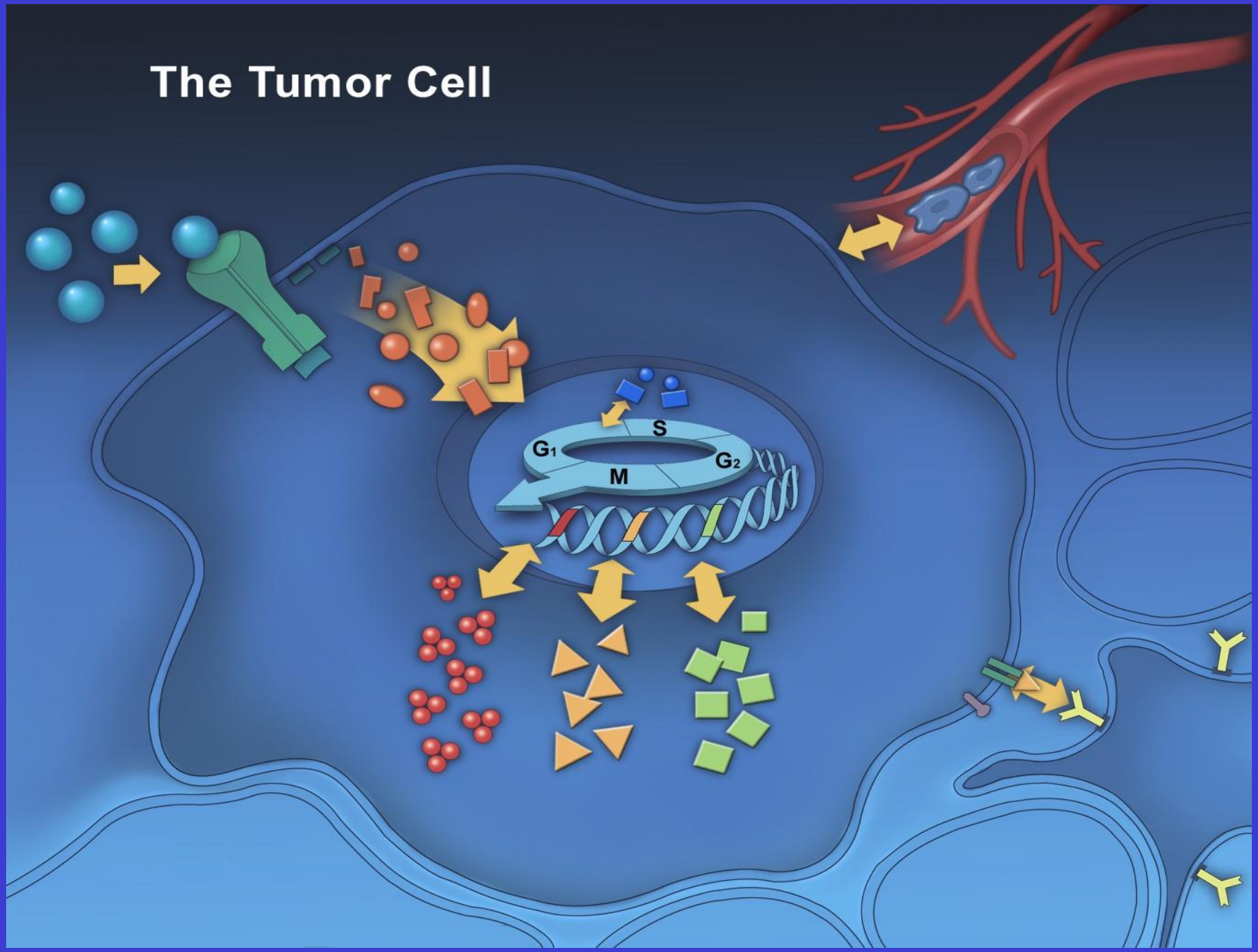
Anti-Angiogenic Therapy for the Treatment of Lung Cancer

ROSWELL PARK CANCER INSTITUTE

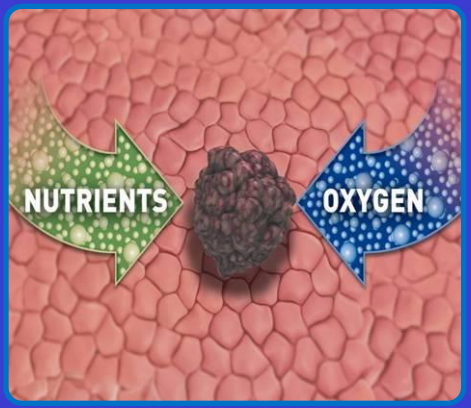
Alex A. Adjei

The Tumor Cell



The role of angiogenesis in cancer

- Angiogenesis
  - Occurs when new blood vessels feed malignant cells
    - Providing oxygen and nutrients
    - Promoting tumour growth
    - Allowing tumour cells to escape into the circulation, leading to metastases



Angiogenic Proteins

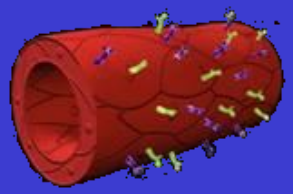
Ligands **Stimulation** **Cell types (proliferation, survival)**

VEGFs

FGFs

PDGFs

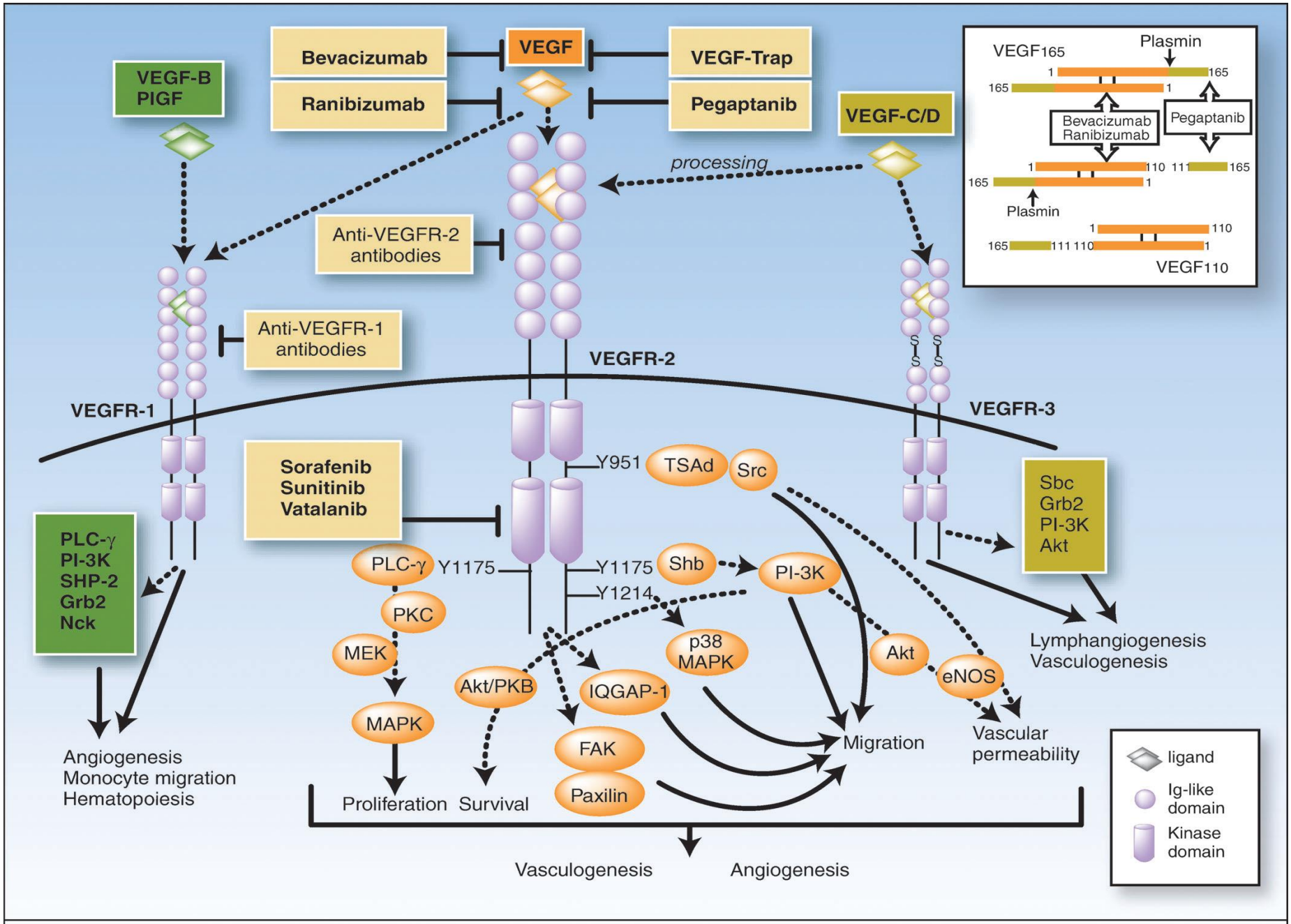
Endothelial cells (VEGFRs, FGFRs)



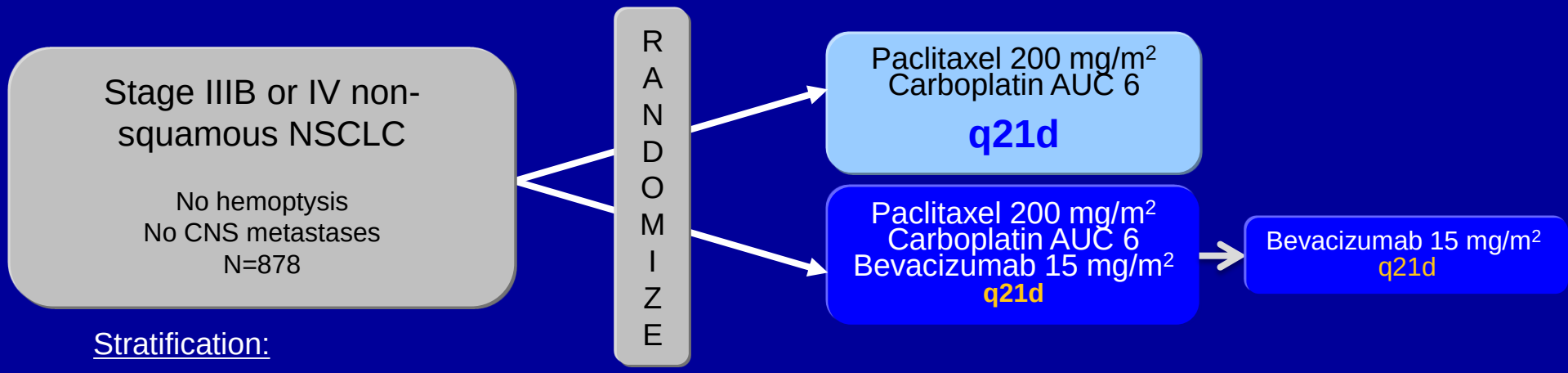
Pericytes (PDGFRs)

Smooth muscle cells (FGFRs, PDGFRs)

Simplified Cartoon of Angiogenic Signaling



ECOG 4599: phase III trial of bevacizumab in nonsquamous NSCLC



Stratification:

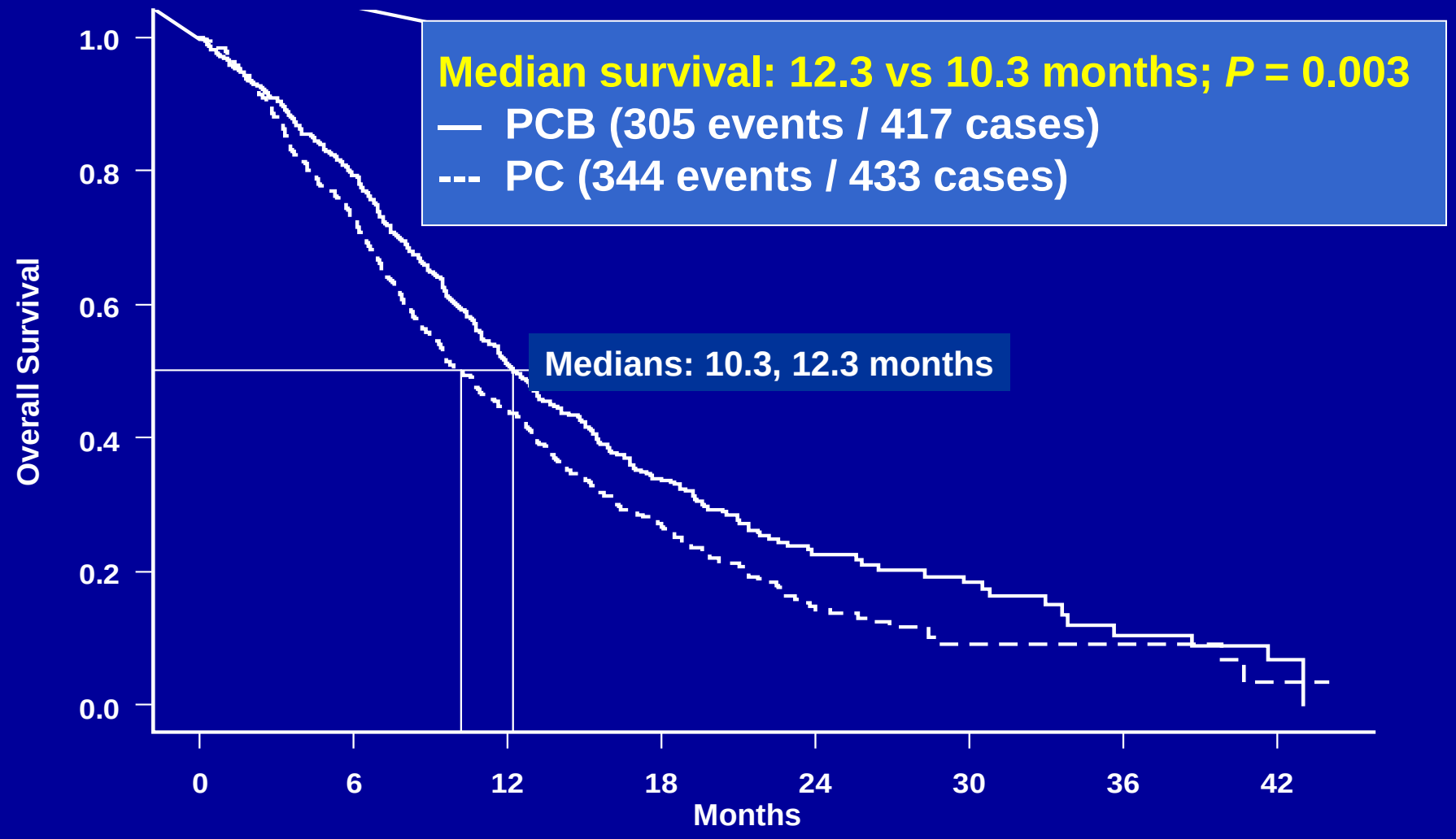
- RT vs. no RT
- Stage IIIB or IV vs. recurrent
- Wt loss <5% vs. ≥5%
- Measurable vs nonmeasurable

	PC	BPC	HR	P
	N = 433	N = 417		
Overall RR (%)	15	35		<.001
OS (months)*	10.3	12.3 (14.2 in adenoca)	0.79	.003
PFS (months)	4.5	6.2	0.66	<.001

* Primary endpoint

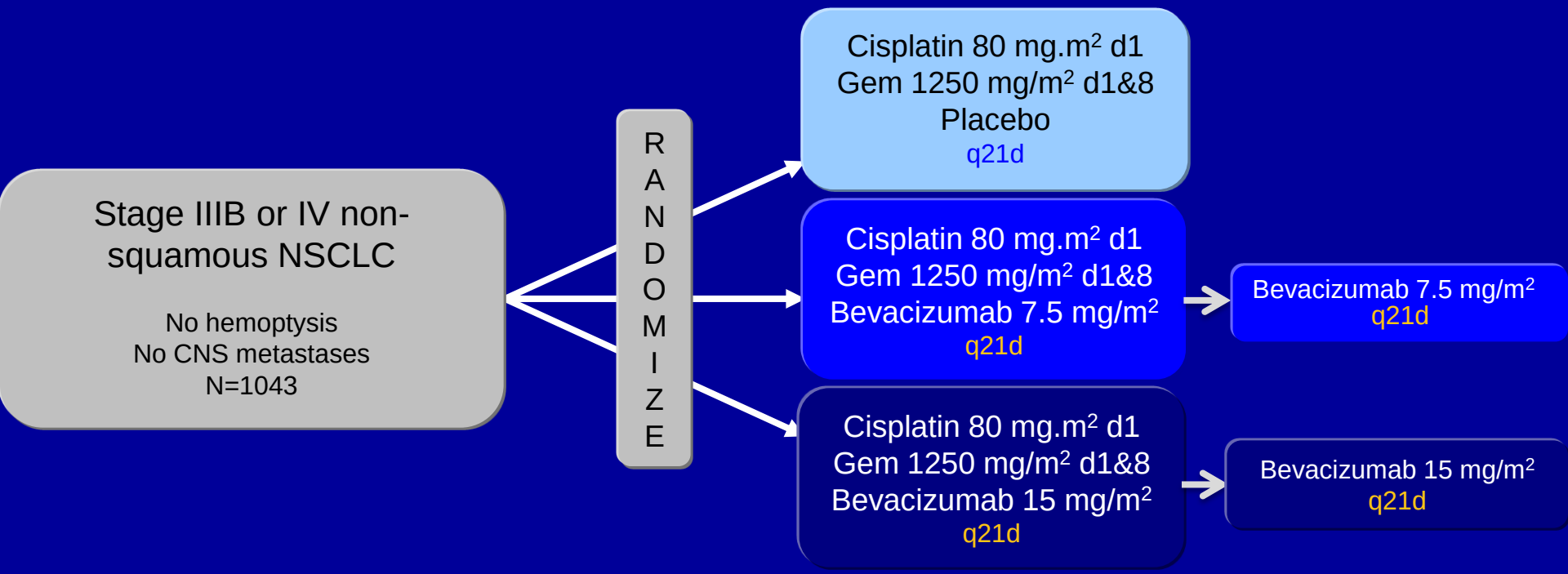
Sandler et al. *N Engl J Med*, 355:2542, 2006.

ECOG 4599: phase III trial of bevacizumab in nonsquamous NSCLC



Sandler et al. *N Engl J Med*. 2006;355(24):2542-2550.

AVAiL (Avastin in Lung Cancer) study

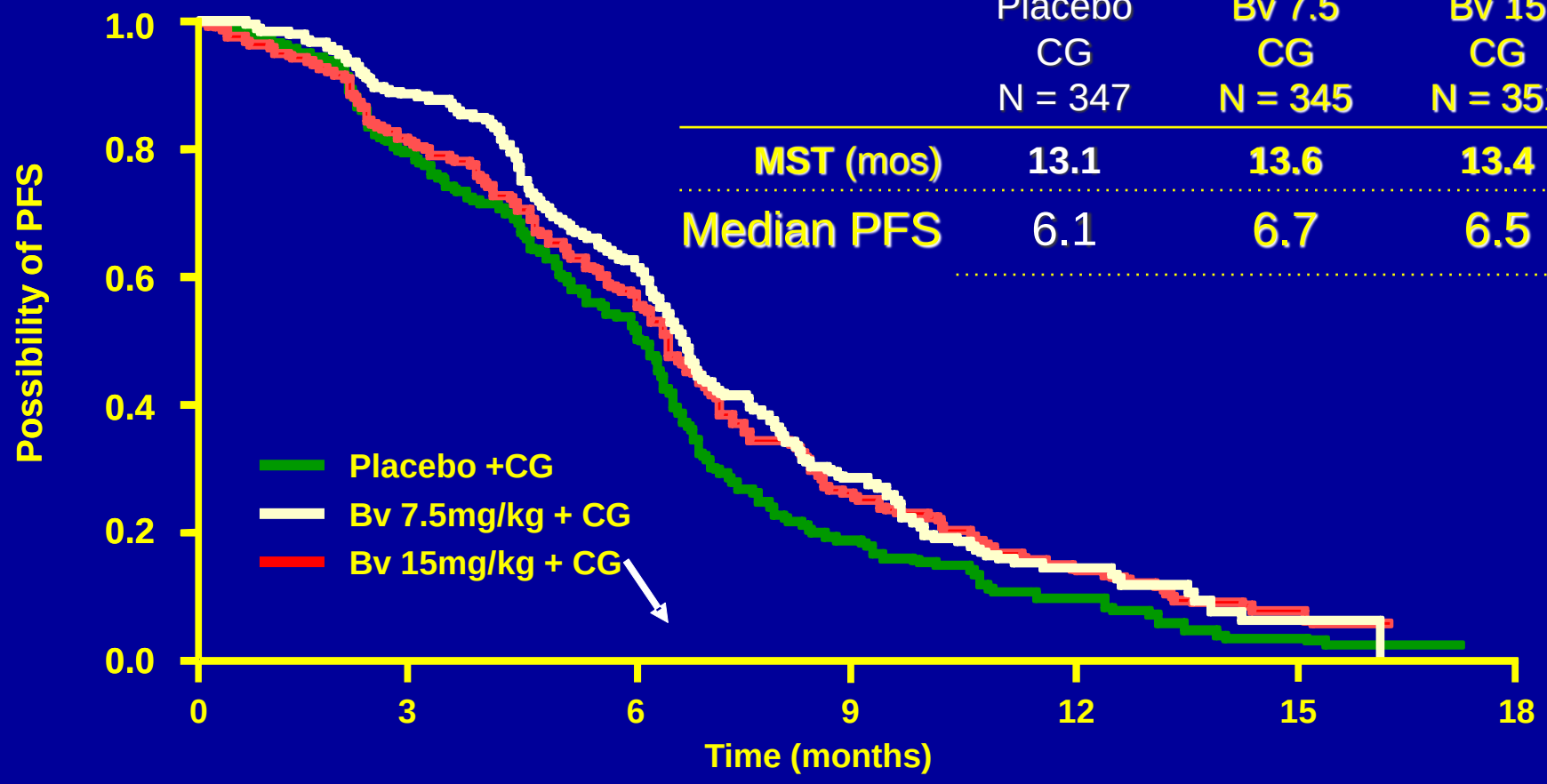


	GC+ placebo	+ Bevacizumab 7.5			+ Bevacizumab 15		
	N = 347	N = 345	HR	p-value	N = 351	HR	p-value
PFS (mos)*	6.1	6.7	0.75	.0003	6.5	0.85	.046
Response (%)	21.6	37.8		<.0001	34.6		.0002
OS (mo)	13.1	13.6	0.93	.42	13.4	1.03	.76

* Primary endpoint

Reck et al. *JCO*, 27(8):1227. 2009. Reck et al. *Ann Oncol*, 21(9):1804. 2010.

AVAiL (Avastin in Lung Cancer) study



	Placebo CG N = 347	Bv 7.5 CG N = 345	Bv 15 CG N = 351
MST (mos)	13.1	13.6	13.4
Median PFS	6.1	6.7	6.5

Reck et al. *JCO*, 27(8):1227. 2009. Reck et al. *Ann Oncol*, 21(9):1804. 2010.

