

ASCO Highlights Lung Cancer



**The University of Texas
MD ANDERSON
CANCER CENTER**

Anne S. Tsao, M.D.

Director, Mesothelioma Program

Assistant Professor

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**Department of Thoracic/Head & Neck
Medical Oncology**

Outline

**Neoadjuvant
& Adjuvant
Chemo**



**Abstract 7500 NATCH trial
Abstract 7501 JBR.10 trial**

ChemoXRT



**Abstract 7505 CALGB 30407 (C225)
Abstract 7503 E3598 (thalidomide)**

Maintenance



**Abstract 8000 pemetrexed
Abstract 8001 SATURN (erlotinib)
Abstract 8002 ATLAS (bevacizumab \pm
erlotinib)**

**Metastatic
Salvage -
Vandetanib**



**Abstract CRA 8003 ZODIAC
Abstract 8009 ZEST
Abstract 8010 ZEAL**

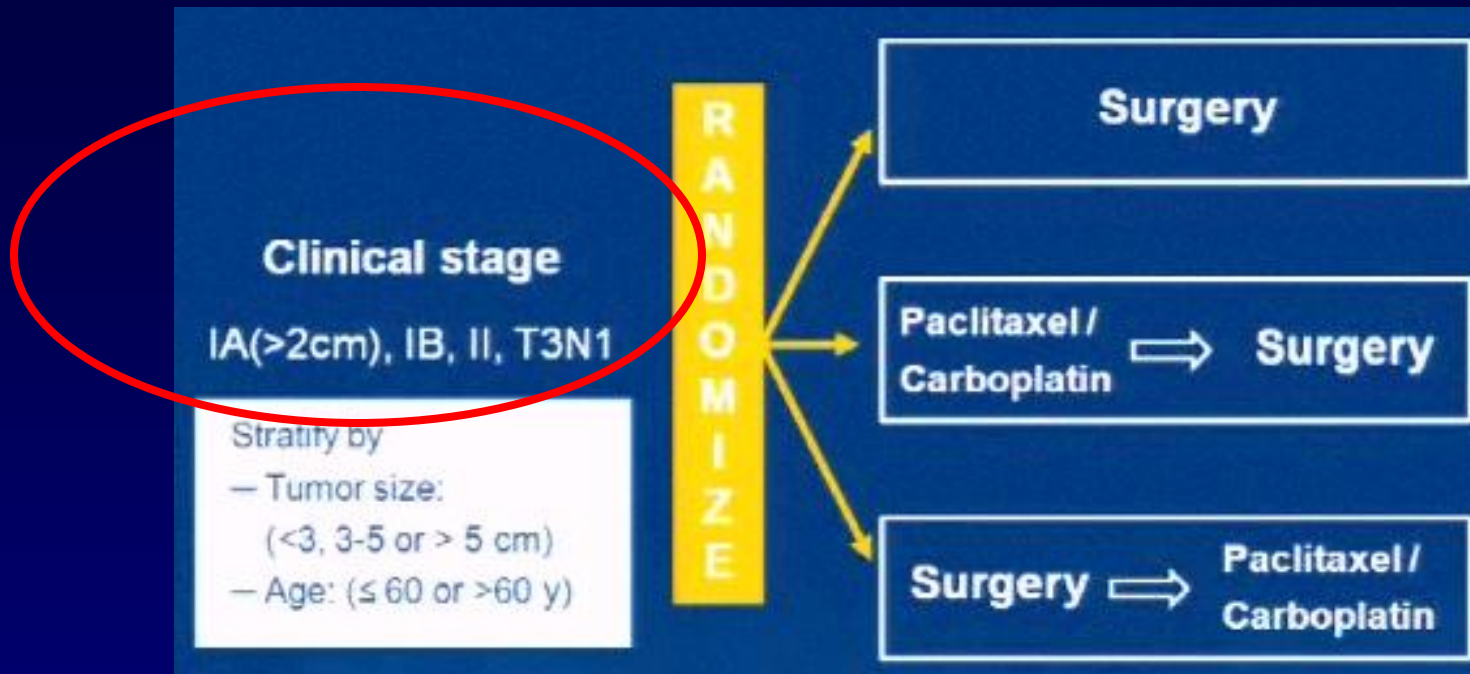
