

ASCO Lung Cancer Review 2009

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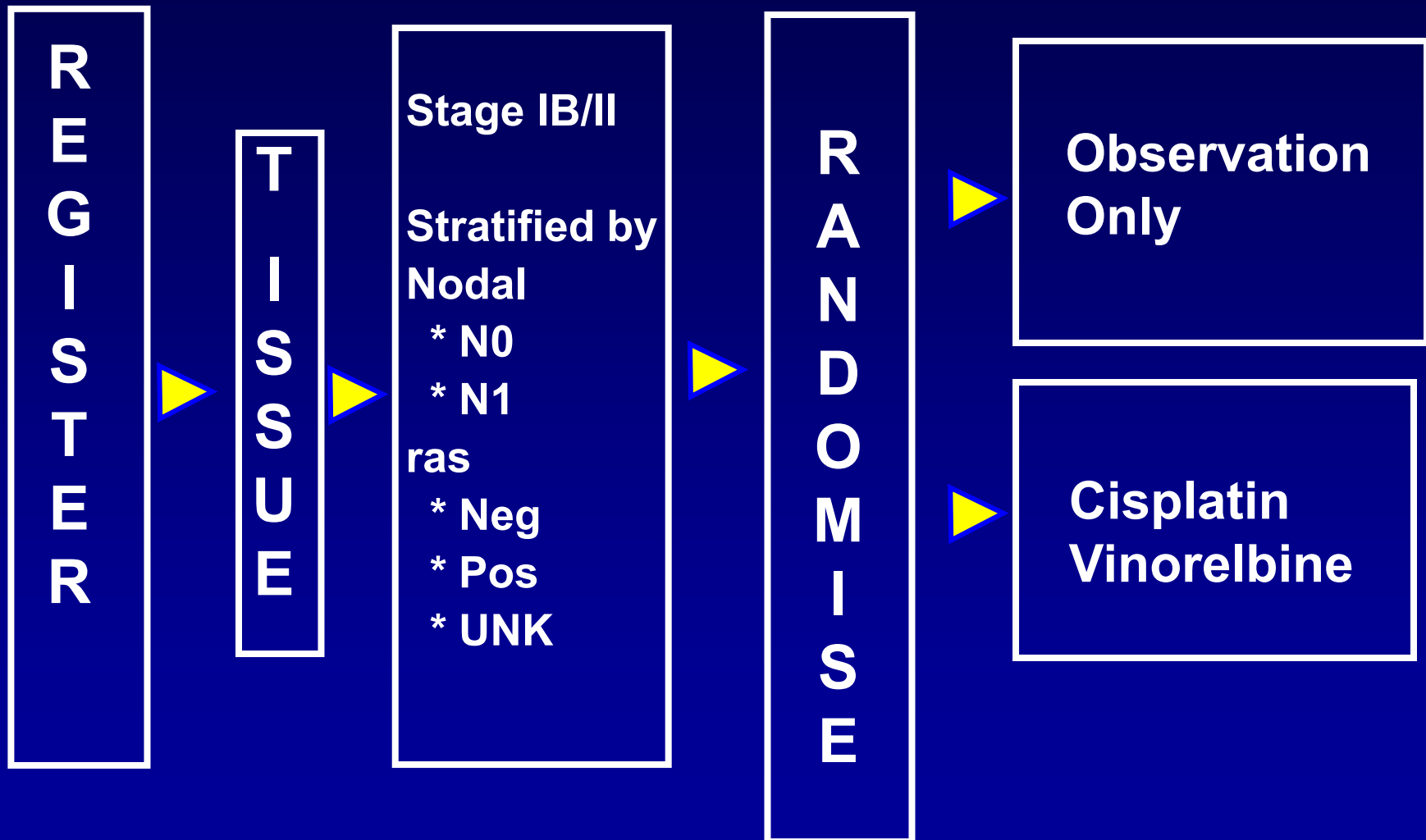
University of North Carolina

Abstracts

- Early stage
 - Adjuvant therapy – BR10 Update (7501)
 - NATCH (7500)
- Stage III
 - ECOG 3598 – thalidomide (7503)
 - CALGB 30407 – cetuximab (7505)
- Stage IV NSCLC
 - “Maintenance” – Pemetrexed, SATURN, ATLAS (8000, 8001, 8002)
 - Biomarkers – FLEX, IPASS (8006, 8007)
 - Vandetinib trials – ZODIAC, ZEST, ZEAL (8003, 8009,8010)

JBR.10 Update - Study Design

Vincent M et al. ASCO 2009, abstr # 7501



Overall Survival: April 2004

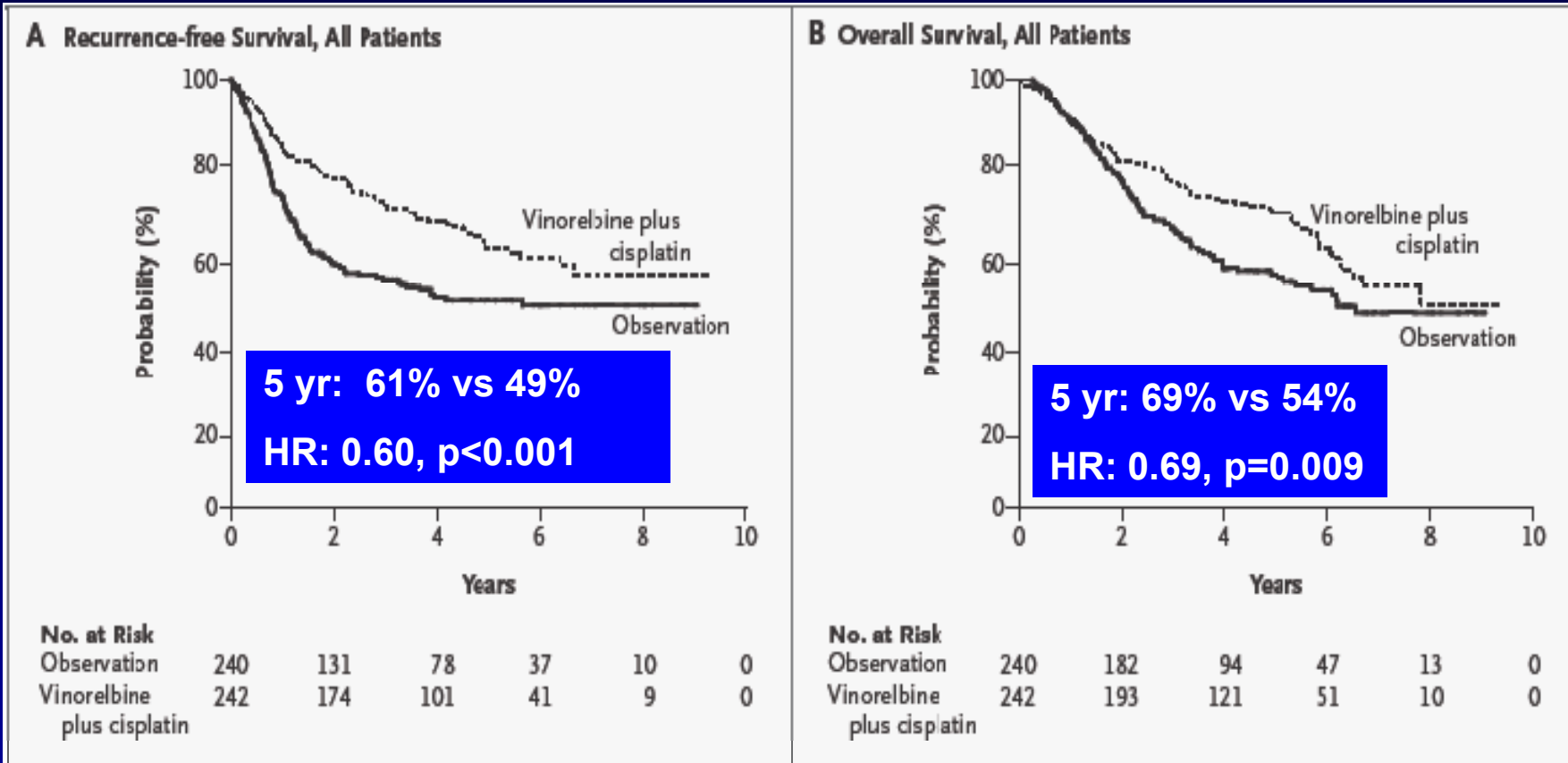


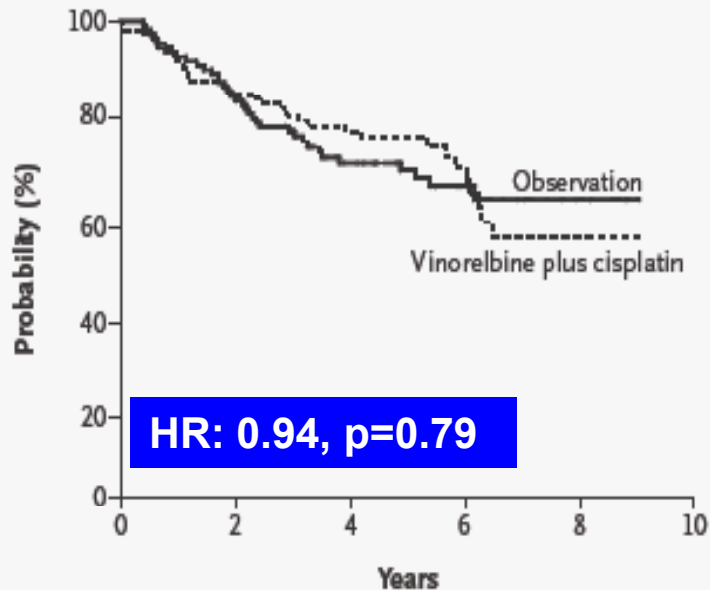
Figure 1. Kaplan–Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone.

P values are based on two-sided statistical analyses of differences between treatment groups after randomization.

Winton et al. NEJM 2005; 352: 2589-97

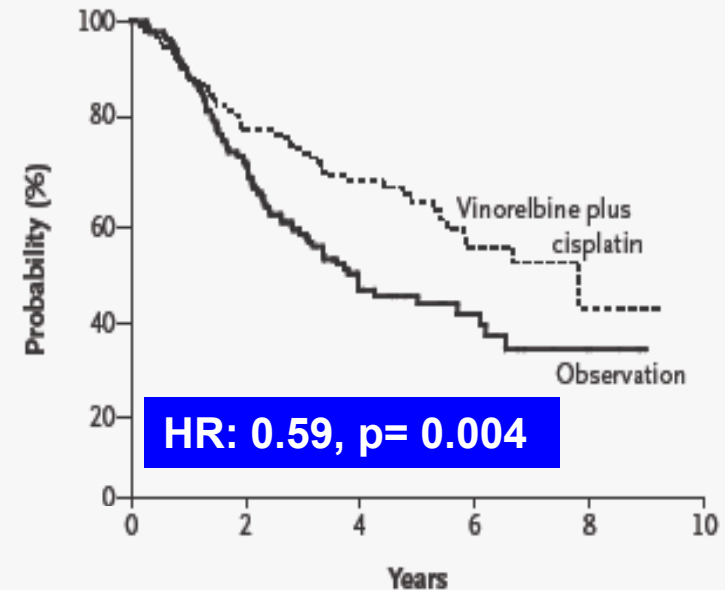
Overall Survival by Stage: April 2004

C Overall Survival, Patients with Stage IB Non-Small-Cell Lung Cancer



No. at Risk						
Observation	108	91	57	29	8	0
Vinorelbine plus cisplatin	111	93	65	27	6	0

D Overall Survival, Patients with Stage II Non-Small-Cell Lung Cancer



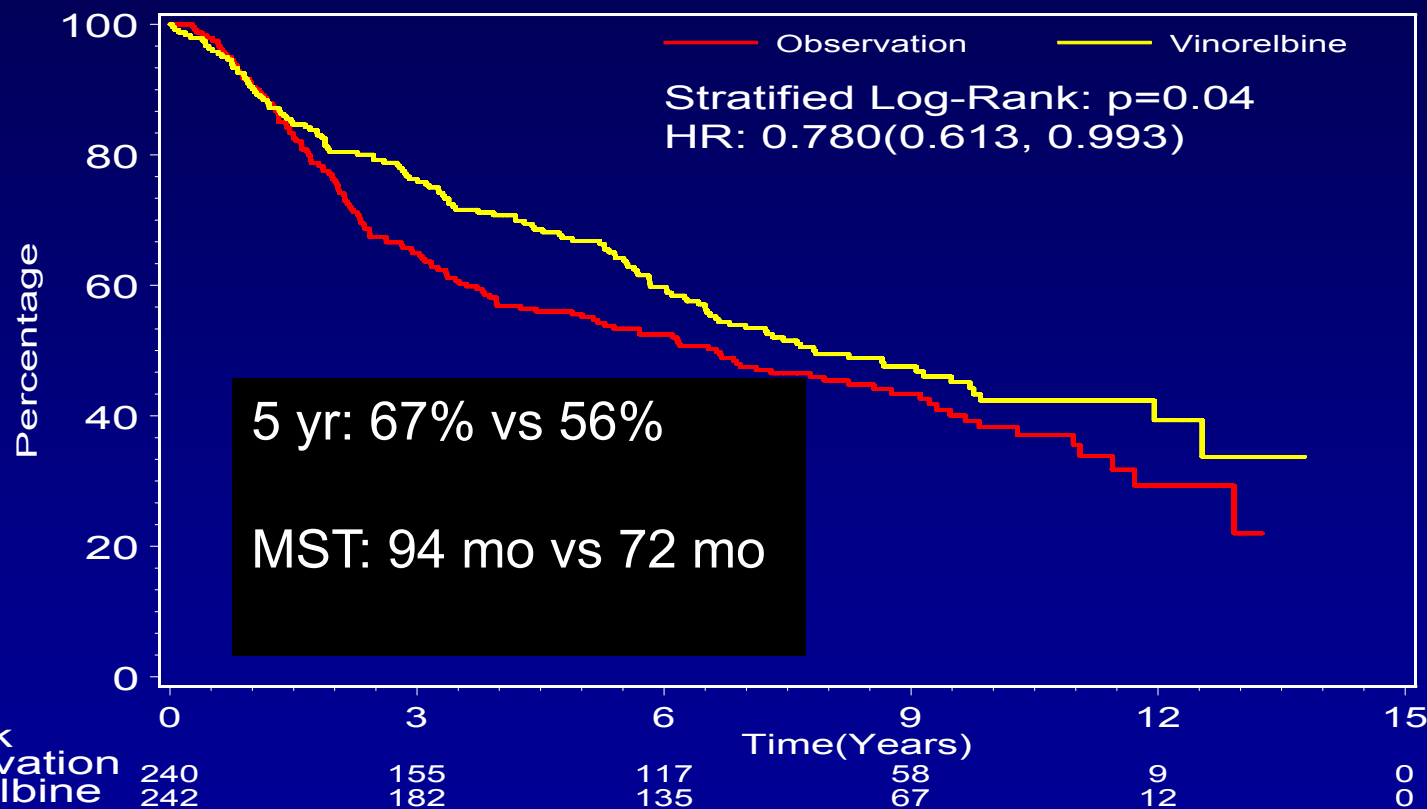
No. at Risk						
Observation	132	91	37	18	5	0
Vinorelbine plus cisplatin	131	100	56	24	4	0

Figure 1. Kaplan–Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone.

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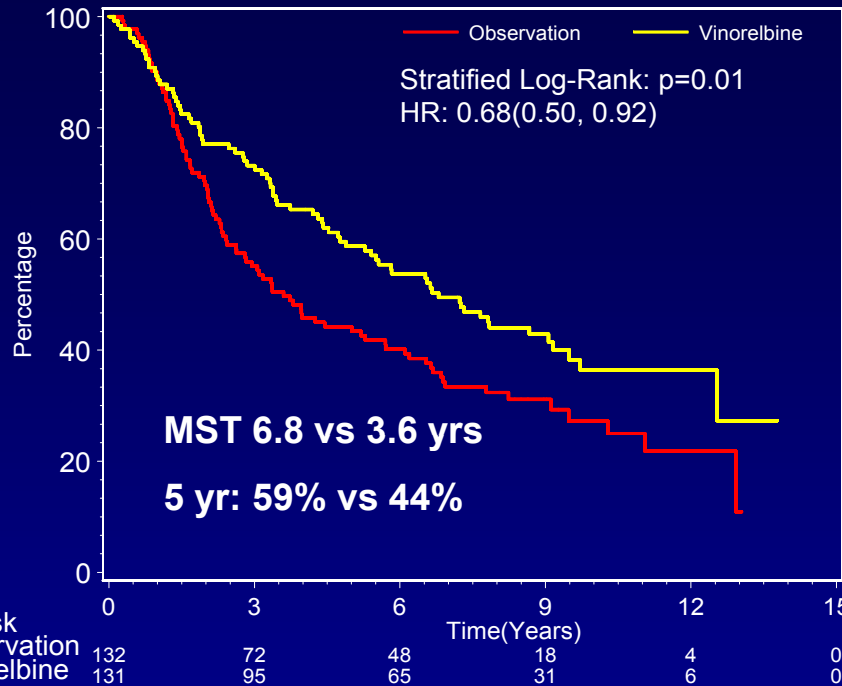
Winton et al. NEJM 2005; 352: 2589-97

Updated Overall Survival by Treatment Arm – ASCO 2009



Absolute improvement in 5 yr OS 11% (67%-56%)

