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

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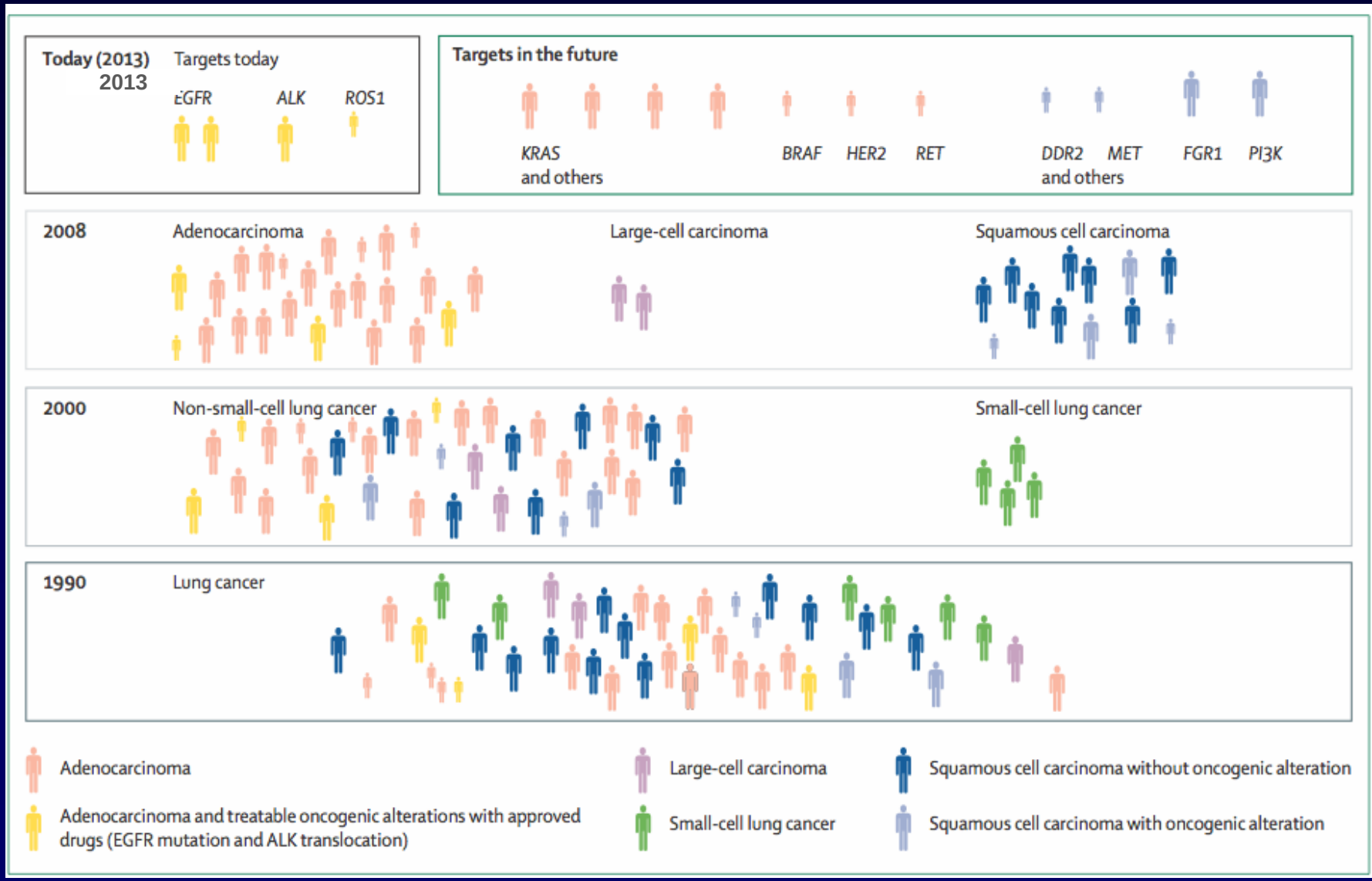
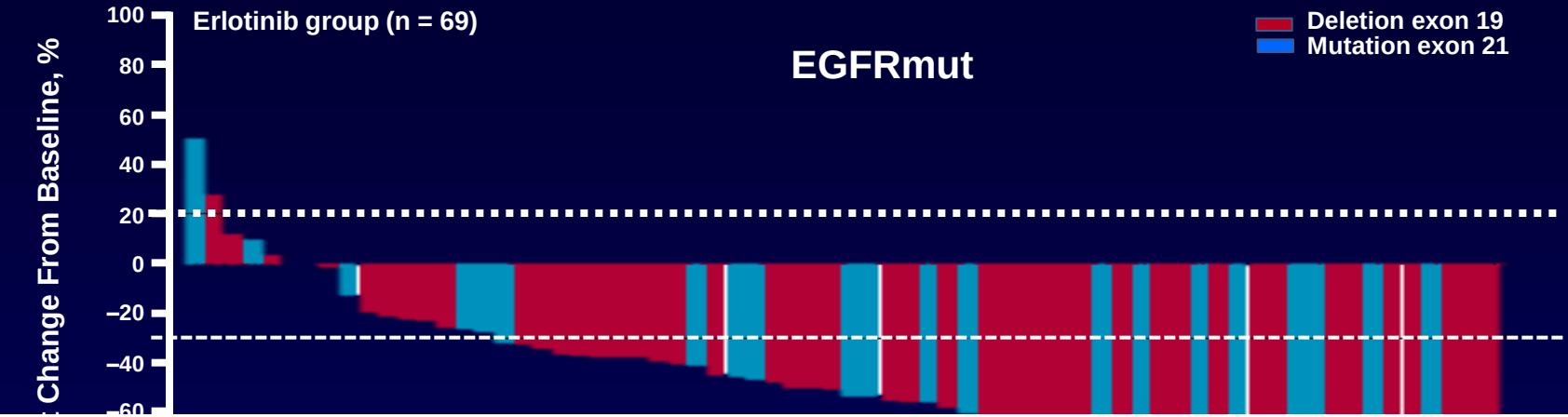
Diagnosis of Lung Cancer Has Changed....

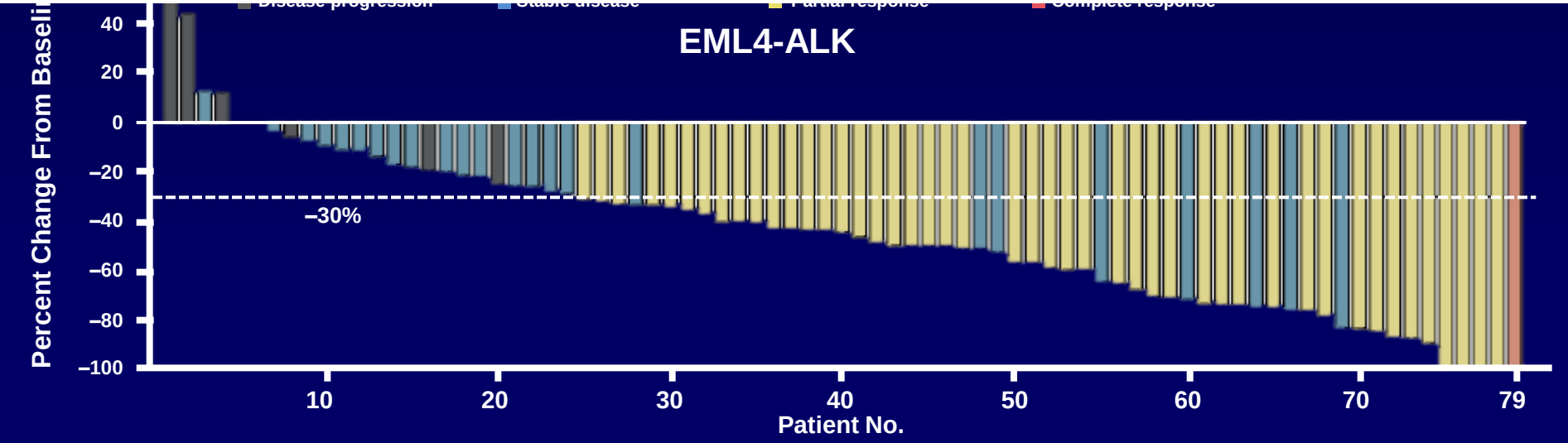


Reck M, et al. *Lancet*. 2013;382(9893):709-719

Dependence on Oncogenic Drivers



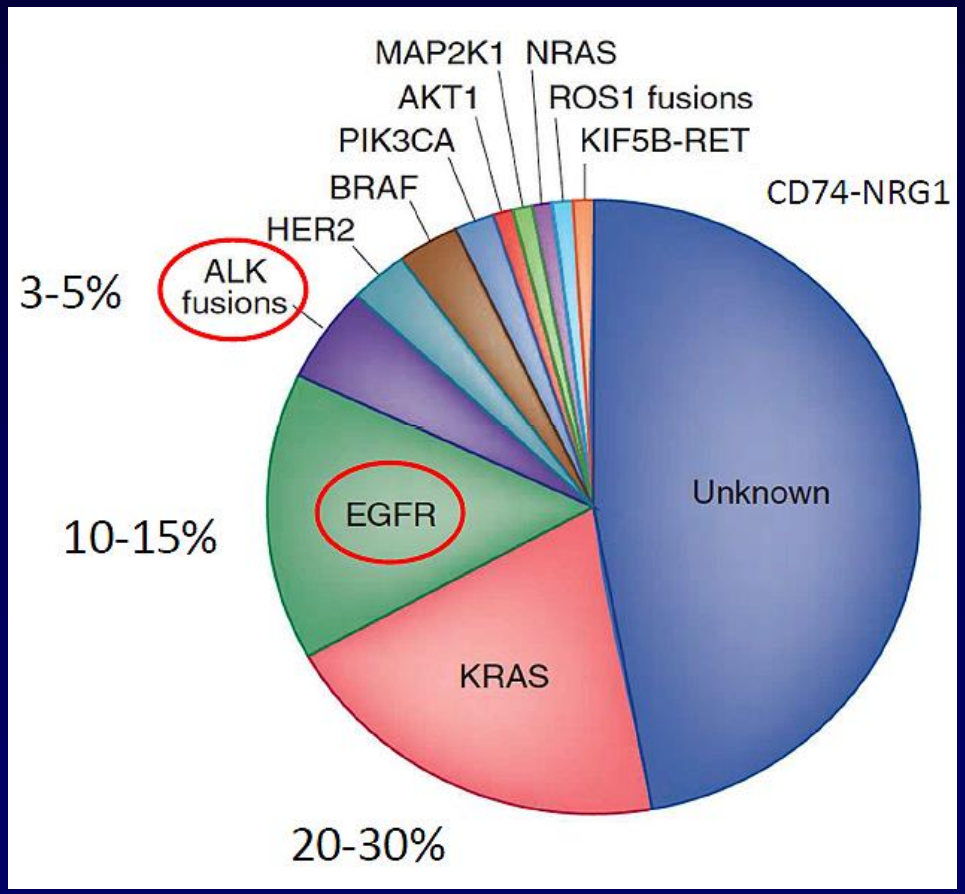
Predominantly Adenocarcinomas



Rosell R, et al. *Lancet Oncol.* 2012;13(3):239-246. Kwak EL, et al. *N Engl J Med.* 2010;363(18):1693-1703.

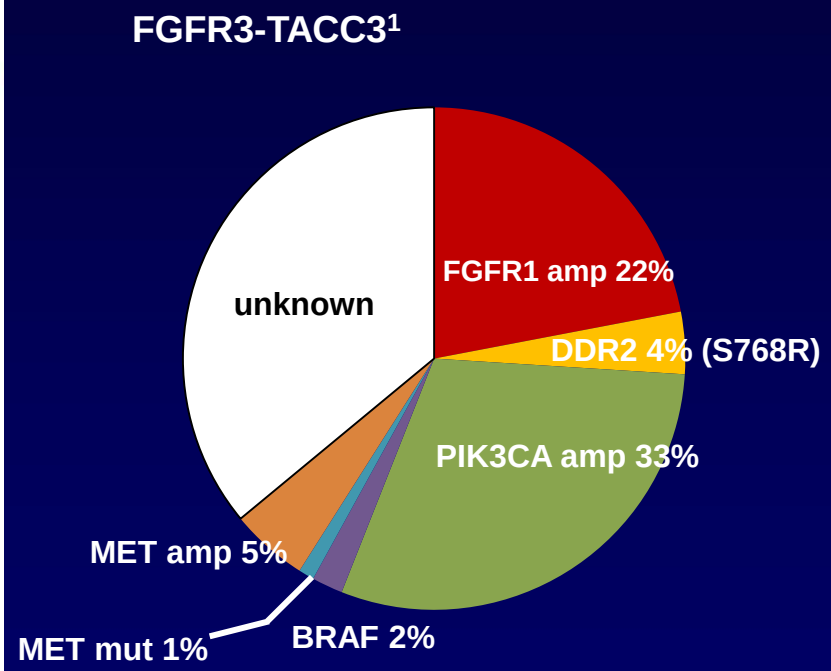
Driver Mutations in NSCLC

Adeno (ca. 75%)



Kris MG. *J Thorac Oncol.* 2013;8(Suppl 2): Abstract PL03.07.

Squamous cell (ca. 20%)



Perez-Moreno P, et al. *Clin Cancer Res.* 2012;18(9):2443-2451.
WCLC 2013

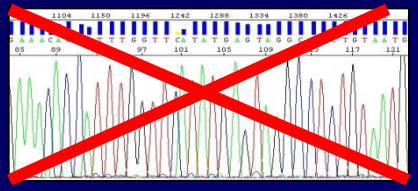
1. Majewski IJ, et al. J Pathol. 2013;230(3):270-276

Which Screening Technology ?

