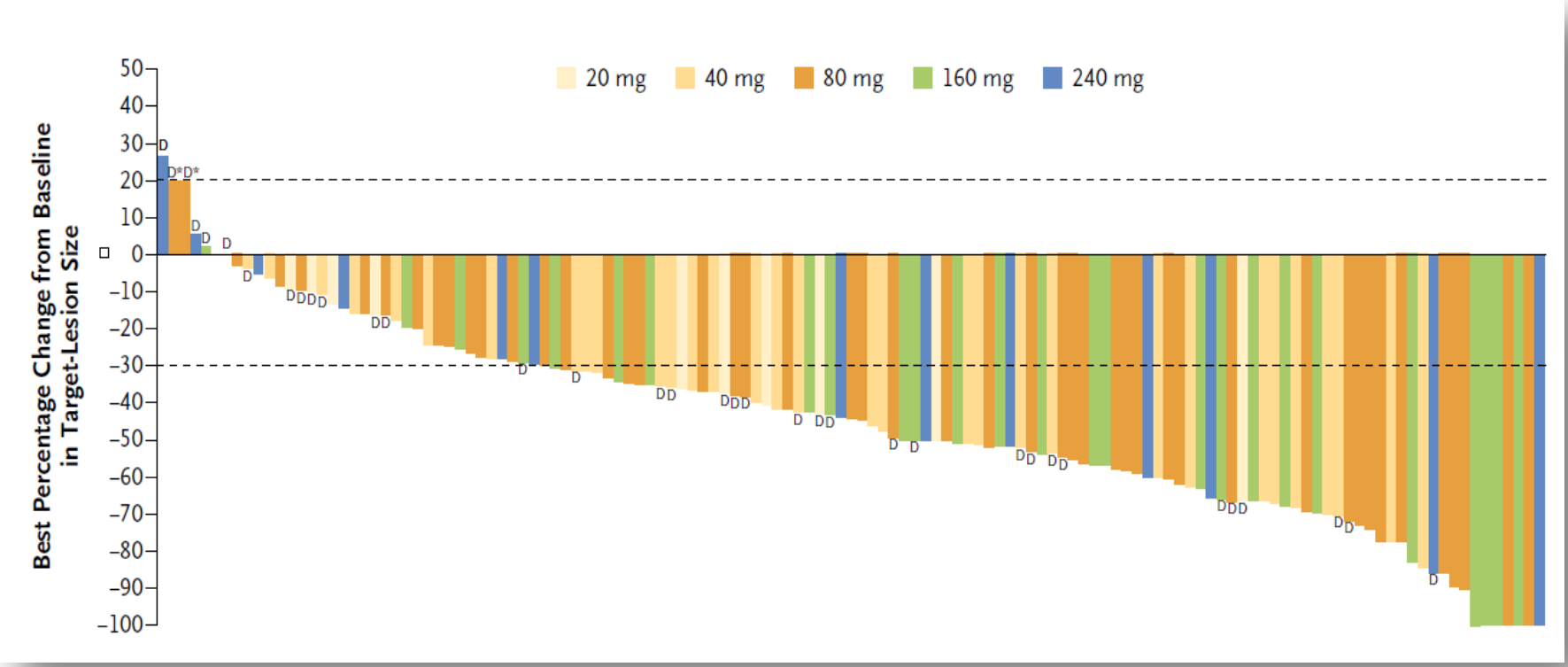
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

H. Borghaei, L. Paz-Ares, N Engl J Med. 2015 Sep 27

Anti PD1/PD-L1 agents: open questions

- How to select patients?
  - Clinical characteristics?
  - PD-L1 expression or other biomarkers?
- Treatment duration
- Best tool(s) to assess drug activity?
- Patient communication