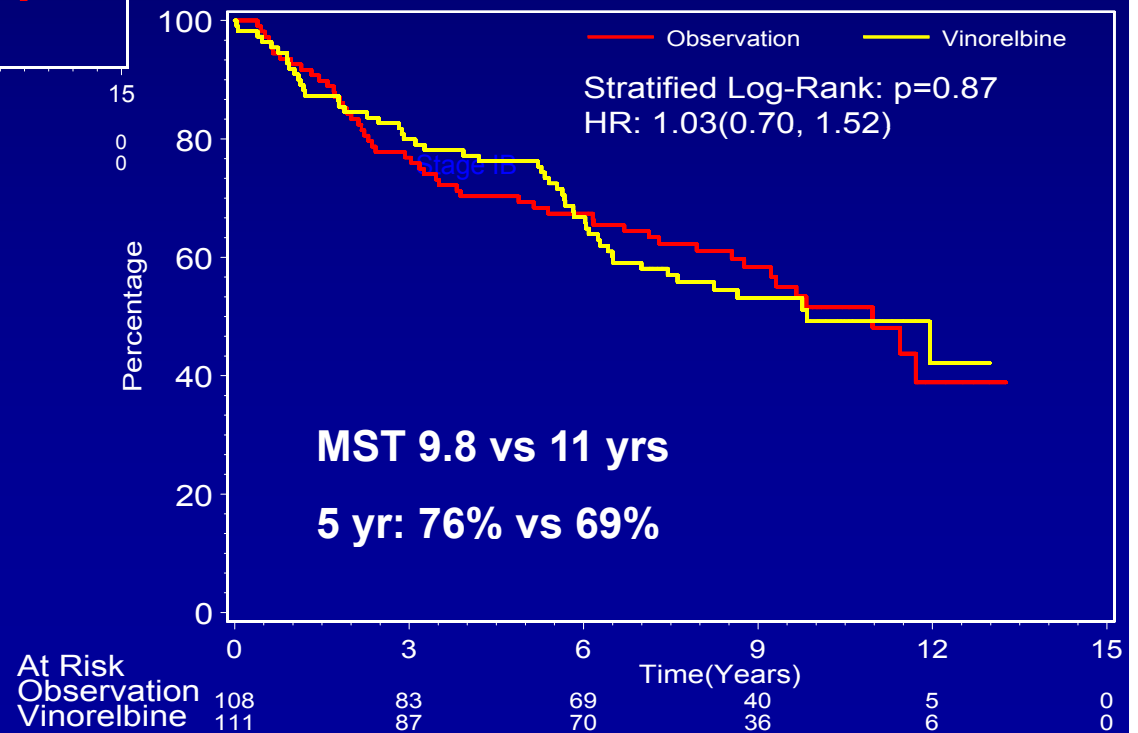
Updated Survival by Stage



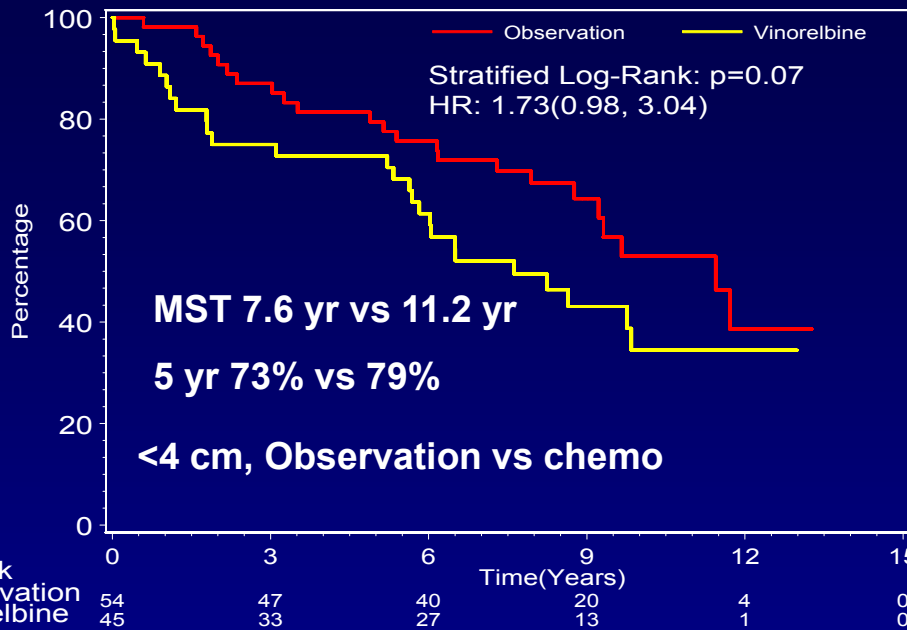
Stage II

Interaction $p=0.09$

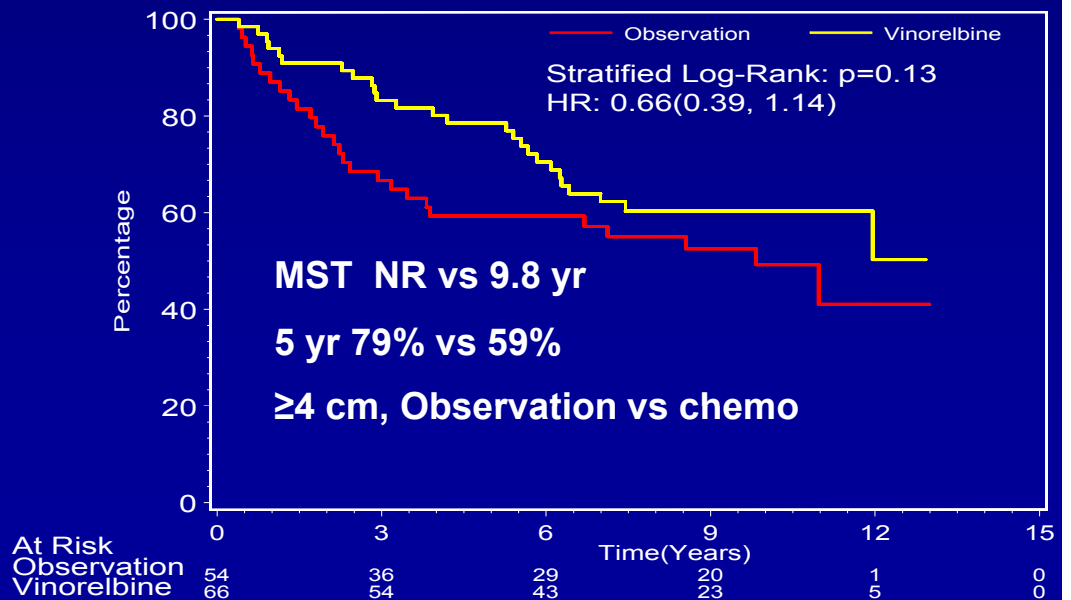
Stage IB



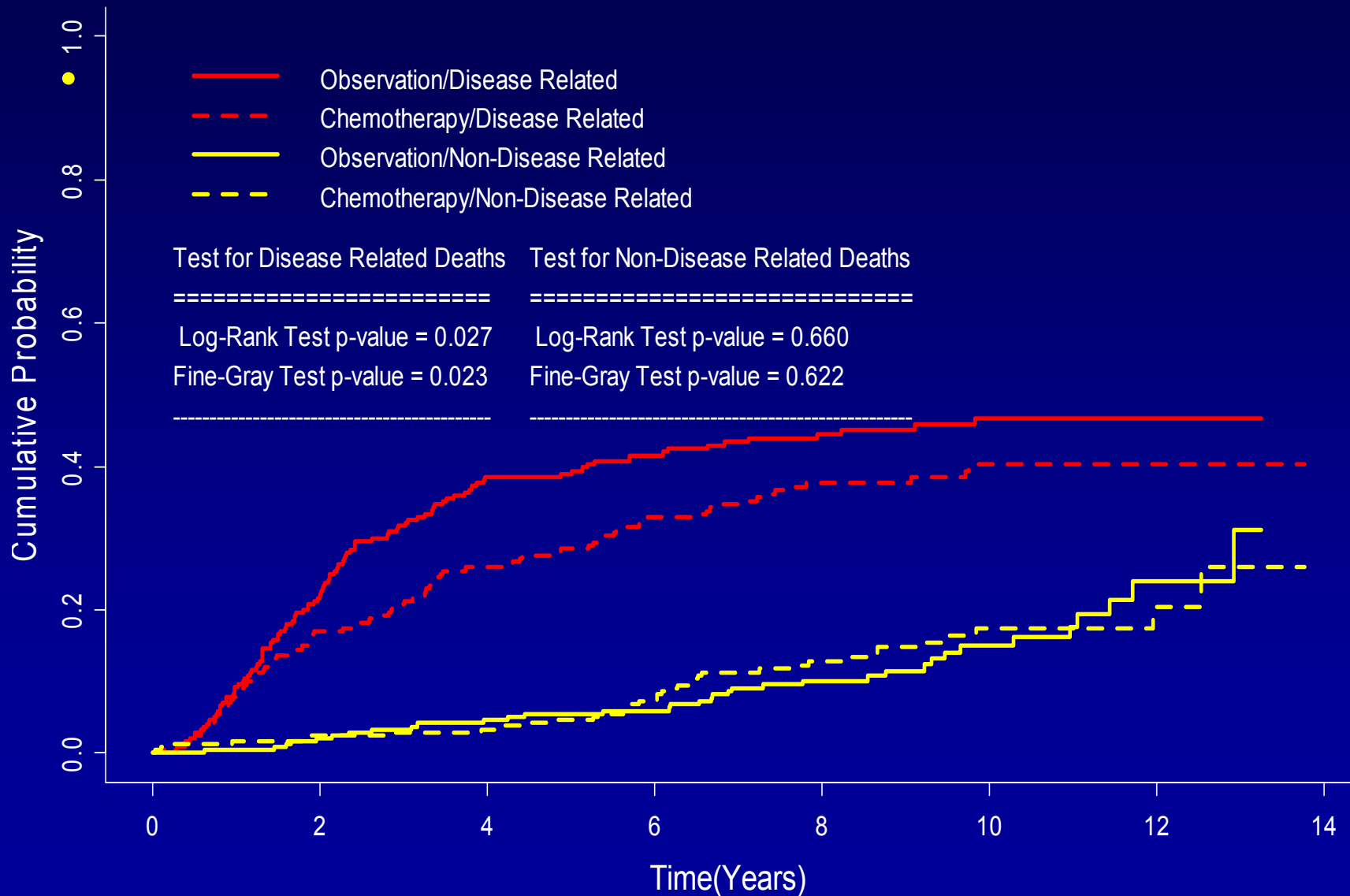
Updated Stage IB Survival By T Size



Interaction $p=0.02$



Cumulative Incidence Plots for Disease and Non-disease Related Deaths

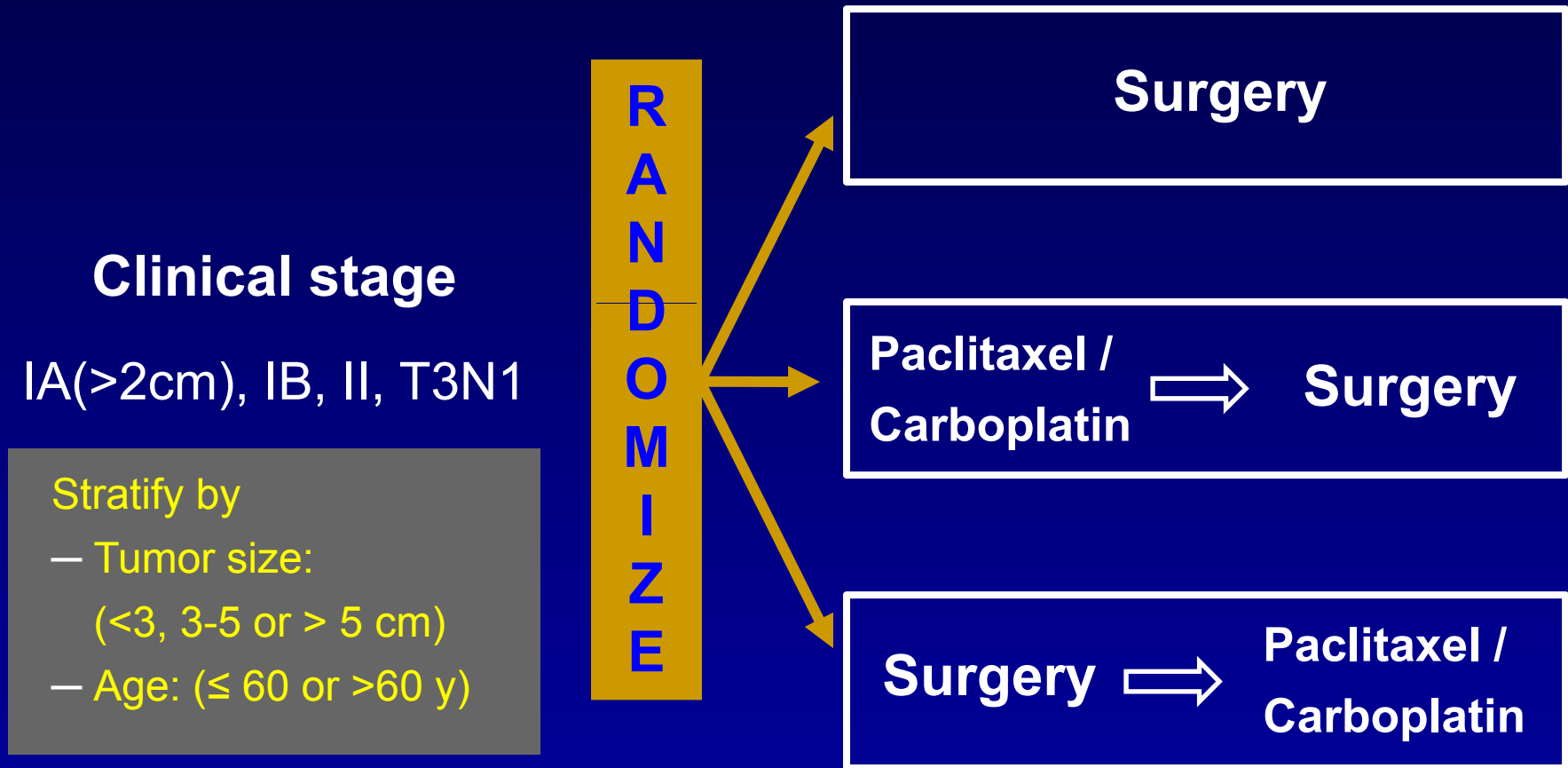


Second Primary Malignancies

	Observation N=239	Chemotherapy N=243
No	218 (91.2%)	226 (93%)
Yes	21 (8.8%)	17 (7.9%)
Head & Neck	4	0
NSCLC	3	0
SCLC	1	1
Bladder	0	1
Kidney	1	1
Miscellaneous	12	14

NATCH Study Design

Felip E et al. ASCO 2009, abstr # 7500



Primary Endpoint:

5 yr DFS (Δ 15%)

- Paclitaxel 200 mg/m² /3h + Carboplatin AUC=6 q3wk for a total of 3 cycles
- Post-op thoracic RT allowed for p-N2 disease

Preop CT Arm: CT Compliance (N=199)

- Preop CT, 193 pts (97%)
 - 180 pts, 3 cycles (90%)
 - 13 pts, < 3 cycles
 - Adverse events, 4 pts
 - Death, 2 pts
 - Progression, 1 pt
 - Other, 4 pts
 - No information, 2 pts
- Dose reductions 9% of pts / delays 11% of pts

Adj CT Arm: CT Compliance (N=210)

No adj CT, 71 pts (34%)

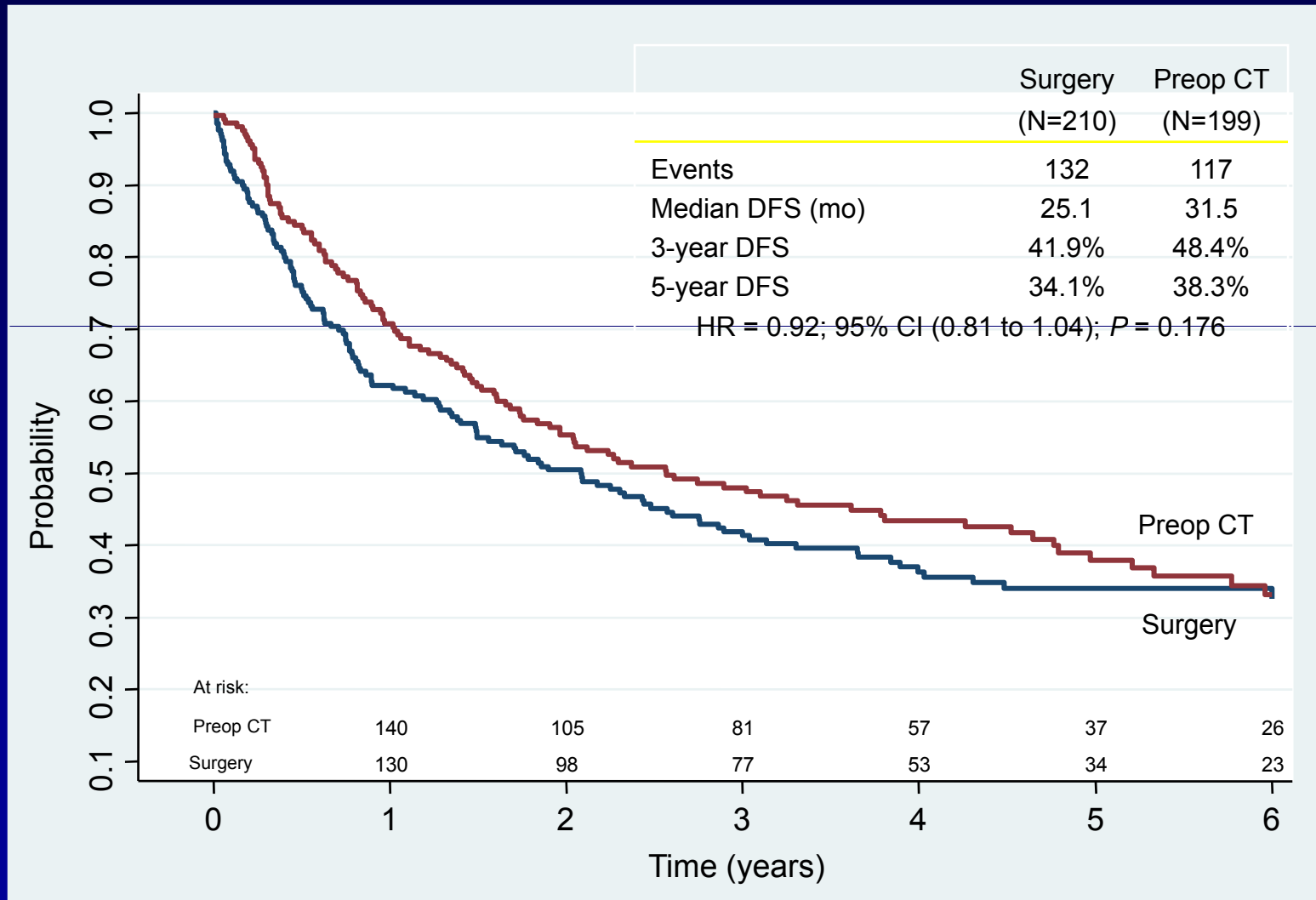
- Post-operative mortality, 15 pts
- Stage IIIB/IV at surgery, 12 pts
- Surgical complications, 9 pts
- Other histologies, 2 pts
- Refused CT, 11 pts
- PI's decision, 4 pts
- Progression, 3 pts
- Other, 5 pts
- Ineligible / cancelled at baseline, 10 pts

Adj CT, 139 pts (66%)

- 129 pts, 3 cycles
- 10 pts, < 3 cycles
 - Adverse events, 4 pt
 - Refusal, 2 pt
 - Progression, 2 pt
 - Death, 2 pt
- Dose reductions 11% of pts / delays 16% of pts

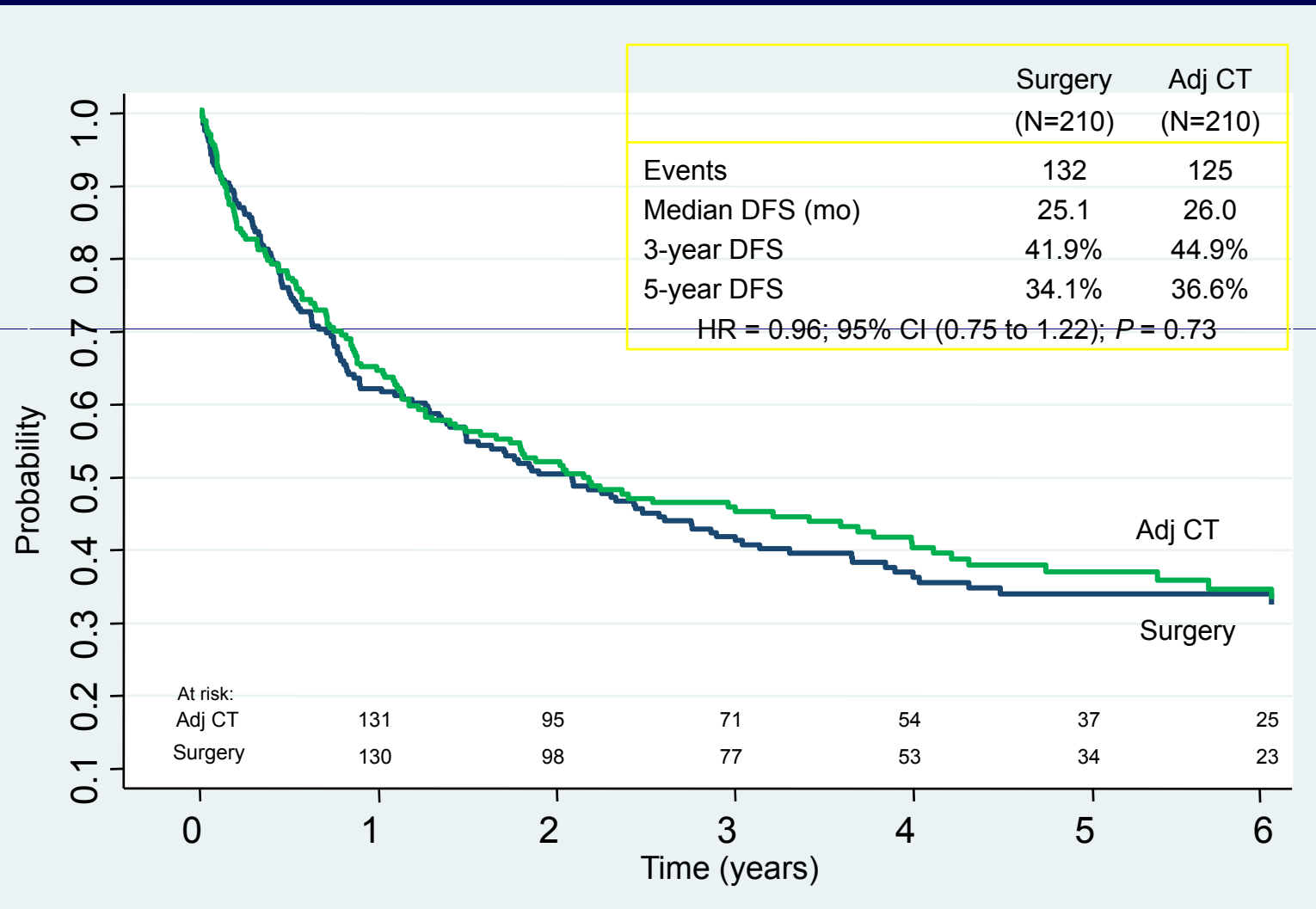
DFS in Preop CT Arm vs Surgery Arm

Median Follow-up 51 Months

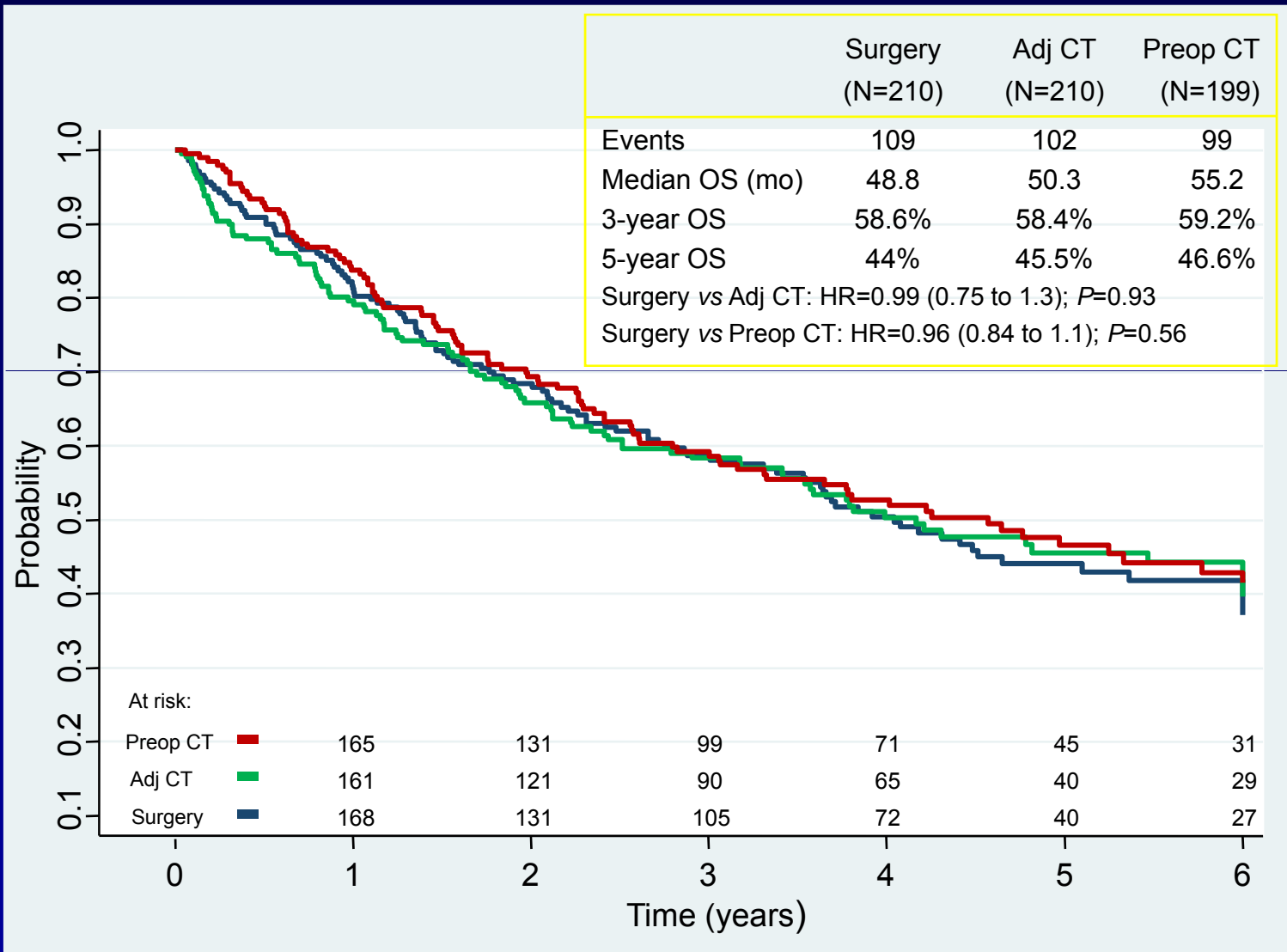


DFS in Adj CT Arm vs Surgery Arm

Median Follow-up 51 Months



Overall Survival by Arm



Abstracts

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ECOG 3598: Rationale for Thalidomide

