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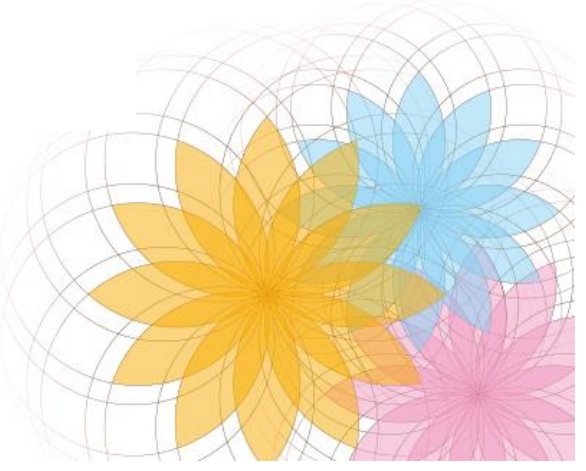
Frances A. Shepherd

Princess Margaret Hospital, Toronto, Canada

“Lung cancer: From nihilism to great advances”



Lung Cancer

From Nihilism to Great Advances

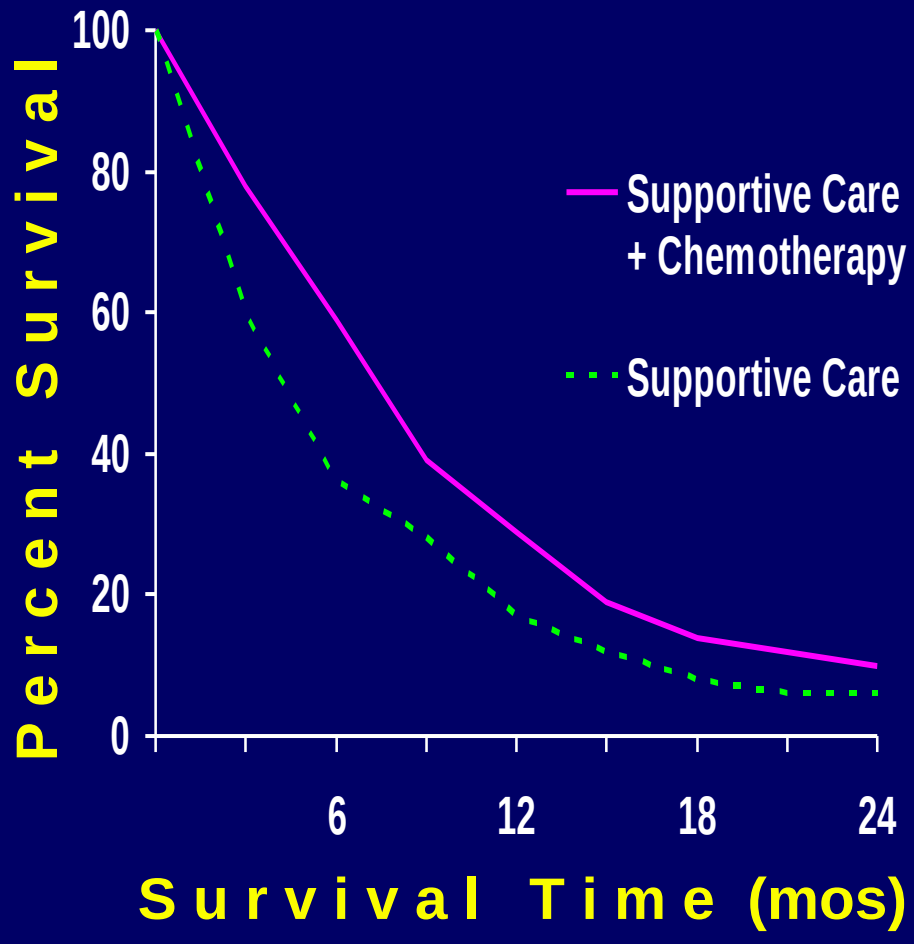
FRANCES A. SHEPHERD
Scott Taylor Chair in Lung Cancer Research
Princess Margaret Cancer Centre
Professor of Medicine, University of Toronto

The Nihilism of Lung Cancer

13 Randomized Trials in Advanced NSCLC of Chemotherapy versus BSC(!!)

Cisplatin, vinblastine (3)
Cisplatin, vindesine (2)*
Cisplatin, etoposide (1)
Carboplatin, etoposide (1)
Mitomycin, ifosfamide, cisplatin (1)
Mitomycin, vinblastine, cisplatin (1)
Gemcitabine, docetaxel, paclitaxel (1 each)
The BIG Lung Trial (1)

Meta-analysis Chemotherapy *versus* BSC - Patient Survival



Chemotherapy for Advanced NSCLC

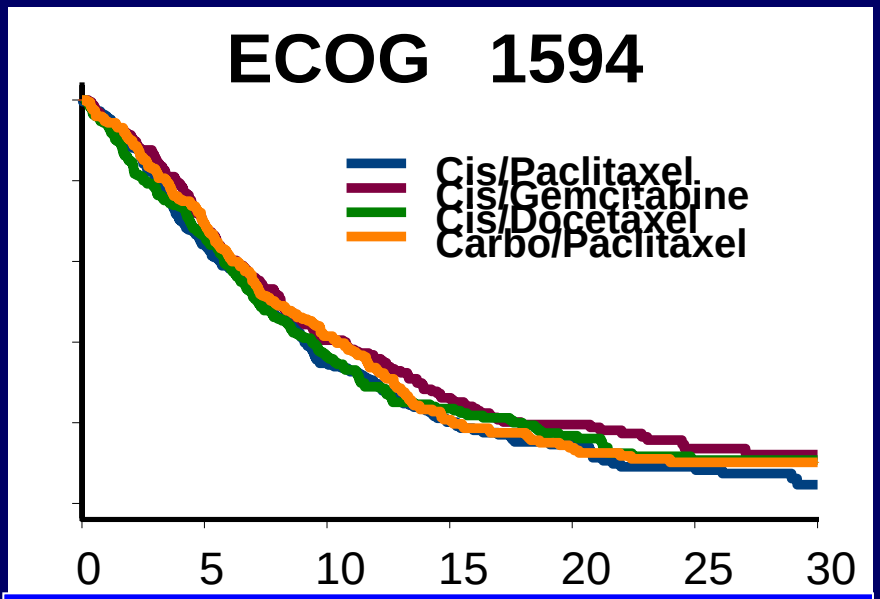
1. **Improves survival**
2. **Improves symptoms**
3. **Maintains QoL**
4. **Is cost-effective**

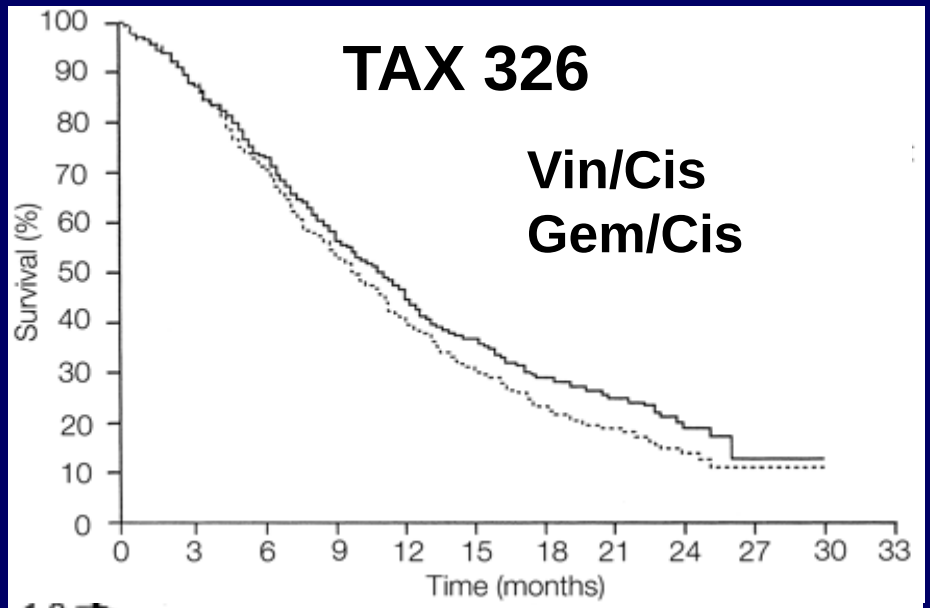
BMJ 311: 899, 1995

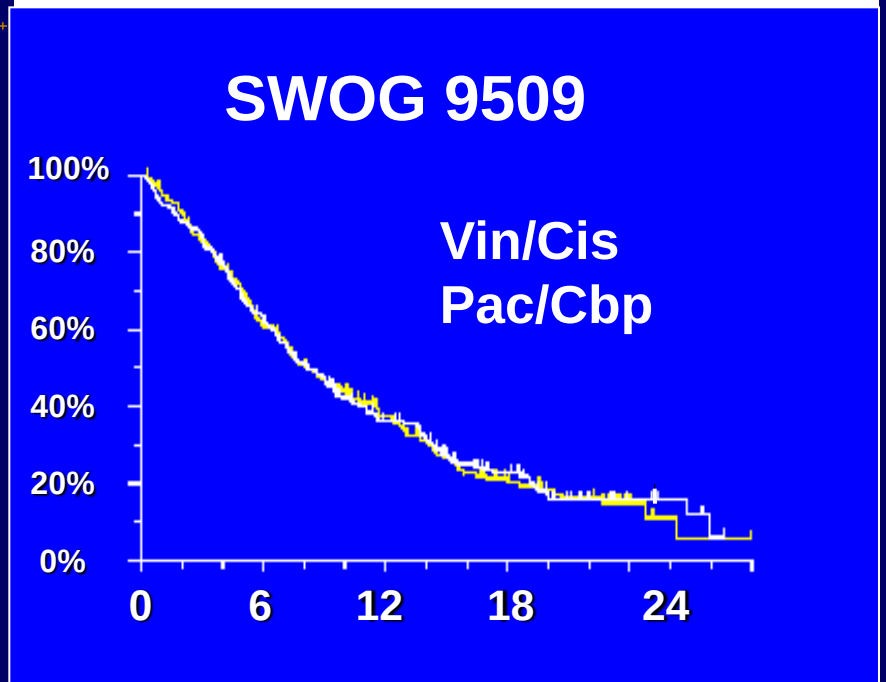
First-Line Chemotherapy Trials of Platinum-based Doublets

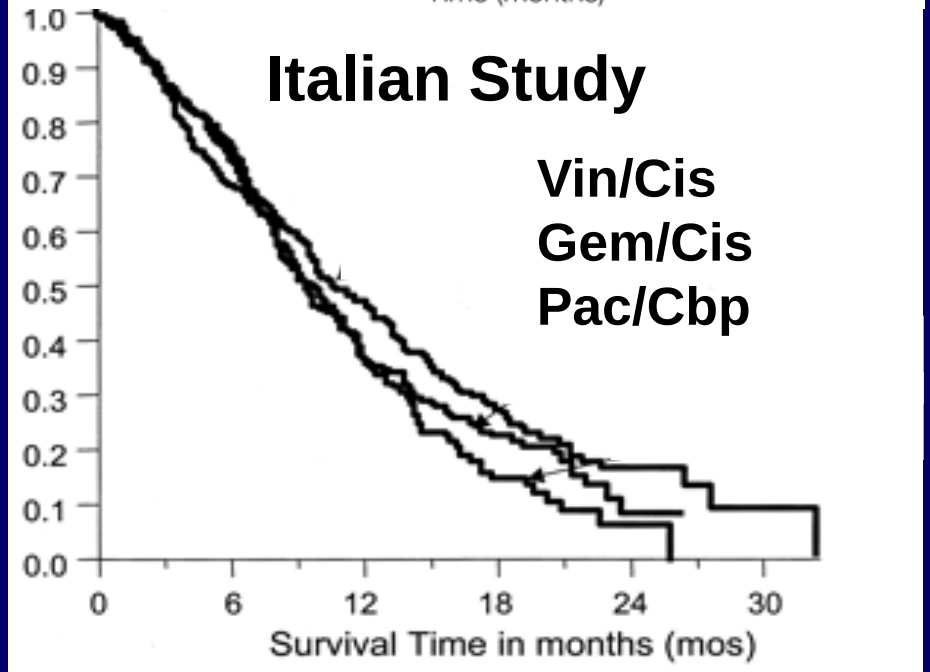
- ECOG 1594
  - Gem/cis v Pac-24/cis v Pac-3/carbo v Doc/cis
- SWOG 9509
  - Pac-3/carbo v Vin/cis
- TAX 326
  - Doc/carbo or Doc/cis v Vin/cis
- Italian Study
  - Gem/cis v Pac-3/carbo v Vin/cis
- JMDB
  - Gem/cis v pemetrexed/cis
- NO significant or meaningful differences

Trials of Third Generation Agents









First-Line Chemotherapy Trials of Platinum-based Do s

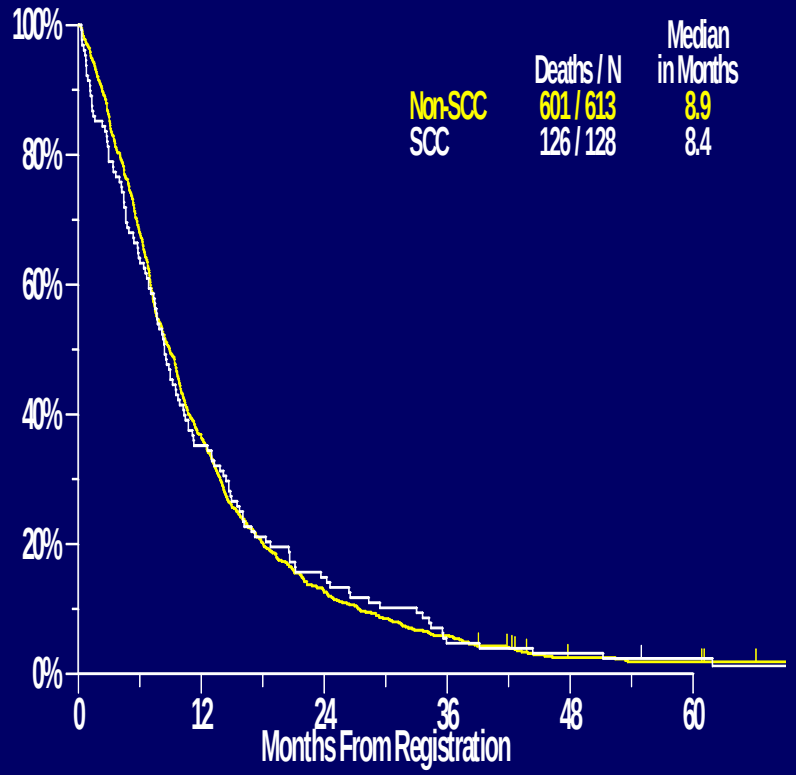
- ECOG 1594
  - Gem/cis v P
- SW
  - P
- TAX
  - Doc
- Italian
  - Gem/c
- JMDB
  - Gem/cis v metrexed/cis
- NO significant or meaningful differences

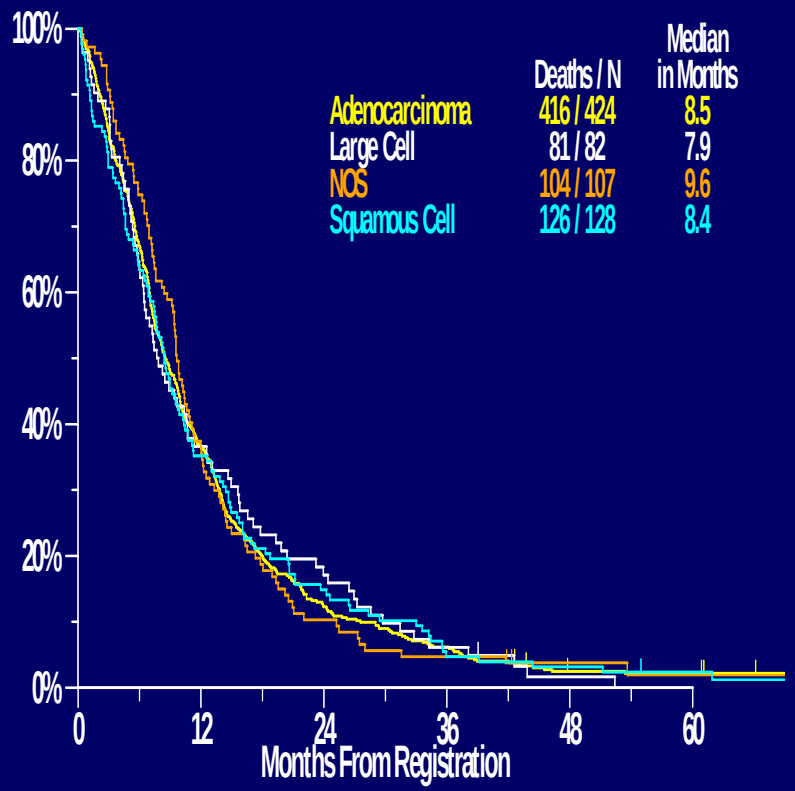
- **All of these trials were performed before the era of molecular testing for driver mutations**
- **Therefore some patients may have had *EGFR* or *ALK* mutations**
- **Were these patients balanced between the arms?**

Selection of Regimen Based on Histology

- Until recently NO selection based on histologic subtype

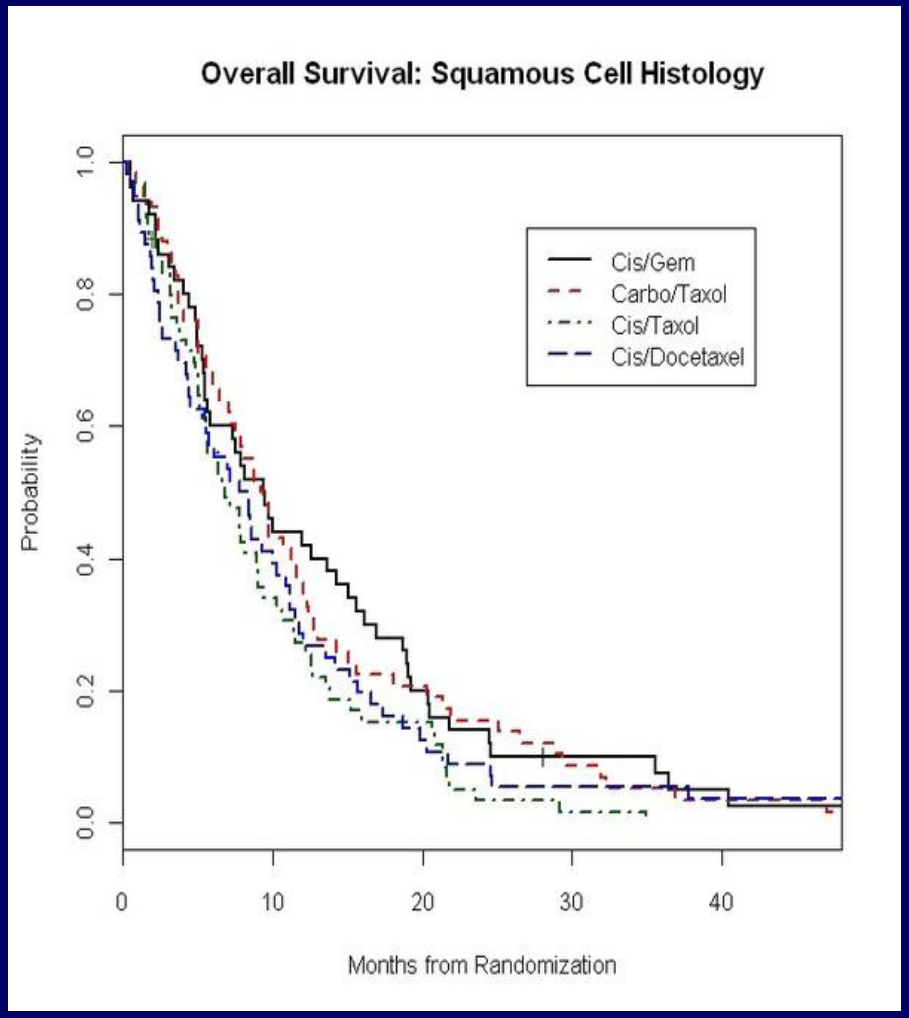
SWOG Tubulin-Targeting Agents Pooled Analysis: OS *by Cell Type*

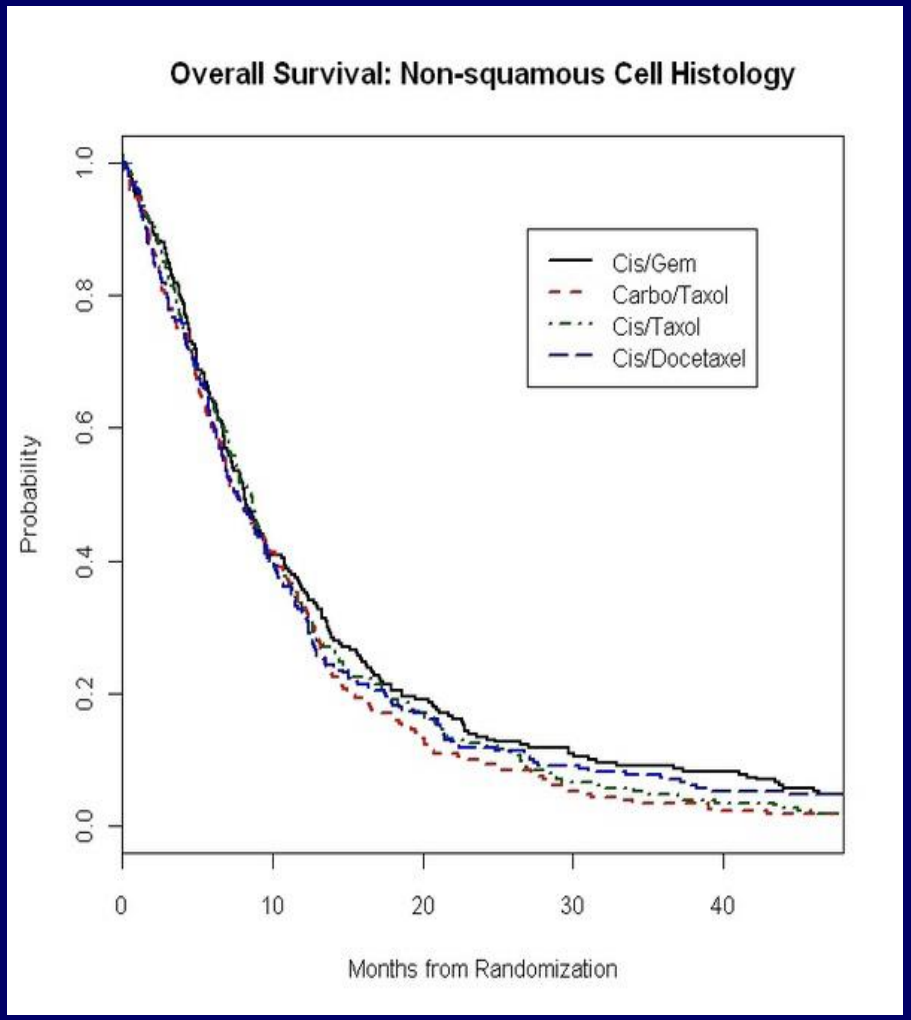




Chansky et al. Proc IASLC, San Francisco, 2009

Effect of *Histology* ECOG 1594



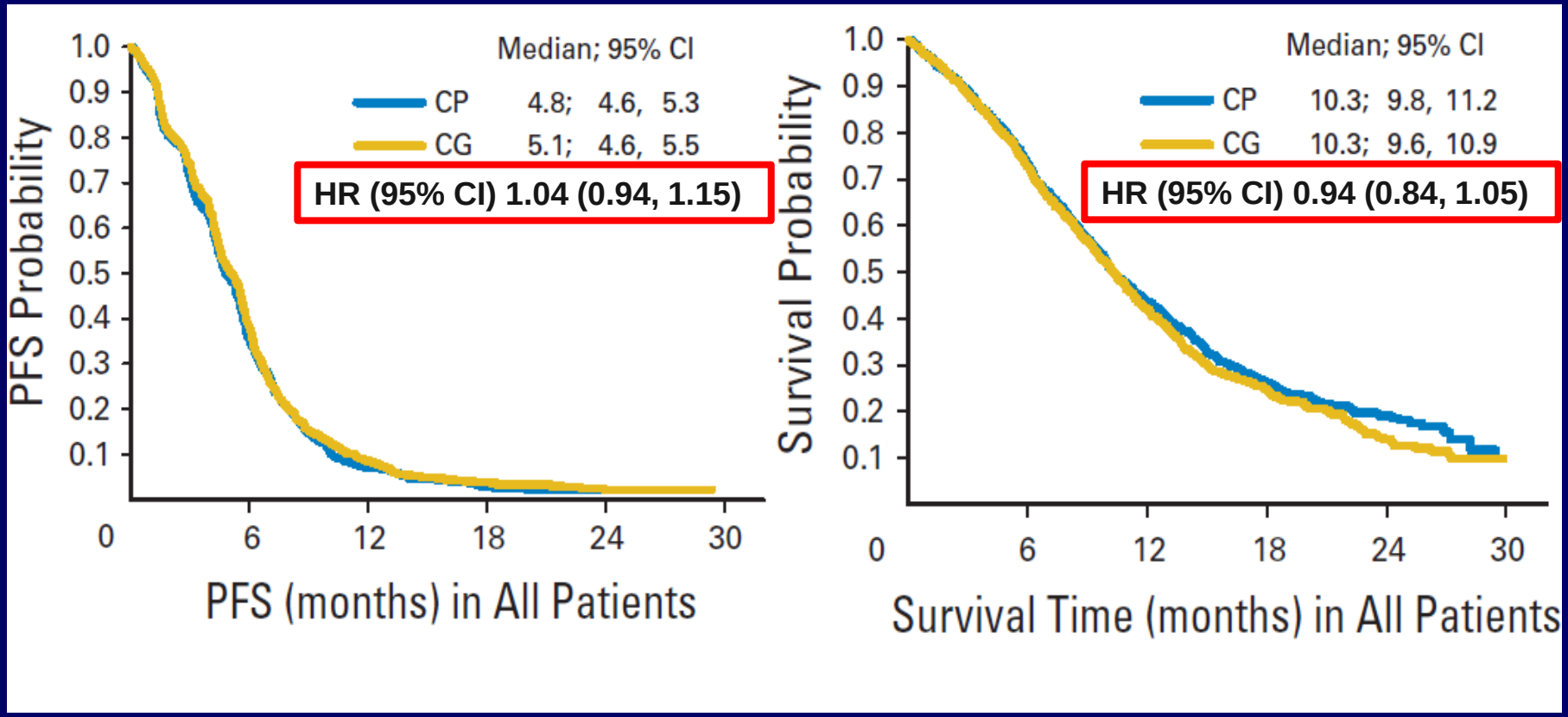


Hoang et al Proc IASLC, San Francisco, 2009

Selection of Regimen Based on Histology

- Until recently NO selection based on histologic subtype
- Patients with squamous histology excluded from bevacizumab therapy based on toxicity (hemoptysis)
- Re-examination of pemetrexed trials revealed inferior results for this agent in patients with squamous histology

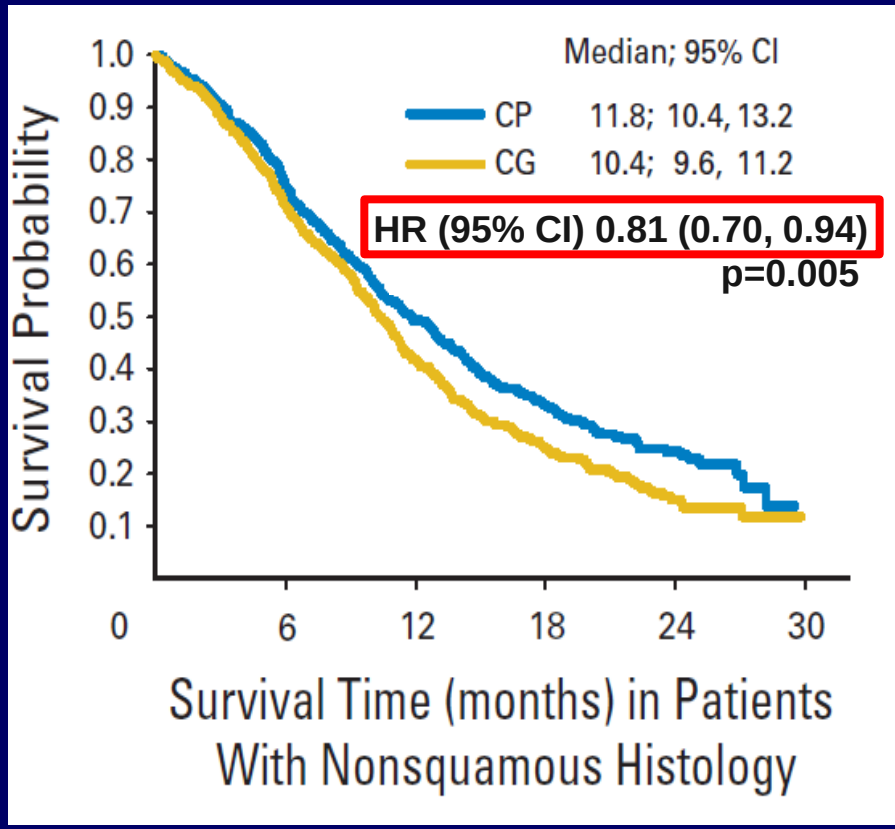
JMDB: Pem/Cis vs Gem/Cis in First-line NSCLC

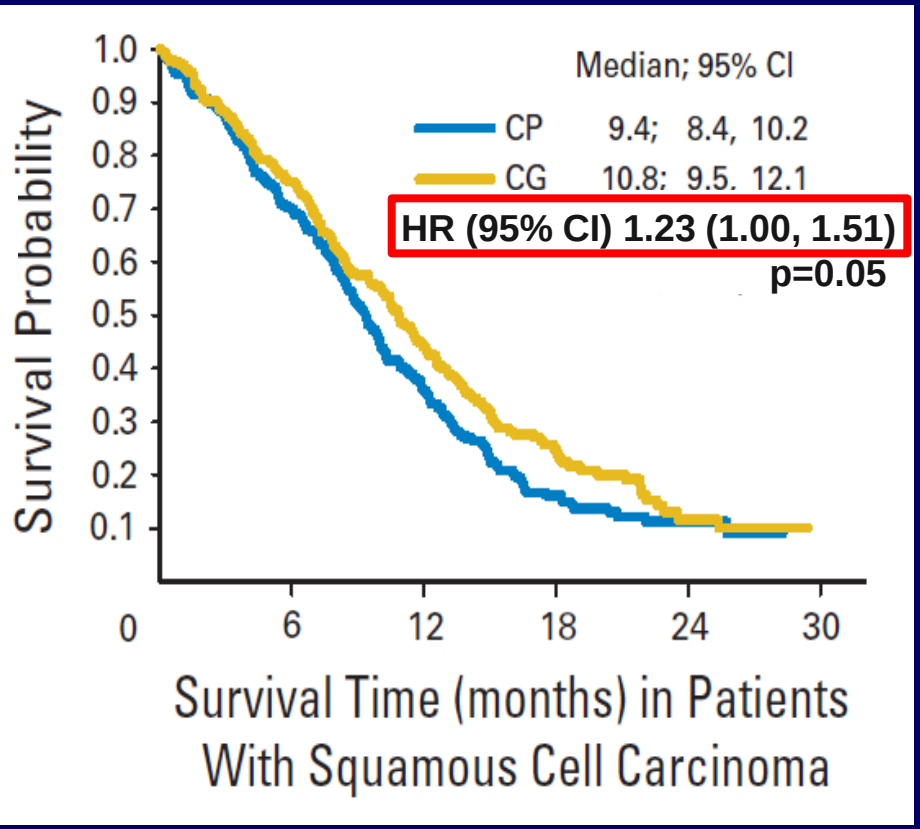


CP, cisplatin/pemetrexed; CG, cisplatin/gemcitabine

Scagliotti et al. J Clin Oncol 26: 3543, 2008

JMDB: Analysis by Histology

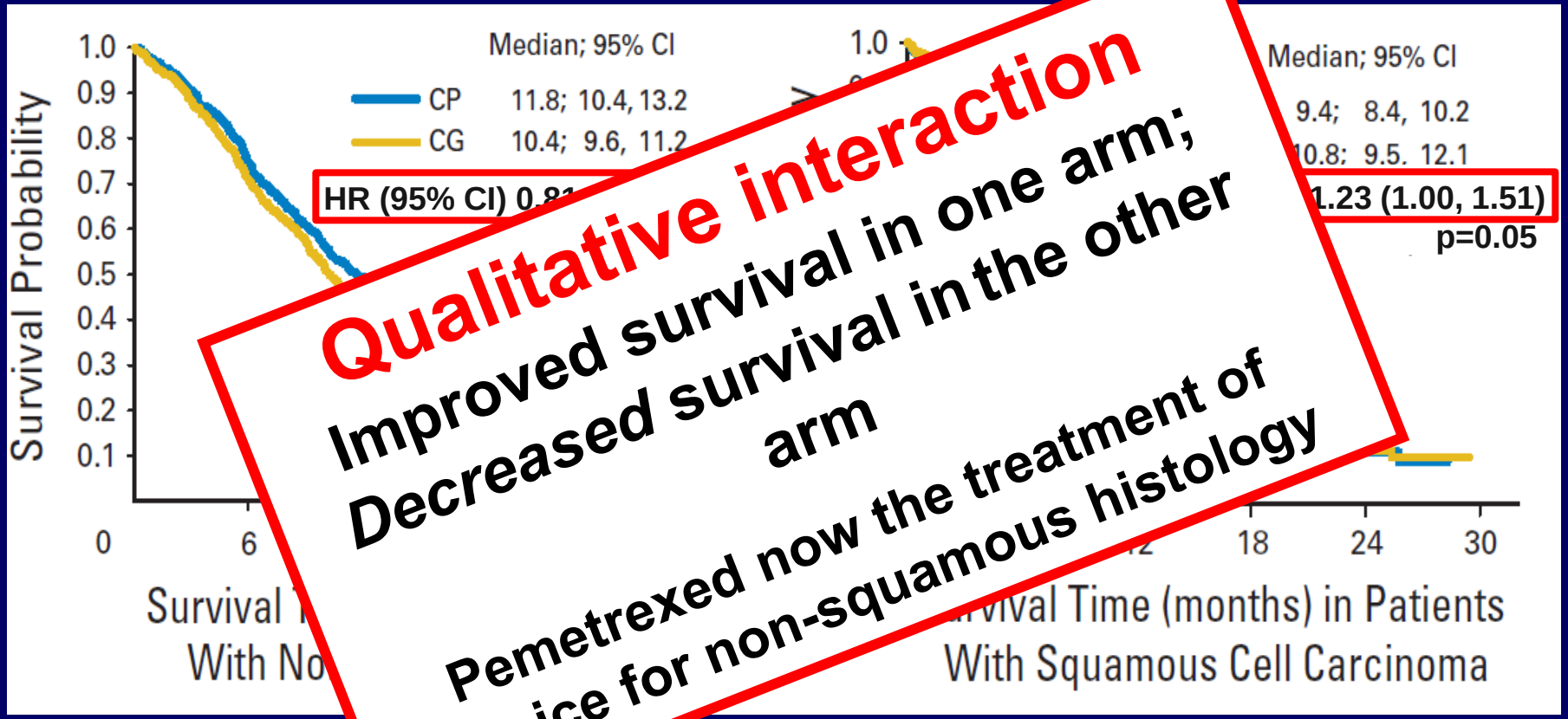




Nonsquamous=adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology

Scagliotti et al. J Clin Oncol 26: 3543, 2008

JMDB: Analysis by Histology



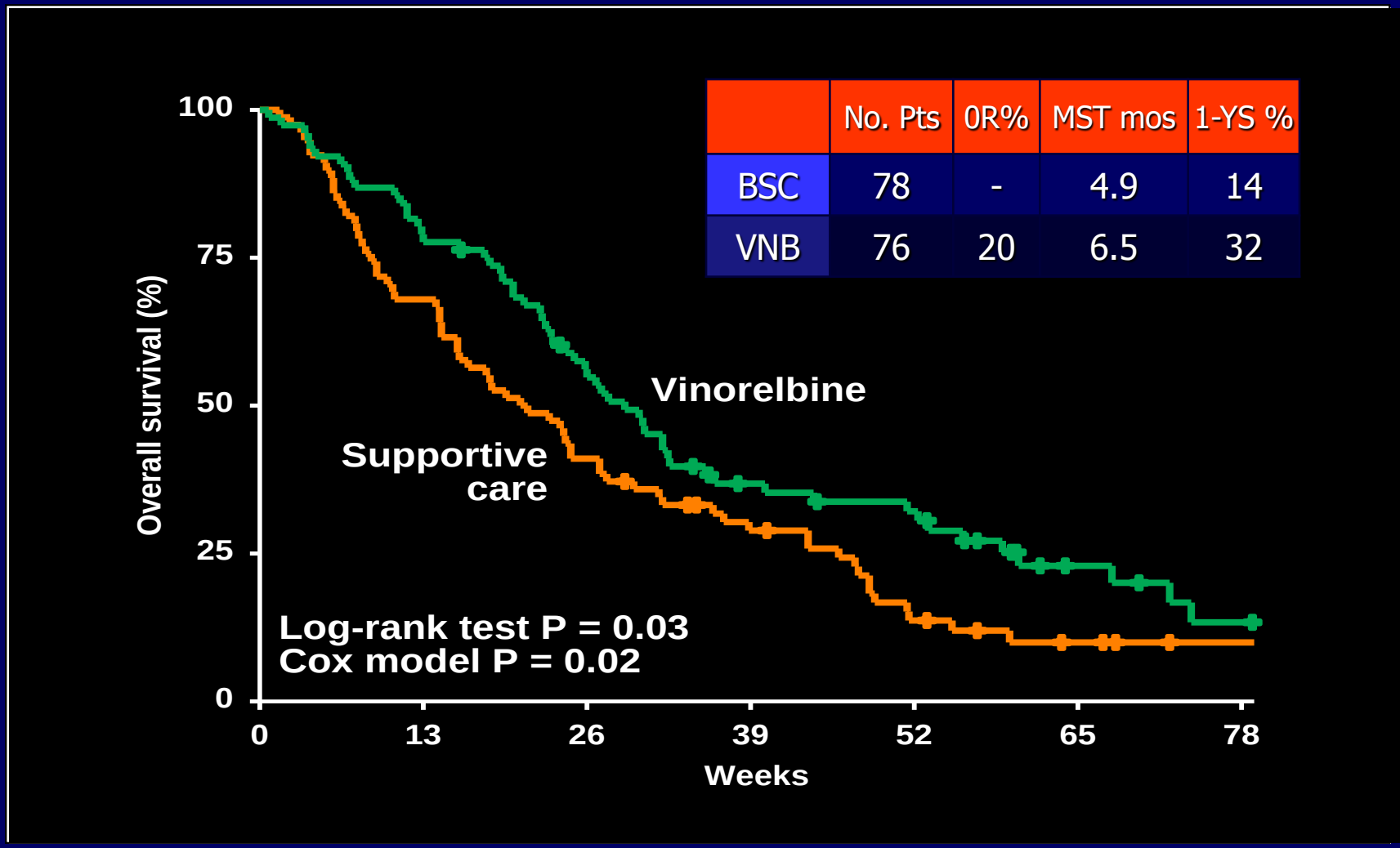
Nonsquamous=adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology

