Case #2—Advanced NSCLC: Treatment Strategies in the Absence of Targetable Driver Mutations

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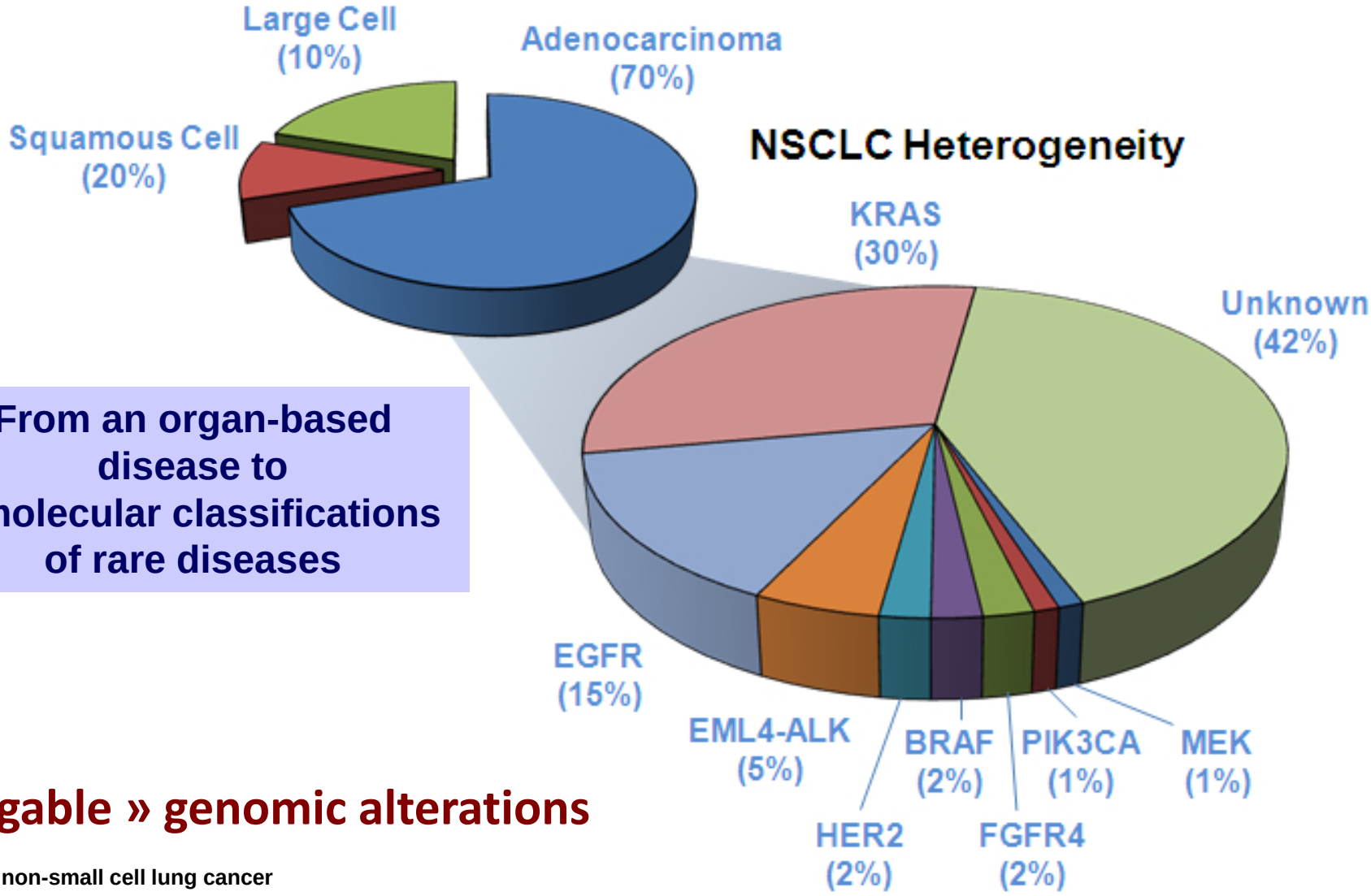
CANCER CAMPUS GRAND PARIS

Disease Segmentation Based on Oncogenic Events

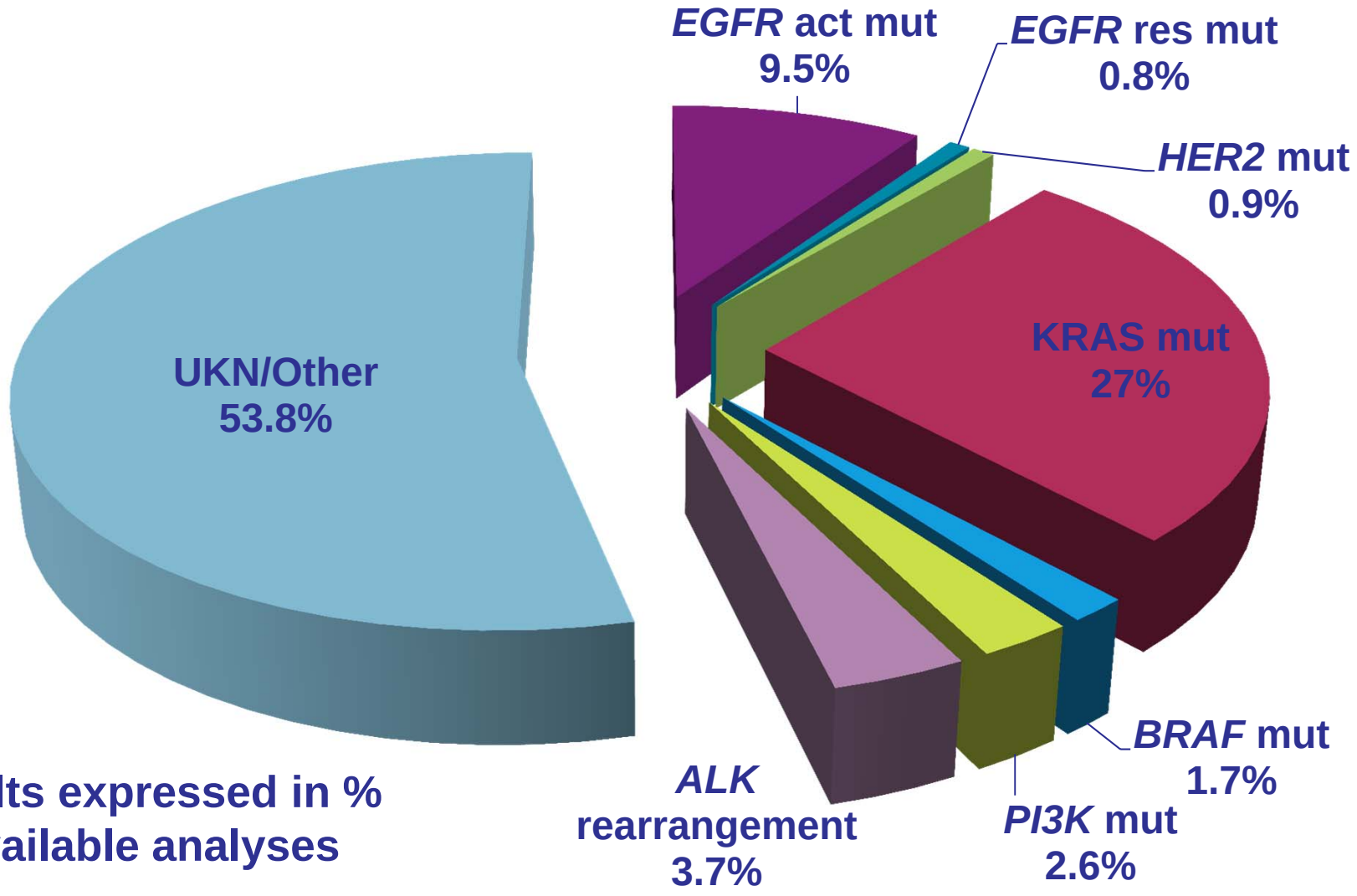


From an organ-based disease to a molecular classifications of rare diseases

« Druggable » genomic alterations

NSCLC, non-small cell lung cancer

Biomarkers France (n = 9911)



Results expressed in % on available analyses

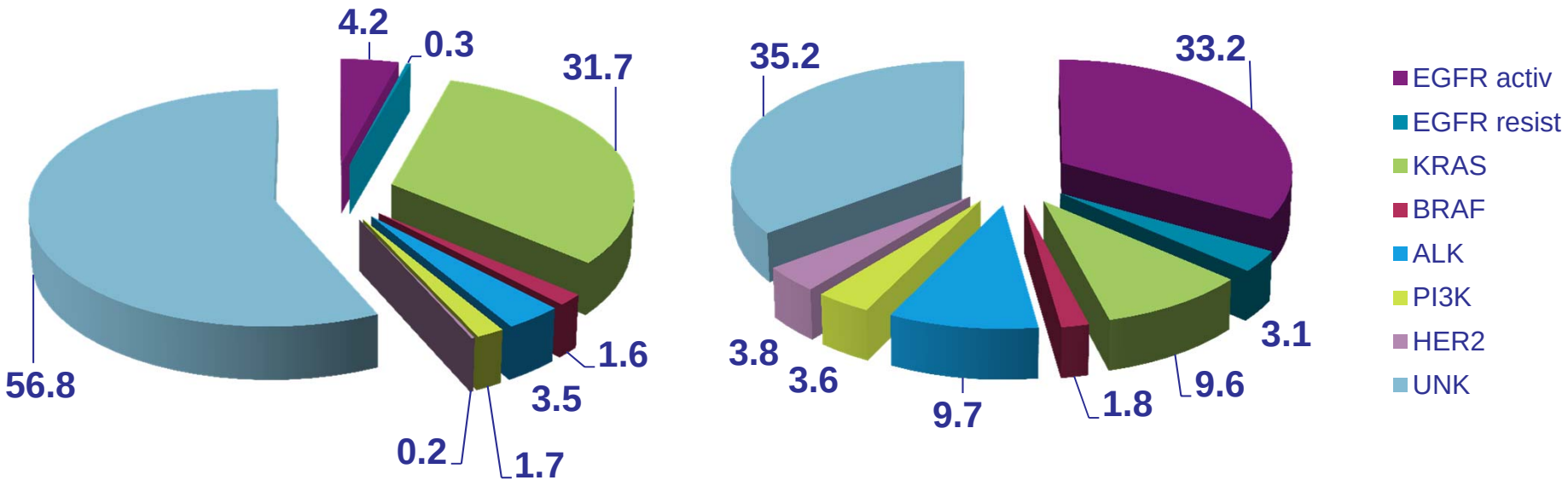
EGFR, epidermal growth factor receptor; UKN, unknown

Barlesi F, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 8000.

Biomarkers by Smoking Status (n = 9911*)

Smokers

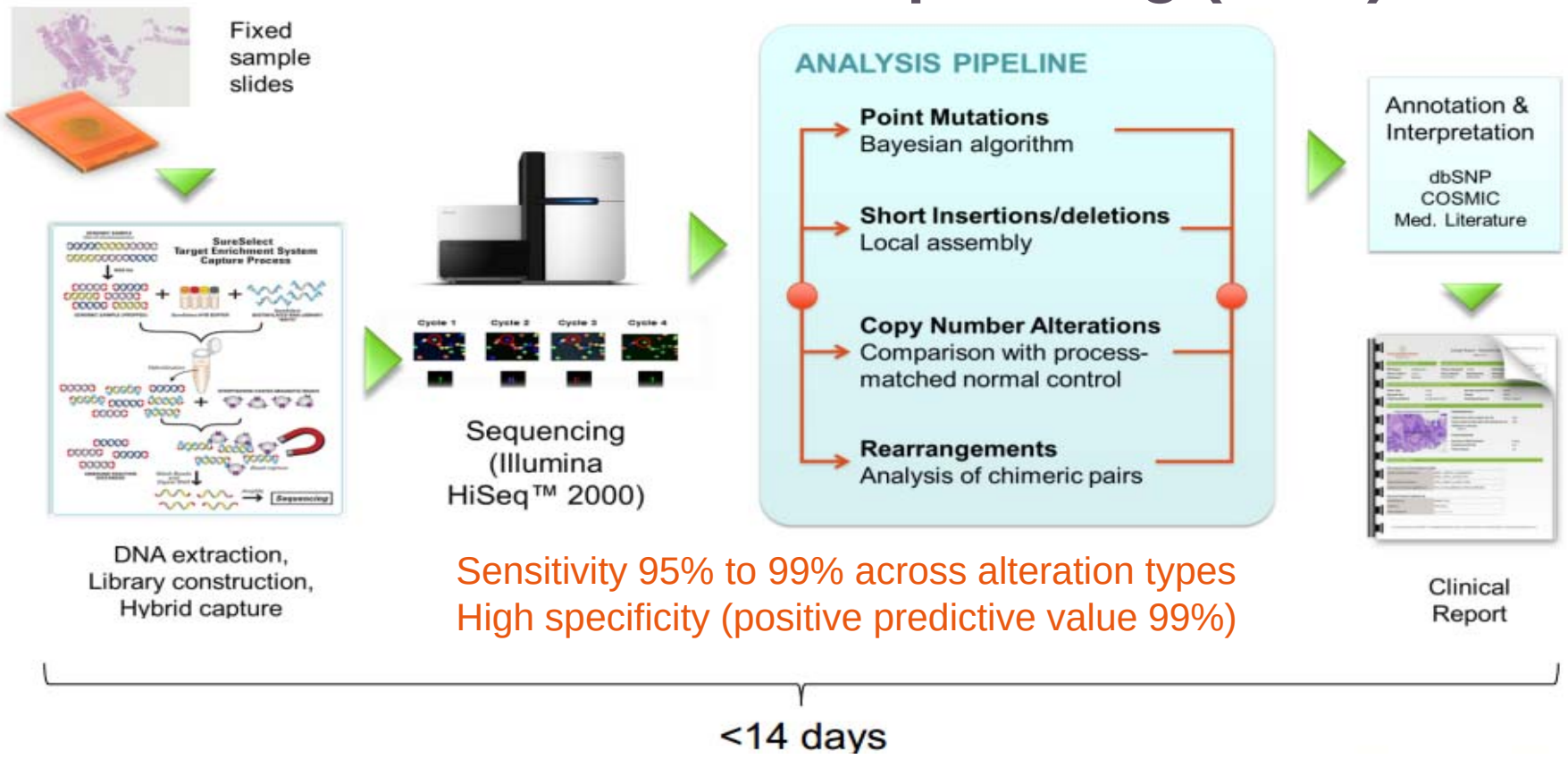
Never Smokers



**** Including 2664 with full clinical data available at the time of this analysis.***

Barlesi F, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 8000.

Genomic Profiling: Next Generation Sequencing (NGS)



- **NGS of clinical NSCLC samples is completely concordant with traditional 'hot-spot" genotyping**
- **NGS uncovers an unexpected genomic alterations that could influence therapy selection for NSCLC**

Frampton GM, et al. *Nat Biotechnol*. 2013;31(11):1023-1031.