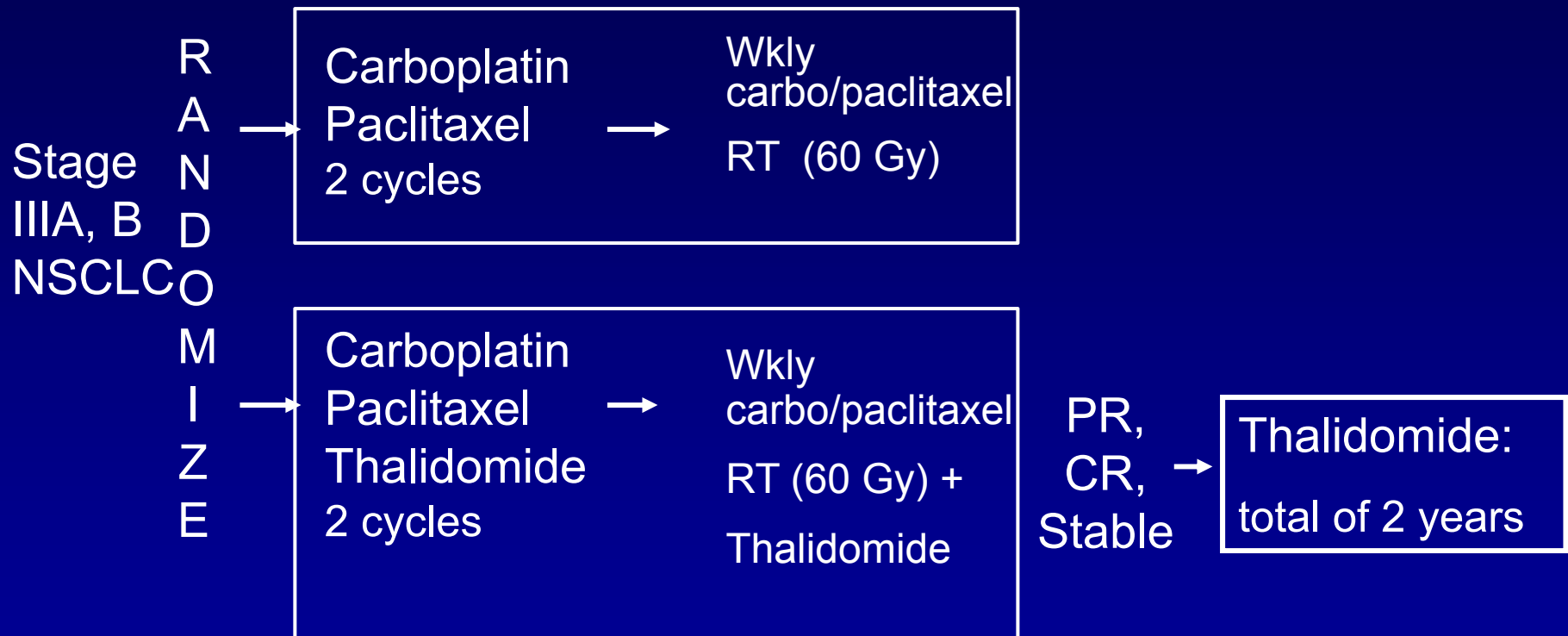
Diverse Properties

- Anti-angiogenic
 - Inhibits expression of a number of angiogenic cytokines: VEGF, bFGF, COX2, TGF beta expression
- Immunomodulatory
 - T cell/NK stimulation
 - Induces expression of immunomodulatory cytokines (IL-12, gamma IFN)
- Anti-proliferative

E3598: Chemo/RT +/- Thalidomide

Schiller J et al. ASCO 2009, abstr # 7503

Amended Schema



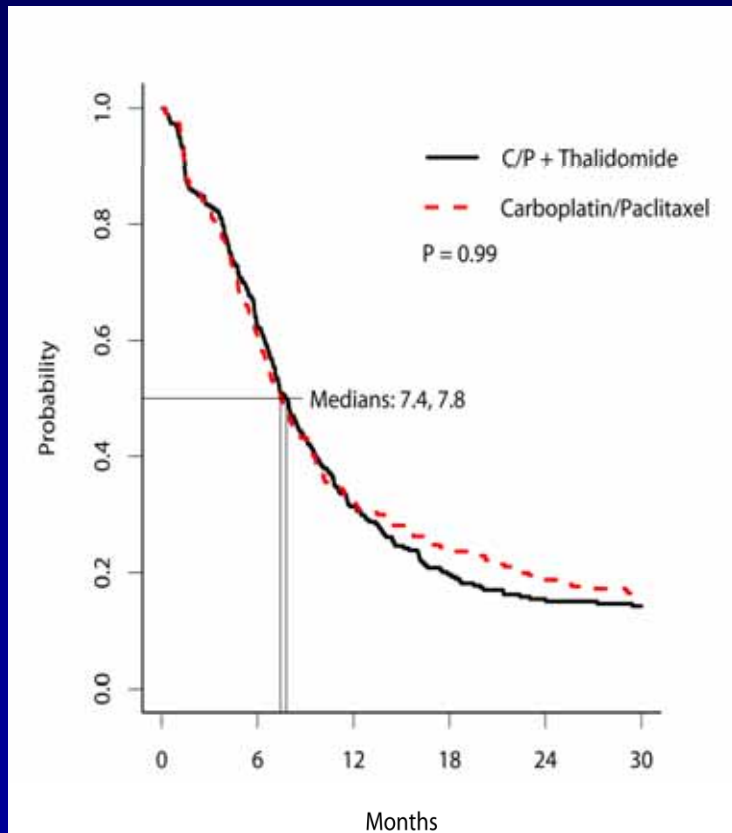
- Amended 6/04/2003 after 288 patients had been registered
- Weekly concurrent carboplatin/paclitaxel added

ECOG 3598: Outcomes

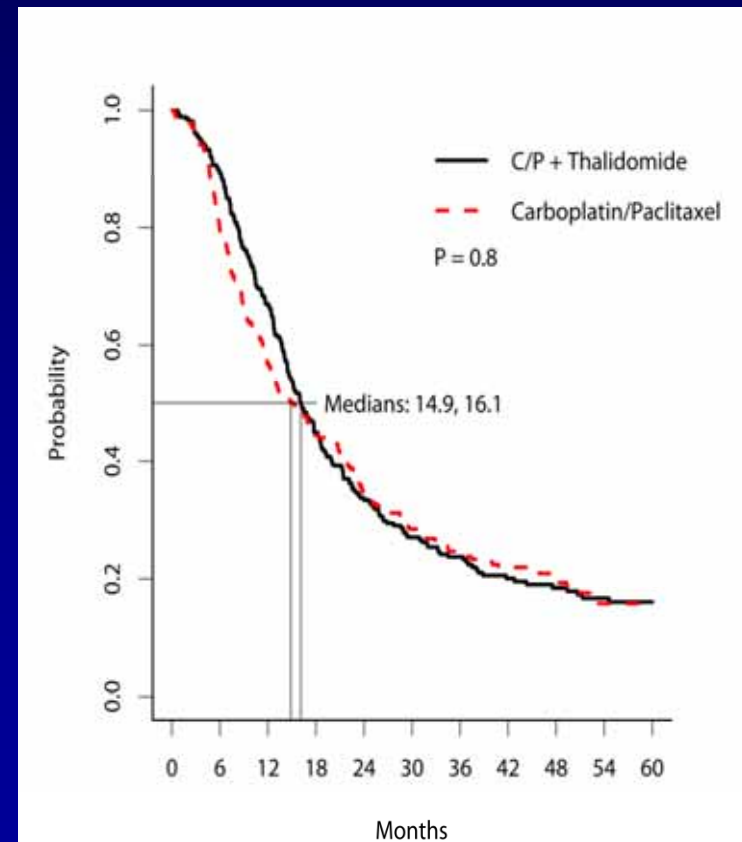
	Carbo/paclitaxel	Carbo/paclitaxel + thalidomide	P (HR)
Response rate	35%	39%	0.36
Survival			
• Median (mo)	14.9 mo (12.4-20.2)	16.1 mo (14.5-18.5)	0.84 (HR= 0.98; 0.81 – 1.18)
• 1 year	57% (51-63%)	67% (62-73%)	
• 2 year	34% (29-41%)	33% (28-40%)	
PFS – median (mo)	7.4 mo (6.6 -8.7)	7.8 mo (7.0-8.8)	0.99 (HR = 1.00; 0.84 – 1.20)

ECOG 3598: Outcomes

Progression Free Survival



Survival

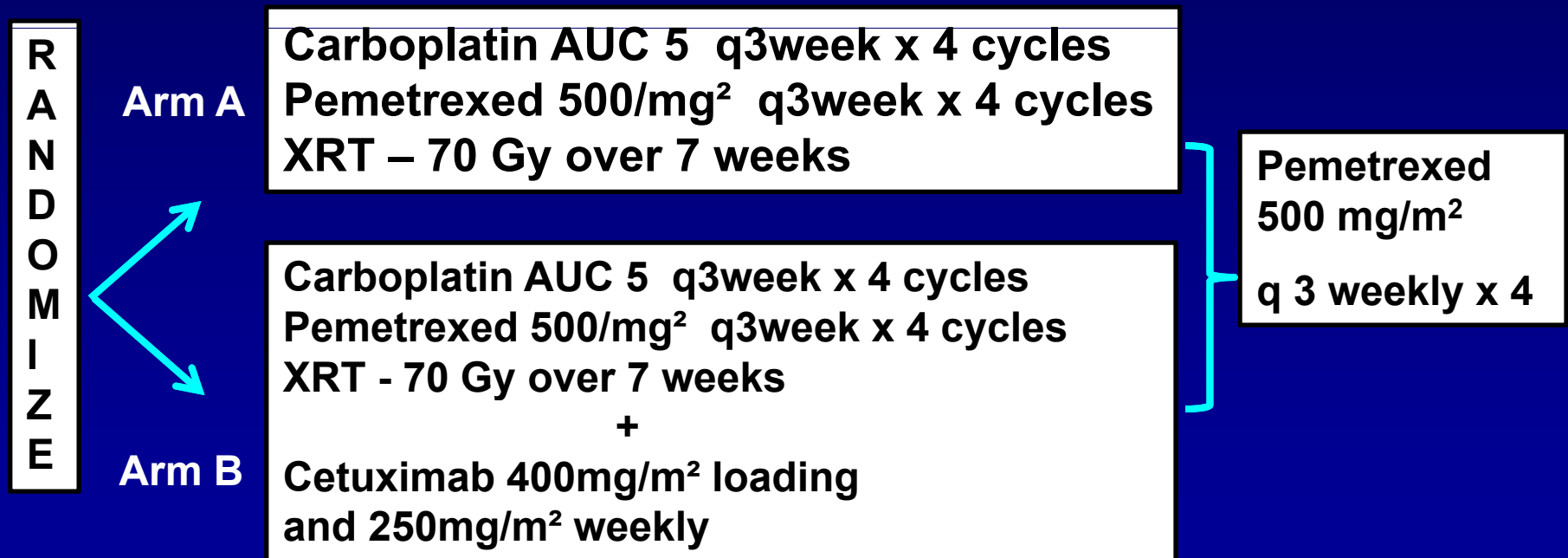


Conclusions

- Thalidomide did not improve the survival of patients with locally advanced NSCLC when administered with carbo/paclitaxel
- Thalidomide was associated with increased thrombotic events, despite the addition of low-dose aspirin.
- Lack of efficacy did not appear to be due to inadequate thalidomide dosing, as patients were titrated to their maximum tolerated dose.
- Identifying effective anti-angiogenic drugs for NSCLC is challenging.

Randomized Phase II Study of Pemetrexed, Carboplatin and Thoracic Radiation with or without Cetuximab in Stage III Non-small Cell Lung Cancer: CALGB 30407 Schema

Govindan R et al. ASCO 2009, abstr # 7505



Primary endpoint: OS (MST > 20.9 months)

CALGB 30407 - Demographics

Characteristic	Pemetrexed and Carboplatin (n- 48)	Pemetrexed, Carboplatin and Cetuximab (n-51)
Male	58%	65%
Median Age in Years (Range)	62 (41-79)	65 (32-81)
Proportion over 70 years	25%	20%
Caucasians	77%	94%
Histology		
Adenocarcinoma	46%	41%
Squamous	33%	35%
Poorly differentiated	19%	18%
Stage III A	58%	55%
Stage III B	40%	45%

CALGB 30407

Treatment Delivery (Post Chemoradiation)

Characteristic	Pemetrexed and Carboplatin (n- 48)	Pemetrexed, Carboplatin and Cetuximab (n-51)
All four cycles	50%	49%
Three cycles	8%	2%
Two cycles	19%	14%
One cycle	6%	6%
None	17%	27%
Missing	0	2%

90% and 80% of patients rec'd all four cycles of Cb/Pem on the Cb/Pem and Cb/Pem/Cetuximab arms, respectively)

CALGB 30407 - Hematological Toxicities (Grade III and IV)

Characteristic	Pemetrexed and Carboplatin n- 48 (%)	Pemetrexed, Carboplatin and Cetuximab n-51 (%)
Anemia	18	14
Neutropenia	50	59
Thrombocytopenia (G3/G4)	36 (22/14)	34(23/11)
Febrile Neutropenia	8	6

CALGB 30407 - Non-hematological Toxicities (Grade II and IV)

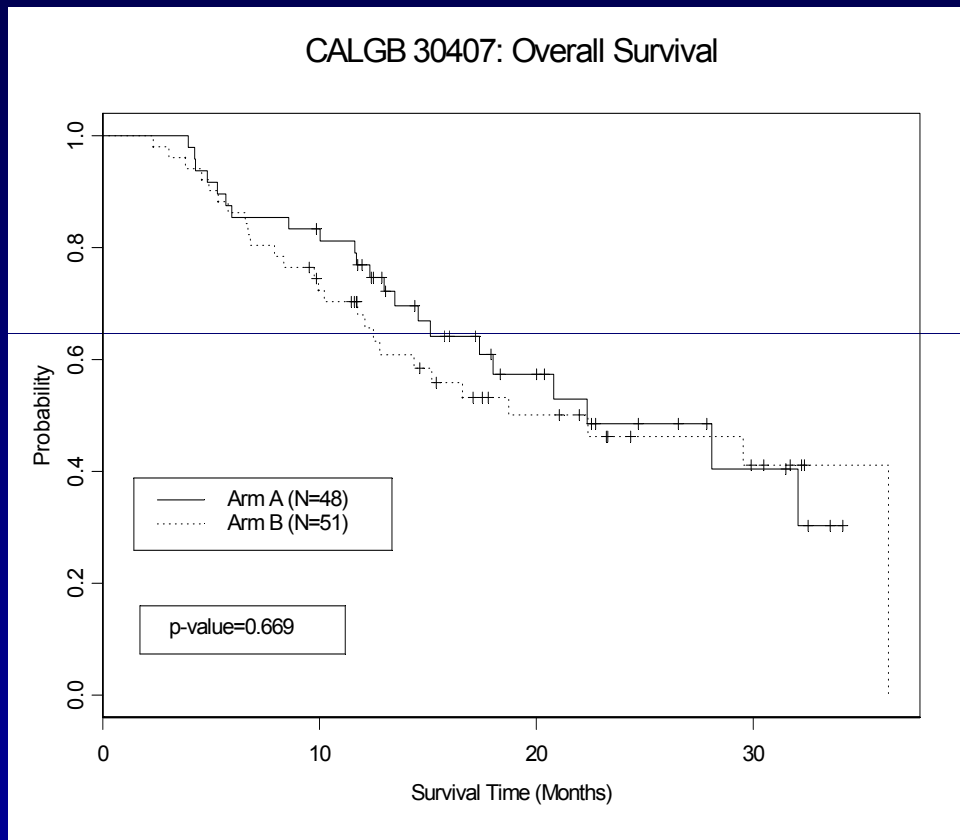
Characteristic	Pemetrexed and Carboplatin n- 48 (%)	Pemetrexed, Carboplatin and Cetuximab n-51 (%)
Dysphagia	32	24
Fatigue	22	17
Pneumonitis	12	8
Rash	2	21
Nausea/Vomiting	8	10
Hypersensitivity	2	8

Deaths

4%

4%

CALGB 30407 - Overall Survival



Median Overall Survival

Arm A 22 months (95% CI: 17-NA)

Arm B 22 months (95% CI: 13-NA)

18 Month Overall Survival

Arm A 57% (95% CI 44-75)

Arm B 50% (95% CI 37-68)

Median follow up: 22 months
H0: $p \leq 0.35$ versus H1: $p \geq 0.55$
p = survival probability at 18 months
registration

CALGB 30407

Summary

- Administration of pemetrexed, carboplatin and thoracic radiation with or without cetuximab produced a median survival of 22 months.
- Both regimens met the pre-defined threshold (median survival of 20.9 months) to be considered worthy for further development.
- Trends toward better outcomes observed with non-squamous NSCLC in this study.
- Toxicities related to concurrent chemoradiation are similar to previous studies