Scagliotti et al. J Clin Oncol 26: 3543, 2008

Treatment of the Elderly

- Single agent therapy
- Combination chemotherapy

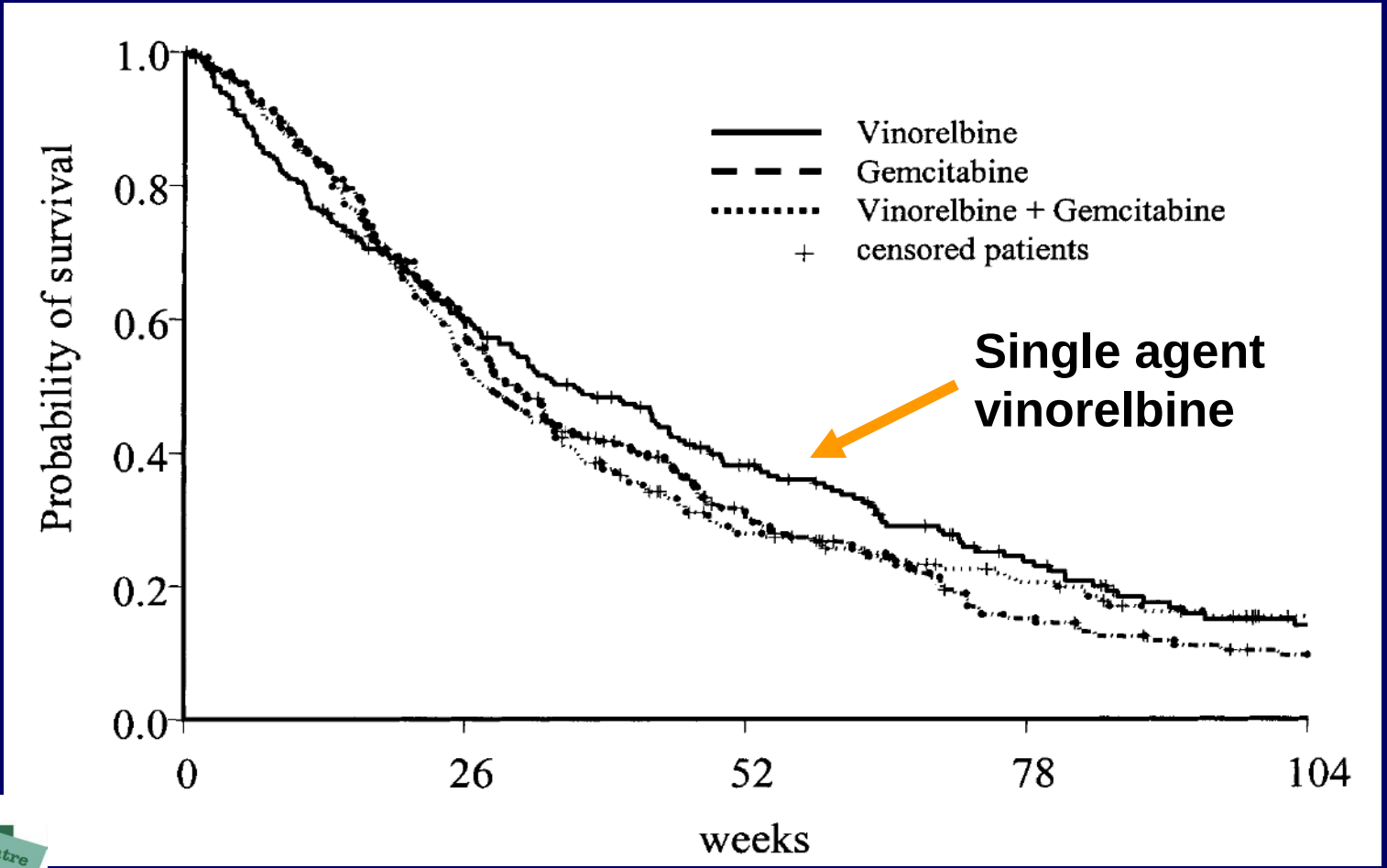
ELVIS: Vinorelbine *versus* BSC



	No. Pts	0R%	MST mos	1-YS %
BSC	78	-	4.9	14
VNB	76	20	6.5	32

Journal of the National Cancer Institute, 1999

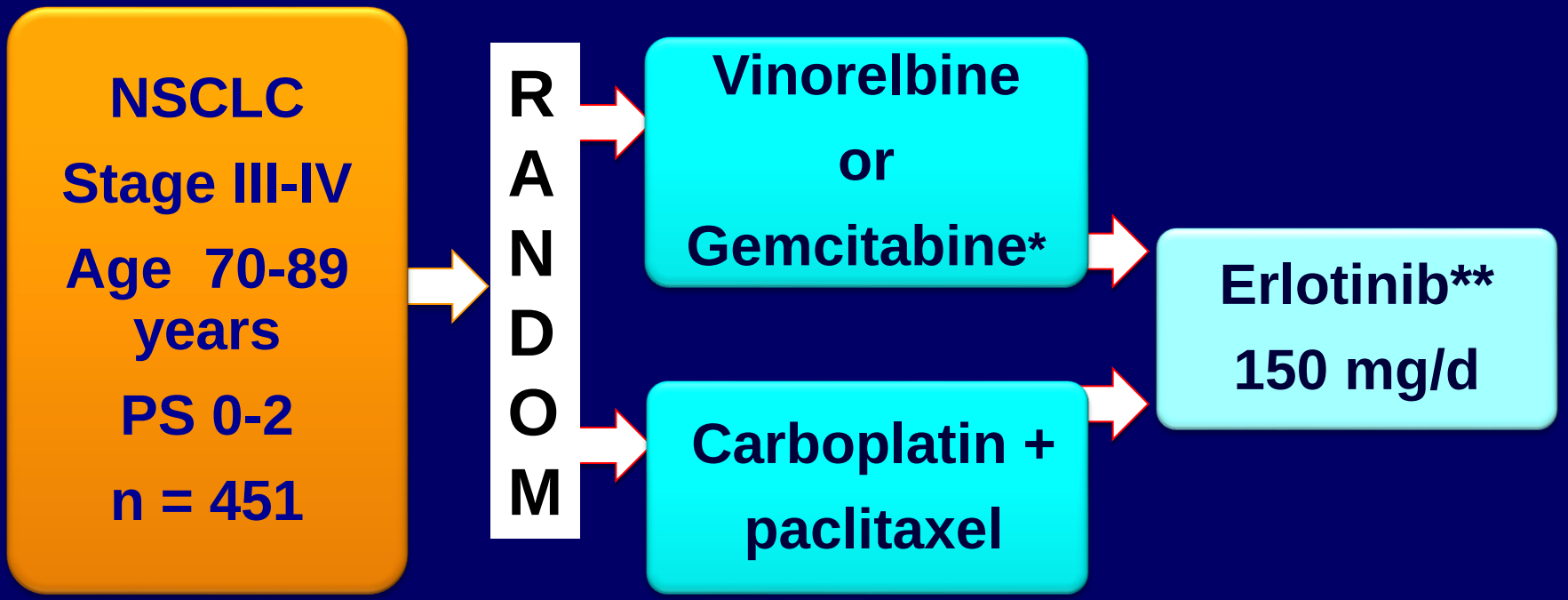
MILES
Gemcitabine *v* Vinorelbine v Gem/Vin



Multicentre Italian Lung cancer in the Elderly Study
MILES

Journal of the National Cancer Institute, Vol. 95, No. 5, March 5, 2003

The Elderly
IFCT-0501 Study Schema



Stratification by centre, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV

*Choice of the center at the beginning of the study
** In case of PD or excessive toxicity

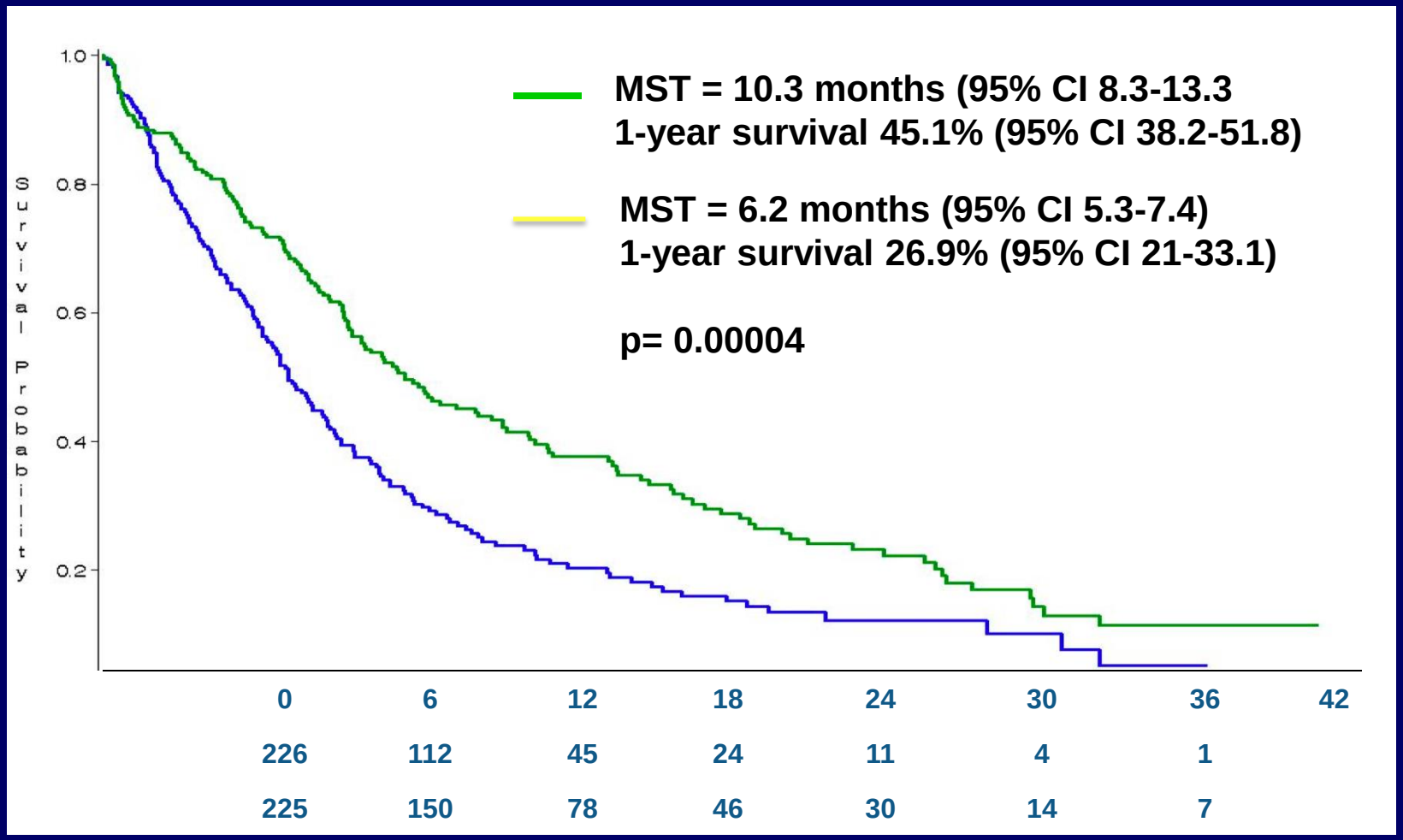
Chemotherapy Schedules

ARM A	V	V		V	V		V	V		V	V		V	V				
	G	G		G	G		G	G		G	G		G	G				
WEEKS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
ARM B	C P	P	P		C P	P	P		C P	P	P		C P	P	P			
EVALUATION																		

V : Vinorelbine : 30 mg/m^2
G : Gemcitabine : 1150 mg/m^2
C : Carboplatin : AUC 6
P : Paclitaxel : 90 mg/m^2

} Choice of the center

Overall Survival (ITT)



Quoix et al. Lancet 378, 1079, 2011

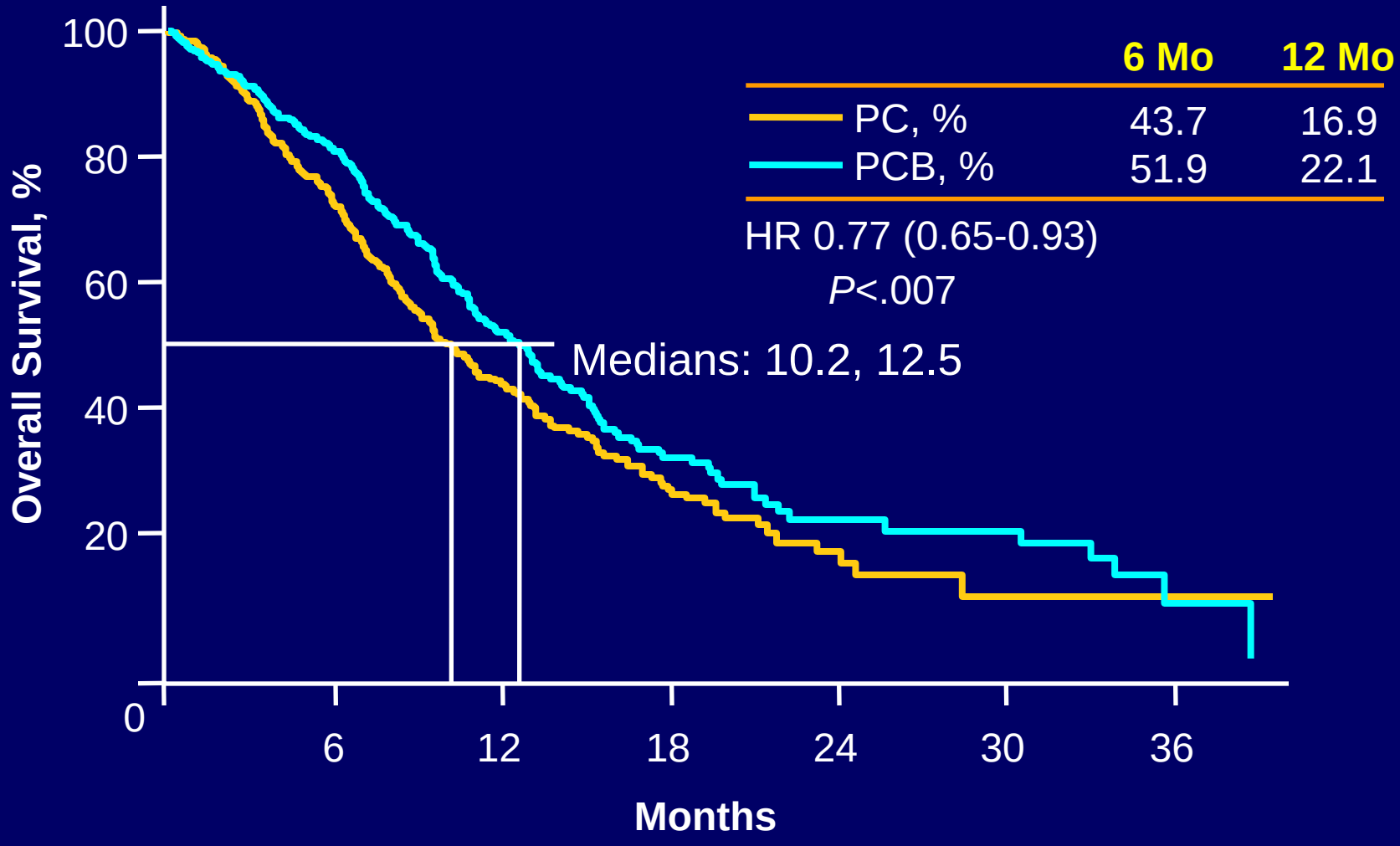
Addition of Targeted Agents to First-Line Chemotherapy Doublets

Bevacizumab

Cetuximab

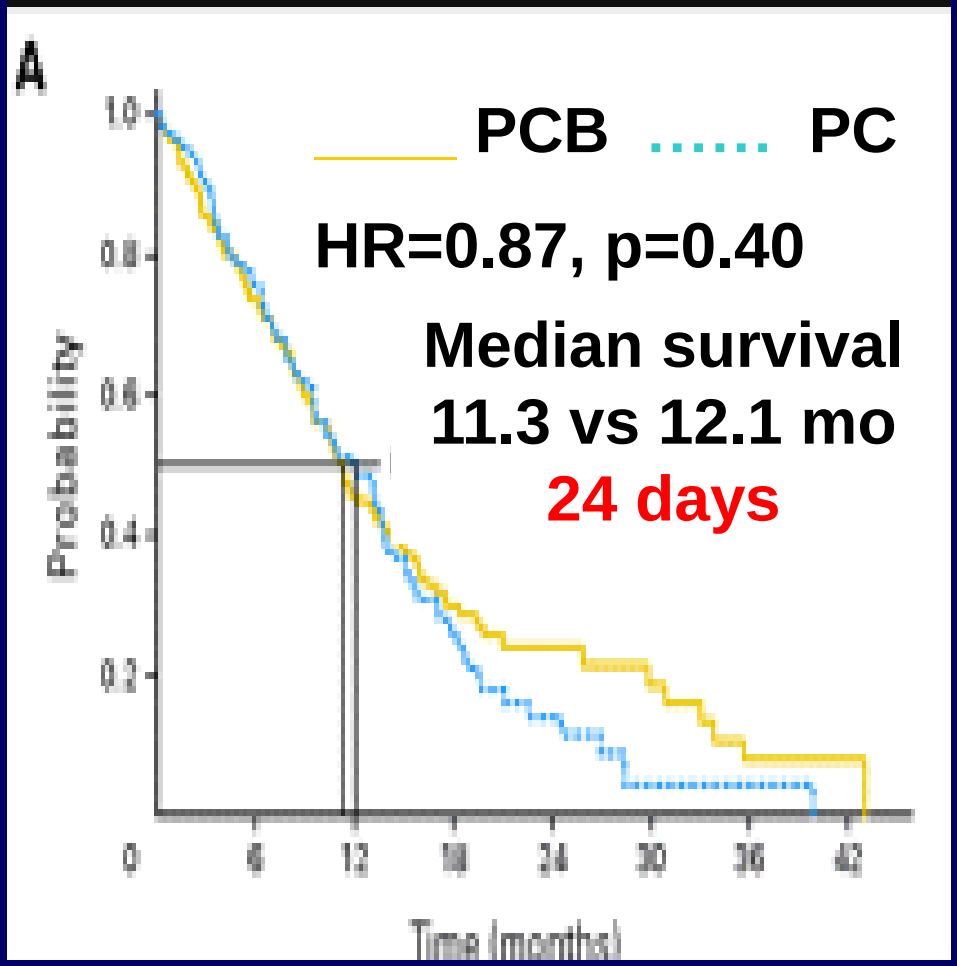
To date everything else has been disastrous!!!

ECOG 4599: Paclitaxel/Carboplatin +/- Bevacisumab



Sandler AB et al. NEJM, 2006

ECOG 4599: Effect of Age



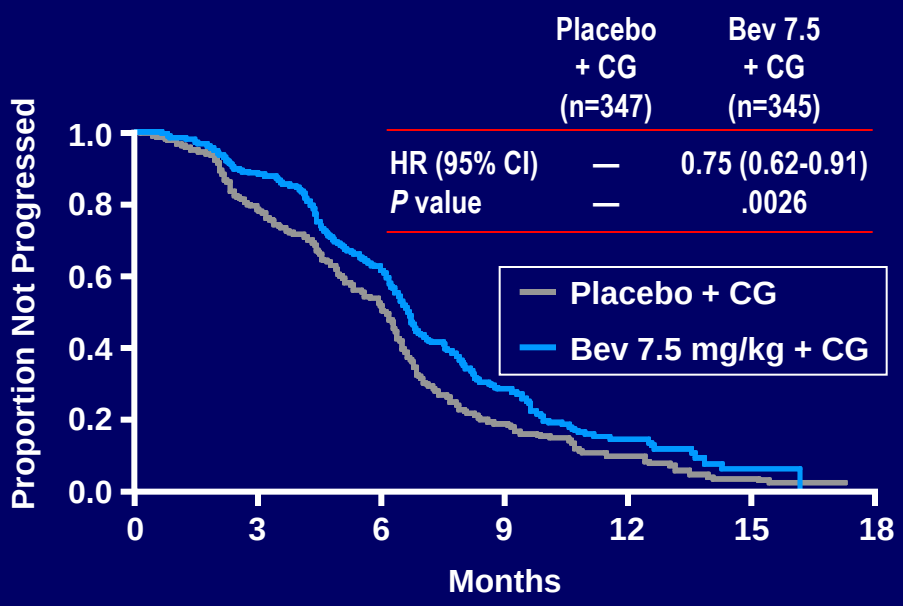
- **Febrile neutropenia**
  0.9 vs 6.2%, p=0.03
- **Hypertension**
  0.9 vs 6.2%, p=0.03
- **Hemorrhage**
  1.7 vs 7.9%, p=0.03
- **Proteinuria**
  0 vs 7.9%, p=0.002

Median age of lung cancer patients is >70

Ramalingham et al. J Clin Oncol 26: 60, 2008

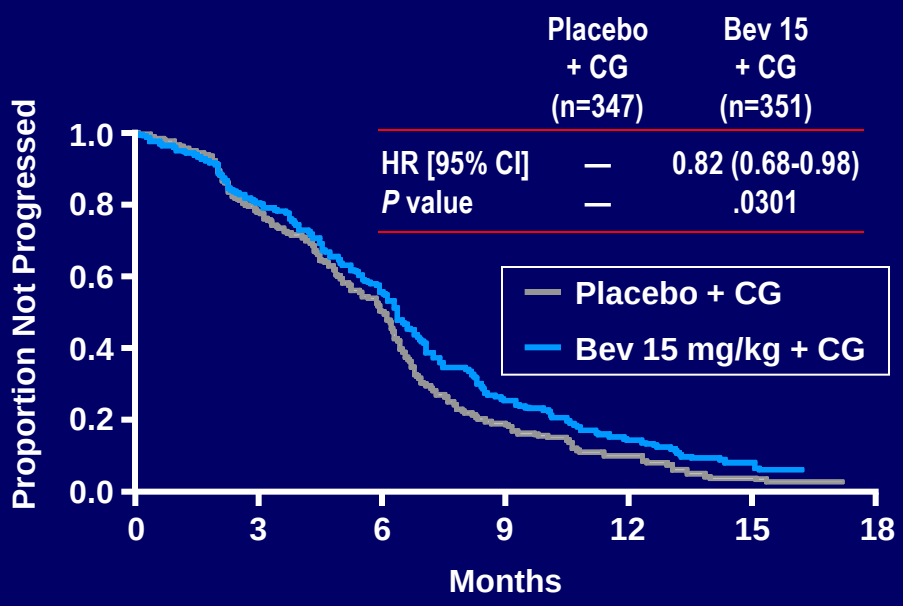
AVAiL: Progression-Free Survival Gemcitabine/Cisplatin +/- Bevacizumab

Primary Analysis (intent-to-treat) of Bevacizumab 7.5 mg/kg Versus Pooled Placebo



No. at Risk							
Placebo + CG	347	228	122	36	12	3	0
Bev 7.5 + CG	345	251	150	52	18	3	0

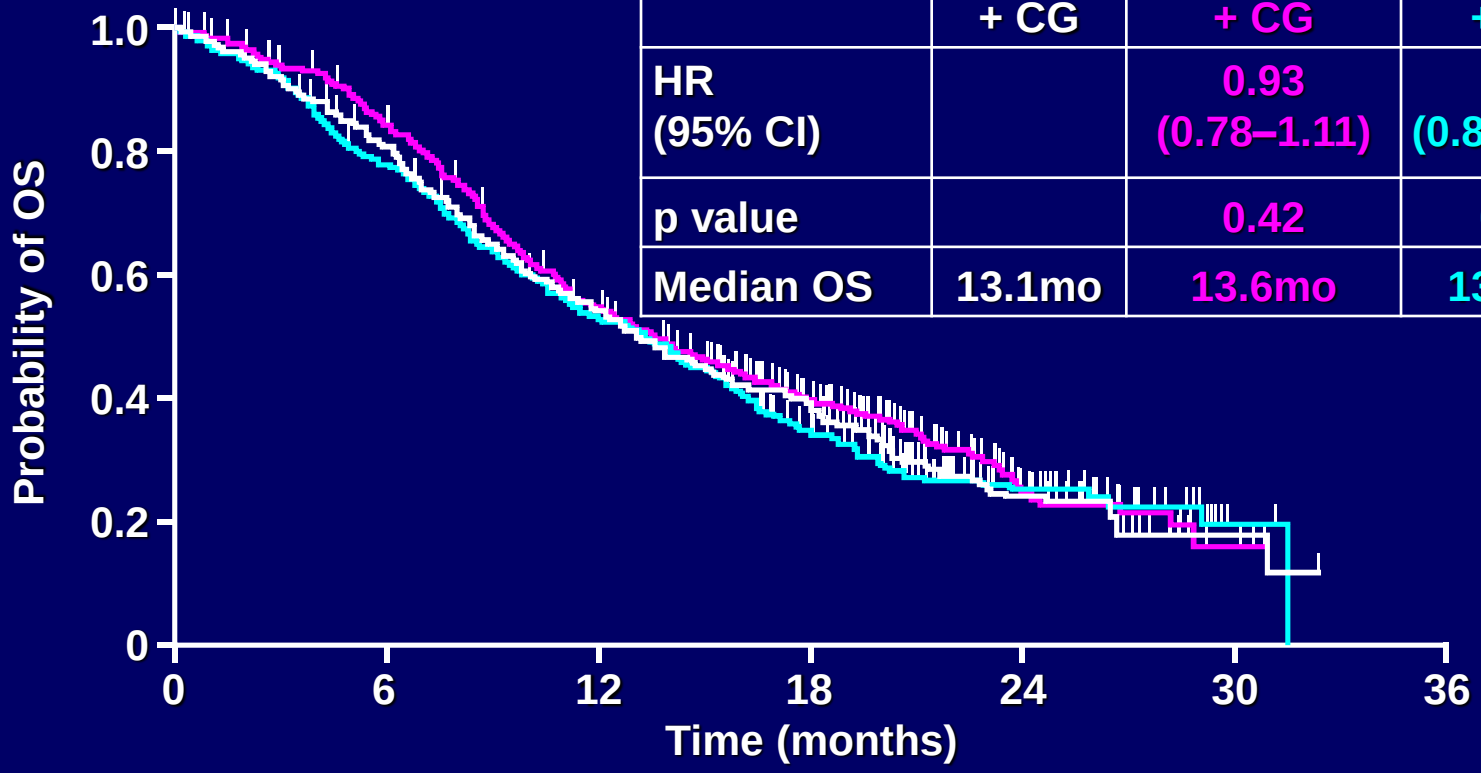
Primary Analysis (intent-to-treat) of Bevacizumab 15 mg/kg Versus Pooled Placebo



No. at Risk							
Placebo + CG	347	228	122	36	12	3	0
Bev 15 + CG	351	238	148	46	16	5	0

AVAiL: Overall Survival

	Placebo + CG	Bev 7.5mg/kg + CG	Bev 15mg/kg + CG
HR (95% CI)		0.93 (0.78–1.11)	1.03 (0.86–1.23)
p value		0.42	0.76
Median OS	13.1mo	13.6mo	13.4mo



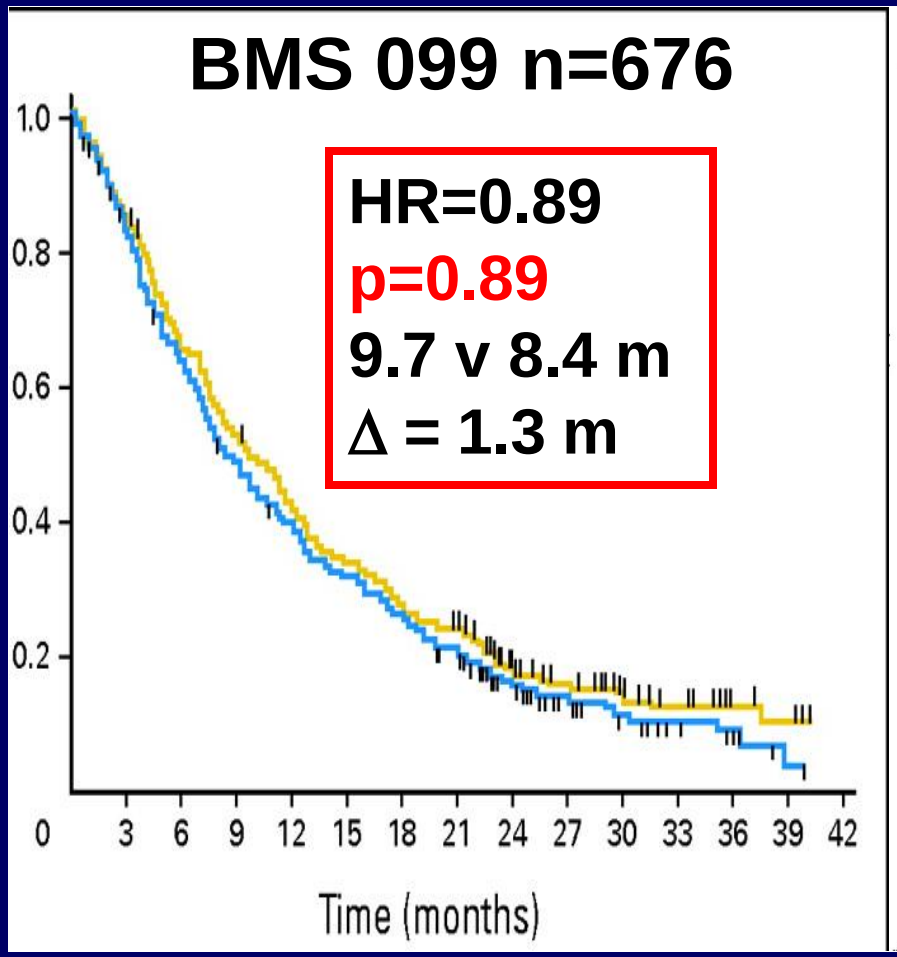
No. at risk							
Placebo + CG	347	272	182	100	36	3	0
Bev 7.5mg/kg + CG	345	286	182	107	34	3	0
Bev 15mg/kg + CG	351	264	177	92	33	2	0

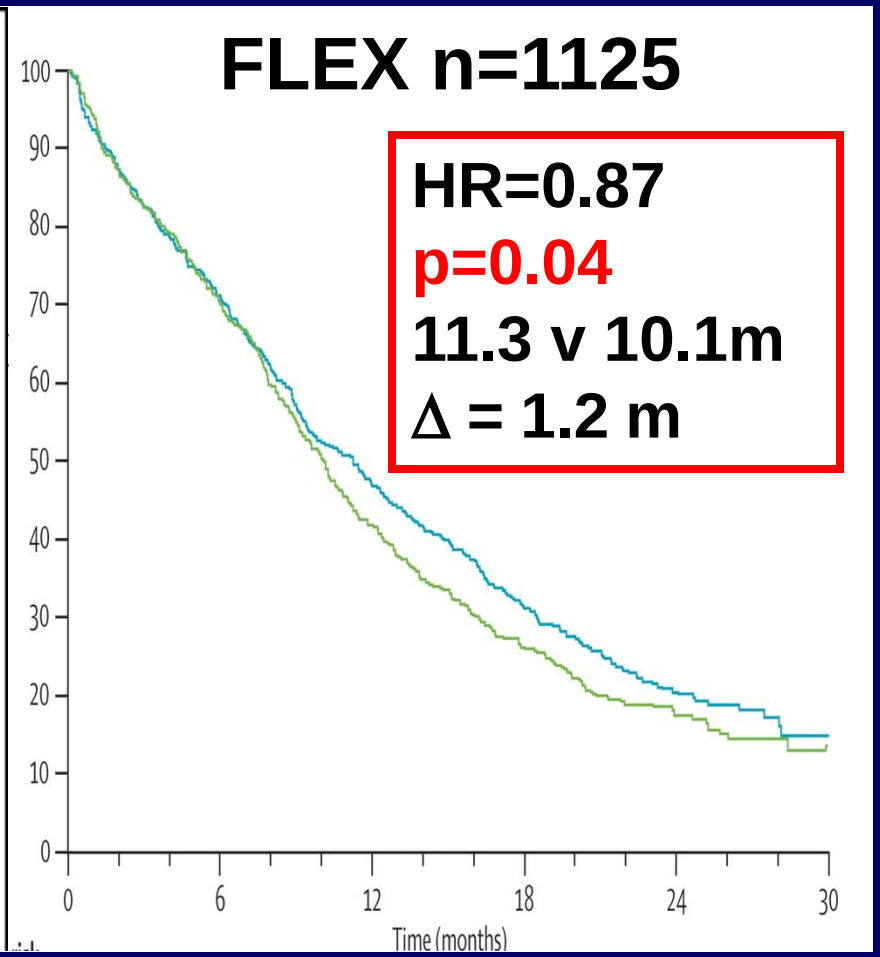
*ITT (intent-to-treat) population

Cetuximab Trials

- **BMS-099: taxane/carboplatin +/- cetuximab**
- **FLEX: vinorelbine/cisplatin +/- cetuximab *in EGFR IHC +ve cases only***
- **SQUIRE: gemcitabine/cisplatin +/- necitumumab in *Squamous* cancer**

Does Size Matter??

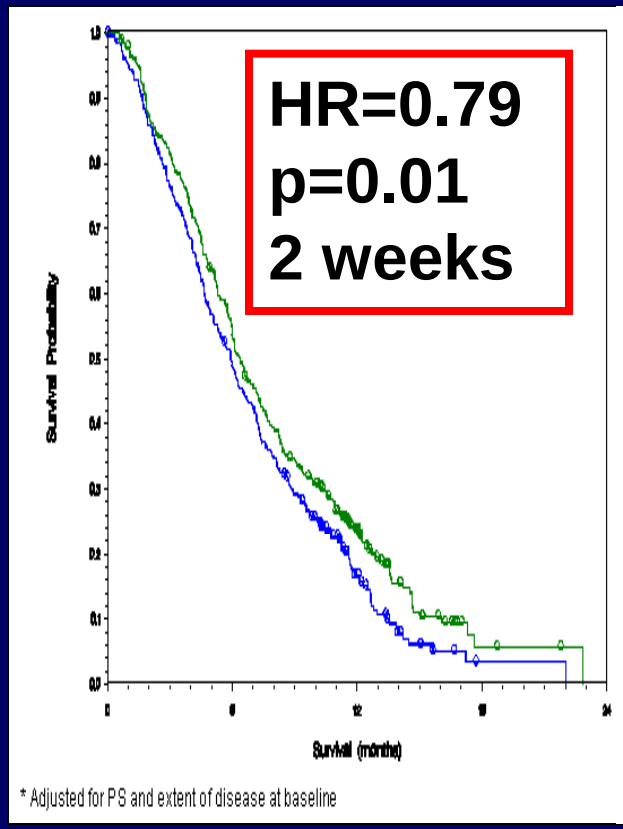


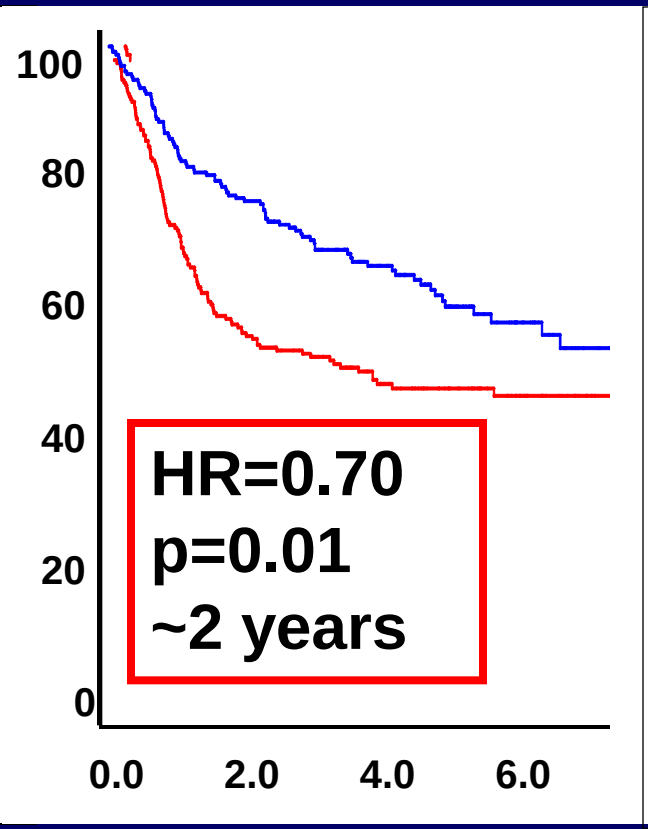


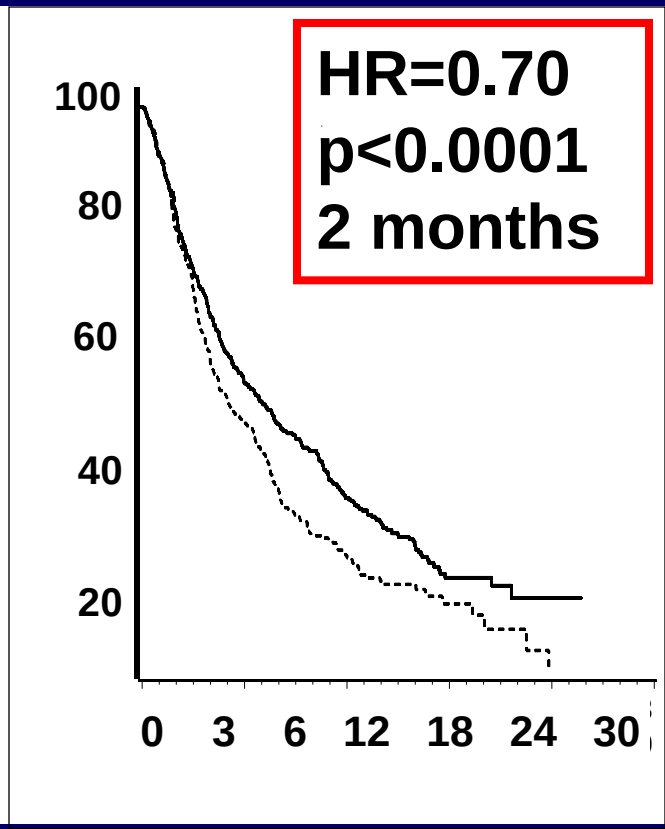
Lynch *et al*
J Clin Oncol 2010

Pirker *et al*
Lancet 2009

Statistically Significant *versus* Clinically Significant or *Relevant*







PA.3

Moore *et al*

J Clin Oncol 2007

BR.10

Winton *et al*

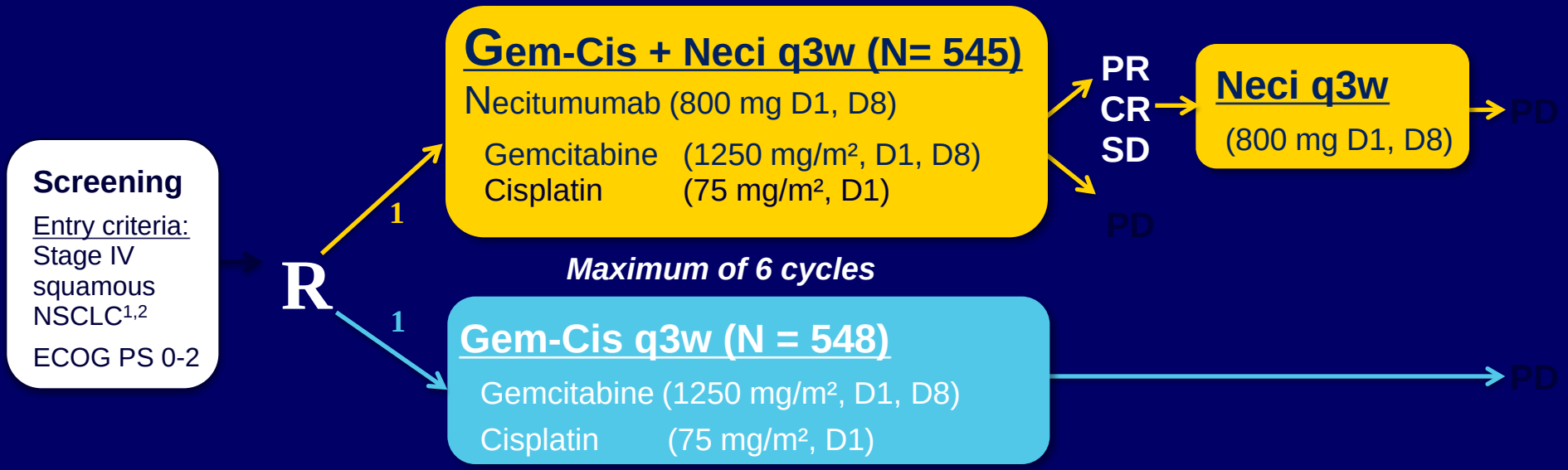
NEJM 2005

BR.21

Shepherd *et al*

NEJM 2005

SQUIRE: Study Design



Randomization (R) stratified by: ECOG PS (0-1 vs. 2) and geographic region (North America, Europe and Australia; vs. South America, South Africa and India; vs. Eastern Asia)

Patient selection not based on EGFR protein expression

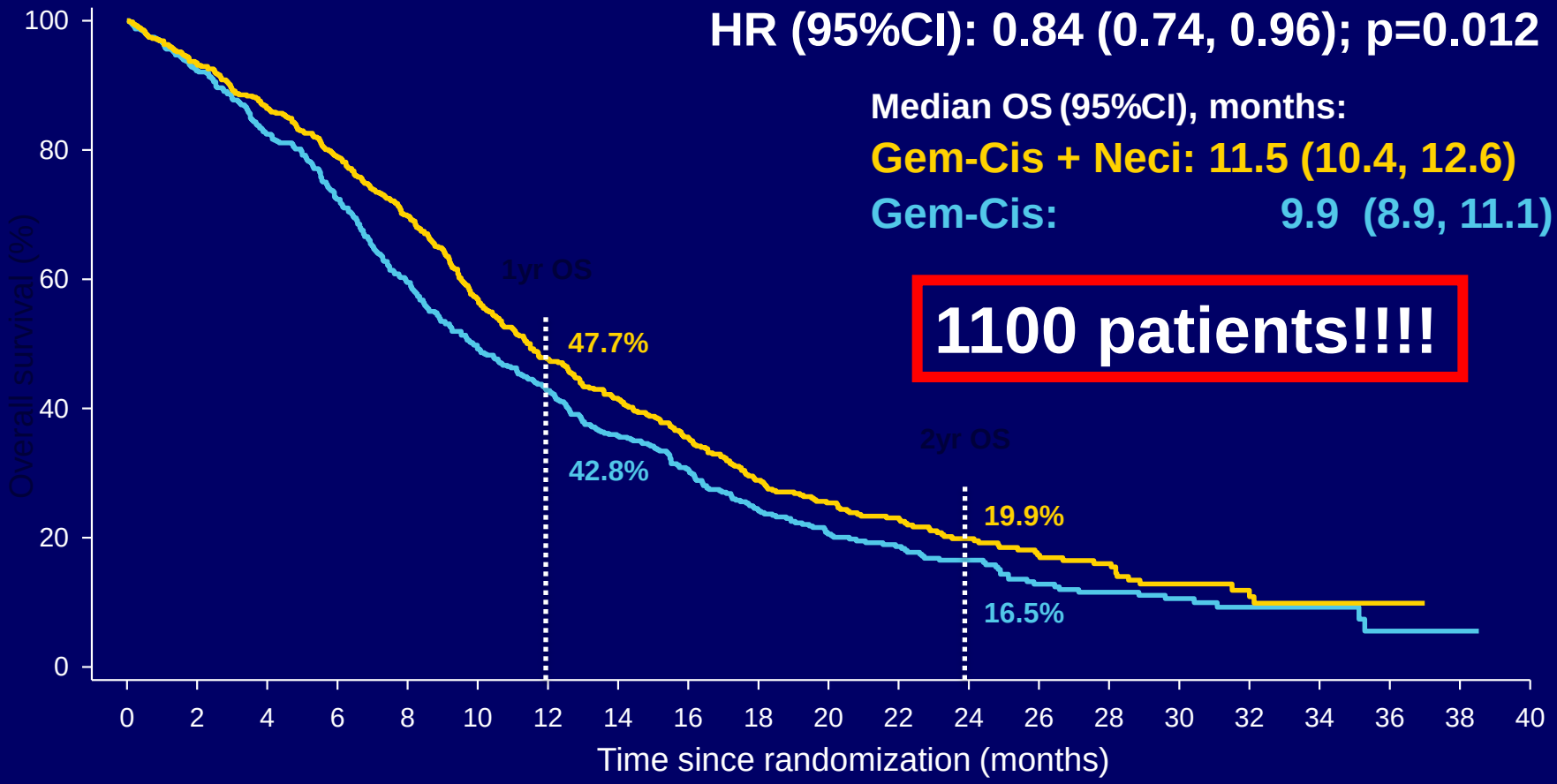
Radiographic tumor assessment (investigator read): at baseline and every 6 weeks until PD