PointBreak: Study Design

- Randomized, open-label, Phase III superiority study conducted in US
- Pemetrexed 500 mg/m^2; Carboplatin AUC 6; Bevacizumab 15 mg/kg
- Paclitaxel 200 mg/m^2; Carboplatin AUC 6; Bevacizumab 15 mg/kg

Inclusion:
- No prior systemic therapy for lung cancer
- PS 0/1
- Stage IIIB-IV NS-NSCLC
- Stable, treated brain metastasis

Exclusion:
- Peripheral neuropathy ≥ Grade 1
- Uncontrolled pleural effusions

R 1:1

Induction Phase q21d, 4 cycles

Pemetrexed (folic acid & vitamin B_{12}) **+ Carboplatin + Bevacizumab**

N=472

Paclitaxel + Carboplatin + Bevacizumab

N=467

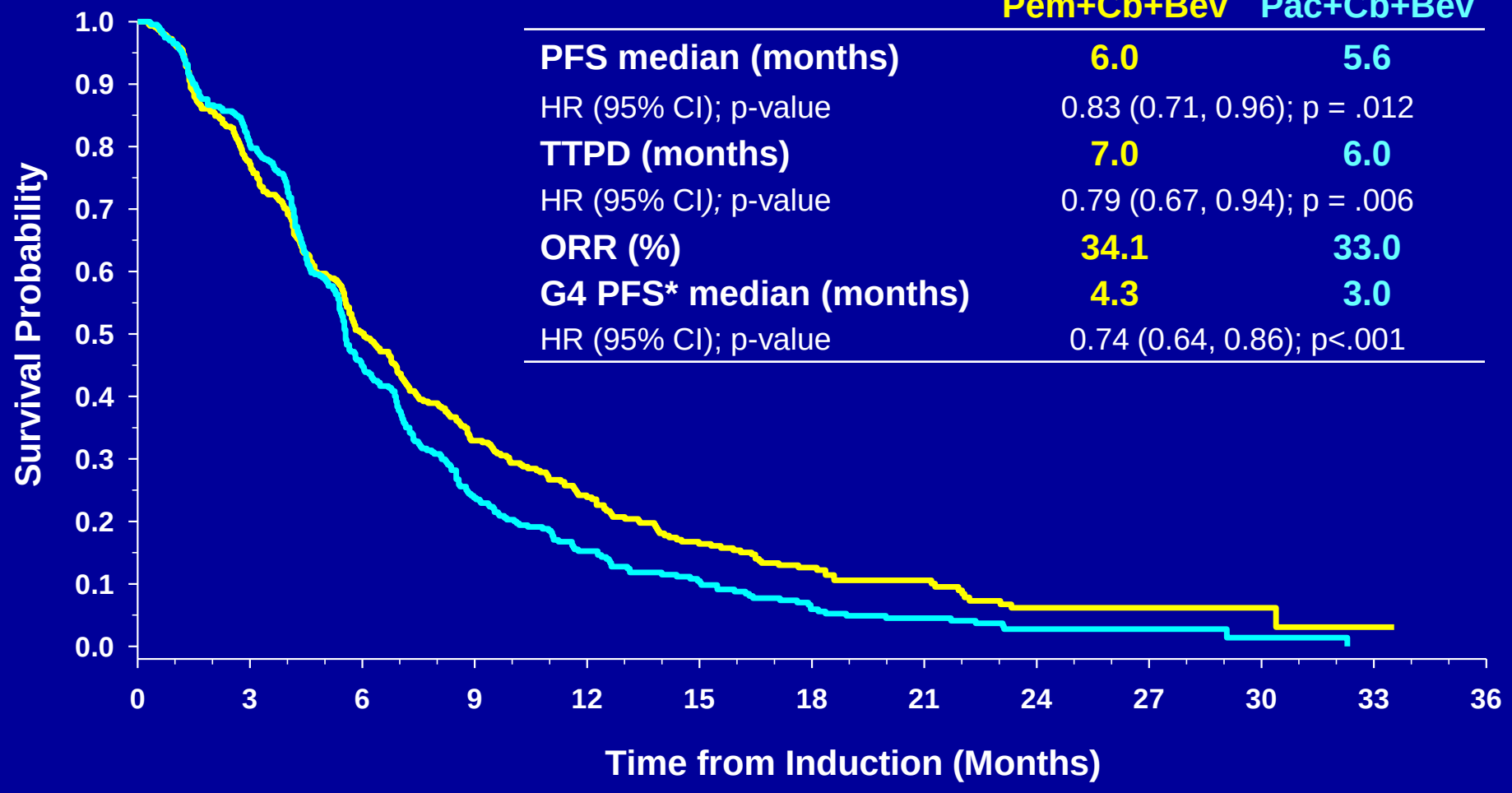
Maintenance Phase q21d until PD

Pemetrexed (folic acid & vitamin B_{12}) **+ Bevacizumab**

Bevacizumab

Stratified for: PS (0 vs. 1); sex (M vs. F); disease stage (IIIB vs. IV); measurable vs. nonmeasurable disease

PointBreak: Kaplan-Meier (KM) PFS from Randomization (ITT)



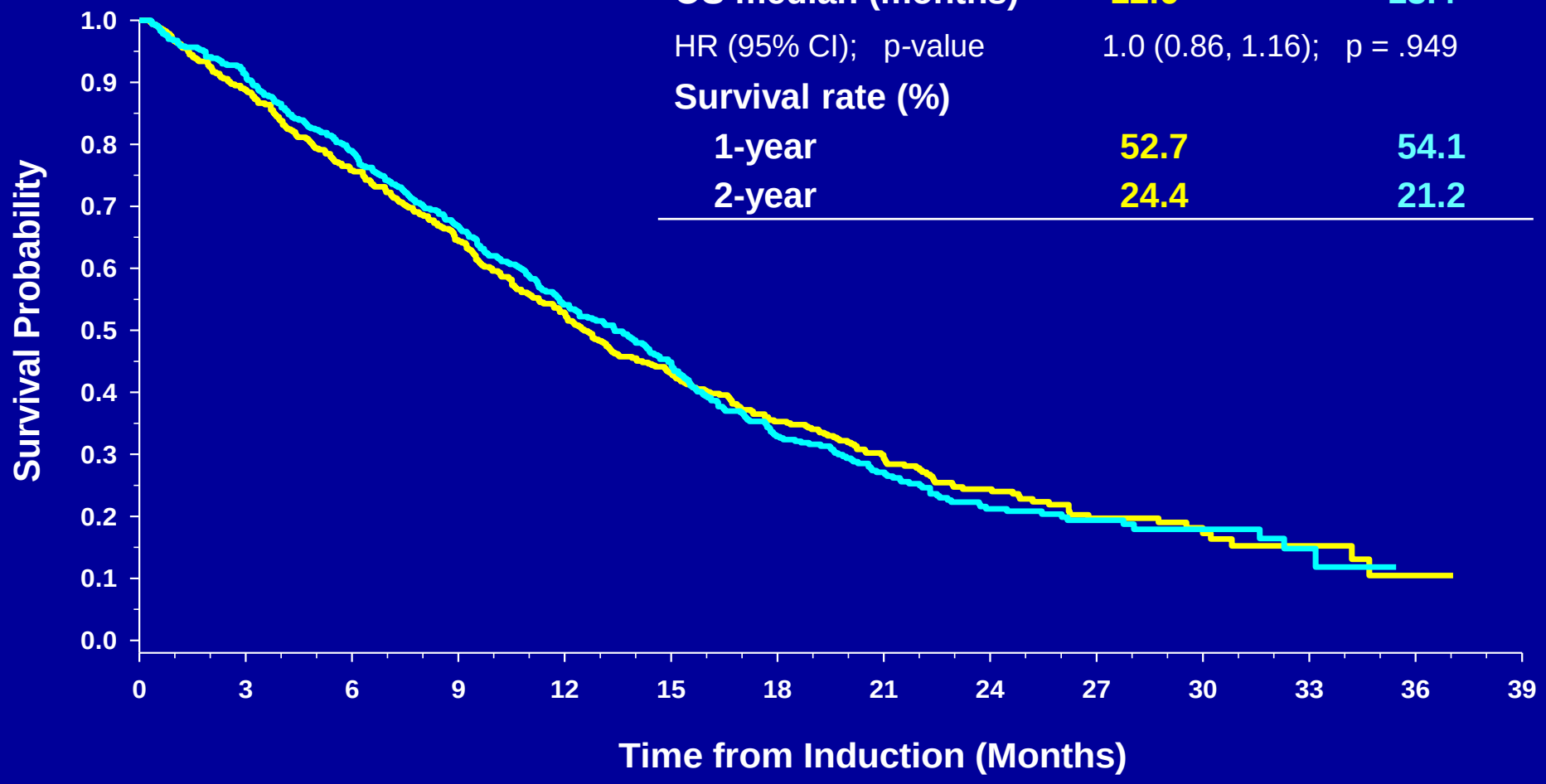
	Pem+Cb+Bev	Pac+Cb+Bev
PFS median (months)	**6.0**	**5.6**
HR (95% CI); p-value	0.83 (0.71, 0.96); p = .012	
TTPD (months)	**7.0**	**6.0**
HR (95% CI); p-value	0.79 (0.67, 0.94); p = .006	
ORR (%)	**34.1**	**33.0**
G4 PFS* median (months)	**4.3**	**3.0**
HR (95% CI); p-value	0.74 (0.64, 0.86); p<.001	

Censoring rate for Pem+Cb+Bev was 26.9; for Pac+Cb+Bev was 23.3; *Exploratory analysis

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

PointBreak: KM OS from Randomization (ITT)

	Pem+Cb+Bev	Pac+Cb+Bev
OS median (months)	**12.6**	**13.4**
HR (95% CI); p-value	1.0 (0.86, 1.16); p = .949	
Survival rate (%)		
1-year	**52.7**	**54.1**
2-year	**24.4**	**21.2**



Censoring rate for Pem+Cb+Bev was 27.8; for Pac+Cb+Bev was 27.2

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

PointBreak

- Both regimens were tolerable, but toxicity profiles differed
  - pemetrexed arm: more grade 3/4 anemia, thrombocytopenia and fatigue
  - paclitaxel arm: more neutropenia, febrile neutropenia, sensory neuropathy and alopecia
- Carboplatin/pemetrexed/bevacizumab combination is an acceptable alternative regimen
- Or is it?

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

PRONOUNCE: Study Design

- Randomized, open-label, Phase III superiority study conducted in US
- Pemetrexed 500 mg/m^2; Carboplatin AUC 6
- Paclitaxel 200 mg/m^2; Carboplatin AUC 6; Bevacizumab 15 mg/kg

Inclusion:
- No prior systemic therapy for lung cancer
- PS 0/1
- Stage IV NS-NSCLC
- Stable, treated brain metastasis

Exclusion:
- Hemoptysis
- Significant effusions

R 1:1

Induction Phase q21d, 4 cycles

Pemetrexed (folic acid & vitamin B_{12}) **+ Carboplatin**

N=179

Paclitaxel + Carboplatin + Bevacizumab

N=182

Maintenance Phase q21d until PD

Pemetrexed (folic acid & vitamin B_{12})

Bevacizumab

Stratified for: PS (0 vs. 1); sex (M vs. F); disease stage (M1a vs. M1b)

Zinner, et al. *Clin Lung Cancer*. 2010;11(5):352-357.

PRONOUNCE

	PemC	BPC	HR	P
	N = 179	N = 182		
Overall RR (%)	23.6	27.4		.414
OS (months)	10.5	11.7	1.07	.615
G4PFS (months)*	3.9	2.9	0.85	.176

- The primary endpoint of PFS without grade 4 toxicity (G4PFS) was not met for superiority of the pemetrexed arm.
- The 2-drug regimen was not better (or worse) than the 3-drug regimen.
- Different but tolerable toxicity profiles.
- Begging question: the additional clinical utility of bevacizumab in the era of contemporary pemetrexed-based chemotherapy for non-squamous NSCLC.