Abstracts

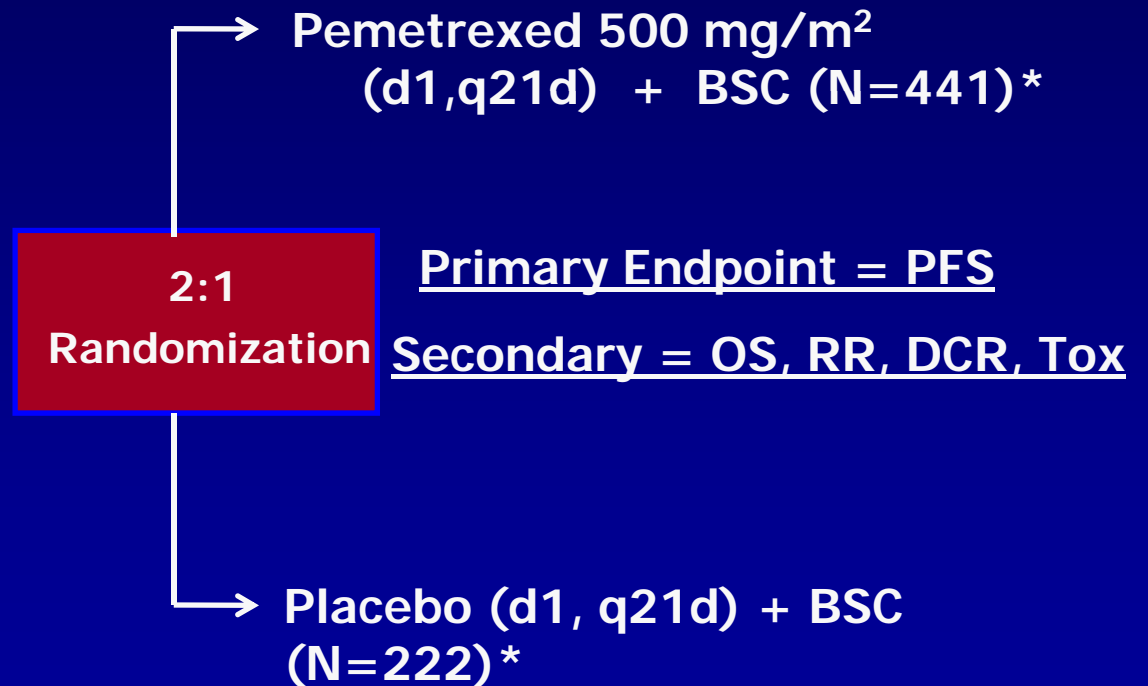
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JMEN – “Maintenance” Pemetrexed Study Design

Belani CP et al. ASCO 2009, abstr #8000

Double-blind, Placebo-controlled, Multicenter, Phase III Trial

- Stage IIIB/IV NSCLC
- ECOG PS 0-1
- 4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD
- Randomization factors:
 - gender
 - PS
 - stage
 - best tumor response
 - non-platinum drug
 - brain mets

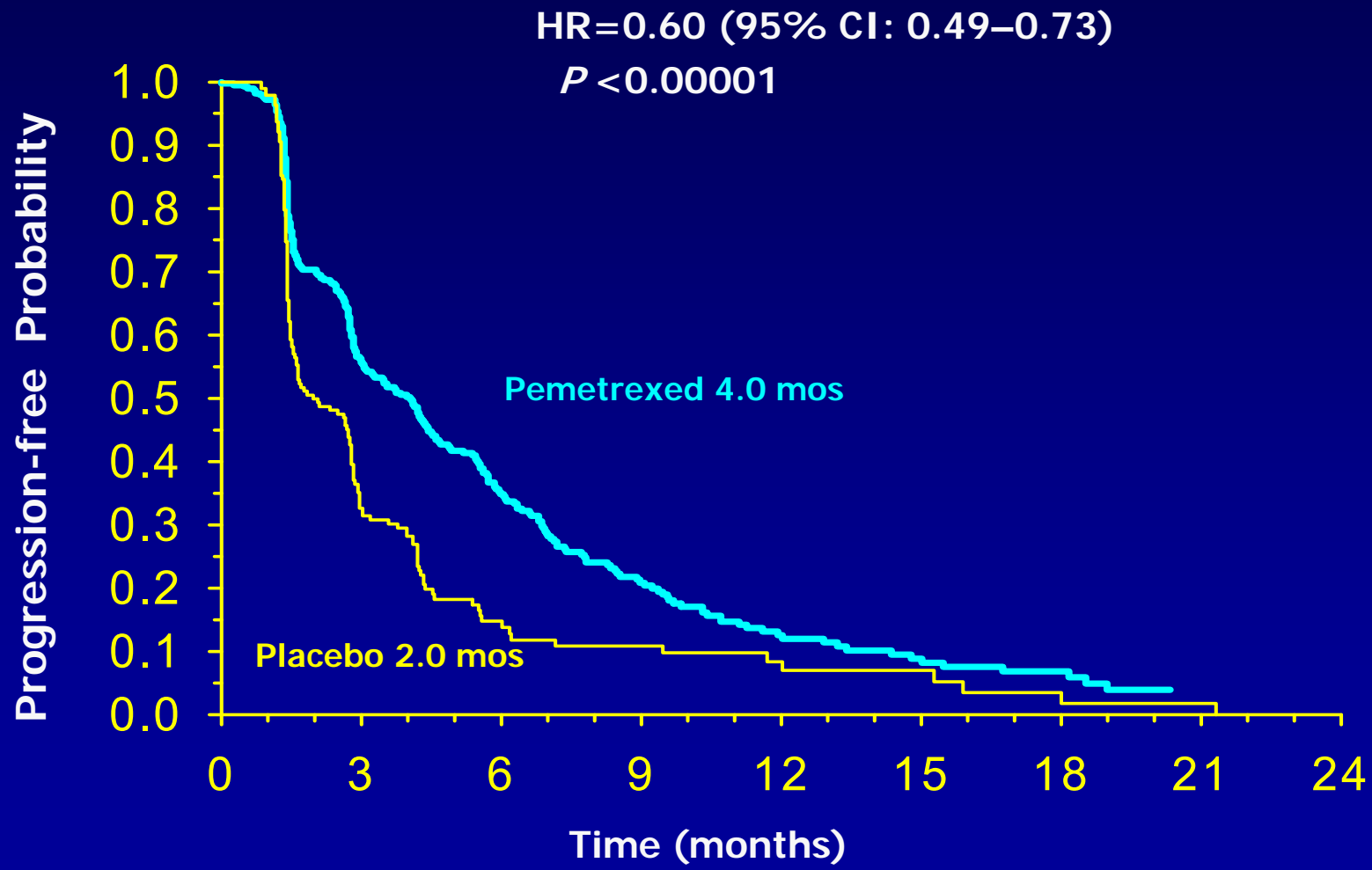


*B₁₂, folate, and dexamethasone given in both arms

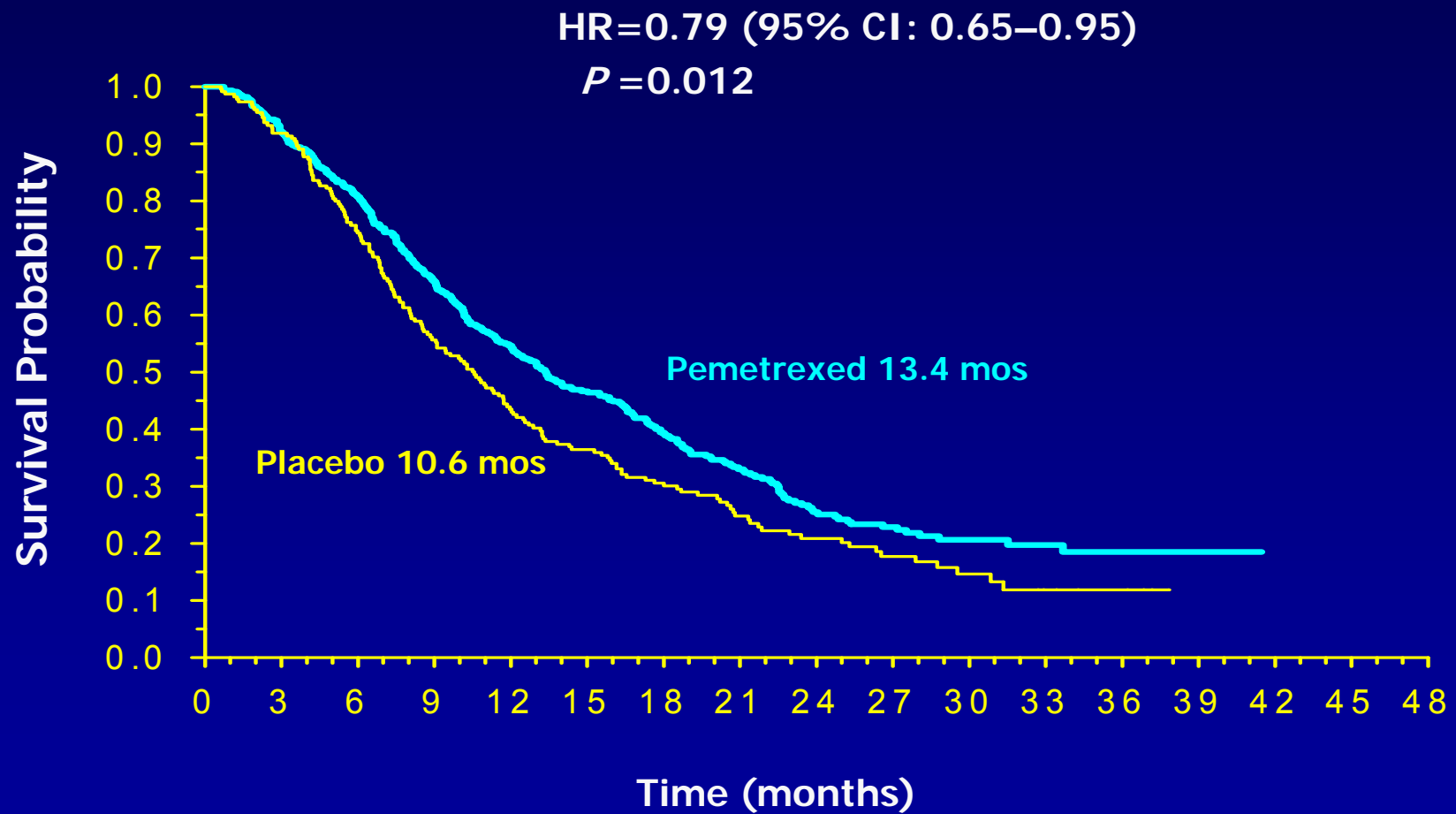
Baseline Characteristics

	Pemetrexed N=441 %	Placebo N=222 %
Median age, years	60.6	60.4
Male/Female	73/27	73/28
Caucasian/Asian/Other	63/32/4	67/30/3
Ever-smoker/Never-smoker	74/26	71/28
Disease stage (IIIB/IV)	18/82	21/79
ECOG PS 0/1	40/60	38/62
Histology		
Non-squamous	74	70
Adenocarcinoma	50	48
Large cell carcinoma	2	5
Other or indeterminate	21	18
Squamous	26	30

Progression-free Survival



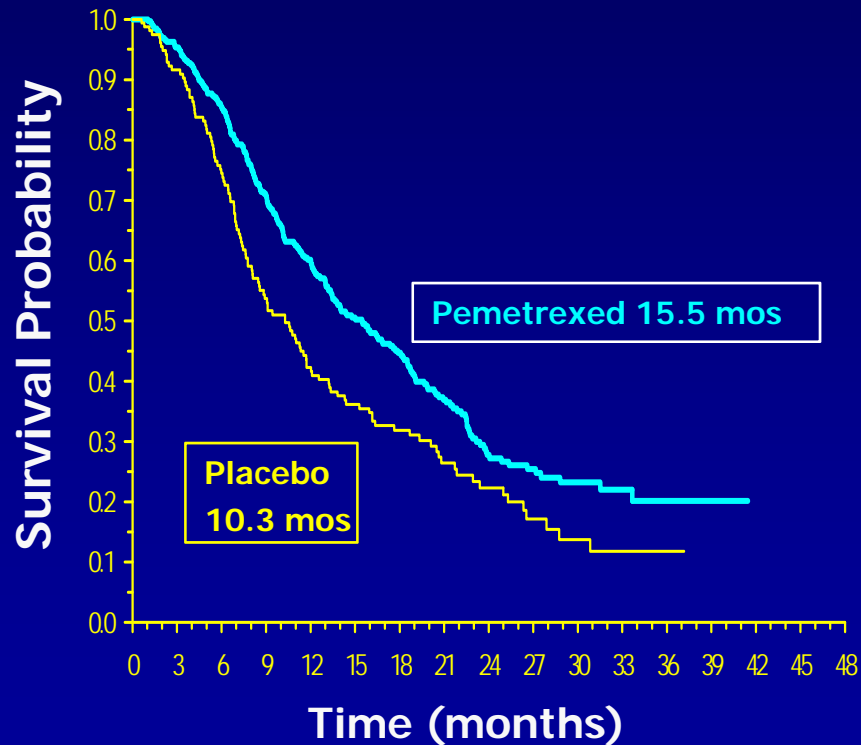
Overall Survival (Intent-to-treat Population)



Overall Survival by Histology

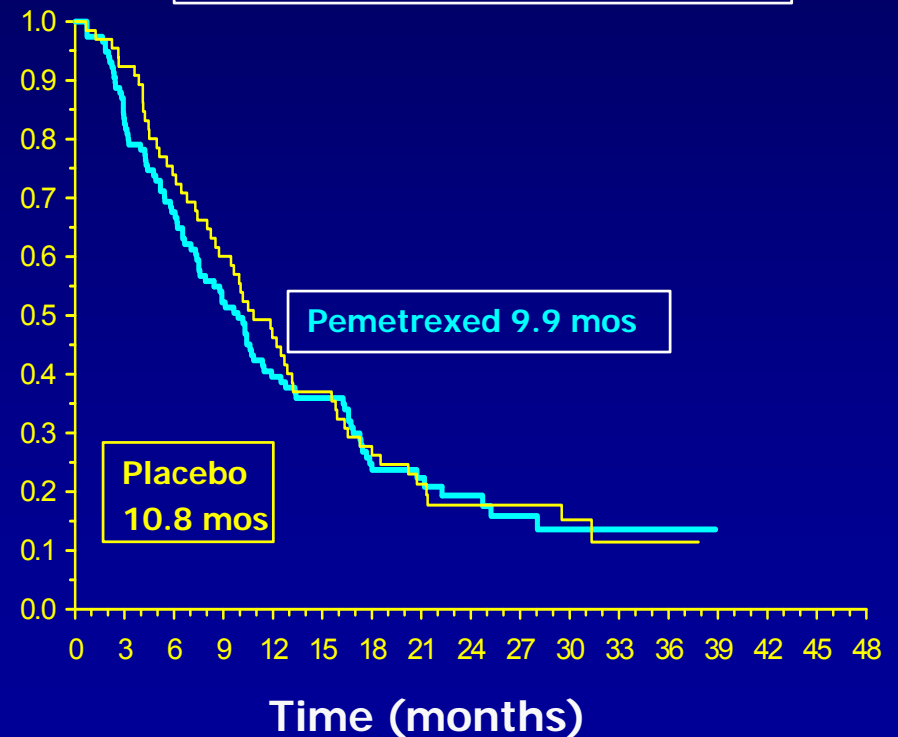
Non-squamous (n=481)

HR=0.70 (95% CI: 0.56-0.88)
P=0.002



Squamous (n=182)

HR=1.07 (95% CI: 0.49-1.73)
P=0.678



Efficacy by Histologic Groups

Histology Groups	Median OS, mos			Median PFS, mos		
	Pem	Plac	<i>P</i> -value (HR)	Pem	Plac	<i>P</i> -value (HR)
Non-squamous (n=481)	15.5	10.3	0.002 (0.70)	4.4	1.8	<0.00001 (0.47)
Adeno (n=329)	16.8	11.5	0.026 (0.73)	4.6	2.7	<0.00001 (0.51)
Large cell (n=20)	8.4	7.9	0.964 (0.98)	4.5	1.5	0.104 (0.40)
Other (n=133)	11.3	7.7	0.025 (0.61)	4.1	1.6	0.0002 (0.44)
Squamous (n=182)	9.9	10.8	0.678 (1.07)	2.4	2.5	0.896 (1.03)

There was a statistically significant treatment-by-histology interaction with both PFS ($P=0.036$) and OS ($P=0.003$)

Systemic Post-study Therapy

	Pemetrexed (N=441) %	Placebo (N=222) %
Patients with post-study therapy	52	67
Most common post-study therapies		
Carboplatin	7	10
Cisplatin	5	6
Docetaxel	22	29
Erlotinib	22	21
Gefitinib	13	10
Gemcitabine	9	14
Paclitaxel	4	6
Pemetrexed	1	19
Vinorelbine	13	17

- Higher rate of follow-up treatment on the placebo arm
- Balanced selection of therapies between arms and low rate of crossover

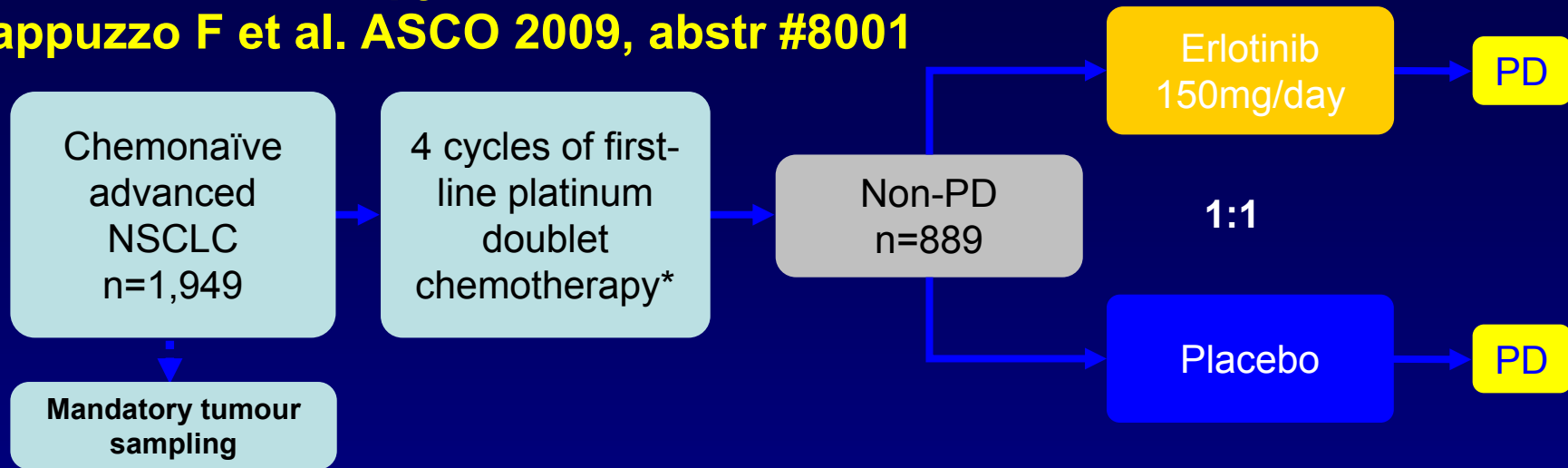
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SATURN– Phase III double-blind, placebo-controlled trial of Maintenance Erlotinib in Non-progressors following 1st Line Platinum-based Chemotherapy

Cappuzzo F et al. ASCO 2009, abstr #8001



Stratification factors:

- EGFR IHC (positive vs negative vs indeterminate)
- Stage (IIIB vs IV)
- ECOG PS (0 vs 1)
- CT regimen (cis/gem vs carbo/doc vs others)
- Smoking history (current vs former vs never)
- Region

Co-primary endpoints:

- PFS in all patients
- PFS in patients with EGFR IHC+ tumours

Secondary endpoints:

- OS in all patients and those with EGFR IHC+ tumours, OS and PFS in EGFR IHC– tumours; biomarker analyses; safety; time to symptom progression; QoL

*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel
cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel
carboplatin/paclitaxel