AURA (AZD9291): best % change in target-lesion size



Janne PA, NEJM 2015

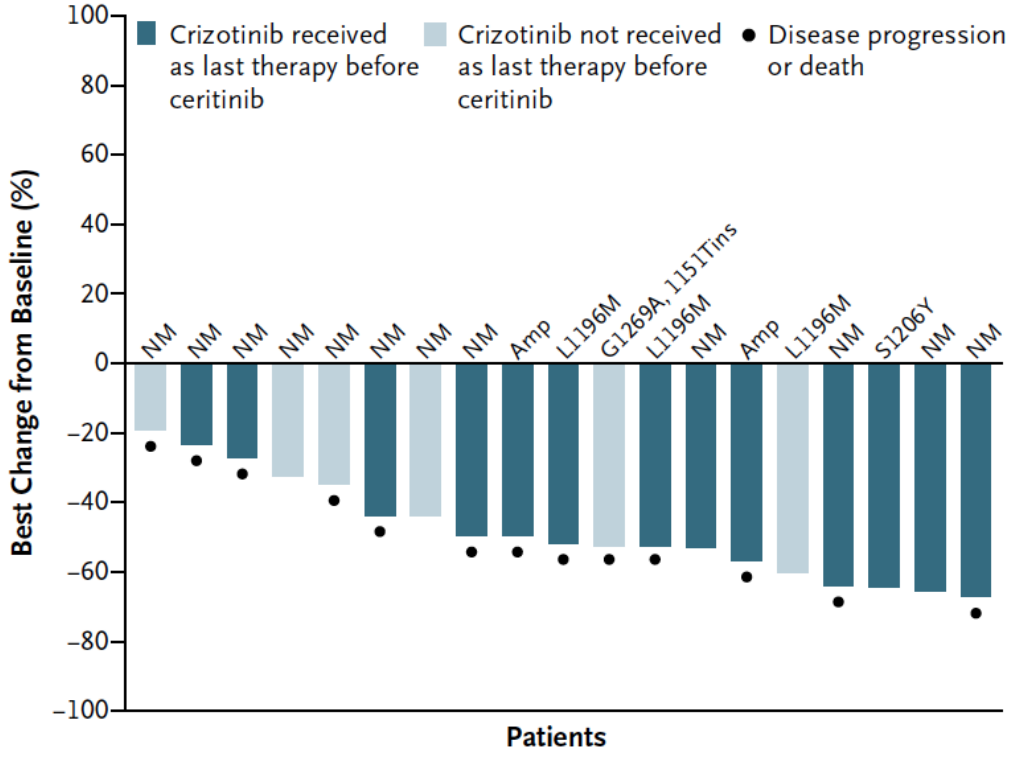
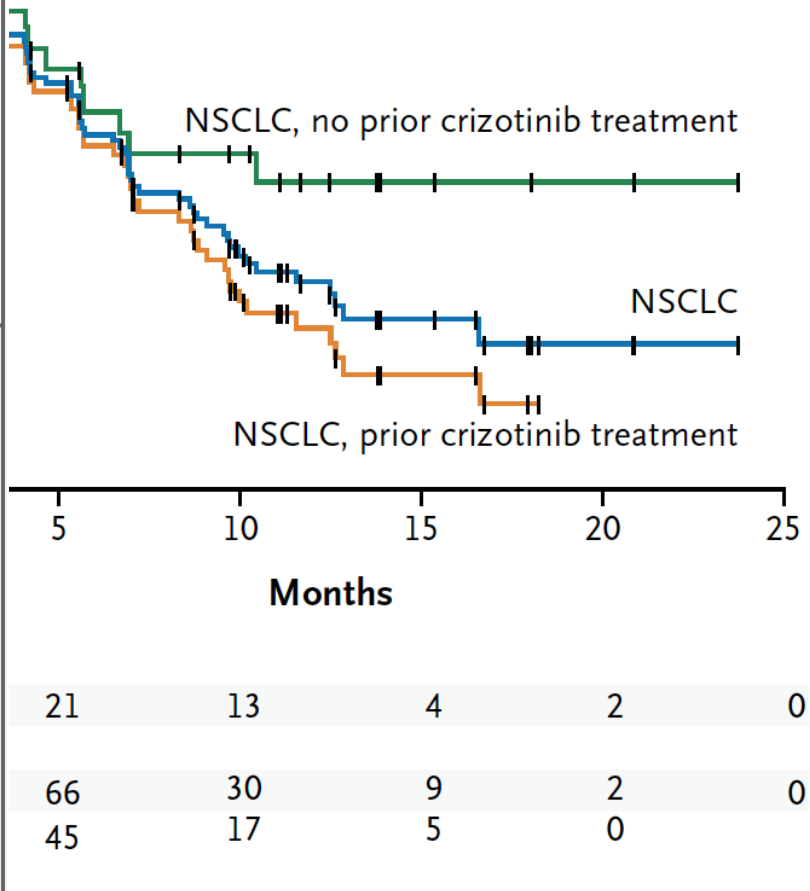