Mandatory tissue collection

[1] AJCC TNM Classification, 7th edition, 2009; [2] UICC TNM Classification of Malignant Tumors, 7th edition, 2009

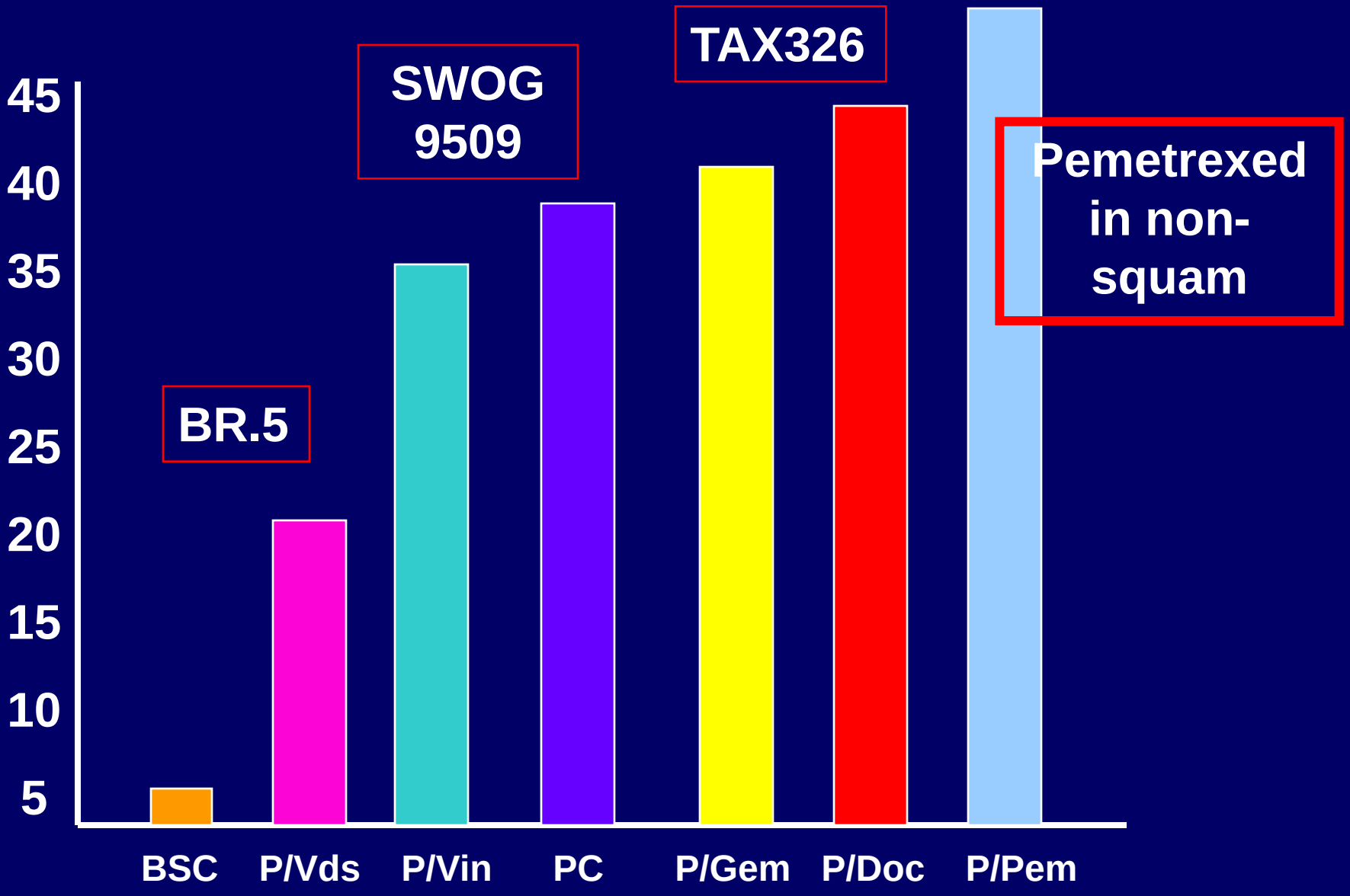
Thatcher et al. ASCO, 2014

Primary Outcome: Overall Survival (ITT)



Follow-up time (median): Gem-Cis + Neci: 25.2 months; Gem-Cis: 24.8 months

Progress in 1-Year Survival Rates

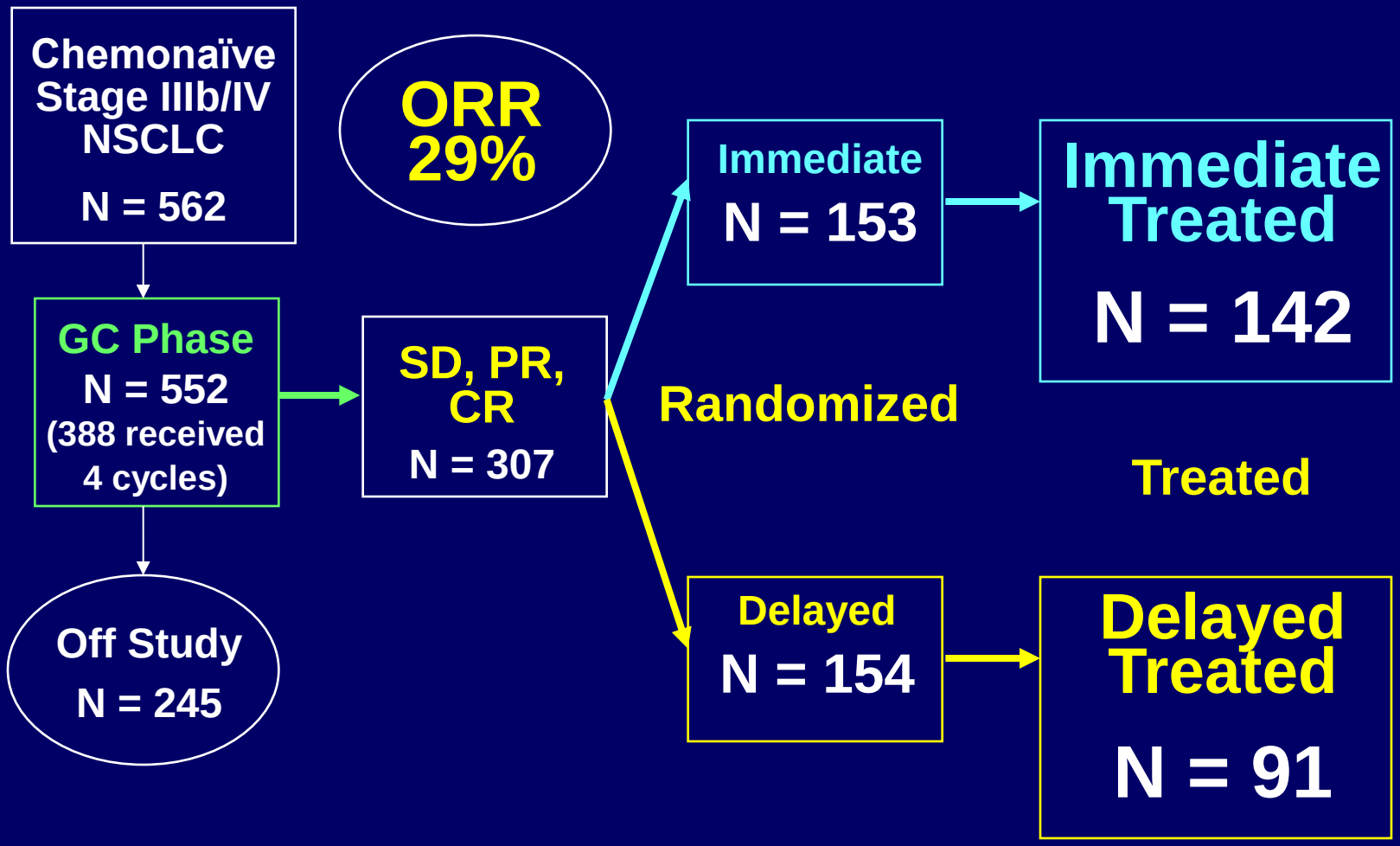


Maintenance Chemotherapy

Switch Maintenance

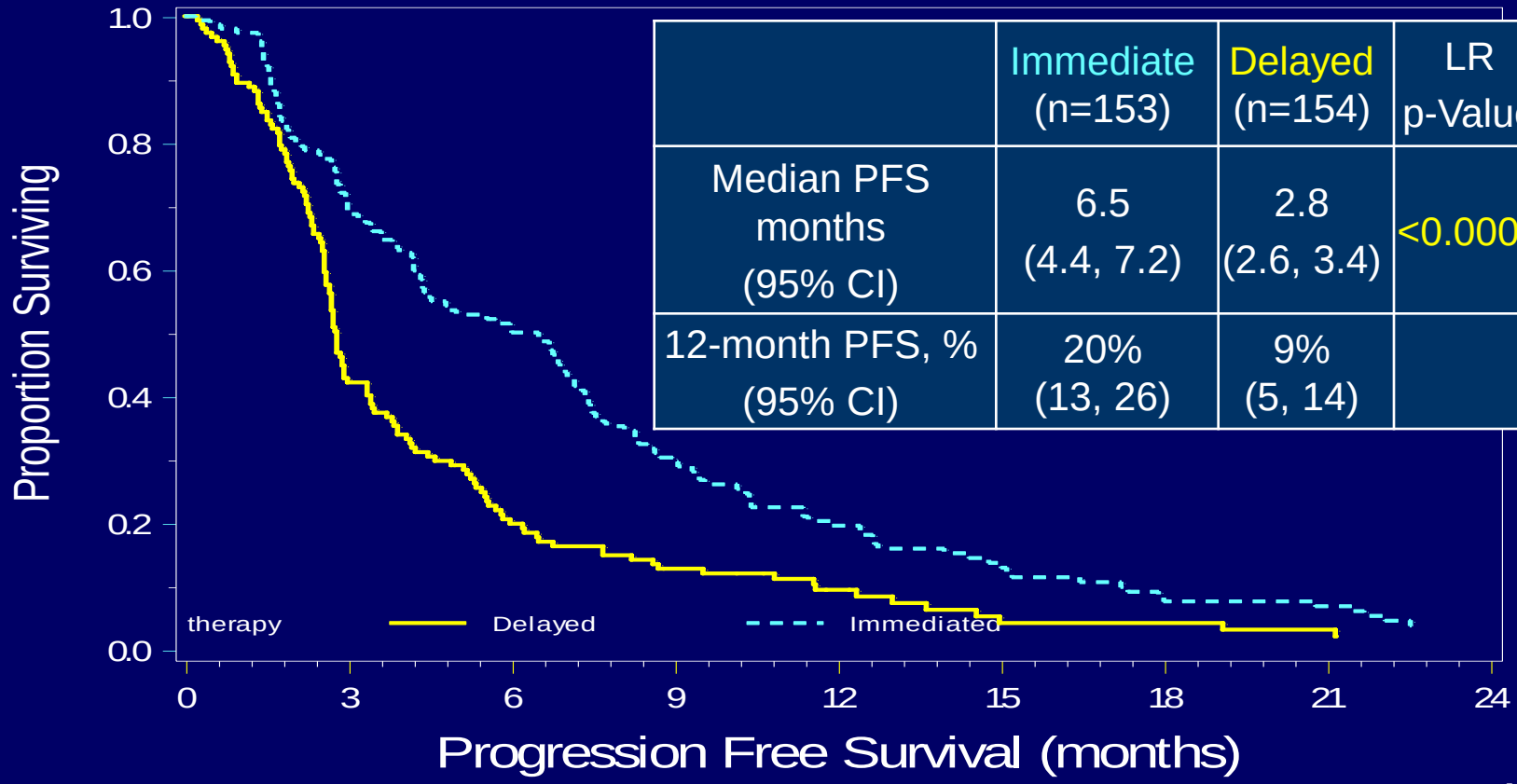
Continuation Maintenance

Immediate *vs* Delayed Docetaxel



Fidias et al. J Clin Oncol 27: 591, Feb, 2009

Progression-Free Survival
Total Randomized Population



	Immediate (n=153)	Delayed (n=154)	LR p-Value
Median PFS months (95% CI)	6.5 (4.4, 7.2)	2.8 (2.6, 3.4)	<0.0001
12-month PFS, % (95% CI)	20% (13, 26)	9% (5, 14)	

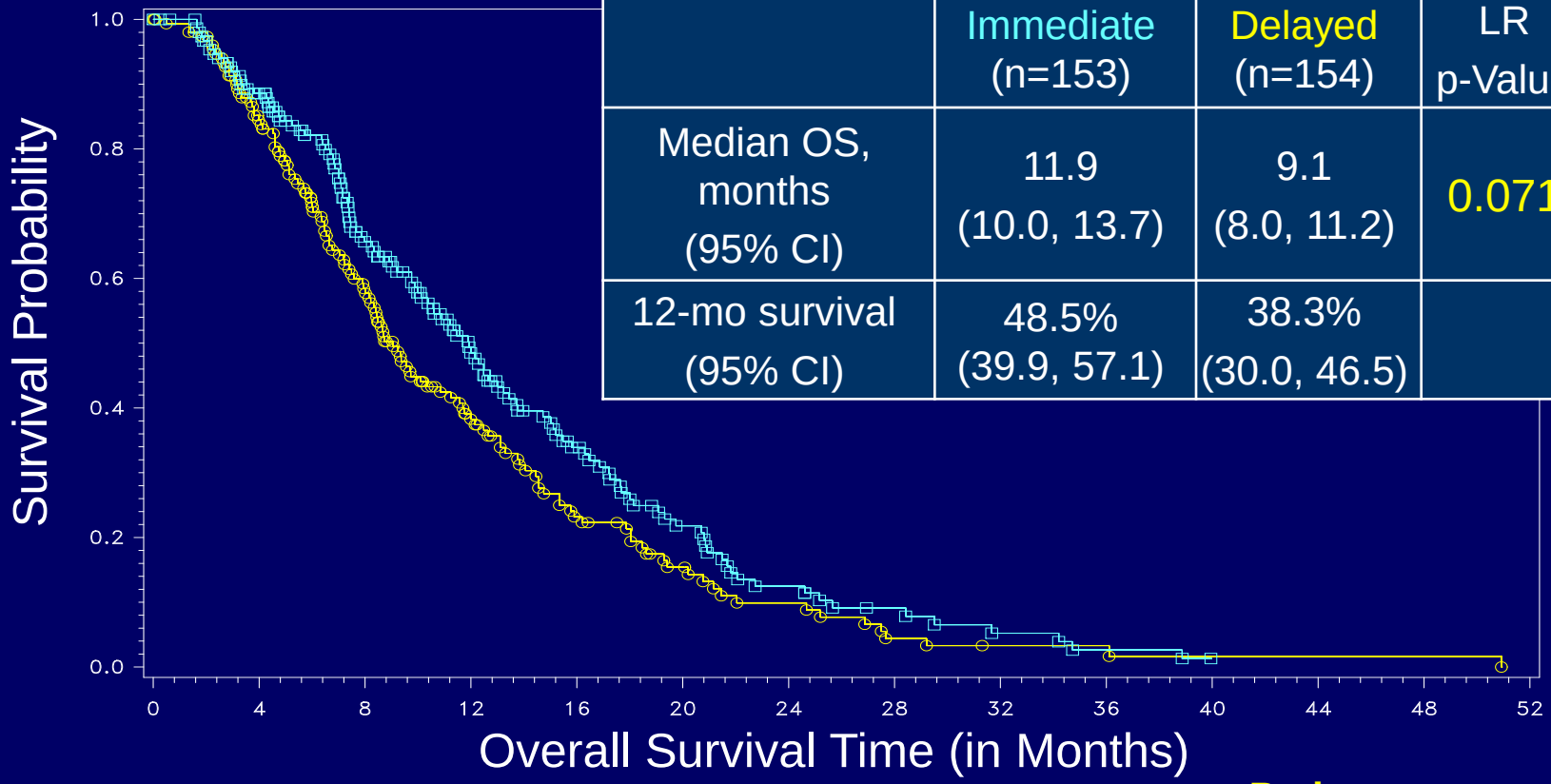
I:	153	72	27	11	5
D	154	28	10	4	2

Patients at Risk

Overall Survival

Total Randomized Population

	Immediate (n=153)	Delayed (n=154)	LR p-Value
Median OS, months (95% CI)	11.9 (10.0, 13.7)	9.1 (8.0, 11.2)	0.071
12-mo survival (95% CI)	48.5% (39.9, 57.1)	38.3% (30.0, 46.5)	

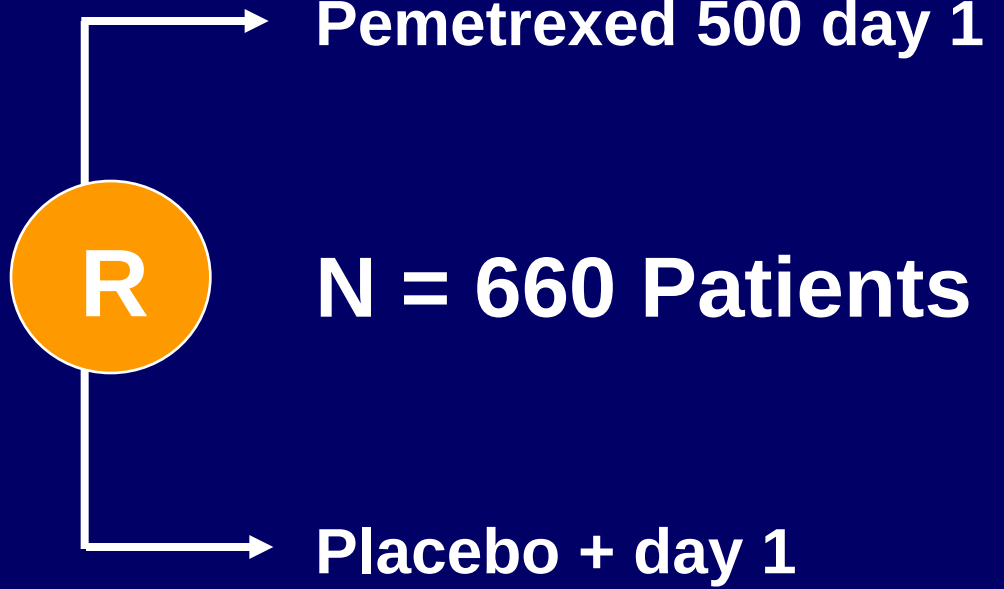


Patients at Risk							
I:	153	111	56	27	12	5	2
D:	154	98	45	22	9	3	2

Is this negative for survival benefit or under-powered??

JMEN: Phase III Study of Maintenance Pemetrexed after Standard First-Line Therapy in Advanced NSCLC

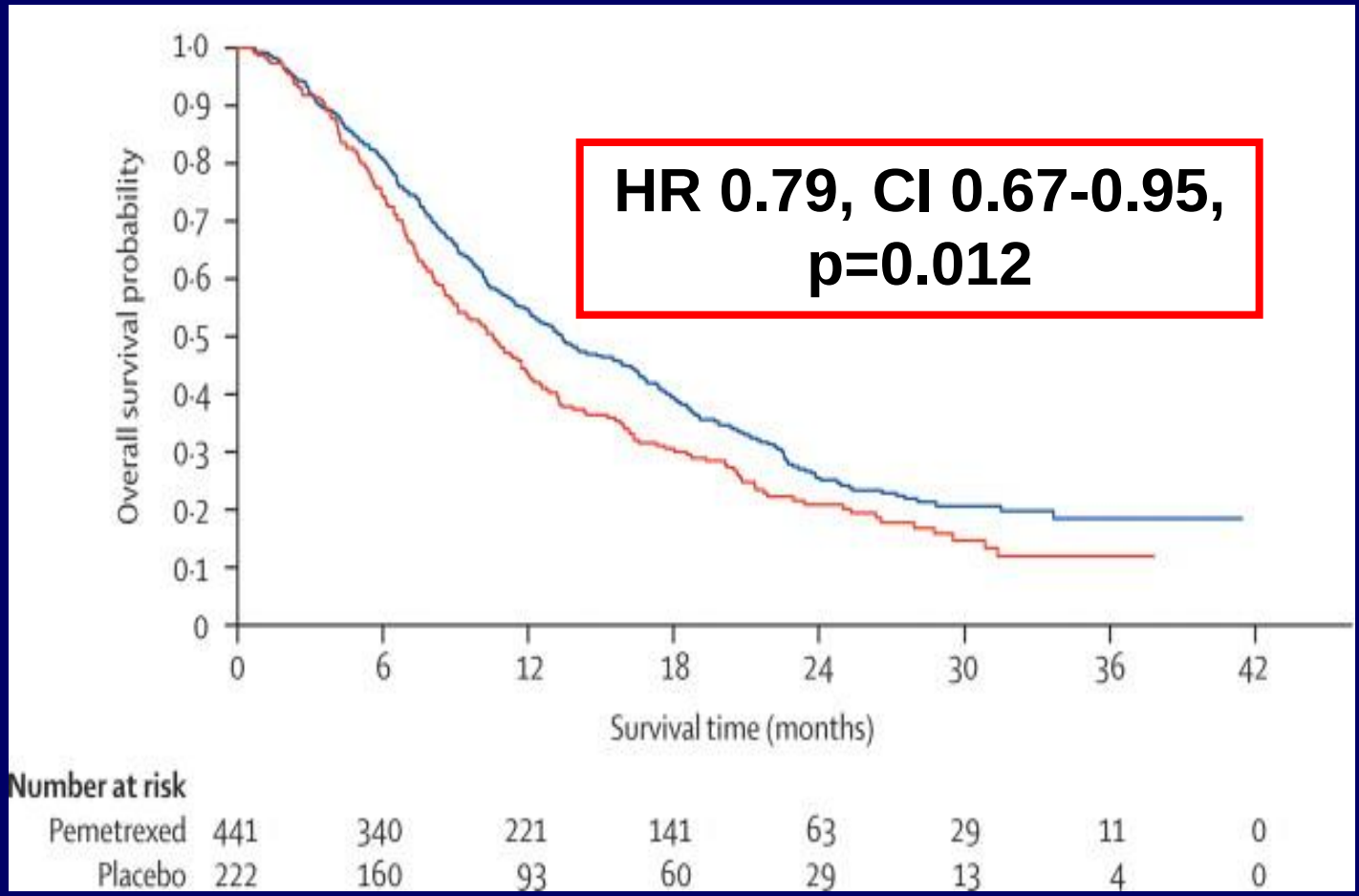
- Stage IIIB or IV NSCLC who has not progressed after 4 cycles of a standard chemotherapy



Primary objective: PFS, Superiority design

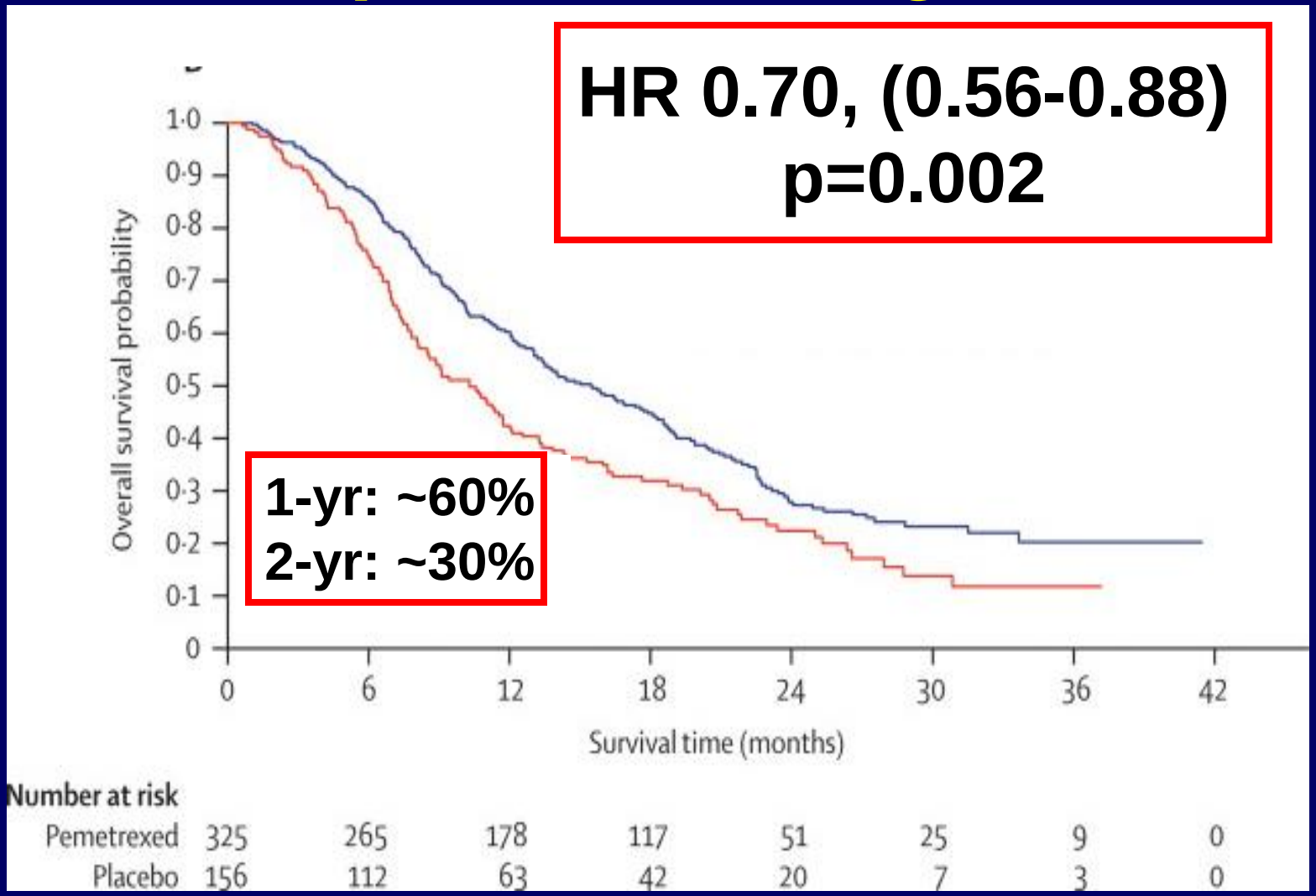
Secondary objectives: RR, OS, TTPD, TWQ (Time to Worsening QOL), QOL based on LCSS

JMEN Overall Survival



Ciulanu et al. Lancet, 2009

Maintenance Pemetrexed in Non-Squamous Lung Cancer



Ciulaneau et al. Lancet 374: 1432, 2009

JMEN: Efficacy by Histology

	Med OS* months		p-value HR	Med PFS* months		p-value HR	CR+PR+SD %		p-value
	Pem	Placebo		Pem	Placebo		Pem	Placebo	
Nonsquamous n=482	14.4	9.4	0.005 0.66 (0.49-0.88)	4.5	2.6	<0.00001 0.44 (0.36-0.55)	57.7	32.7	<0.001
Adeno n=329	16.4	11.7	0.091 0.728 (0.50, 1.05)	4.7	2.6	<0.00001 0.452 (0.35, 0.59)	61.0	33.0	<0.001
Large Cell n=20	9.1	5.5	0.154 0.424 (0.13, 1.38)	3.5	2.1	0.109 0.400 (0.13, 1.22)	45.5	33.3	0.670
Other n=133	11.3	7.0	0.005 0.469 (0.28, 0.80)	4.2	2.8	0.0002 0.433 (0.28, 0.67)	51.1	31.7	0.041
Squamous n=181	9.6	11.9	0.231 1.284 (0.85, 1.93)	2.8	2.6	0.039 0.692 (0.49, 0.98)	34.8	34.8	1.000

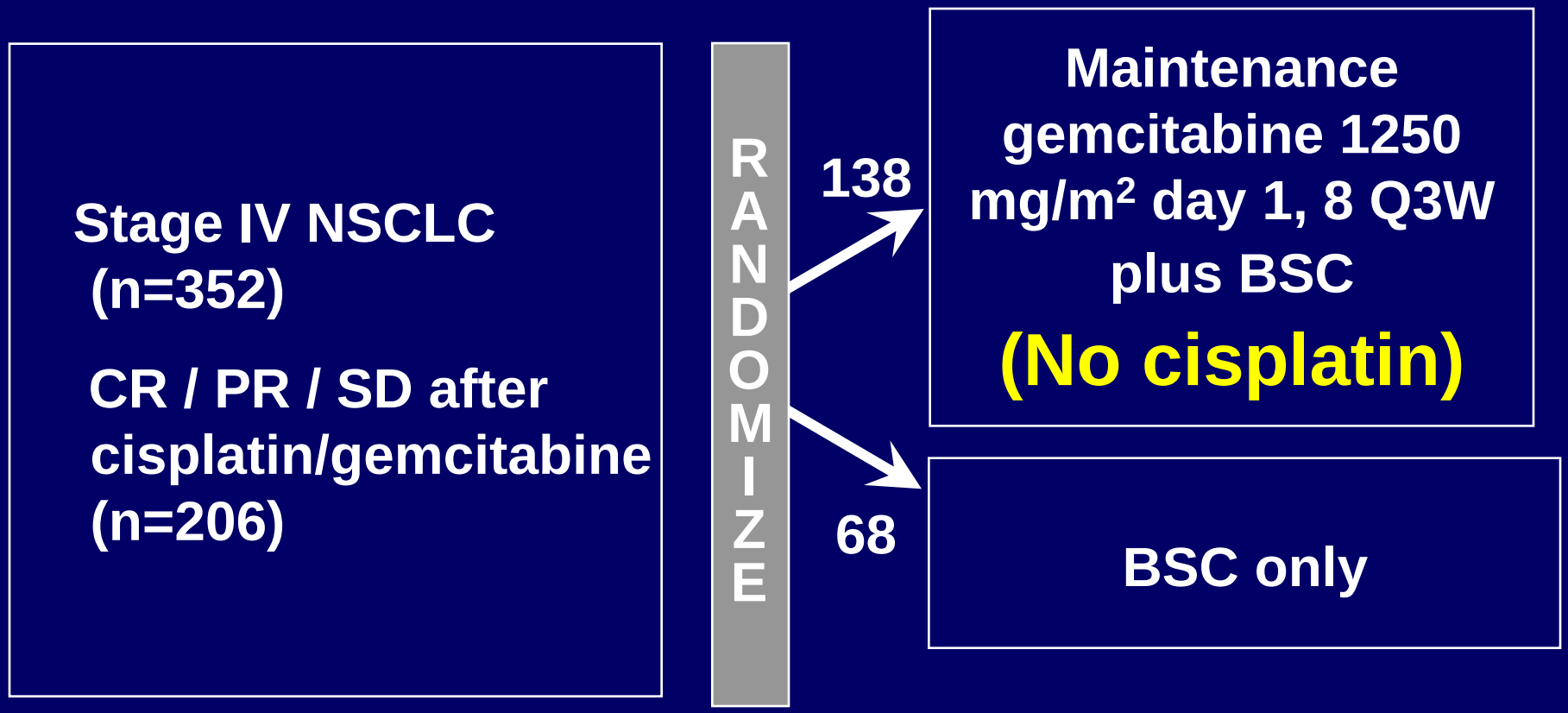
* Treatment-by-histology interaction tests significant for OS and PFS.

Source: SMPOSA(12/13/14/15),
SMPFSA (12/13/14/15), FQRESA (12/13/14/15)

Maintenance Chemotherapy

Continuing Same First-Line Single Agent Induction Chemotherapy *Without the Platinum Analogue*

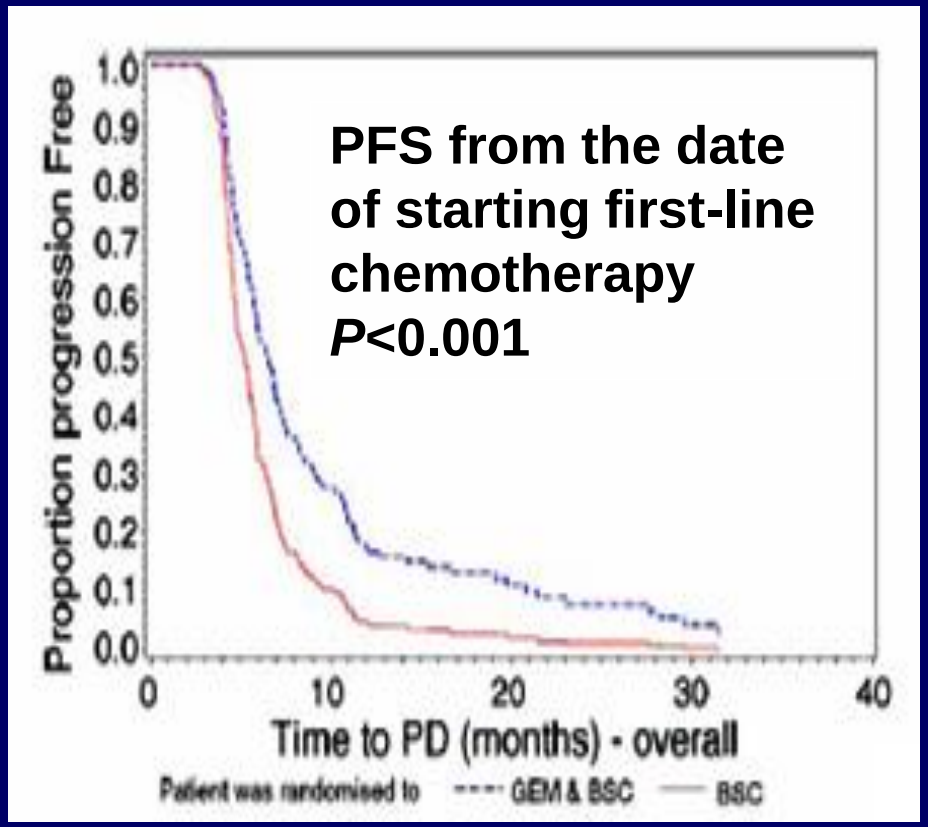
Advanced NSCLC
Gemcitabine Maintenance Therapy



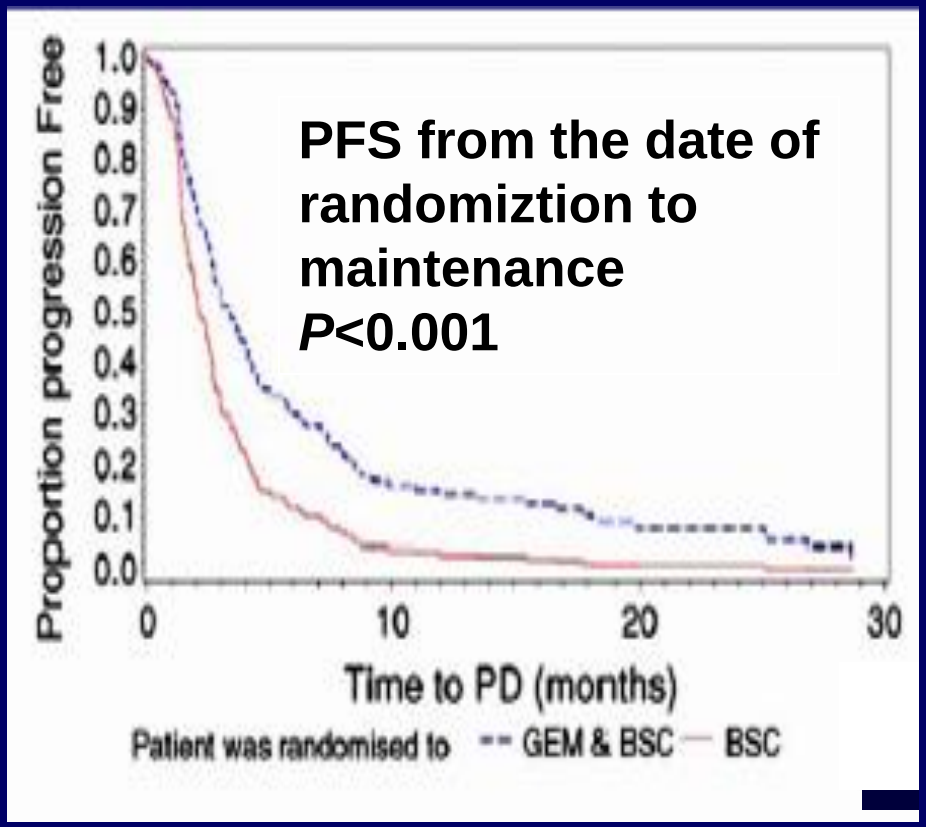
Primary endpoint: median time to progression

Brodowicz et al, Lung Cancer 2006; 52: 155-163

Gemcitabine Maintenance
Progression-Free Survival



PFS from the date of starting first-line chemotherapy
***P*<0.001**

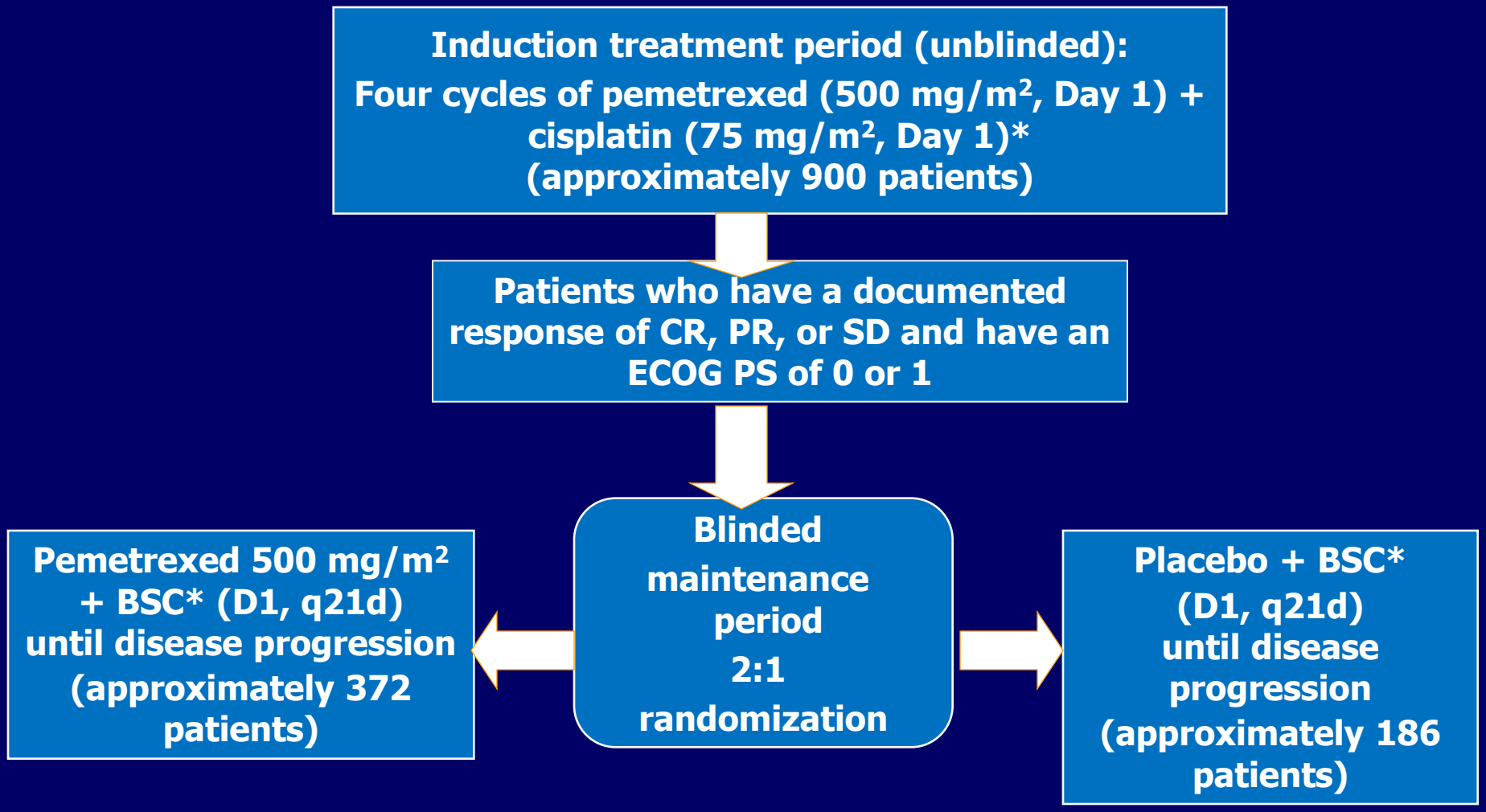


PFS from the date of randomiztion to maintenance
***P*<0.001**

Overall survival: 13.0 mos vs 11.0 mos, p= 0.19

Brodowicz et al, Lung Cancer 2006; 52: 155-163

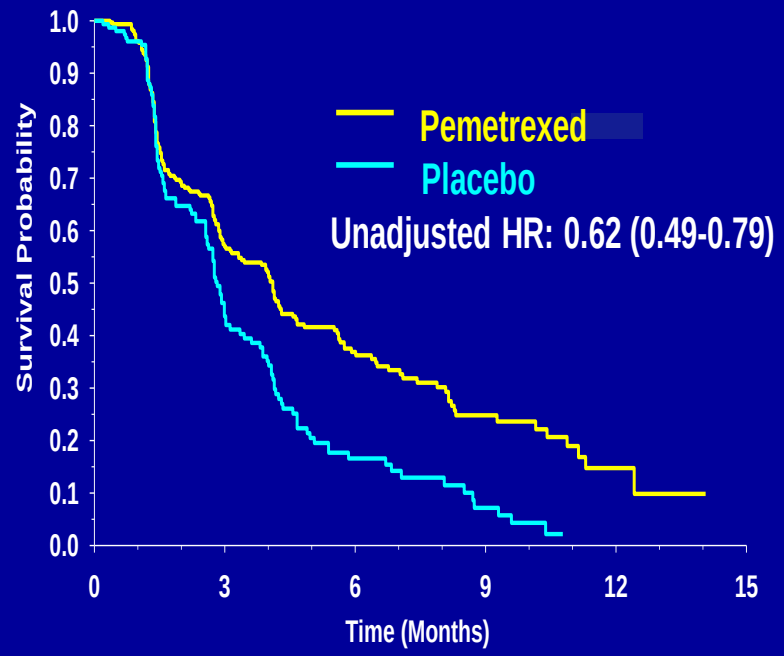
PARAMOUNT Study Design



*Patients received folic acid, vitamin B_{12}, and dexamethasone.