Platinum-Based Doublets for NSCLC

North American Experience (SWOG + ECOG)

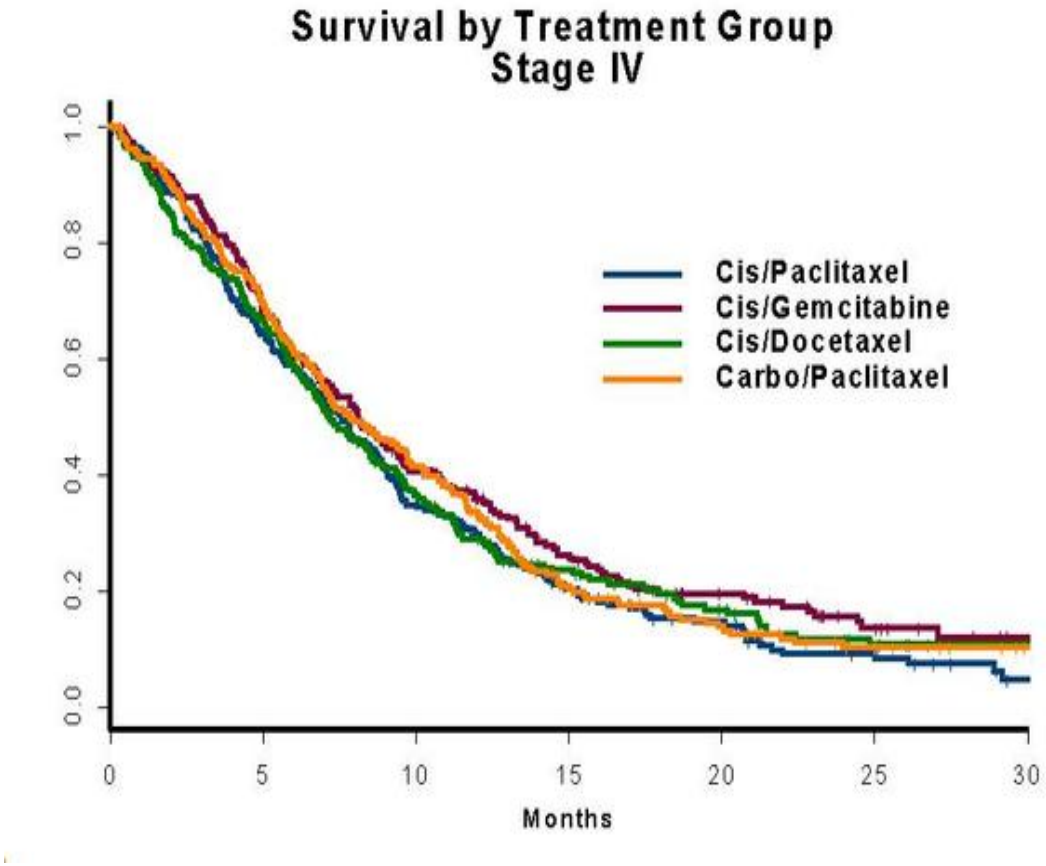
SWOG[1]	N	ORR, %	Median Survival, Months	1-Year Survival, %
Cisplatin + vinorelbine	202	28	8.6	36
Paclitaxel + carboplatin	206	25	8.1	38
ECOG[2]				
Paclitaxel + carboplatin	290	17	8.1	34
Gemcitabine + cisplatin	288	22	8.1	36
Paclitaxel + cisplatin	288	21	7.8	31
Docetaxel + cisplatin	289	17	7.4	31

ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; SWOG, Southwest Oncology Group

1. Kelly K, et al. *J Clin Oncol.* 2001;19(13):3210-3218. 2. Schiller JH, et. al. *N Engl J Med.* 2002;346(2):92-98.

Platinum-Based Doublets for NSCLC

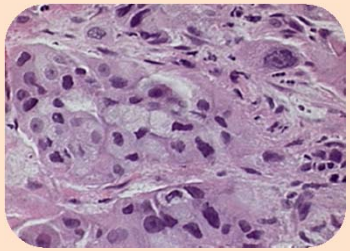
North American Experience (SWOG[1] + ECOG)

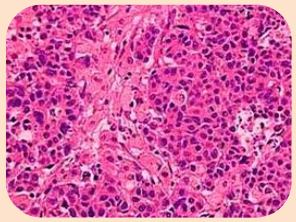


Schiller JH, et. al. *N Engl J Med.* 2002;346(2):92-98.

Histologic Classification of NSCLC

Classification		Characteristics[1]

Nonsquamous‡	**Adenocarcinoma (AC) 30% to 50%***
	 
		• Malignant epithelial tumors with glandular differentiation
		• IASLC classification of invasive AC[2]:
		  • Lepidic, acinar, papillary, micropapillary, or solid pattern predominant
		  • Variants: Invasive mucinous AC, colloid, fetal, and enteric

	Large cell carcinoma 10%* 	• Involves large cells (subtypes are giant cell, clear cell) with large nuclei • No evidence of squamous or glandular differentiation

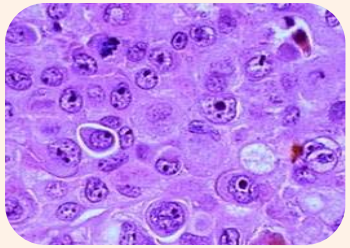
Squamous	**Squamous cell carcinoma 30%†**
	 
		• Involves cells of the squamous epithelium
		• Two variants of clinicopathologic significance[3]
		  • Papillary variant
		  • Basaloid variant

*Image from www.surgical-pathology.com; †Image from www.lmp.ualberta.ca/resources/pathoimages/PC-S.htm.
‡Other less common subtypes of nonsquamous NSCLC include adenosquamous carcinoma and sarcomatoid carcinoma.[3]

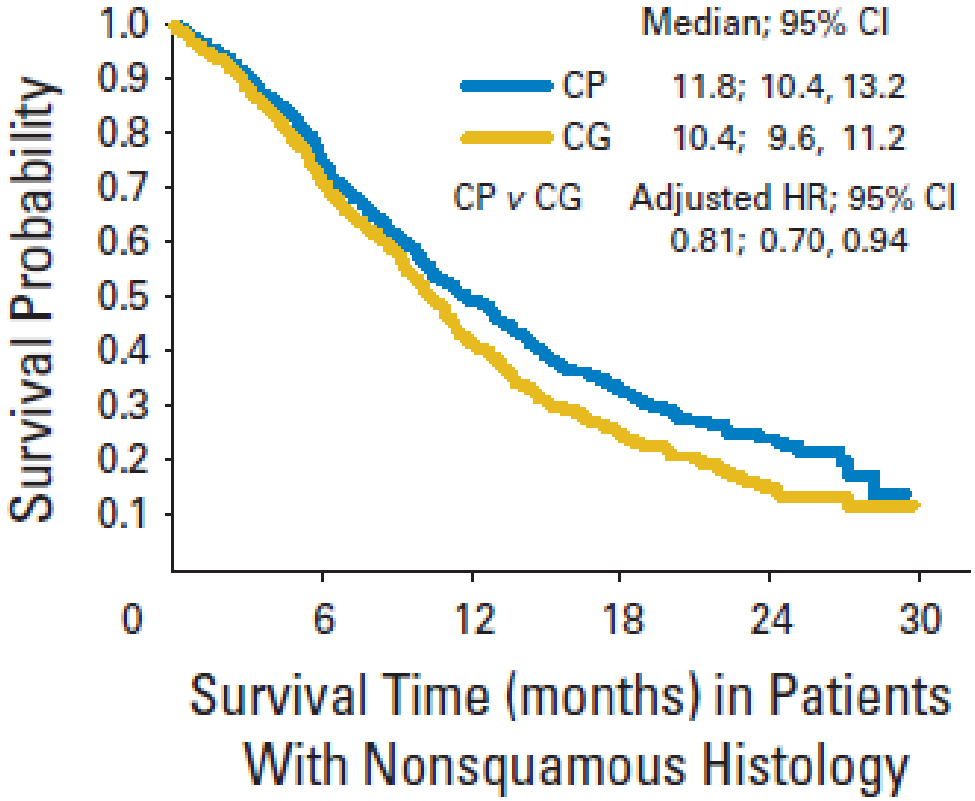
1. Langer CJ, et al. *J Clin Oncol.* 2010;28(36):5311-5320. 2. Travis WD, et al. *J Thorac Oncol.* 2011;6(2):244-285.
3. WHO 2004.

Pemetrexed vs Gemcitabine (+CDDP)

- **Pemetrexed** **500 mg/m² on day 1**
- **Cisplatin** **75 mg/m² on day 1**

- **Adenocarcinoma+LCC**
  → Pemetrexed better

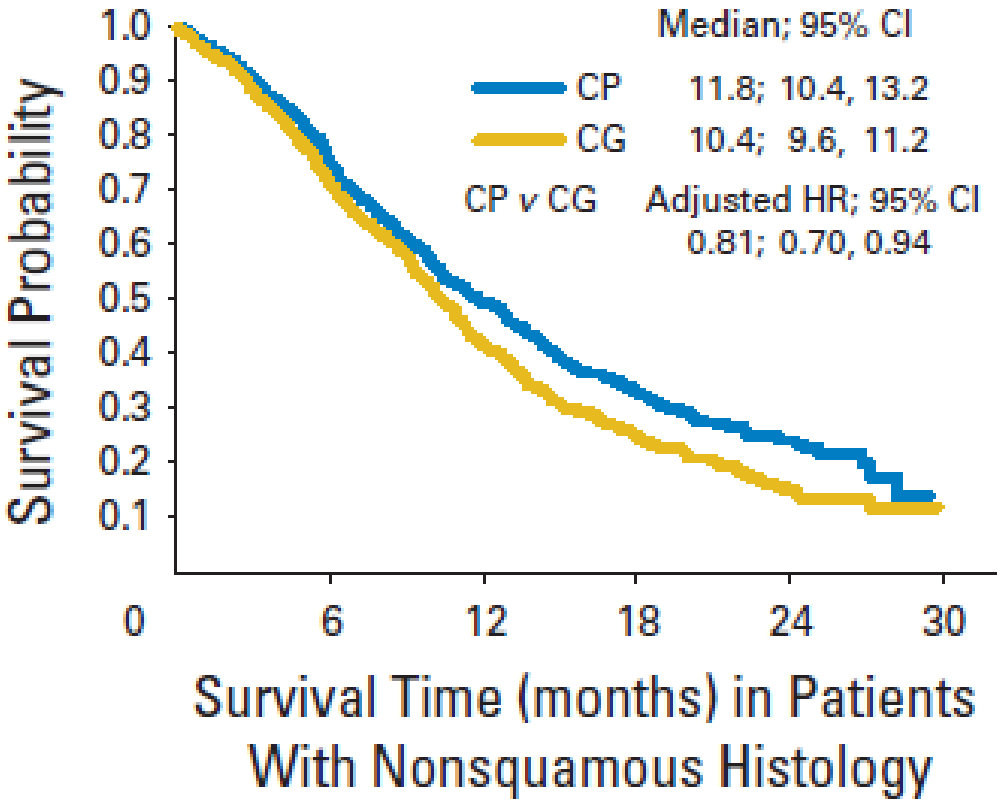
- **SCC**
  → Gemcitabine better



CI, confidence interval; HR, hazard ratio

Scagliotti GV, et al. *J Clin Oncol.* 2008;26(21):3543-3551.

Pemetrexed vs Gemcitabine (+CDDP)



- **Post-treatment**
- **56.1% of gem/cis**
  - Pem 13.4%
  - Gem 8.6%
  - Docetaxel 27.6%
  - EGFR TKI 22.5%
- **52.6% of pem/cis**
  - Pem 3.5%
  - Gem 16.7%
  - Docetaxel 25.4%
  - EGFR TKI 24.9%

Only 13.4% patients crossed over to pemetrexed!

TKI, tyrosine kinase inhibitor

Scagliotti GV, et al. *J Clin Oncol.* 2008;26(21):3543-3551.

Antiangiogenic?

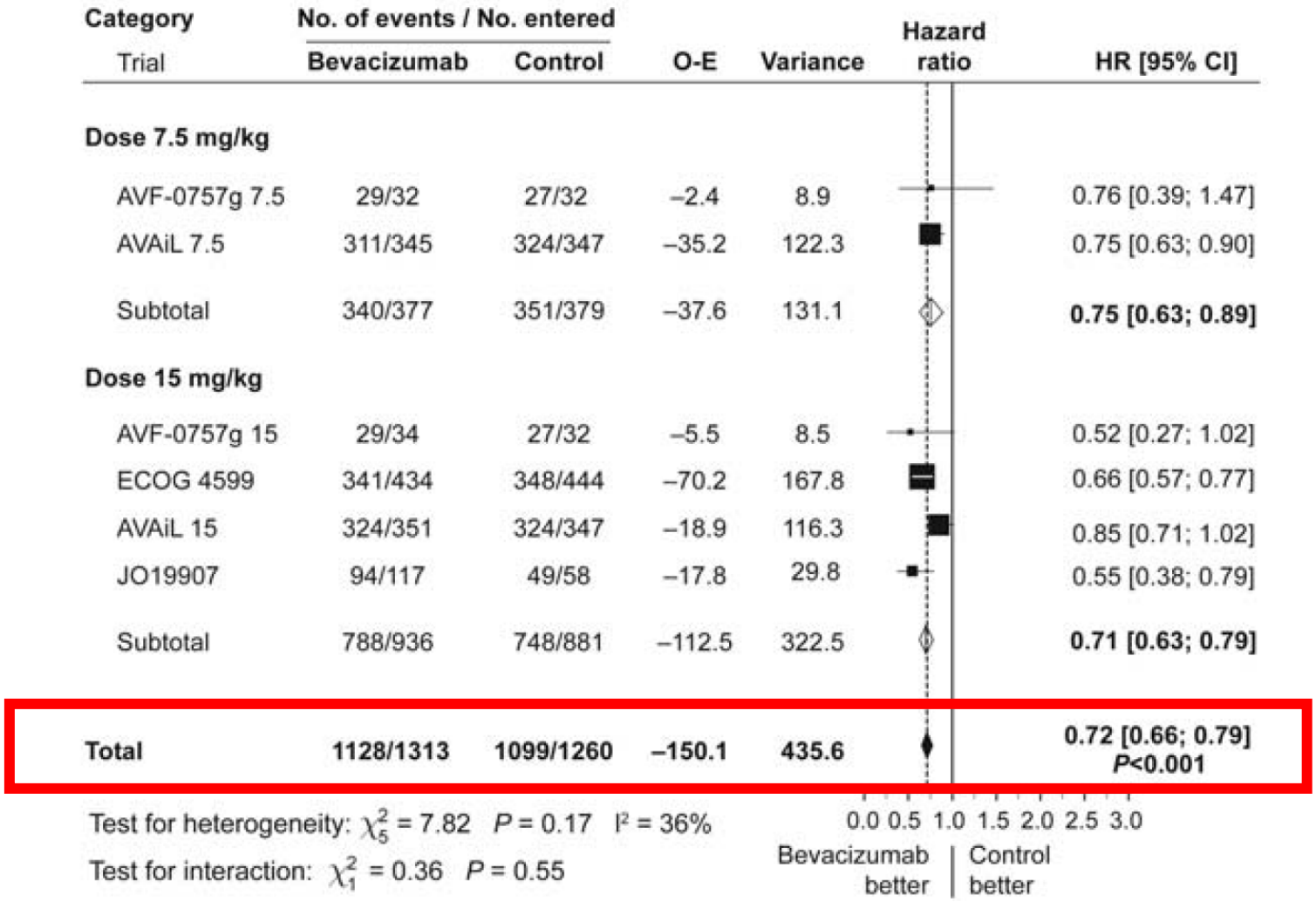
Bevacizumab in Nonsquamous NSCLC: Key Results

	E4599[1]		AVAiL[2,3]			JO19907[4]	
Outcome	PAC-CP-BEV	PAC-CP	CP-GEM (7.5)	CP-GEM (15)	PAC	PAC-CP-BEV	PAC-CP
ORR, %	35	15	34.1	30.4	20.1	60.7	31.0
	P<.001		*P*<.0001	*P* = .0002		.001	
HR for PFS	0.66 (*P*<.001)		0.75 (*P* = .003)	0.82 (*P* = .03)		0.61 (*P* = .009)	
Median PFS, months	6.2	4.5	6.7	6.5	6.1	6.9	5.9
HR for OS	0.79 (*P* = .003)		0.93 (NS)	1.03 (NS)		0.99 (*P* = .95)	
Median OS, months	12.3	10.3	13.6	13.4	13.1	22.8	23.4

OS, overall survival; PFS, progression-free survival

1. Sandler A, et al. *N Engl J Med.* 2006;355(24):2542-2550. 2. Reck M, et al. *J Clin Oncol.* 2009;27(8):1227-1234.
3. Reck M, et al. *Ann Oncol*. 2010;21(9):1804-1809. 4. Ichinose Y, et al. *Eur J Cancer Suppl.* 2009;7(2): Abstract O-9008.