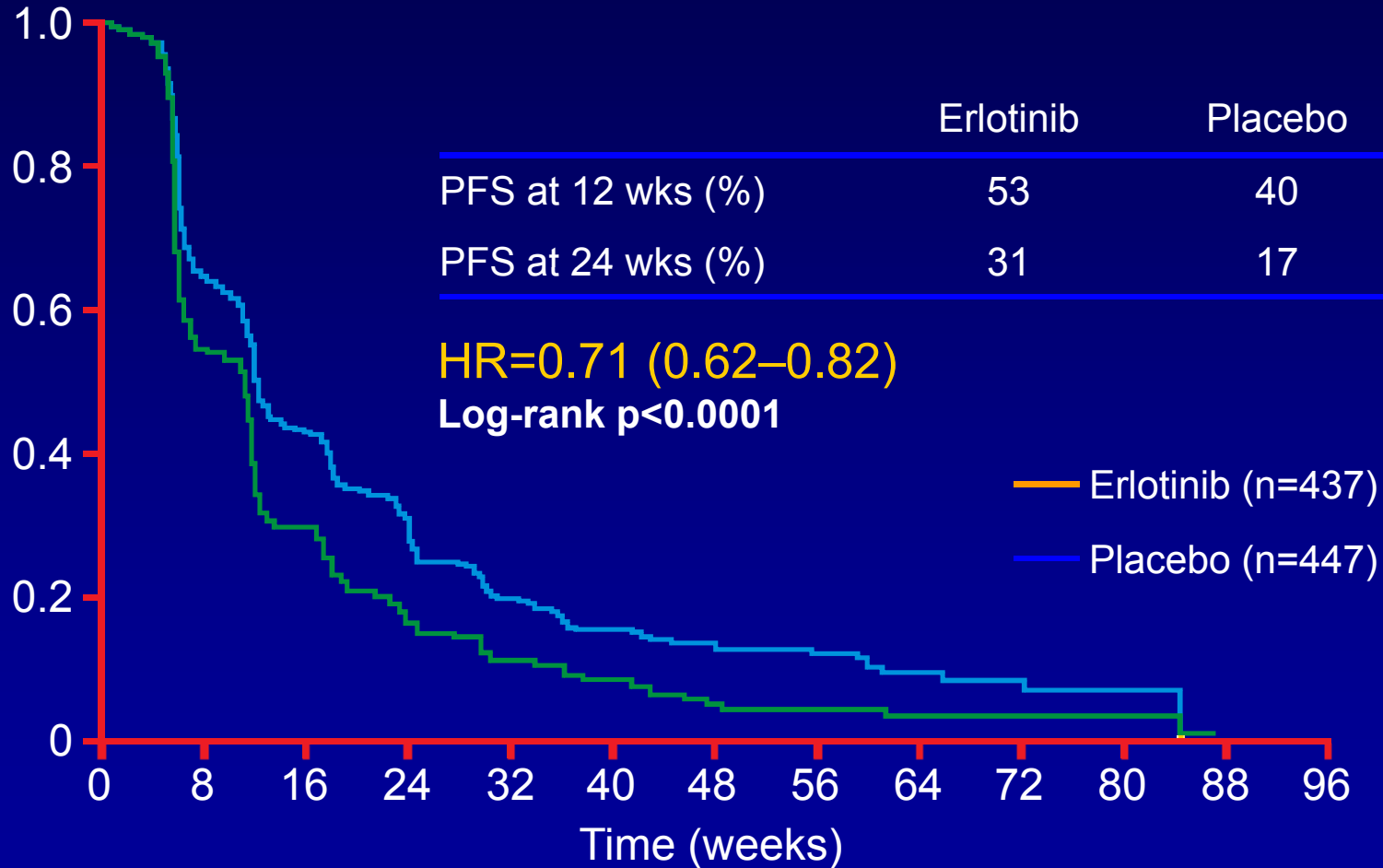
Baseline characteristics

	Erlotinib (n=438)	Placebo (n=451)
Age, median (range), years	60 (33–83)	60 (30–81)
Male / female, %	73 / 27	75 / 25
Stage IIIB / IV, %	26 / 74	24 / 76
Caucasian / Asian / Other, %	84 / 14 / 1	83 / 15 / 1
ECOG PS 0 / 1, %	31 / 69	32 / 68
Current / former / never smoker, %	55 / 28 / 18	56 / 27 / 17
Adenocarcinoma / squamous / other, %	47 / 38 / 15	44 / 43 / 13
Response to prior chemotherapy, CR / PR/ SD, %	<1 / 42 / 58	<1 / 47 / 52

CR = complete response; PR = partial response; SD = stable disease

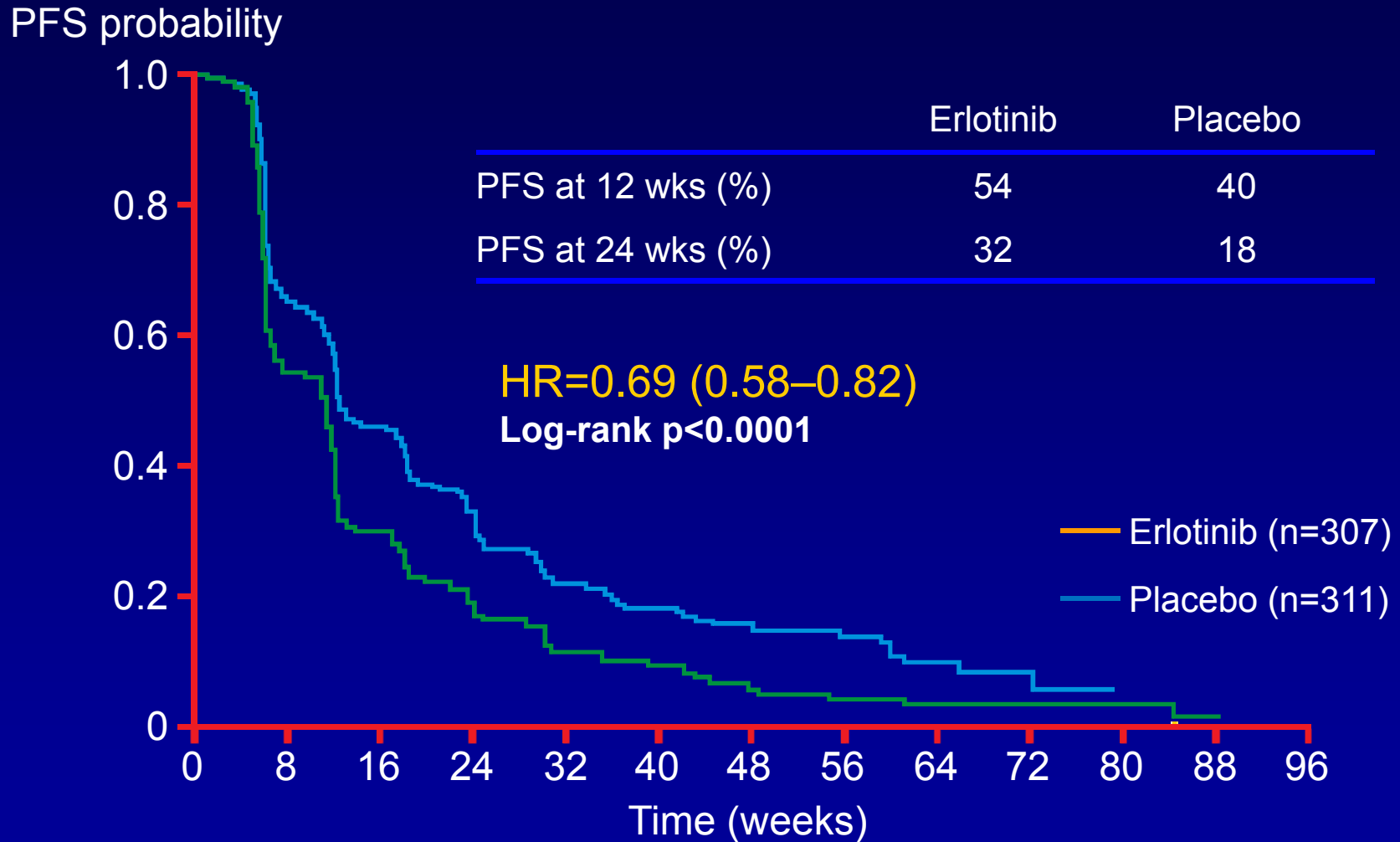
PFS*: all patients (ITT)

PFS probability



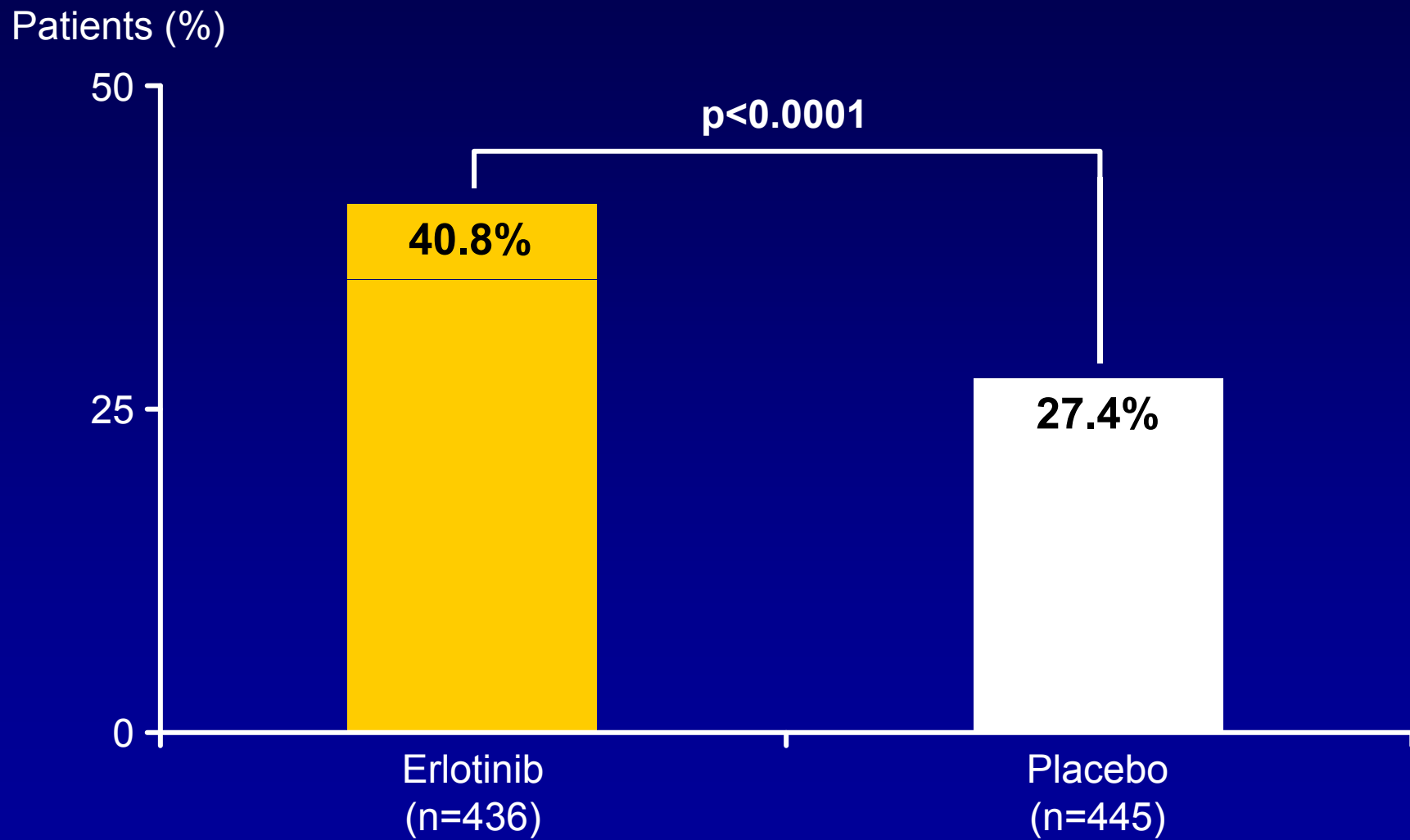
*PFS is measured from time of randomisation into the maintenance phase; assessments were every 6 weeks; ITT = intent-to-treat population

PFS*: EGFR IHC+ tumours (co-primary endpoint)



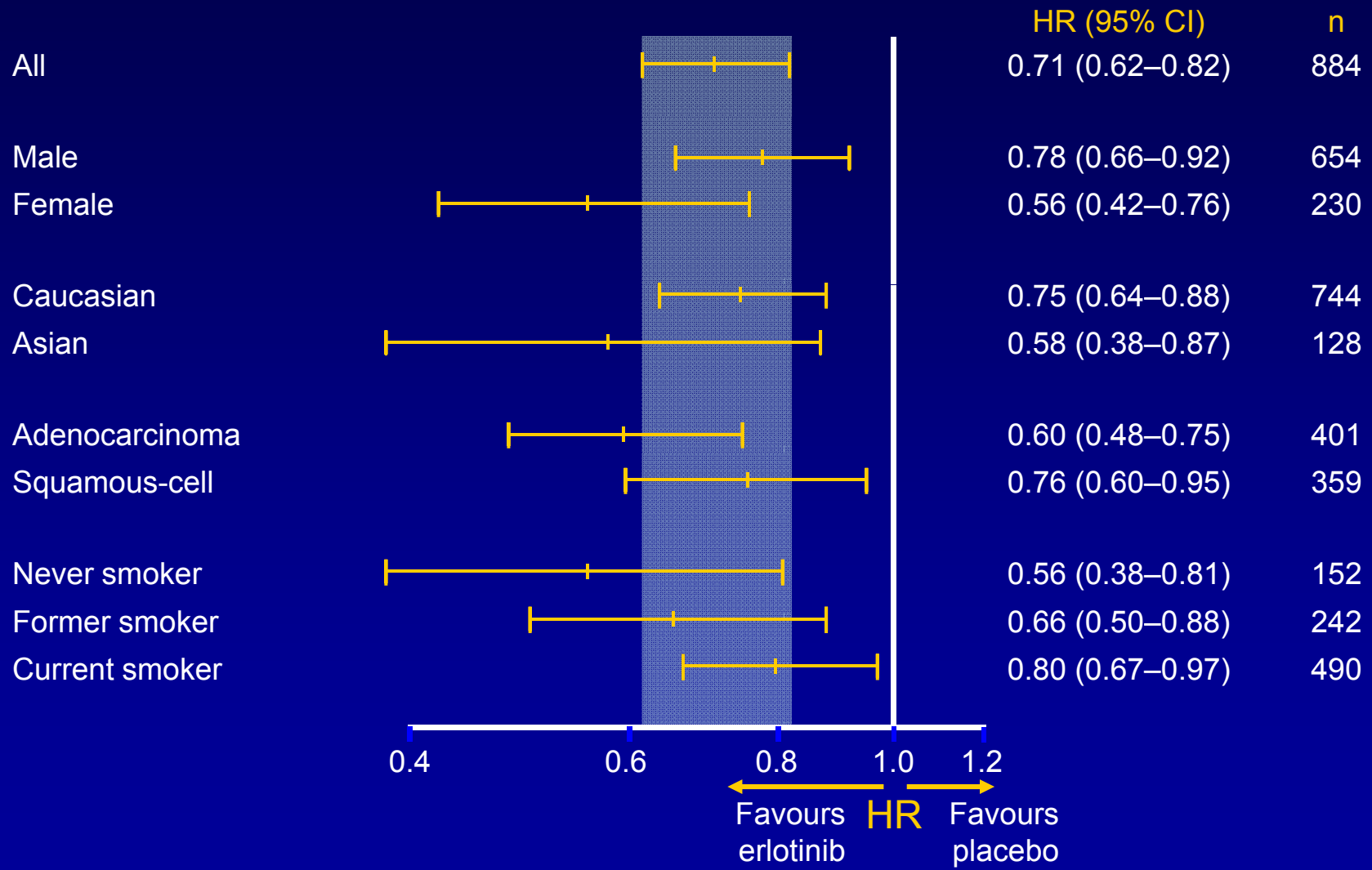
*PFS is measured from time of randomisation into the maintenance phase;
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Disease control rate ≥ 12 weeks*



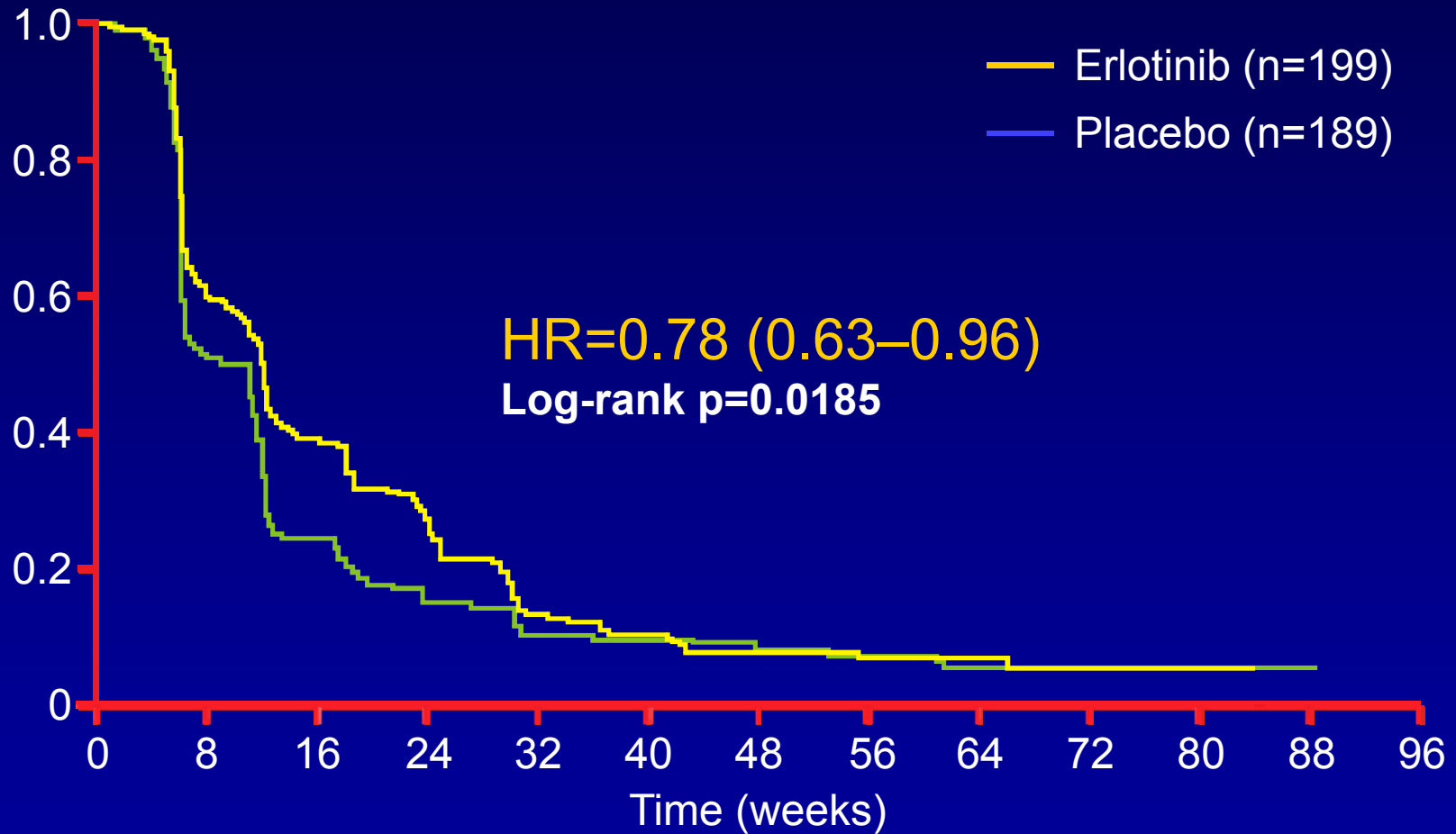
* CR + PR + SD ≥ 12 weeks

Subgroup analysis of PFS



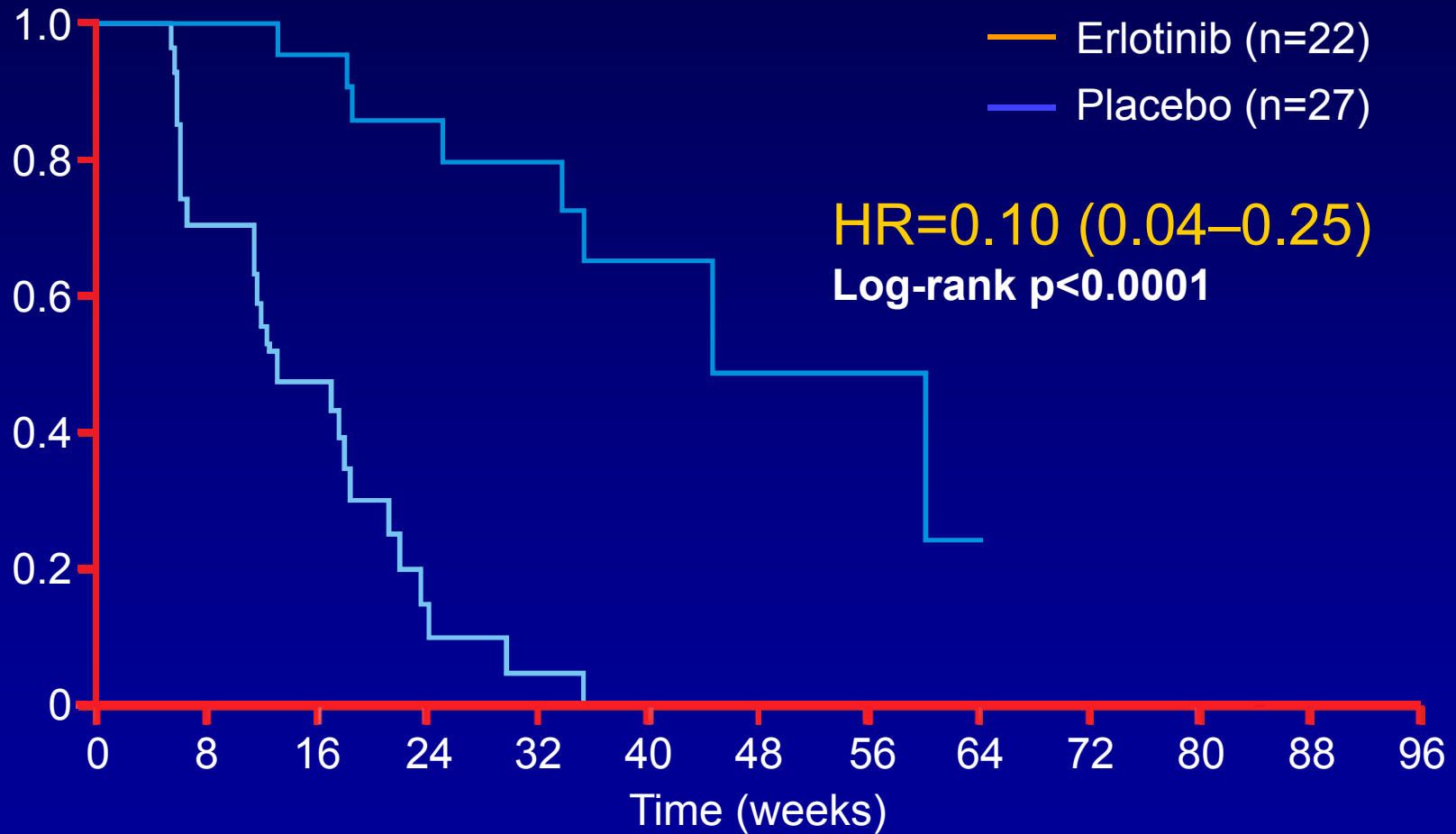
PFS in EGFR wild-type tumours

PFS probability



PFS in *EGFR* mutation+ tumours*

PFS probability



*60% censored

Summary of safety data

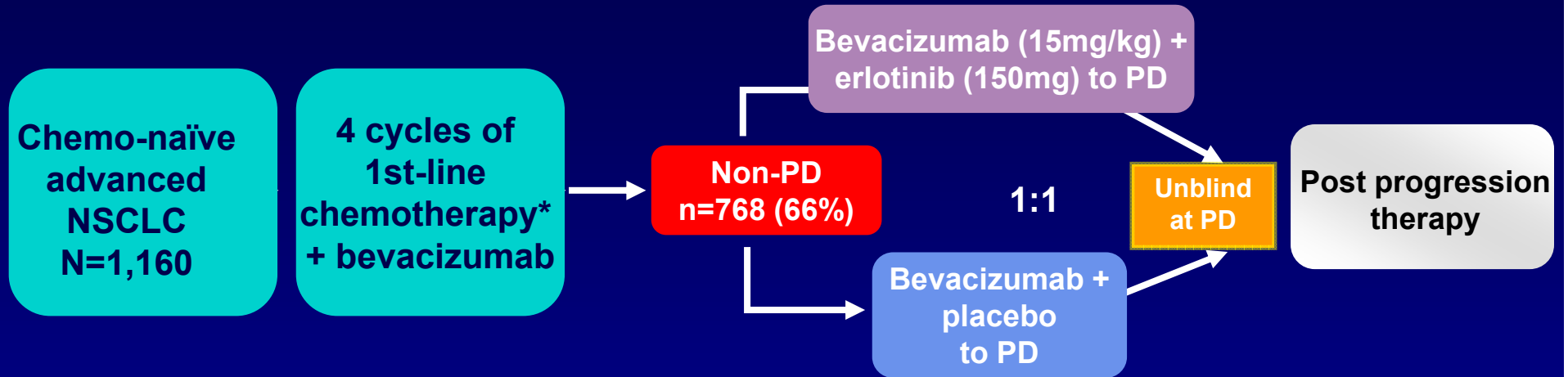
	Erlotinib (n=433)	Placebo (n=445)
Withdrawal due to any AE, %	5	2
Dose modification/interruption due to any AE, %	16	3
AEs occurring in $\geq 10\%$ of patients		
Rash, %	60	9
grade 3/4*	9	0
Diarrhoea, %	20	4
grade 3/4*	2	0