ABI 3130 (Sanger Sequencing)

Sensitivity 10% to 20%

Insufficient for ctDNA



Cobas (RT-PCR)

Sensitivity 1% to 2%

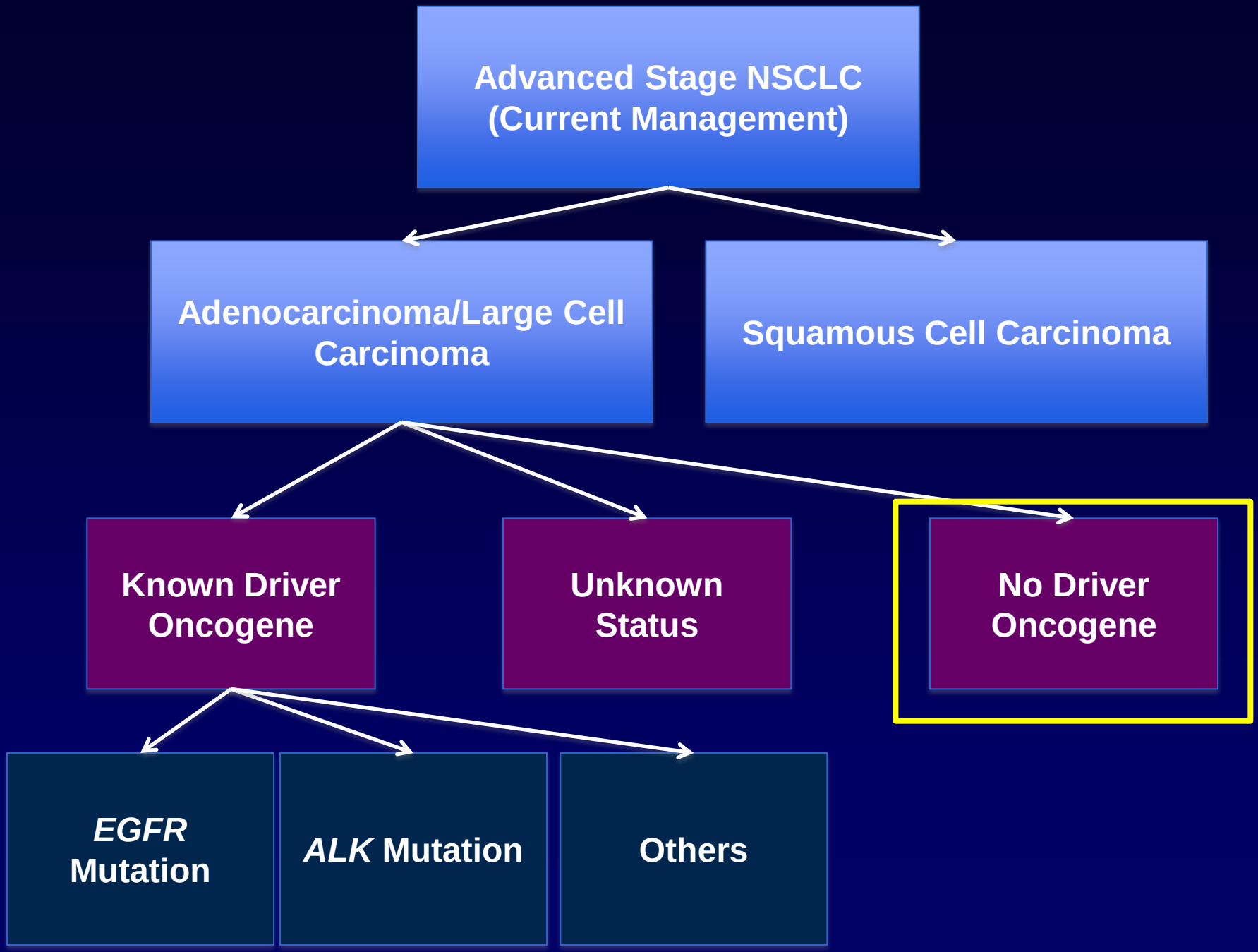
State of the art

Miseq (NGS)

Sensitivity 1% to 2%

Future (present)

Pyrosequencing: 10%
BEAMing, Digital PCR, TAM-seq: 0,01% or lower


Advanced Stage NSCLC (Current Management)
Adenocarcinoma/Large Cell Carcinoma
Squamous Cell Carcinoma
Known Driver Oncogene
Unknown Status
No Driver Oncogene
EGFR Mutation
ALK Mutation
Others

The Most Important Selection Factors

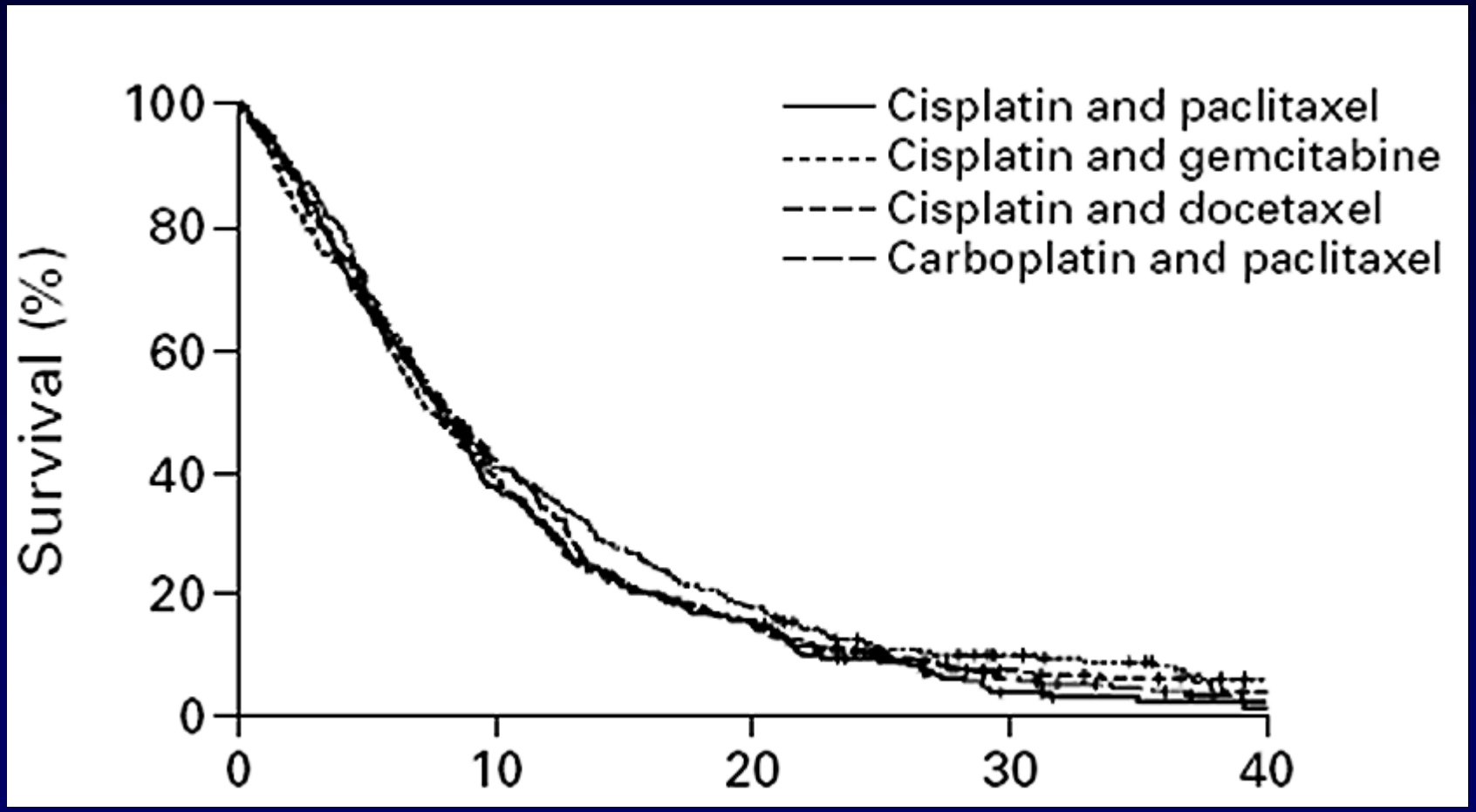
- Age
- Performance Status
- Stage

"Classic Factors"

- Histology / Eligibility for bevacizumab
- Maintenance Therapy
- Molecular Screening

"New Factors"

Comparison of Four Chemotherapy Regimens

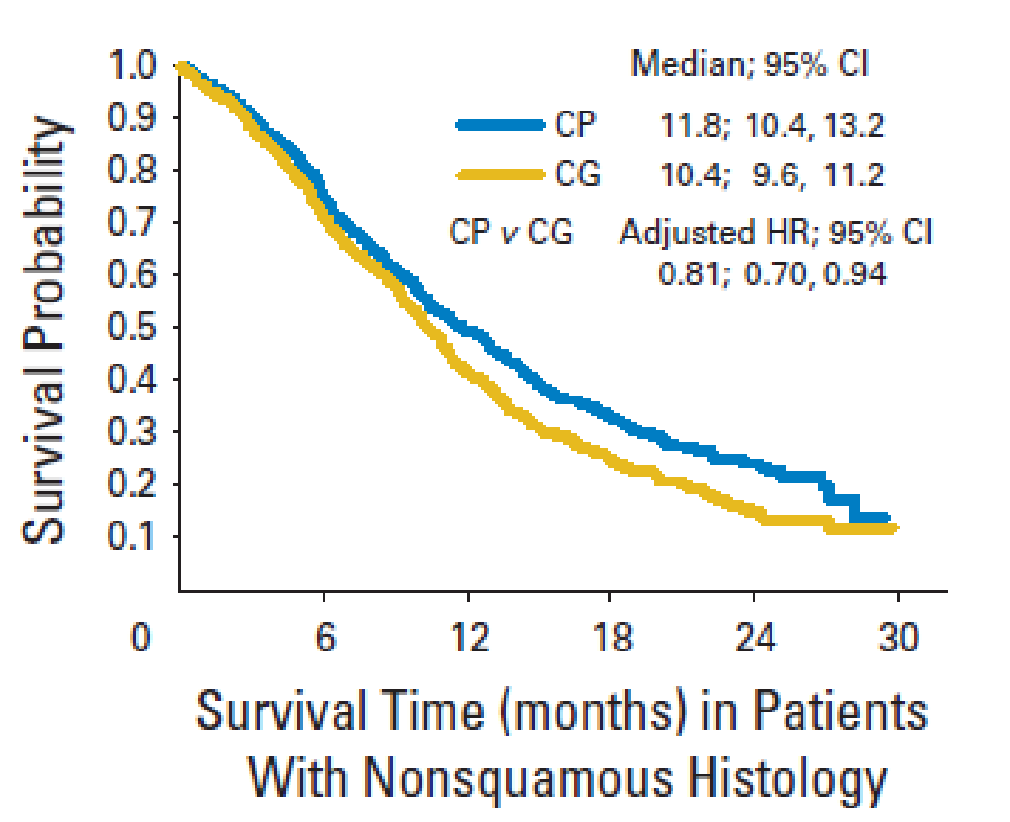


Schiller JH, et al. *N Engl J Med.* 2002;346(2):92-98

Pemetrexed vs Gemcitabine (+CDDP)

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

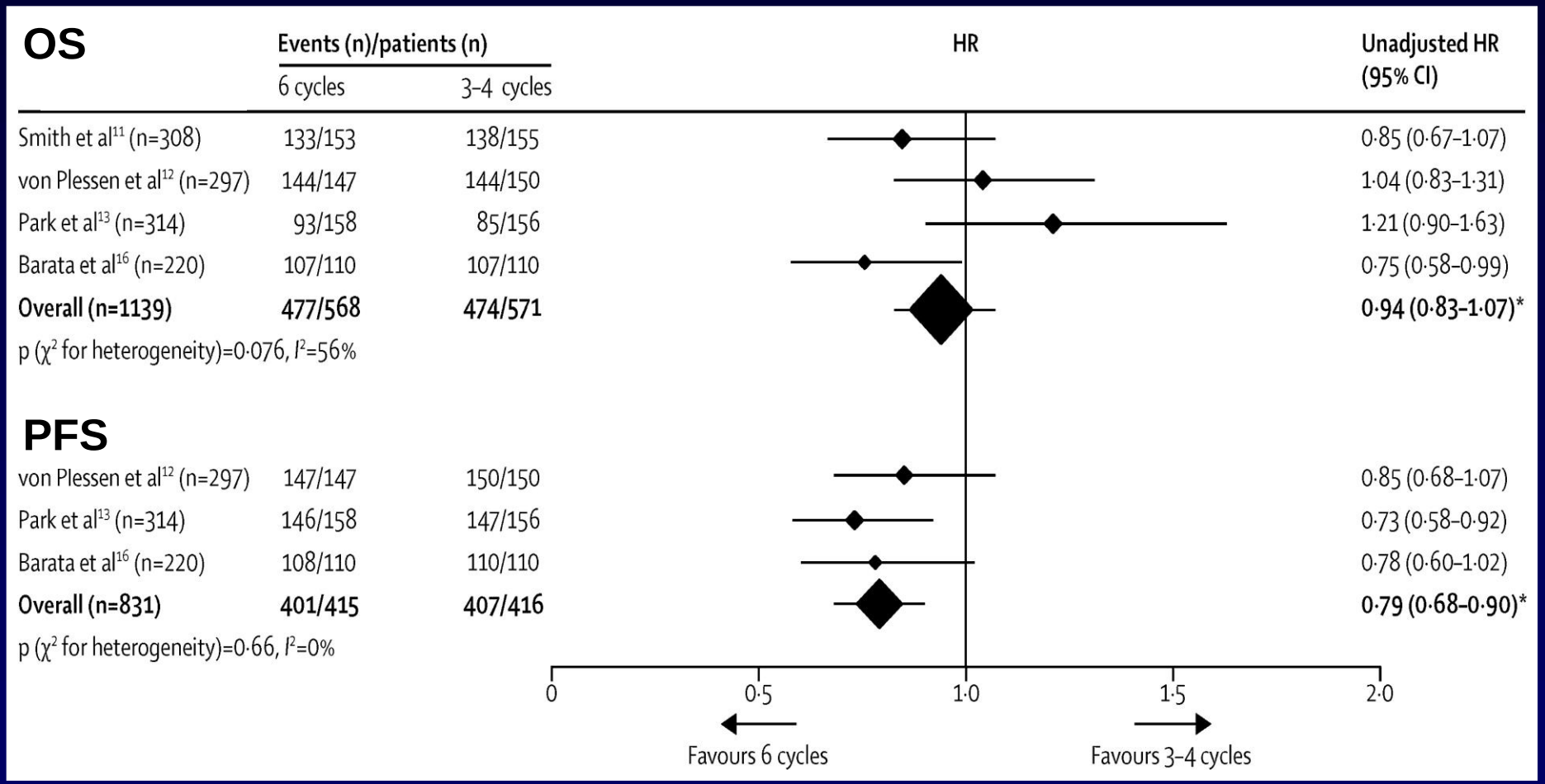
- Adenocarcinoma + LCC
  → Pemetrexed better
- SCC
  → Gemcitabine better