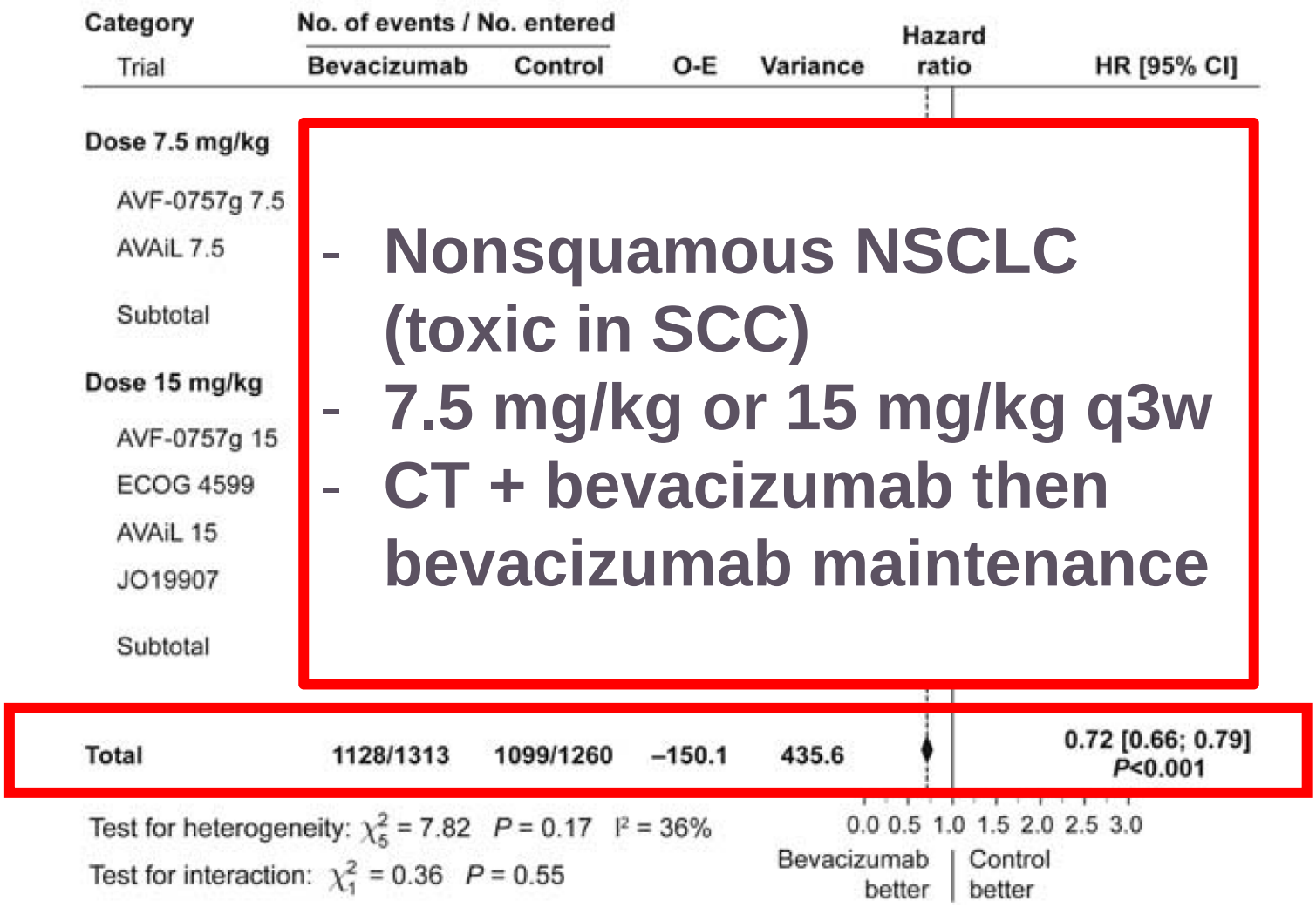
Bevacizumab—Pooled Analysis for PFS



CT chemothherapy

Soria JC, et al. *Ann Oncol.* 2013;24(1):20-30.

Bevacizumab—Pooled Analysis for PFS



CT chemothherapy

Soria JC, et al. *Ann Oncol.* 2013;24(1):20-30.

First-Line Metastatic NSCLC

Treatment Options

Gemcitabine	**1250 mg/m²**	**d 1, 8**	**q3w**
Cisplatin	**80 mg/m²**	**d 1**	

All histologies

Vinorelbine	**25 mg/m²**	**d 1, 8, 15, 22**	
Cisplatin	**100 mg/m²**	**d 1**	**d1 = d28**

Historic design, all histologies

Pemetrexed	**500 mg/m²**	**d 1**	
Cisplatin	**75 mg/m²**	**d 1**	**d1 = d21**

Nonsquamous NSCLC

+/- bevacizumab if non SCC
7,5 mg/kg or 15 mg/kg d1=d21

First-Line Metastatic NSCLC

Treatment Options

Docetaxel	**75 mg/m²**	**d 1**	**d1 = d21**
Cisplatin	**75 mg/m²**	**d 1**	
Paclitaxel	**135 mg/m² (24 h)**	**d 1**	**d1 = d21**
Cisplatin	**75 mg/m²**	**d 2**	
Paclitaxel	**225 mg/m² (3 h)**	**d 1**	**d1 = d21**
Carboplatin	**AUC 6**	**d 1**	

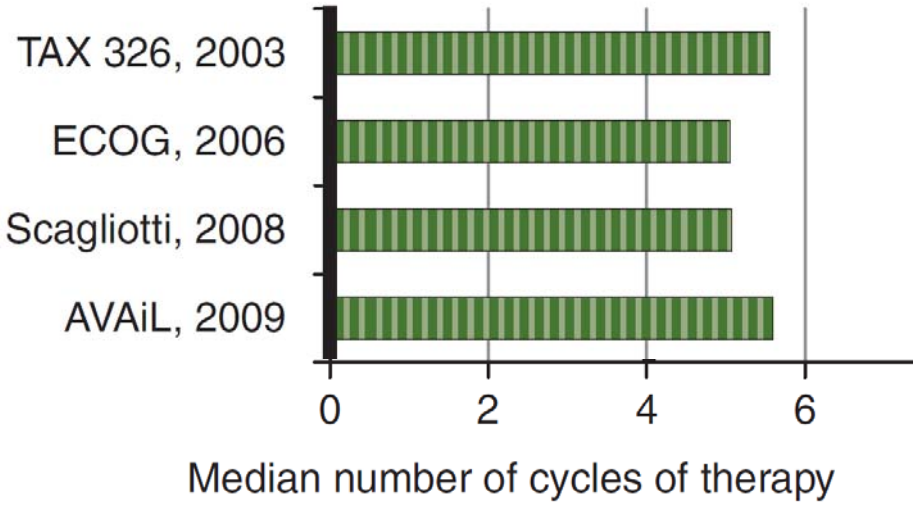
All histologies, induce alopecia

+/- bevacizumab if non SCC
7,5 mg/kg or 15 mg/kg d1=d21

How Many Cycles of Chemotherapy?

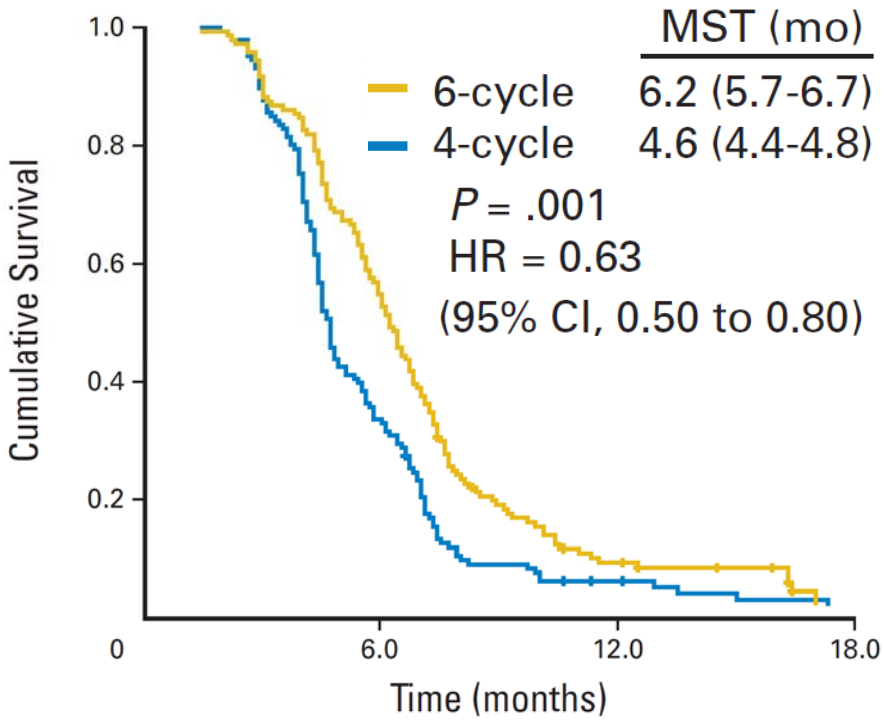
Optimal Duration of Chemotherapy

First-line registration trials



Docetaxel ; TAX 326
Bevacizumab ; ECOG, AVAIL
Pemetrexed ; Scagliotti

PFS: 4 cycles vs 6 cycles of cisplatin-based CT

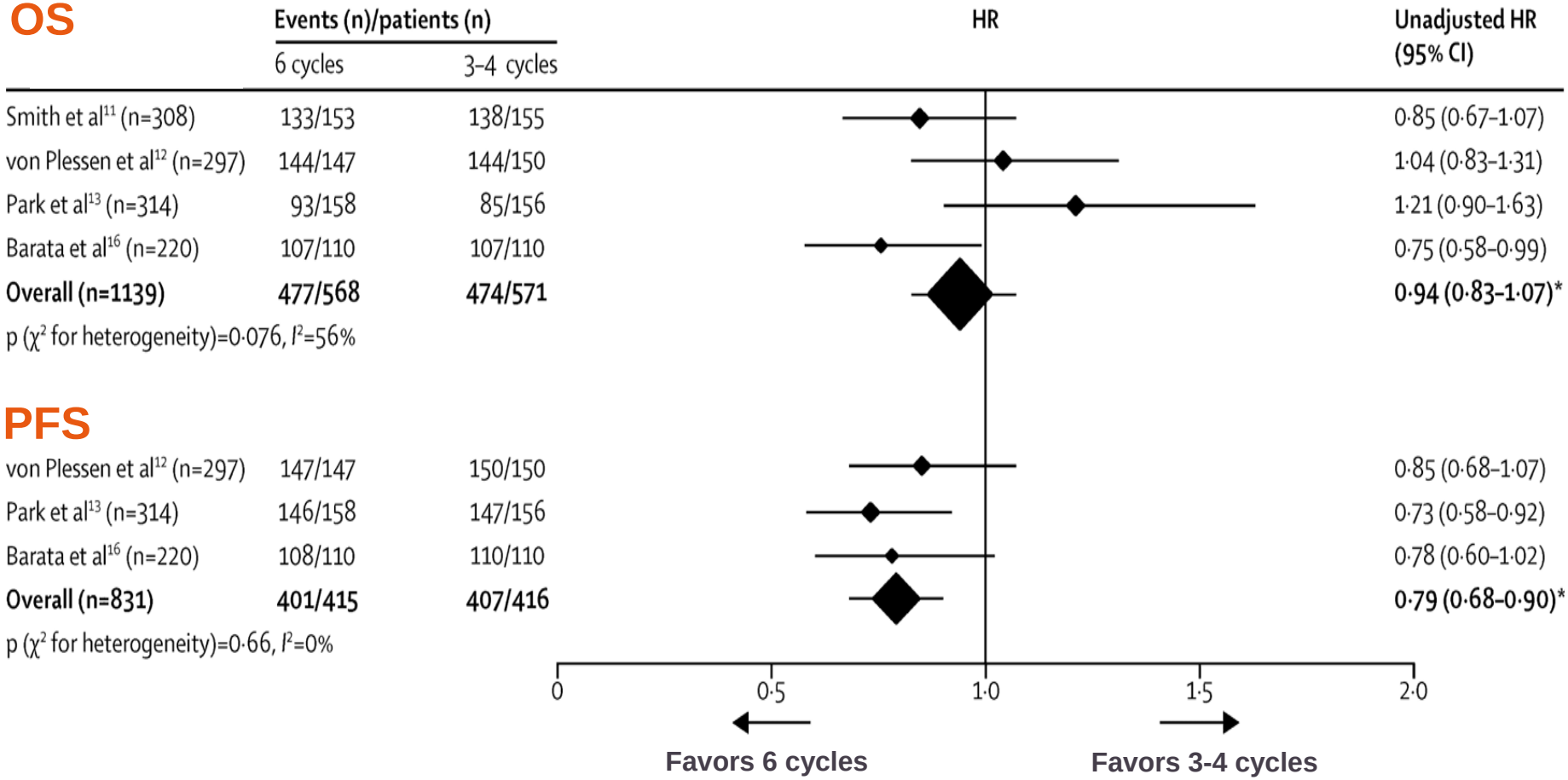


Nonprogressive patients after 2 cycles

MST, median survival time

Polo V, Besse B. *Ann Oncol.* 2014;25(7):1283-1293. Park JO, et al. *J Clin Oncol.* 2007;25(33):5233-5239.