Biomarkers



**Abstract 8006 I-PASS (EGFR mutation)
Abstract 8007 FLEX (EGFR FISH)**

Abstract #7500 NATCH trial

Preop vs. Adjuvant chemotherapy



Carboplatin AUC 6 + paclitaxel 200 mg/m² Q3wk for 3 cycles

Post-op thoracic XRT allowed for pN2 disease

Primary endpoint: 5-year DFS

Secondary endpoints: toxicity, OS, molecular markers

Stats: 80% power to detect 15% improvement in 5-yr DFS, n=624

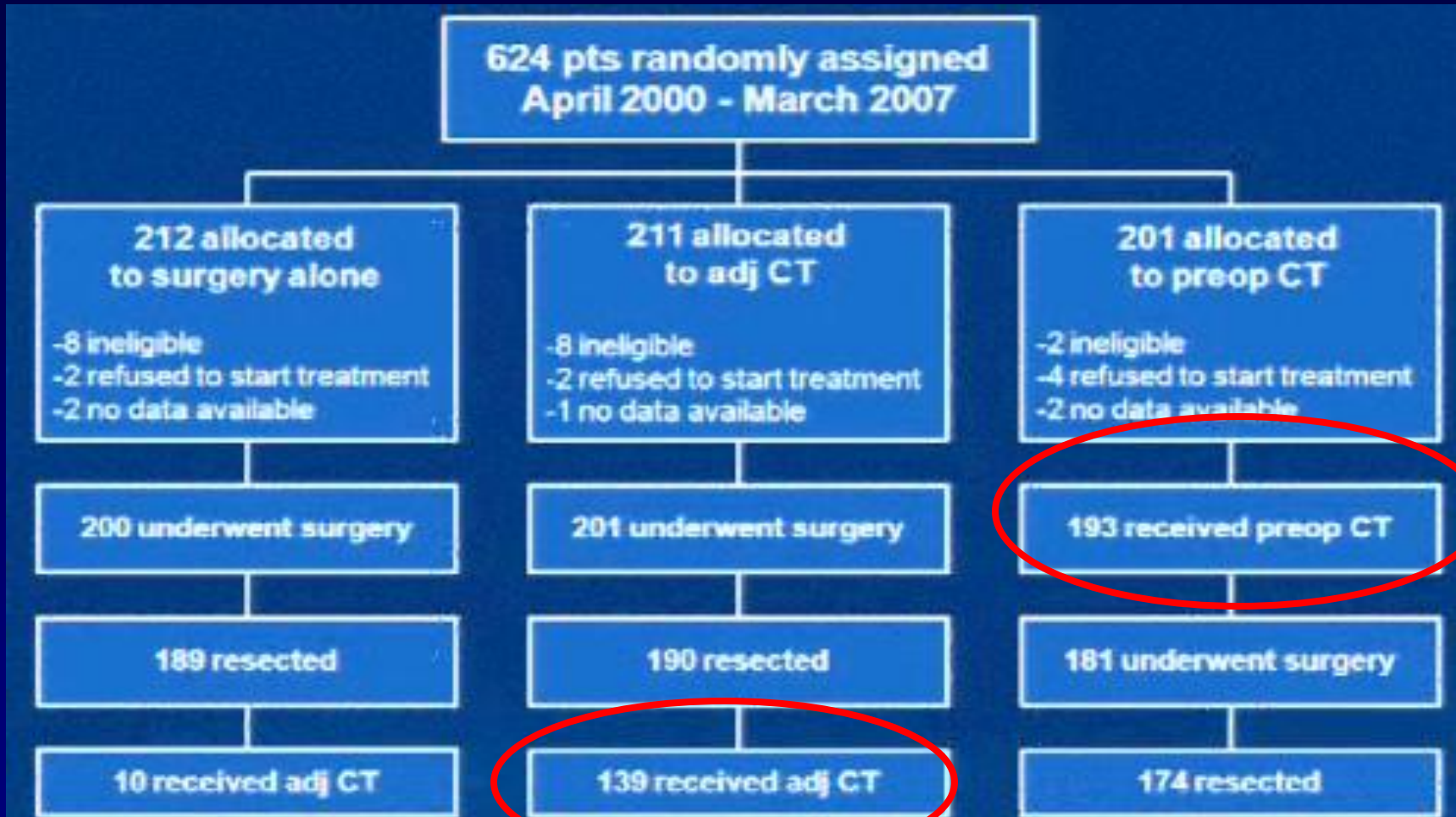
Patient Demographics (n=624)

Characteristic	Surgery alone (n=210)	Adjuvant chemo (n=210)	Preop chemo (n=199)
Median age	64	64	65
Male	87%	86%	87%
PS 0/1/2	49%/50%/1%	45%/53%/1%	44%/54%/0.5%
SCC	50%	49%	54%
Adenocarcinoma	34%	33%	29%
Large cell	10%	11%	10%
Other	6%	7%	7%