PARAMOUNT: PFS from Randomization

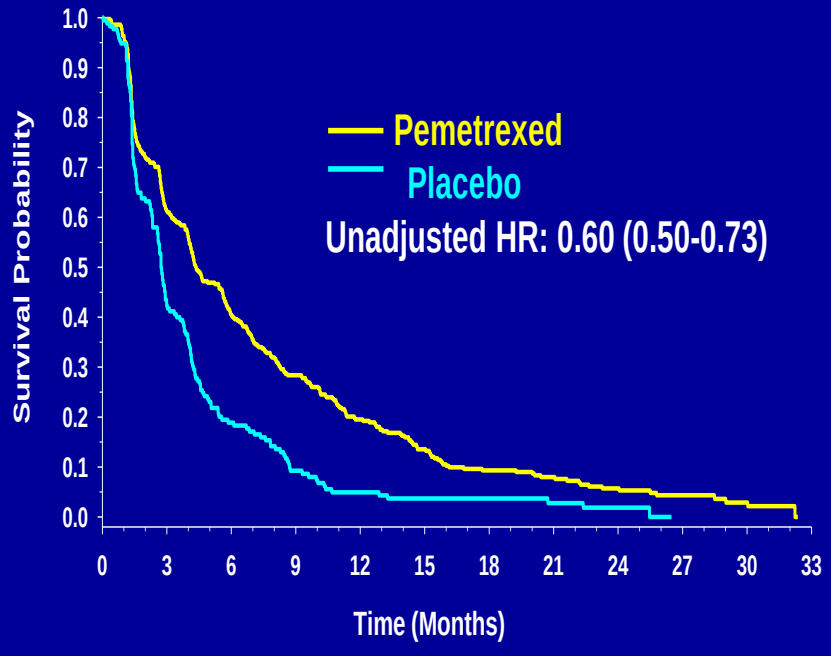
PFS: Primary Efficacy Endpoint



Patients at Risk

Pem + BSC	359	132	57	21	4	0
Plac+ BSC	180	52	15	5	0	0

PFS: Reassessed at Time of Final OS

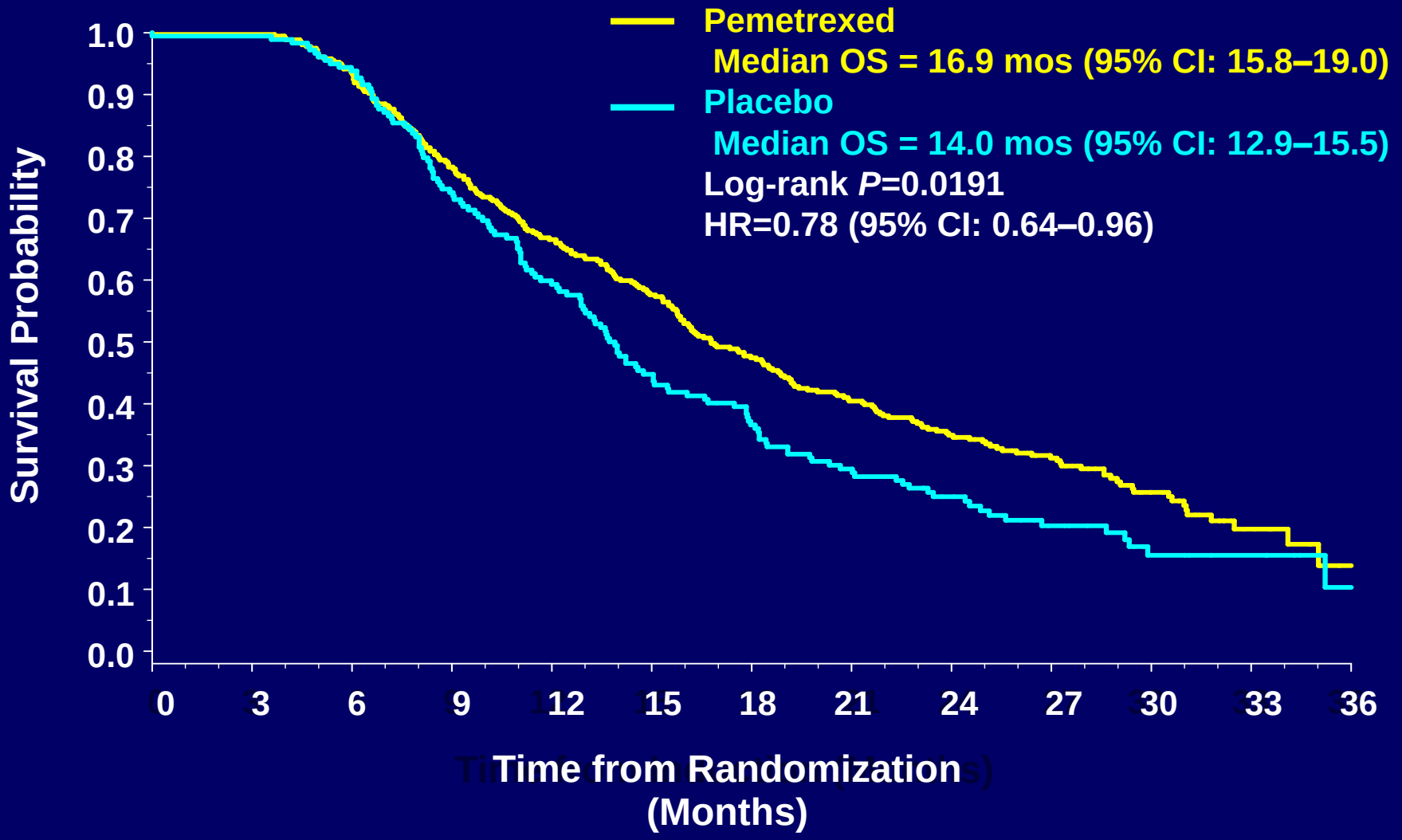


Patients at Risk

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

Paz-Ares, Proc ASCO, 2012

PARAMOUNT: Final OS from Induction



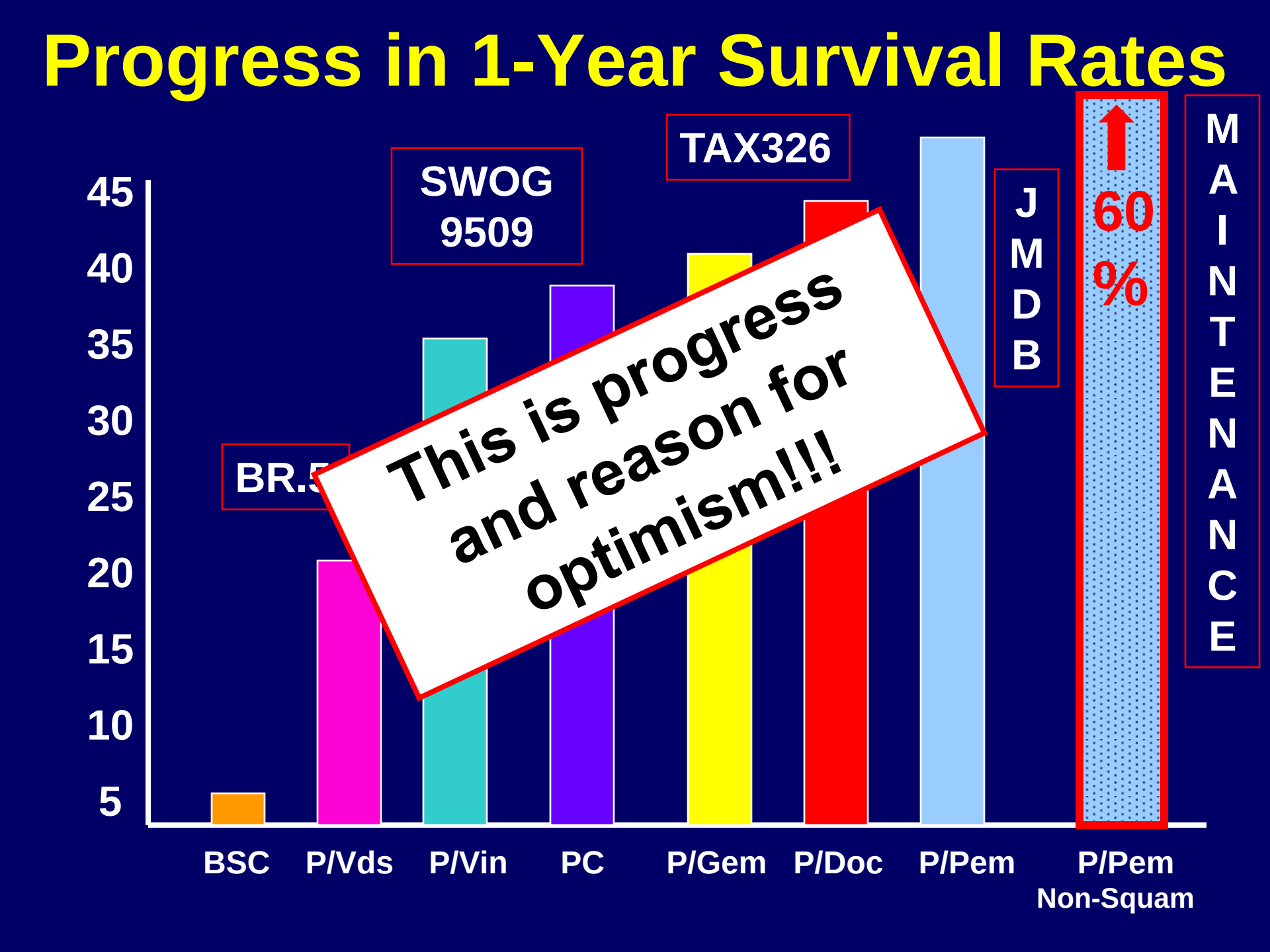
Paz-Ares, Proc ASCO, 2012

Conclusions

- Survival is improved significantly when patients are treated with pemetrexed continu
maintenance therapy com ebo (HR=0.78)
- The s nally consistent across ps, including response to induction

PARAMOUNT led to EMA and FDA approval

Progress in 1-Year Survival Rates



Second-Line Chemotherapy

The Nihilism Continues

1997

ASCO Guidelines for NSCLC

"…there is **no current evidence** that either confirms or refutes that **second-line chemotherapy** improves survival in … patients with advanced NSCLC."*

* *Treatment Guidelines For Unresectable NSCLC. JCO 15: 2996-3019, 1997.*

Study Design - TAX 317

NSCLC

Stratified by:

ECOG PS

(0,1 vs. 2)

and

Best response to prior platinum

(PD vs. non-PD)

RANDOMIZE

317 A

Taxotere 100 mg/m^2, one-hour IV infusion on Day 1, every 21 days

Premedication: Dexamethasone 8 mg x 10 doses, beginning 12 hours before Taxotere

By Protocol Amendment 6:

317 B

Taxotere 75 mg/m^2, one-hour IV infusion on Day 1, every 21 days

Premedication: Dexamethasone 8 mg x 5 doses, beginning 12 hours before Taxotere

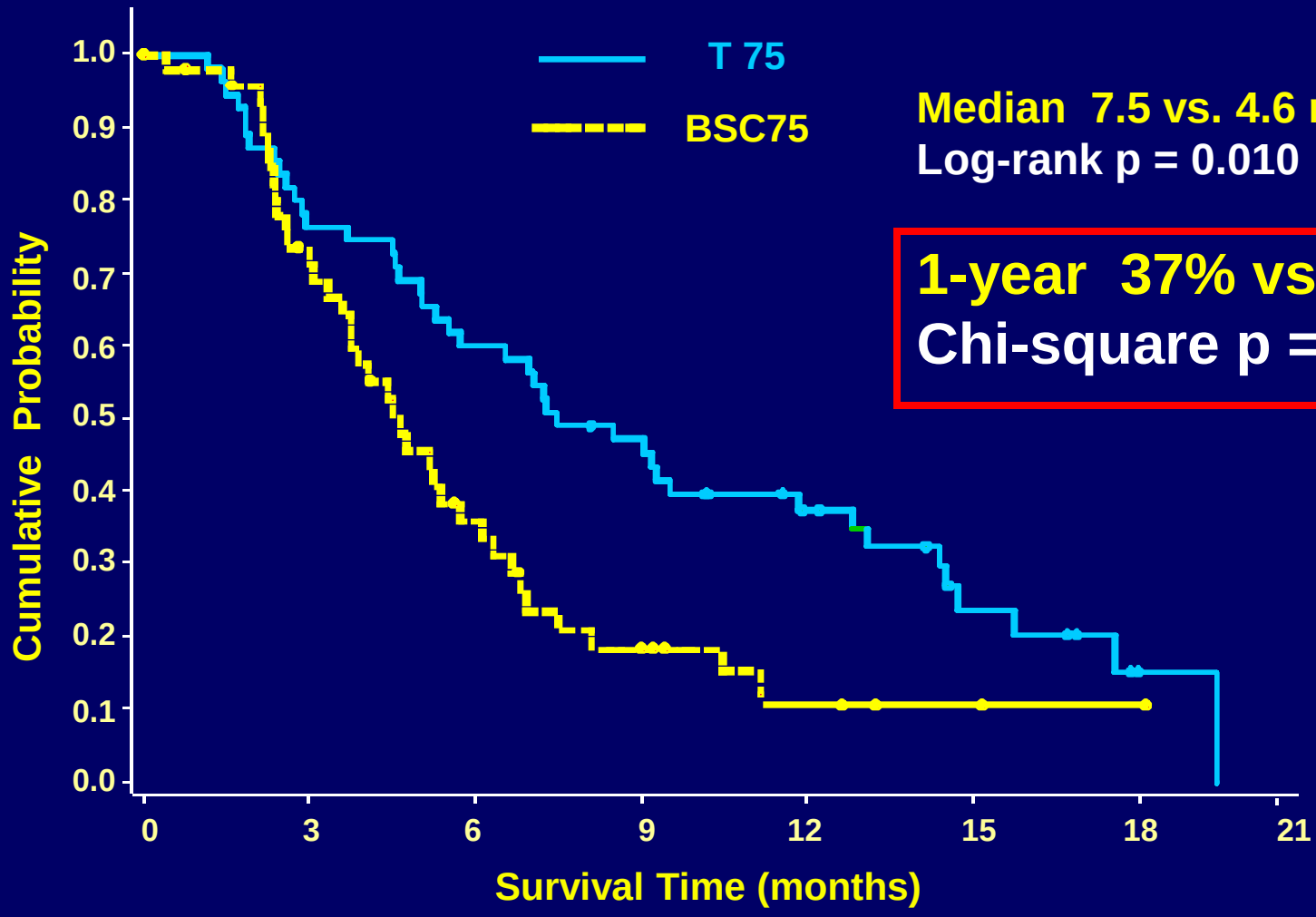
Best Supportive Care

without chemotherapy

Shepherd et al. J Clin Oncol 18: 2095, 2000

Survival - TAX 317B

Taxotere 75 mg/m^2 vs. BSC

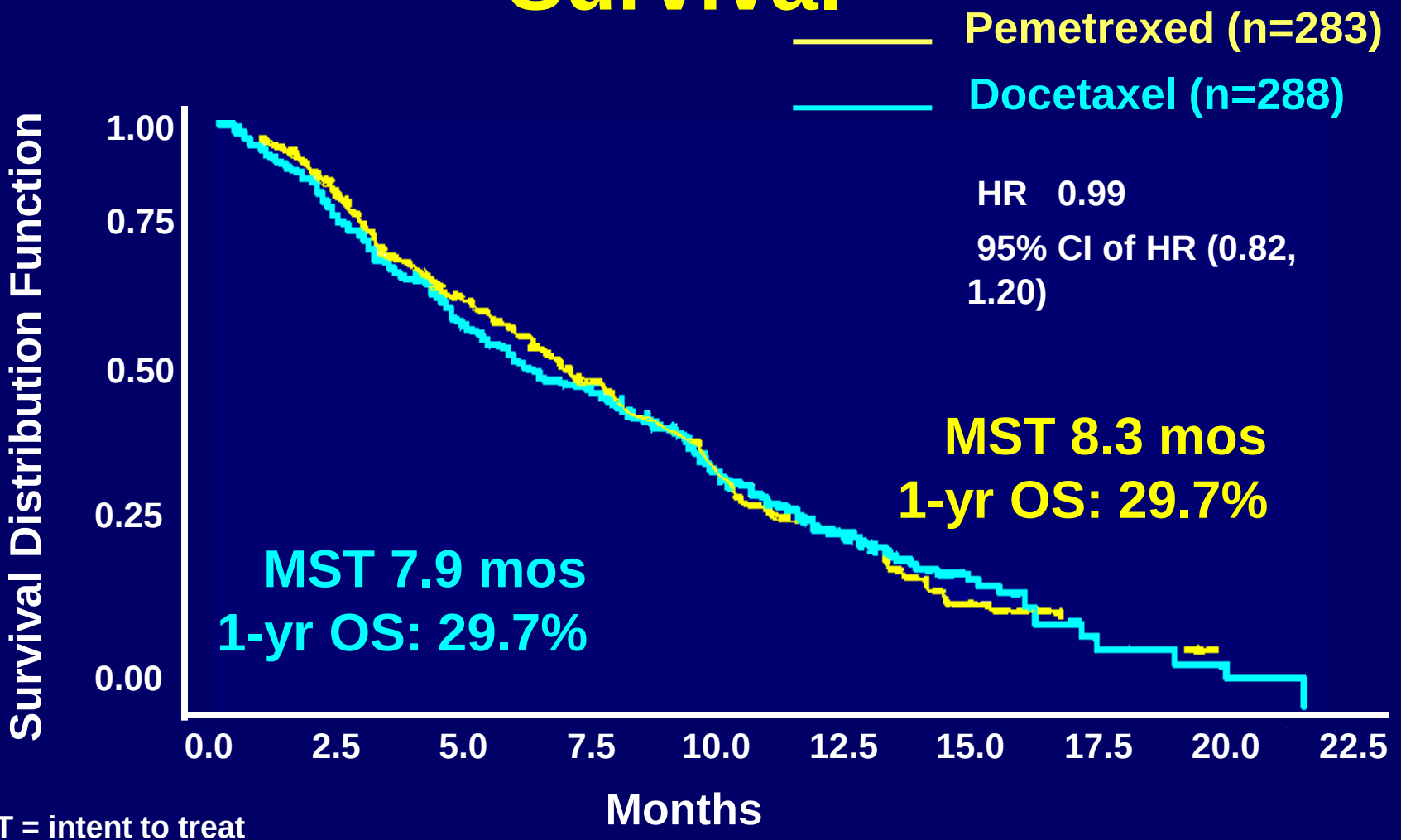


Median 7.5 vs. 4.6 mos.
Log-rank p = 0.010

1-year 37% vs. 12%
Chi-square p = 0.003

Shepherd et al. J Clin Oncol 18: 2095, 2000

JMEI: Pemetrexed *vs* Docetaxel: Survival



ITT = intent to treat
HR = hazard ratio
CI = confidence interval
MST = median survival time

Hanna et al. J Clin Oncol 22: 1589, 2004

JMEI: Efficacy by Histology

Efficacy Parameters	Second-Line Pemetrexed vs. Docetaxel ($N = 571$)	
	Nonsquamous[a] ($n = 399$)	Squamous ($n = 172$)
Overall survival		
Adjusted HR[b] (95% CI)	0.78 (0.61–1.00)	1.56 (1.08–2.26)
Superiority p	0.048	0.018
Treatment-by-histology interaction test p^c	0.001	
Progression-free survival		
Adjusted HR[b] (95% CI)	0.82 (0.66–1.02)	1.40 (1.01–1.96)
Superiority p	0.076	0.046
Treatment-by-histology interaction test p^c	0.004	

Scagliotti et al. T Thorac Oncol 6: 64, 2011

2003 ASCO Guidelines for NSCLC

"Docetaxel is ***recommended*** as second-line therapy for patients with advanced or metastatic NSCLC with adequate performance status who have progressed on first-line platinum-based therapy."*

July 27, 2004 – ODAC committee voted 13:0 to recommend **accelerated approval** of pemetrexed

* ASCO Treatment of Unresectable NSCLC Guideline. JCO 22-: 330-353, 2004

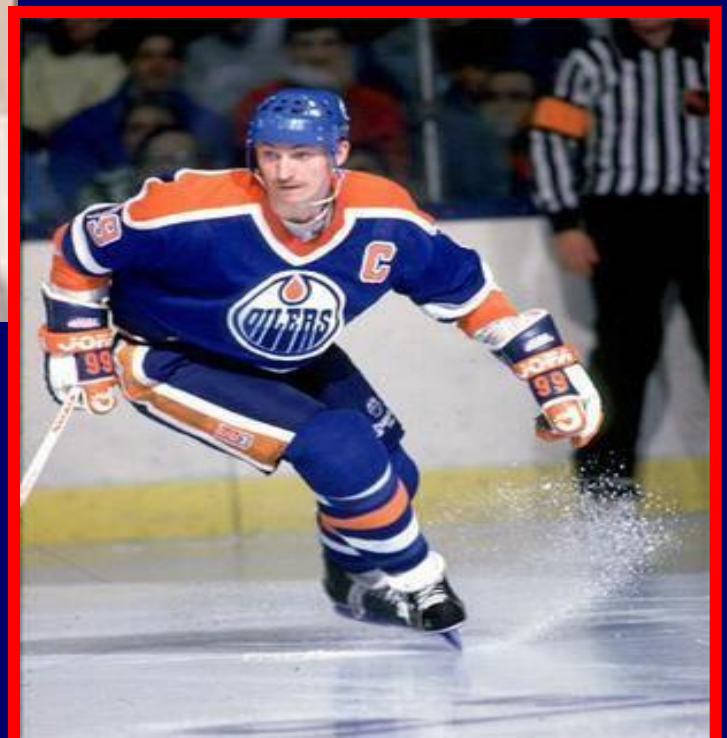
Why Continue to Study Chemotherapy for Advanced Non-SCLC in View of the Modest Survival Benefits???

Even Wayne Gretzky Had to Crawl Before He Could Skate!!!

Second and third-line

First-line

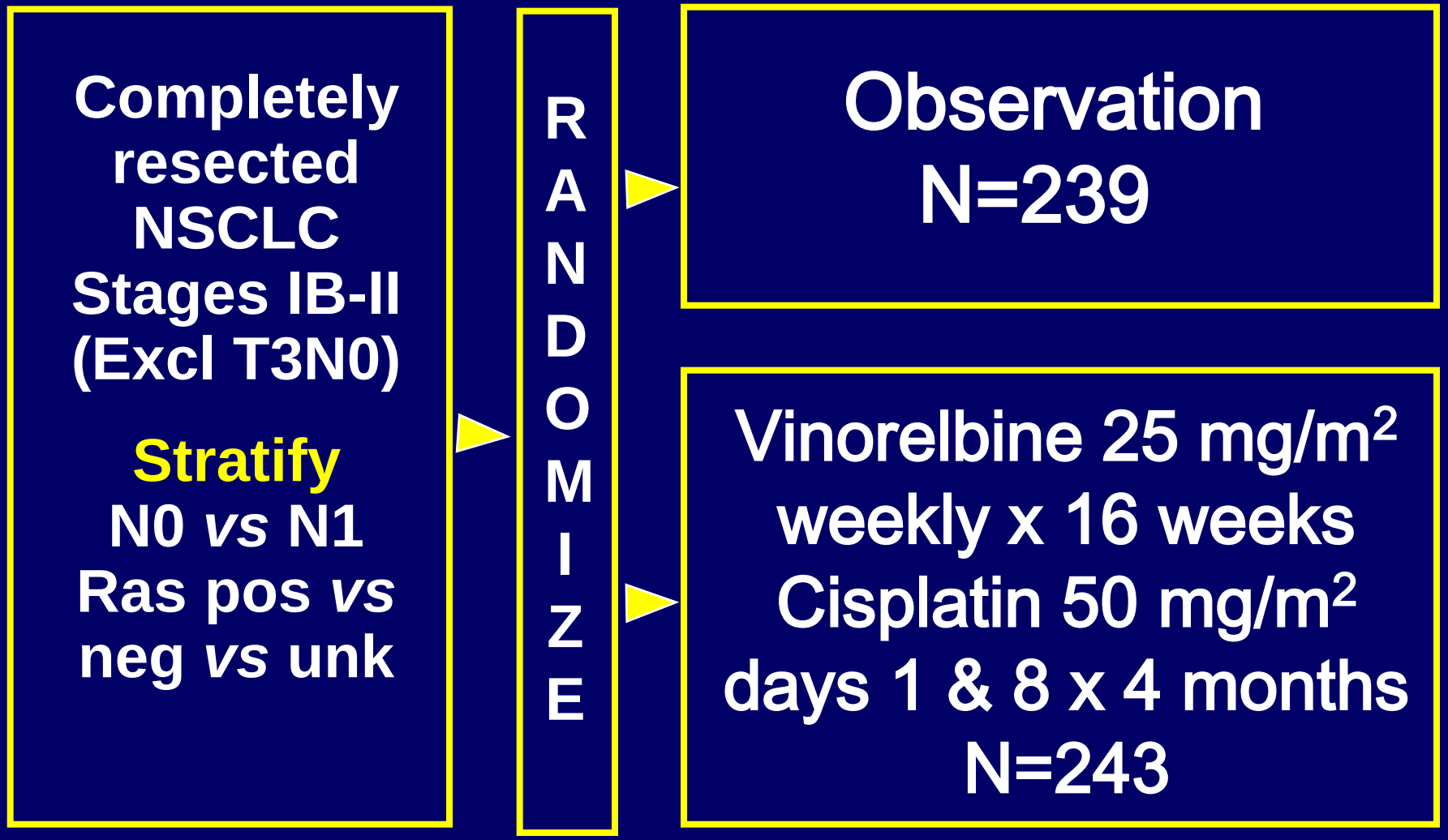
Adjuvant



The Nihilism of Adjuvant Chemotherapy After Surgery for Lung Cancer

- 52 (!!!!) randomized trials of chemotherapy versus observation
- 13% reduction in the risk of death, yet difference not significant
- Chemotherapy versus observation trials continued for another decade!!
- Yet this is where we have a chance to improve the CURE rate

NCIC-CTG Intergroup Trial BR.10

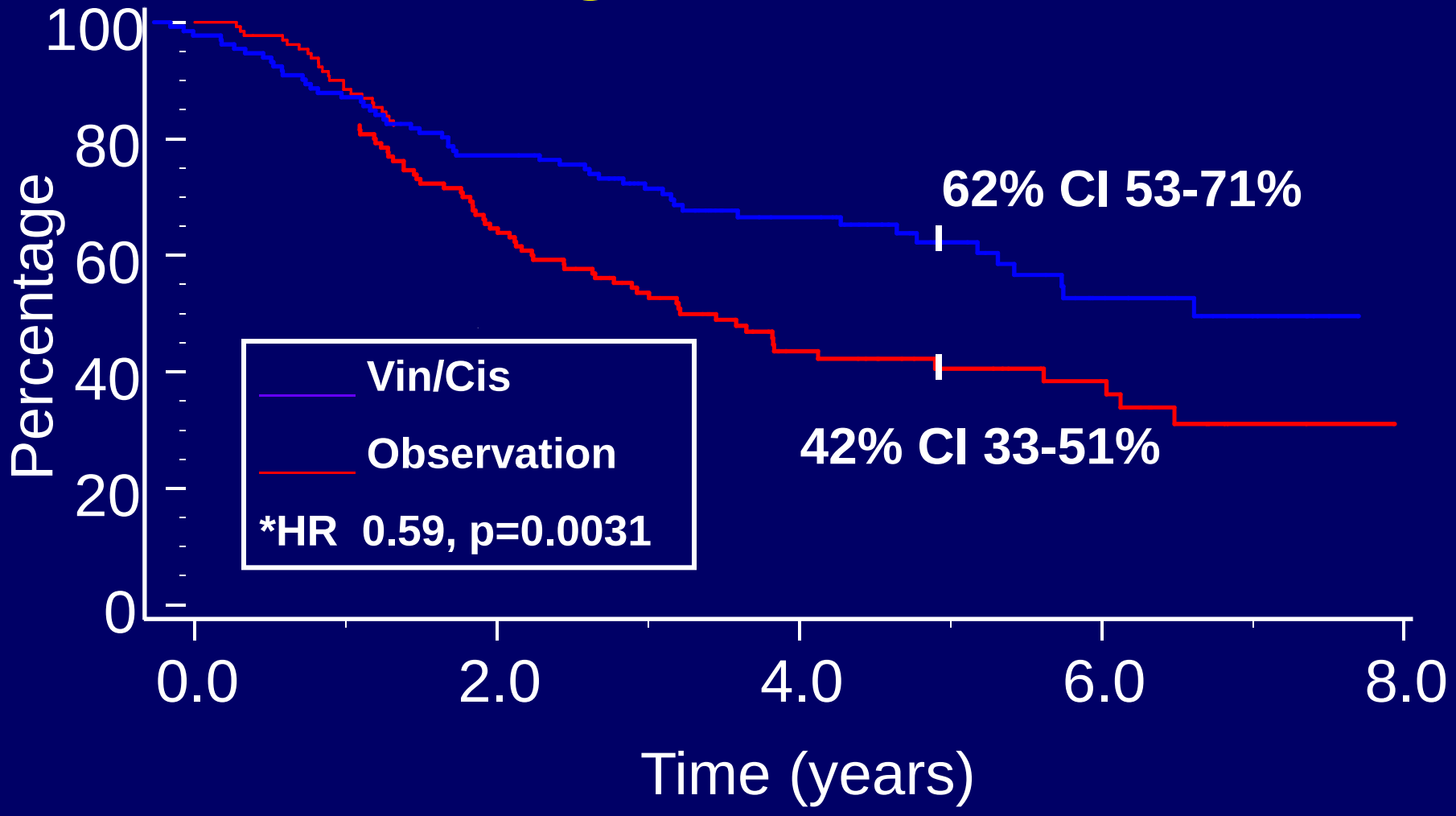


Winton et al. N Engl J Med 353: 2589, 2005

NCIC CTG BR.10 : A Landmark, Paradigm-Shifting Study

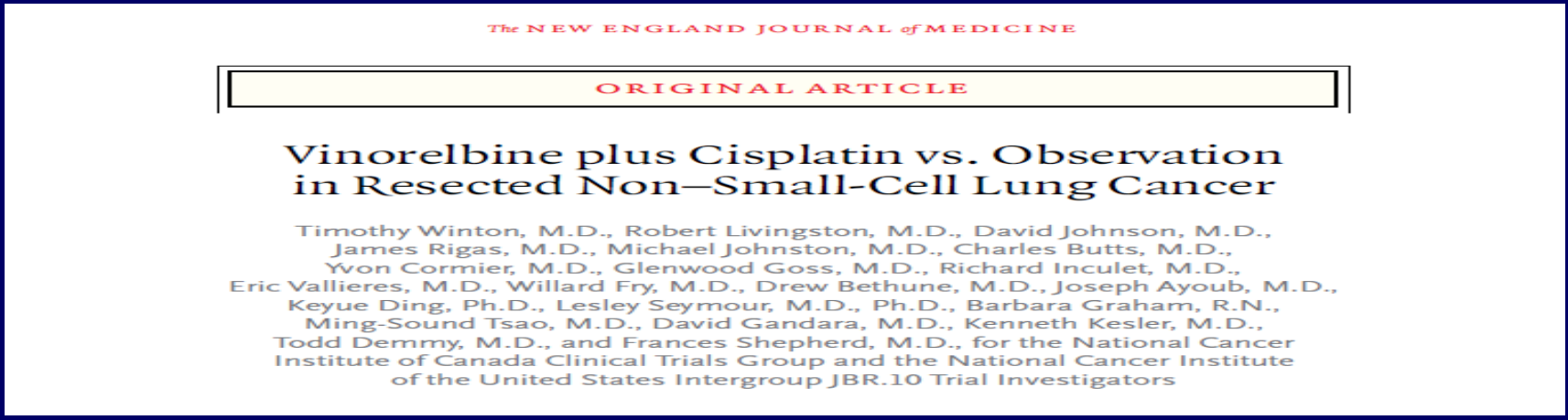
Winton et al. N Engl J Med 353: 2589, 2005

BR.10 Overall Survival
Stage T1-2 N1



Winton et al. N Engl J Med 353: 2589, 2005

NCIC CTG BR.10



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

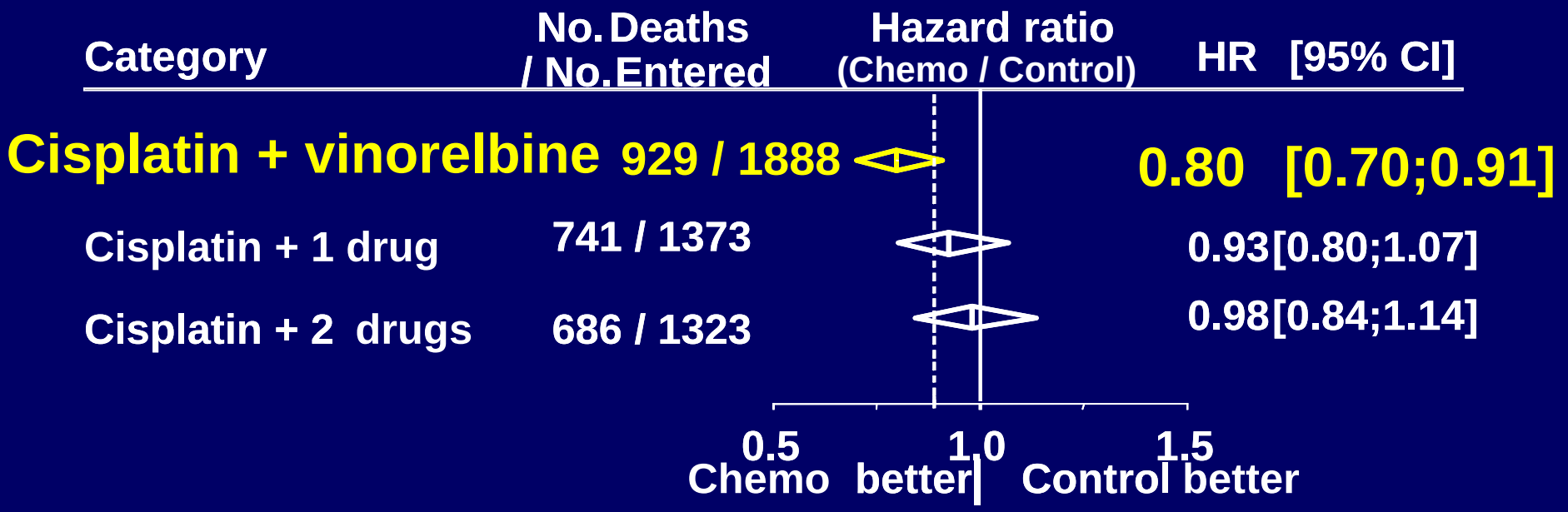
Vinorelbine plus Cisplatin vs. Observation in Resected Non–Small-Cell Lung Cancer

Timothy Winton, M.D., Robert Livingston, M.D., David Johnson, M.D., James Rigas, M.D., Michael Johnston, M.D., Charles Butts, M.D., Yvon Cormier, M.D., Glenwood Goss, M.D., Richard Inculet, M.D., Eric Vallieres, M.D., Willard Fry, M.D., Drew Bethune, M.D., Joseph Ayoub, M.D., Keyue Ding, Ph.D., Lesley Seymour, M.D., Ph.D., Barbara Graham, R.N., Ming-Sound Tsao, M.D., David Gandara, M.D., Kenneth Kesler, M.D., Todd Demmy, M.D., and Frances Shepherd, M.D., for the National Cancer Institute of Canada Clinical Trials Group and the National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators

- **BR.10 was a landmark trial**
- **It changed practice at a global level**
- **It changed the *cure rate* for resected lung cancer**

Was it a fluke?????