Meta-Analysis of Individual Patient Data: 6 Cycles vs 3-4 Cycles of First-Line Chemotherapy



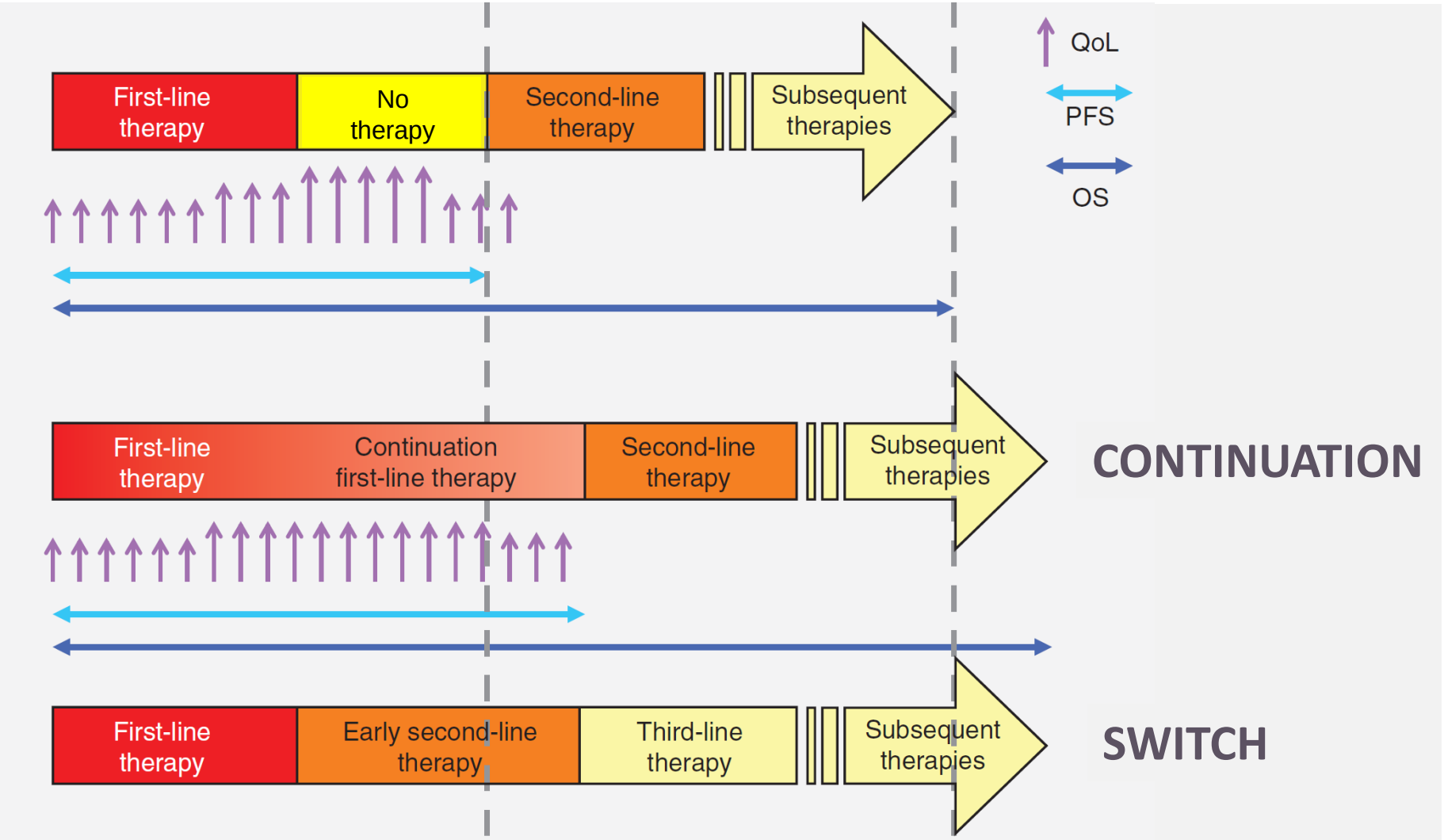
OS; HR = 0.94 (95% CI, 0.83 to 1.07; *P* = .33 (stratified by trial)

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.

Maintenance?

Maintenance Therapy Strategies

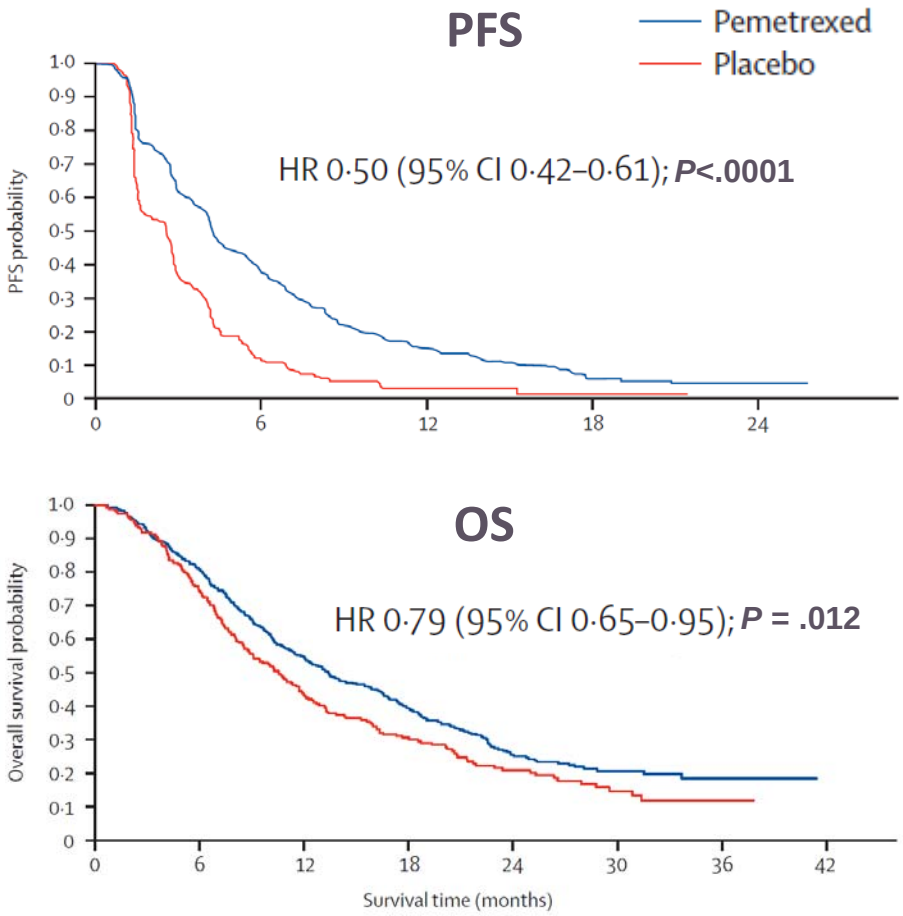


QoL, quality of life

Polo V, Besse B. *Ann Oncol.* 2014;25(7):1283-1293.

Switch Maintenance

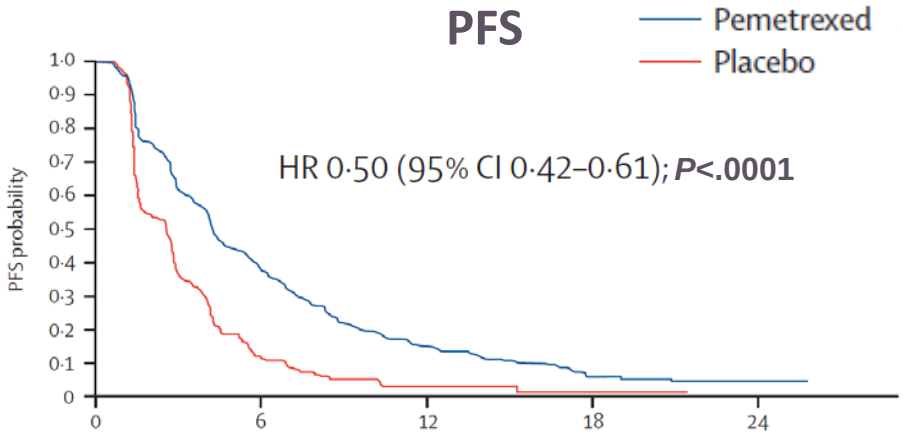
Pemetrexed vs Placebo
Induction CT Without Pemetrexed

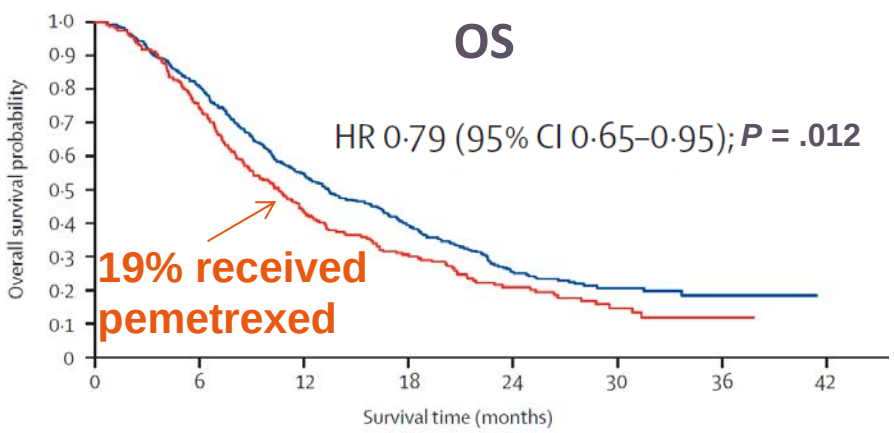


Ciuleanu T, et al. *Lancet.* 2009;374(9699):1432-1440.

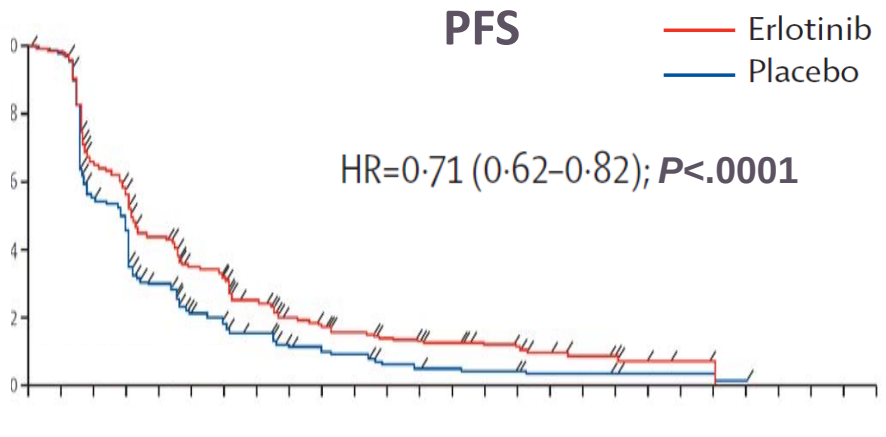
Switch Maintenance

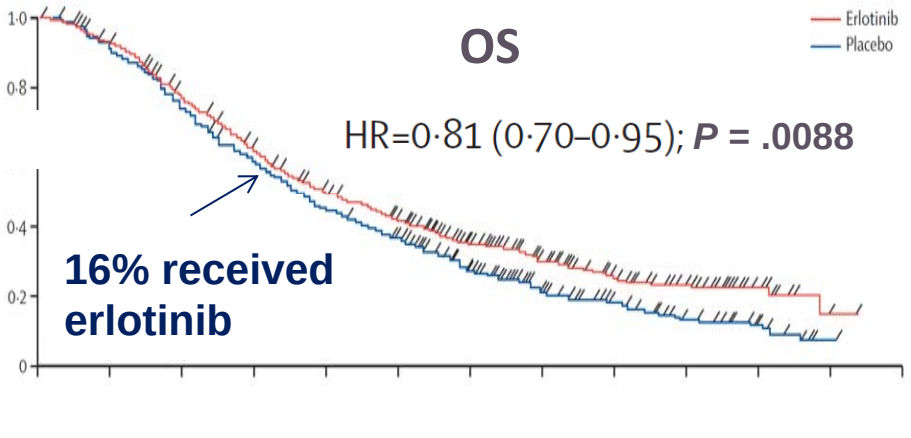
Pemetrexed vs Placebo[1]
Induction CT Without Pemetrexed





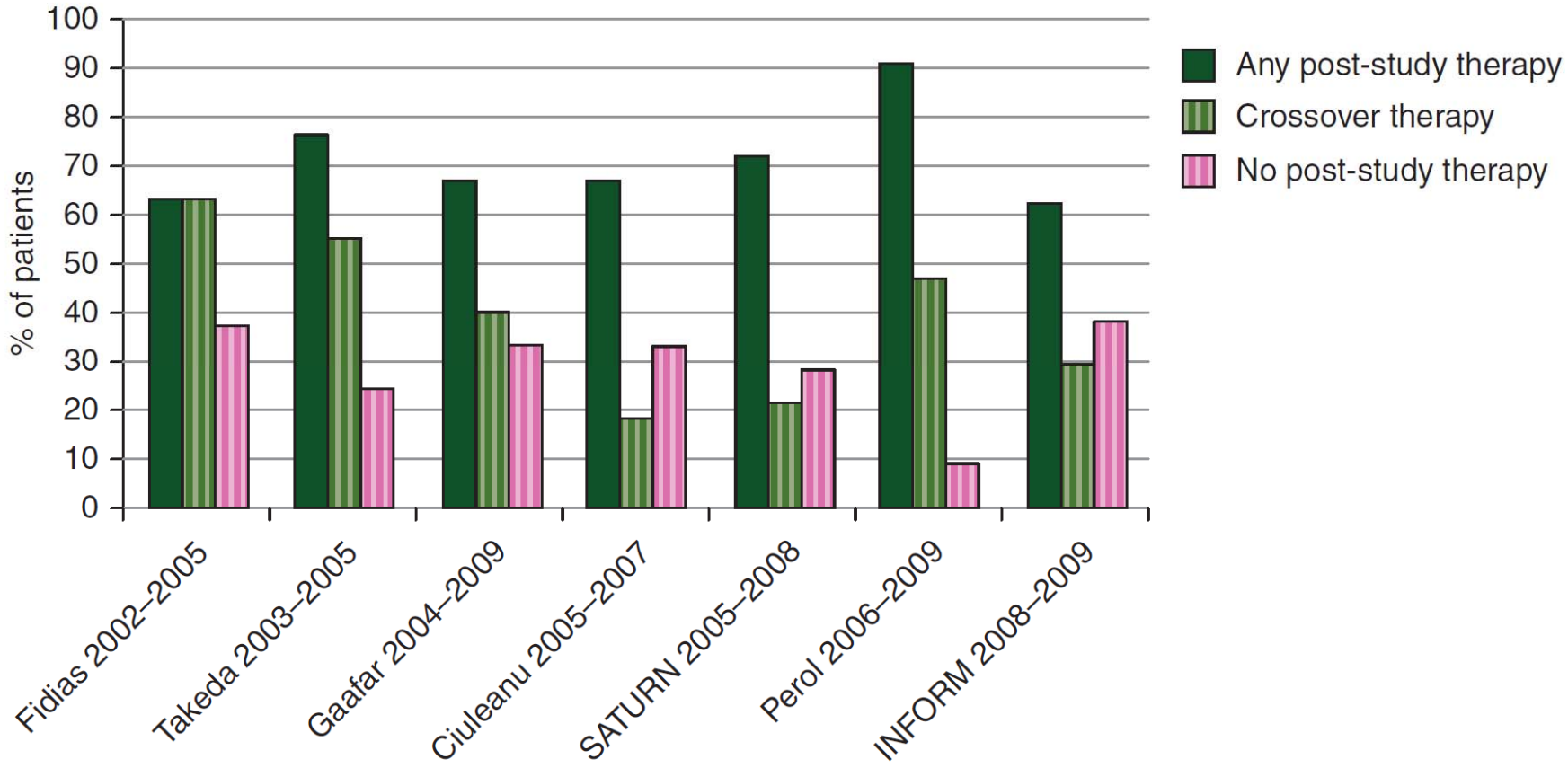
Erlotinib vs Placebo[2]