CI, confidence interval; HR, hazard ratio; CDDP, cisplatin; LCC,large cell carcinoma; SCC, squamous cell carcinoma

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

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



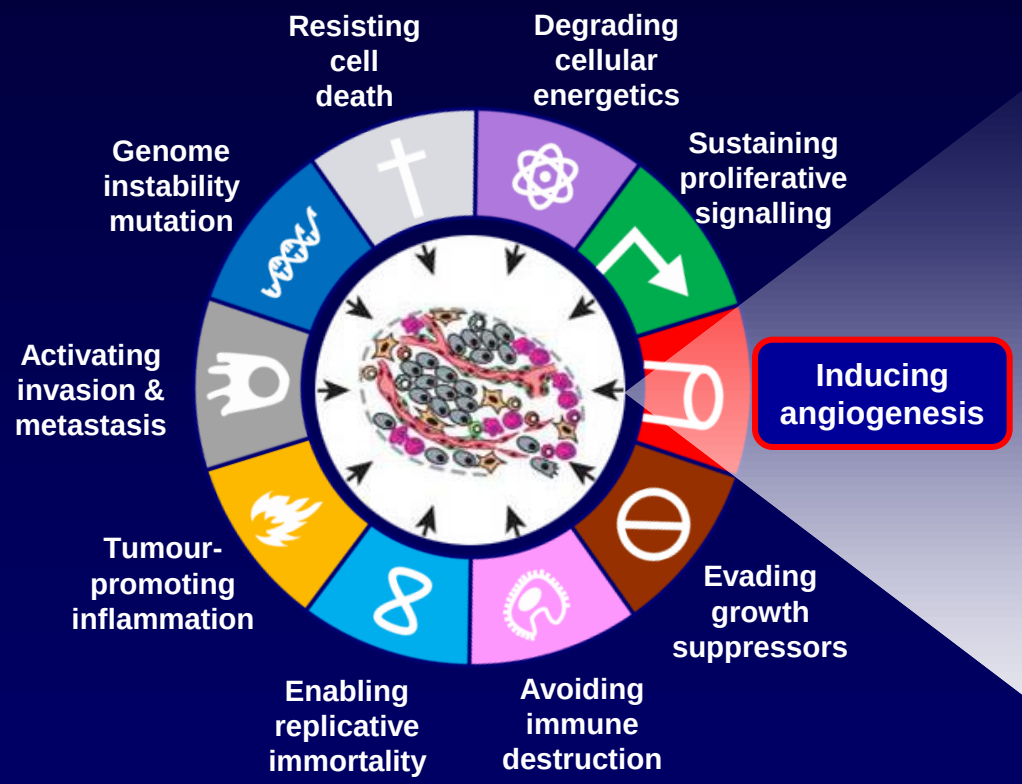
OS; HR = 0.94 (95% CI, 0.83 to 1.07; *P* = .33 (stratified by trial)

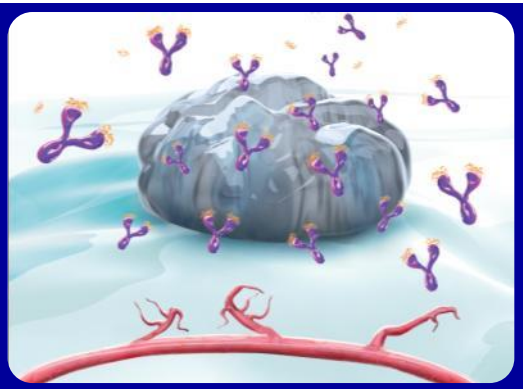
PFS; HR = 0.79 (95% CI 0.68 to 0.90), *P* = .0007 (stratified by trial)

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

Antiangiogenic?

Angiogenesis: a Hallmark of Cancer





Anti-VEGF therapy

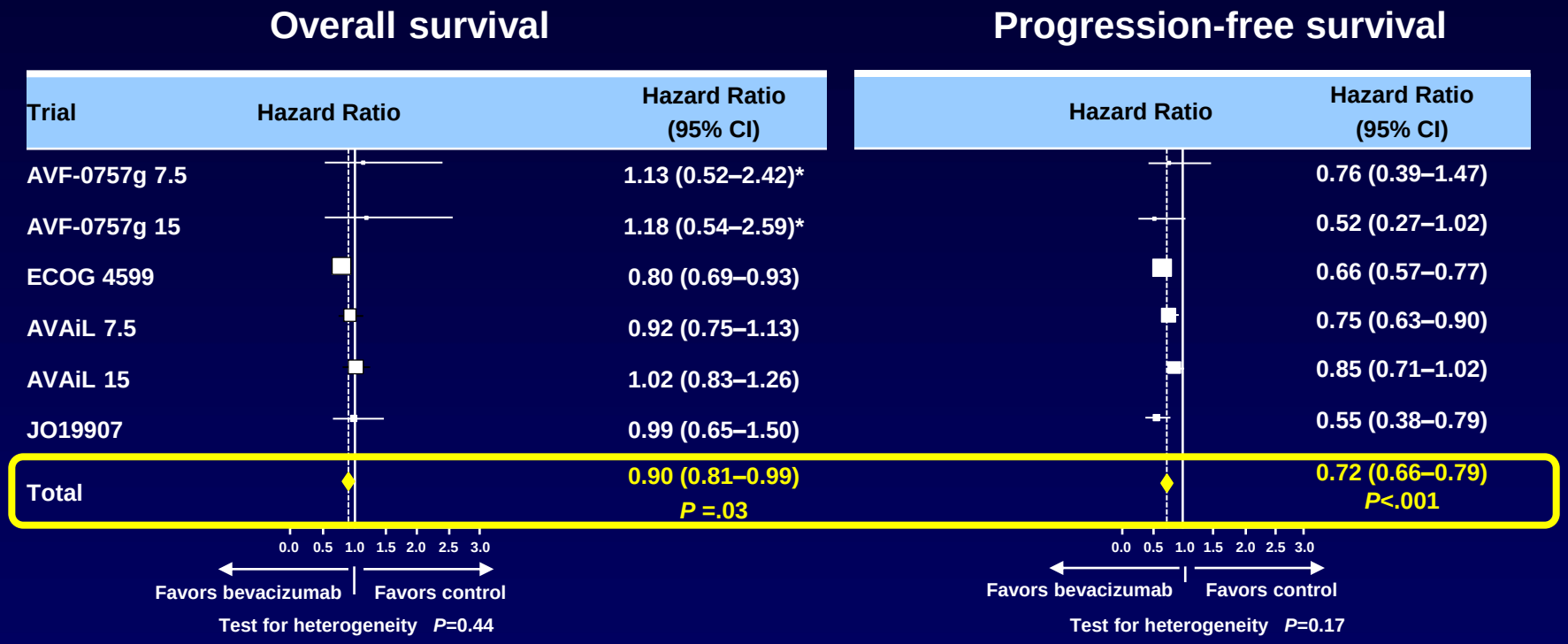
- Regression of existing tumour vasculature
- Inhibition of new vessel growth
- No bone marrow suppression
- No cumulative toxicities

Improved efficacy in combination with a well-established safety profile

Hanahan D, et al. *Cell.* 2011;144(5):646-674.

Bevacizumab + Platinum-Based Chemotherapy: First-Line Treatment of Advanced Nonsquamous NSCLC

Meta-analysis of efficacy data from first-line RCTs

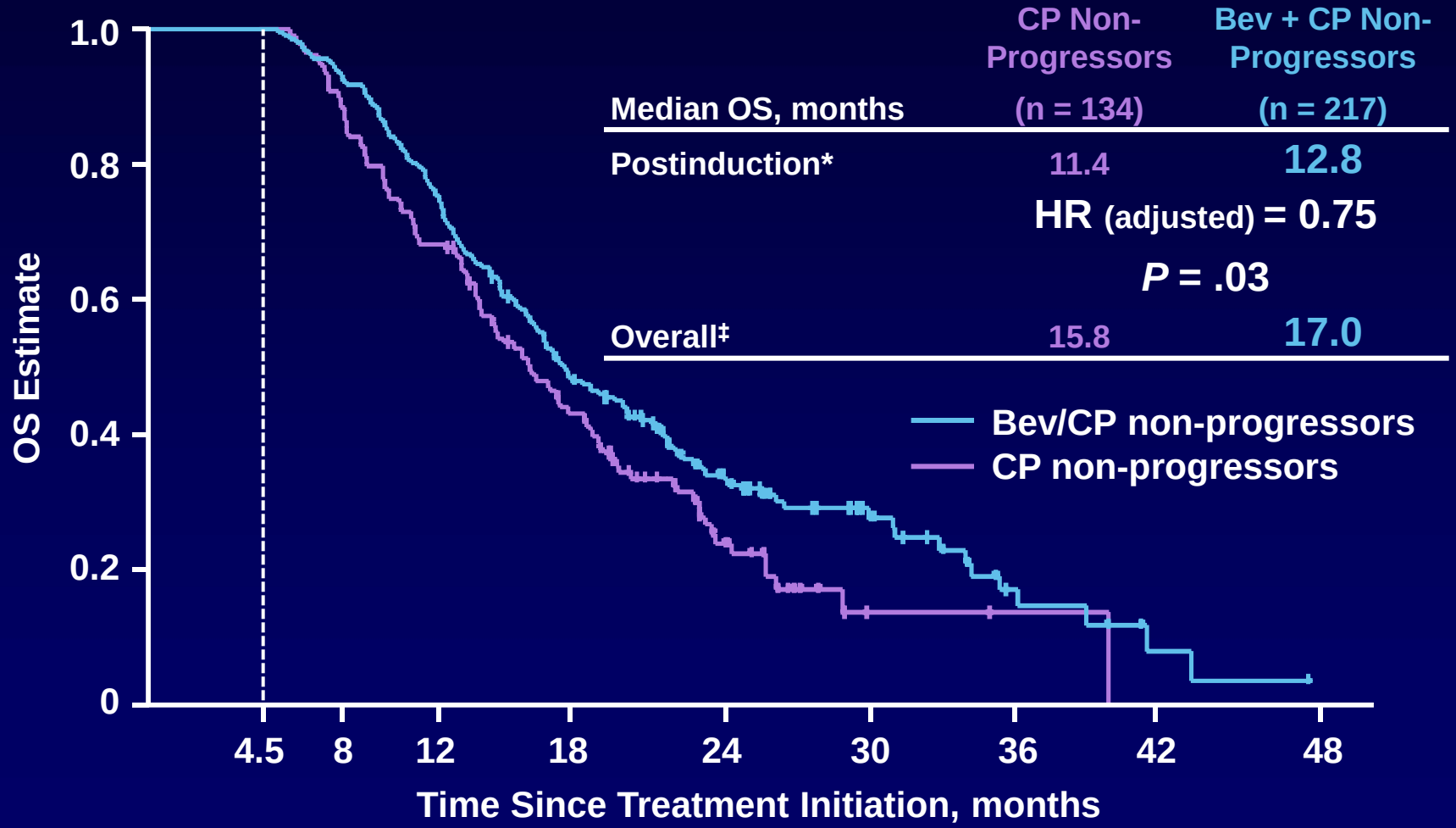


Overall survival and progression-free survival significantly improved by addition of bevacizumab to chemotherapy in NSCLC (primarily nonsquamous) patients

*AVF-0757g trial: direction of OS HR unknown, worst scenario chosen
RCTs, randomized controlled trials; CI, confidence interval. Results as reported in meta-analysis