Patient Stage

Clinical Stage	Surgery alone (n=210)	Adjuvant chemo (n=210)	Preop chemo (n=199)
Stage 1	73%	77%	74%
T1N0	10%	14%	8%
T2N0	64%	63%	66%
Stage II	25%	22%	23%
T1N1	0.5%	1%	2%
T2N1	12%	12%	12%
T3N0	12%	9%	9%
Stage III	2%	0.5%	3%
T3N1	2%	0.5%	2%
T4N0	0%	0%	0.5%

Compliance



Chemo Compliance

	Adjuvant chemo (n=210)	Preop chemo (n=199)
% received chemo	66%	97%
% 3 cycles	93%	90%
% < 3 cycles	7%	7%
% Dose reductions	11%	9%
% Dose delay	16%	11%

More patients received neoadjuvant chemotherapy (97%) compared to adjuvant chemotherapy (66%)

Pre-op chemo efficacy

- 53% ORR (9% CR + 44% PR)
- 32% SD
- 5% PD
- 10% inevaluable

Surgery Results

	Surgery alone (n=210)	Adjuvant chemo (n=210)	Preop chemo (n=199)
Patients having surgery	200	201	181
Lobectomy/ bilobectomy	65%	69%	72%
Pneumonectomy	26%	24%	23%
< 1 lobe	4%	1%	0.5%
Exploratory thoracotomy	5%	5%	4%
Surgery-related deaths	6%	7%	5%

There was no difference in type of surgery or surgery related deaths. Preop chemo with 3 cycles carbo-paclitaxel did not decrease rate of pneumonectomy.

Felip et al. ASCO abstract #7500

Grade 3/4 Toxicity to Chemo

Adverse Event	Adjuvant (n=139)	Preoperative (n=193)
Neutropenia	7.2%	12.4%
Thrombocytopenia	1.4%	1%
Anemia	1.4%	0.5%
Nausea/vomiting	2.9%	1.6%
Febrile neutropenia	0.7%	0.5%
Diarrhea	3.6%	0.5%
Hyperglycemia	2.9%	2.1%
Arthralgia	2.1%	1.6%
Myalgia	0.7%	1%
Fatigue	2.2%	2.6%
Sensory neuropathy	1.4%	0.5%
Allergic reaction	0.7%	0.5%
Treatment related death	1	1

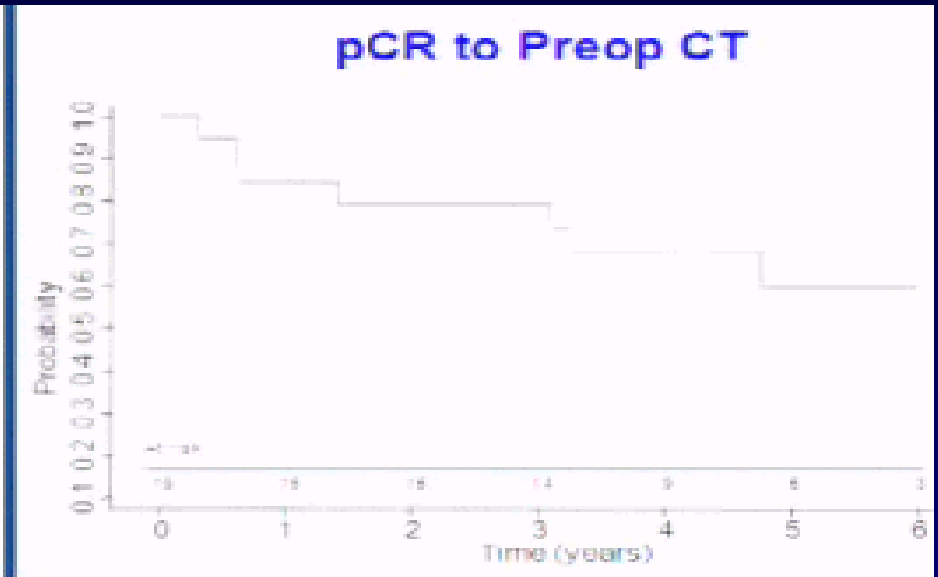
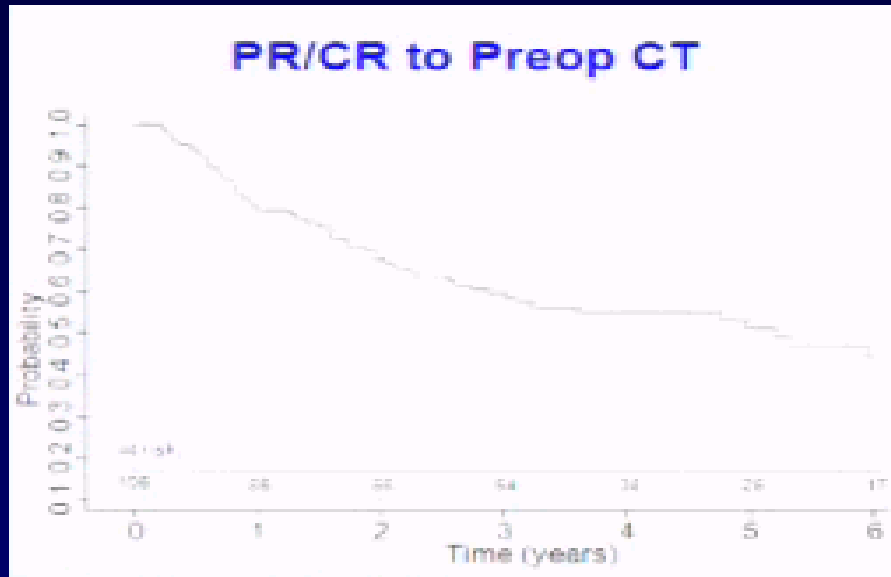
DFS by Stage