1. Ciuleanu T, et al. *Lancet.* 2009;374(9699):1432-1440. 2. Cappuzzo F, et al. *Lancet Oncol.* 2010;11(6):521-529.

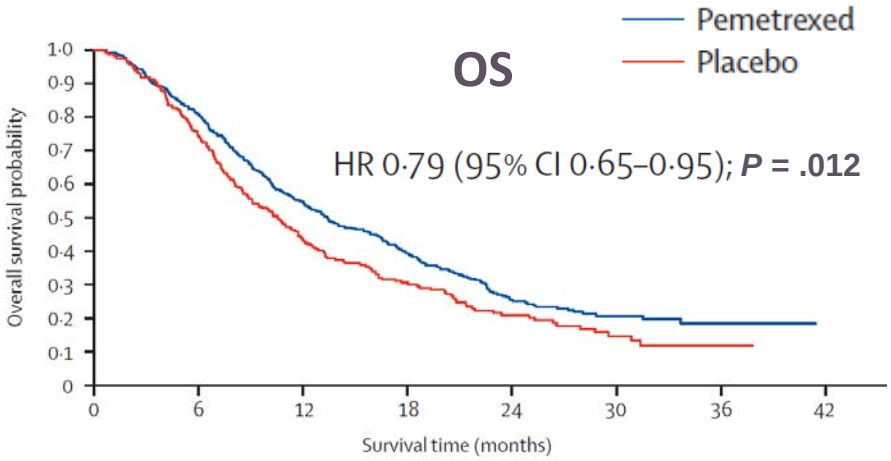
Crossover Therapy

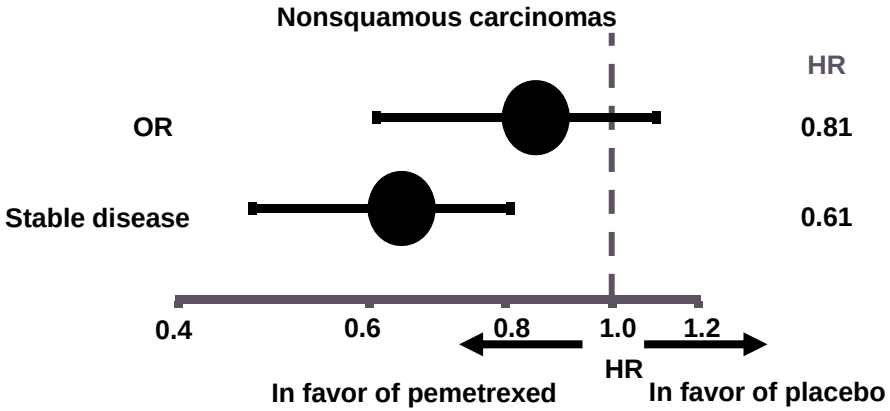


Polo V, Besse B. *Ann Oncol.* 2014;25(7):1283-1293.

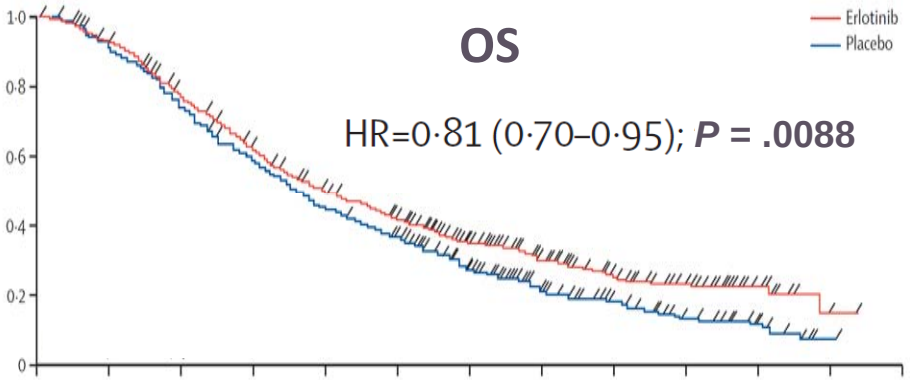
Switch Maintenance vs Response to First-Line Chemotherapy

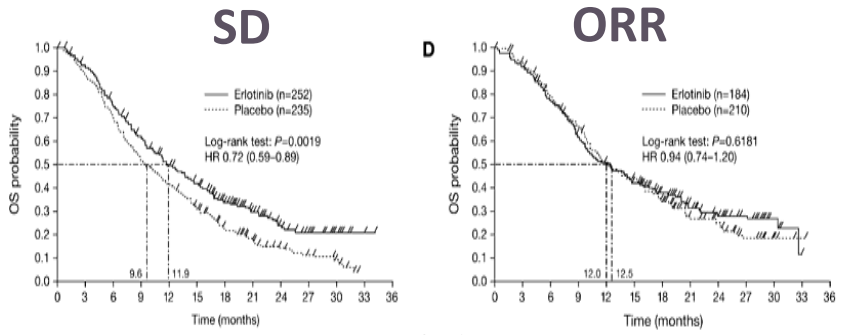
Pemetrexed vs Placebo
Induction CT Without Pemetrexed





Erlotinib vs Placebo





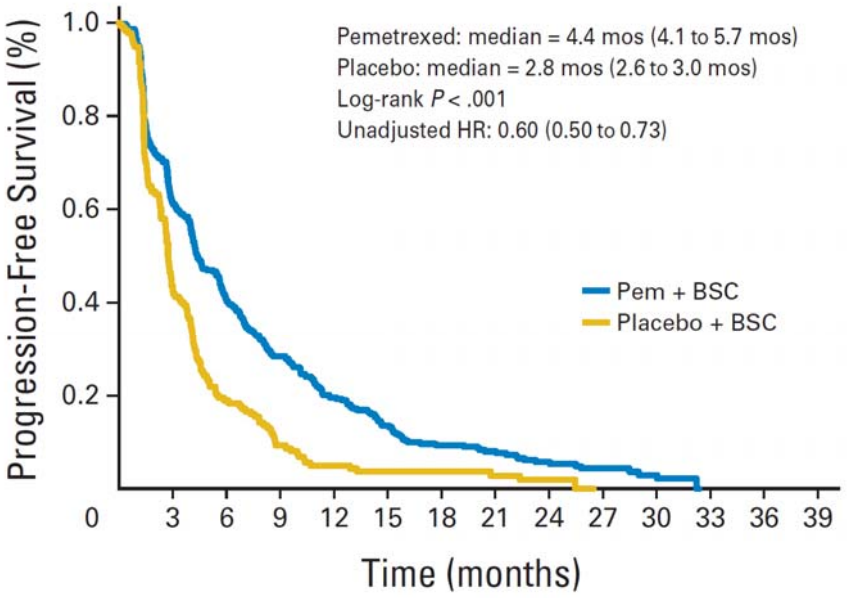
HR = 0.72 (0.59-0.89) **HR = 0.94 (0.74-1.20)**

SD, stable disease

Ciuleanu T, et al. *Lancet.* 2009;374(9699):1432-1440. Cappuzzo F, et al. *Lancet Oncol.* 2010;11(6):521-529. Belani CP, et al. *J Clin Oncol.* 2009;27(19S): Abstract CRA8000. Coudert B, et al. *Ann Oncol.* 2012;23(2):388-394.

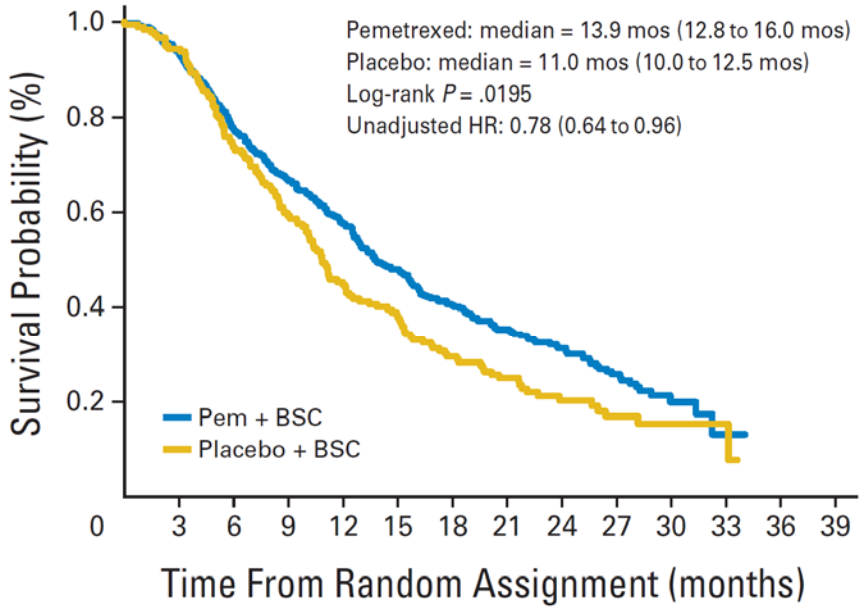
Pemetrexed vs Placebo After 4 Cycles Pemetrexed/Cisplatin

PFS



No. at risk												
Pem + BSC	359	215	139	97	67	47	32	22	16	10	5	0
Placebo + BSC	180	75	33	16	9	7	6	4	2	0	0	0

OS



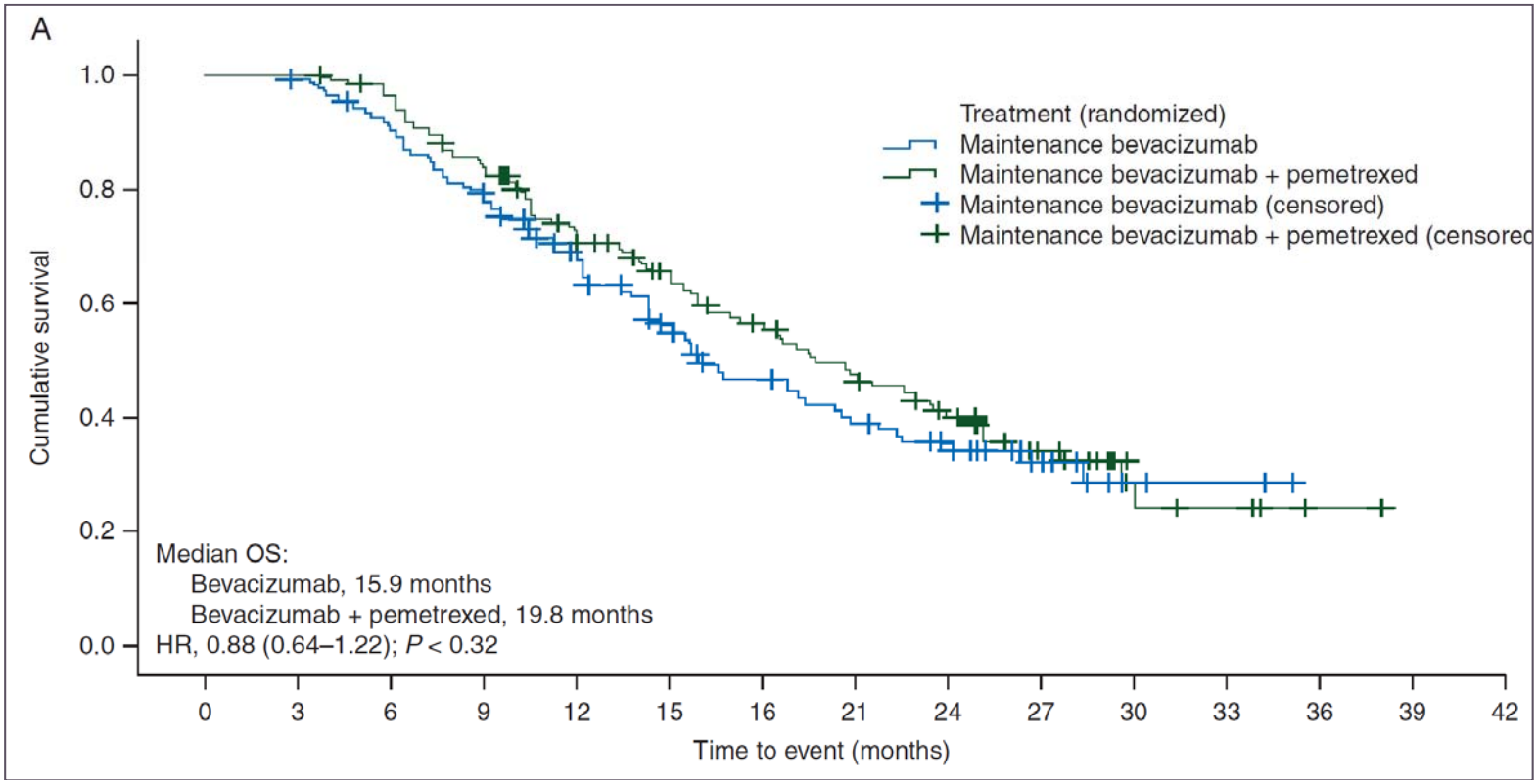
No. at risk													
Pem + BSC	359	333	272	235	200	166	138	105	79	43	15	2	0
Placebo + BSC	180	169	131	103	78	65	49	35	23	12	8	3	0

PARAMOUNT

OS maintenance pemetrexed: 13.9 months

Paz-Ares LG, et al. *J Clin Oncol.* 2013;31(23):2895-2902.