- Erlotinib has a well-characterised safety profile; no unexpected safety signals were seen in this study
- No deterioration in QoL was seen in the erlotinib and placebo arms (FACT-L questionnaire)

*no grade 4 events reported

ATLAS – Phase III Randomized, Double-Blind, Placebo-controlled Trial of Maintenance Erlotinib in Non-Progressors Following 1st Line Platinum-based Chemotherapy

Miller V et al. ASCO 2009, abstr # 8002



Eligibility

- Stage IIIB^{**}/IV NSCLC
- ECOG performance status 0-1

Stratification factors

- Gender
- Smoking history (never vs former/current)
- ECOG performance status (0 v ≥ 1)
- Chemotherapy regimen

Primary endpoint

- PFS in all randomized pts

Secondary endpoints

- Overall survival
- Safety

Exploratory endpoints

- Biomarker analyses (IHC, FISH, EGFR & K-Ras mutation)

*Carbo/paclitaxel; cis/vinorelbine; carbo or cis/gemcitabine; carbo or cis/docetaxel.

**IIIB with pleural effusion

ATLAS: Baseline Characteristics

(ITT population)

	Bevacizumab + Placebo (n=373)*	Bevacizumab + Erlotinib (n=370)*
Median age, years (range)	64 (23-83)	64 (31-88)
Sex, %		
Male	52.3	52.2
Female	47.7	47.8
Race, %		
Caucasian	77.7	79.2
Asian	12.1	11.6
Other	10.2	9.2
Disease Stage, %		
IIIB	10.2	8.7
IV	83.3	85.6
Recurrent	6.5	5.7
ECOG PS, %		
0	46.1	48.1
1	53.6	51.9

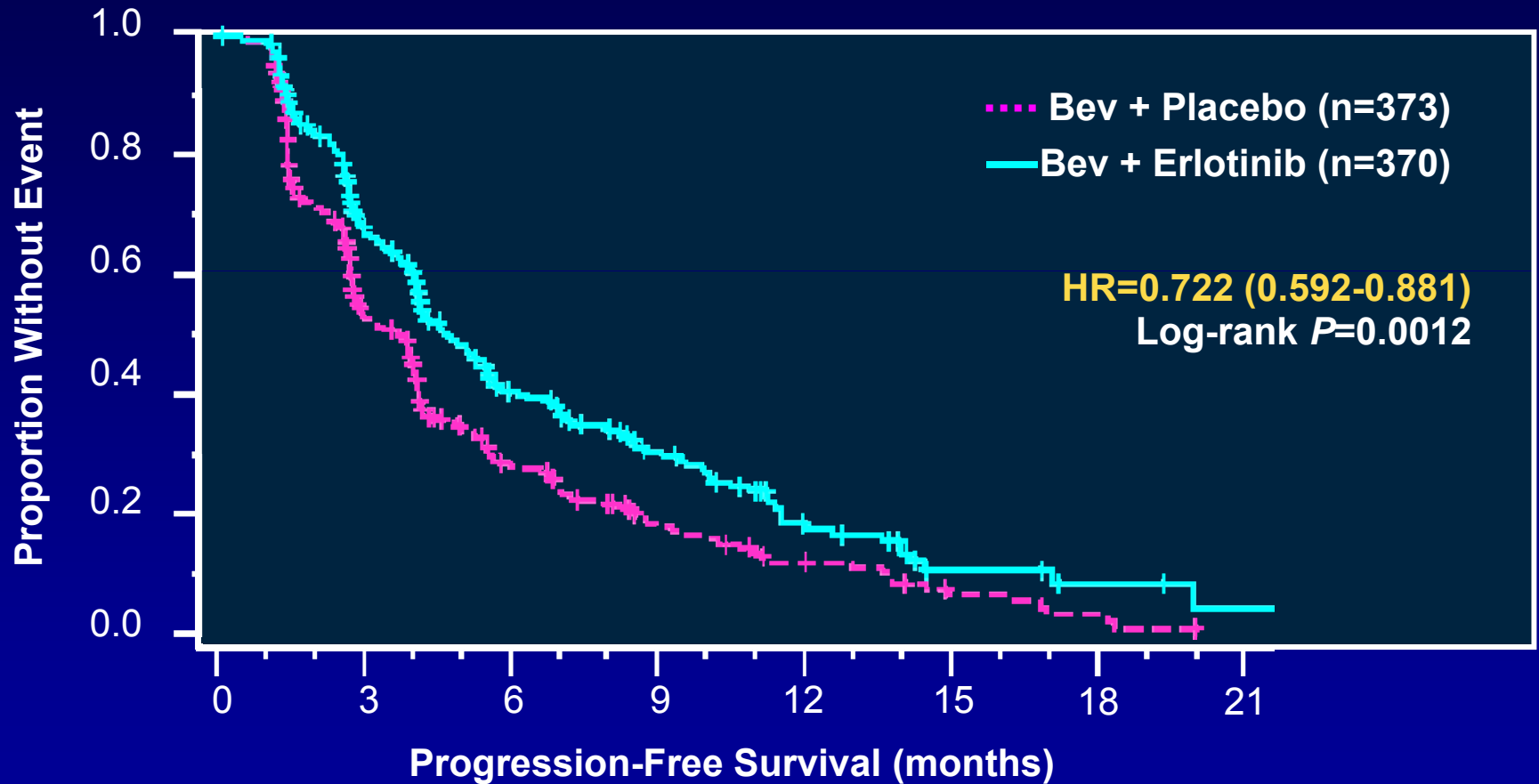
*Patients randomized as of July 18 2008.

ATLAS: Baseline Characteristics (cont.)

	Bevacizumab + Placebo (n=373)	Bevacizumab + Erlotinib (n=370)
Smoking status, %		
Current	34.6	34.9
Former	47.7	48.6
Never	17.7	16.5
Histology, %		
Adenocarcinoma	82.5	81.3
Squamous (peripheral)	1.6	3.0
Other	15.9	15.7
Prior radiotherapy, yes, %	15.3	17.3

ATLAS: Progression-Free Survival

(ITT population, investigator assessment)



No. of patients at risk:

Bev + Placebo	373	142	58	27	15	6	3	0
Bev + Erlotinib	370	178	81	43	20	6	3	1

ATLAS: Additional PFS Outcome Measures

Progression Free Survival: HR=0.722 (0.592-0.881) Log-rank *P*=0.0012
(ITT population, investigator assessment)

	Bev + Placebo (n=370)	Bev + Erlotinib (n=373)
Median PFS, mos (95% CI)	3.75 (2.83, 4.04)	4.76 (4.14, 5.52)
PFS rate, % (95% CI)		
3 mos	53.4 (47.5, 58.9)	67.7 (61.9, 72.7)
6 mos	28.4 (23.0, 34.1)	40.3 (34.2, 46.3)

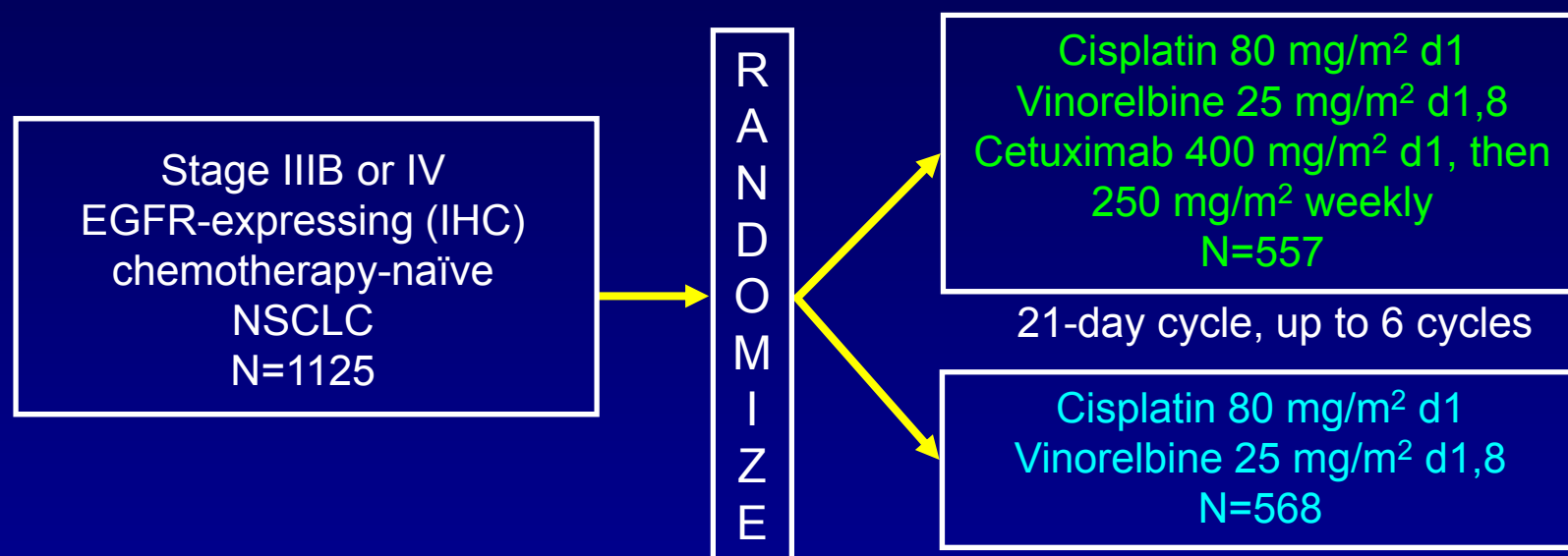
ATLAS: Grade 3-4 Adverse Events of Special Interest during the Post Chemotherapy Phase (Cont.)

	Bev + Placebo, n (%) (n=368)	Bev + Erlotinib, n (%) (n=367)
	Grade 3–4	Grade 3–4
Rash	2 (0.5%)	38 (10.4%)
Diarrhea	3 (0.8%)	34 (9.3%)
Infection	17 (4.6%)	15 (4.1%)
ILD-like events	0	2 (0.5%)
Renal failure/ deficiency*	0	2 (0.5%)
Hepatic events*	1 (0.3%)	1 (0.3%)

Grade 5 events: Bev + Placebo: 1 (0.3%) infection.

FLEX Phase III Trial: Cisplatin/Vinorelbine ± Cetuximab in EGFR IHC-Positive Advanced NSCLC – Biomarker Analysis

O'Byrne K et al. ASCO 2009, abstr # 8006

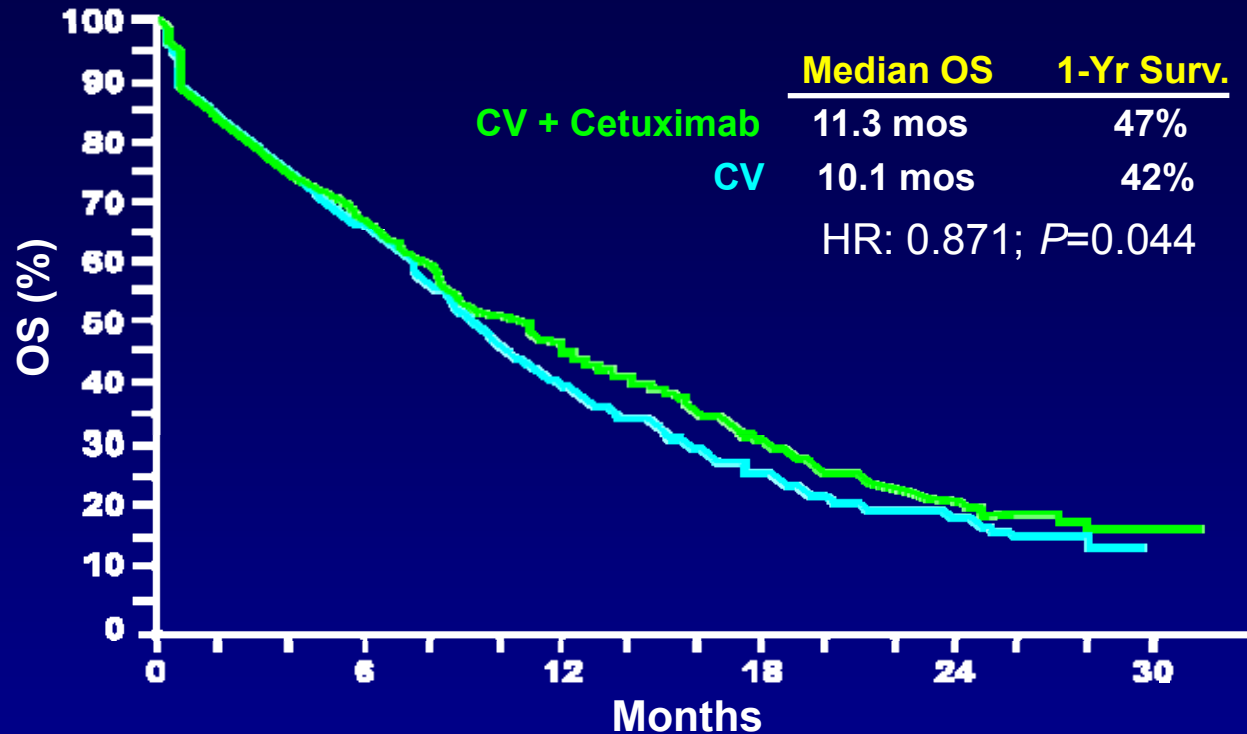


Primary endpoint: OS

Secondary endpoints: 1- and 2-year survival rates, 6-month and 12-month PFS rates, RR, safety, QOL

Patient Selection Criteria: EGFR-expressing (IHC) stage IIIB/IV NSCLC, PS 0-2, all histologies included; known brain metastases excluded

FLEX: Results



	CV + Cetuximab	CV	<i>P</i>
RR	36%	29%	0.01
PFS	4.8 mos	4.8 mos	NS
TTF	4.2 mos	3.7 mos	0.015

NS=not significant; TTF=time to treatment failure.

Pirker R et al. Lancet, 373:1525-33, 2009.

FLEX FISH analysis: OS

By FISH status

	FISH status	CT + cetuximab	CT	HR (95% CI)	p-value
Median OS	FISH -	10.6 mo	10.0 mo	0.91 (0.65–1.26)	0.56
	FISH +	11.6 mo	9.9 mo	0.85 (0.56–1.29)	0.44

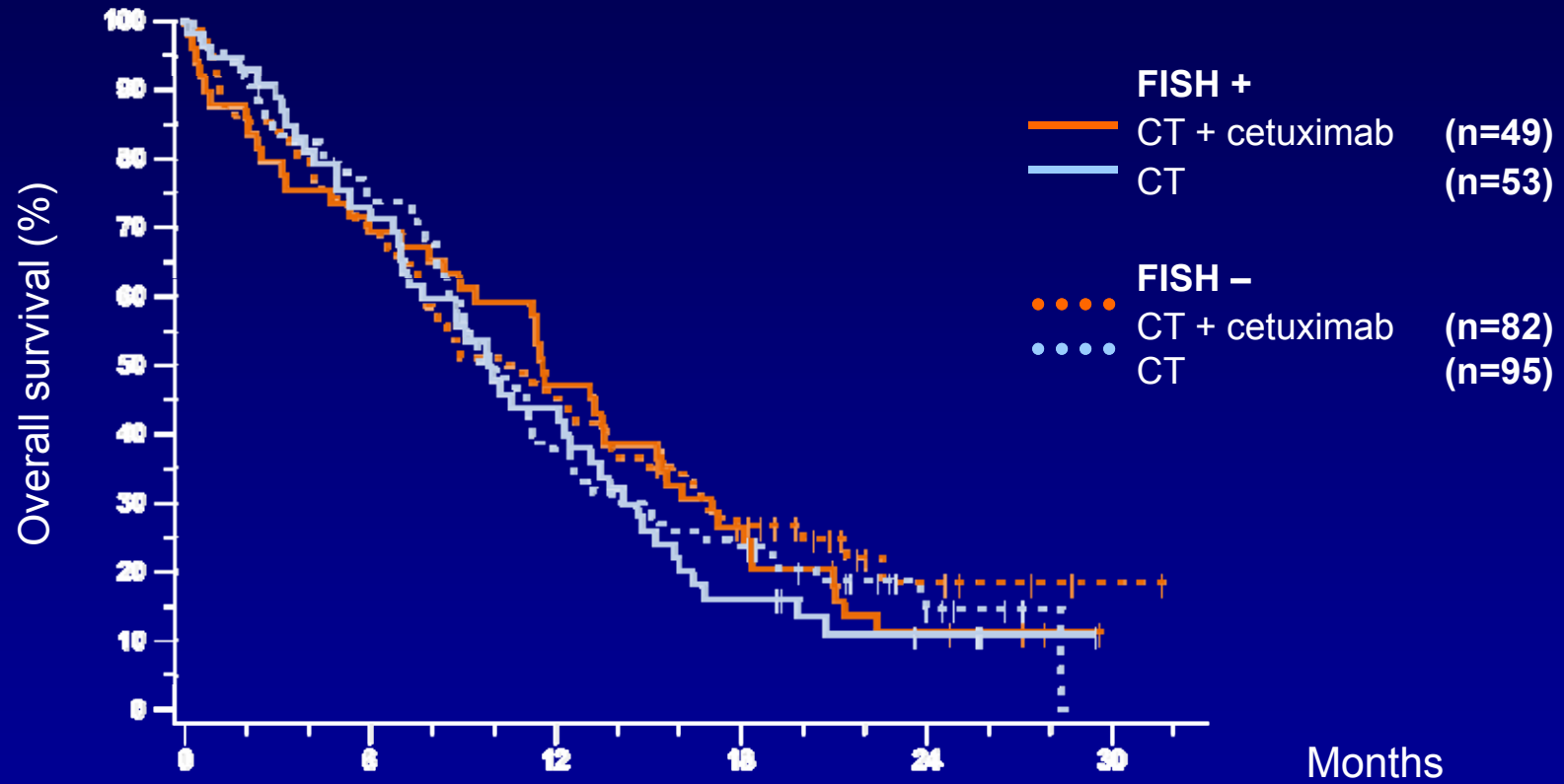
By treatment

	Arm	FISH -	FISH +	HR (95% CI)	p-value
Median OS	CT + cetuximab	10.6 mo	11.6 mo	1.09 (0.74–1.61)	0.66
	CT	10.0 mo	9.9 mo	1.10 (0.76–1.58)	0.62

CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival

O'Byrne K et al. ASCO 2009, abstract #8007.