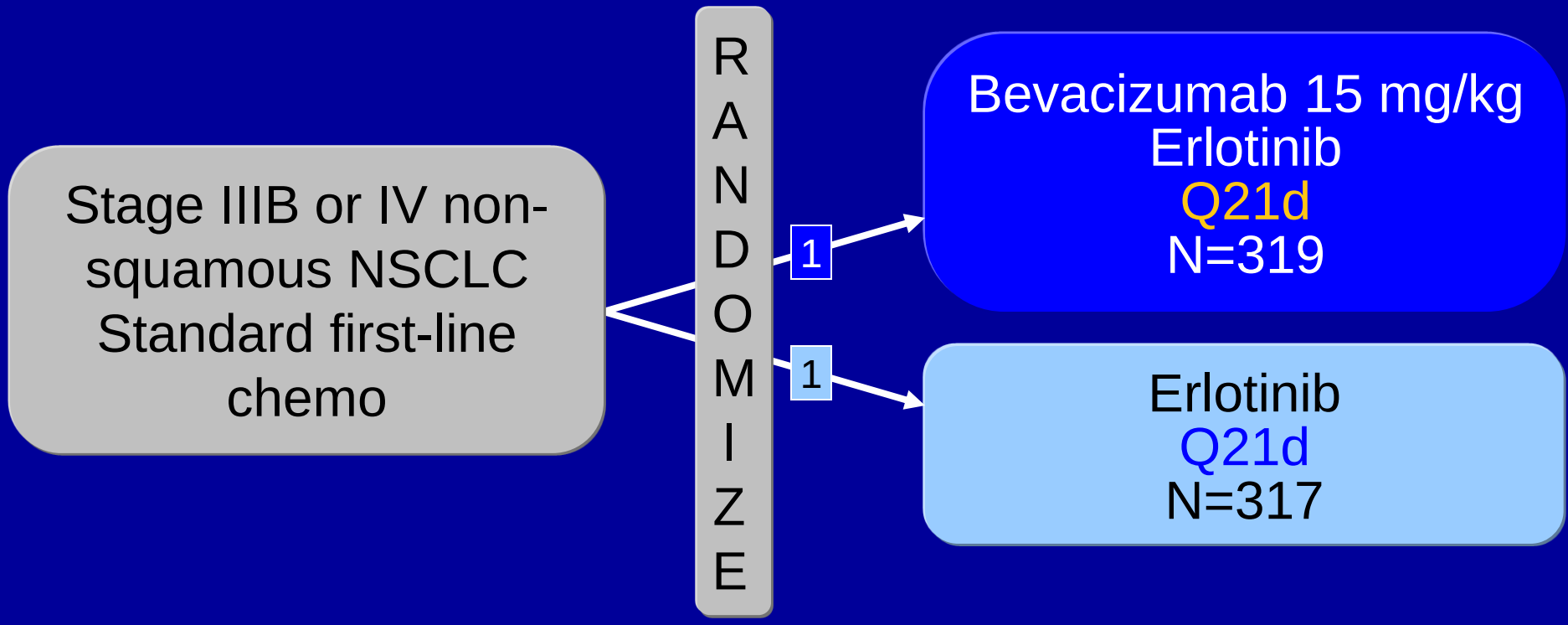
Zinner, et al. *J Clin Oncol*. 2013;31(suppl):LBA8003.

Some very simplified mathematical equations

- Carboplatin/Paclitaxel/Bevacizumab **>** Carboplatin/Paclitaxel (ECOG 4599)
- Carboplatin/Paclitaxel/Bevacizumab **≈** Carboplatin/Pemetrexed/Bevacizumab (PointBreak)
- Carboplatin/Paclitaxel/Bevacizumab **≈** Carboplatin/Pemetrexed (Pronounce)
- Carboplatin/Pemetrexed/Bevacizumab **> or ≈** Carboplatin/Pemetrexed?
- Will there ever be a head-to-head trial?

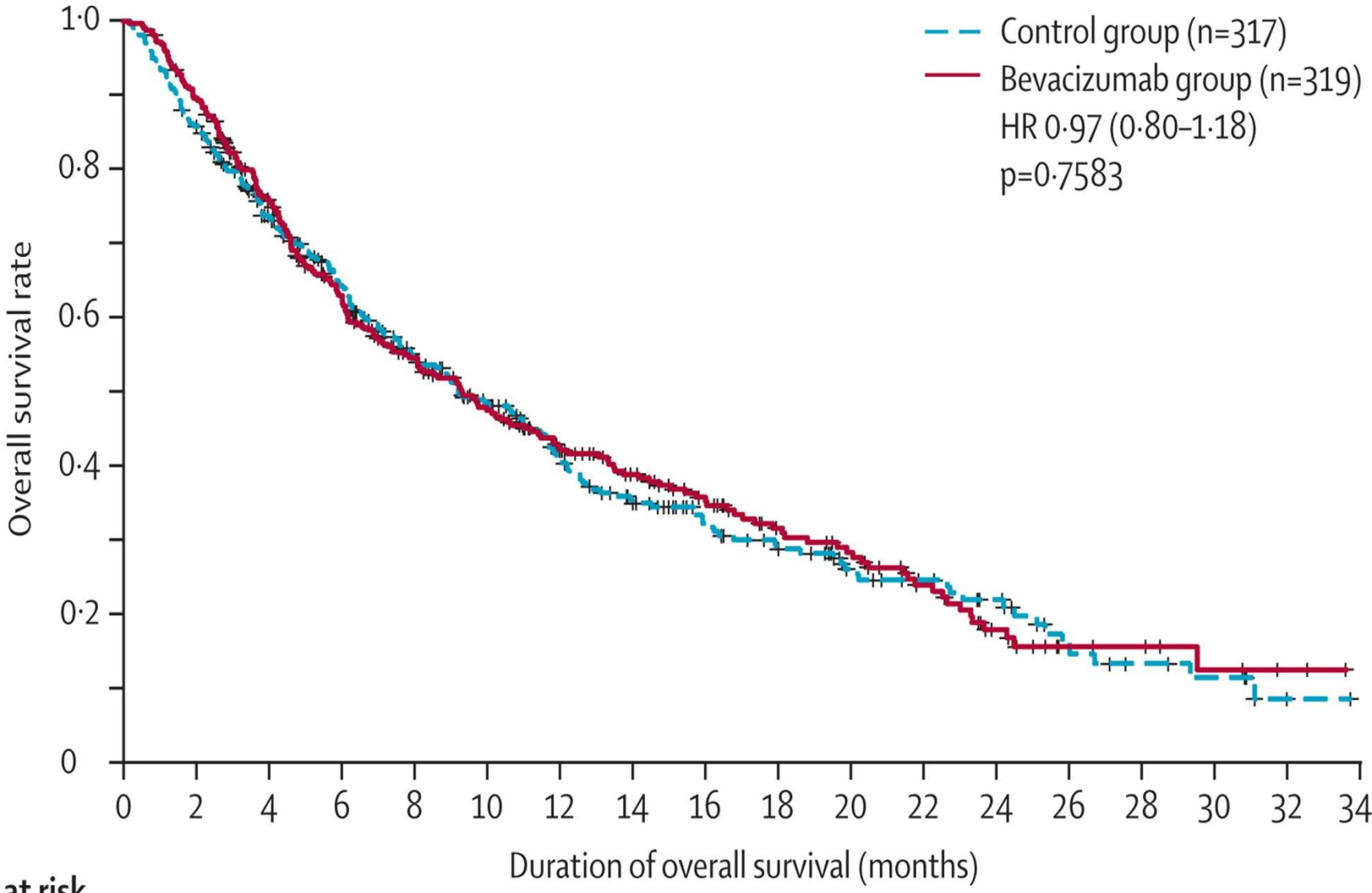
BeTa Trial

- **Primary endpoint: OS**



Herbst, **et al.** *Lancet*. 2011;377(9780):1846-1854.

BeTa Trial



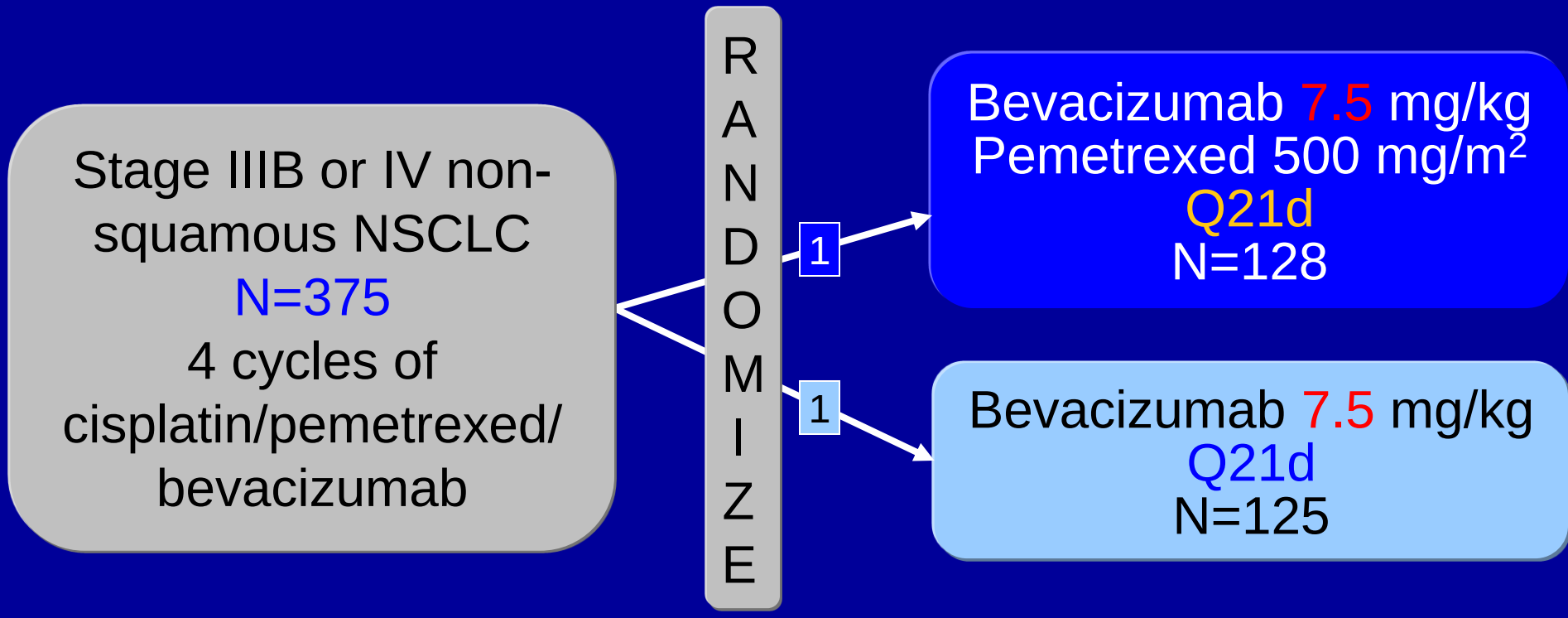
Number at risk

Control group	317	271	216	180	142	120	93	73	58	48	35	29	22	11	8	6	1	0
Bevacizumab group	319	284	223	174	143	118	97	81	65	49	42	29	16	8	7	4	2	0

Herbst, **et al.** *Lancet*. 2011;377(9780):1846-1854.

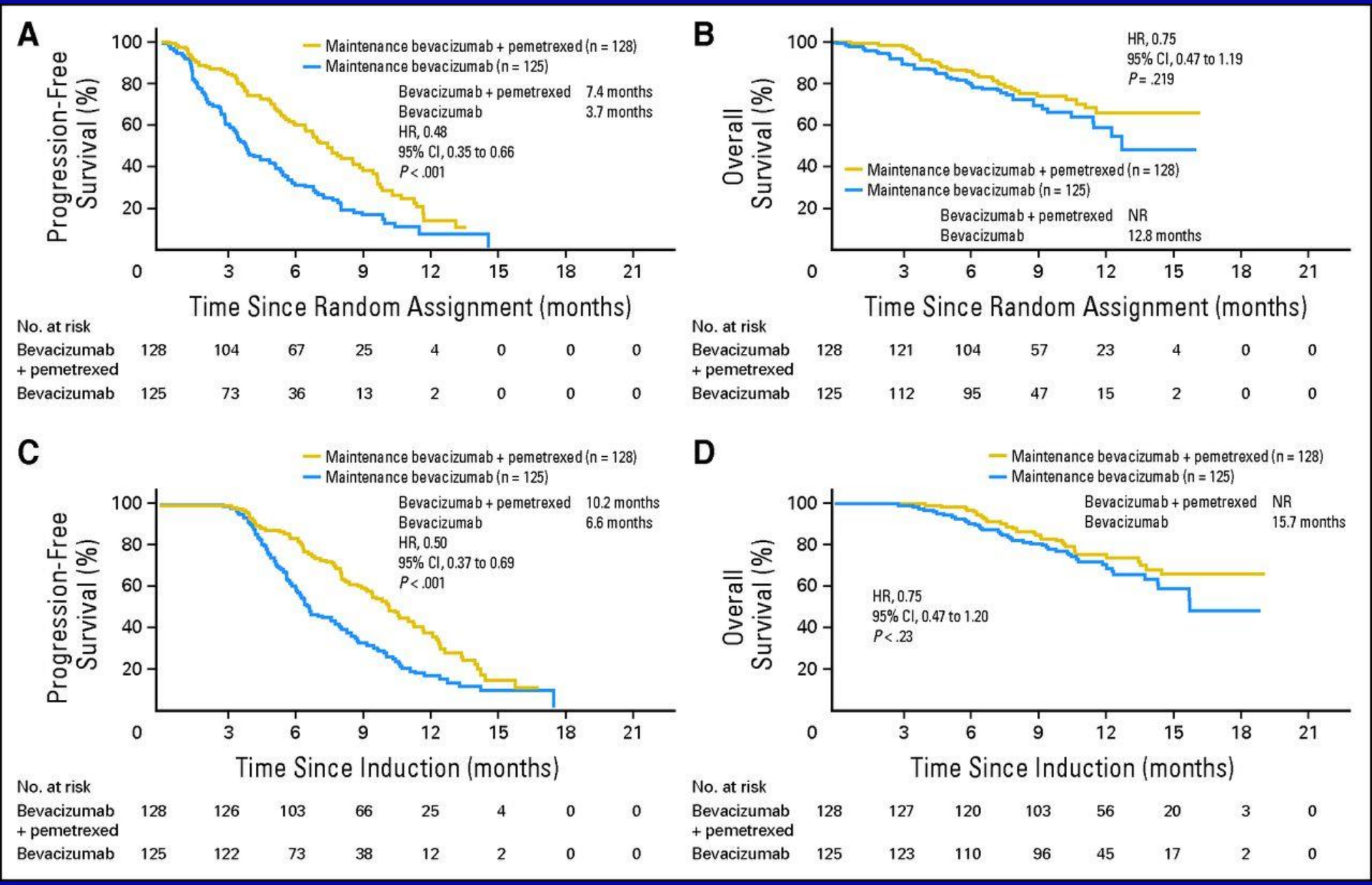
AVAPERL (MO22089)