LACE: Chemotherapy Effect & Associated Drugs

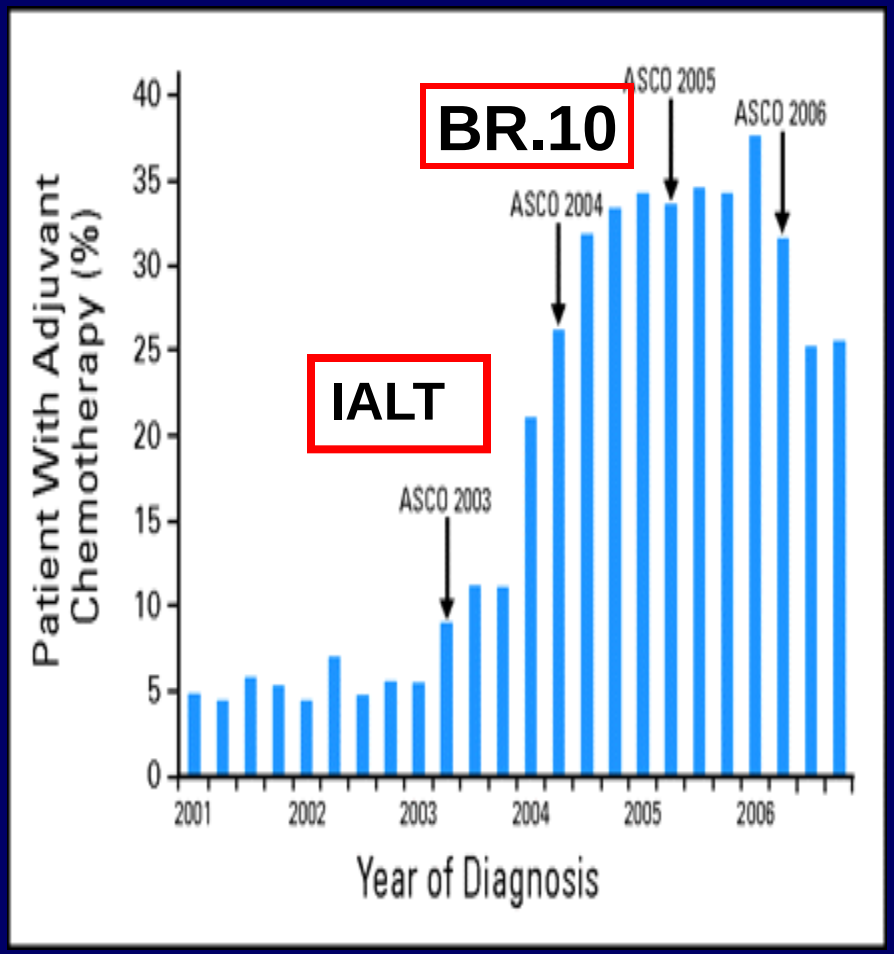


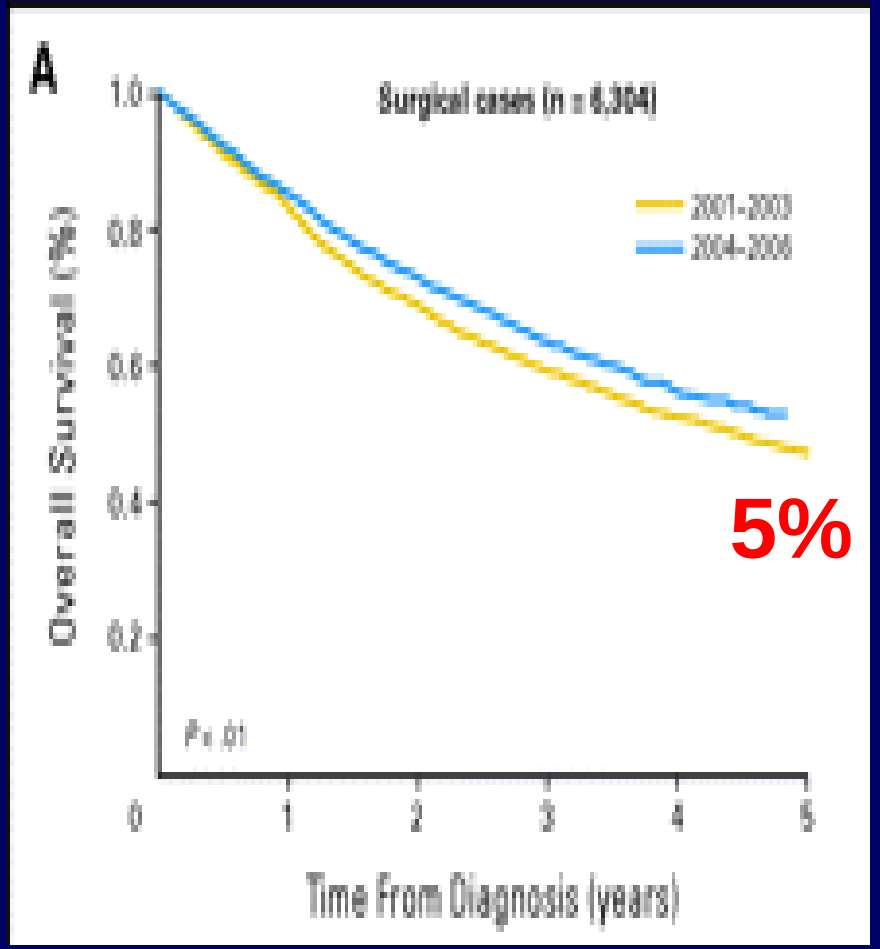
Test for interaction: p = 0.104

The effect of cisplatin+vinorelbine was marginally better than the effect of other drug combinations, this is significant when the other combinations are pooled (p=0.04, post-hoc analysis)

Pignon et al J Clin Oncol 2008

Changing the CURE RATE at the Population-Based Level





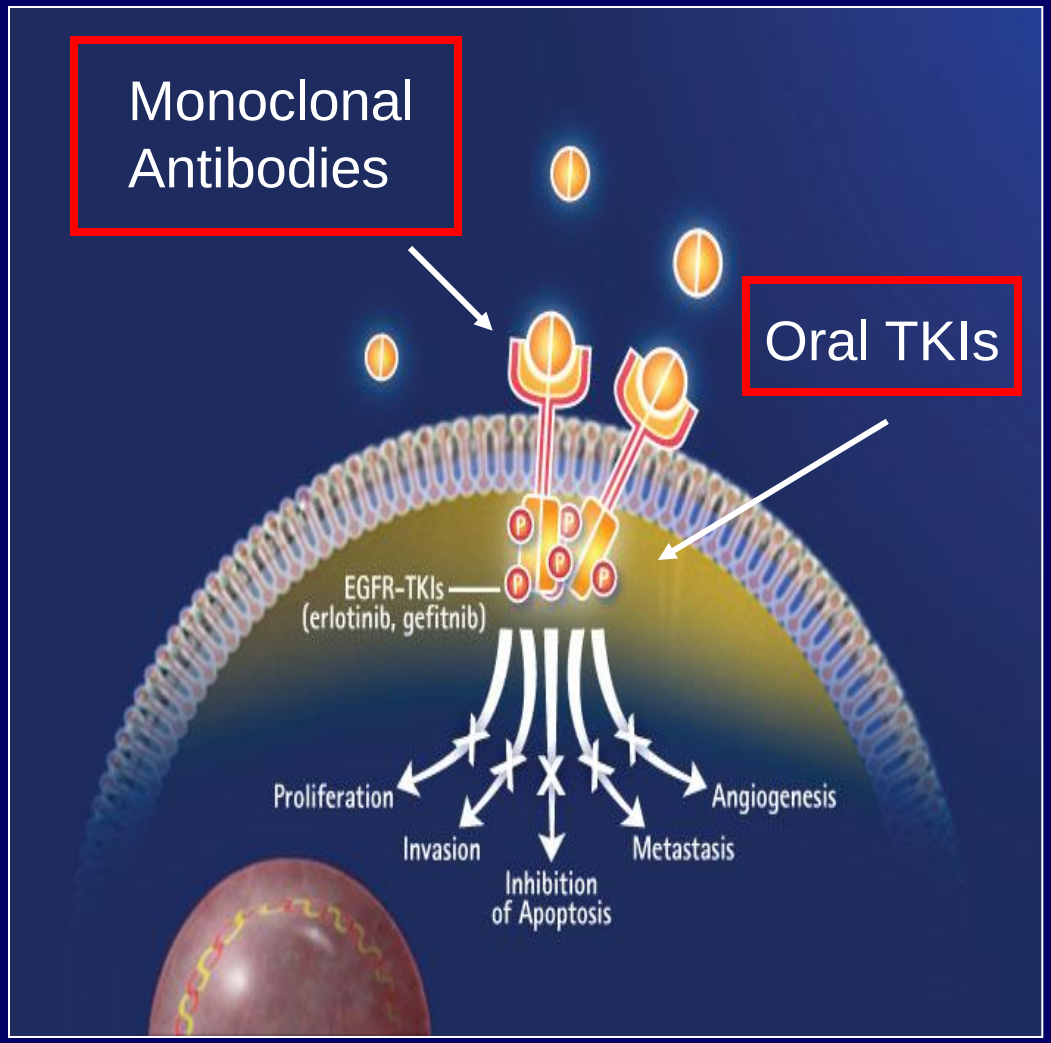
Booth et al. J Clin Oncol 28: 3472, 2010

Third-Line and Now Even Fourth-Line Therapy

The Nihilism Continues

Diverse Antitumor Effects of EGFR Inhibition

- Proliferation
- Invasion
- Inhibition of apoptosis
- Metastasis
- Angiogenesis
- **Frequently expressed and over-expressed in lung cancer**
- **Associated with poor prognosis**



NCIC CTG BR.21: Study Design

Stratified by:
- Centre
- PS, 0/1 *vs* 2/3
- Response to prior Rx (CR/PR:SD:PD)
- Prior regimens, (1 *vs* 2)
- Prior platinum, (Yes *vs* no)

▶ RANDOMIZE ▶

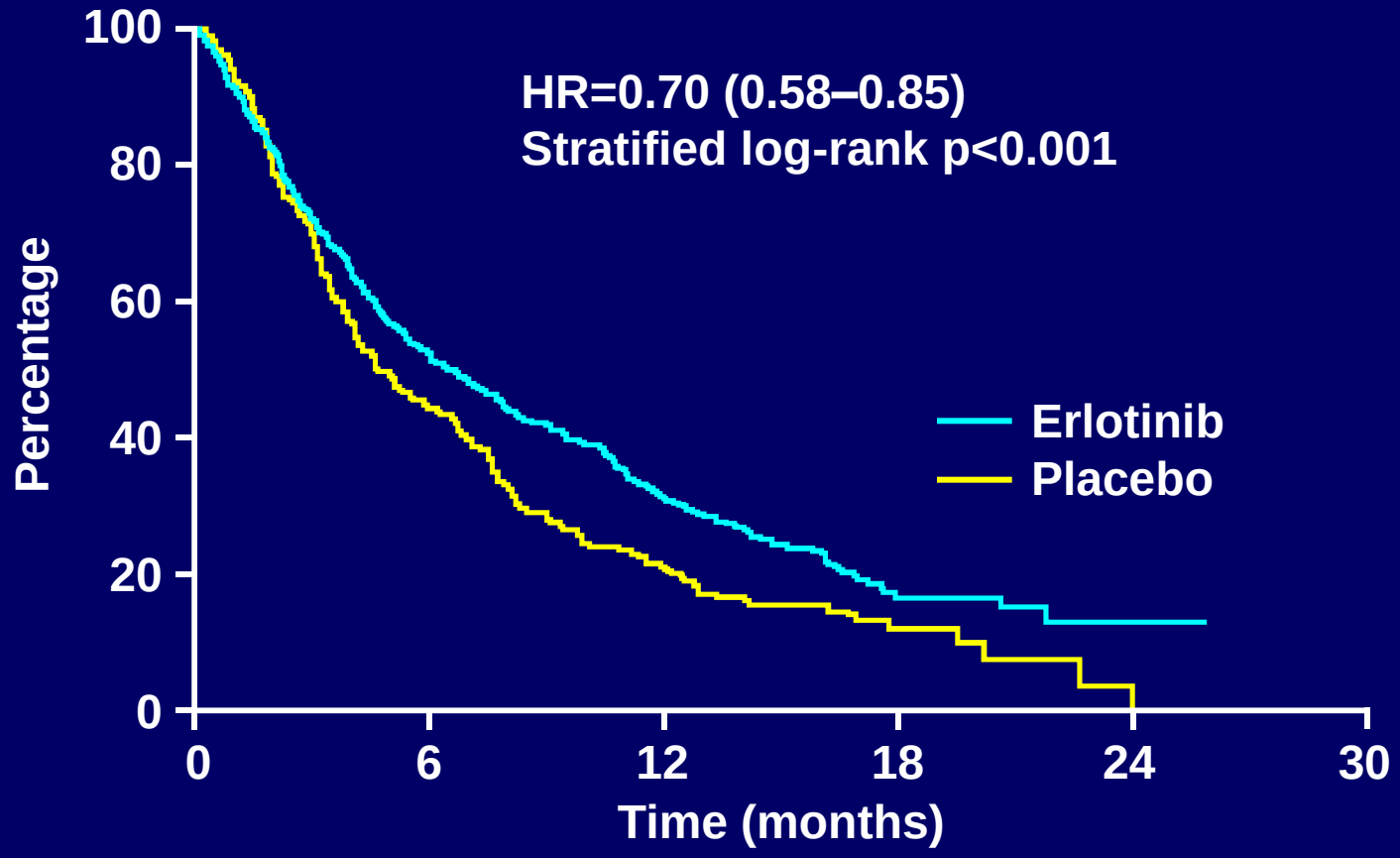
- Erlotinib* 150 mg daily
- Placebo "150 mg" daily

*2:1 Randomization

Shepherd et al. N Engl J Med 353: 132, 2005

National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

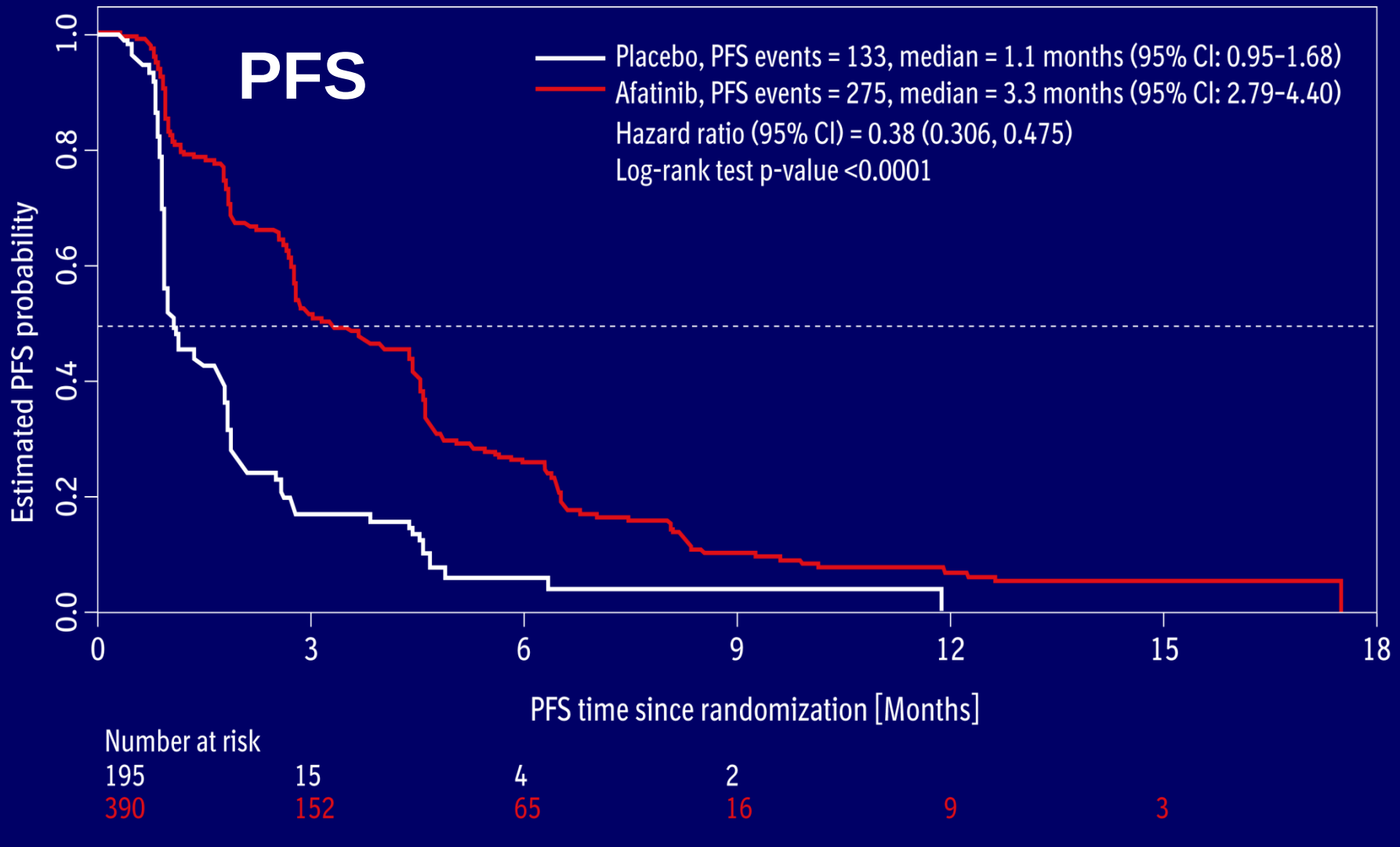
BR.21: The first Trial to Demonstrate a Survival Advantage for a Molecularly-Targeted Agent in Lung Cancer



At risk						
Erlotinib	488	255	145	23	4	0
Placebo	243	107	50	9	0	0

Shepherd, et al. N Engl J Med 353: 132, 2005.

LUX- Lung 1: Afatinib *vs* Placebo in Fourth-Line!!!



Thanks to Two Decades of Clinical Trials…

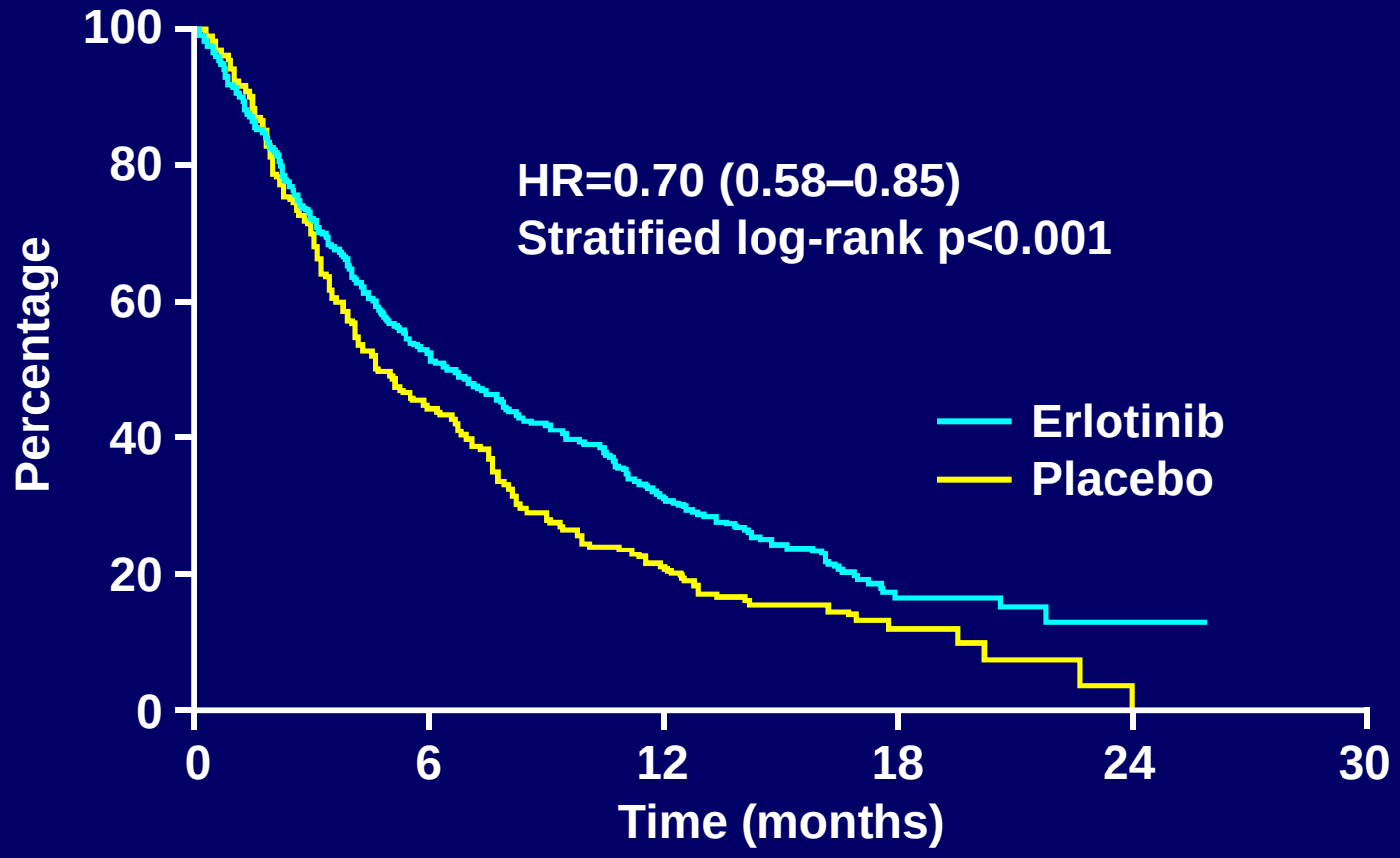
- Patients with lung cancer can now expect to derive a survival benefit from
  - First-line chemotherapy
  - Second-line chemotherapy
  - Third-line molecularly targeted Rx
- They can expect to derive symptom benefit from treatment
- The toxicity of treatment does not have a negative effect on overall QoL
- New drugs must be evaluated in 4th-line (!!) or 1) added to or 2) compared to other Rx

How Can We Improve the Cure Rate for Lung Cancer??

- *Prevention goes without saying*
- Early Detection
- Molecular targeting
- Identifying the appropriate populations to treat
  - Molecular markers of prognosis
  - Molecular predictors of response
  - Genomic markers of response
  - Genomic markers of toxicity

National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

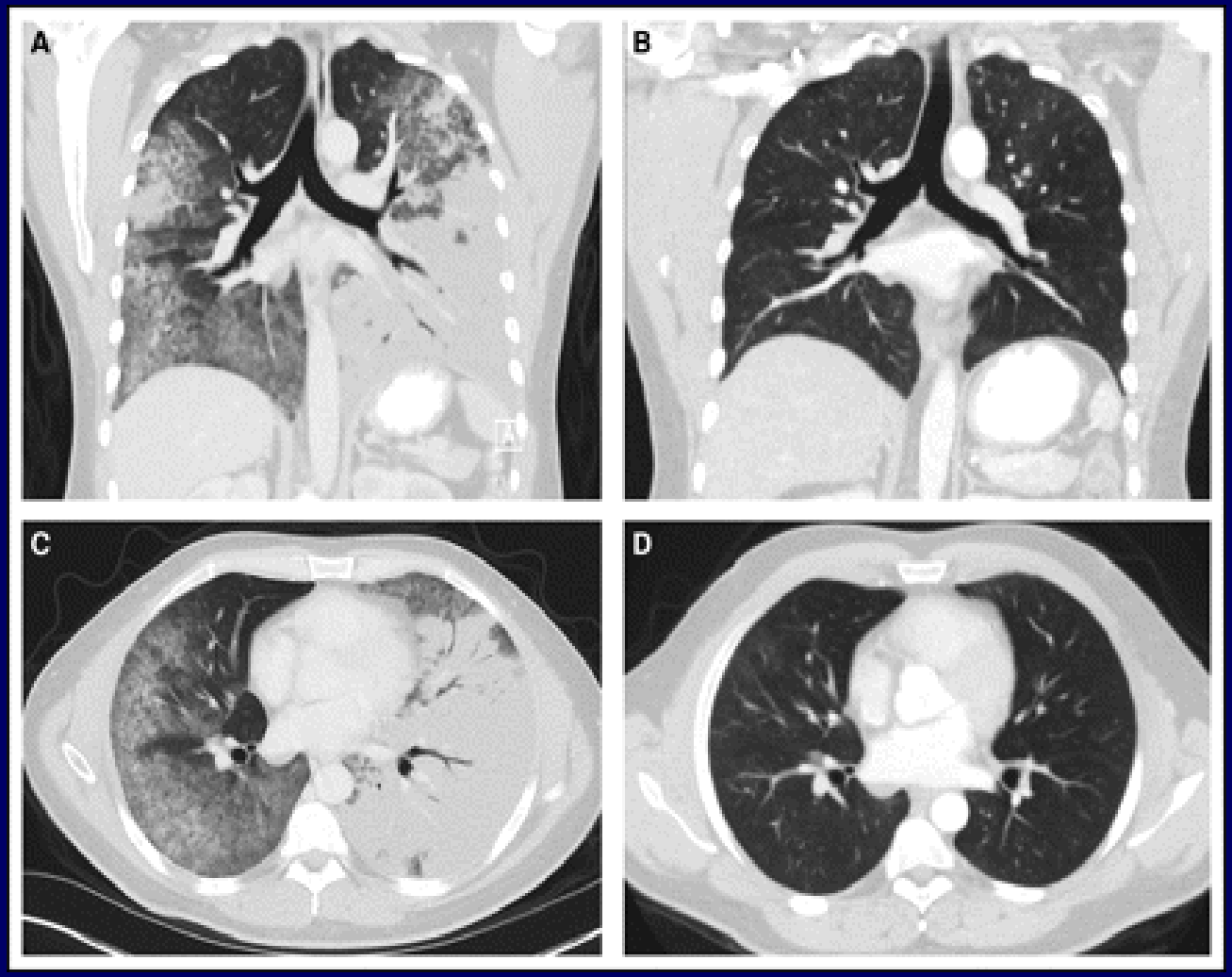
BR.21: The First Trial to Demonstrate a Survival Advantage for a Molecularly-Targeted Agent in NSCLC



At risk						
Erlotinib	488	255	145	23	4	0
Placebo	243	107	50	9	0	0

Shepherd, et al. N Engl J Med 353: 132, 2005.

Dramatic and Rapid Response to EGFR Inhibitor Therapy.

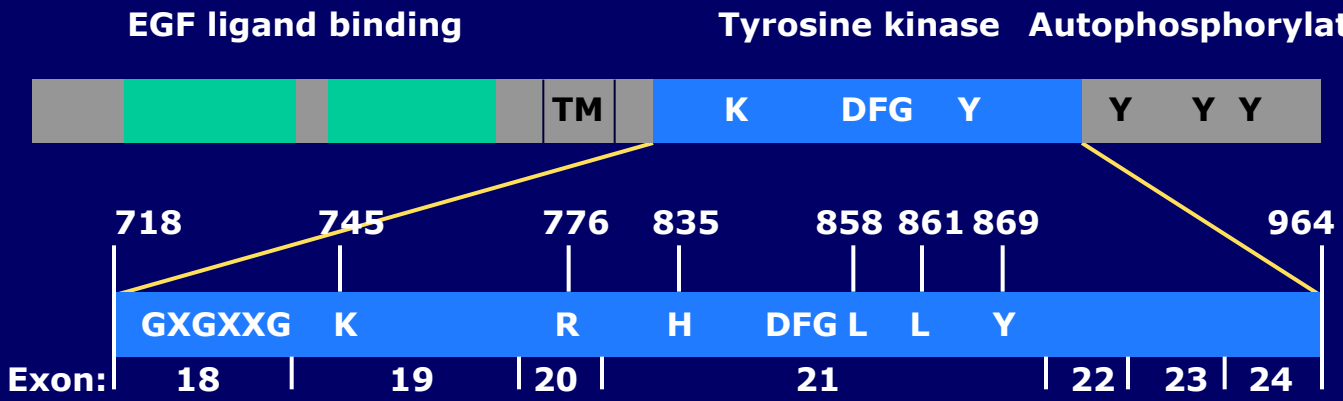


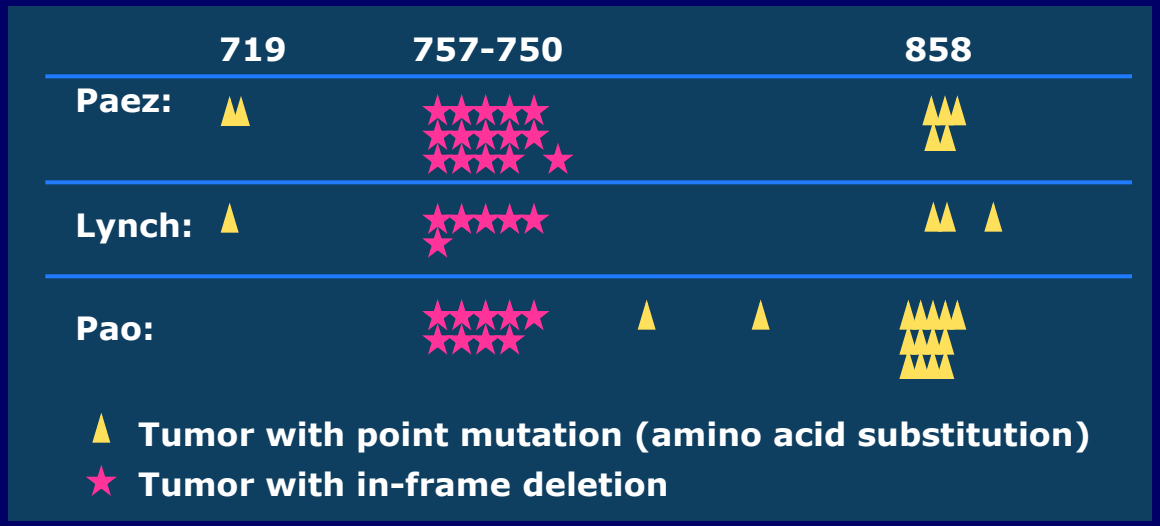
Characteristics of NSCLC Patients Who Respond to EGFR TKIs

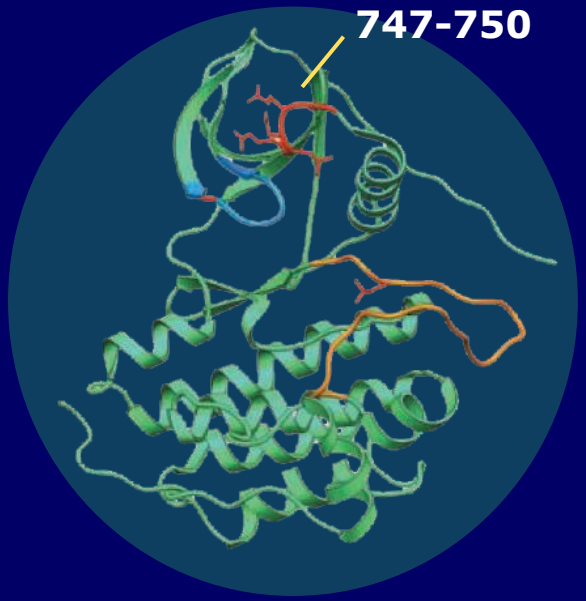
- Females
- Adenocarcinoma
- Asian
- Non-smokers

~60% of these patients will have *EGFR* driver mutations

Somatic Mutations In The *EGFR* Tyrosine-Kinase (TK) Domain

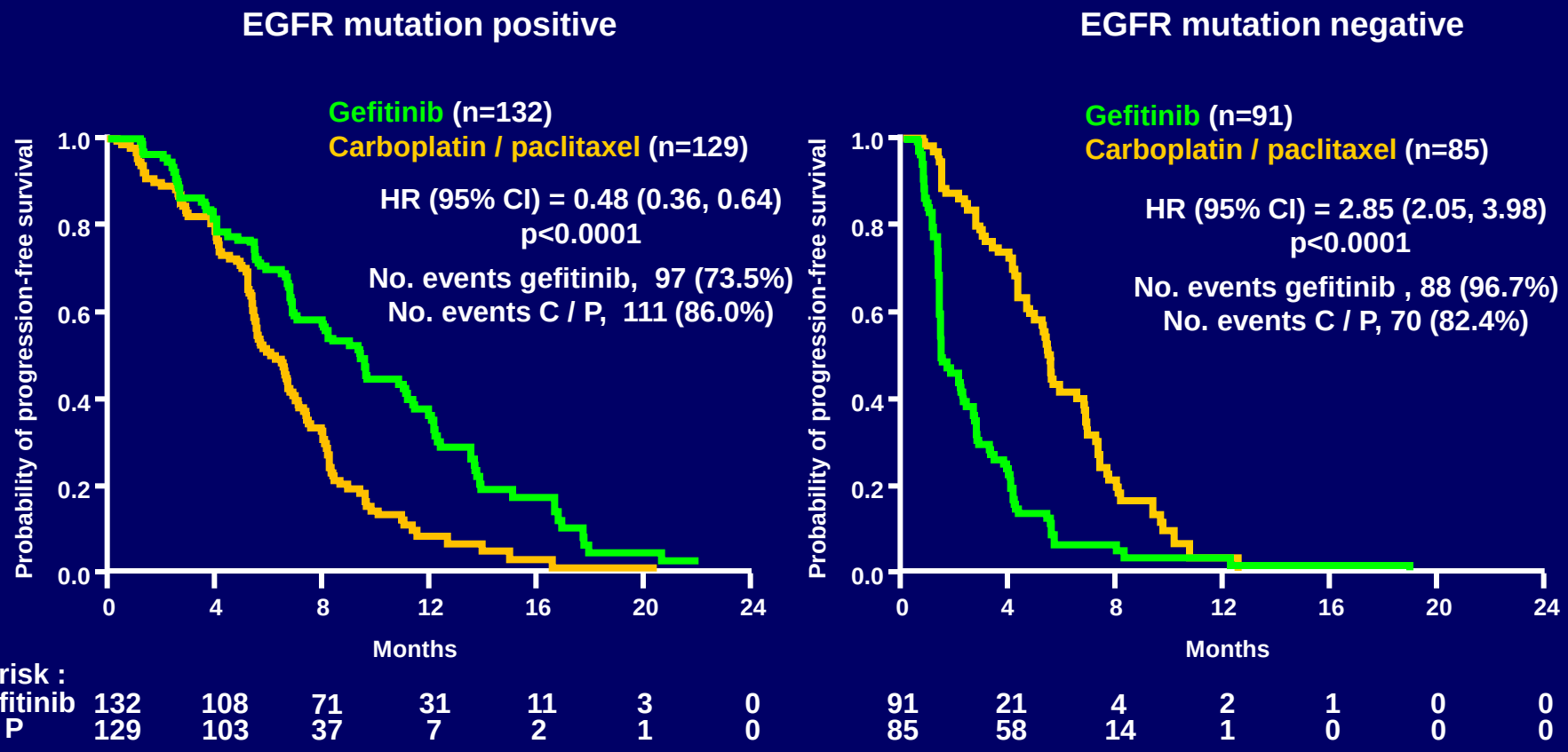






Adapted from: Pao et al. Proc Natl Acad Sci U S A. 2004;101:13306; Lynch et al. N Engl J Med. 2004;350:2129; Paez et al. Science. 2004;304:1497.

IPASS: Progression-Free Survival in EGFR Mutation Positive and Negative Patients

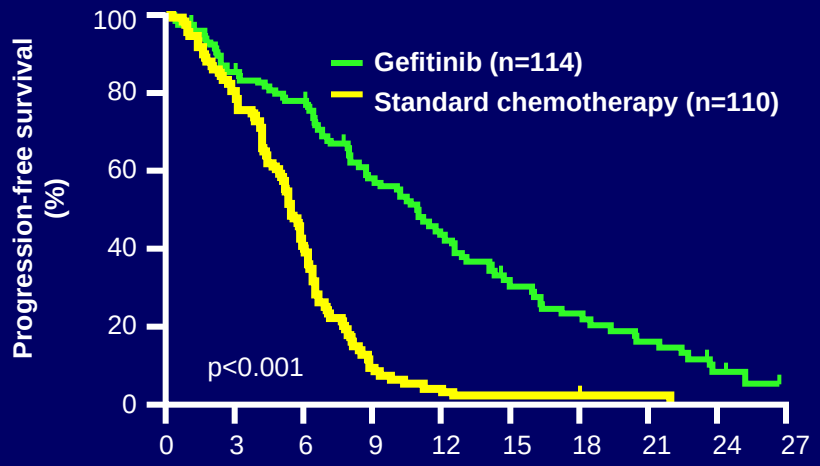


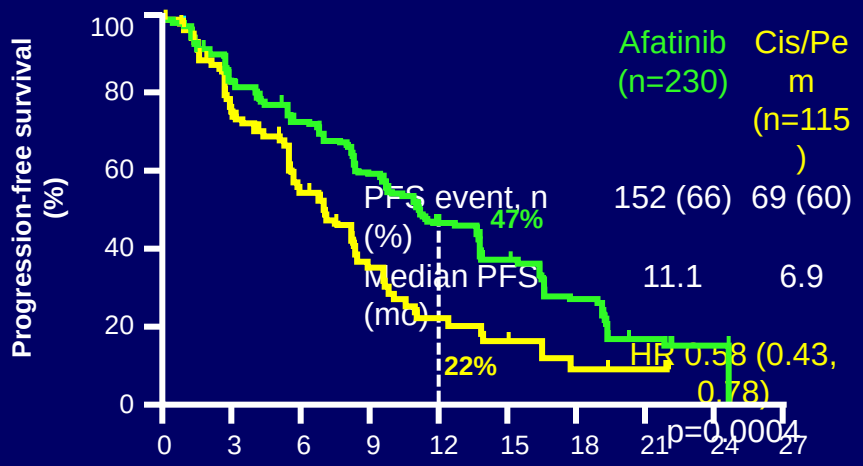
Treatment by subgroup interaction test, p<0.0001

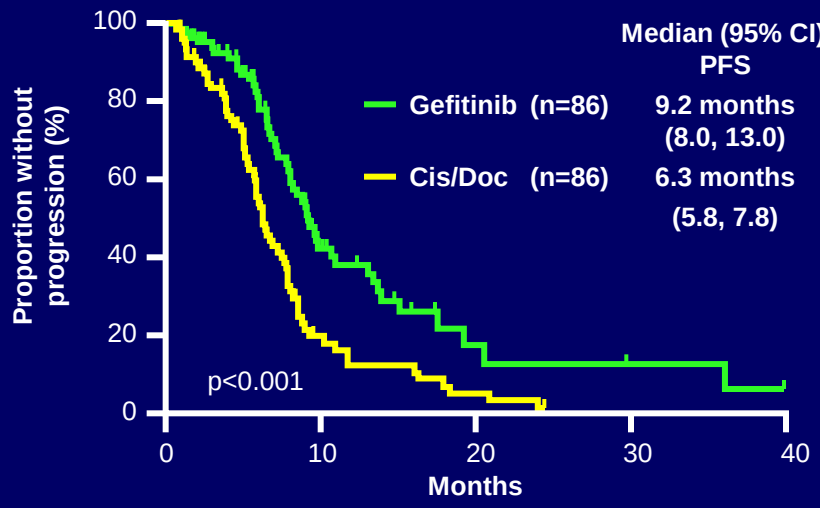
Qualitative interaction!!!!

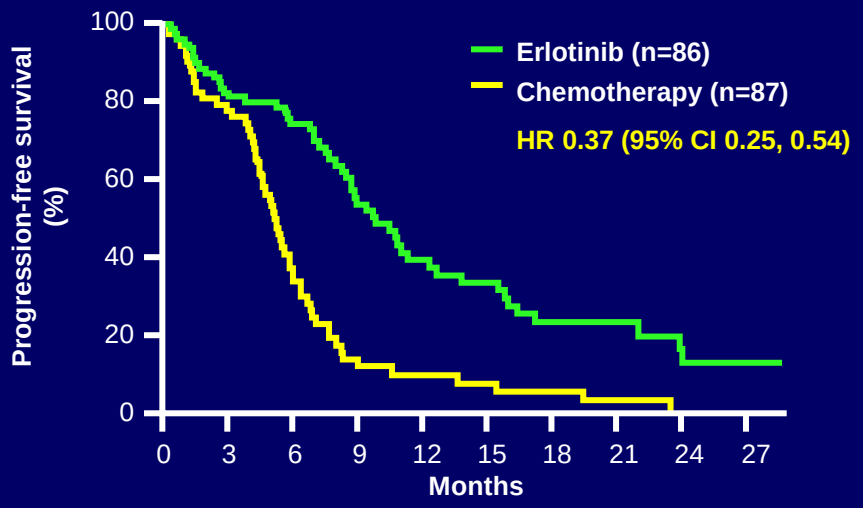
Fukuoka et al. Proc ASCO, 2009

TKI Activity in *EGFR*-mutant NSCLC







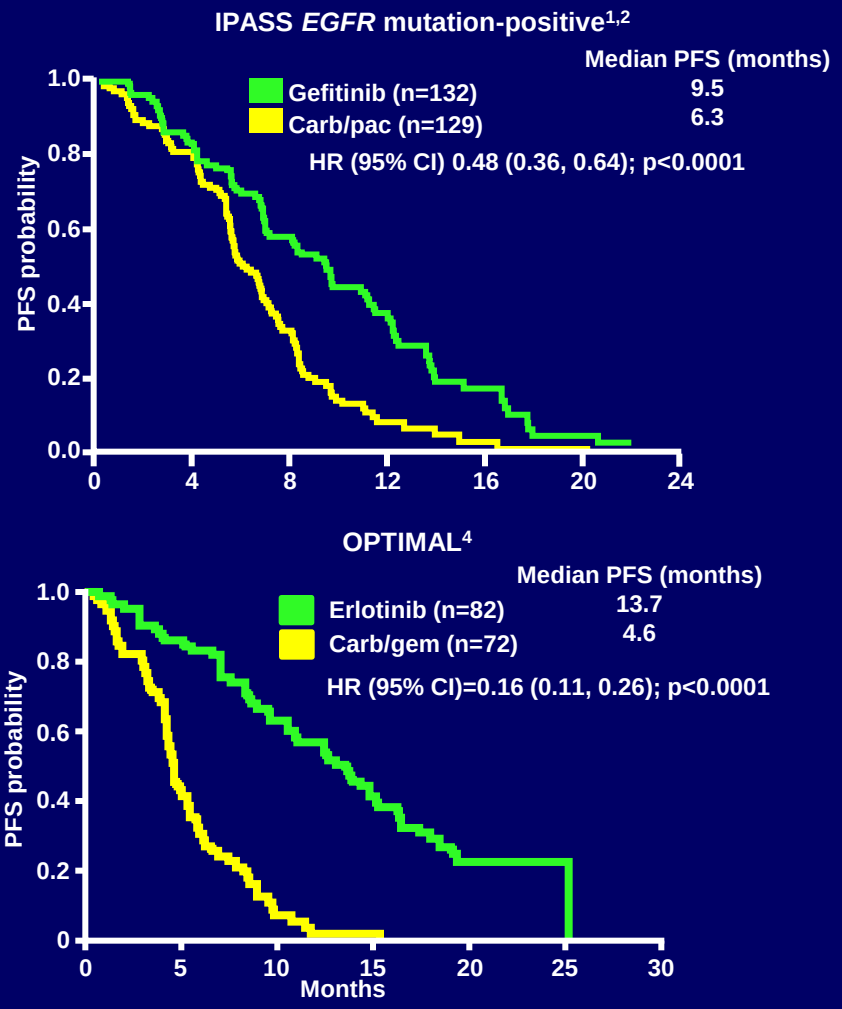


Doc, docetaxel

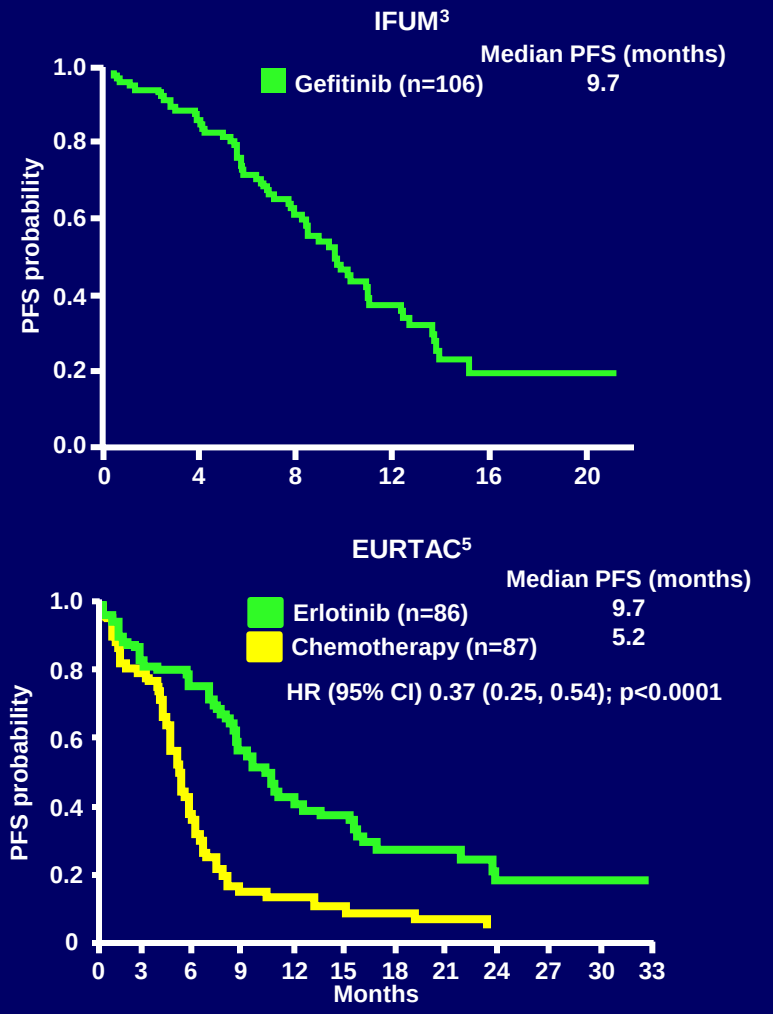
Maemondo et al. New Engl J Med 2010; Yang et al. J Clin Oncol 2012; Mitsudmoi et al. Lancet Oncol 2010; Rosell at al. Lancet Oncol 2012; Sequist et al. J Clin Oncol 2013; Yang et al. Presented at ASCO 2012

Activity of EGFR-TKIs Irrespective of Ethnicity

Asian population



Caucasian population



1. Mok et al, N Engl J Med 2009; 2. AstraZeneca, Gefitinib Summary of Product Characteristics; 3. Douillard, EMCTO 2013; 4. Chen et al, Ann Oncol 2013; 5. Rosell et al, Lancet Oncol 2012

LUX-Lung 3 and 6: design

- Stage IIIB/IV adenocarcinoma of the lung
- Presence of *EGFR* mutation in the tumor tissue*
- No prior treatment with chemotherapy for advanced/metastatic disease or EGFR inhibitors
- ECOG PS 0 or 1

Randomization

2:1

Stratification by EGFR mutation type: Del19/L858R/other and by race (LUX-Lung 3 only): Asian/non-Asian

Afatinib
40 mg orally once daily

LUX-Lung 3[1]:
Cisplatin + pemetrexed
up to 6 cycles

LUX-Lung 6[2]:
Cisplatin + gemcitabine
up to 6 cycles

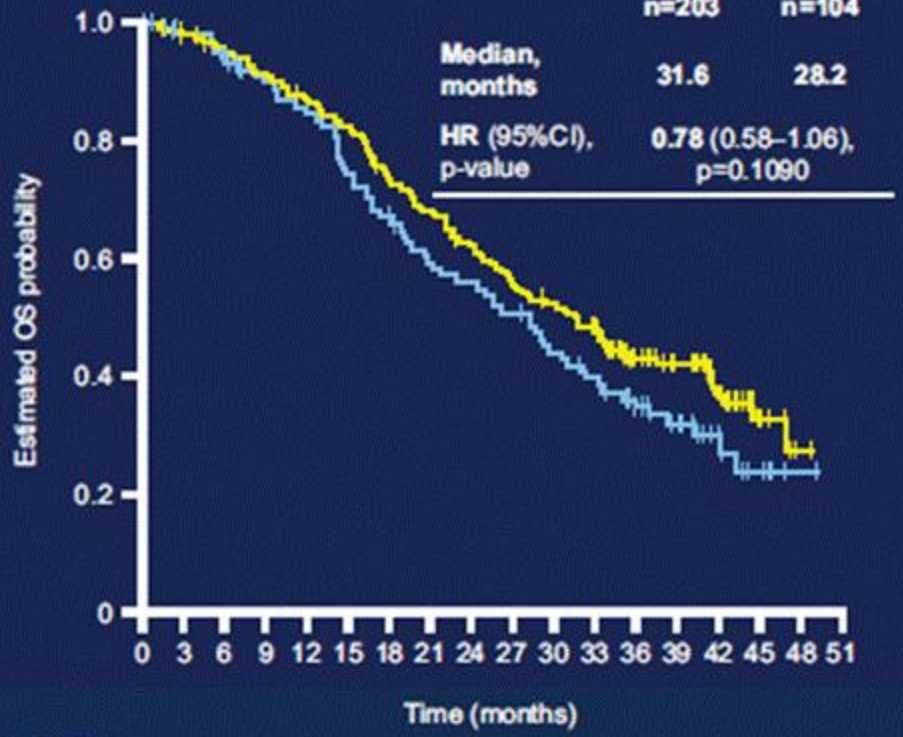
Primary endpoint: PFS (independent review)
Secondary end points: ORR, DCR, OS, PRO, safety

*EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.