FLEX: FISH analysis: OS



CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival

***FLEX KRAS* mutation analysis: OS**

By mutation status

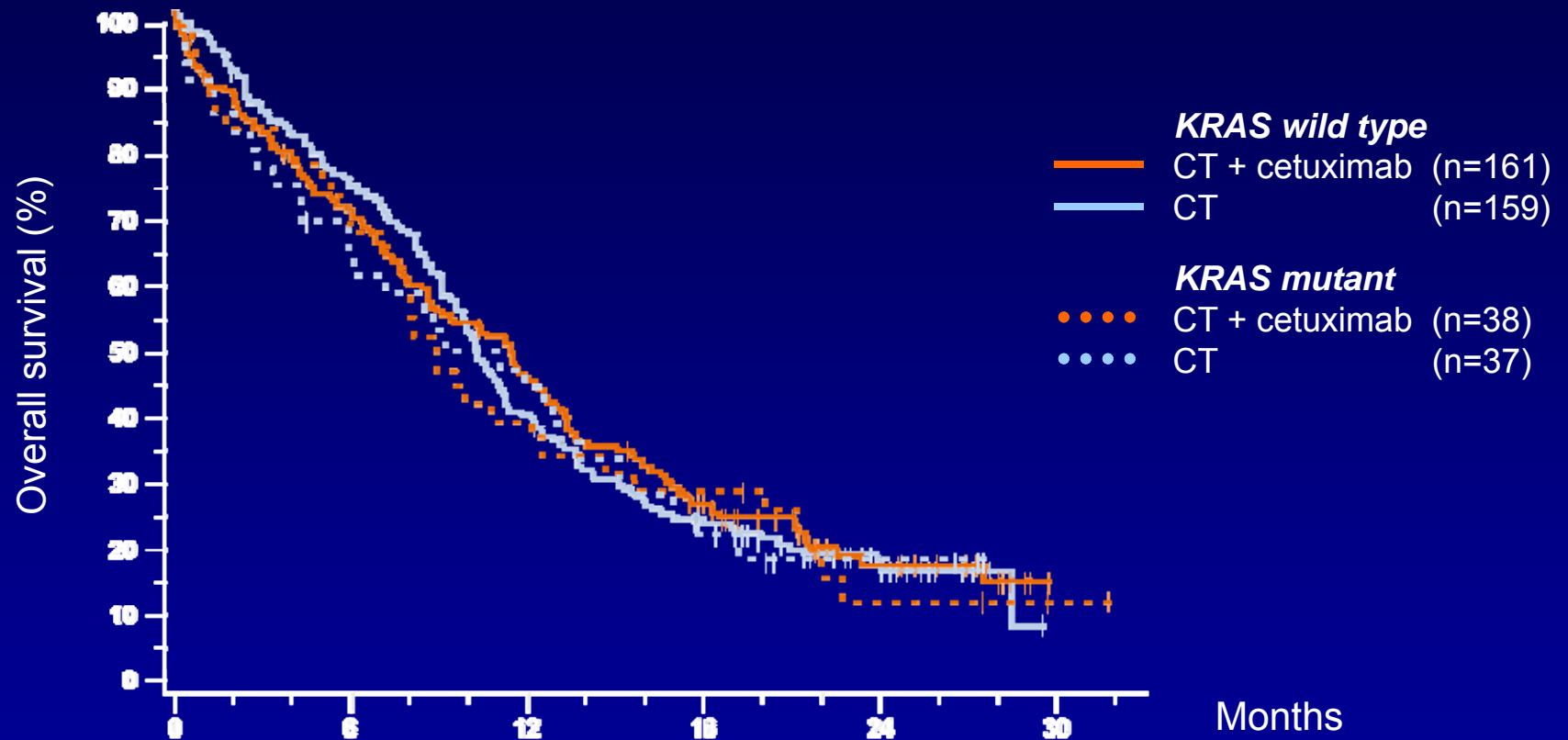
	<i>KRAS</i> status	CT + cetuximab	CT	HR (95% CI)	p-value
Median OS	Wild type	11.4 mo	10.3 mo	0.96 (0.75–1.23)	0.75
	Mutant	8.9 mo	11.1 mo	1.00 (0.60–1.66)	1.00

By treatment

	Arm	<i>KRAS</i> Wild type	<i>KRAS</i> Mutant	HR (95% CI)	p-value
Median OS	CT + cetuximab	11.4 mo	8.9 mo	1.06 (0.72–1.56)	0.77
	CT	10.3 mo	11.1 mo	1.02 (0.68–1.54)	0.91

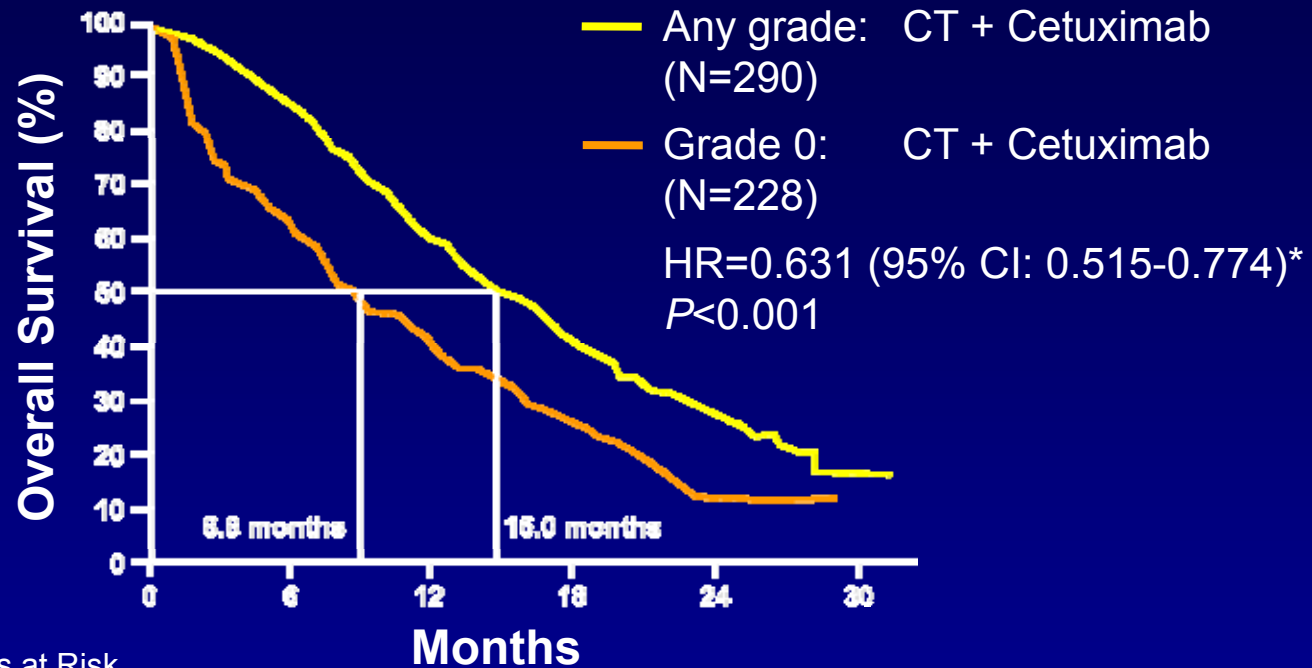
CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival

FLEX KRAS mutation analysis: OS



CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival

FLEX: OS Early acne-like rash (1st cycle) Pre-planned Analysis



Patients at Risk

Grade 0	228	145	88	54	15	0
Any Grade	290	238	163	101	38	3

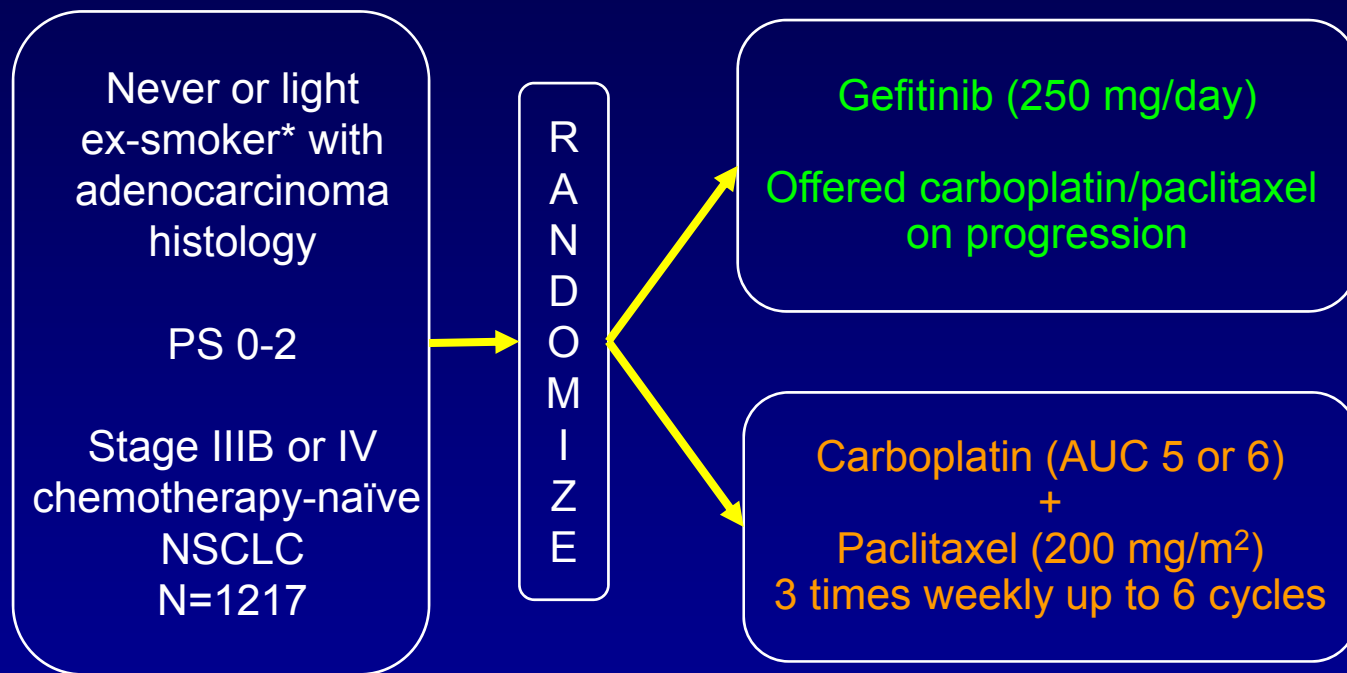
CV + Cetuximab	Any grade	Grade 0
OS	15.0 mos	8.8 mos
RR	44%	28%
PFS	5.4 mos	4.3 mos

*Landmark analysis.

Gatzemeier. 2008 Chicago Multidisciplinary Symposium in Thoracic Oncology (abstr 8).

Iressa Pan Asian Study (IPASS) Phase III Trial: Gefitinib vs Carboplatin/Paclitaxel in Selected Pts With Advanced NSCLC – Biomarker Analysis

Fukouka et al. ASCO 2009, abstr # 8007



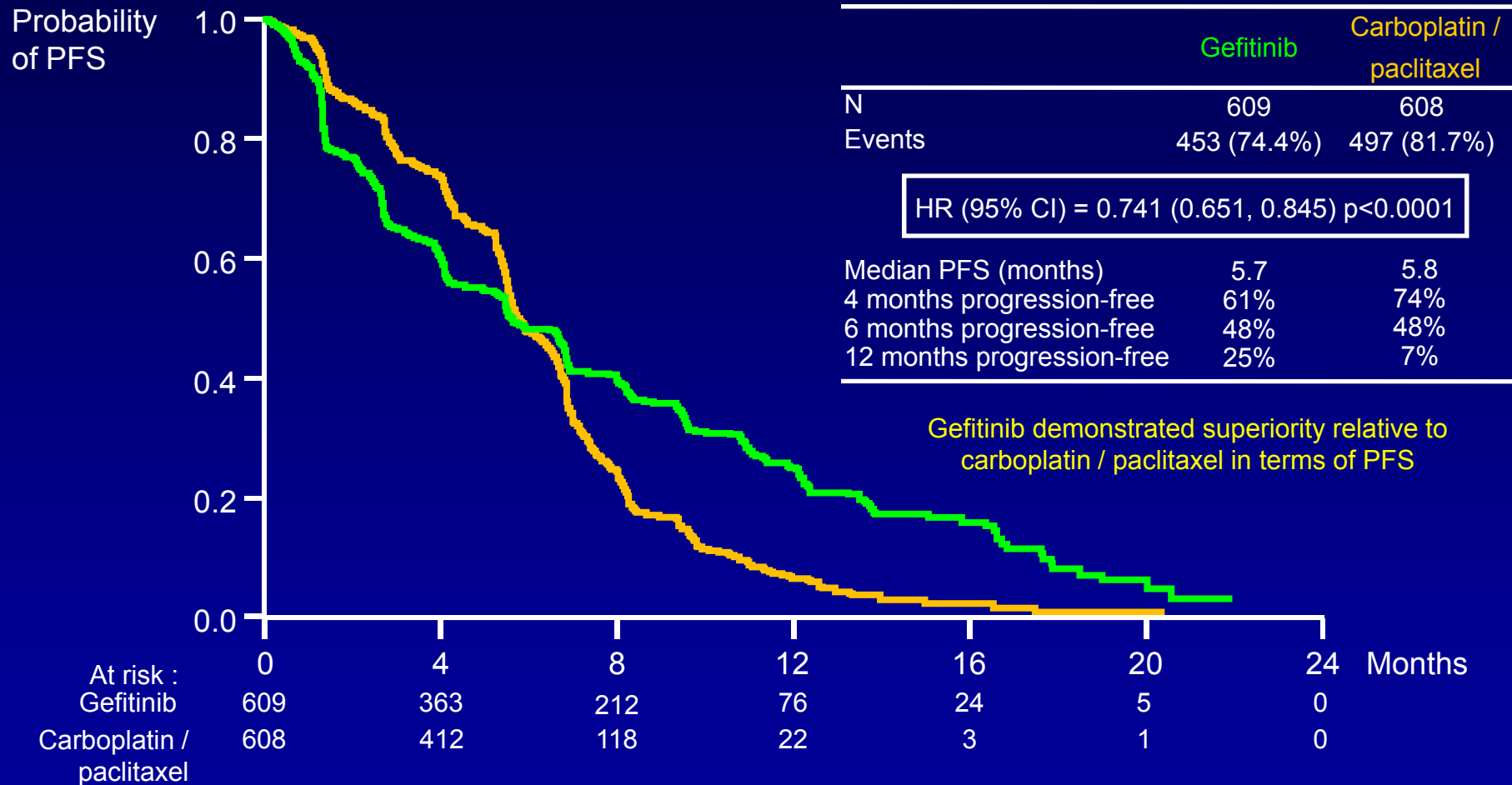
Primary endpoint: PFS (noninferiority)

Secondary endpoints: ORR, OS, QOL, disease-related symptoms, safety, and tolerability

Exploratory: biomarkers – EGFR mutation, gene copy number, and protein expression

*Never smoker=smoked <100 cigarettes in lifetime; light ex-smoker=stopped ≥15 years ago and smoked ≤10 pack-years.

Progression-free survival in ITT population

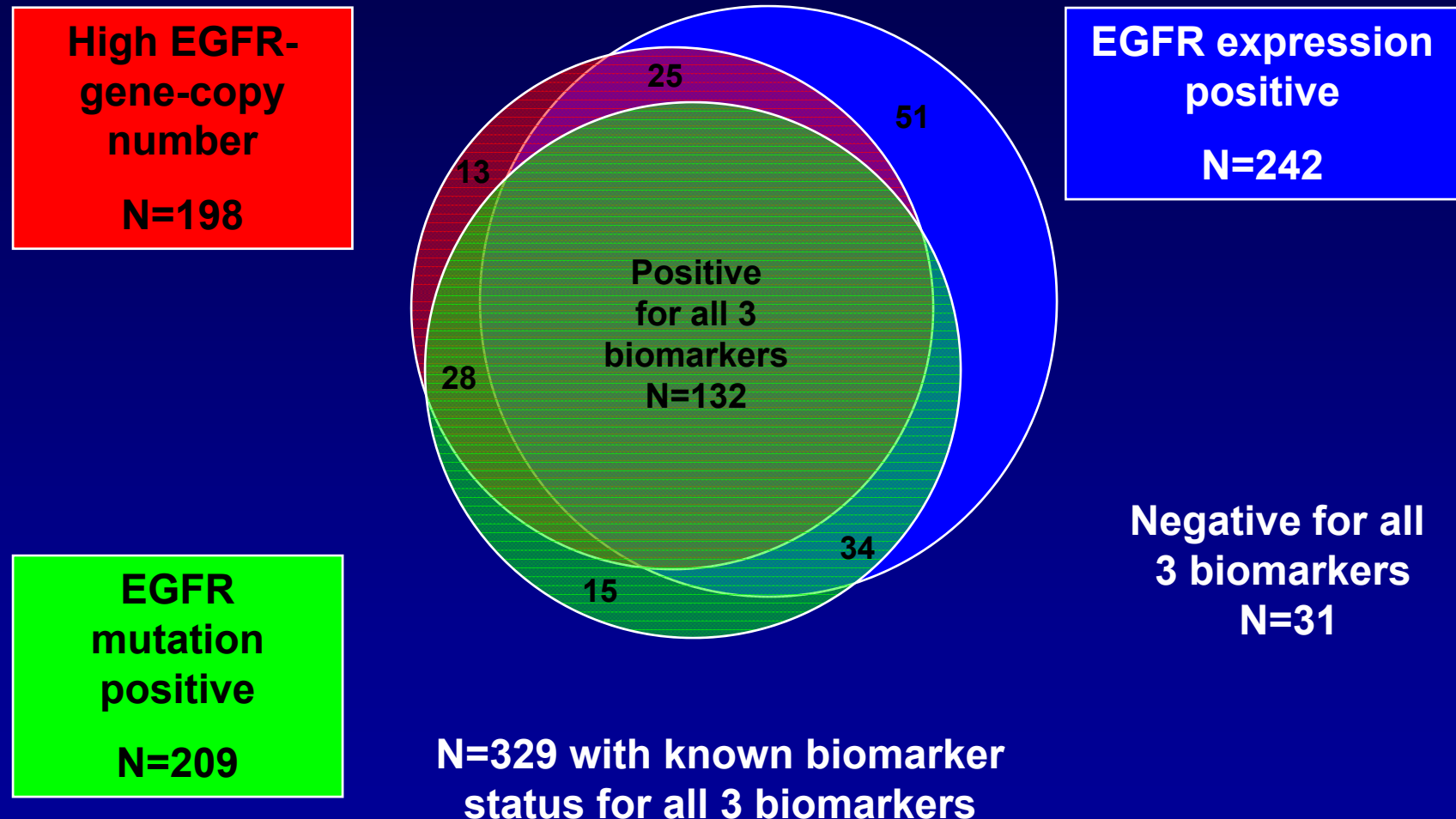


Primary Cox analysis with covariates
 HR <1 implies a lower risk of progression on gefitinib

Patients with evaluable (known) biomarker data

Biomarker	Status	N (% of total known)		
		Gefitinib	Carboplatin / paclitaxel	Overall
EGFR mutation	Positive	132 (59%)	129 (60%)	261 (60%)
	Negative	91 (41%)	85 (40%)	176 (40%)
EGFR-gene-copy number	High	124 (60%)	125 (62%)	249 (61%)
	Low	81 (40%)	76 (38%)	157 (39%)
EGFR expression	Positive	132 (71%)	134 (74%)	266 (73%)
	Negative	53 (29%)	46 (26%)	99 (27%)

Overlap of biomarkers



EGFR mutation status

EGFR mutation status	N (% of all patients) [% of patients with EGFR mutation positive]	
	Gefitinib (n=609)	Carboplatin/paclitaxel (n=608)
Negative ^a	91 (14.9)	85 (14.0)
Positive ^b	132 (21.7)	129 (21.2)
Exon 19 deletions	66 [50.0]	74 [57.4]
Exon 21 L858R	64 [48.8]	47 [36.4]
Exon 20 T790M	5 [3.8]	6 [4.7]
Other ^c	3 [2.3]	7 [5.4]
Unknown ^d	386 (63.4)	394 (64.8)