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

E4599: Retrospective Analyses of Non-Progressors on Study 21 Days After Cycle 6

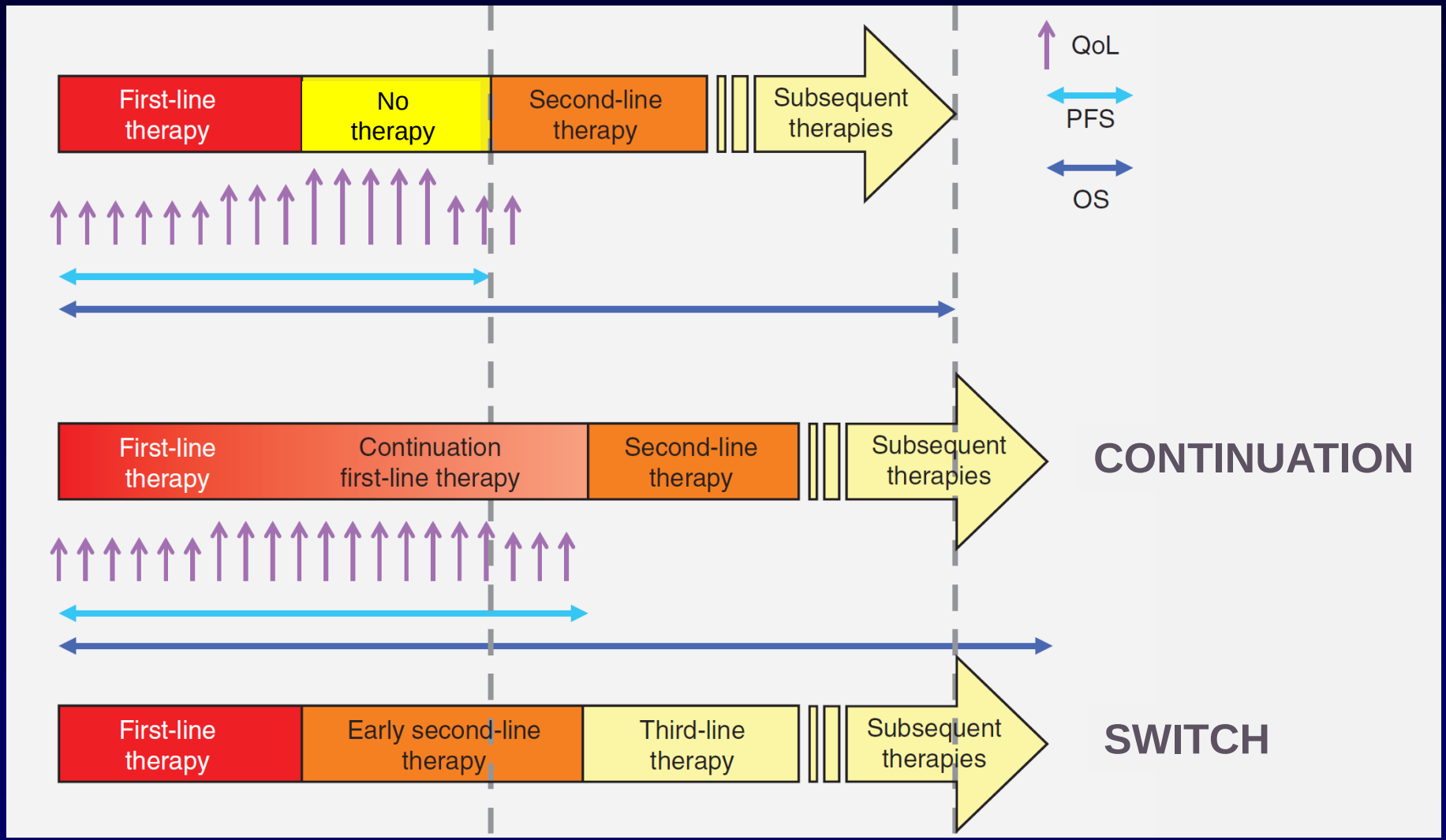


*Calculated from the landmark date +21 days; ‡Calculated from start of induction treatment

Sandler A. et al. *J Thoracic Oncol.* 2011;6(Suppl 2): Abstract P3.216

Maintenance?

Maintenance Therapy Strategies

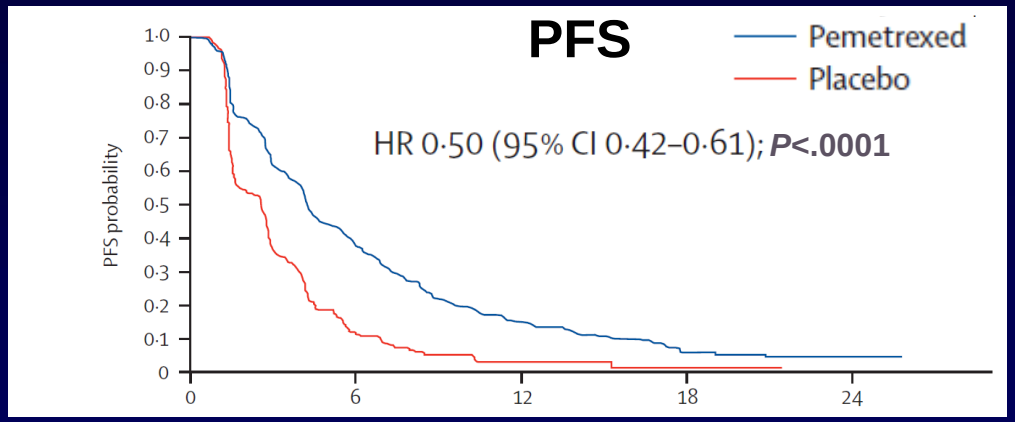


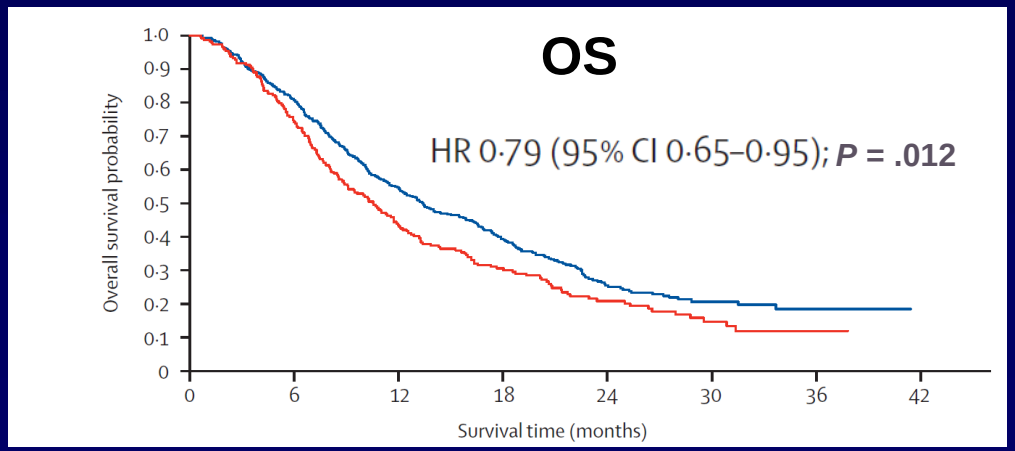
QoL, quality of life

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

Switch Maintenance

Pemetrexed vs Placebo,
(induction CT without pemetrexed)

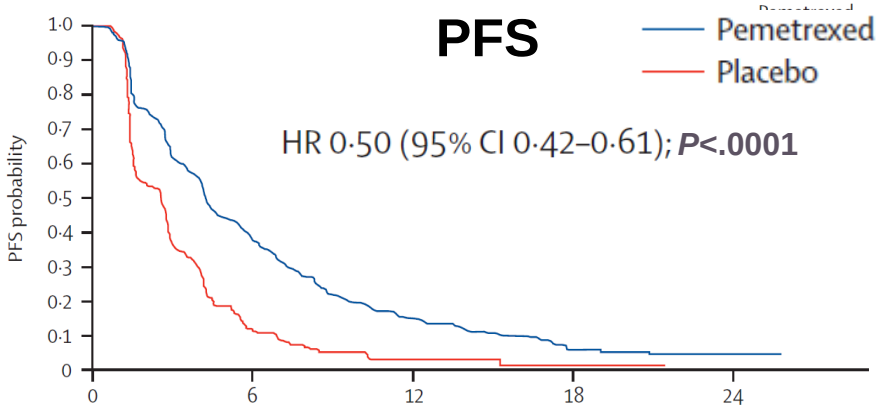


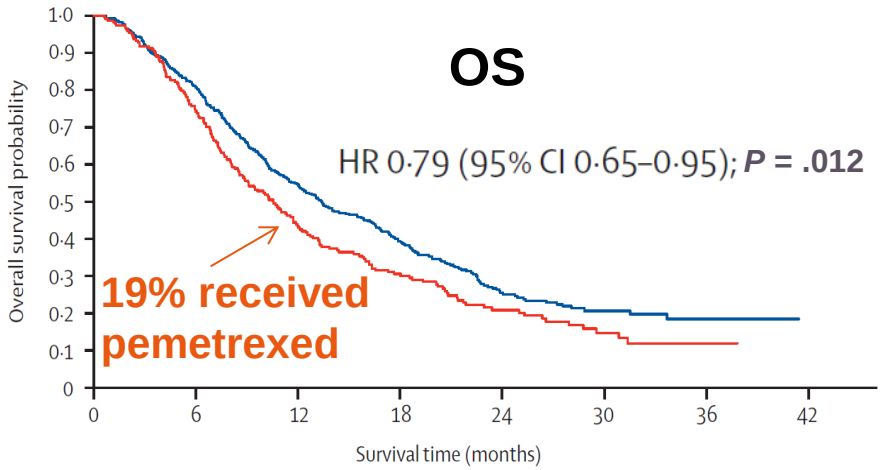


Ciuleanu T, et al. *Lancet.* 2009;374(9699):1432-1440.

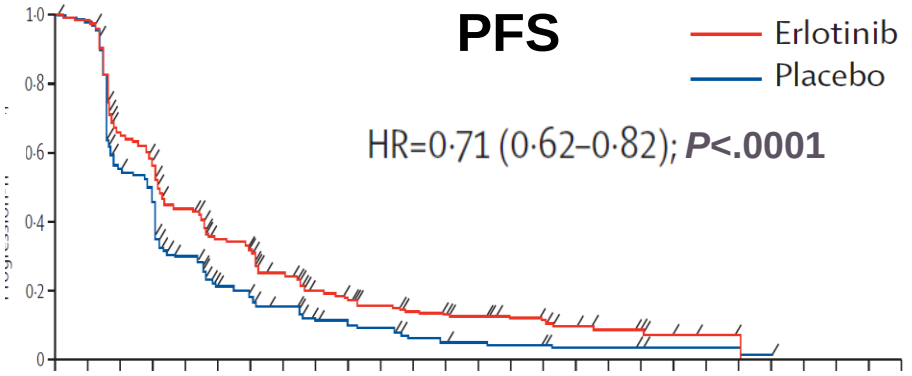
Switch Maintenance

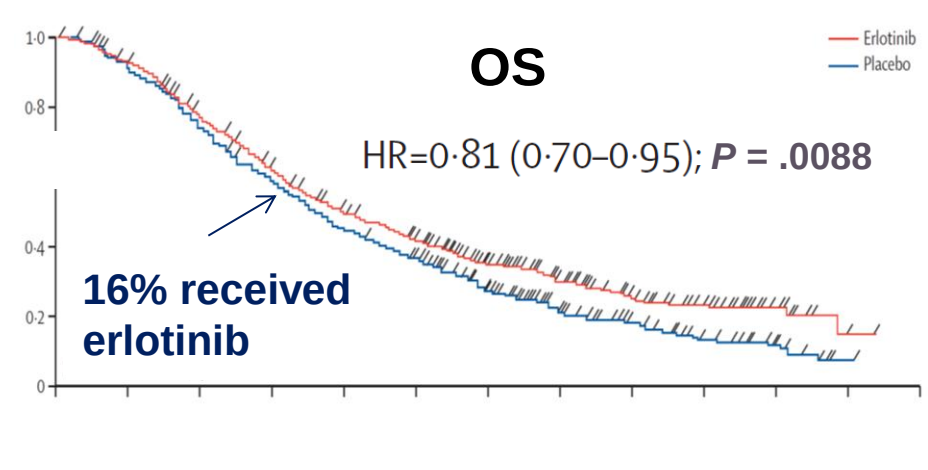
Pemetrexed vs Placebo[1], (induction CT without pemetrexed)





Erlotinib vs Placebo[2]