1. Sequist et al. *J Clin Oncol.* 2013;31:3327; 2. Wu et al. *Lancet Oncol.* 2014;15:213.

LUX-Lung 3 and 6: OS in common mutations

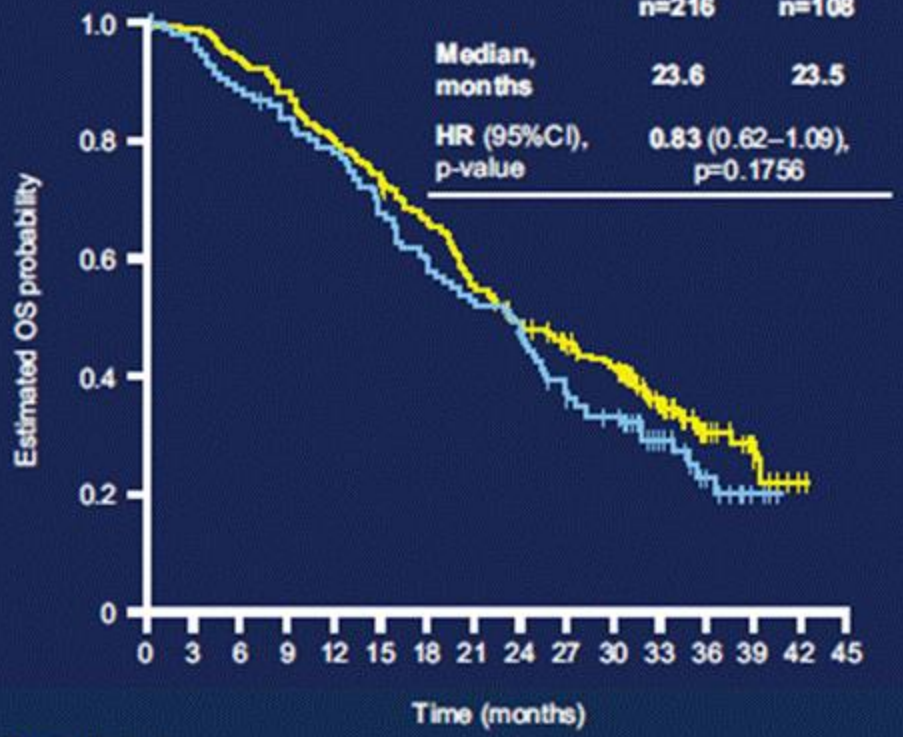
LUX-Lung 3



	Afatinib n=203	Pem/Cis n=104
Median, months	31.6	28.2
HR (95%CI), p-value	0.78 (0.58–1.06), p=0.1090	

No of patients																	
Afatinib	203	197	188	181	171	162	143	133	121	108	101	90	58	49	32	9	1	0
Pem/Cis	104	98	92	86	81	71	63	55	52	47	40	35	26	20	10	5	1	0

LUX-Lung 6



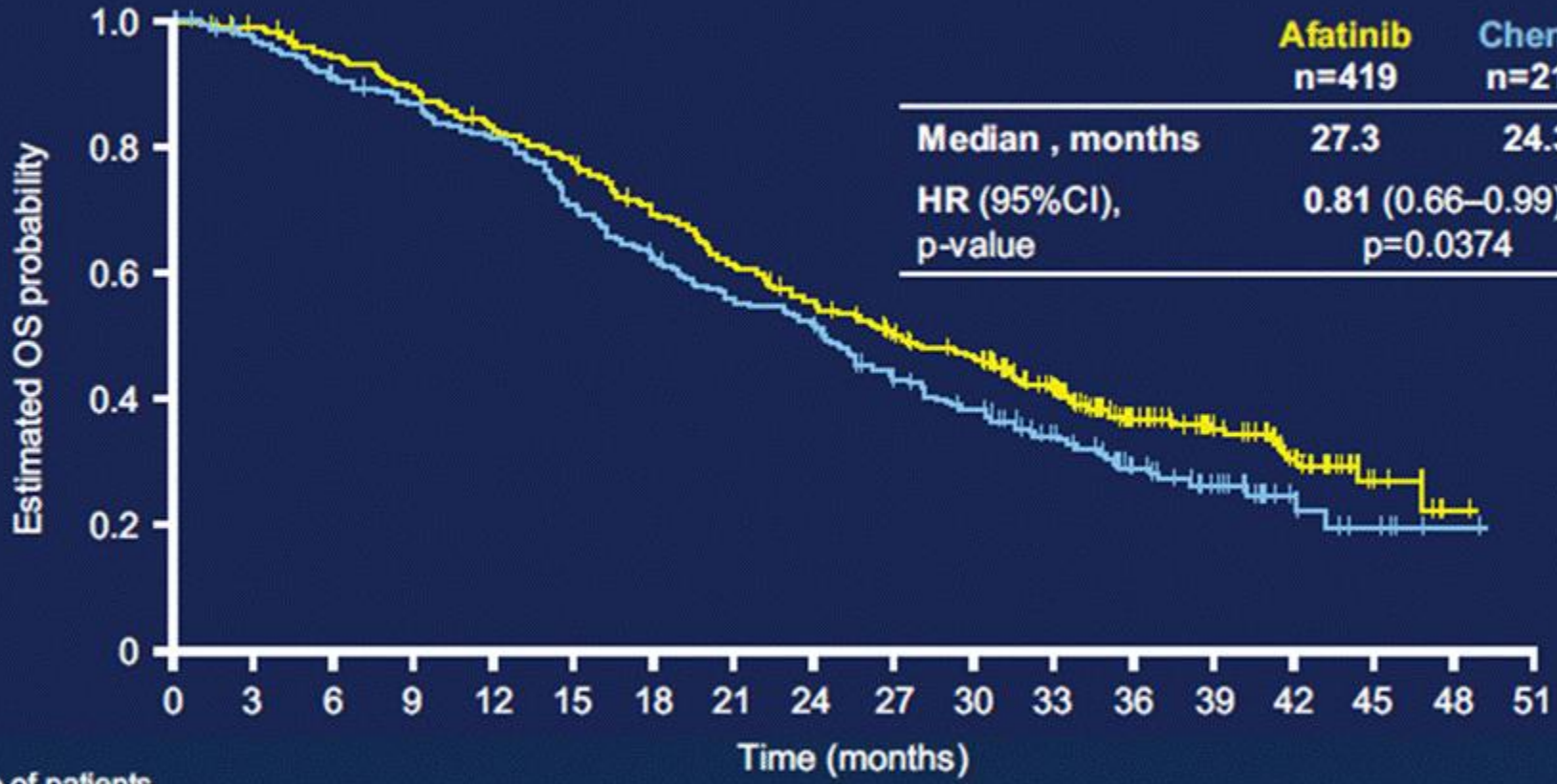
	Afatinib n=216	Gem/Cis n=108
Median, months	23.6	23.5
HR (95%CI), p-value	0.83 (0.62–1.09), p=0.1756	

No of patients																	
Afatinib	216	214	202	190	172	158	141	118	104	93	80	51	19	9	1	0	
Gem/Cis	108	101	93	87	81	70	61	55	49	36	30	17	8	3	0	0	

Presented by: James Chih-Hsin Yang

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Combined OS analysis: common mutations (n=631)



	Afatinib n=419	Chemo n=212
Median , months	27.3	24.3
HR (95%CI), p-value	0.81 (0.66–0.99), p=0.0374	

No of patients

Afatinib	419	411	390	371	343	320	284	251	225	201	181	141	77	58	33	9	1	0
Chemo	212	199	185	173	162	141	124	110	101	83	70	52	34	23	10	5	1	0

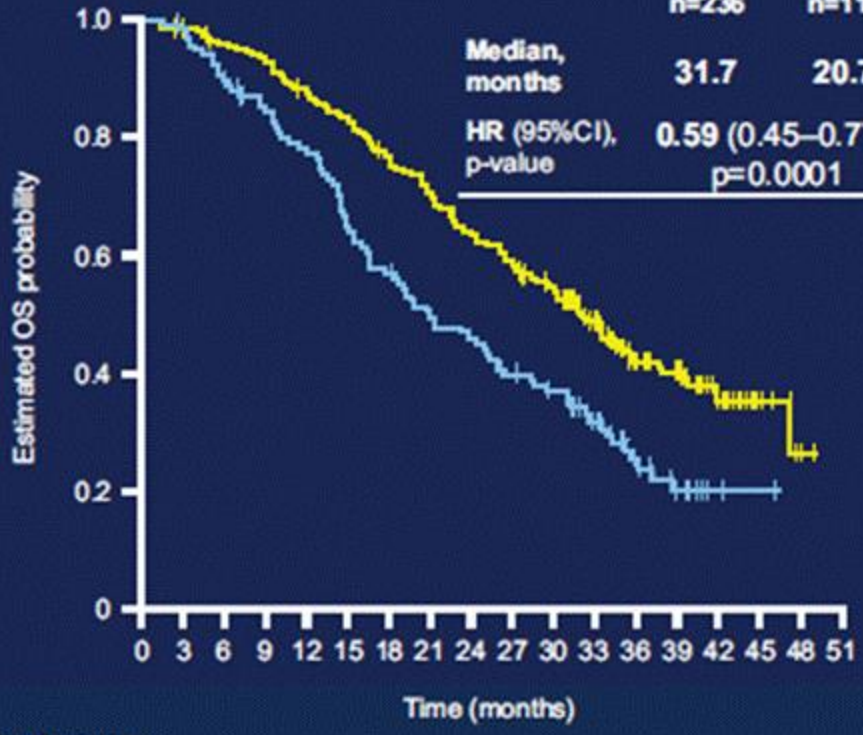
Presented by: James Chih-Hsin Yang

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Combined OS analysis: mutation categories

Del19

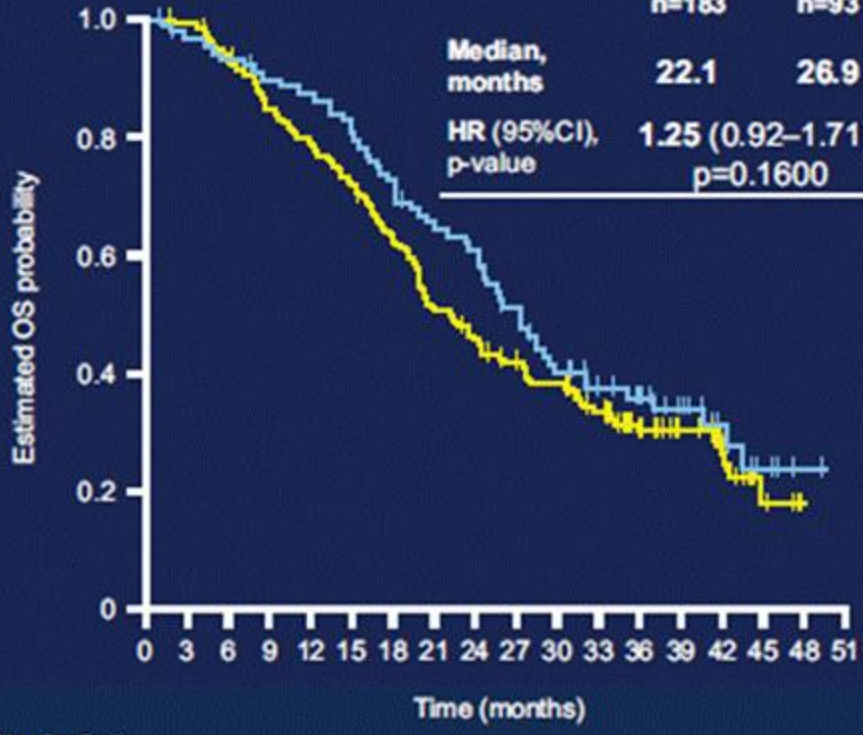
	Afatinib n=236	Chemo n=119
Median, months	31.7	20.7
HR (95%CI), p-value	0.59 (0.45–0.77), p=0.0001	



No of patients																	
Afatinib	236	230	223	217	202	192	173	160	145	131	117	90	50	38	22	6	1	0
Chemo	119	113	103	95	87	72	63	55	51	43	38	27	14	9	1	1	0	0

L858R

	Afatinib n=183	Chemo n=93
Median, months	22.1	26.9
HR (95%CI), p-value	1.25 (0.92–1.71), p=0.1600	

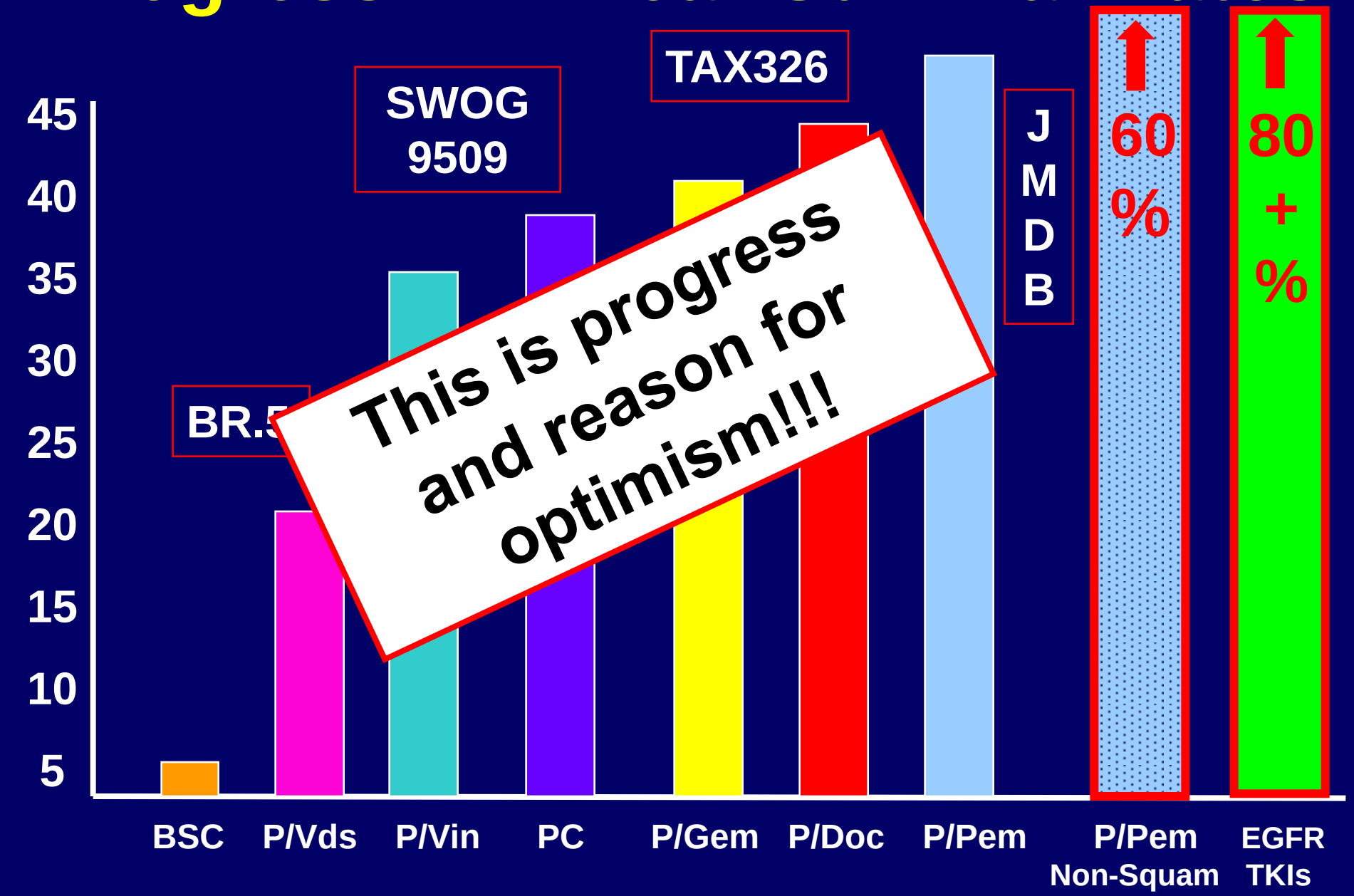


No of patients																	
Afatinib	183	181	167	154	141	128	111	91	80	70	64	51	27	20	11	3	0	0
Chemo	93	86	82	78	75	69	61	55	50	40	32	25	20	14	9	4	1	0

Presented by: James Chih-Hsin Yang

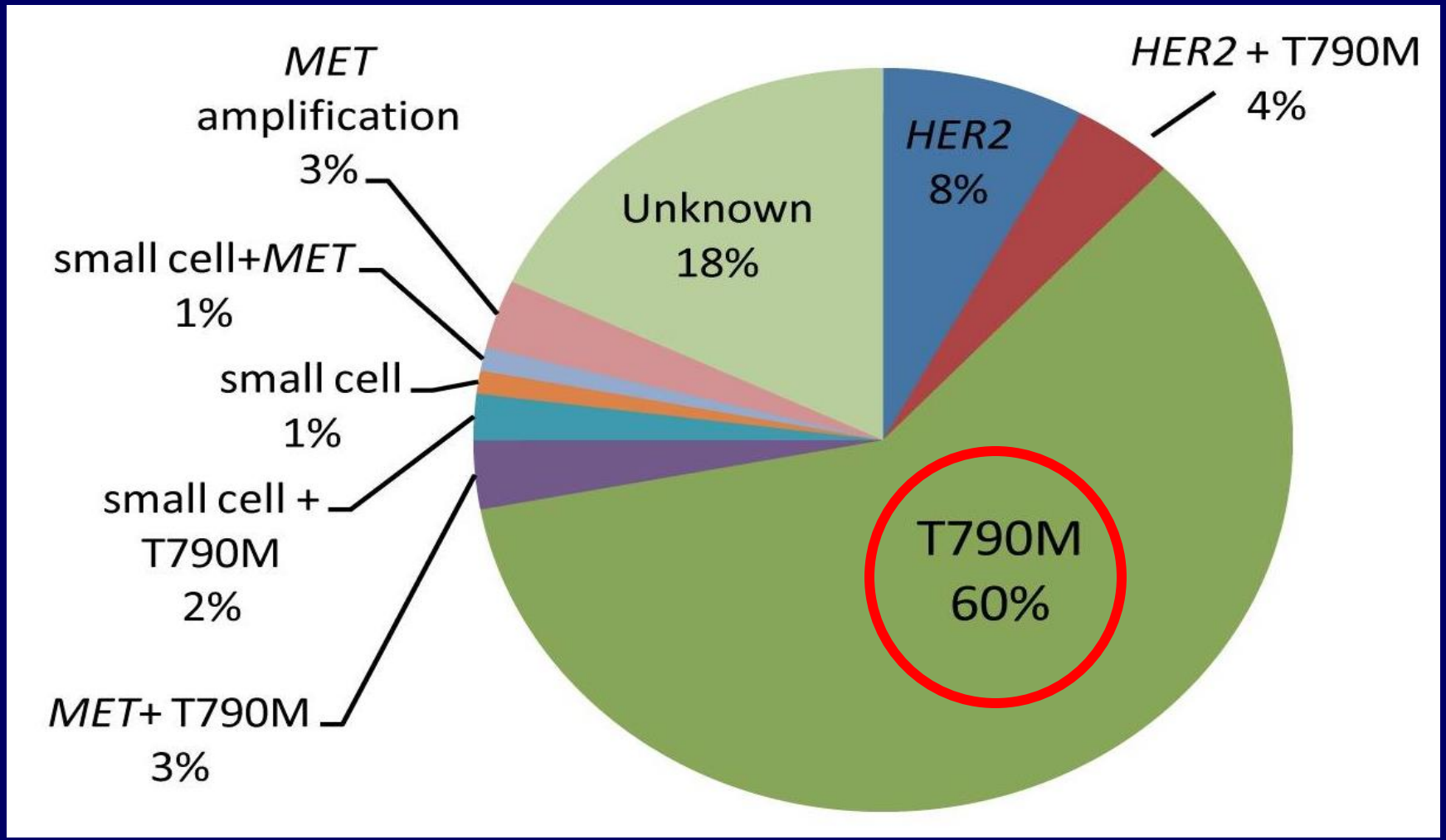
PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Progress in 1-Year Survival Rates



EGFR and the Molecular Basis For Resistance to EGFR TKIs

Mechanisms of Resistance to EGFR TKI Therapy



Yu H et al. Clin Cancer Res. 2013 Apr 15;19(8):2240-7

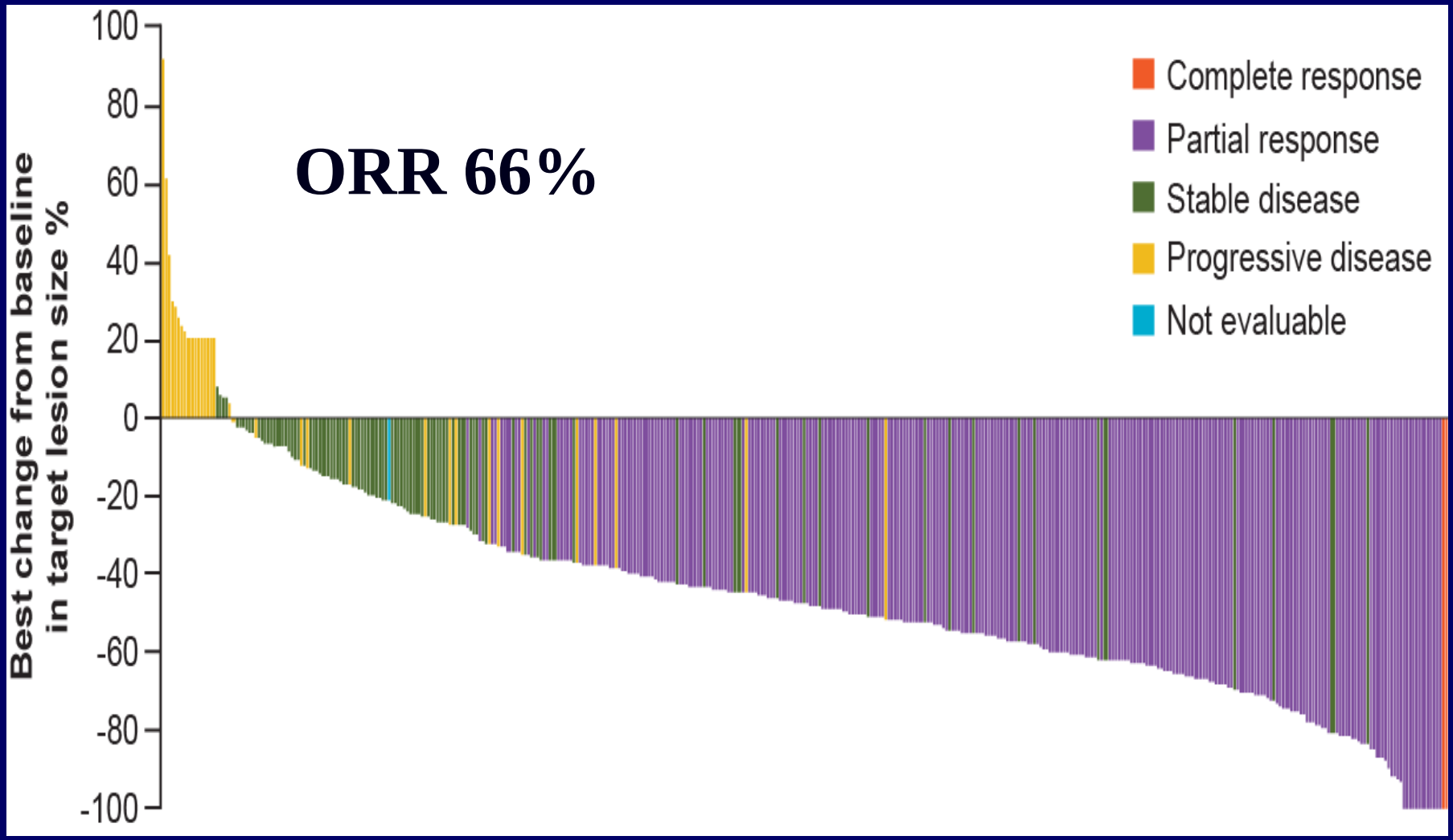
EGFR TKIs

1st Generation -EGFR (WT, mutant) -Reversible	2nd Generation -panHER -Irreversible	3rd Generation -Mutant EGFR - Irreversible
Gefitinib	Afatinib	**Osimertinib (Tagrisso™) AZD9291**
Erlotinib	Dacomitinib	**Rociletinib (CO-1686)**
Icotinib	Neratinib (HER2)	**HM61713**
		EGF816
		ASP8273
		BI1482649

AZD 9291

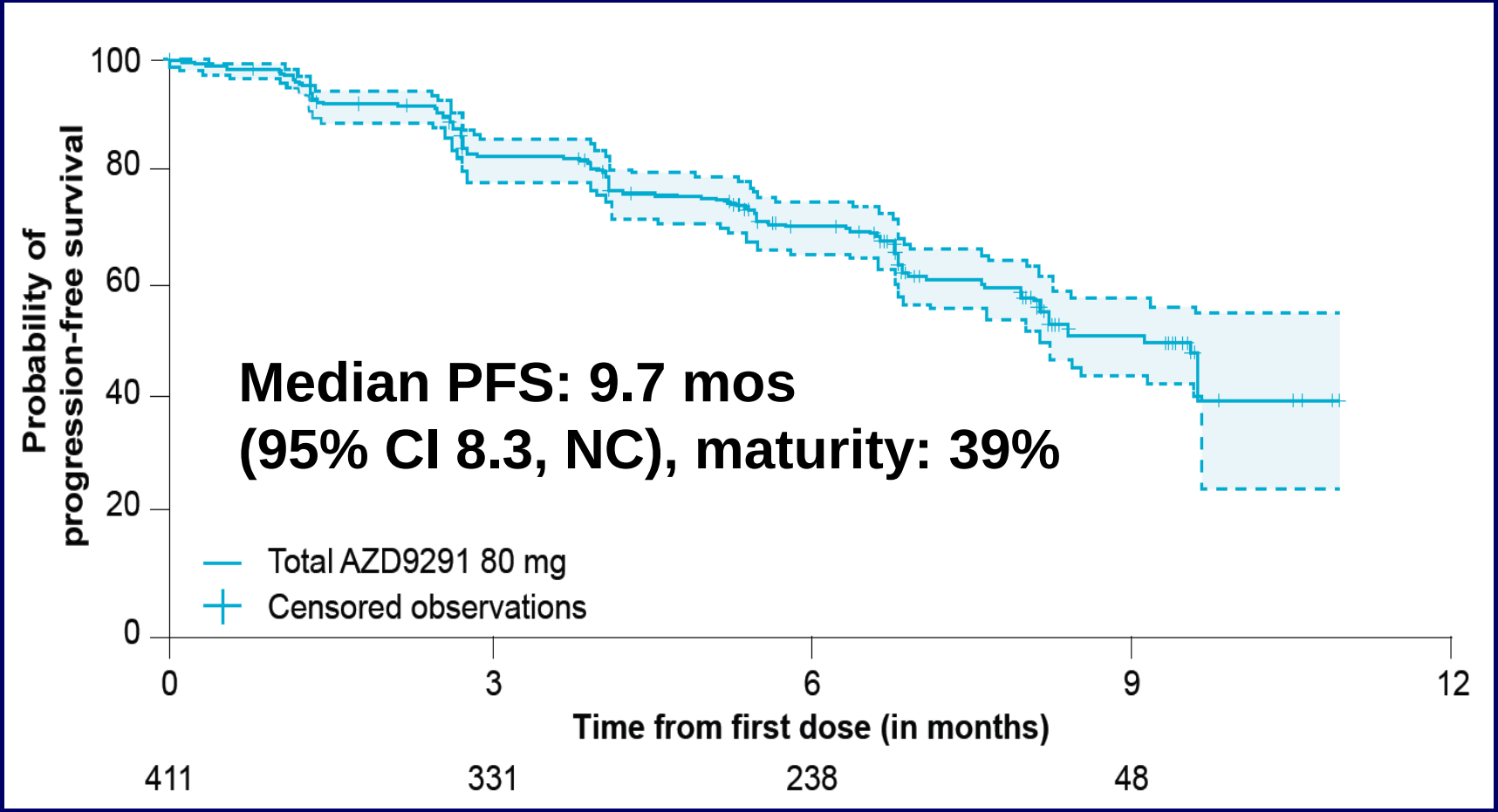
- AURA
- AURA2
- AURA3
- FLAURA
- CAURAL

AURA 1 & 2
Percent Change From Baseline



Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress

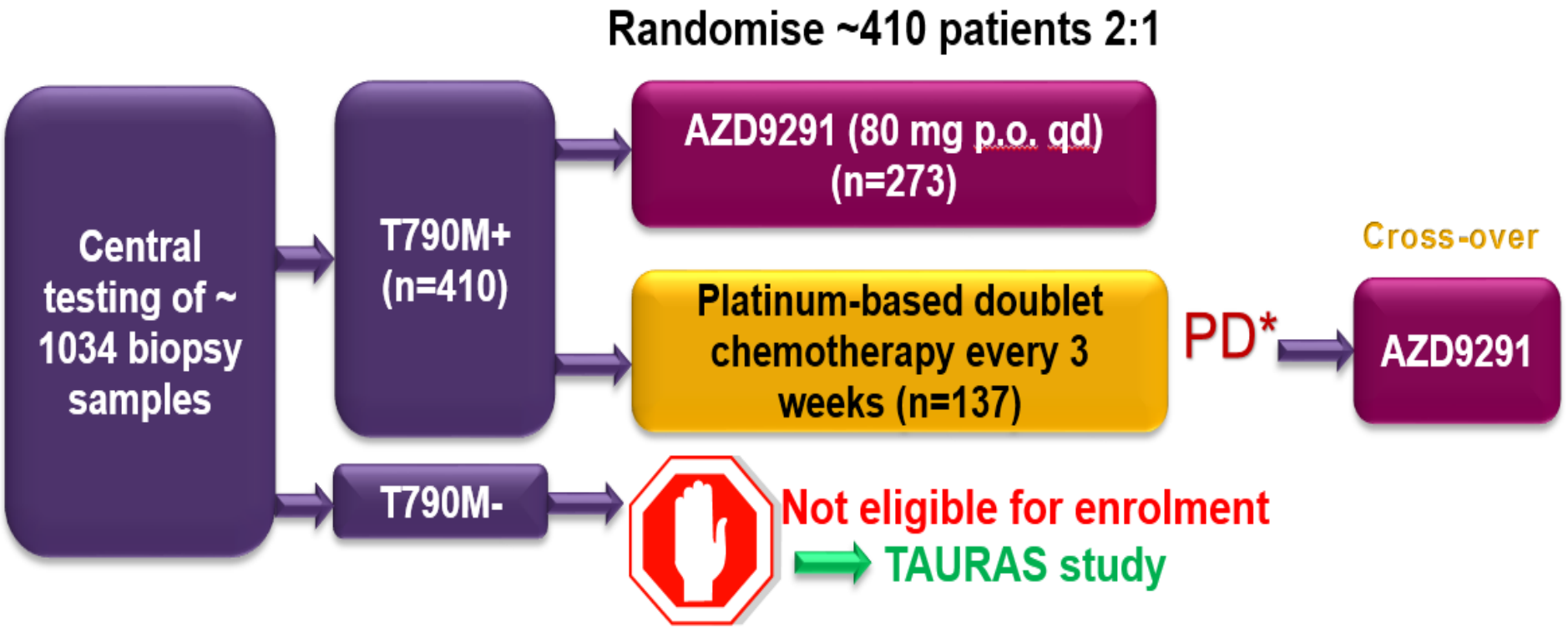
AURA 1 & 2
Progression-free Survival



By blinded independent central review. Patients with confirmed objective response (n=263), maturity 23%. Blue dotted lines represent 95% CI
CI, confidence interval; NC, not calculated

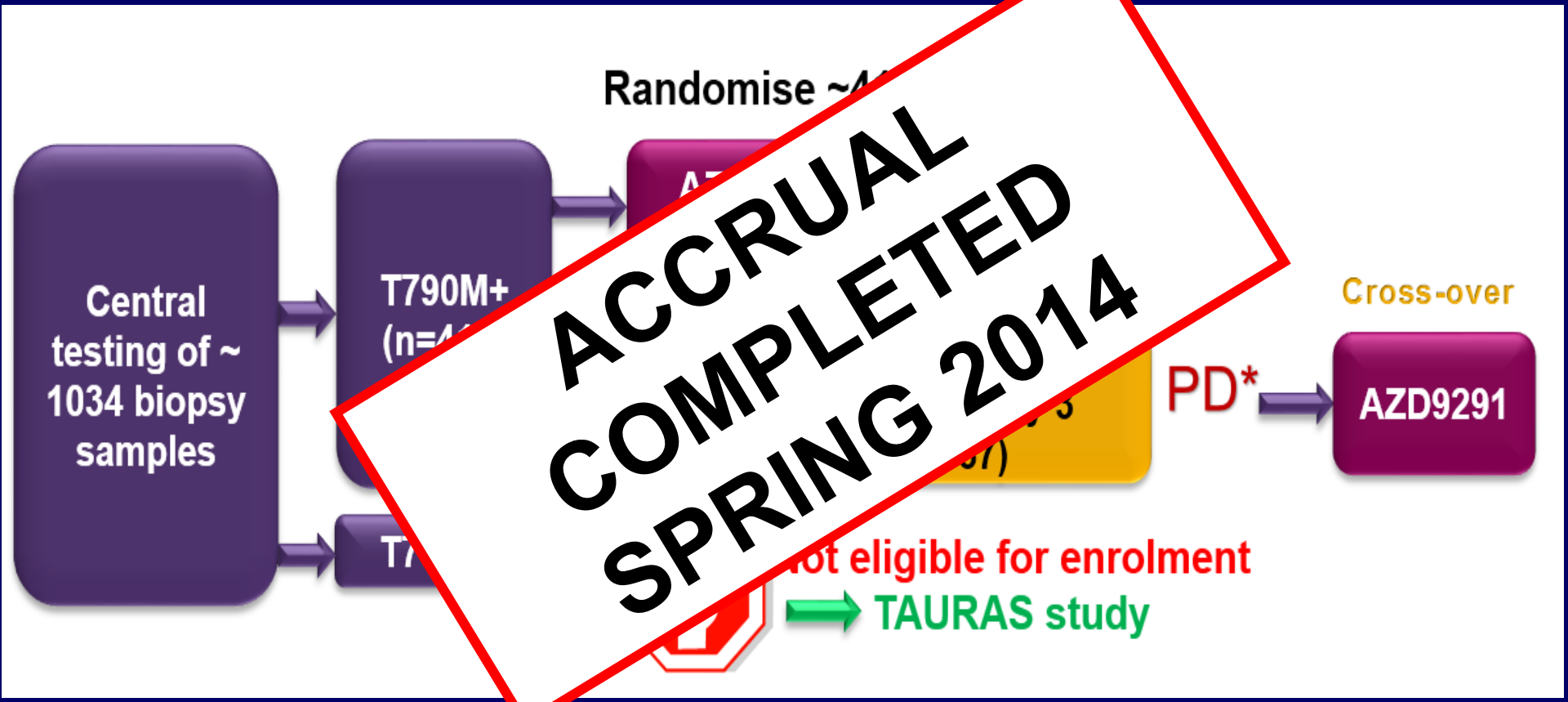
Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress

AURA 3 - Study Design



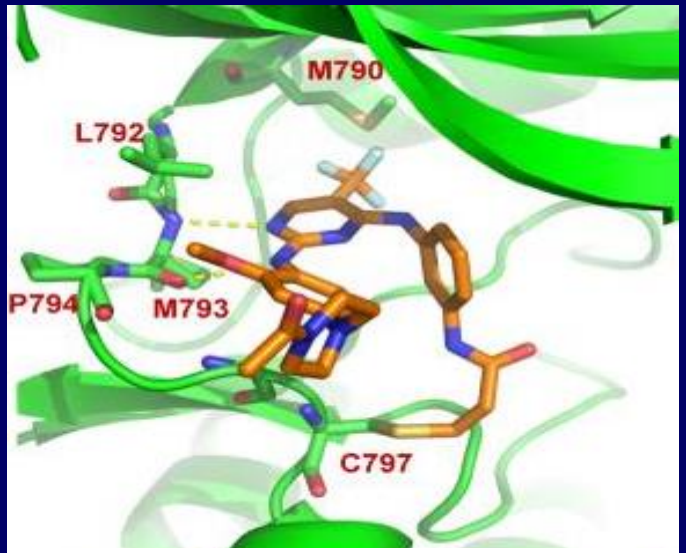
* Once subjects on the platinum-based doublet chemotherapy arm are determined to have objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review, they will be eligible to cross-over to AZD9291 80,g, once daily.

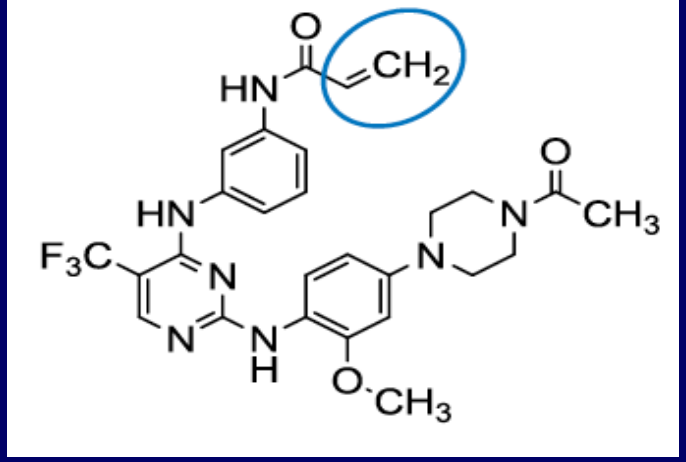
AURA 3 - Study Design



* Once subjects on the platinum-based doublet chemotherapy arm are determined to have objective radiological progression according to RECIST 1.1 by the investigator and confirmed by independent central imaging review, they will be eligible to cross-over to AZD9291 80,g, once daily.