- **Primary endpoint: PFS**



Barlesi, et al. *J Clin Oncol* .2013,31(24):3004-3011

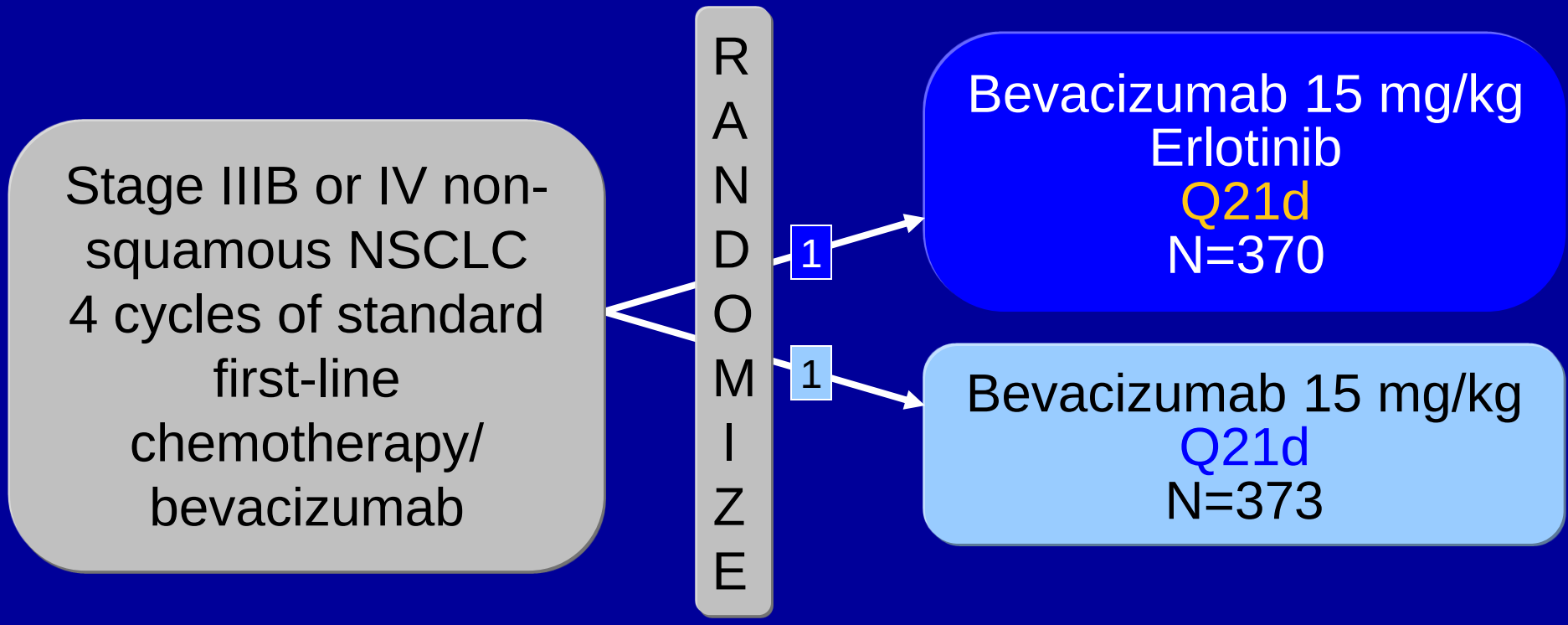
AVAPERL (MO22089)



Barlesi, et al. *J Clin Oncol* .2013,31(24):3004-3011

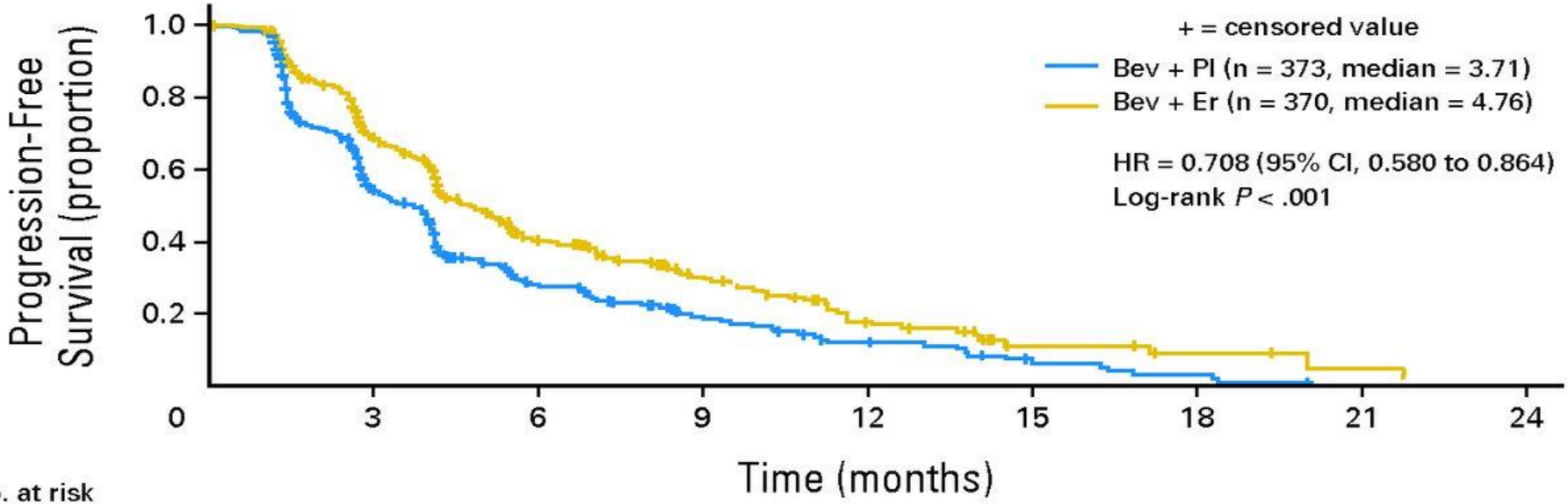
Avastin Tarceva Lung Adenocarcinoma Study (ATLAS)

- **Primary endpoint: PFS**



Johnson, et al. *J Clin Oncol*. 2013;31(31):3926-3934.

Avastin Tarceva Lung Adenocarcinoma Study (ATLAS)

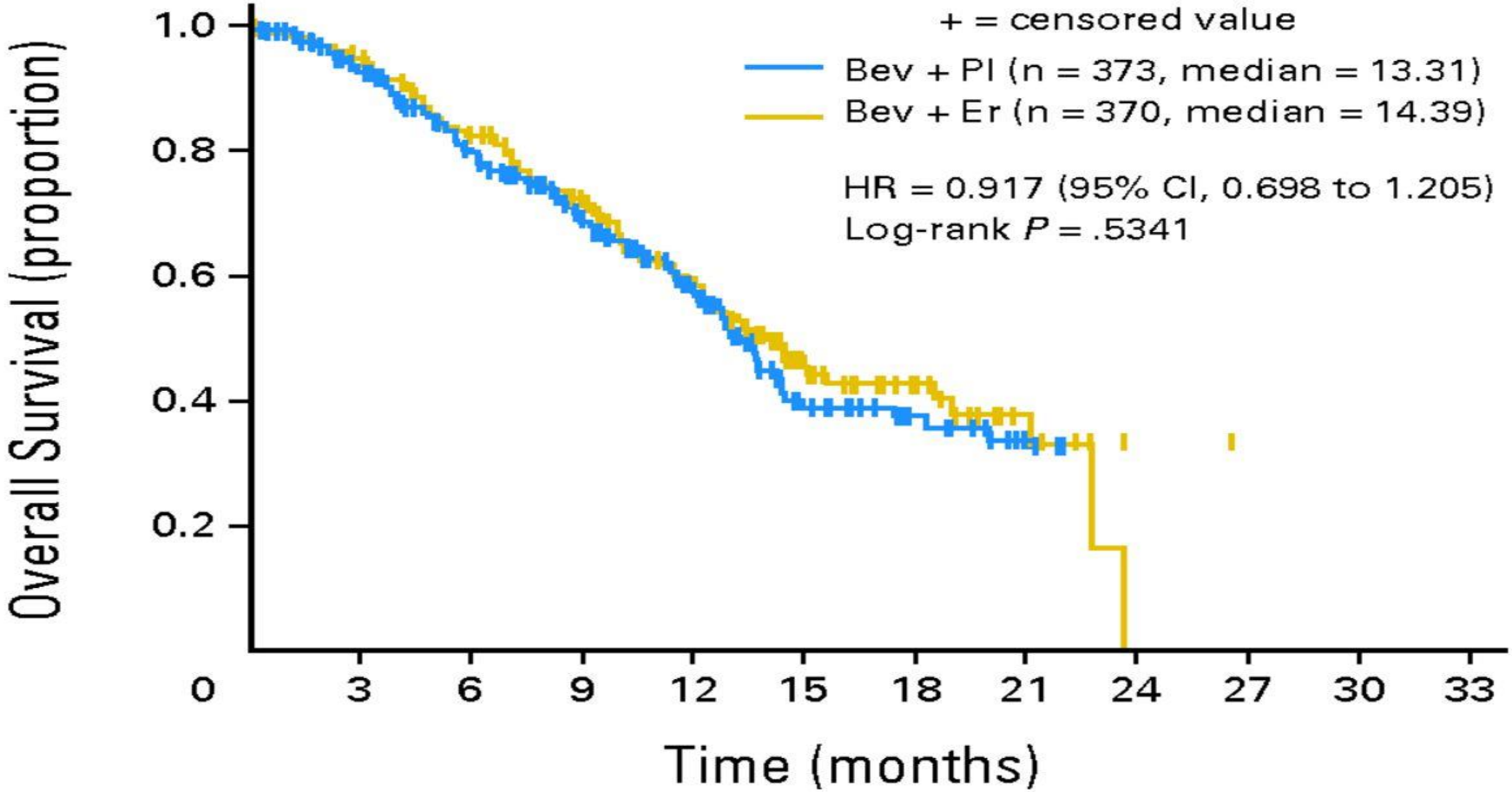


No. at risk									
Bev + Er	370	180	80	43	20	6	3	1	0
Bev + Pl	373	143	57	28	15	6	3	0	0

	Bevacizumab + Placebo (n = 373)		Bevacizumab + Erlotinib (n = 370)	
Time Since Random Allocation	Patients With Event	Kaplan–Meier Percent Event Free (Pointwise 95% CI)	Patients With Event	Kaplan–Meier Percent Event Free (Pointwise 95% CI)
3 months	138 (37.0%)	54.1 (48.2 to 59.6)	92 (24.9%)	68.4 (62.7 to 73.4)
6 months	200 (53.6%)	28.2 (22.7 to 33.9)	160 (43.2%)	40.2 (34.1 to 46.2)
9 months	216 (57.9%)	19.3 (14.3 to 24.9)	177 (47.8%)	30.2 (24.2 to 36.5)
12 months	226 (60.6%)	12.1 (7.8 to 17.5)	193 (52.2%)	17.8 (12.3 to 24.1)

Johnson, et al. *J Clin Oncol*. 2013;31(31):3926-3934.