Pemetrexed + Bevacizumab vs Bevacizumab After 4 Cycles Pemetrexed/Cisplatin/Bevacizumab

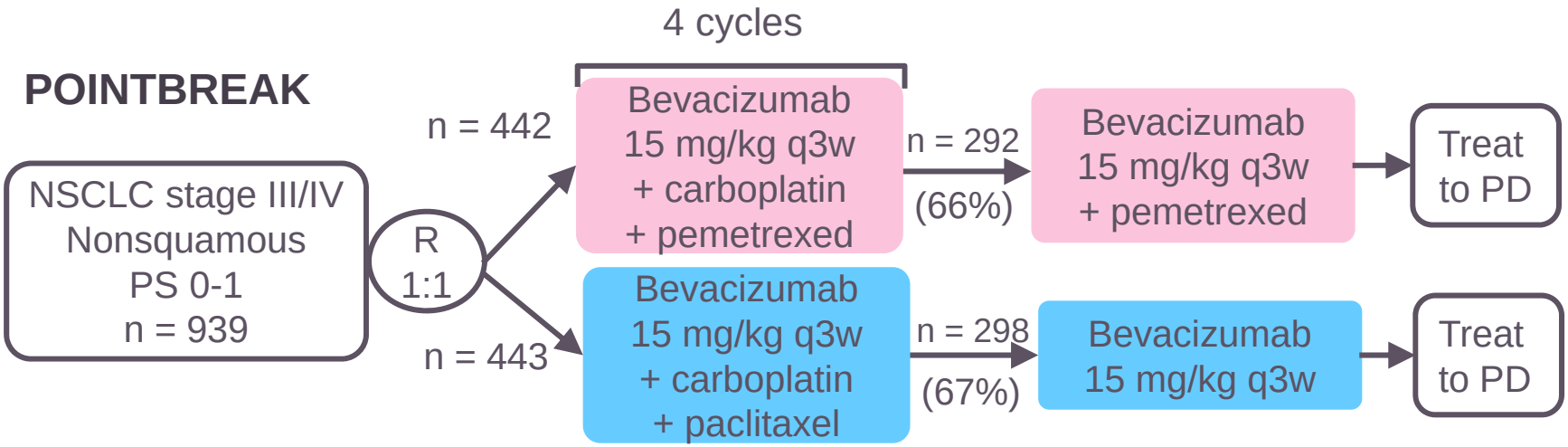


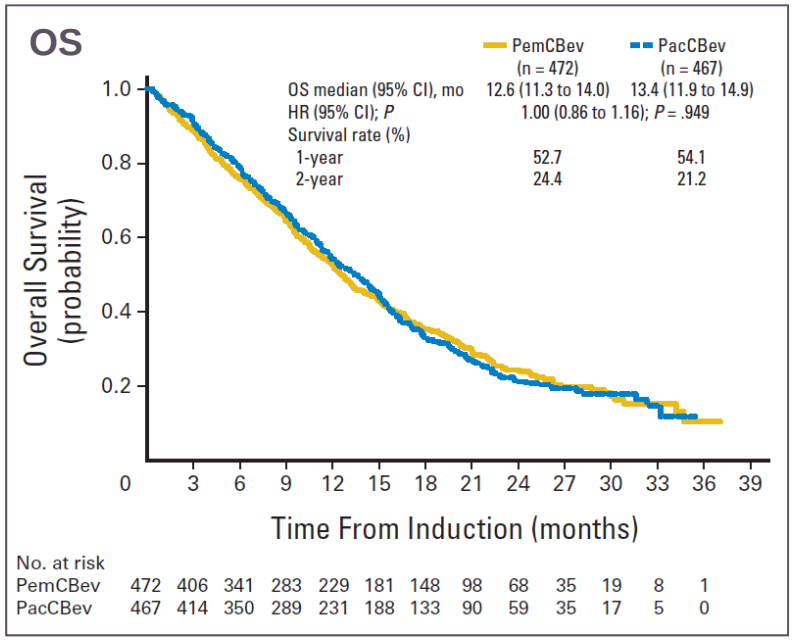
AVAPERL

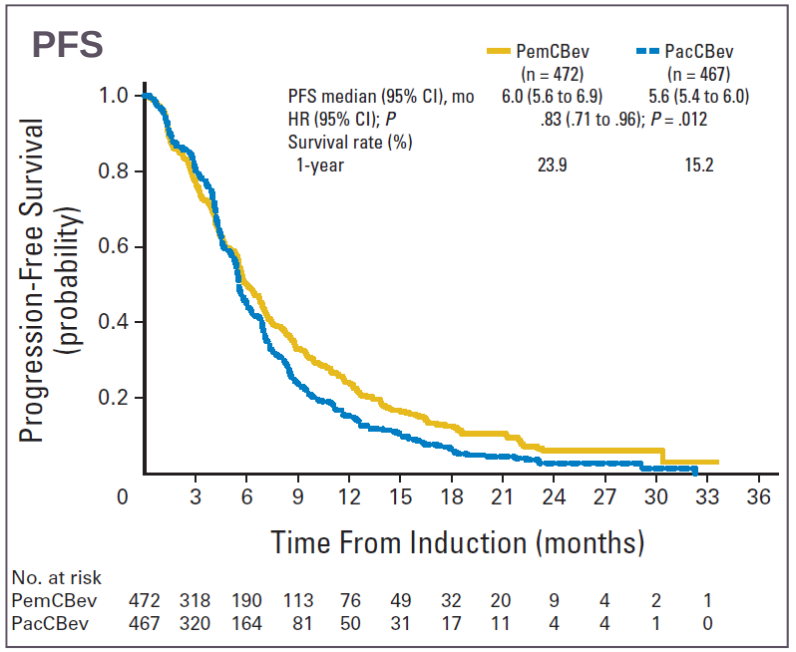
OS maintenance pemetrexed/bevacizumab: 19.8 months

Barlesi F, et al. *Ann Oncol.* 2014;25(5):1044-1052.

Maintenance Pemetrexed + Bevacizumab?





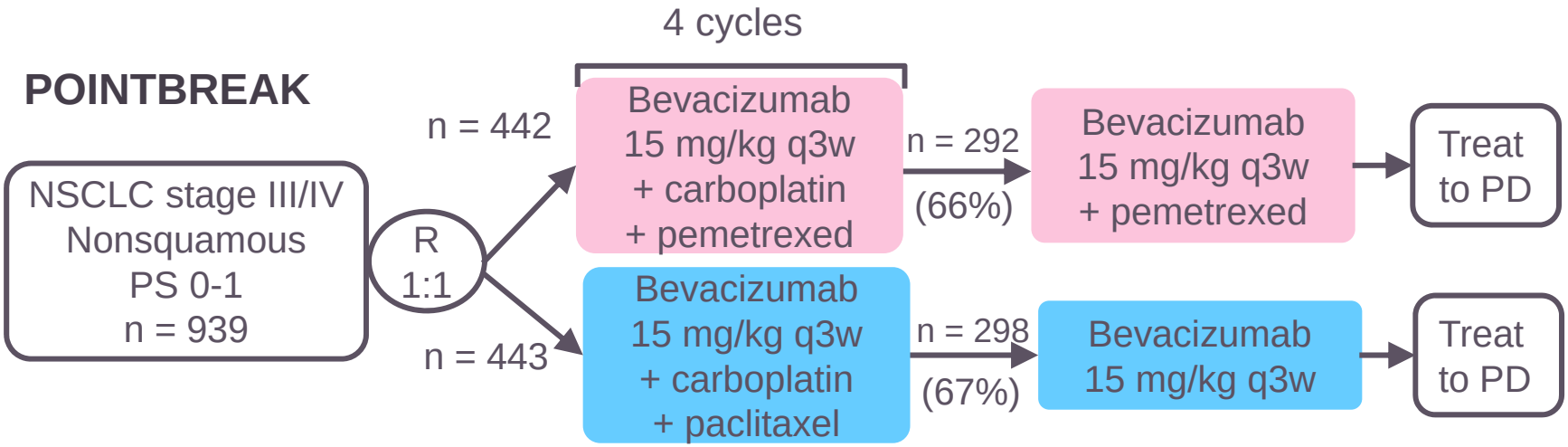


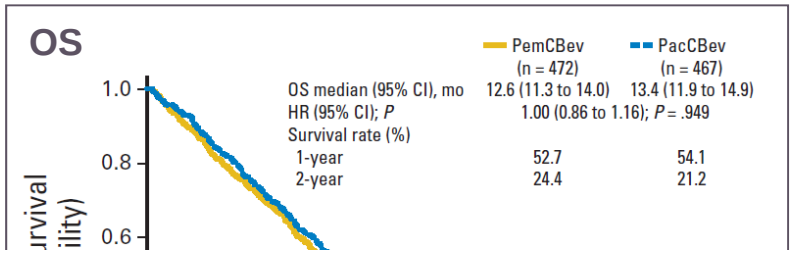
Post-continuation therapy: 36.2% in pem/bev arm *vs* 14%

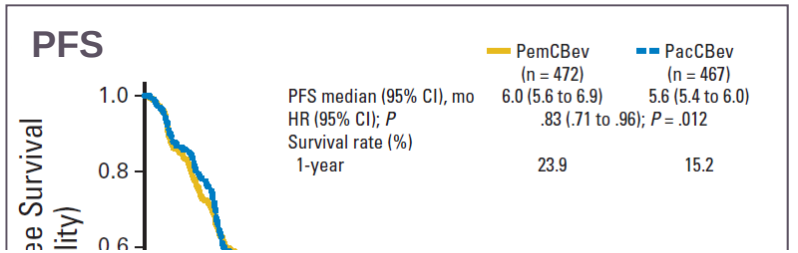
PD, progressive kisease

Patel JD, et al. *J Clin Oncol.* 2013;31(34):4349-4357. Barlesi F, et al. *Ann Oncol.* 2014;25(5):1044-1052.

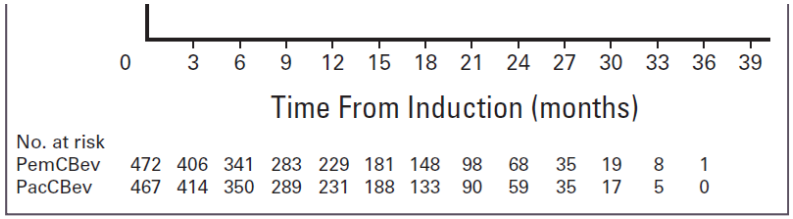
Maintenance Pemetrexed + Bevacizumab?

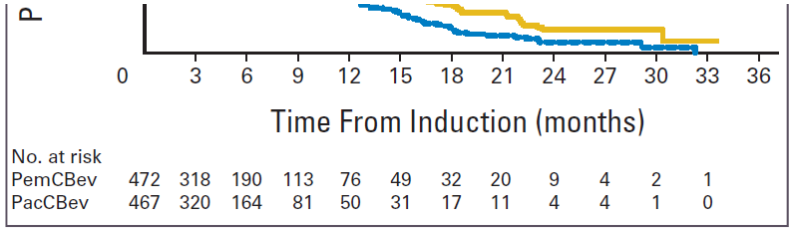






OS maintenance pemetrexed/bevacizumab: 12.6 months (POINTBREAK) vs 19.8 months in AVAPERL



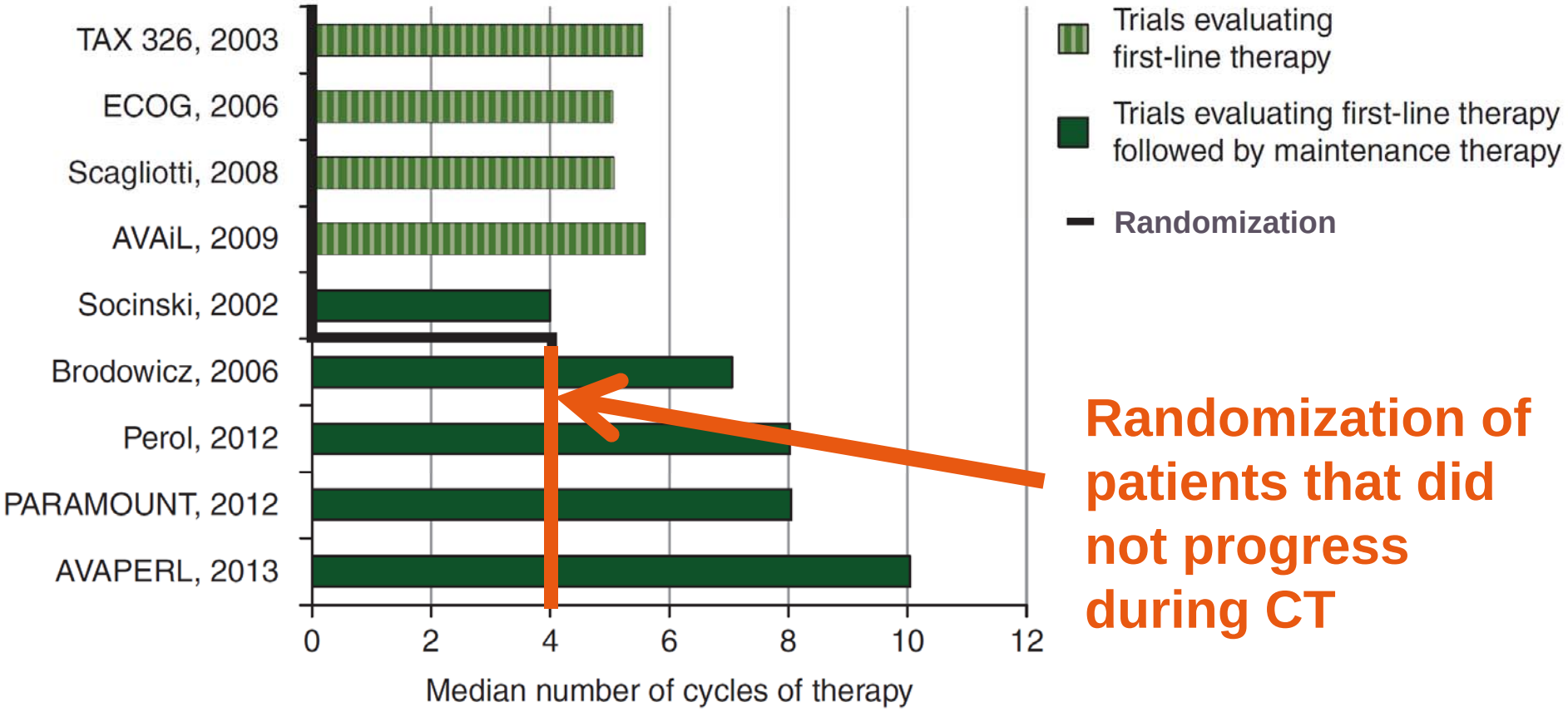


Post-continuation therapy: 36.2% in pem/bev arm *vs* 14%

PD, progressive kisease

Patel JD, et al. *J Clin Oncol.* 2013;31(34):4349-4357. Barlesi F, et al. *Ann Oncol.* 2014;25(5):1044-1052.