Rociletinib (CO-1686)



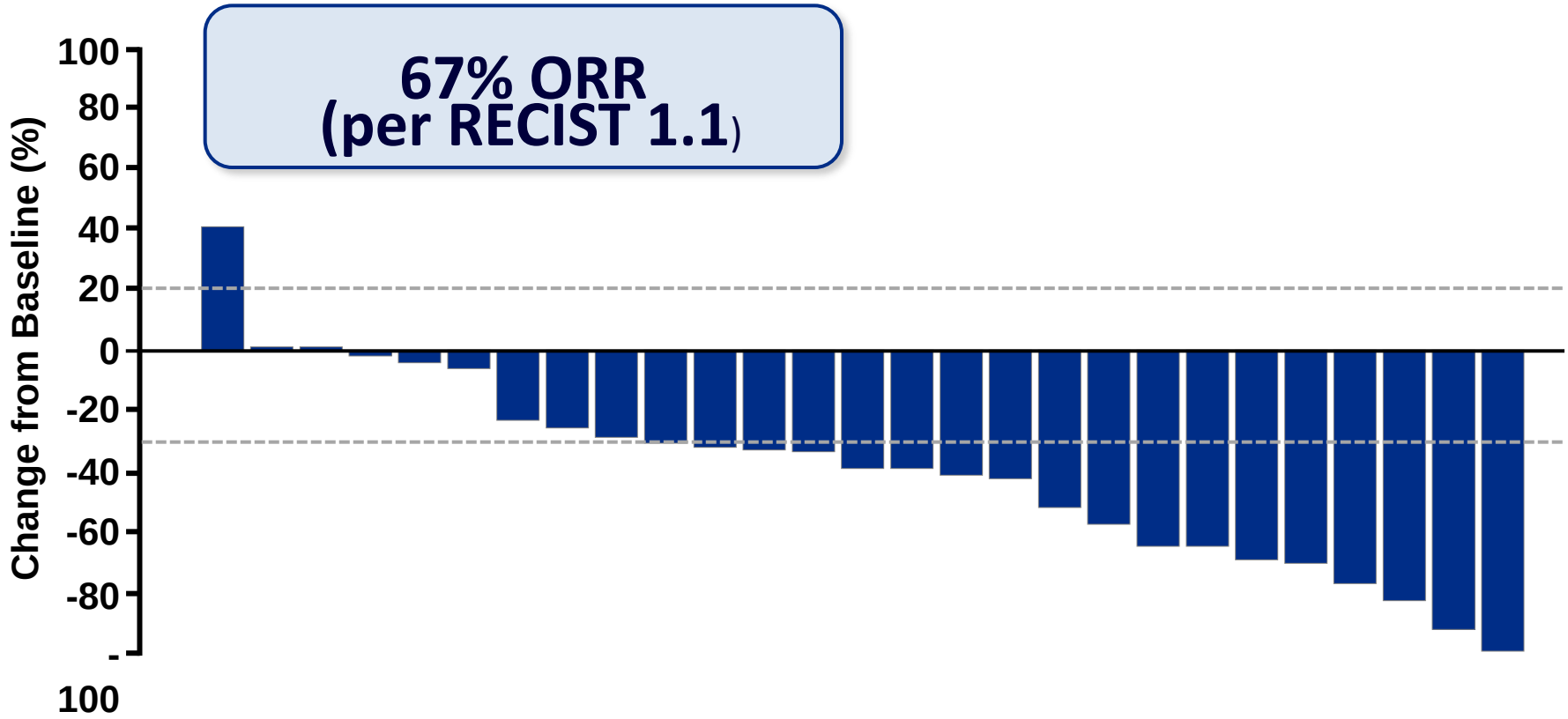


- Irreversible covalent binding to ATP site Cys797, hinge M793 (active acrylamide site)
- Highly selective for mEGFR including T790M

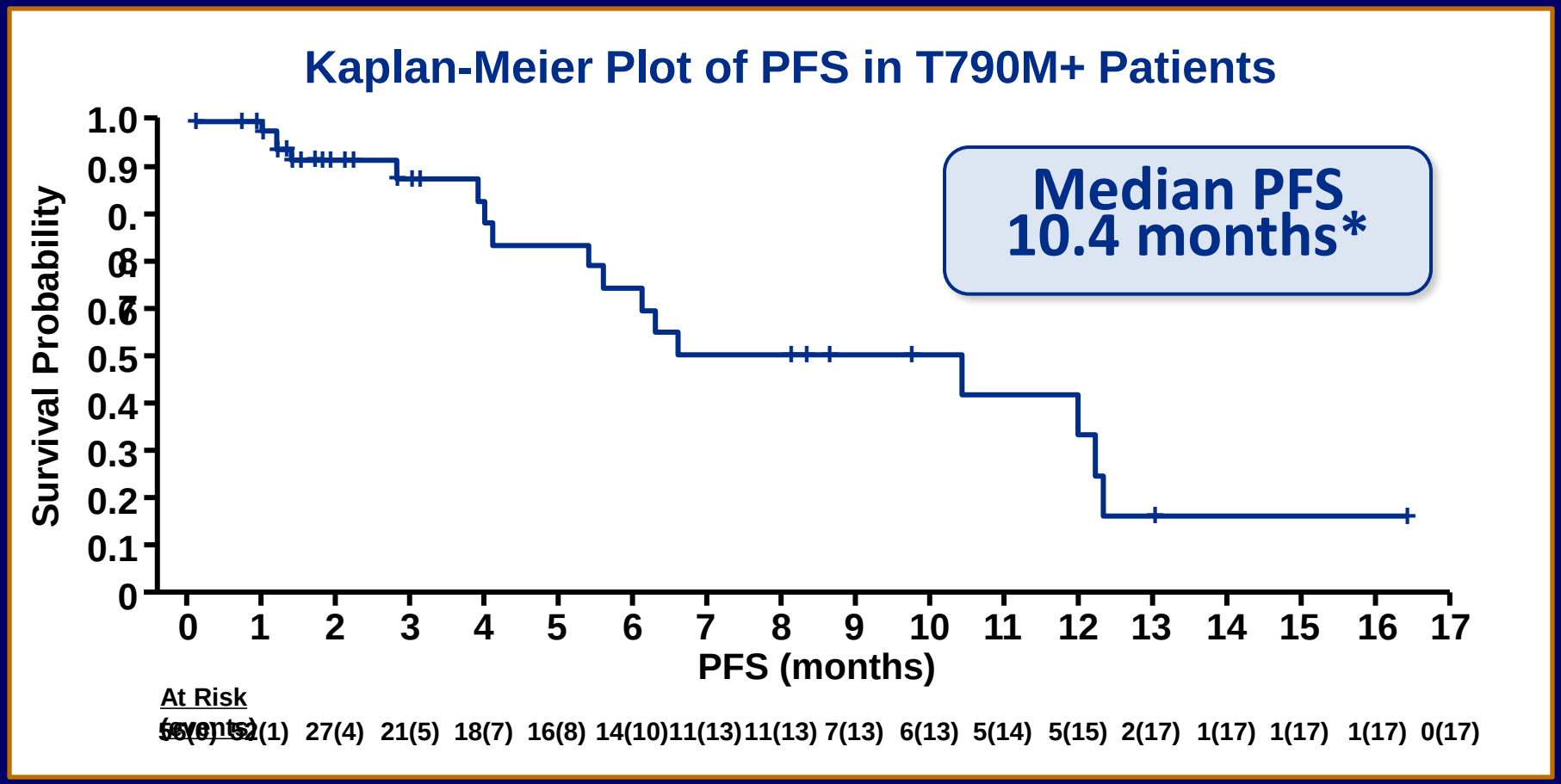
Cell lines	EGFR mutation	Other mutation	Erlotinib pEGFR IC_{50} [nM]	CO-1686 pEGFR IC_{50} [nM]
NCI-H1975	L858R / T790M		>5000	62±34
HCC827	Del 19		<14	187±88
HCC827-EPR	Del 19 / T790M		ND	180±55
PC9	Del 19		21	211
A431	wild-type		<7	> 4331
NCI-H1299	wild-type	NRAS	ND	>2000
NCI-H358	wild-type	KRAS	ND	>2000

Walter et al. Cancer Discov 2013

TIGER-X Clinical Dose Group Responses in T790M+ Group



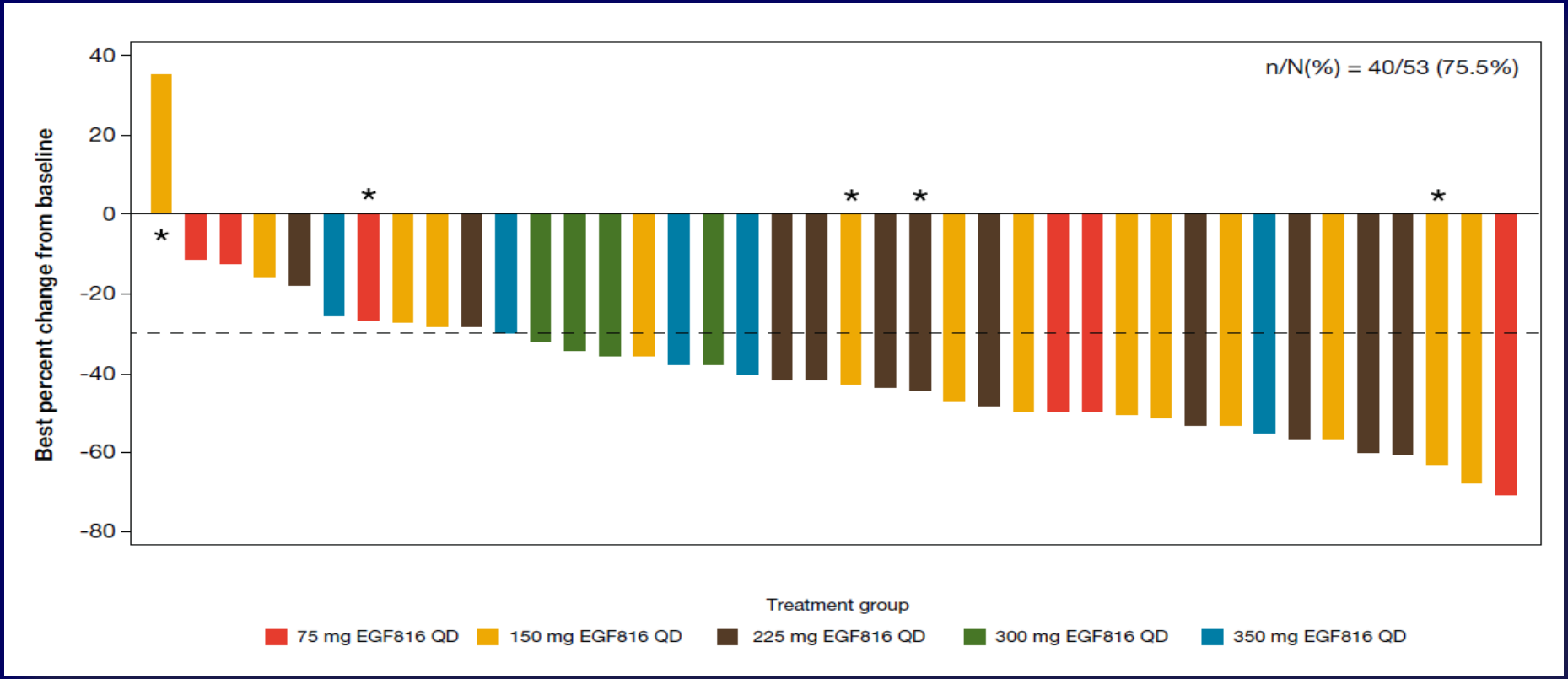
TIGER-X Clinical Dose Group: Progression-Free Survival



*Data as of 25 September 2014 reflecting 31% data maturity.
PFS=progression-free survival.

EGF816: Phase II Efficacy

Best %Change From Baseline in Target Lesions

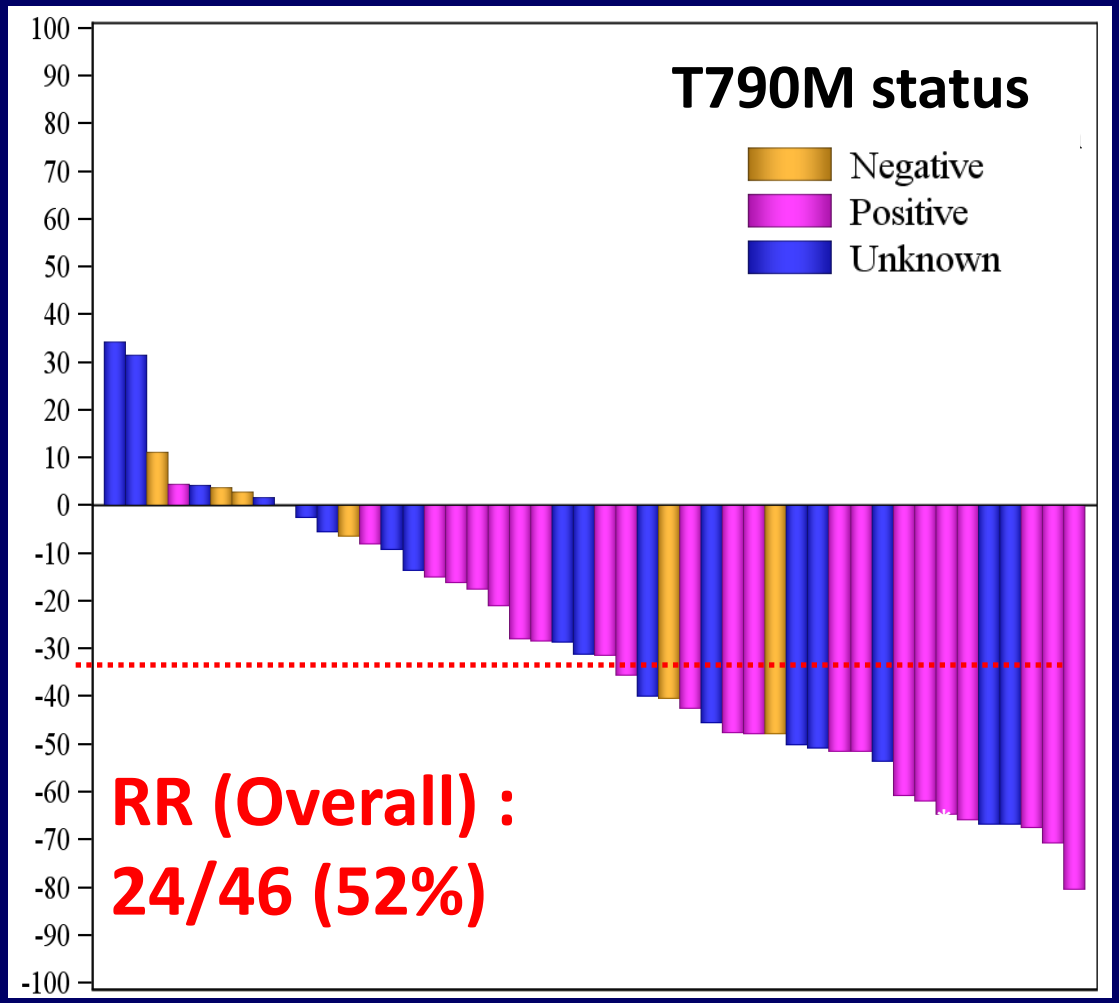


* Discontinued.

† Evaluable patients include those who are ongoing with study treatment and have at least one post-baseline response assessment, or who have discontinued study treatment. This total is used for percentage calculation. cPR, complete PR; CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; QD, once daily; SD, stable disease; uPR, unconfirmed PR; WT, wild type. Data cut-off, 2 February 2015.

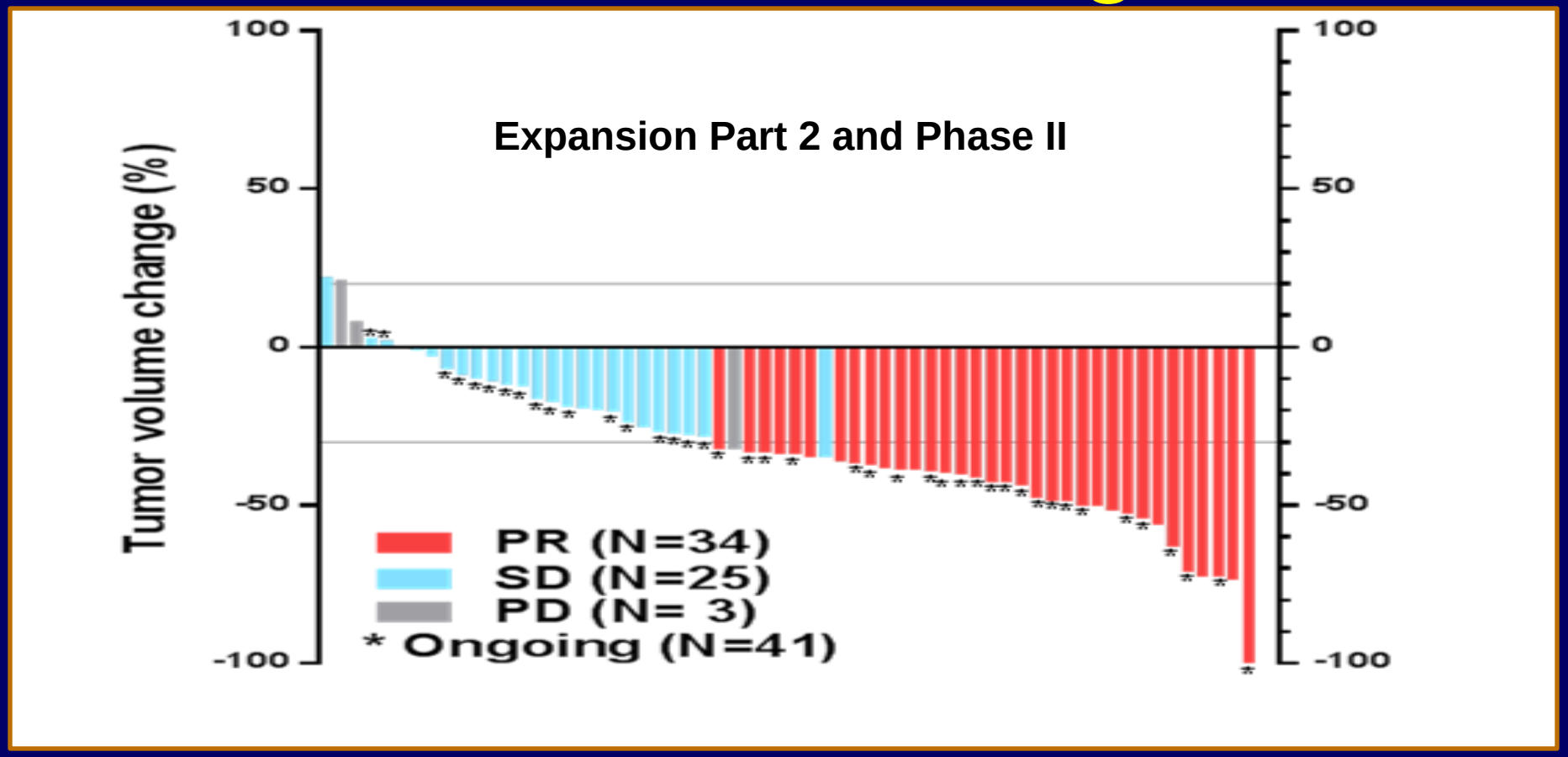
- ***One patient on 150 mg QD had progressive disease at first evaluation. Repeat testing revealed the tumor to be EGFR WT***

Antitumor Activity of ASP8273



- Tumor responses seen ≥ 100 mg.
- Overall : 24/46 (52%).
- T790M positive : 14/23 (61%).
- T790M negative : 2/6 (33%).
- T790M unknown : 8/17 (47 %).

EMSI-101 Trial: Activity in T790M + Subset at 800 mg



	ORR (%)	DCR (%)	Median PFS
N=62	54.8	95.2	Not reached

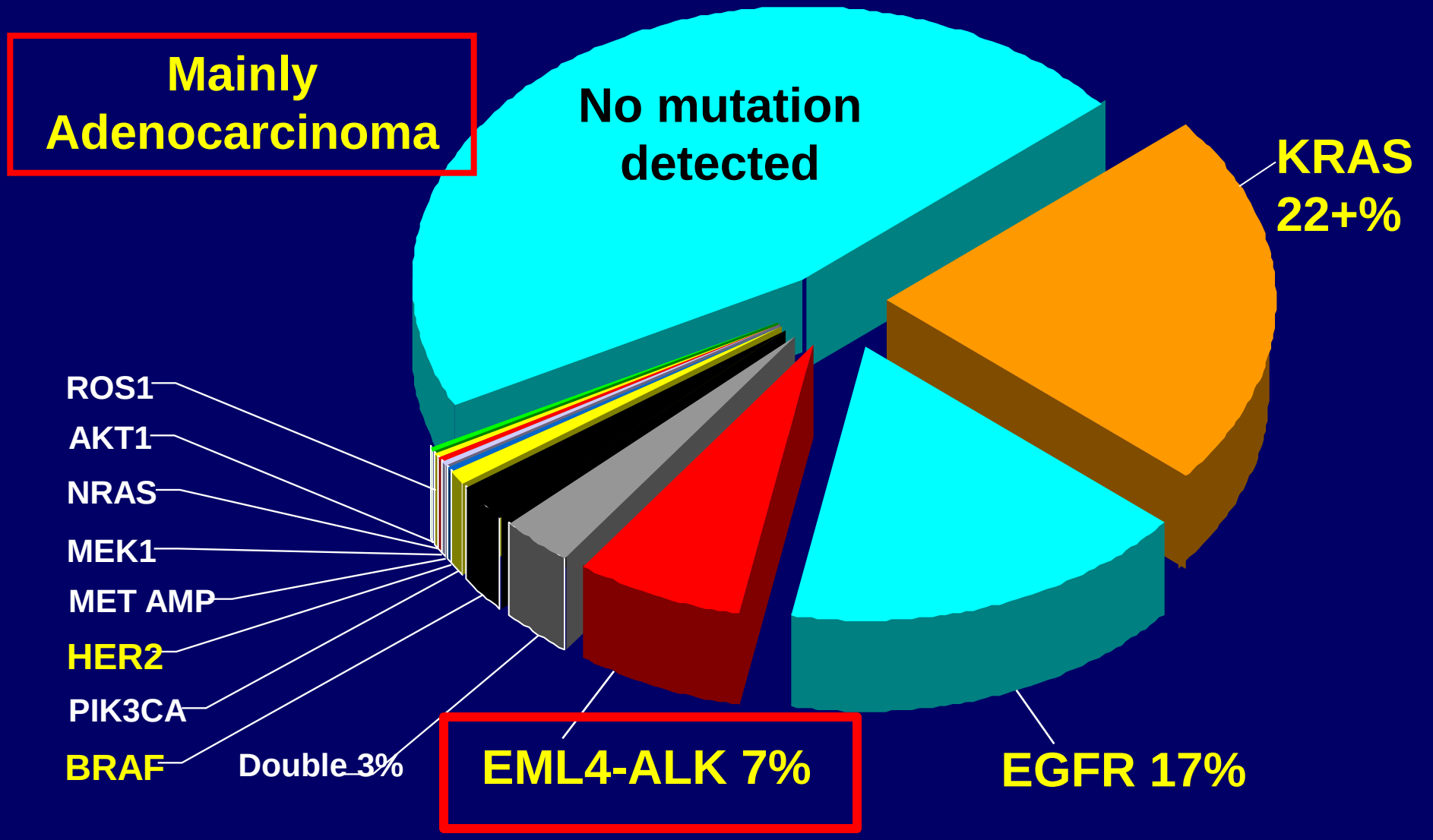
3rd Generation EGFR TKIs

Agent	N	RR* T790M-	RR T790M+	PFS	Toxicity
Osimertinib AZD 9291	253	21%	66%	~8.2 m	Mild Diarrhea
Rociletinib (CO-1686)	256	37%	53%	~8.0 m	**Hyper-glycemia**
HM61713 (800mg) BI1482694	62	12%(300 mg)	55%	NR	**Diarrhea, Nausea Rash**
EGF816X	53	-	60%	NR	**Rash Diarrhea**
ASP8273	47	~33%	61%	NR	**Hypo-Na Diarrhea**

My Bet Is Going On AZD 9291

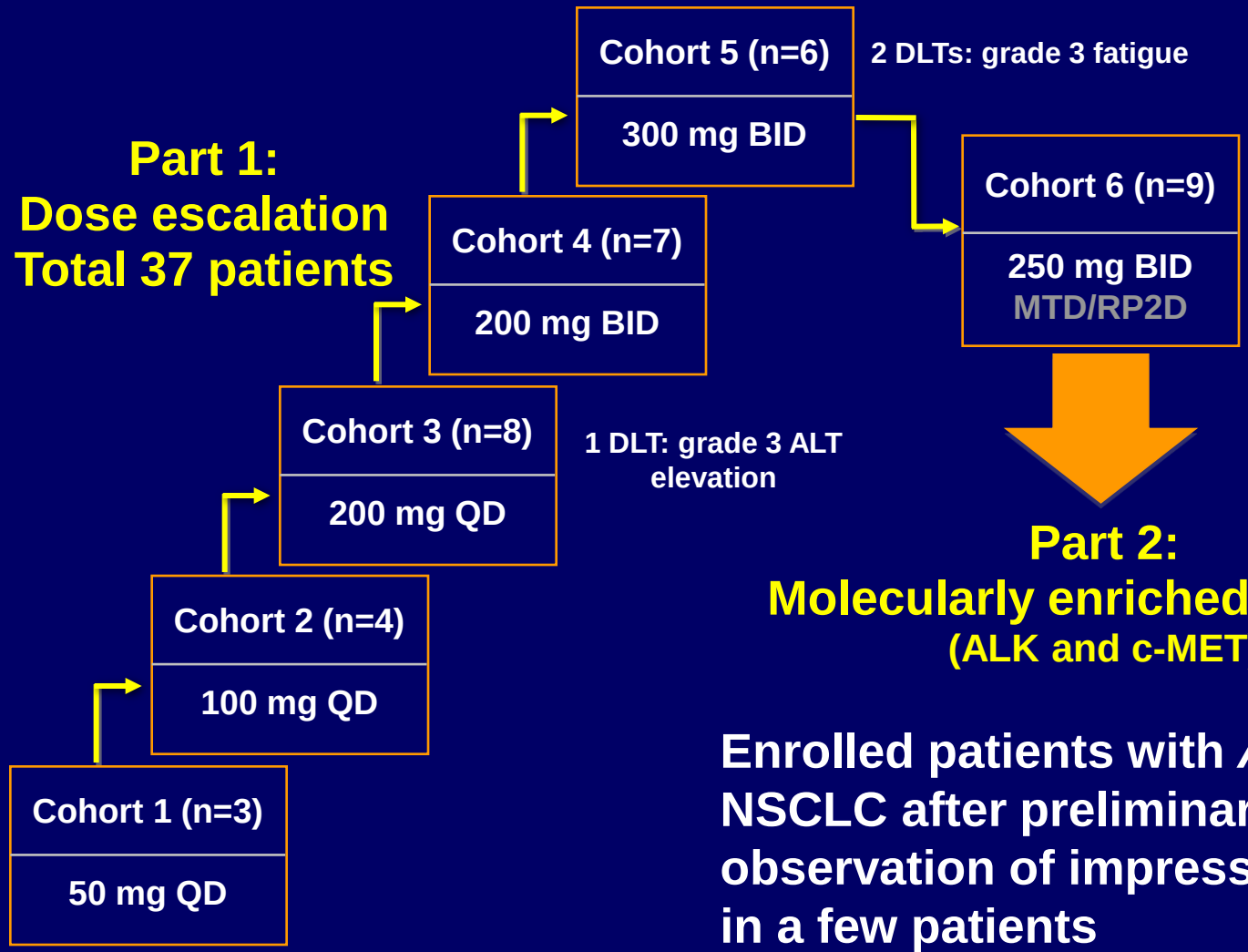
My Bet Is Going On AZD 9291

Numerous Molecular Changes Drive Lung Cancer



Kris, et al. J Clin Oncol 2011;29:Suppl(Abstr 7506).

Crizotinib: First-in-Human Trial

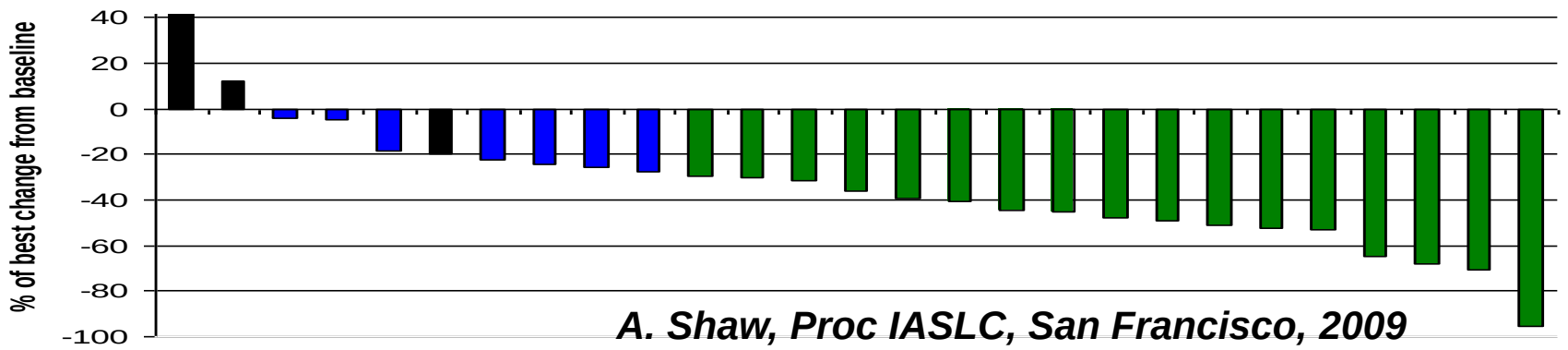


Enrolled patients with *ALK*-positive NSCLC after preliminary observation of impressive activity in a few patients

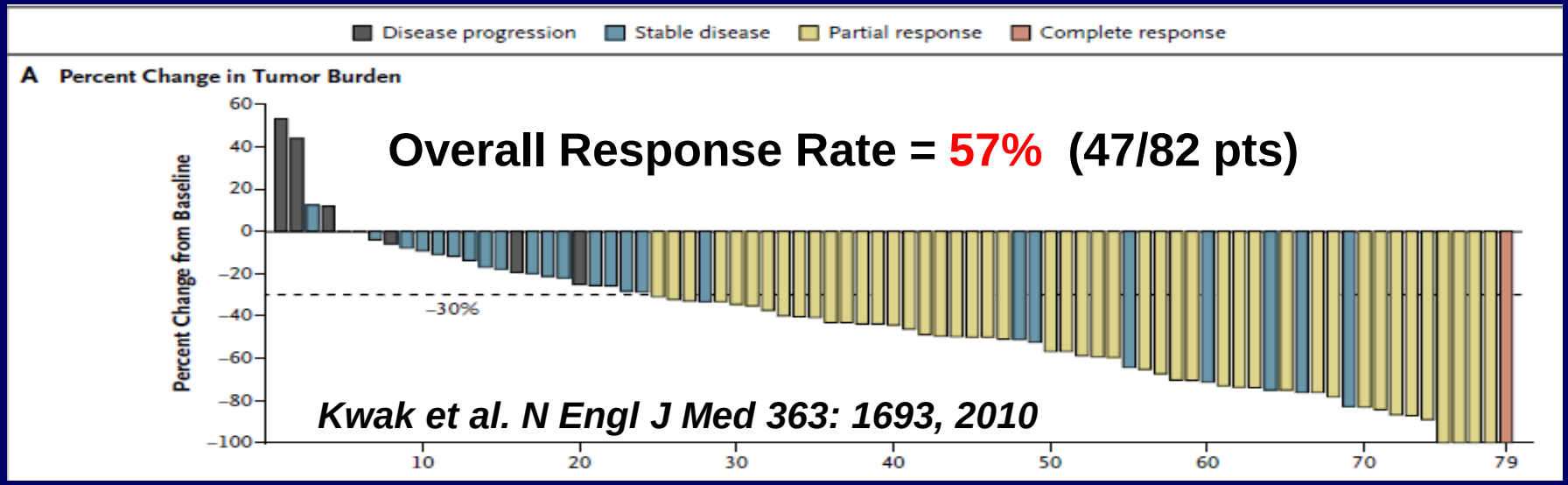
ALT = alanine aminotransferase

Tumor Response to Crizotinib in Patients With *ALK* Mutations

Overall Response Rate = 63% (10/19 pts)



A. Shaw, Proc IASLC, San Francisco, 2009



Overall Response Rate = 57% (47/82 pts)

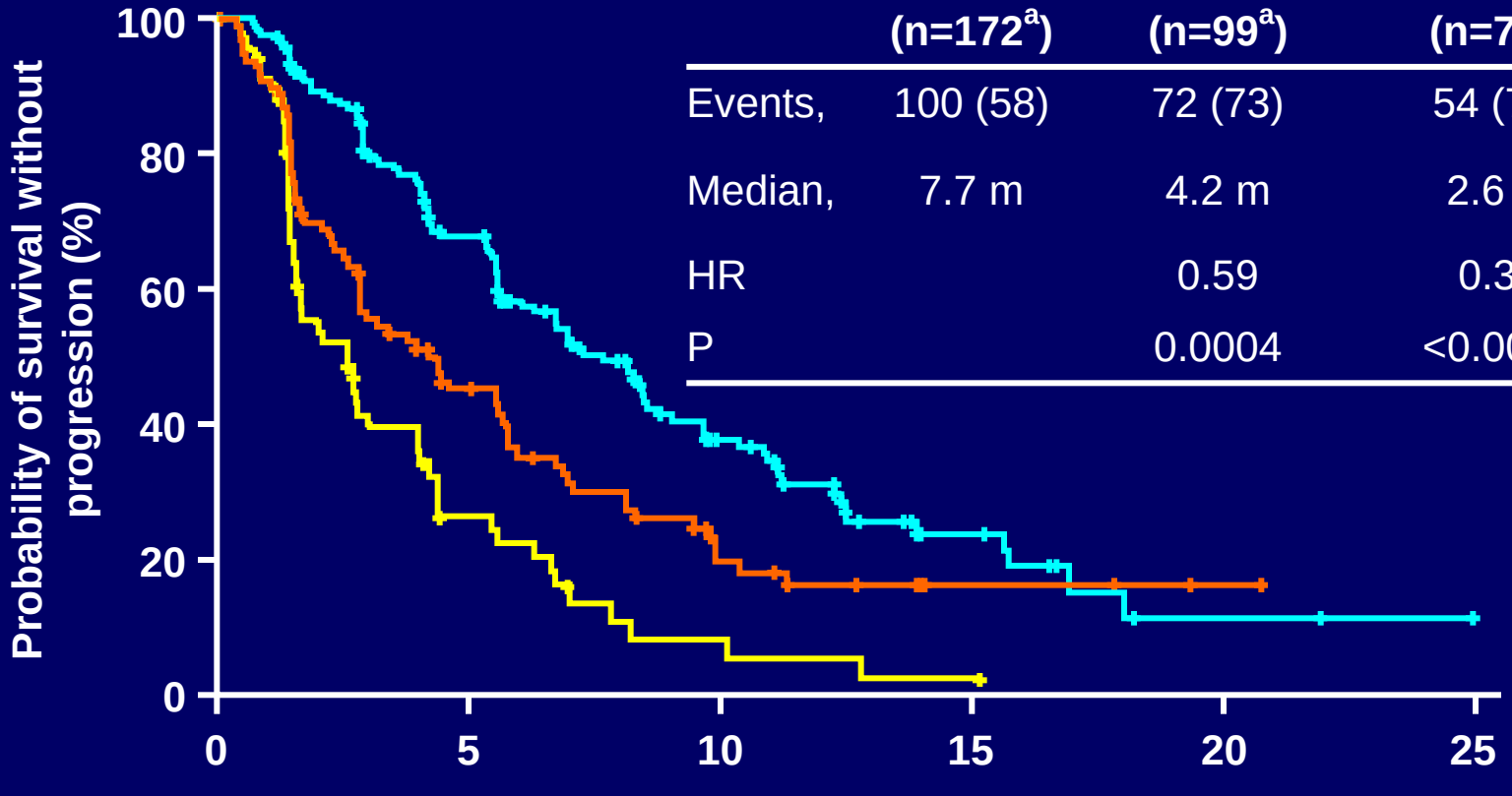
Kwak et al. N Engl J Med 363: 1693, 2010

Crizotinib

- Approved by FDA in Fall, 2011 for treatment of patients with *EML4-ALK* mutations
- Post-approval commitment trials are ongoing in patients with mutations
  - Paclitaxel/carboplatin vs crizotinib
  - Pemetrexed vs crizotinib

PROFILE 1: PFS Crizotinib *vs* Pemetrexed or Docetaxel

	Crizotinib (n=172[a])	Pemetrexed (n=99[a])	Docetaxel (n=72[a])
Events,	100 (58)	72 (73)	54 (75)
Median,	7.7 m	4.2 m	2.6 m
HR		0.59	0.30
P		0.0004	<0.0001



No. at risk						
Crizotinib	172	93	38	11	2	0
Pemetrexed	99	36	12	3	1	0
Docetaxel	72	13	3	1	0	

Shaw et al., N Engl J Med 2013; 368: 2385-94

From Response to Resistance in 41 Pages!!!!