Avastin Tarceva Lung Adenocarcinoma Study (ATLAS)

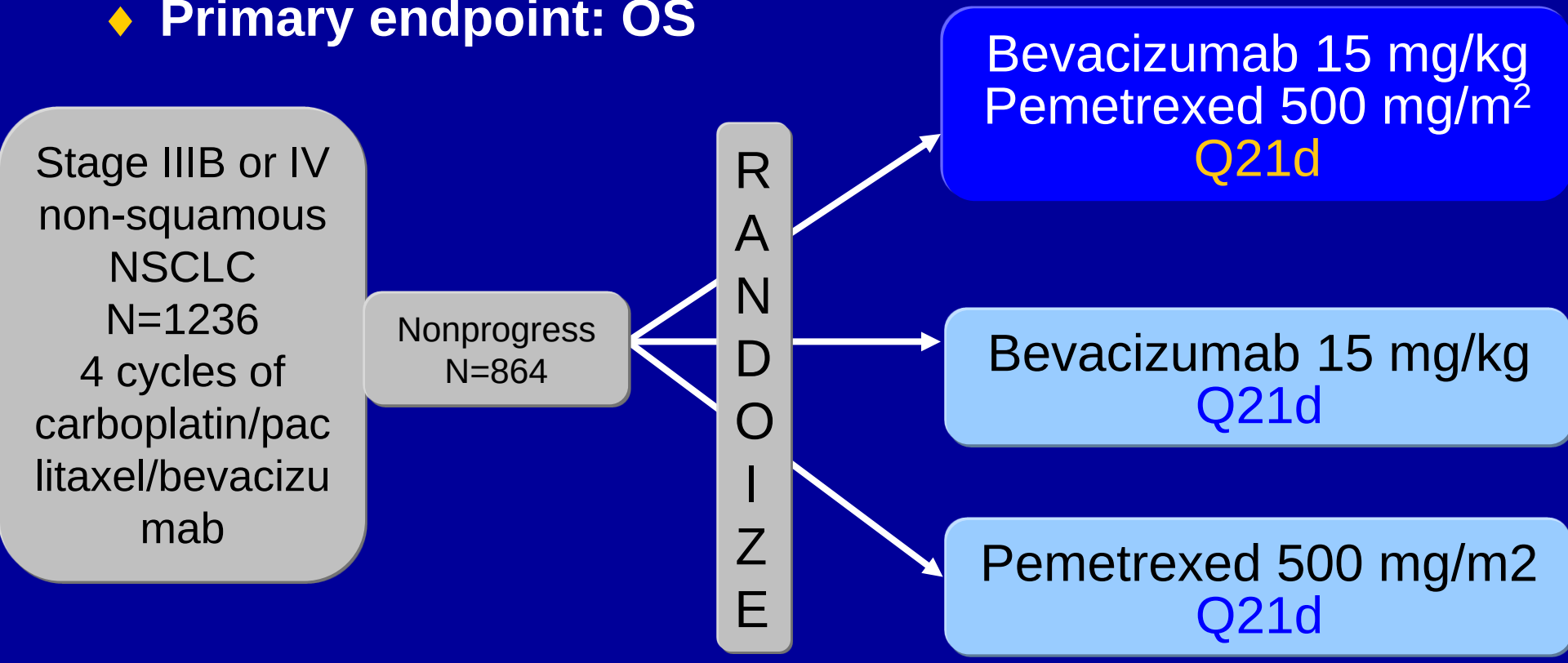


No. at risk												
Bev + Er	370	282	192	132	85	38	22	7	0	0	0	0
Bev + Pl	373	280	184	121	73	37	21	9	1	0	0	0

Johnson, et al. *J Clin Oncol*. 2013;31(31):3926-3934.

ECOG 5508

- **Primary endpoint: OS**



Early Stage Disease

Early Stage NSCLC

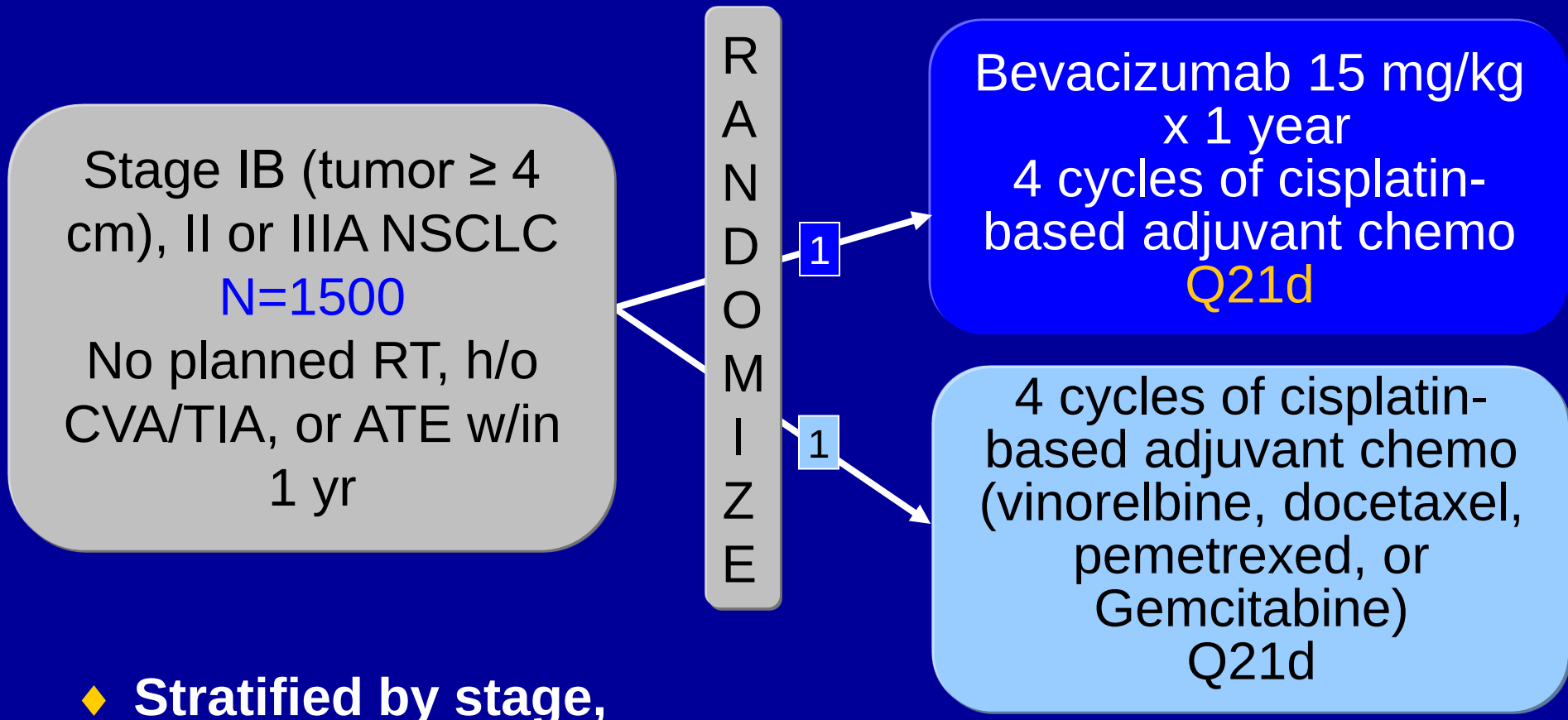
- Combined-modality treatment of stage III NSCLC
  - A phase I/II study: incorporating bevacizumab and erlotinib with a complex sequence of induction chemotherapy and then concurrent chemoradiotherapy followed by consolidation therapy
  - esophageal toxicity: 29% grade 3/4 esophagitis, with 1 grade 3 tracheoesophageal fistula
  - lack of efficacy signal

- SWOG S0533: closed due to poor accrual
  - cisplatin/etoposide/radiotherapy followed by consolidation docetaxel and the addition of bevacizumab in three cohorts of patients with inoperable locally advanced stage III NSCLC

Socinski, et al, *J Clin Oncol*. 2012 ;30(32):3953-3959.

ECOG 1505

- **Primary endpoint: OS**



- **Stratified by stage, Histology (sq vs ns), gender, And chemo type**

Other Anti-Angiogenic Antibodies

Aflibercept

- A recombinant fusion protein consisting of portions of human VEGFR extracellular domains fused to the Fc portion of human immunoglobulin G1
- Second-line setting
  - phase III Vital trial (N=913)
  - aflibercept/docetaxel vs docetaxel
  - primary endpoint: OS (10.1 vs 10.4 months)

- First-line setting
  - phase II single arm, open label, multicenter trial
  - aflibercept/cisplatin/pemetrexed
  - terminated: 3/42 confirmed and 2/42 suspected cases of reversible posterior leukoencephalopathy syndrome (RPLS)
  - RPLS may be related to declining renal function and/or hypertension associated with anti-angiogenic therapy.

Ramlau, et al. *J Clin Oncol*. 2012;30(29):3640-3647. Chen, et al. *Br J Cancer*. 2014;110(3):602-608.

Ramucirumab

- IMC-1121B: a fully human IgG1 mAb targeting VEGFR-2
- First-line setting
  - A randomized phase II study: platinum/pemetrexed ± ramucirumab (10 mg/kg every 21 days)
    - primary endpoint: PFS in nonsquamous (7.2 vs 5.6 months)
  - Another phase II study: carboplatin/paclitaxel/ramucirumab
    - RR 52%
    - PFS 7.8 months (ESMO 2012)
- Second-line setting
  - phase III REVEL study (NCT01168973): ramucirumab/docetaxel vs docetaxel

Doebele, et al. *J Thorac Oncol*. 2013;8(suppl 2):S290, abstr MO06.08. Camidge, et al. *J Clin Oncol*. 2010;28(
et al. *Clin Lung Cancer*. 2012;13(6):505-509.

Bavituximab

- Vascular disrupting agent (VDA): chimeric IgG1 mAb directed against the membrane phospholipid phosphatidylserine
- First-line setting
  - A randomized, open-label, phase II study: carboplatin/paclitaxel ± bavituximab
    - primary endpoint: RR (32% vs 31%)
- Second-line setting
  - A randomized, blinded, placebo-controlled phase II study: bavituximab/docetaxel vs docetaxel
    - primary endpoint: RR (17.1% vs 11.3%)
    - Median OS (11.7 vs 7.3 months)
  - Phase III SUNRISE trial (NCT01999673): bavituximab/docetaxel vs docetaxel

Gerber, et al. *Clin Cancer Res*. 2011;17(21):6888-6896. Dragnev, et al. *J Thorac Oncol*. 2012;7(suppl):abstr 180. Shtivelband, et al. *J Clin Oncol*. 2013;31(suppl):abstr 8095.