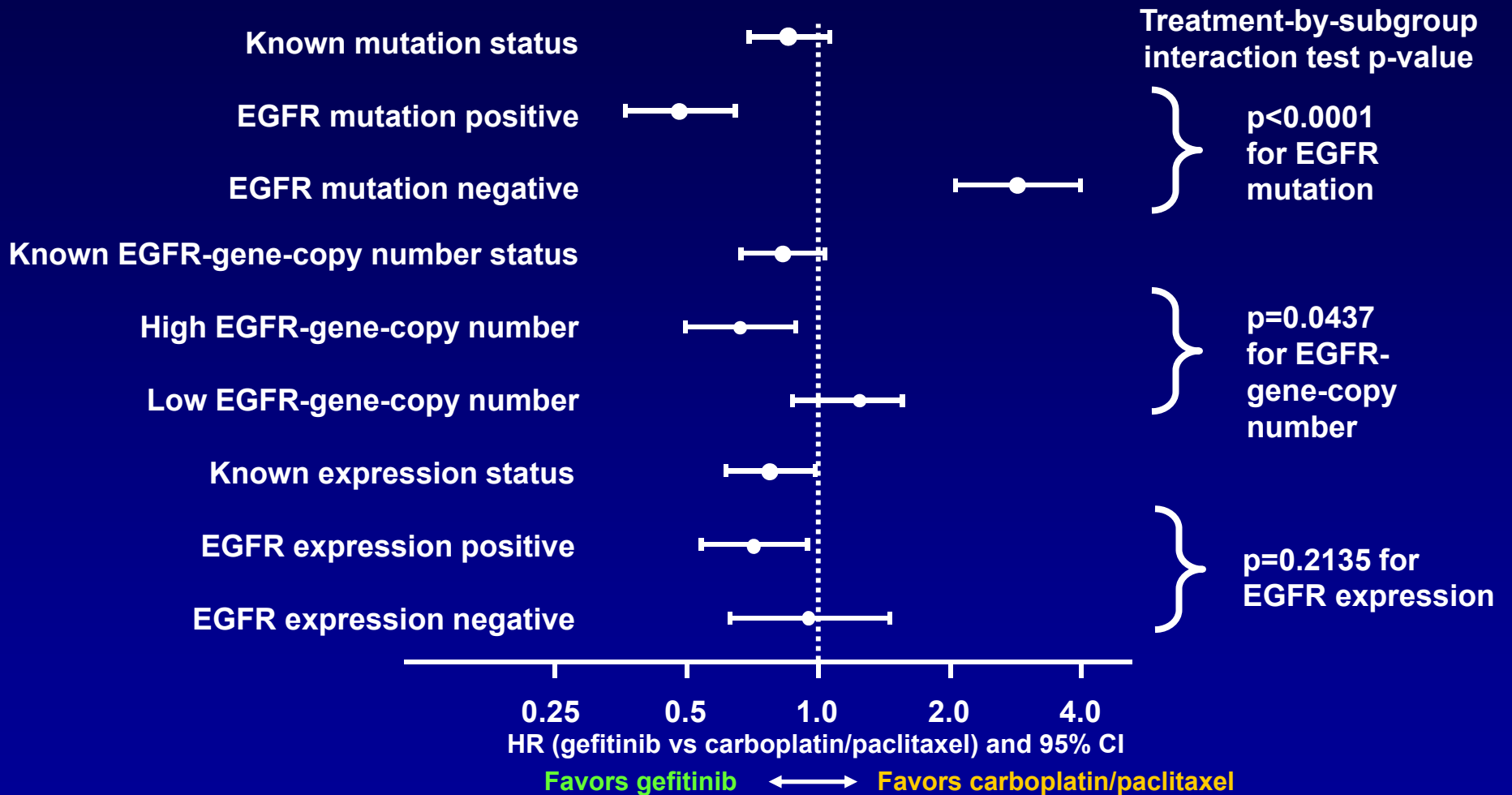
^aNo mutation detected

^bEleven patients had multiple mutations and are counted more than once

^cIncludes 3 patients with exon 18 G719X, 5 with exon 20 S768I, and 2 with exon 21 L861Q

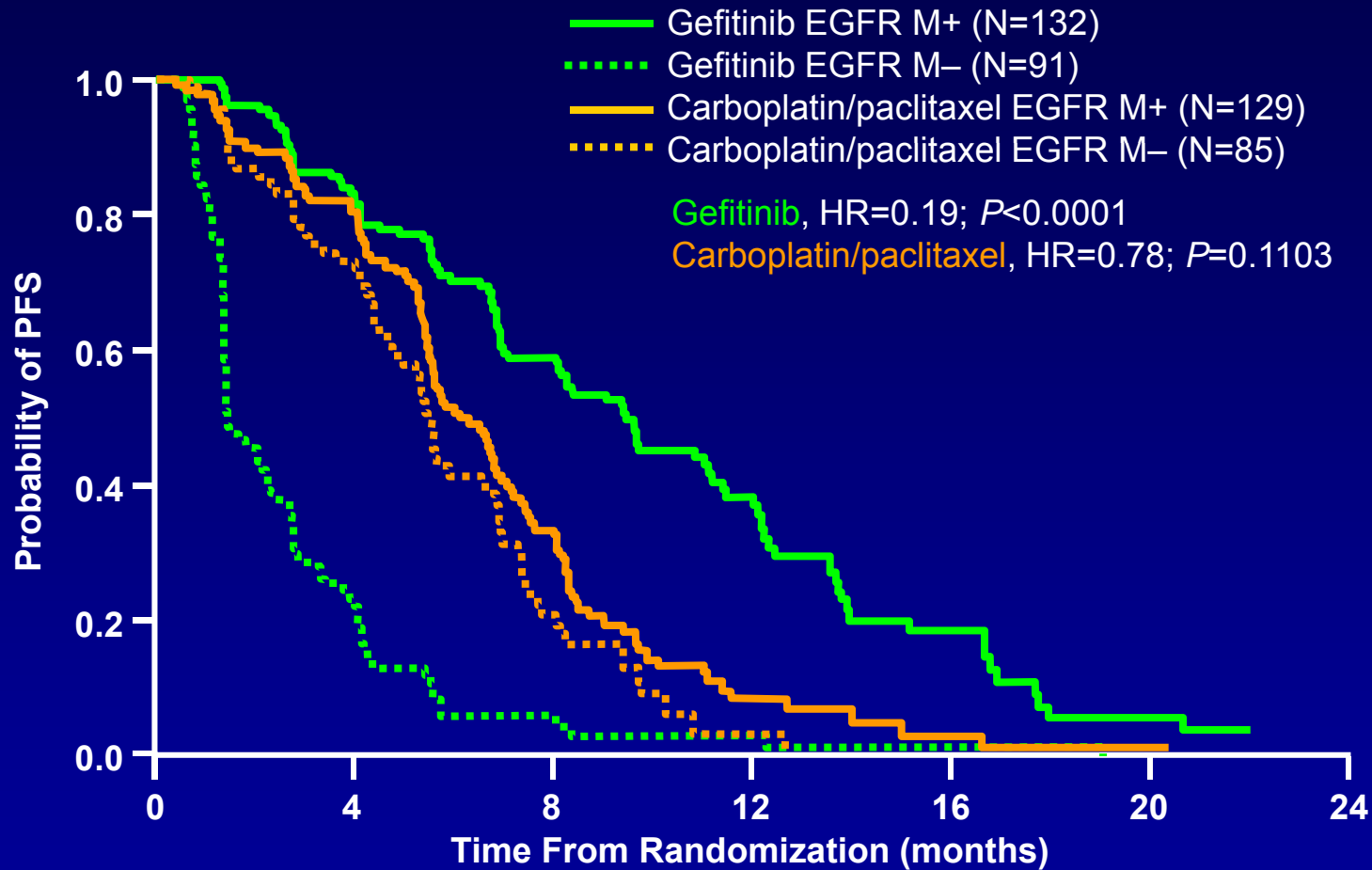
^dPatients without a tumour sample evaluable for EGFR mutation analysis, and samples which were not successfully analysed for EGFR mutation status were classified as unknown.

Progression-free survival by biomarkers



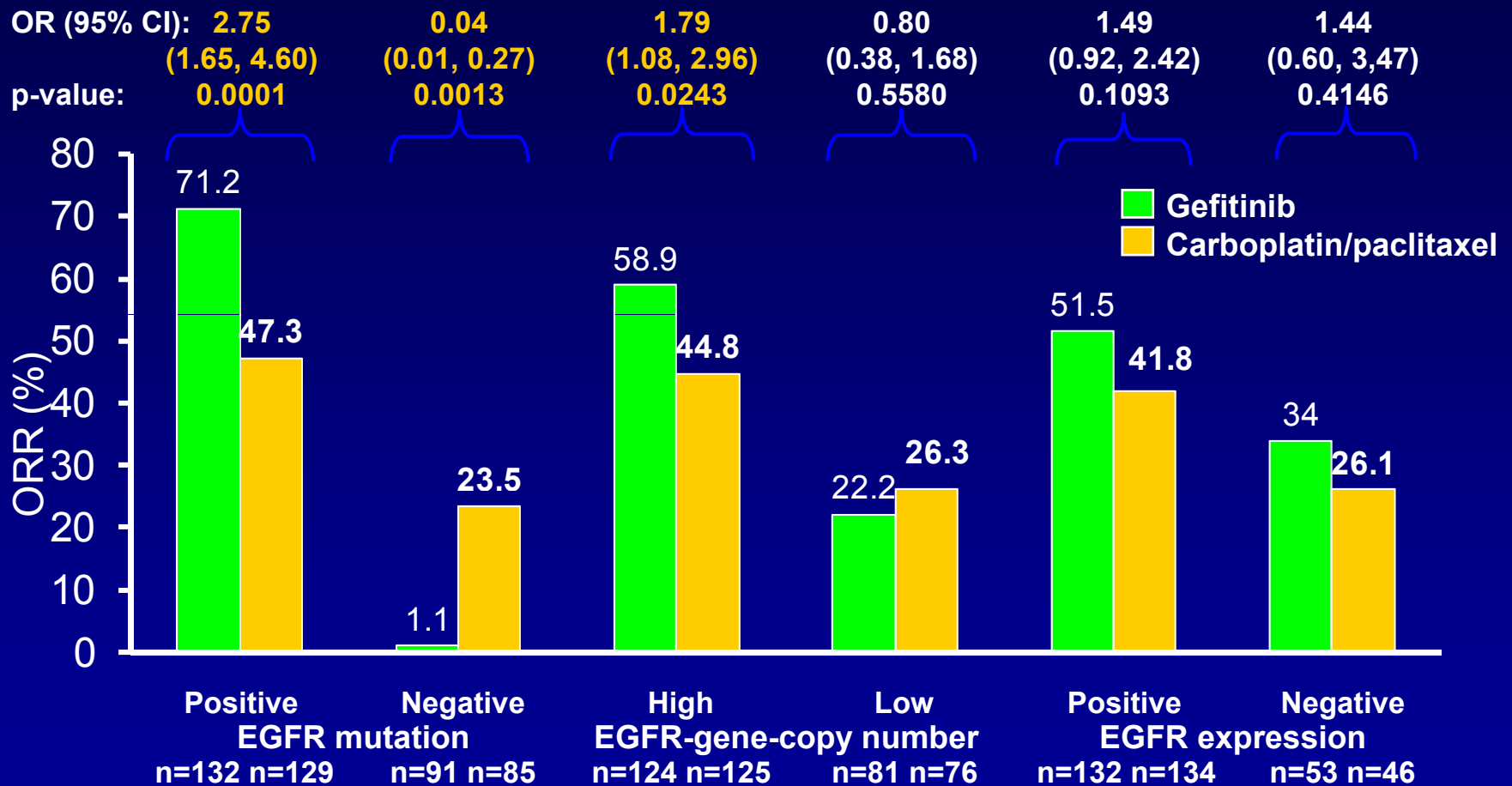
ITT population; Cox analysis with covariates; HR <1 implies a lower risk of progression on gefitinib

IPASS: PFS by EGFR Mutation Status



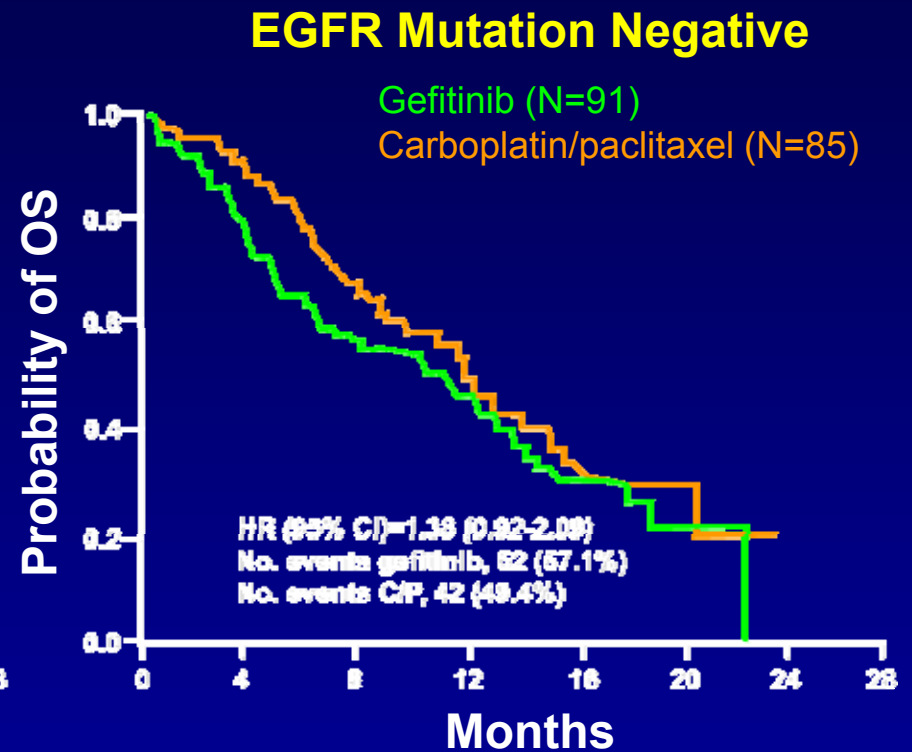
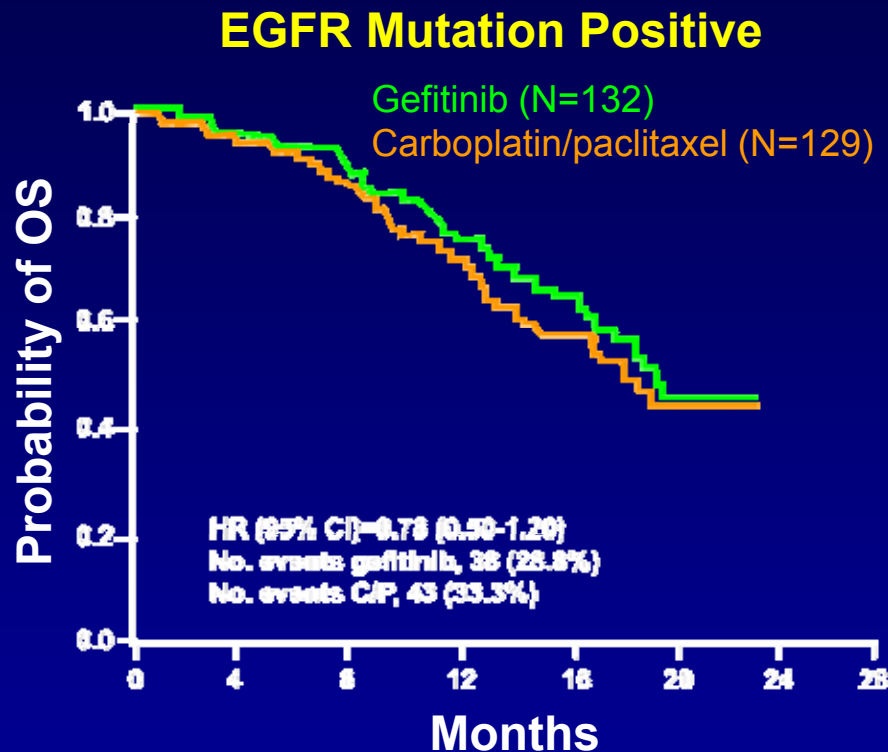
Hazard ratio <1 implies a lower risk of progression in the M+ group than in the M- group

Objective response rates by treatment and biomarker status



p-values from logistic regression with covariates; OR >1 implies greater chance of response on gefitinib; ITT population

IPASS: OS by EGFR Mutation Status



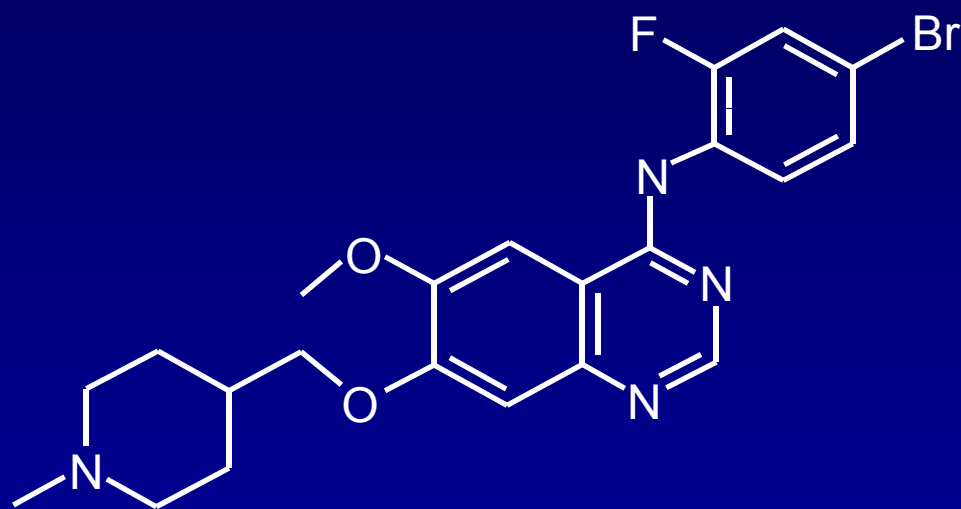
Patients at Risk		EGFR Mutation Positive								EGFR Mutation Negative							
	0	4	8	12	16	20	24	28	0	4	8	12	16	20	24	28	
Gefitinib	132	126	114	73	41	17	0	0	91	69	44	25	13	5	0	0	
Carboplatin/ paclitaxel	129	123	105	67	38	15	1	0	85	75	55	24	9	4	0	0	

- Cox analysis with covariates
- HR < 1 implies a lower risk of death on gefitinib
- ITT population
- Post-hoc analysis of OS by EGFR mutation status

Summary

- **EGFR mutation status**
 - In mutation positive patients, PFS was significantly longer with gefitinib than with carboplatin/paclitaxel
 - In EGFR mutation negative patients, PFS was significantly shorter with gefitinib than with carboplatin/paclitaxel
- **EGFR-gene-copy number**
 - A possibly related trend in PFS was observed. Post hoc explorations suggest this effect was driven by the overlap of high EGFR-gene-copy number with a positive EGFR mutation status
- **EGFR protein expression**
 - This was found to be less of a differentiator between the two treatment arms in terms of PFS
- **ORR results were consistent with PFS results**

Vandetinib is a Selective Inhibitor of Key Signaling Pathways in Cancer



M Wt = 475 Da

Kinase	IC ₅₀ (μM)
VEGFR-2 (KDR)	0.04
VEGFR-3 (Flt-4)	0.11
RET	0.13
EGFR	0.50
VEGFR-1 (Flt-1), PDGFR-β, Tie-2, FGFR1	>1
MEK, CDK2	>10
c-Kit, erbB2, FAK, PDK1	>20
Akt	>100
IGF-1R	>200

Adapted from Wedge SR *et al. Cancer Res* 2002;62:4645–4655

ZEAL

de Boer RH et al. ASCO 2009, abstr # 8010

- 534 2nd line pts randomized to pemetrexed \pm vandetinib
- Primary endpoint – PFS
- PFS HR – 0.86, $p=0.108$
- RR – 19% vs 8% favoring Pem + vandetinib ($p<0.001$)
- Delayed time to symptom progression (HR=0.61, $p=0.004$)
- No difference in overall survival
- Conclusion: Negative trial but largely consistent with the ZODIAC results
- Issue: Inclusion of squamous cell carcinoma (21%)

ZEST

Natale RB et al. ASCO 2009, abstr # 8009

- 1240 2nd+ line pts randomized to erlotinib vs vandetinib
- Primary endpoint – PFS (superiority)
- PFS HR – 0.98, p=0.7
- RR – 12% vs 12% erlotinib vs vandetinib (p=ns)
- Vandetinib was more toxic (diarrhea, QT_c interval, overall incidence of \geq grade 3 AEs)
- No difference in overall survival; planned non-inferiority test for PFS and OS showed vandetinib was “not inferior” to erlotinib
- Conclusion: Negative superiority trial; positive non-inferiority trial (secondary)

Vandetinib

Trial	Comparator	#Pts	PFS*	RR (%)	Comment
ZODIAC (abstr # 8003)	Docetaxel \pm Vandetinib	1391	0.79 p<0.001	17 vs 10 p<0.001	TDS 0.78 p=0.002 OS 0.91 p=0.196
ZEAL (abstr # 8010)	Pemetrexed \pm Vandetinib	534	0.86 p=0.108	19 vs 8 p<0.001	TDS 0.61 p=0.004 OS 0.86 p=0.2
ZEST (abstr # 800^9)	Vandetinib Vs Erlotinib	1240	0.98 p=0.7	12 vs 12 p=ns	OS 1.01 p=0.83

* PFS was primary endpoint in all three trials: RR, OS and TDS (time to deterioration of symptoms) were secondary endpoints

Thank you