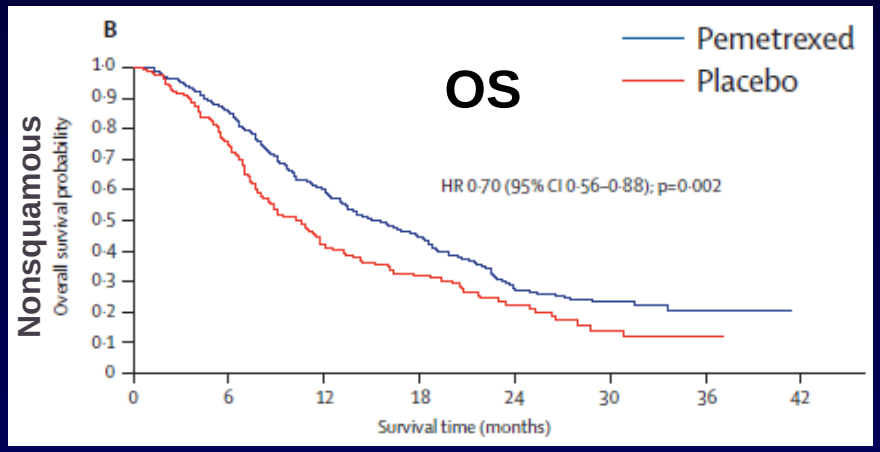


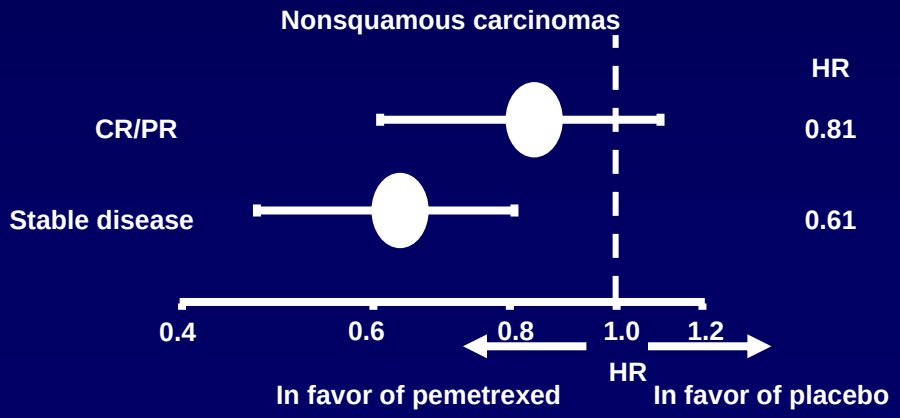


1. Ciuleanu T, et al. *Lancet.* 2009;374(9699):1432-1440; 2. Cappuzzo F, et al. *Lancet Oncol.* 2010;11(6):521-529.

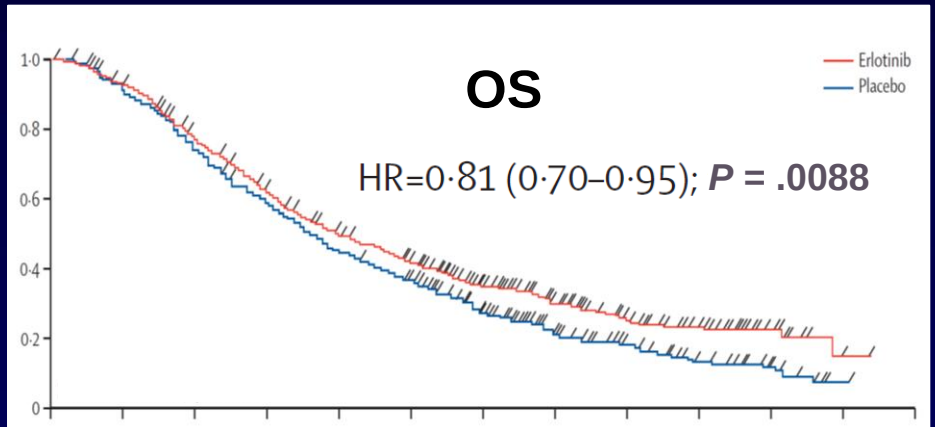
Switch Maintenance vs Response to First-Line Chemotherapy

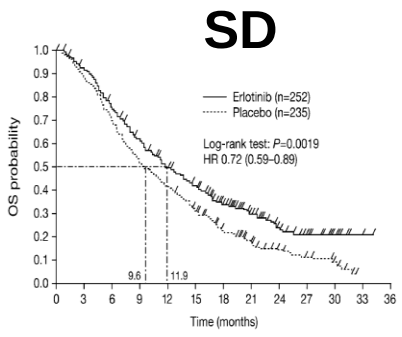
Pemetrexed vs Placebo (induction CT without pemetrexed)

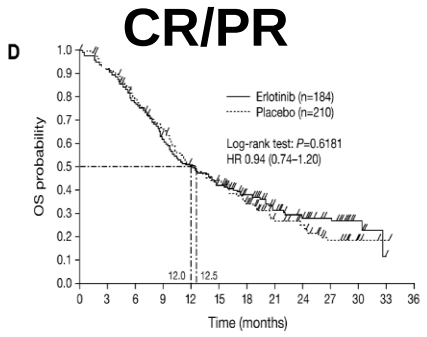




Erlotinib vs Placebo







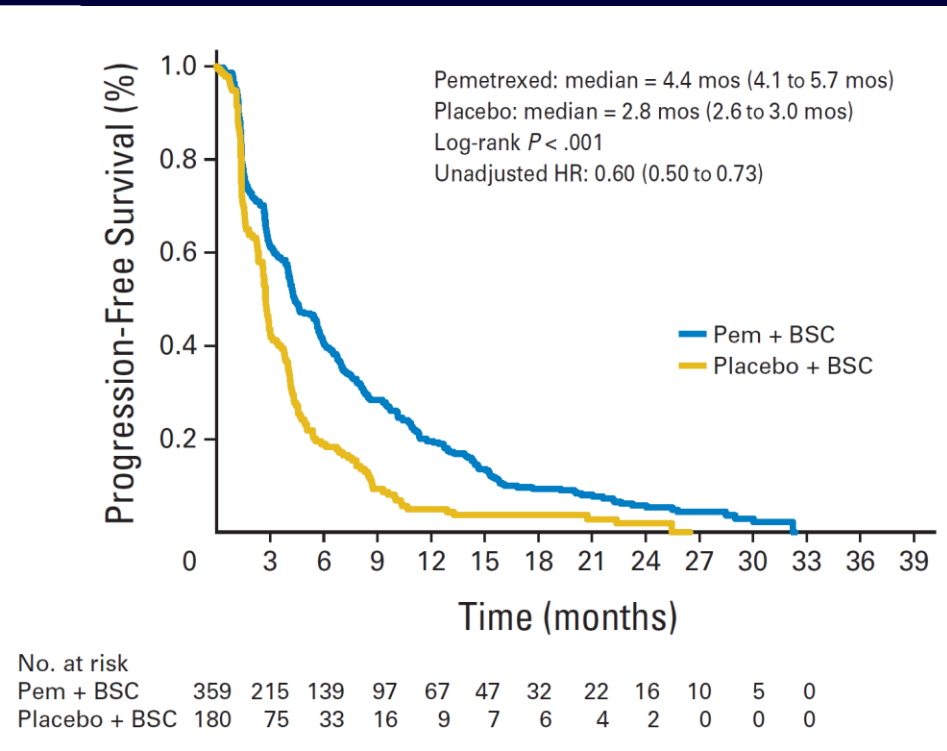
HR = 0.72 (0.59-0.89) **HR = 0.94 (0.74-1.20)**

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.

PARAMOUNT Trial: Pemetrexed vs Placebo After 4 Cycles Pemetrexed/Cisplatin

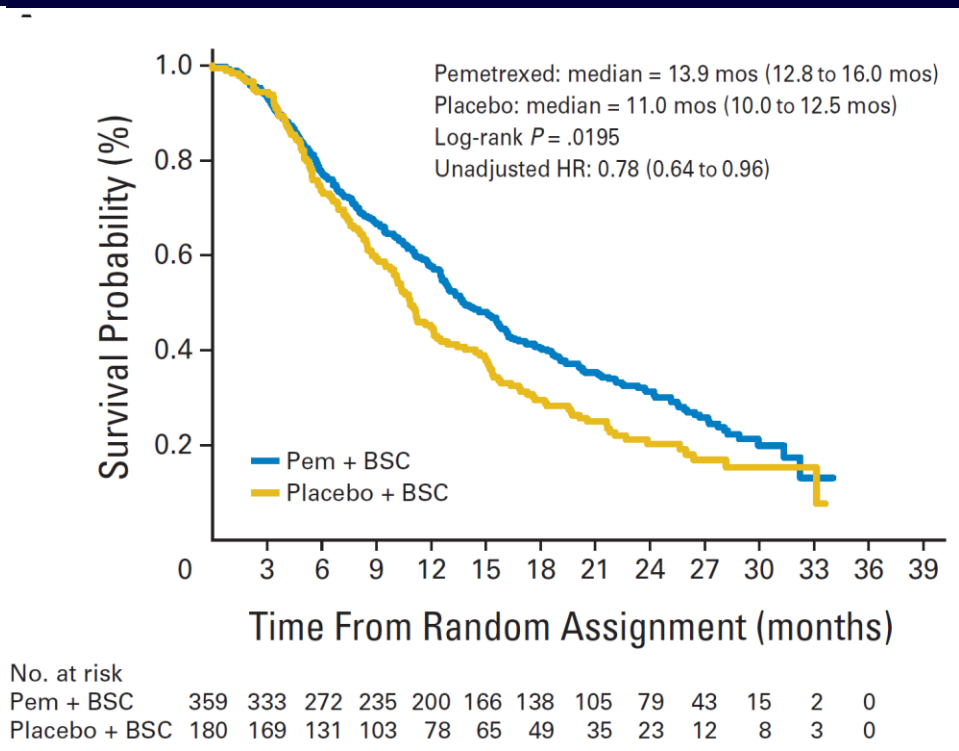
PFS



No. at risk

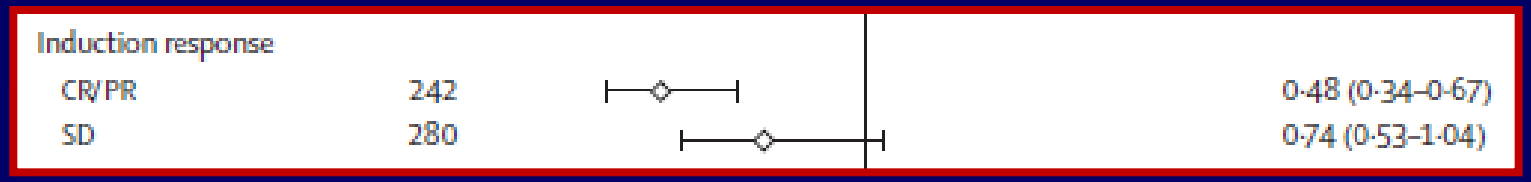
Pem + BSC	359	215	139	97	67	47	32	22	16	10	5	0
Placebo + BSC	180	75	33	16	9	7	6	4	2	0	0	0