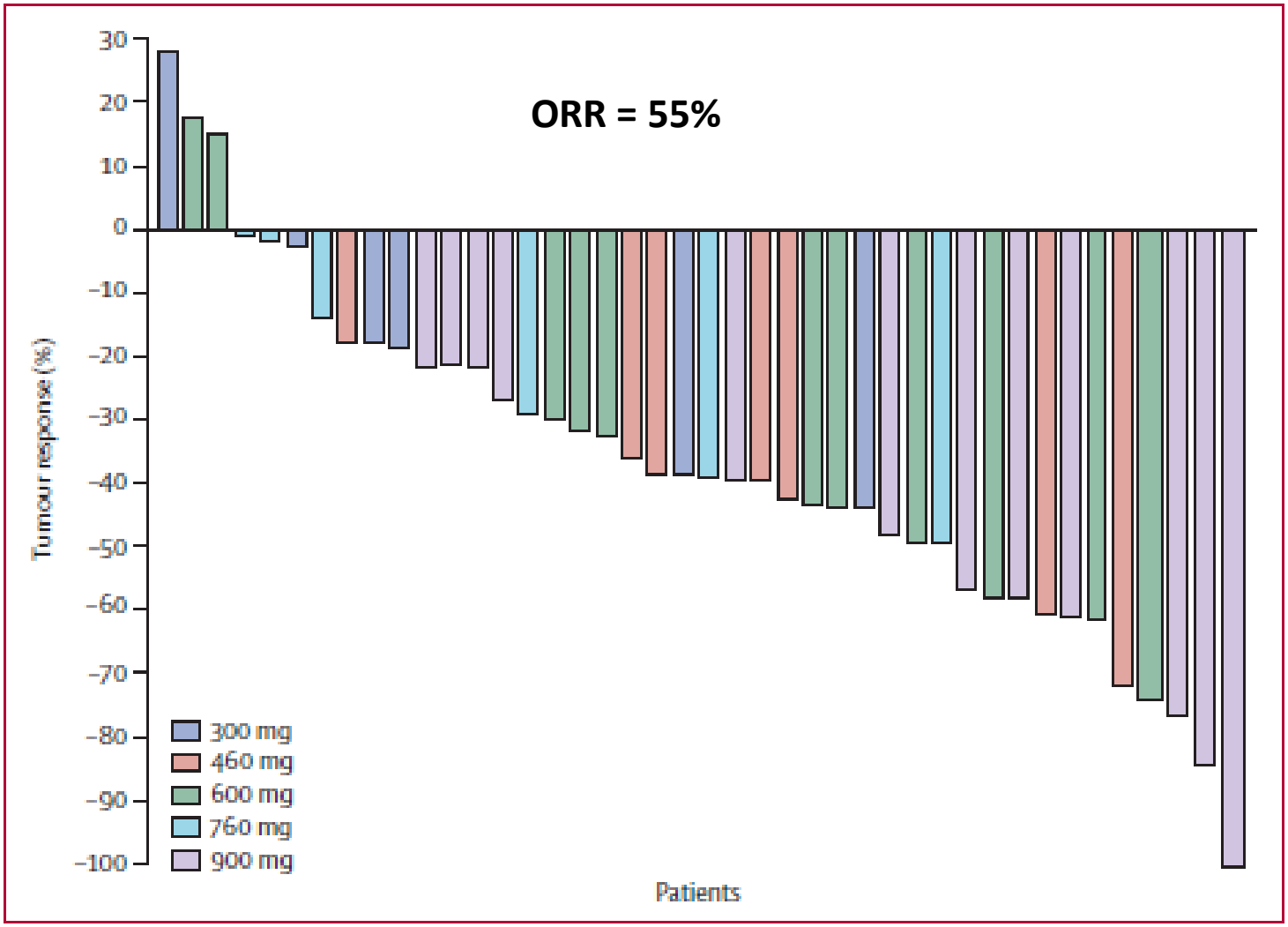
Figure 3. Correlation of Response to Ceritinib with *ALK* Gene Alteration among Patients with Crizotinib Resistance.

A total of 19 patients with crizotinib-resistant, *ALK*-rearranged non–small-cell lung cancer underwent biopsy at one study site before the initiation of ceritinib. Shown here is the largest percentage decrease in target lesions in these 19 patients. All the tumors were positive for *ALK* rearrangement, on the basis of the standard fluorescence in situ hybridization (FISH) assay with the use of break-apart probes. *ALK* genotypes are shown above the bars. Amp denotes amplification of the *ALK* fusion gene as determined by means of FISH, and NM no *ALK* mutation or amplification. Data are shown for patients who had received crizotinib as the last therapy before ceritinib treatment (dark blue bars) and for patients who received any intervening systemic therapy between crizotinib and ceritinib (light blue bars). Dots below individual bars indicate patients with disease progression or death at the time of data cutoff.