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

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BRIEF REPORT

EML4-ALK Mutations in Lung Cancer That Confer Resistance to ALK Inhibitors

Young Lim Choi, M.D., Ph.D., Manabu Soda, M.D., Ph.D., Yoshihiro Yamashita, M.D., Ph.D., Toshihide Ueno, Ph.D., Junpei Takashima, M.D., Takahiro Nakajima, M.D., Ph.D., Yasushi Yatabe, M.D., Ph.D., Kengo Takeuchi, M.D., Ph.D., Toru Hamada, M.D., Hidenori Haruta, M.D., Ph.D., Yuichi Ishikawa, M.D., Ph.D., Hideki Kimura, M.D., Ph.D., Tetsuya Mitsudomi, M.D., Ph.D., Yoshiro Tanio, M.D., Ph.D., and Hiroyuki Mano, M.D., Ph.D., for the ALK Lung Cancer Study Group

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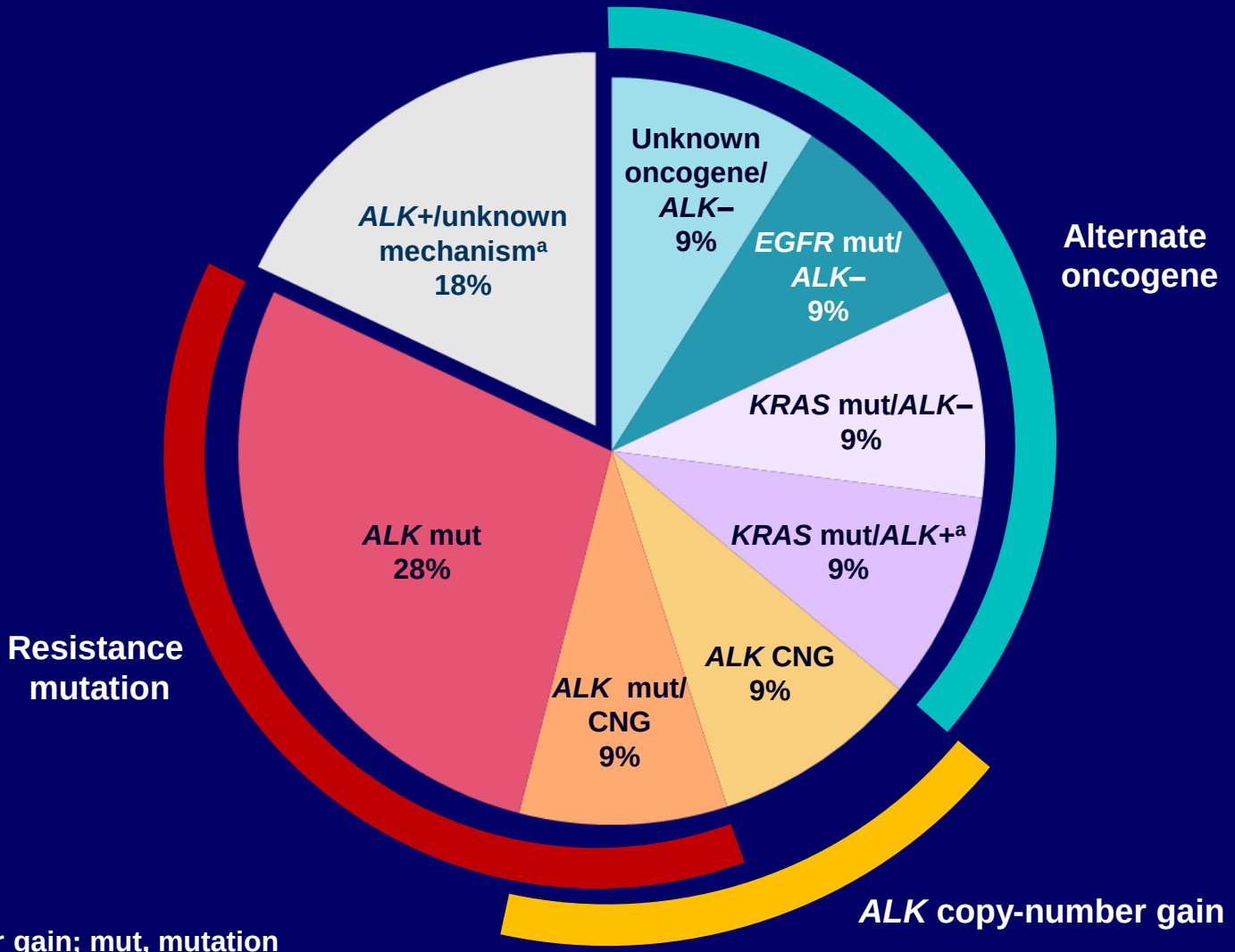
Crizotinib Resistance Mechanisms



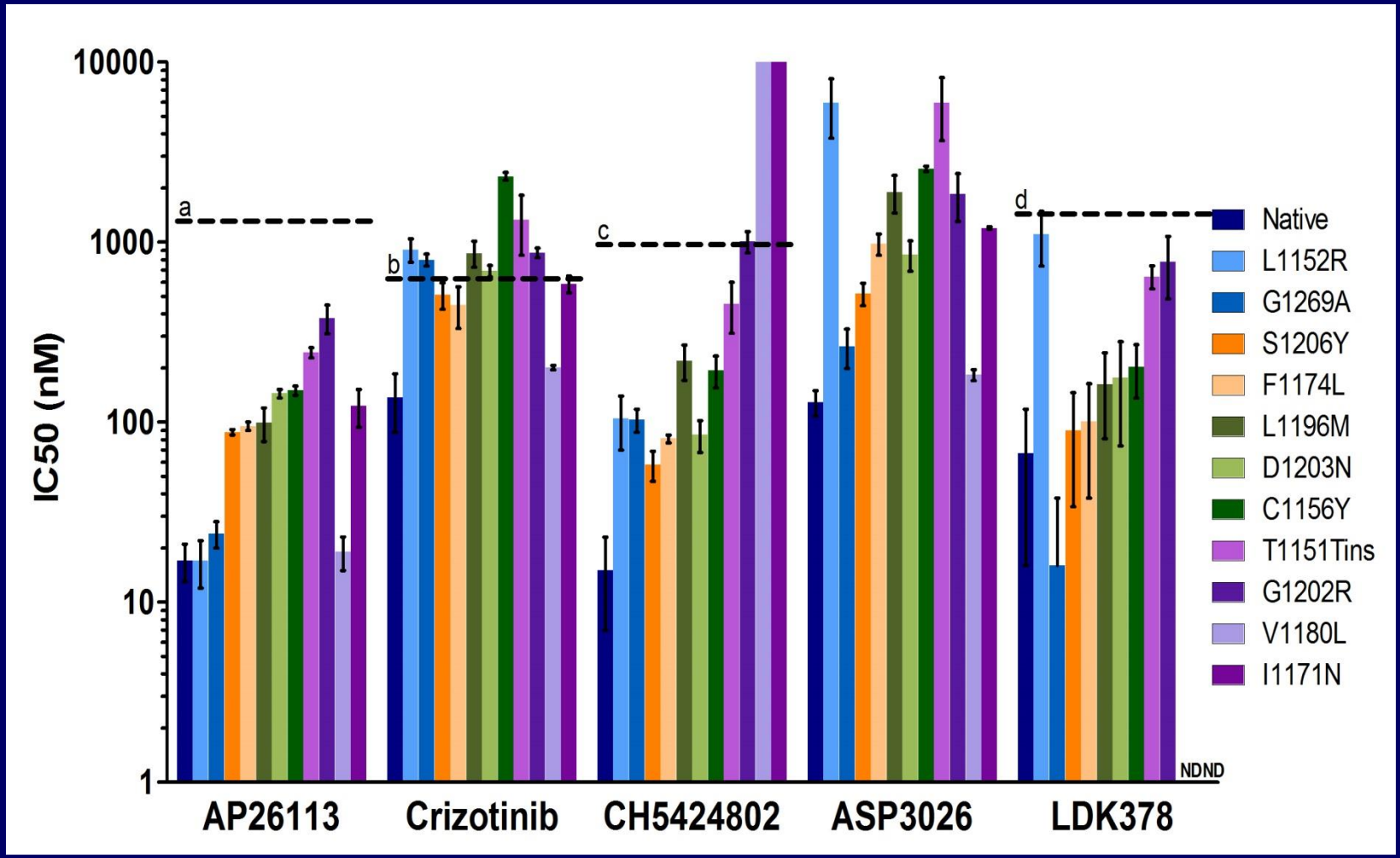
CNG, copy-number gain; mut, mutation
[a]One patient had intrinsic resistance within this category

Doebele RC, et al. *Clin Cancer Res* 2012;18:1472–1482

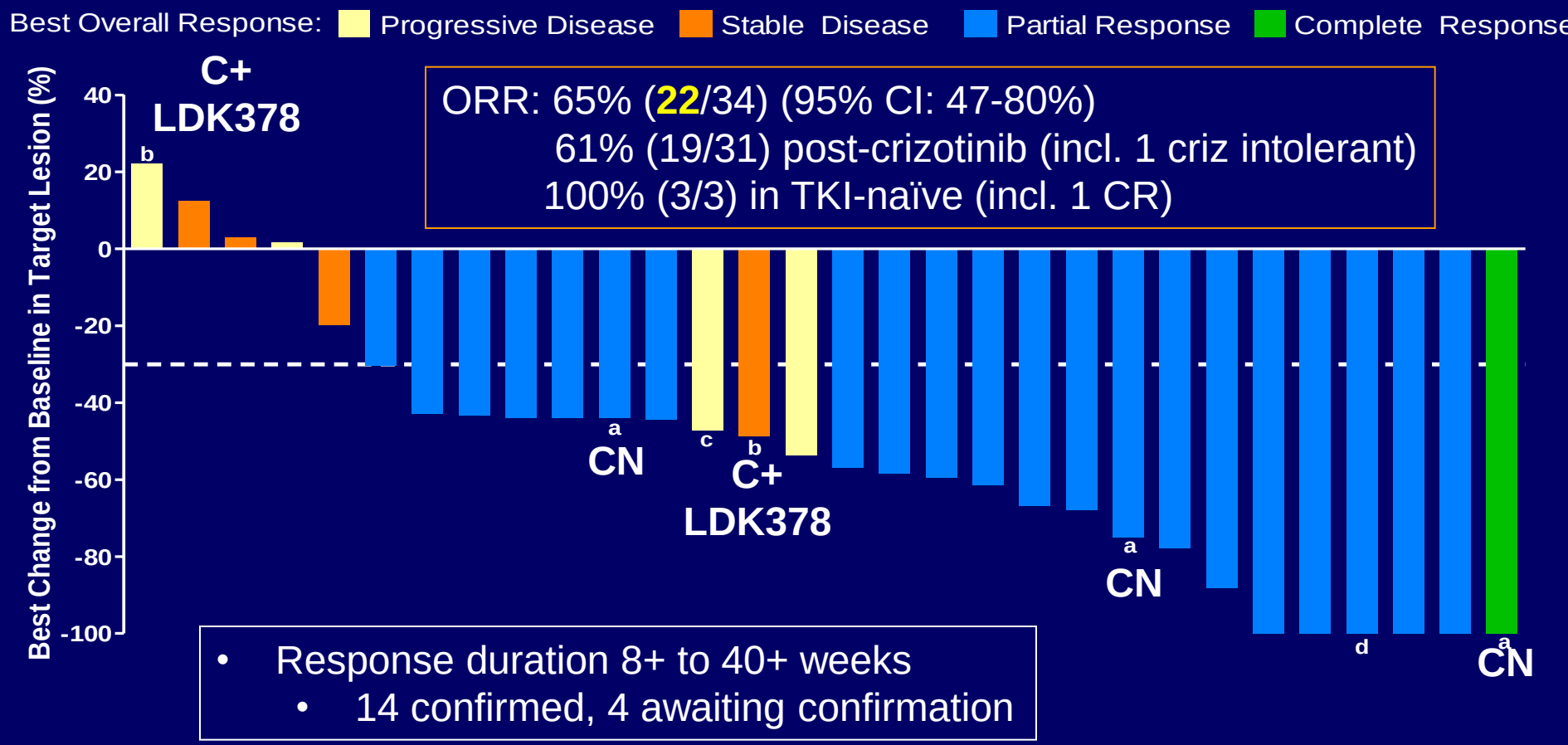
The Competition is Fierce!!

AP26113 (ALK/EGFR)
CH5424802 (Selective ALK)
LDK378 (Ceritinib, Selective ALK)
ASP3026 (ALK/EGFR)

All Agents Demonstrate ALK Inhibitory Effects

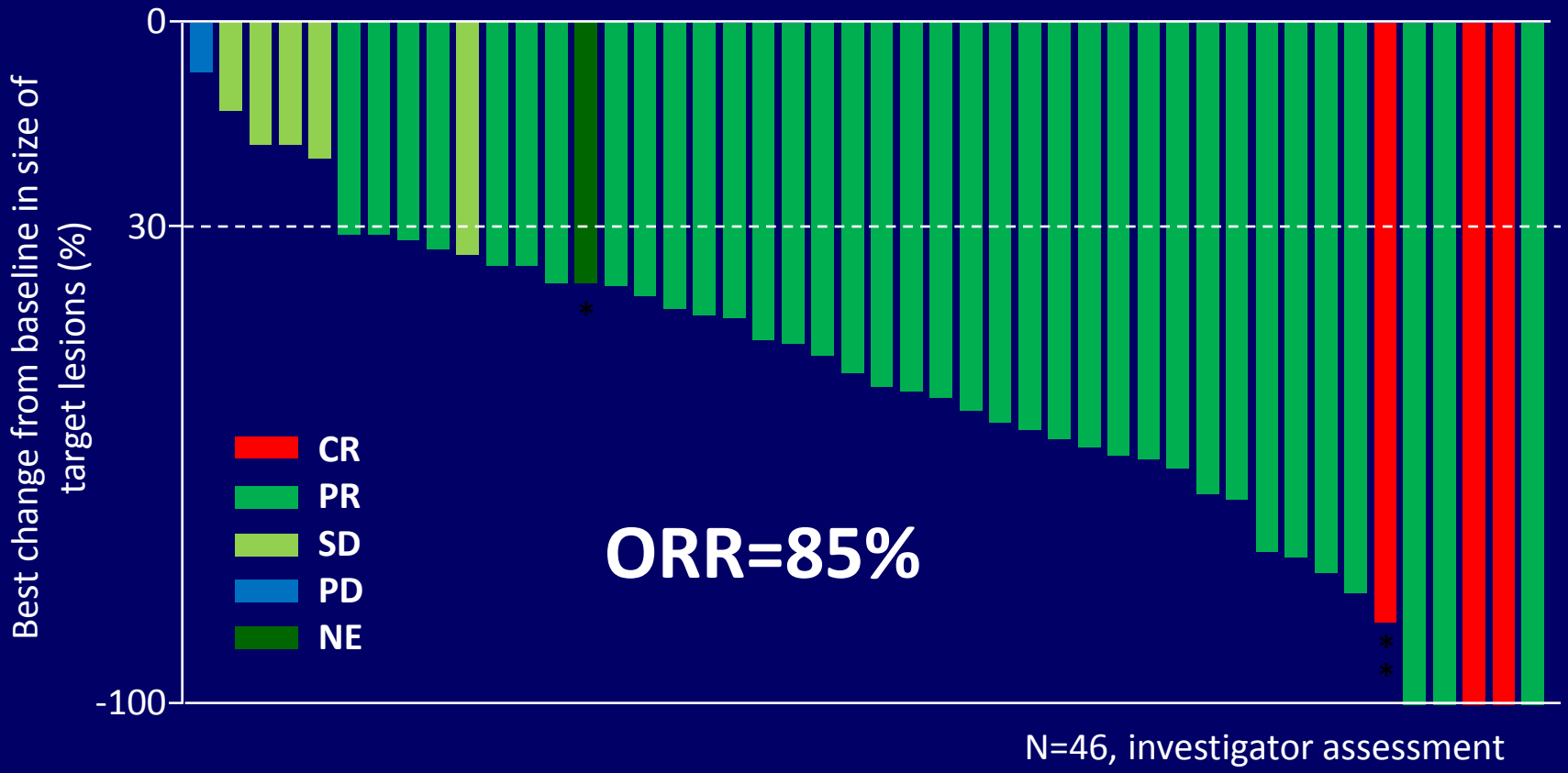


AP26113: Anti-Tumor Activity Target Lesions (N=34)



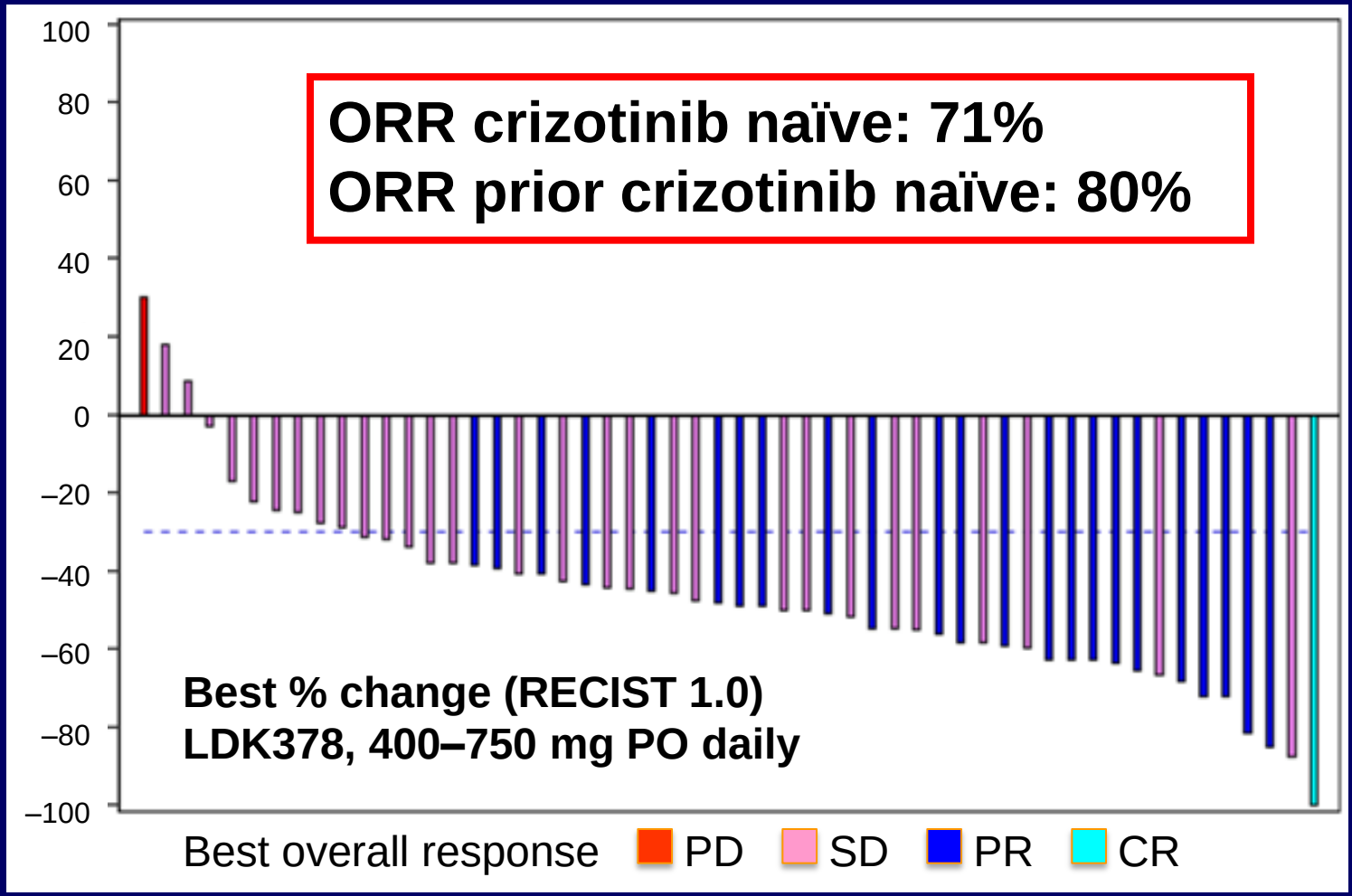
Camidge et al. Proc ECCO/ESMO, 2013

CH5424802: Waterfall Plot of Tumor Shrinkage



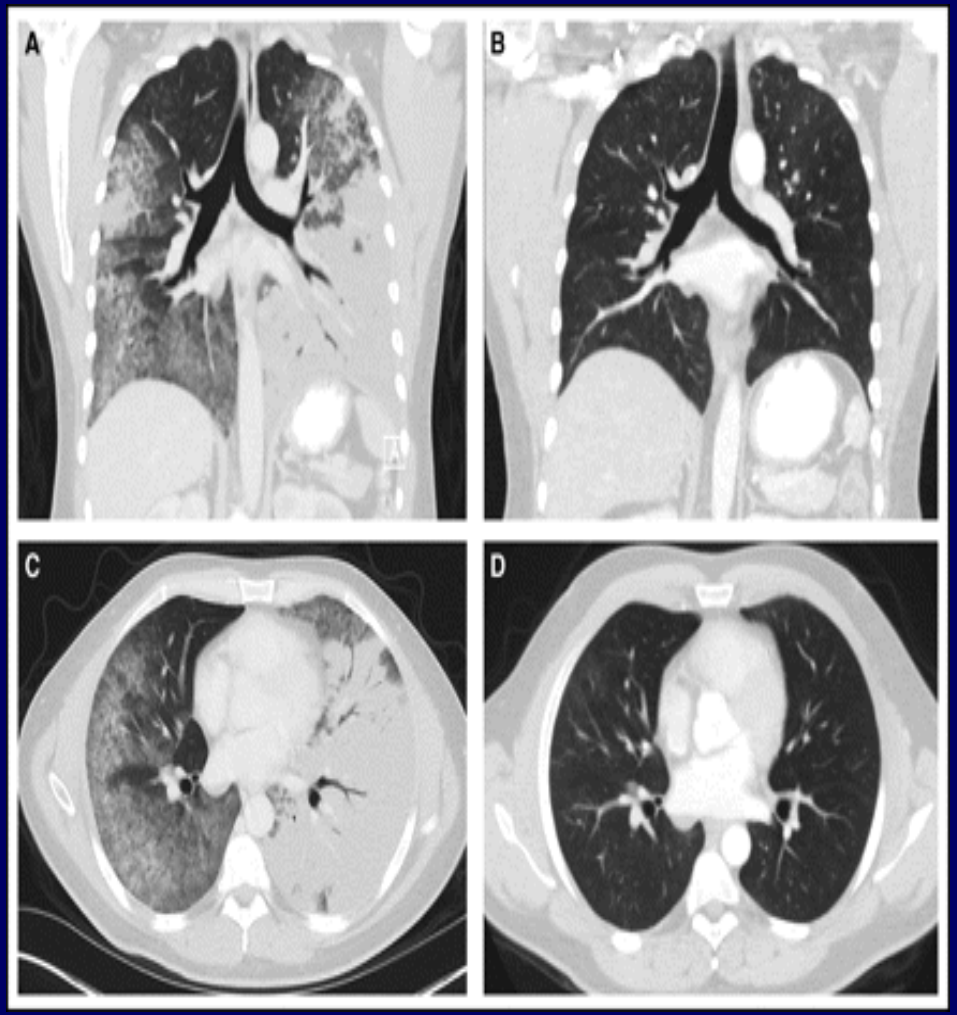
Nishio M, et al. Presented at ESMO 2012. Abstract number: 441O

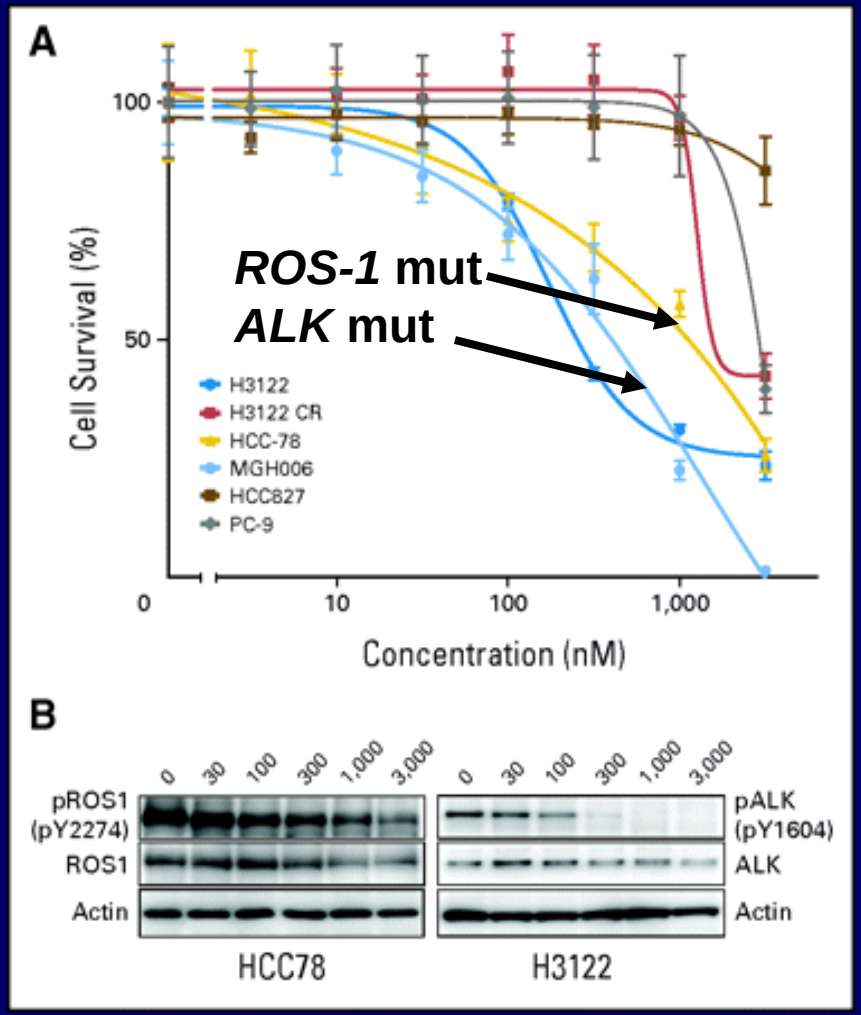
Activity of Ceritinib in Advanced ALK+ NSCLC



Shaw et al. Proc ESMO, 2012

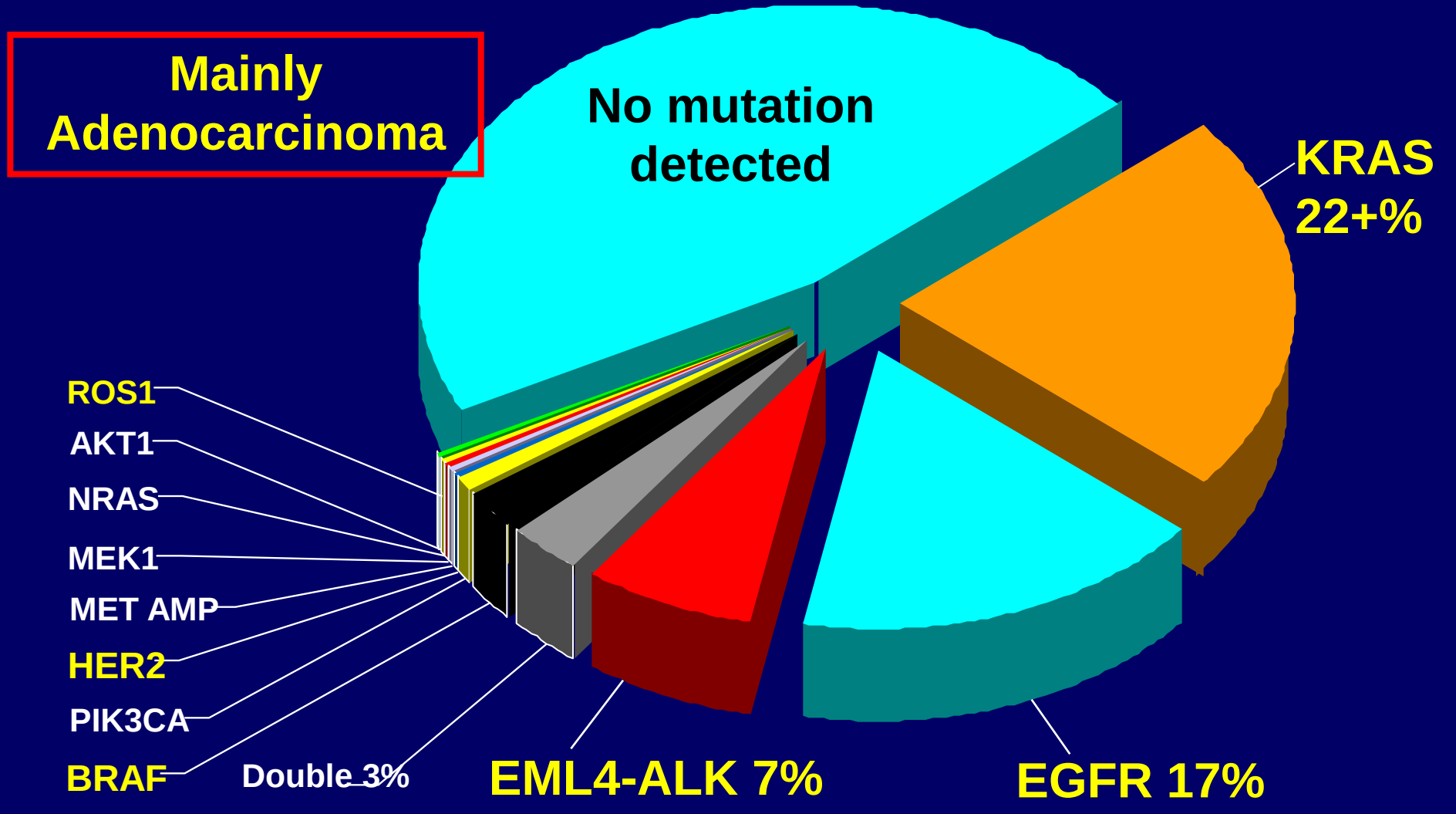
ROS-1 Mutated Tumours are Sensitive *In Vitro* and *In Vivo* to Crizotinib





Bergethon et al. J Clin Oncol 30: 863, 2012

Numerous Molecular Changes Drive Lung Cancer

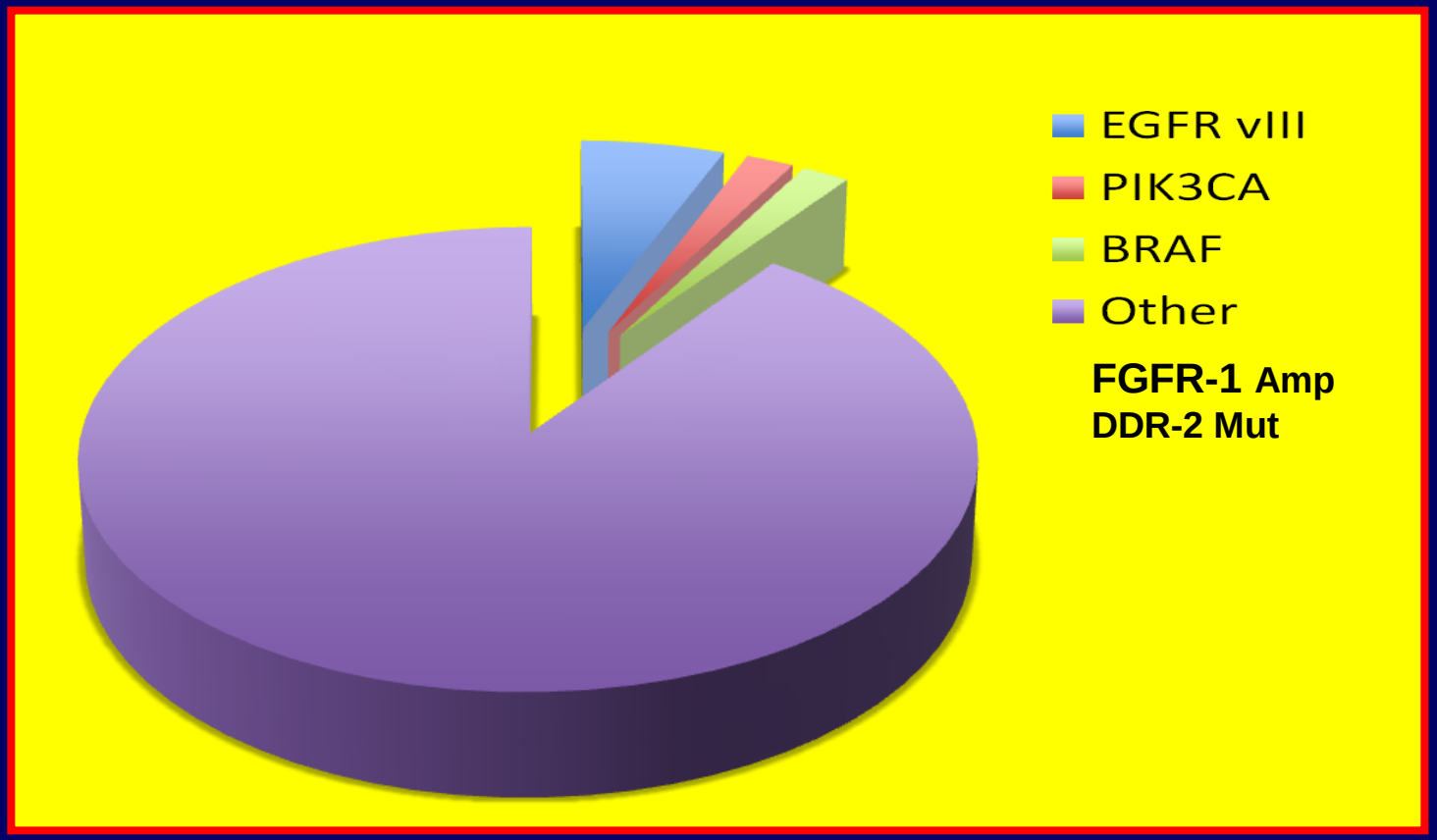


Kris, et al. J Clin Oncol 2011;29:Suppl(Abstr 7506).

Will Adenocarcinoma of the Lung Become a Collection of "Orphan Diseases"?

More Cosettes than Olivers!!

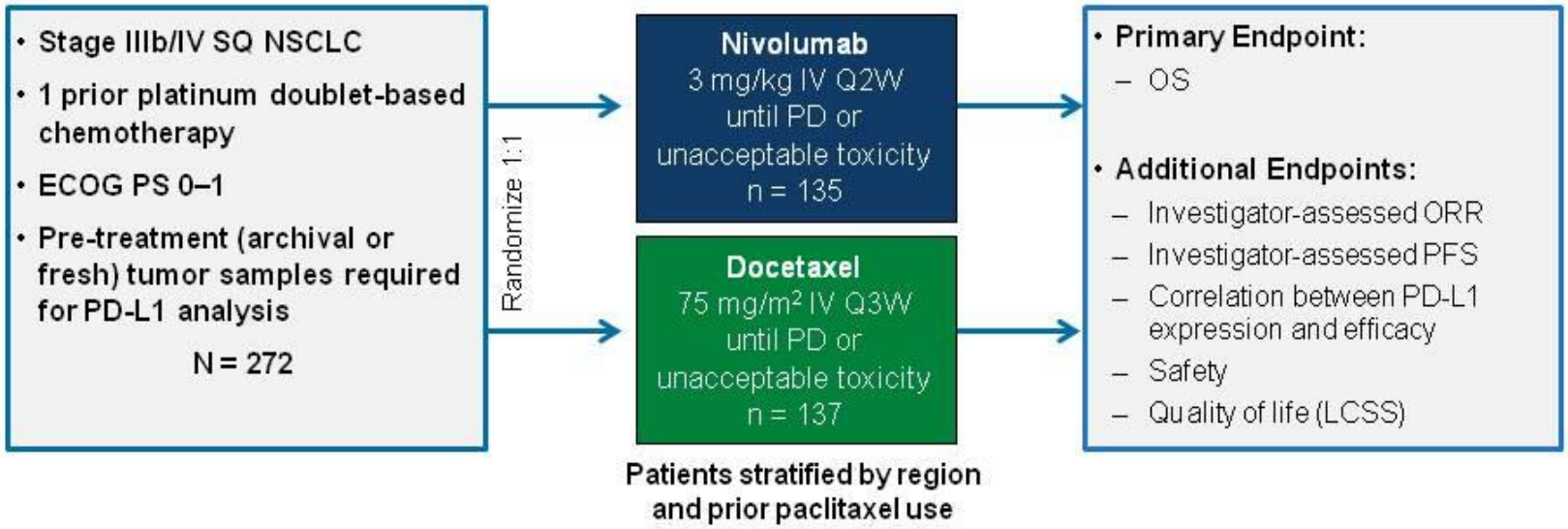
Dominant Mutations in Squamous Cell Lung Cancer



- Compared to adenocarcinoma, there are NO proven molecularly targeted therapies for squamous cell carcinoma and fewer potential targets

CheckMate 017: Study Design

CheckMate 017 (NCT01642004) - Study Design

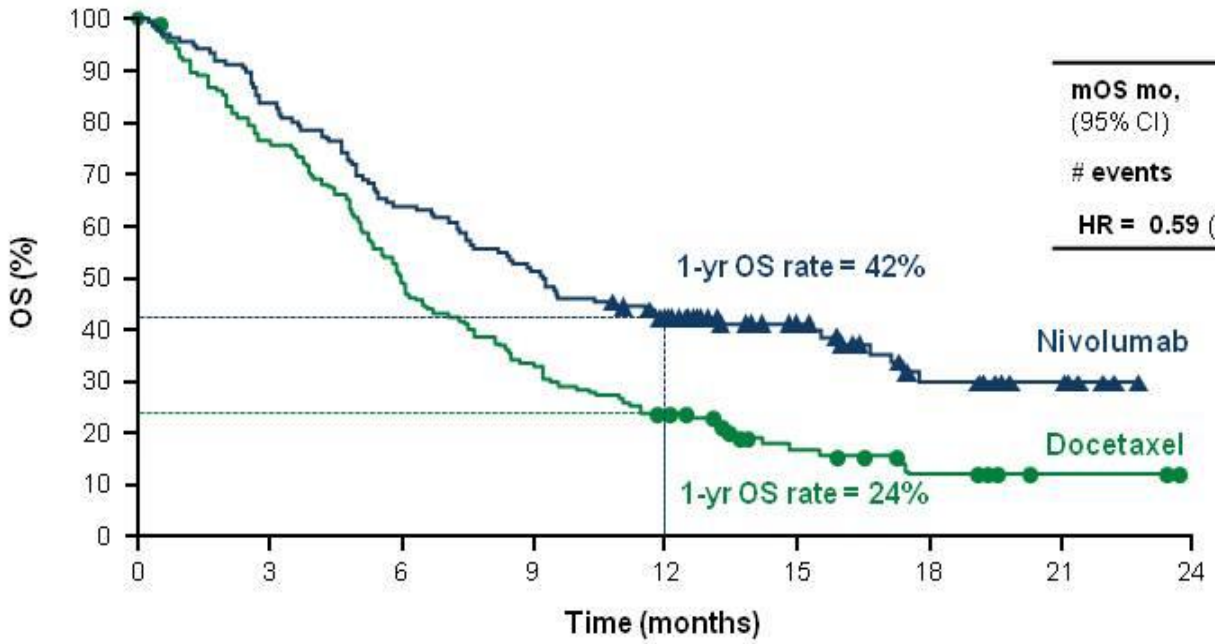


- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

LCSS = Lung cancer symptom scale

CheckMate 017: Overall Survival

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), ***P* = 0.00025**

Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

PRESENTED AT: ASCO Annual '15 Meeting

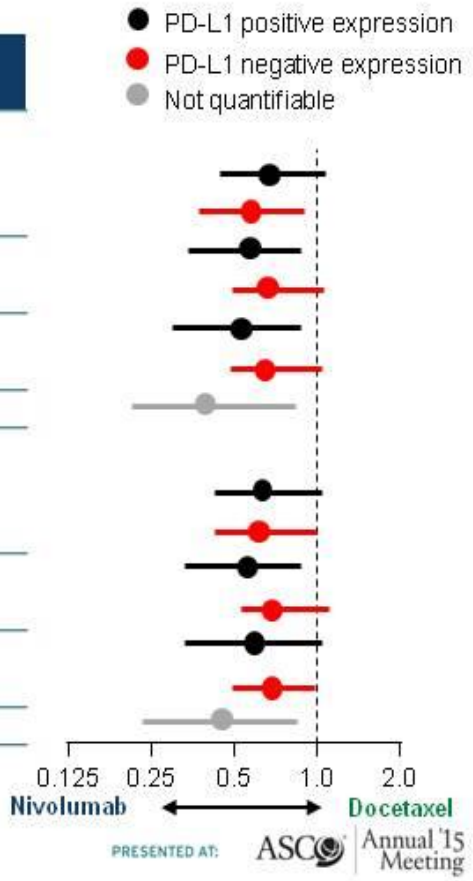
David Spigel at 2015 ASCO

OS and PFS by PD-L1 Expression

- Survival benefit with nivolumab was independent of PD-L1 expression level

PD-L1 expression	Patients, n Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	63	56	0.69 (0.45, 1.05)	**0.56**
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	**0.47**
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	**0.41**
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
≥1%	63	56	0.67 (0.44, 1.01)	**0.70**
<1%	54	52	0.66 (0.43, 1.00)	
≥5%	42	39	0.54 (0.32, 0.90)	**0.16**
<5%	75	69	0.75 (0.52, 1.08)	
≥10%	36	33	0.58 (0.33, 1.02)	**0.35**
<10%	81	75	0.70 (0.49, 0.99)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	

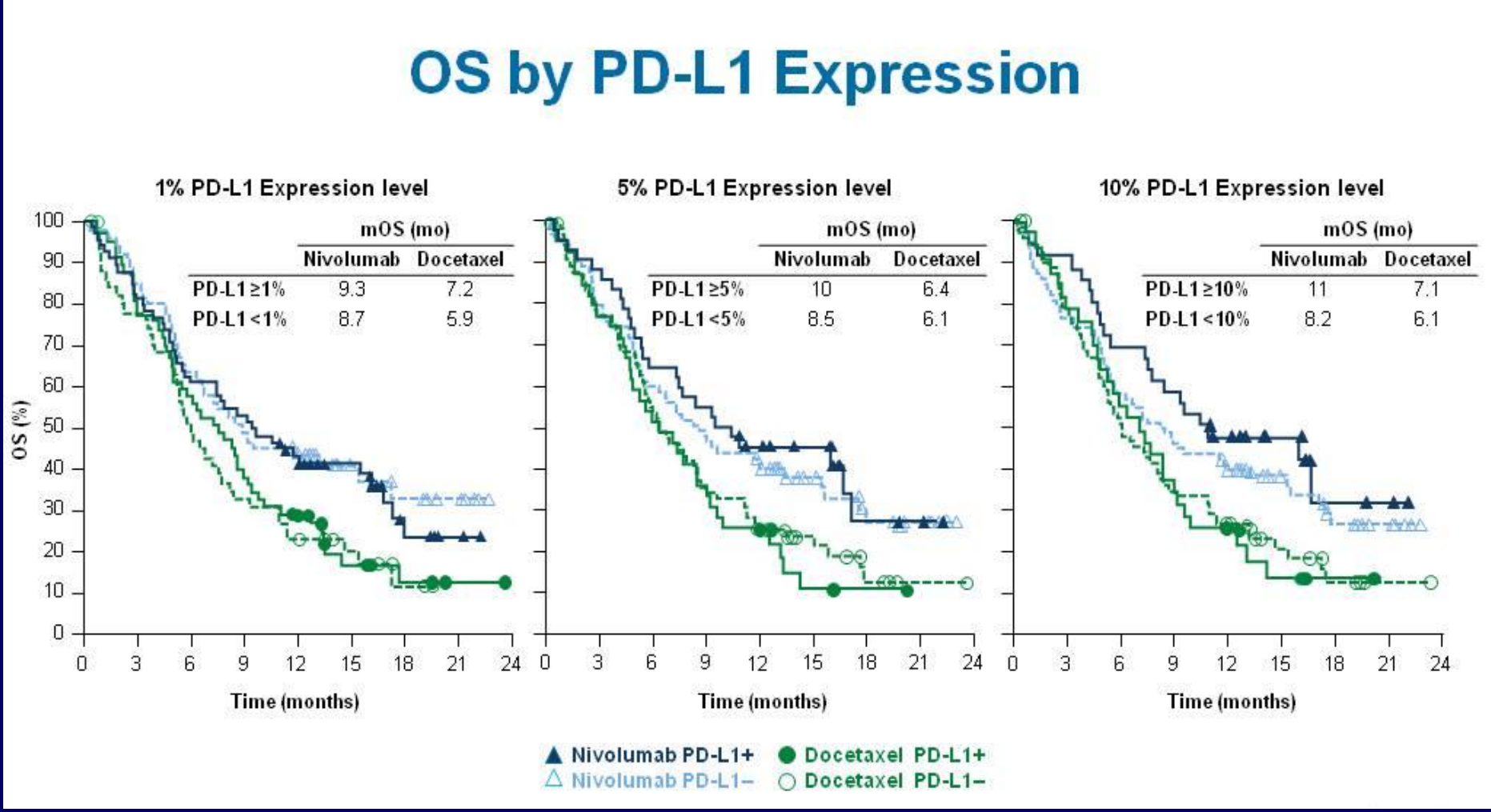
- PD-L1 expression was measured in pre-treatment tumor biopsies (DAKO automated IHC assay)[15]



PRESENTED AT: ASCO Annual '15 Meeting

Presented By David Spigel at 2015 ASCO Annual Meeting

Overall Survival by PD-L1 Expression



David Spigel at 2015 ASCO

From Bench to Bedside

- Critical pathways for lung cancer have been identified
- New treatments now specifically target the most important pathways
- Patient selection by genetic analysis should lead to improved outcomes and avoid the toxicity of treatment for those not likely to benefit
- Harnessing the immune system has shown impressive results to date

Although the Speed is Dizzying, We Are In This Race Together

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