	Surgery alone (n=210)	Adjuvant chemo (n=210)	Preop chemo (n=199)
Stage 1	N=154	N=163	N=146
3-yr DFS	46%	48%	52%
5-yr DFS	37%	38%	39%
Stage II	N=56	N=47	N=51
3-yr DFS	29%	35%	39.4%
5-yr DFS	25%	31%	36.6%

Surgery vs Adjuvant Chemo HR 0.87, p=0.54

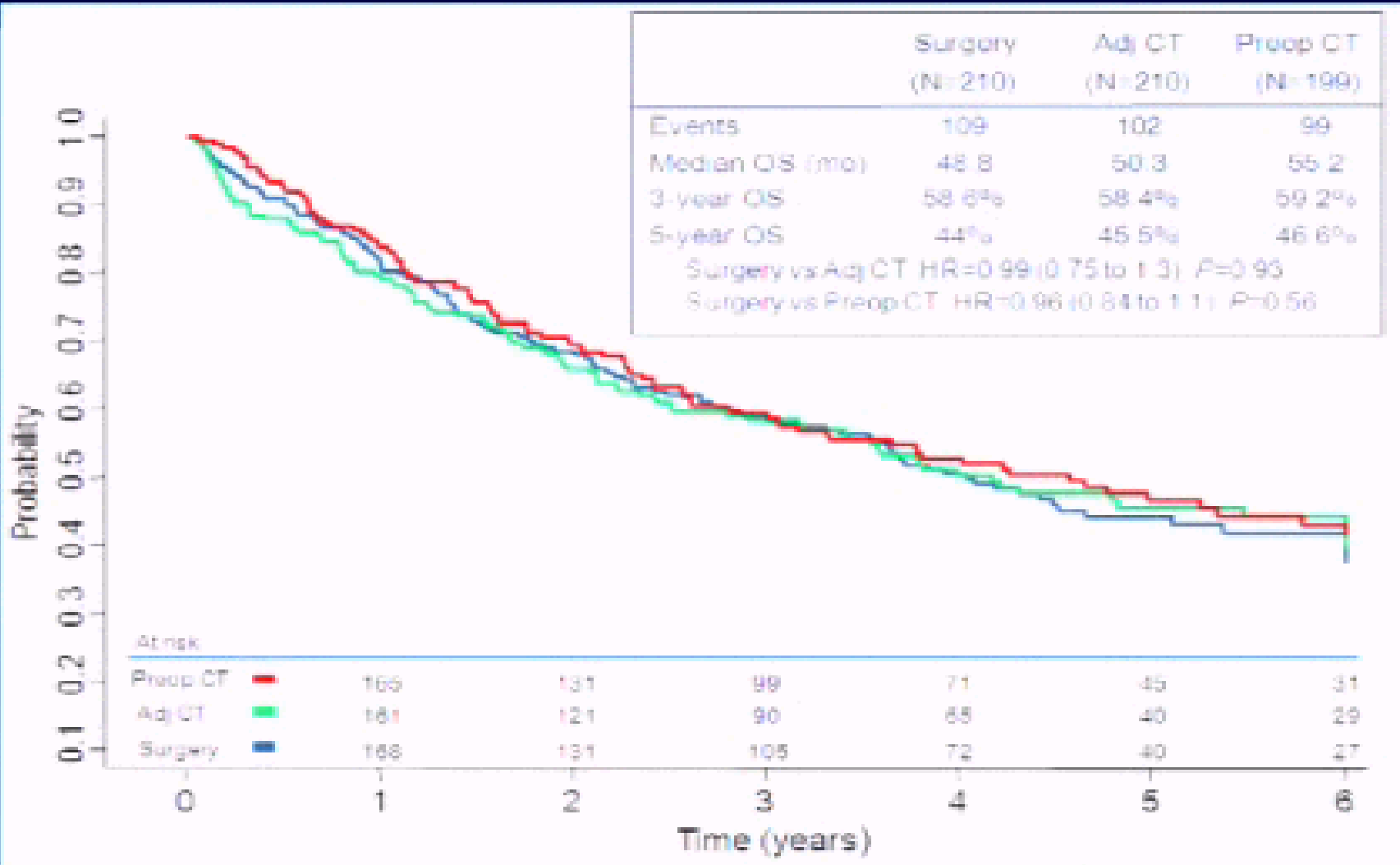
Surgery vs Preop Chemo HR 0.81, p=0.07