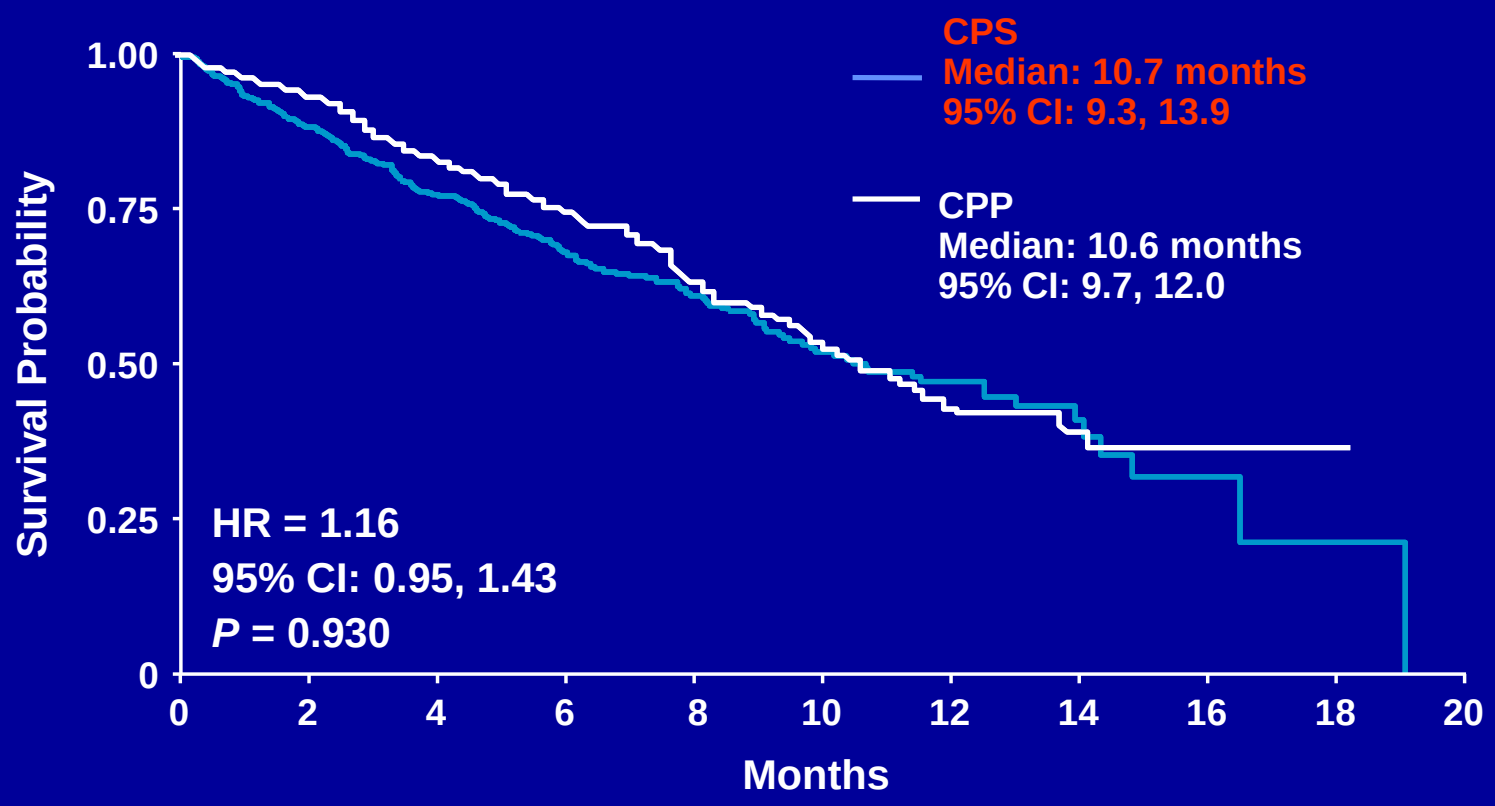
Efficacy results of phase III trials of multi-targeted TKIs in the treatment of advanced/metastatic NSCLC

Trials	Line of treatment	Treatment arms	Number of patients	RR (%)	PFS (months)	OS (months)
Sorafenib ESCAPE¶	First	carboplatin/paclitaxel	462	24	5.4	10.6*
		carboplatin/paclitaxel/ sorafenib (400 mg bid days 2-19) + maintenance sorafenib (400 mg bid)	464	27.4 (P=.101)	4.6 (HR, 0.99; P=.433)	10.7 (HR, 1.15; P=.915)
Sorafenib NExUS	First	cisplatin/gemcitabine	387	26	5.5	12.5*
		cisplatin/gemcitabine/ sorafenib (400 mg bid) + maintenance sorafenib	385	28 (P=.27)	6.0 (HR, 0.83; P=.008)	12.4 (HR, 0.98; P=.401)
Sorafenib MISSION	Third/fourth	placebo	353	0.9	1.4	8.3*
		Sorafenib (400 mg bid)	350	4.9 (P=.0009)	2.8 (HR, 0.61; P<.0001)	8.2 (HR, 0.99; P=.469)

* Primary endpoint. ¶ Terminated early due to futility analysis or toxicity.

Paz-Ares LG, et al. *J Clin Oncol*. 2012;30(25):3084-3092.

ESCAPE - Overall Survival (Intent-to-Treat Population)

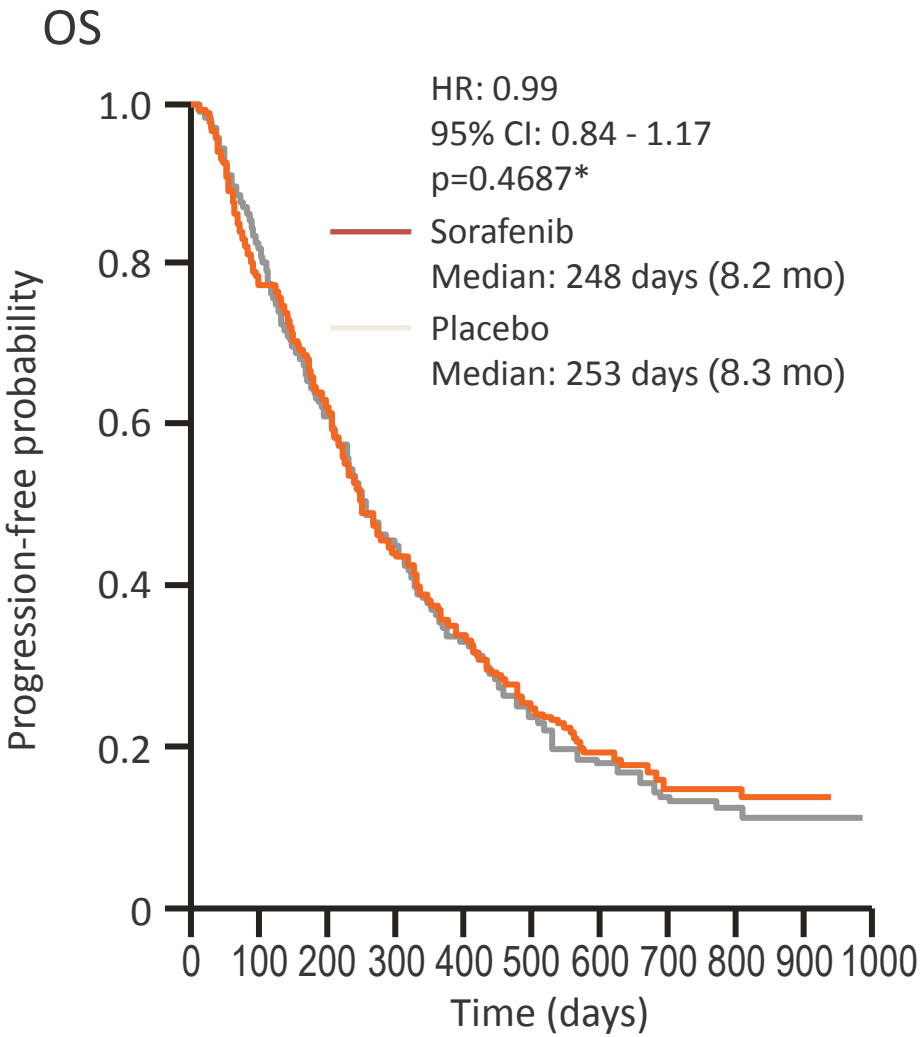


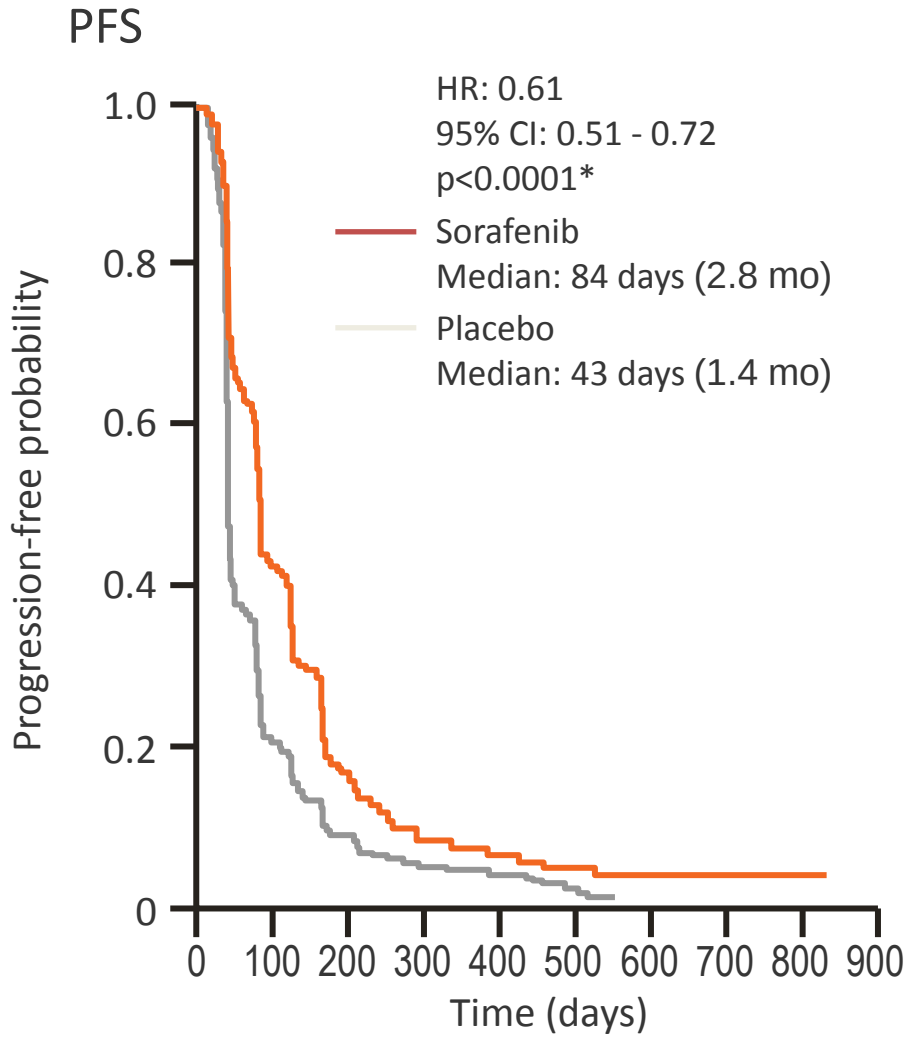
Patients at Risk

CPS	464	406	354	268	155	86	47	16	7	1
CPP	462	426	377	300	157	83	34	13	5	1

Scagliotti, et al. *J Clin Oncol*. 2010;28(11):1835-1842.

MISSION: PFS but not OS improved with sorafenib





[a]one-sided stratified log-rank test

Paz-Ares et al. Ann Oncol 2012;Vol (suppl; abstr LBA33_PR)

Efficacy results of phase III trials of multi-targeted TKIs in the treatment of advanced/metastatic NSCLC

Trials	Line of treatment	Treatment arms	Number of patients	RR (%)	PFS (months)	OS (months)
Sunitinib	Second/third	erlotinib	480	6.9	2	8.5*
		erlotinib + sunitinib (37.5 mg/day)	480	10.6 (P=.047)	3.6 (HR, 0.81; P=.002)	9.0 (HR, 0.92; P=.139)
Cediranib BR24¶ (only the phase II portion of this phase II/III study completed)	First	carboplatin/paclitaxel	125	16	5*	10.1
		carboplatin/paclitaxel/cediranib (30 mg/day)	126	38 (P<.0001)	5.6 (HR, 0.77; P=.13)	10.5 (HR, 0.78; P=.11)
Cediranib BR29¶	First	carboplatin/paclitaxel	153	34	5.5	12.1*
		carboplatin/paclitaxel/cediranib (20 mg/day) + maintenance cediranib	152	50 (P=.001)	5.5 (HR, 0.91; P=.49)	12.2 (HR, 0.94; P=.72)

* Primary endpoint. ¶ Terminated early due to futility analysis or toxicity. Paz-Ares, et al. *J Clin Oncol*. 2012 ;30(17):2070-2078. Goss, et al. *J Clin Oncol*. 2010;28(1):49-55. Laurie, et al. *Eur J Cancer*. 2014.