OS



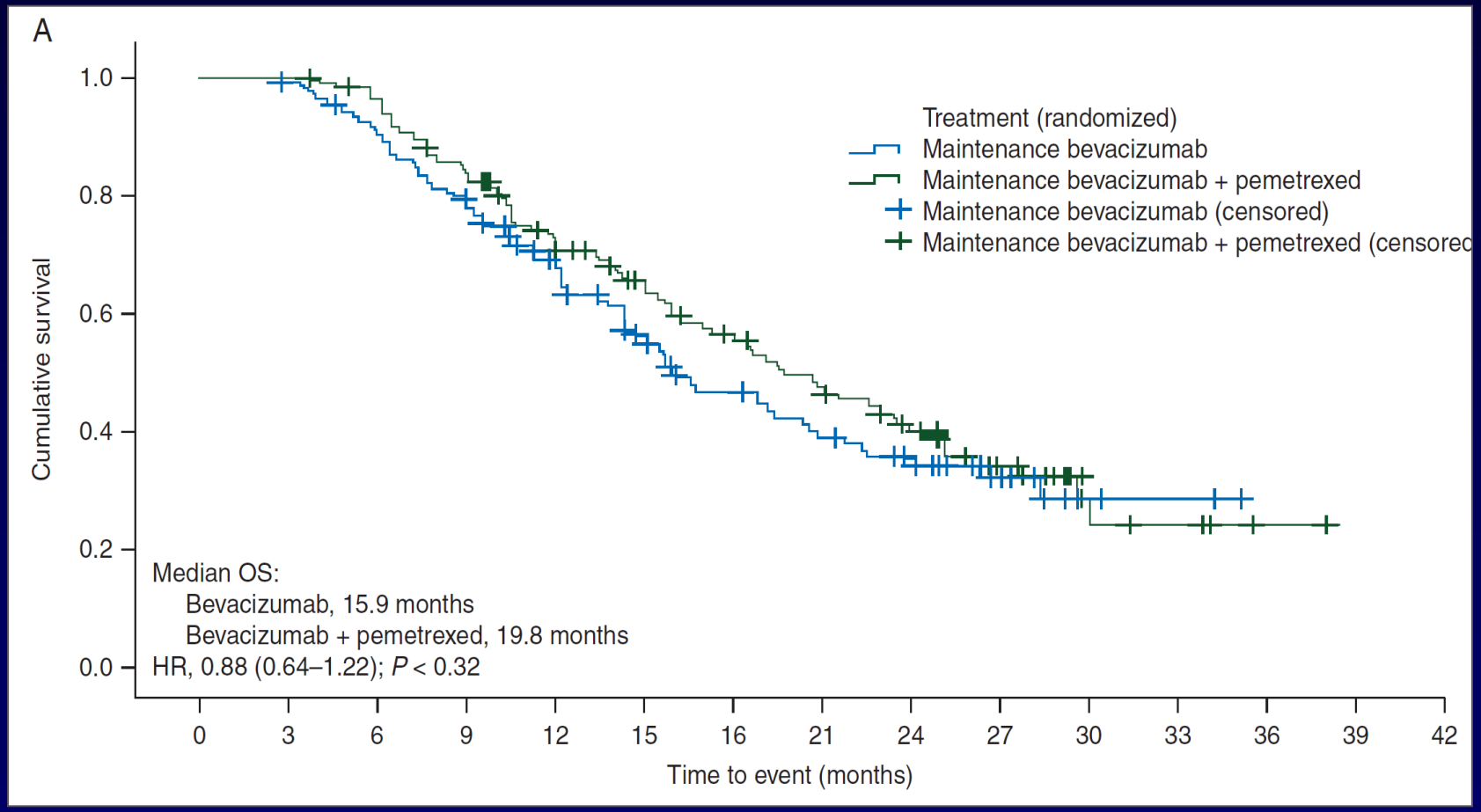
No. at risk

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



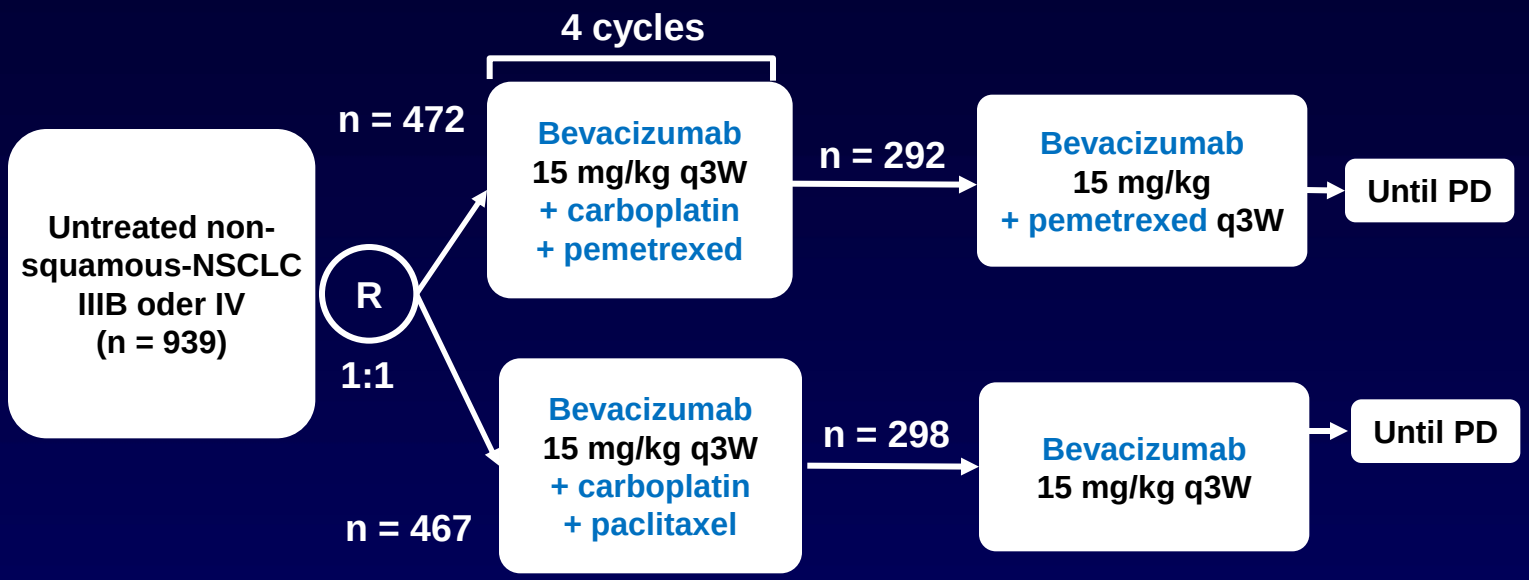
Paz-Ares LG, et al. *J Clin Oncol.* 2013;31(23):2895-2902.

AVAPERL Trial: Pemetrexed + Bevacizumab vs Bevacizumab After 4 Cycles Pemetrexed/Cisplatin/Bevacizumab



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

Bevacizumab Combinations: The Pointbreak-Trial



	OS	TTP	DCR
	Prim.	Sec.	
Beva/Carbo/Pem – Beva/Pem	12.6 months	6.0 months	65.9%
Beva/Carbo/Tax – Beva	12.4 months	5.4 months	69.8%

PD, progressive disease

Patel JD, et al. *J Clin Oncol.* 2013;31(34):4349-4357.

Second Line

NSCLC—Second Line Therapy Options

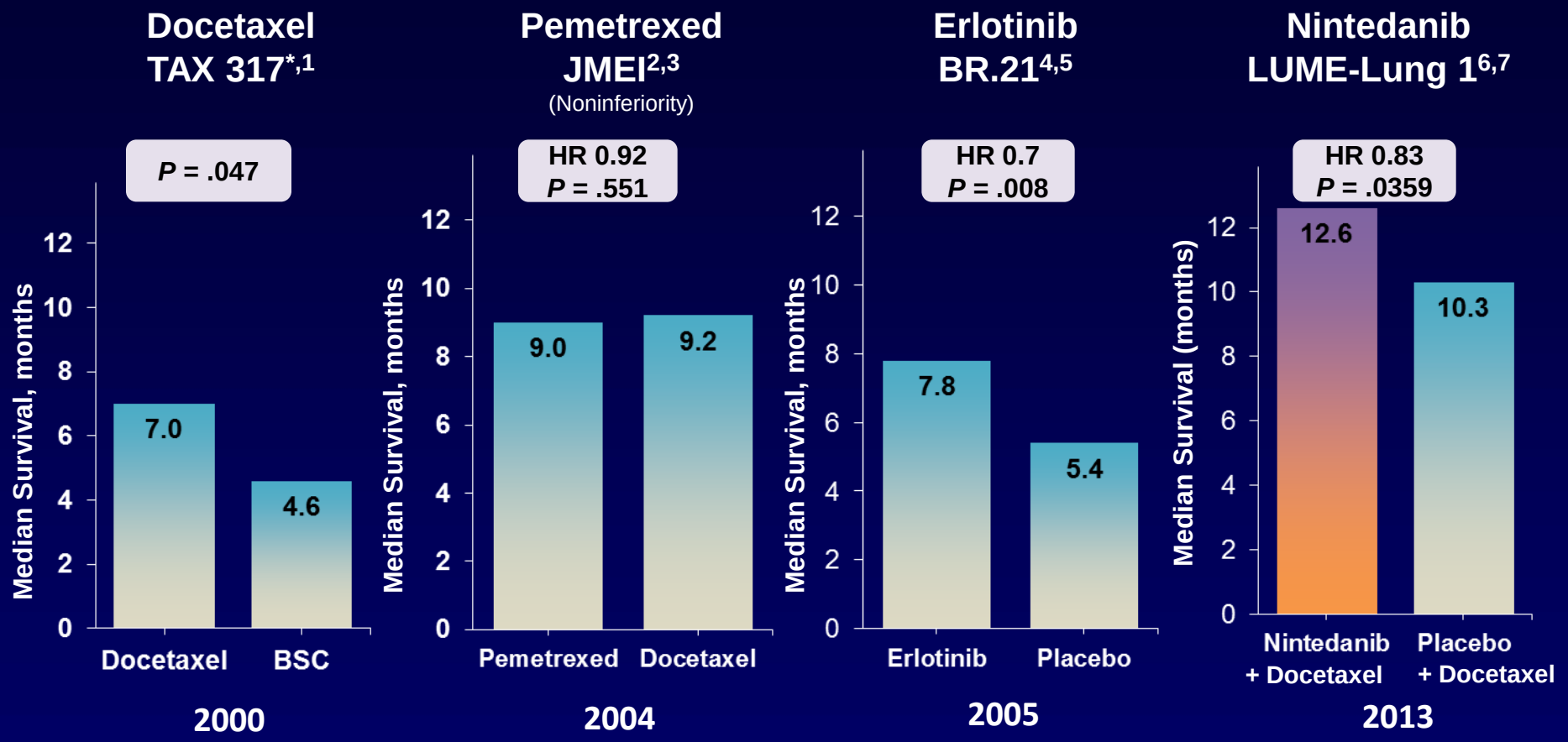
BSC (BR.21 Study): Median OS 4.7 months[1]

Approved in Europe:

- **Docetaxel**
- **Nintedanib + docetaxel (adenocarcinoma)**
- **Pemetrexed (adenocarcinoma)**
- **Erlotinib**
- **Gefitinib (*EGFR* mutation)**
- **Crizotinib (*ALK* translocation)**

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

Adenocarcinoma: Second-Line Treatment Options



BSC, best supportive care; HR, hazard ratio

1. Shepherd FA, et al. *J Clin Oncol.* 2000;18(10):2095-2103. 2. Hanna N, et al. *J Clin Oncol.* 2004;22(9):1589-1597. 3. Scagliotti G, et al. *Oncologist.* 2009;14(3):253-263. 4. Shepherd FA, et al. *N Engl J Med.* 2005;353(2):123-132. 5. Wojtowicz-Praga S, et al. *Ann Oncol.* 2012;23(suppl 9): Abstract 1277P. 6. Reck M, et al. *J Clin Oncol.* 2013;(suppl): Abstract LBA8011. 7. Reck M, et al. *Lancet Oncol.* 2014;15(2):143-155.

Second-Line Therapy of NSCLC: Novel Therapeutic Approaches

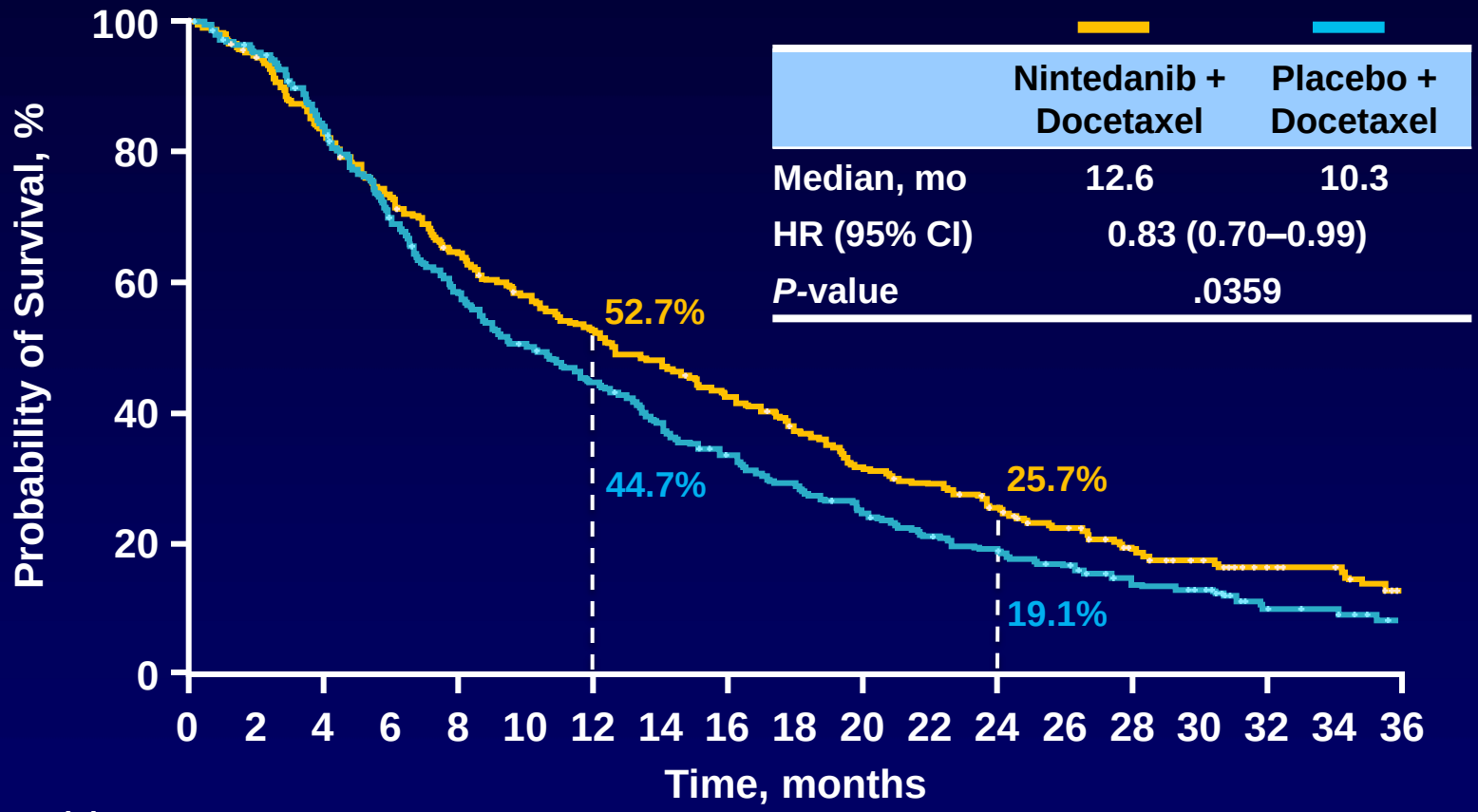
Drug	Target	Phase	
Nintedanib	Inhibitor of VEGFR1, 2, 3; PDGFRα, β; FGFR1, 2, 3; FLT3; RET, Src	III	Approved in EU
Pazopanib	Inhibitor of VEGFR1, 2, 3; PDGFRα, β; c-KIT	II/III	
Ramucirumab	VEGFR2- Antibody	III	Approved in US

Drug (Immunotherapy)	Target	Phase
Nivolumab	PD-1 Checkpoint-Inhibitor	III
Ipilimumab	Anti-CTLA-4 Antibody	III
MPDL3280A	PD-1 Checkpoint-Inhibitor	II/III
MK-3475	Anti-PD-1 Antibody	II/III
BMS-936559	Anti-PD-L1 Antibody	I

https://clinicaltrials.gov

LUME-LUNG 1: Positive OS in Patients With Adenocarcinoma Histology (Key Secondary Endpoint)