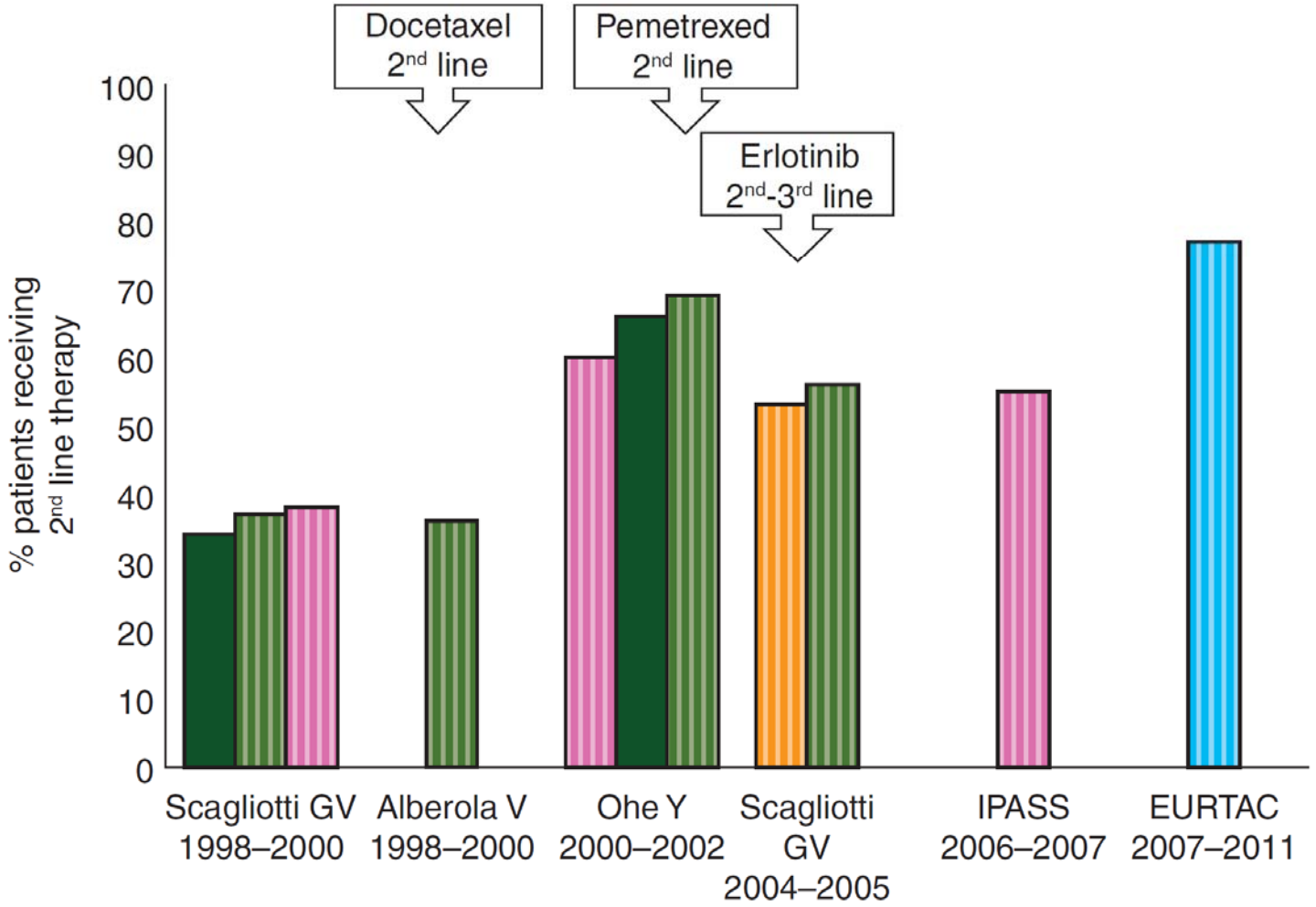
Mind the Randomization!



Polo V, Besse Bl. *Ann Oncol.* 2014;25(7):1283-1293. Park JO, et al. *J Clin Oncol.* 2007;25(33):5233-5239.

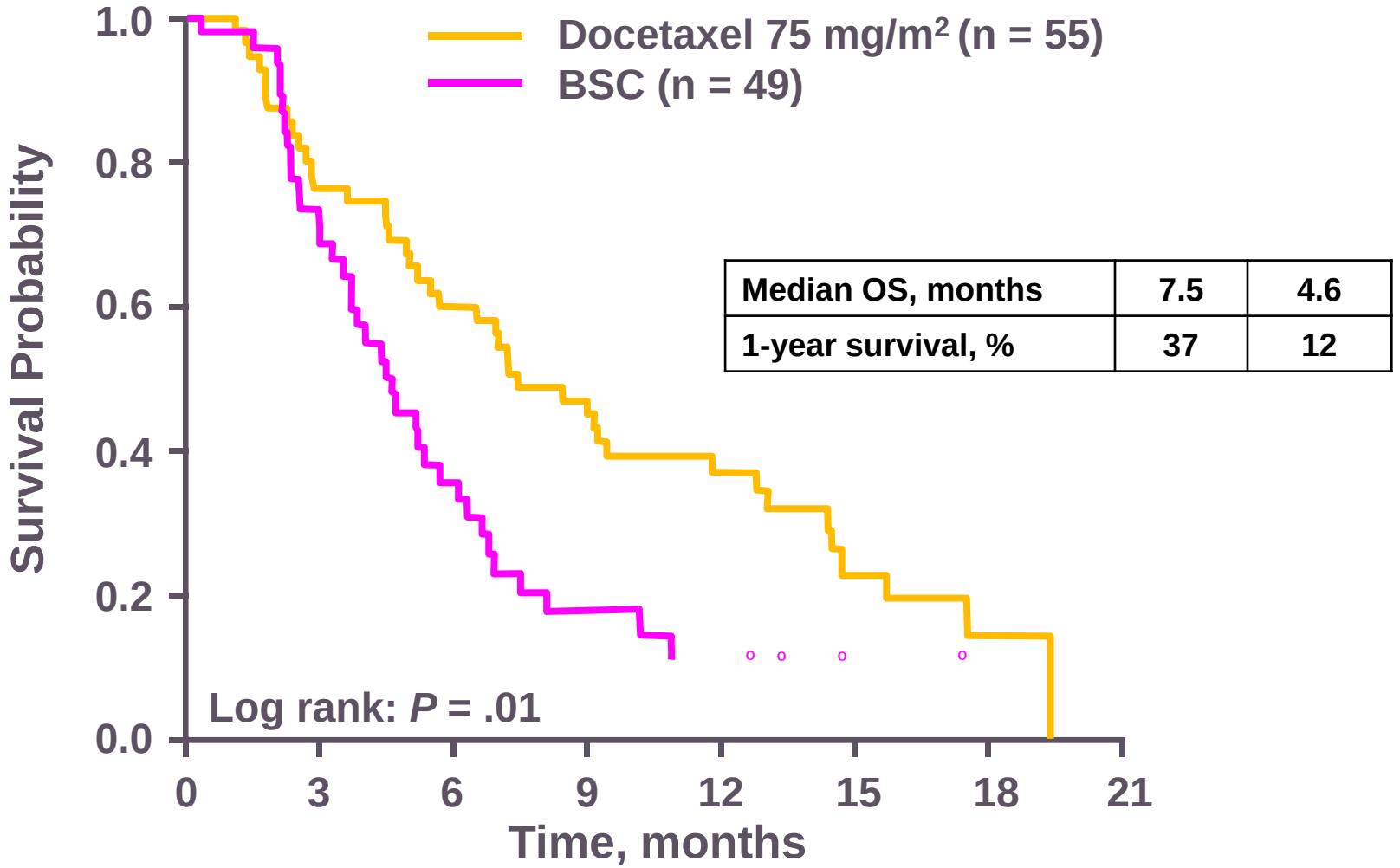
Second Line

Second-Line Uptake



Polo V, Besse BI. *Ann Oncol.* 2014;25(7):1283-1293.

Docetaxel—2000



Median OS, months	7.5	4.6
1-year survival, %	37	12

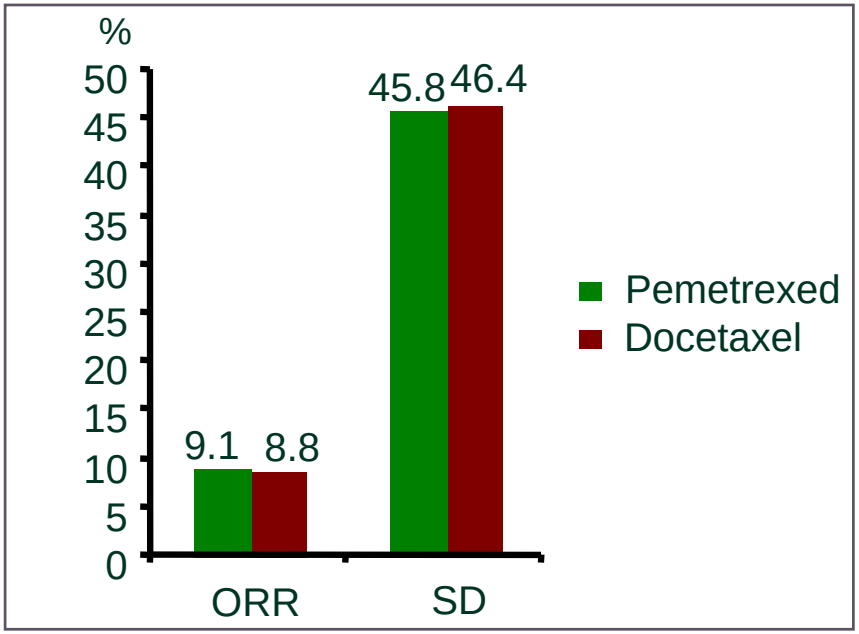
Shepherd FA, et al. *J Clin Oncol.* 2000;18(10):2095-2103.

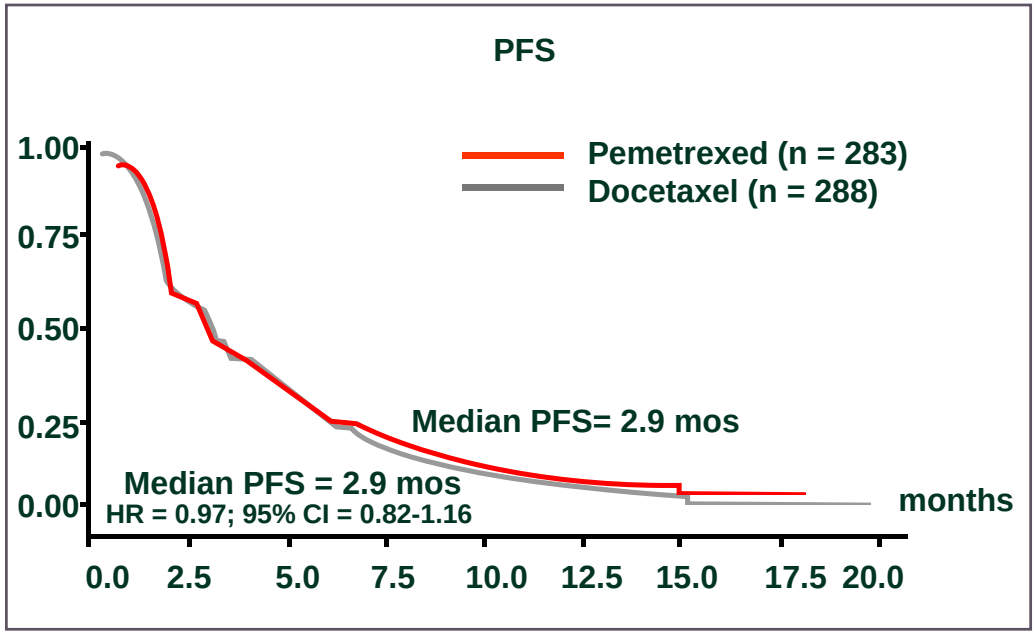
Pemetrexed—2003

R → Docetaxel 75 mg/m^2 q3w

R → Pemetrexed 500 mg/m^2 q3w

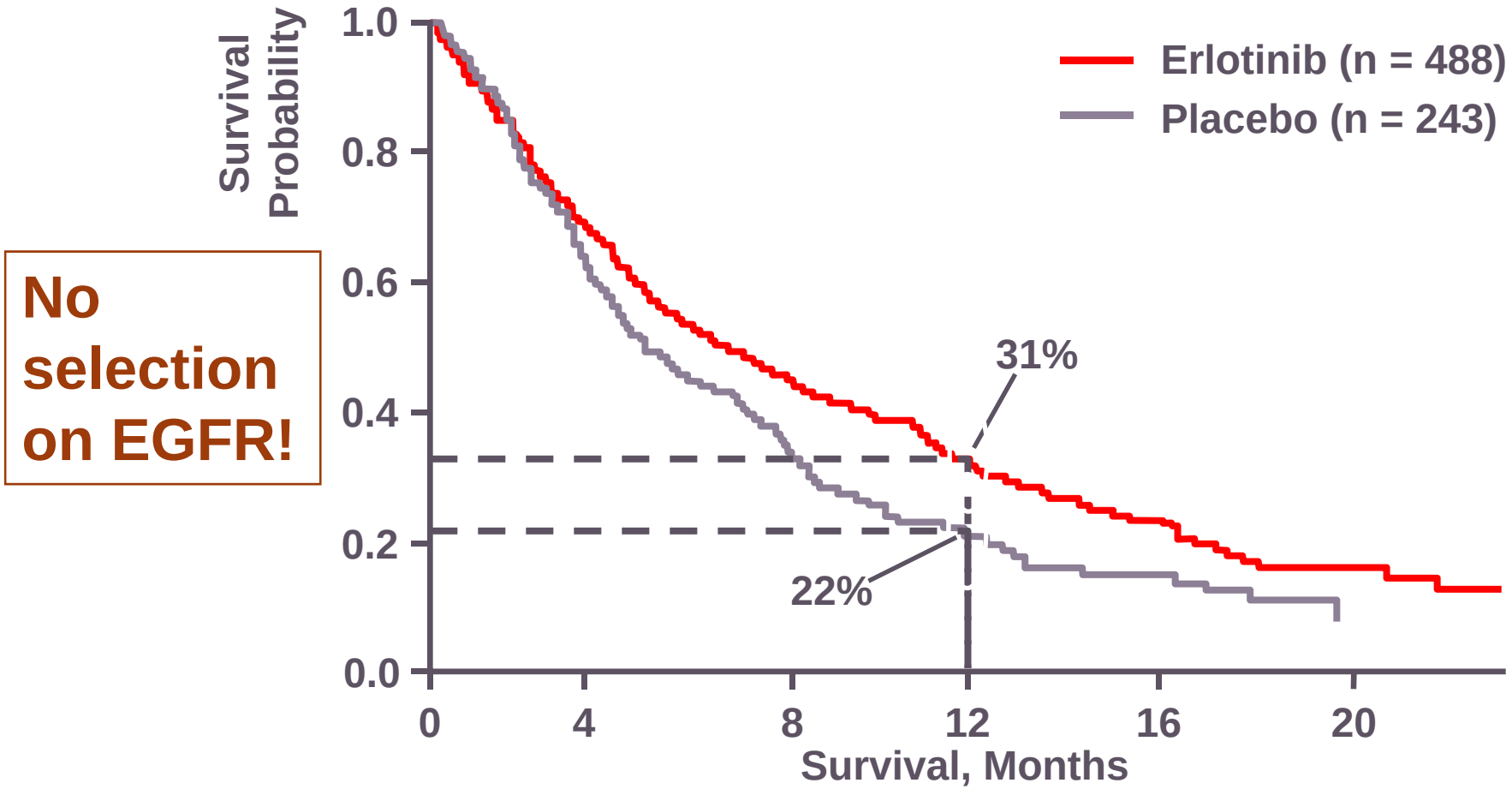
+ Vit. B12 and folates





Hanna N, et al. *J Clin Oncol.* 2004;22(9):1589-1597

Erlotinib—2005



No selection on EGFR!

Shepherd FA, et al. *N Engl J Med.* 2005;353(2):123-132.

Second-Line for Advanced NSCLC

A best choice?

Docetaxel: 75 mg/m² - d1 = d21
ORR: 9% - PFS: 2.9 months

But if paclitaxel is given first line?