Efficacy results of phase III trials of multi-targeted TKIs in the treatment of advanced/metastatic NSCLC

Trials	Line of treatment	Treatment arms	Number of patients	RR (%)	PFS (months)	OS (months)
Vandetanib ZODIAC	Second	docetaxel	697	10	3.2*	10
		docetaxel + vandetanib (100 mg/day)	694	17 (P=.0001)	4.0 (HR, 0.79; P<.0001)	10.6 (HR, 0.91; P=.196)
Vandetanib ZEPHYR	Second	placebo	307	0.7	1.8	7.8*
		vandetanib (300 mg/day)	617	2.6 (P=.028)	1.9 (HR, 0.63; P<.001)	8.5 (HR, 0.95; P=.527)
Vandetanib ZEAL	Second	pemetrexed	278	8	11.9 weeks*	9.2
		pemetrexed + vandetanib (100 mg/day)	256	19 (P<.001)	17.6 weeks (HR, 0.86; P=.108)	10.5 (HR, 0.86; P=.2198)
Vandetanib ZEST	Second/third	erlotinib	617	12	2*	7.8
		Erlotinib + vandetanib (300 mg/day)	623	12 (P=.98)	2.6 (HR, 0.98; P=.721)	6.9 (HR, 1.01; P=.83)

* Primary endpoint. Herbst, et al. *Lancet Oncol*. 2010;11(7):619-626. Lee, et al. *J Clin Oncol*. 2012;30(10):1114-1121. de Boer, et al. *J Clin Oncol*. 2011;29(8):1067-1074 . Natale, et al. *J Clin Oncol*. 2011;29(8):1059.

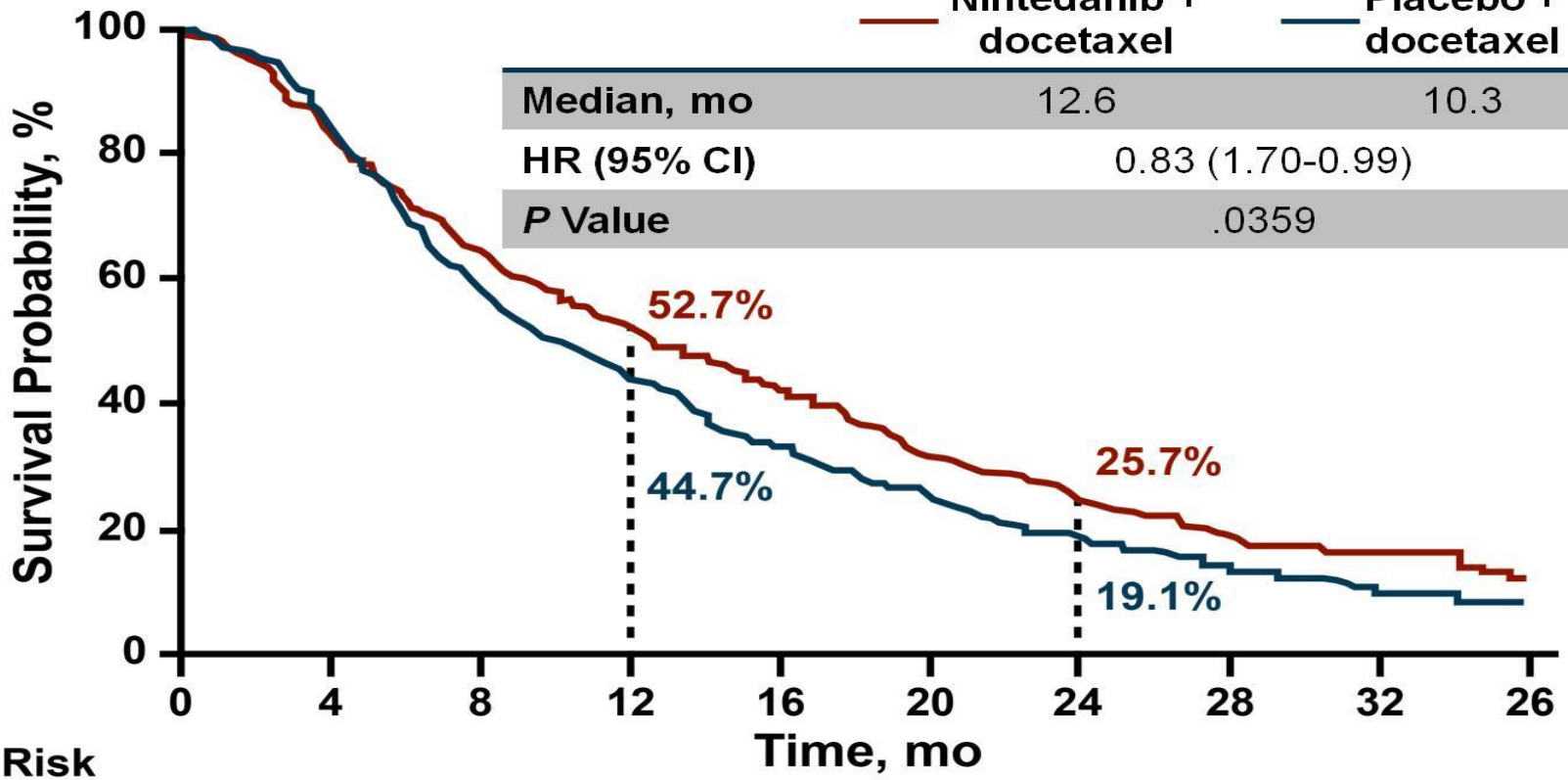
Efficacy results of phase III trials of multi-targeted TKIs in the treatment of advanced/metastatic NSCLC

Trials	Line of treatment	Treatment arms	Number of patients	RR (%)	PFS (months)	OS (months)
Motesanib MONET1	First	carboplatin/paclitaxel	549	26	5.4	11*
		carboplatin/paclitaxel/ motesanib (125 mg/day)	541	40 (P<.001)	5.6 (HR, 0.79; P<.001)	13 (HR, 0.90; P=.14)
Nintedanib LUME-Lung 1	Second	docetaxel	659	3.3	2.7*	9.1 (10.3 in adenocarcinoma)
		docetaxel + nintedanib (200 mg bid, days 2-21)	655	4.4 (P=.0307)	3.4 (HR, 0.79; P=.0019)	10.1 (HR, 0.94; P=.272) (12.6 in adenocarcinoma, HR, 0.83; P=.036)
Nintedanib LUME-Lung 2¶	Second	pemetrexed	360	9	3.6*	NR
		pemetrexed + nintedanib (200 mg bid)	353	9	4.4 (HR, 0.83; P=.04)	NR (HR, 1.03; P=.NR)

* Primary endpoint. ¶ Terminated early due to futility analysis or toxicity. Scagliotti, et al. *J Clin Oncol*. 2012;30(23):2829-2836. Reck, et al. *Lancet Oncol*. 2014;15(2):143-155. Hanna, et a. *J Clin Oncol*. 2013;31(suppl):abstr 8034.

Nintedanib: an oral inhibitor of VEGF, FGFR and PDGFR---triple angiokinase inhibition

LUME Lung 1: Overall Survival Adenocarcinoma



	Nintedanib + docetaxel	Placebo + docetaxel
Median, mo	12.6	10.3
HR (95% CI)	0.83 (1.70-0.99)	
P Value	.0359	

No. at Risk										
Nintedanib	322	263	203	163	131	96	72	46	25	10
Placebo	336	269	184	139	101	73	55	33	15	7

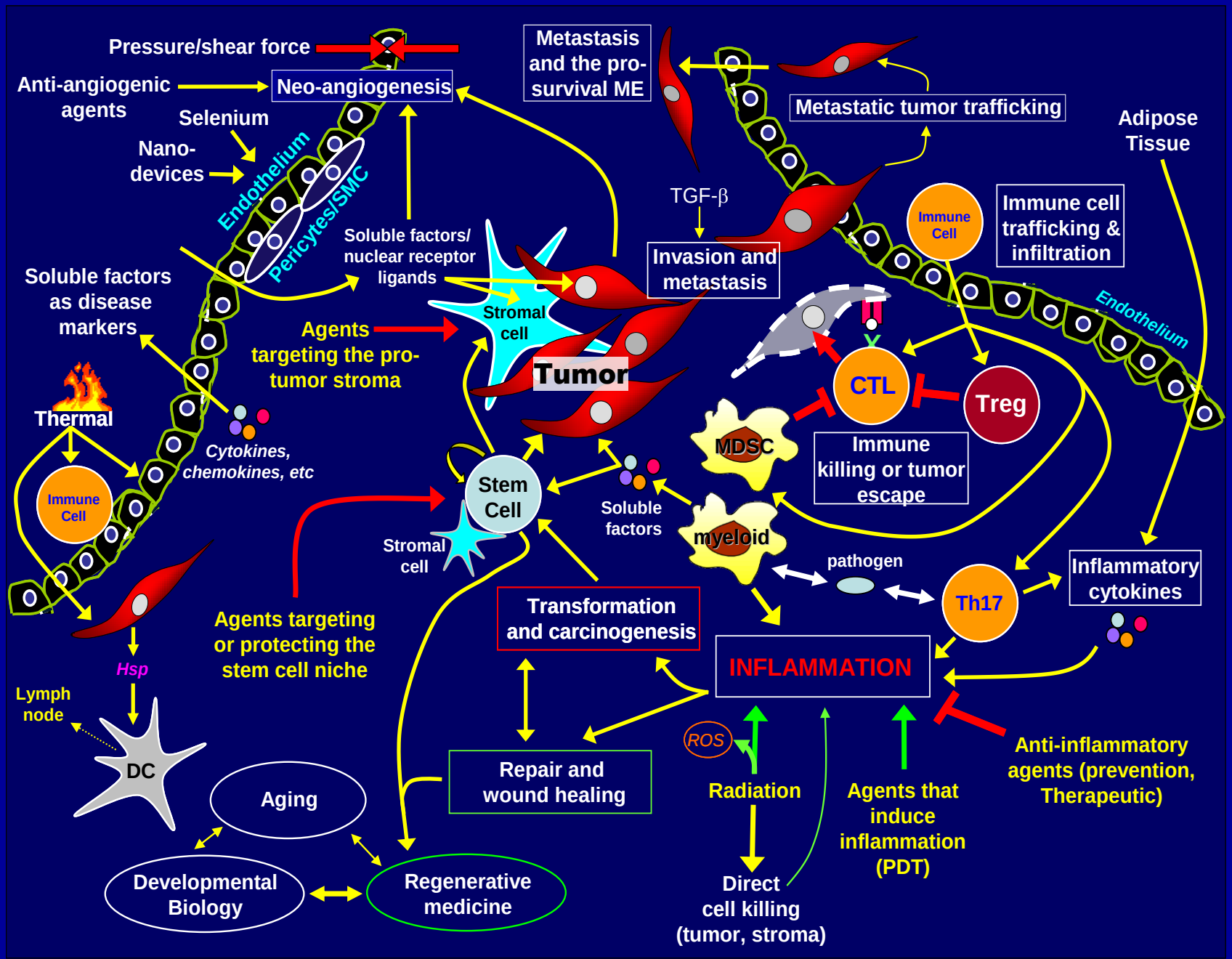
Reck M, et al. ASCO® 2013. Abstract LBA8011.[7]

Dual targeting of EGFR and VEGF pathways

- Bevacizumab + erlotinib
  - Second-line setting: BeTa
  - Maintenance setting: ATLAS
- Bevacizumab + cetuximab
  - SWOG0536: carboplatin/paclitaxel+bevacizumab+cetuximab
    - primary endpoint: 2% grade ≥ 4 hemorrhage
    - PFS 7 mo, OS 15 mo, RR 56%
  - SWOG S0819: phase III carboplatin/paclitaxel+bevacizumab±cetuximab
- Vandetanib: negative
- BMS-690514
  - reversible oral inhibitor of EGFR/HER-1, HER-2 and -4, and VEGFRs-1 to -3
  - phase I–IIa study: manageable safety profile and antitumor activity (RR of 3.3 %) in NSCLC

Kim, et al. *J Thorac Oncol*. 2013;8(12):1519-1528. Redman, et a. *Clin Cancer Res*. 2012;18(15):4004-4012. Soria, et al. *Eur J Cancer*. 2013;49(8):1815-1824.

Tumor Microenvironment and Host Factors



Thank You!