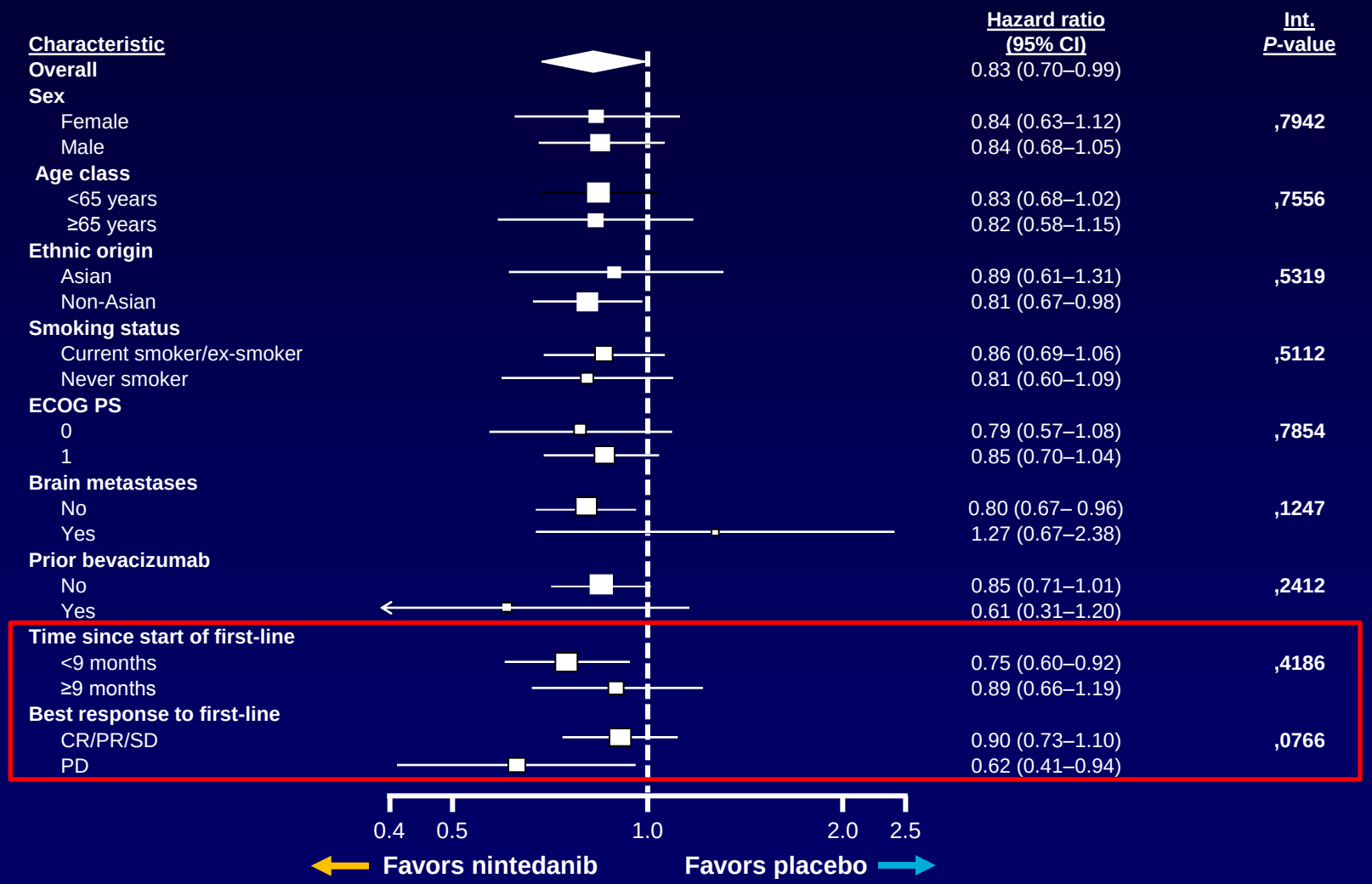
Patients with adenocarcinoma histology



Reck M, et al. *Lancet Oncol*. 2014;15(2):143-155.

LUME-LUNG 1: Subgroup Analyses on Survival Patients With Adenocarcinoma Histology

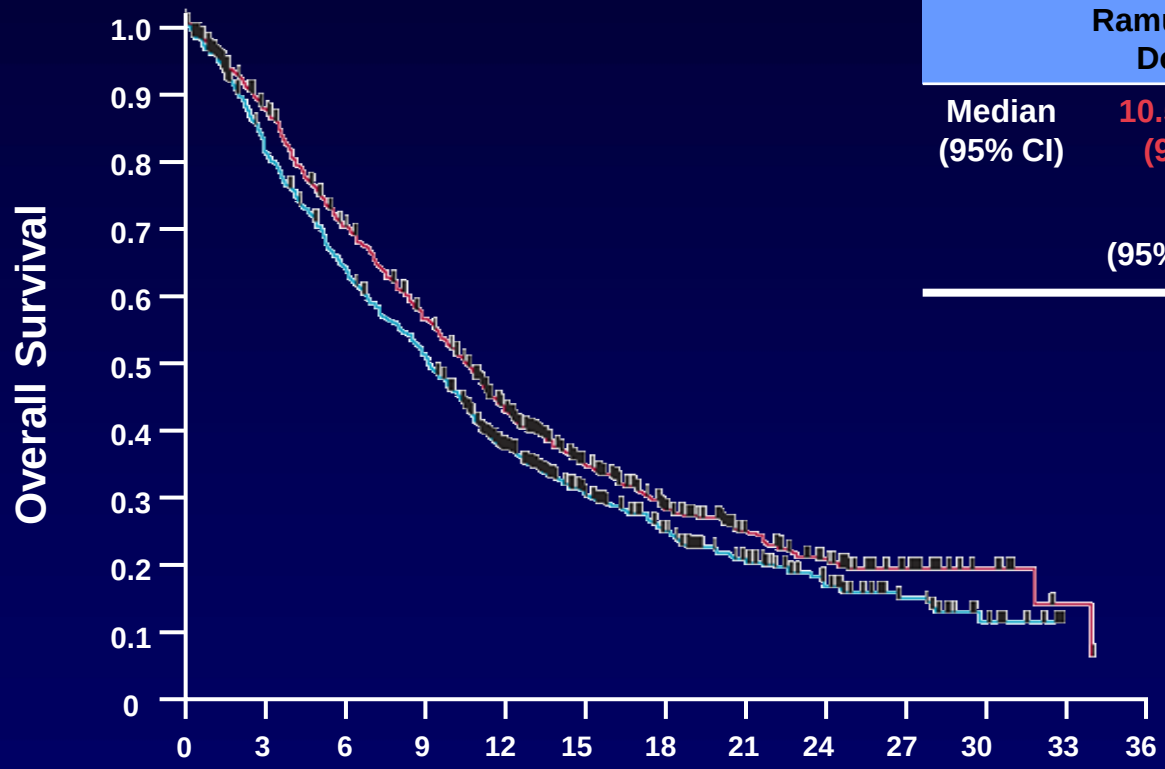
Patients with adenocarcinoma histology



Reck M, et al. *Lancet Oncol*. 2014;15(2):143-155.

REVEL Trial: Overall Survival

All Patients (Primary Endpoint)



	Ramucirumab + Docetaxel	Placebo + Docetaxel
Median (95% CI)	10.5 months (9.5-11.2)	9.1 months (8.4-10.0)

Stratified HR 0.86 (95% CI 0.75-0.98); *P* = .023

Number at risk													
Ramucirumab + docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo + docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

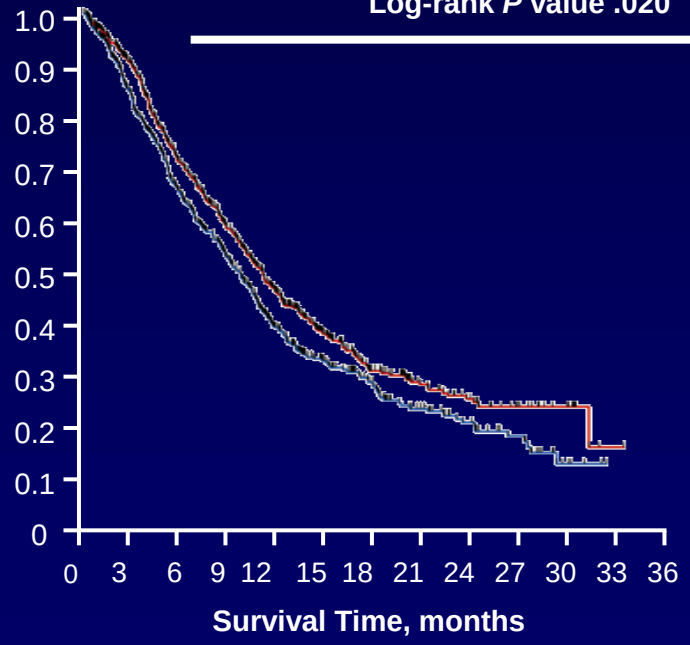
Garon EB, et al. *Lancet.* 2014;384(9944):665-673.

REVEL Trial: Overall Survival

Nonsquamous histology

	Ramucirumab + Docetaxel	Placebo + Docetaxel
Median (95% CI)	11.1 (9.9,12.3)	9.7 (8.5,10.6)

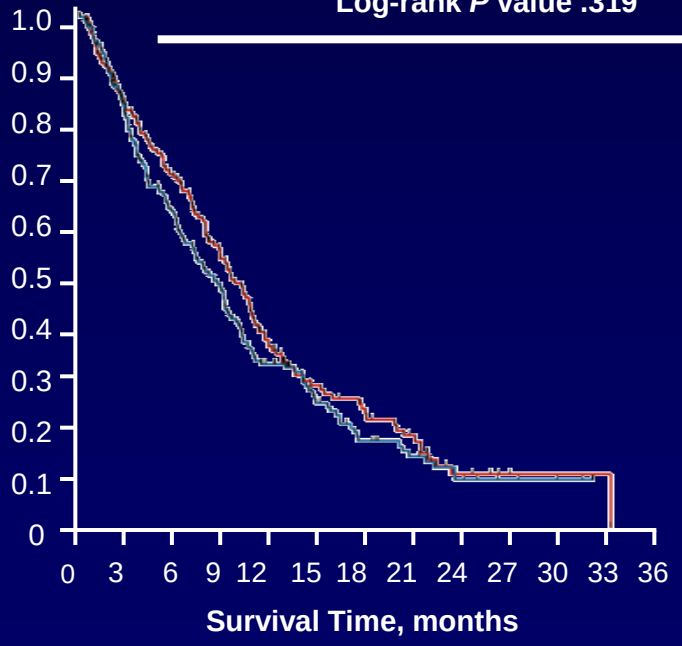
HR (95% CI) = 0.830 (0.708,0.972)
Log-rank *P* value .020



Squamous histology

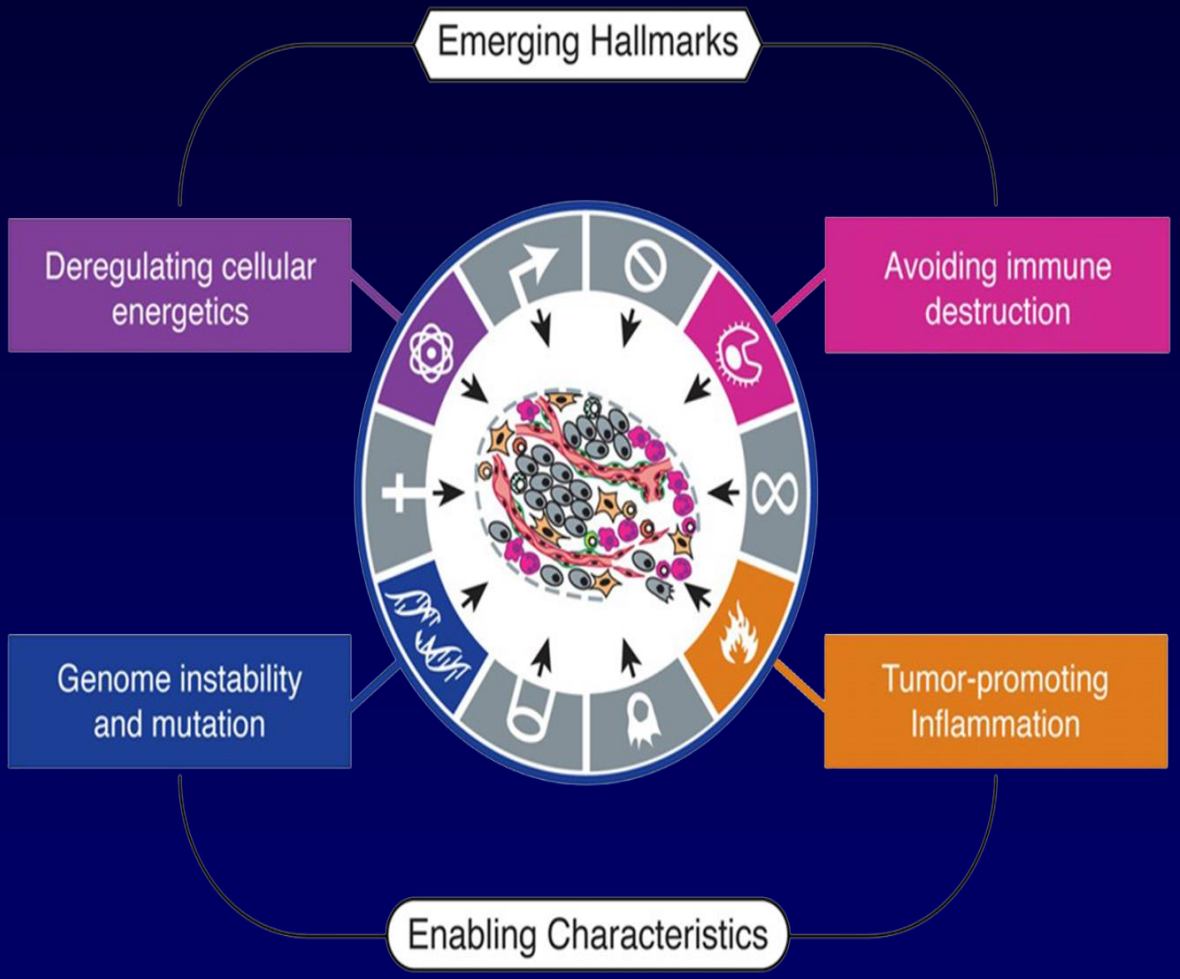
	Ramucirumab + Docetaxel	Placebo + Docetaxel
Median (95% CI)	9.5 (8.0,10.8)	8.2 (6.3, 9.4)