Pemetrexed: 500 mg/m² - d1 = d21
ORR: 9% - PFS: 2.9 months

Non SCC only

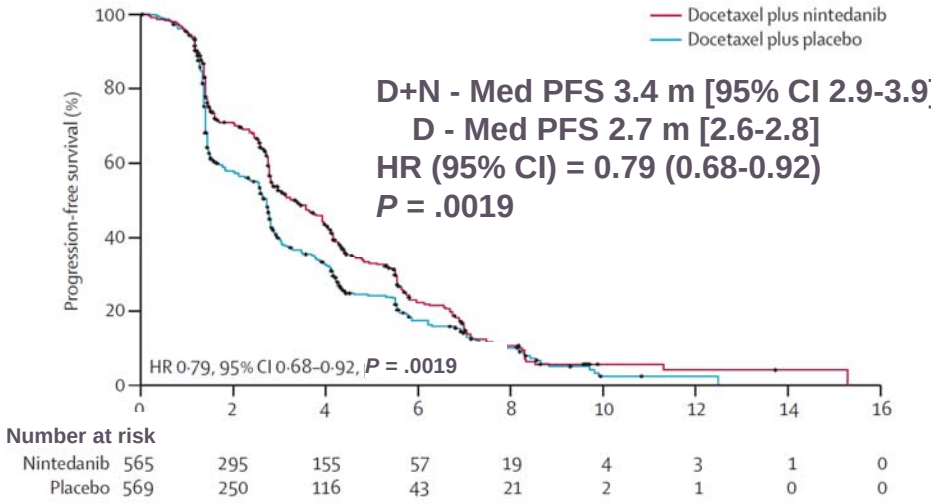
Erlotinib: 150 mg/d
ORR: 9% - PFS: 2.2 months

All histology

Antiangiogenic Agents in Second-Line?

LUME-LUNG 1 Trial[1]: Docetaxel +/- nindetanib (VEGFR TKI)

- PFS (primary endpoint)



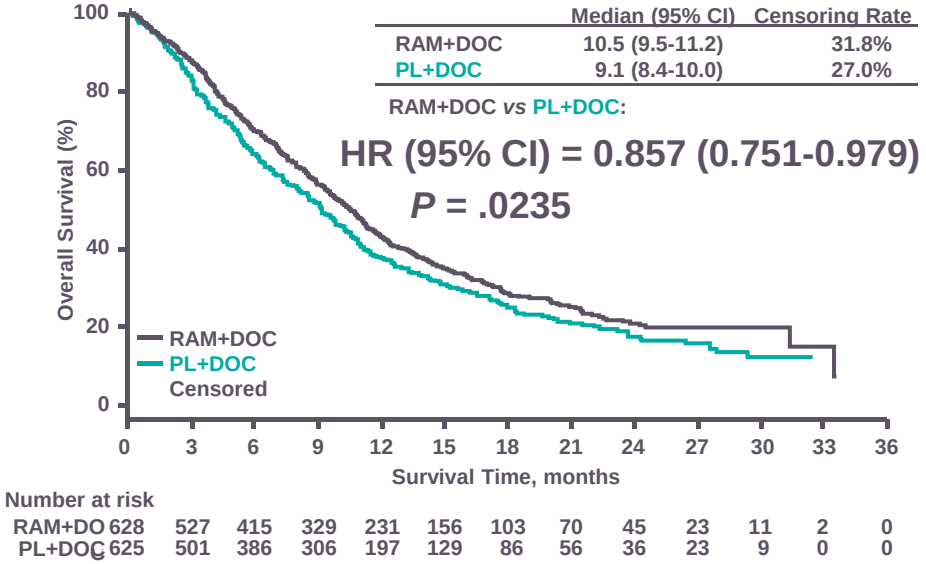
D+N - Med PFS 3.4 m [95% CI 2.9-3.9]
D - Med PFS 2.7 m [2.6-2.8]
HR (95% CI) = 0.79 (0.68-0.92)
P = .0019

OS benefit in adenocarcinoma

PFS benefit in first-line refractory patients (HR= 0.67 [0.43-1.04], P = .0725)

REVEL Trial[2]: Docetaxel +/- ramucirumab (VEGFR2 Ab)

- OS (primary endpoint)



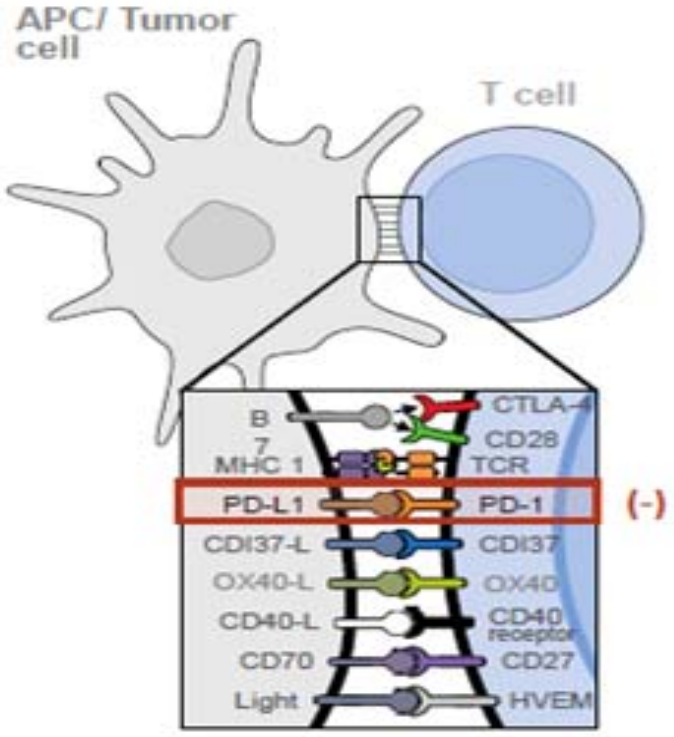
OS benefit in SCC and non SCC

VEGFR, vascular endothelial growth factor receptors

Reck M, et al. *Lancet Oncol.* 2014;15(2):143-155. Perol M, et al. *J Clin Oncol.* 2014;32(5S): Abstract LBA8006.

Immunotherapy

Immune checkpoint inhibition



Similar Response Regardless Histology

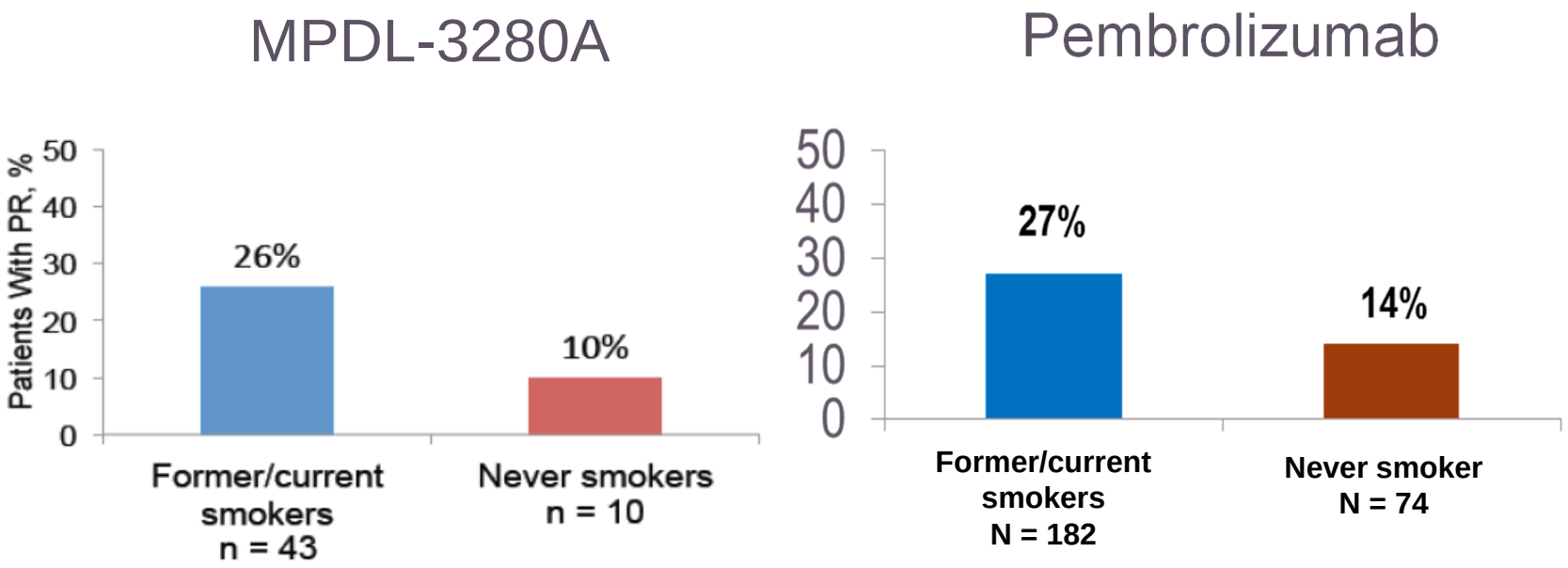
	Adenocarcinoma	Squamous Carcinoma
Nivolumab (PD-1)	17.6% (13/74)	16.7% (9/54)
MK-3475 (PD-1)	23% (7/31)	33% (2/6)
BMS-936559 (PD-L1)	11% (4/36)	8% (1/13)
MPDL3280A (PD-L1)	21% (9/42)	27% (3/11)

- **Durable responses beyond 1 year observed in some responding patients**

Brahmer JR, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 8030. Garon EB, et al. *Clin Cancer Res.* 2014;20(2Suppl): Abstract A20. Brahmer JR, et al. *N Engl J Med*. 2012;366(26):2455-2465. Soria JC, et al. *Eur J Cancer*. 2013;49(Suppl 2): Abstract 3408.

PD-1 and PD-L1 Ab : Response by Smoking History in NSCLC Patients

Response by Smoking Status (ORR)



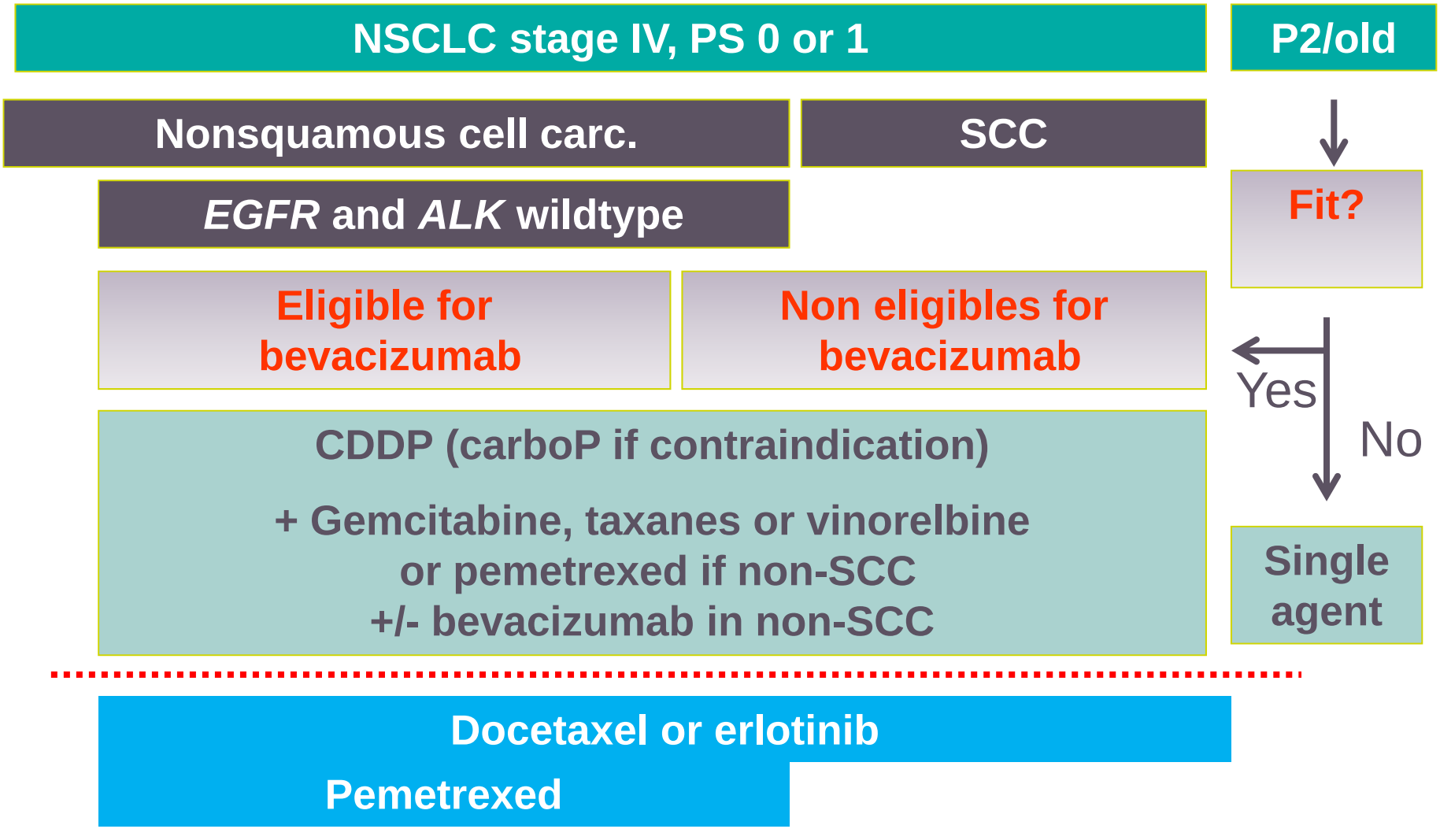
Soria JC, et al. *Eur J Cancer.* 2013;49(Suppl 2): Abstract 3408; Garon EB, et al. *J Clin Oncol.* 2014;21(5s): Abstract 8020.

Some Immune Checkpoint Inhibitors Ongoing Trials in Late Stage Development for Advanced NSCLC

	Study/ No.	Phase	Indication(s)	N	Comparator	Primary Endpoint
PD-1						
Nivolumab	**CheckMate 057** NCT01673867/ CA209-057	III	Advanced/metastatic nonsquamous NSCLC, second/third-line	574	Docetaxel	OS
	CheckMate 153 NCT02066636	IIIb/IV	Advanced/metastatic after progression during or after at least 1 therapy	780		Safety
	CheckMate 026 NCT02041533/ CA209-026	III	Advanced/metastatic PD-L1 positive NSCLC, first-line	495	Investigator's Choice of chemotherapy	PFS
MK-3745	**MK-3475-010/ KEYNOTE-010** NCT01905657	II/III	Previously treated PD-L1 positive NSCLC	920	Docetaxel	OS, PFS, Safety
	MK-3475-024 NCT02142738	III	Metastatic NSCLC PD-L1 strong; first-line	300	Platinum-based chemotherapy	PFS
PD-L1						
MPDL3280A	**OAK** NCT01903993	III	Locally advanced or metastatic NSCLC, after progression on platinum-based chemo	1100	Docetaxel	OS
	BIRCH NCT02031458	II	Locally advanced or metastatic NSCLC, PD-L1 positive	635	Single arm study	ORR
MEDI4736	**ATLANTIC** NCT02087423	II	Third-line therapy in locally advanced or metastatic NSCLC PD-L1-positiive	184	None	ORR

https://clinicaltrials.gov/

Treatment Algorithm for Nonsquamous Advanced NSCLC With Not Identified Targetable Mutation



Always consider clinical trial!