JGLAND MEDICINE

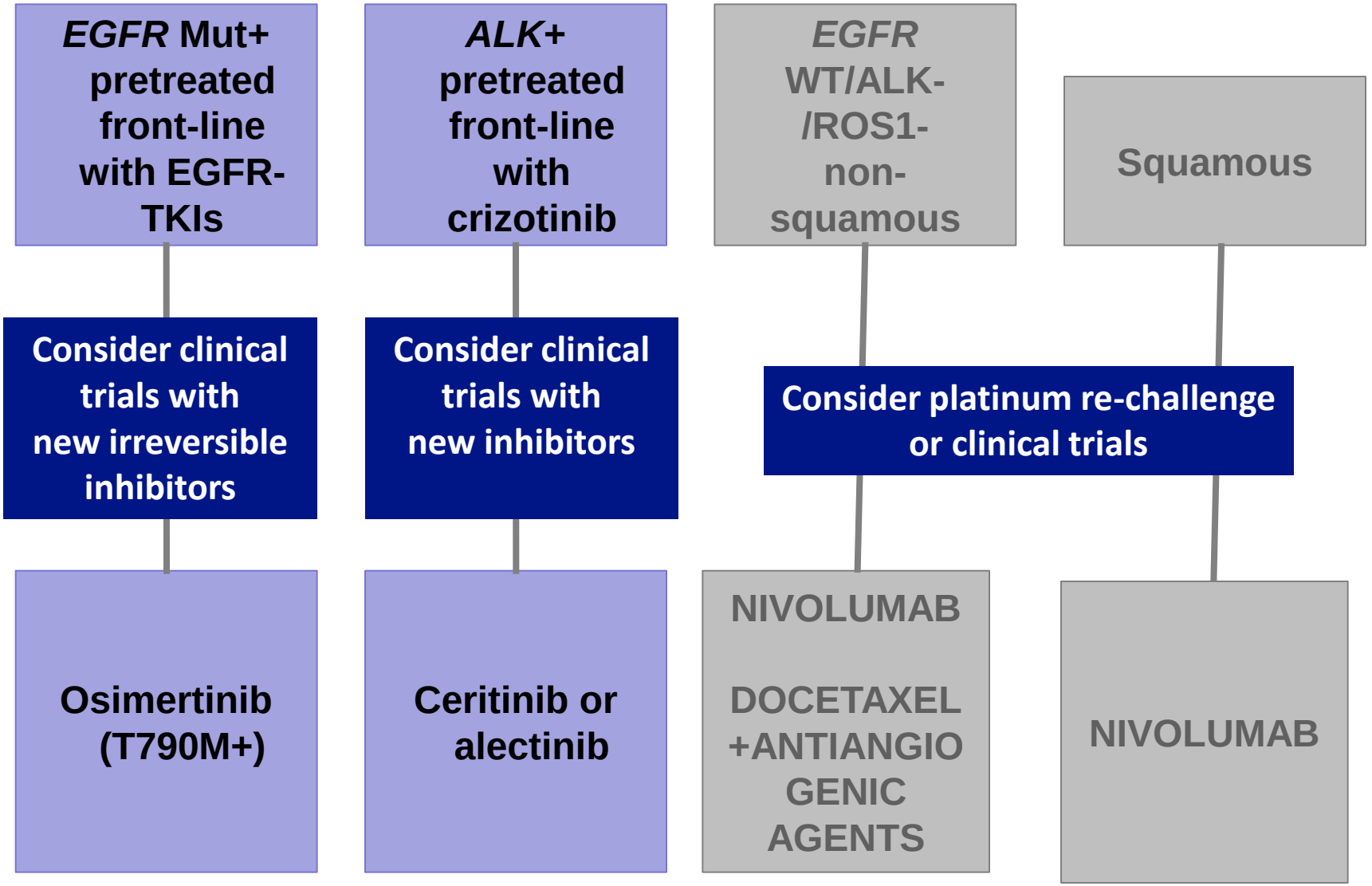


Alectinib: Best systemic and best tumor response



Gadgeel SM et al; Lancet Oncology 2014; 15: 1119-28

Second-line options for metastatic NSCLC in 2016



“Benchè i dottori lo curassero,

gli cavassero sangue e gli facessero prendere molte medicine, tuttavia guarì”.

LEV NIKOLAEVIC TOLSTOJ