HR (95% CI) = 0.883 (0.692,1.127)
Log-rank *P* value .319



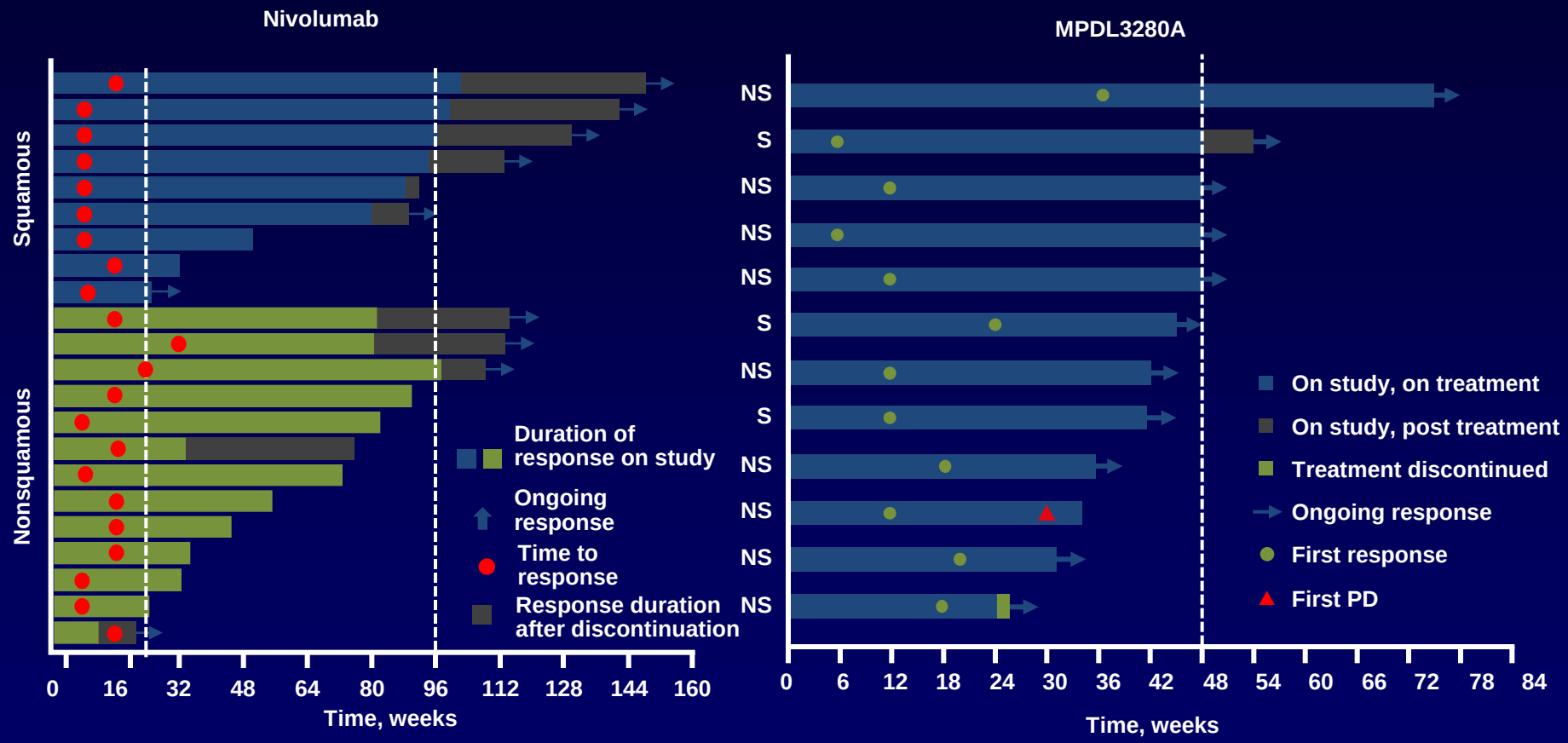
Garon EB, et al. *Lancet.* 2014;384(9944):665-673.

Immuno-Oncology and “Hallmarks of Cancer”



Hanahan D, et al. *Cell.* 2011;144(5):646-674.

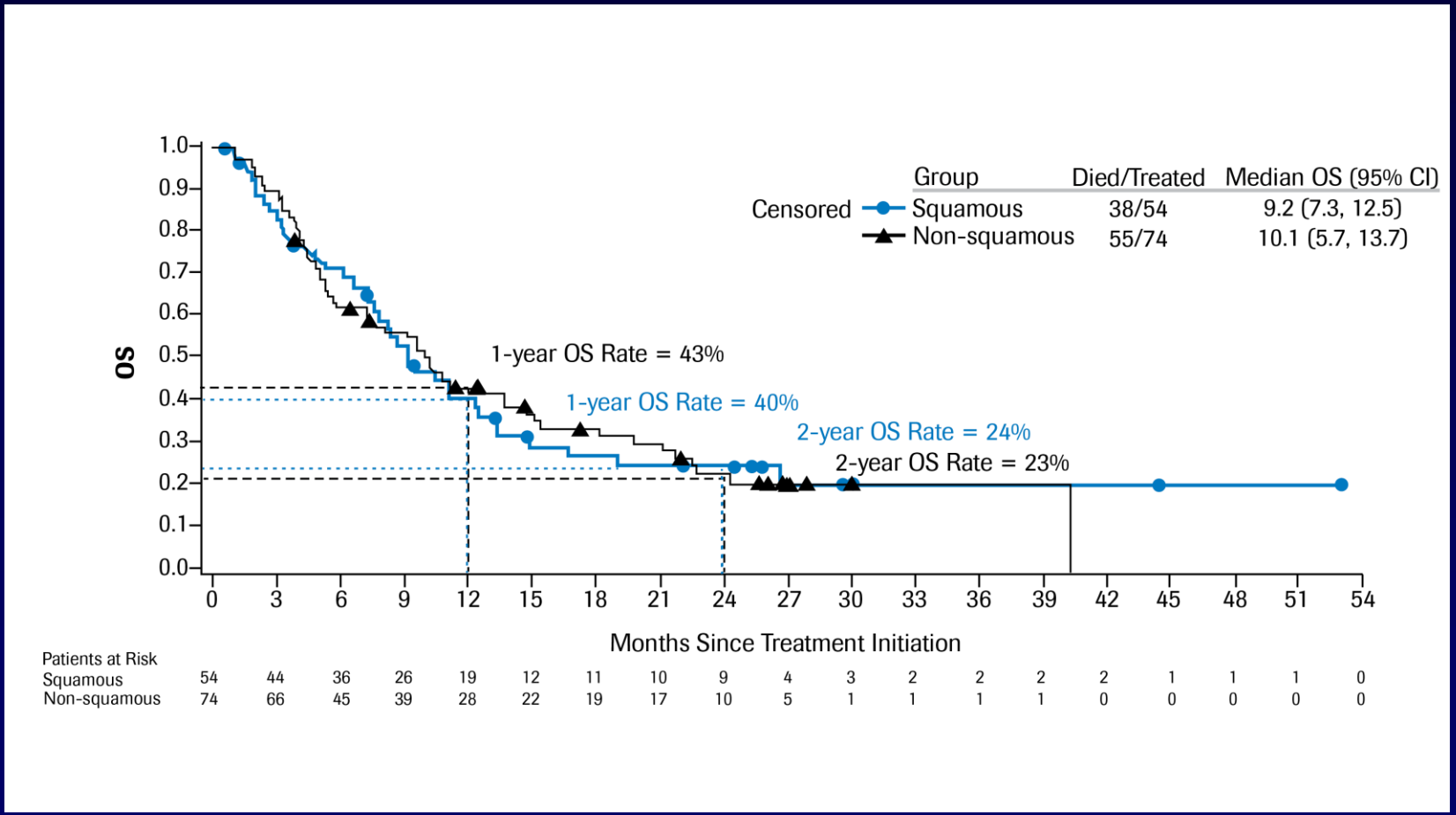
Impact of Histology: Efficacy of Anti-PD1/PD-L1 Antibodies



Brahmer JR, et al. *J Thorac Oncol.* 2013;8(Suppl 2): Abstract: MO18.03. Horn L, et al. *J Thorac Oncol.* 2013;8(Suppl 2): Abstract: MO18.01.

Overall Survival by Histology in Patients With NSCLC
Nivolumab, Phase I Data

Previously treated patients with advanced NSCLC received IV nivolumab (1 mg/kg, 3 mg/kg, or 10 mg/kg)



Brahmer JR, et al. *J Clin Oncol.* 2014;32(5S): Abstract 8112.

Efficacy According to PDL-1 Immunohistochemistry

	Anti PD1		Anti PD-L 1	
	MK-3475 ORR n/N (%)	Nivolumab ORR n/N (%)	MEDI4736 ORR n/N (%)	MPDL3280A ORR n/N (%)
All patients	(21%)	22/129 (17.1%)	9/58 (16%)	12/53 (23%)
PD-L1 Status (evaluable pts)				
Positive	37/159 (23%)	5/31 (16%)	5/20 (25%)	8/26 (31%)
Negative	3/35 (9%)	4/32 (13%)	1/29 (3%)	4/20 (20%)

Key questions about PD-L1 assessment:

- Variability in tissue collection timing
- Cell sampling
- mAb used for staining
- IHC criteria

Horn L, et al. *J Thorac Oncol.* 2013;8(Suppl 2): Abstract MO18.01. Brahmer JR, et al. *J Thorac Oncol.* 2013;8 (Suppl2): Abstract MO1803. Antonia SJ, et al. *J Thorac Oncol.* 2013;8(Suppl 2): AbstractP2 11-034. Garon E, et al. *J Clin Oncol.* 2014;32(5S): Abstract 8020. Brahmer J, et al. *J Clin Oncol.* 2014;32(5S): Abstract 8021.

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/

How I Would Treat This Patient

Nonsquamous NSCLC stage IV, 63 years, PS1

History: Adjuvant Chemotherapy With Cisplatin/Vinorelbine

Routine Molecular Testing: EGFR, ALK, ROS1

Consider Clinical Study

Eligible for Bevacizumab?

Carboplatin + Paclitaxel + Bevacizumab for 4 Cycles Followed by Bevacizumab Maintenance

PD

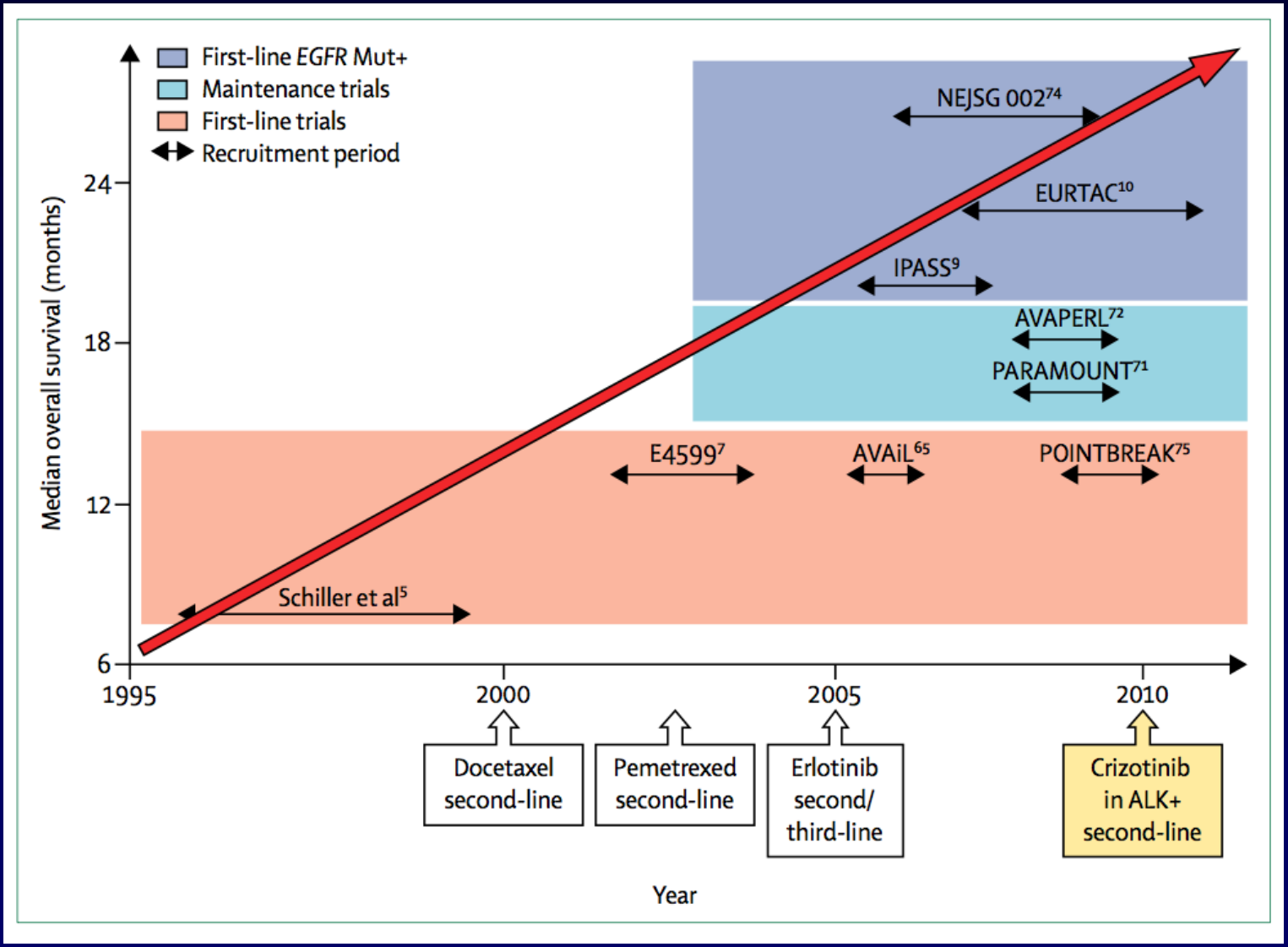
Pemetrexed

Docetaxel + Nintedanib/Ramucirumab

(Erlotinib)

Consider Clinical Study

OS in NSCLC: We Are Making Progress



Reck M, et al. *Lancet.* 2013;382(9893):709-719.