Patients with a response to Pre-op chemotherapy have higher DFS



	PR/CR to Preop Chemo (n=106)	pCR to Preop Chemo (n=19)
3 year DFS	59%	79%
5 year DFS	51%	59%

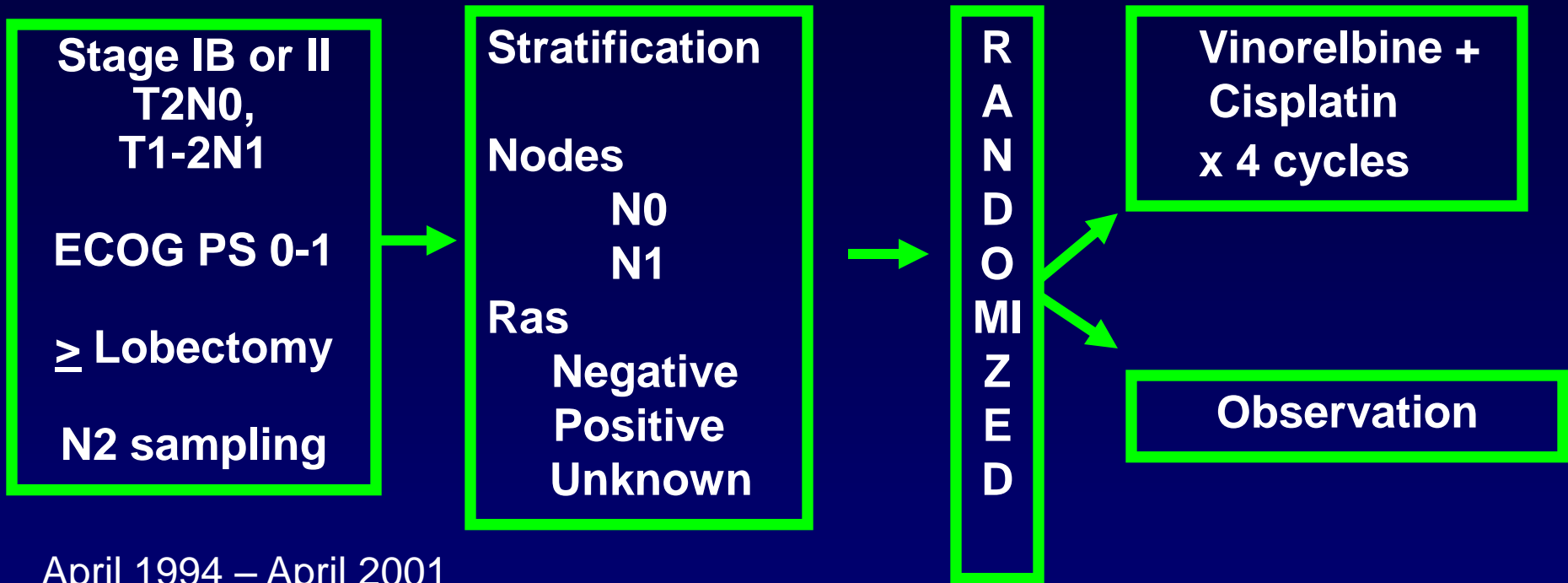
Overall Survival



Summary Abstract #7500

- Although more patients received preoperative chemo (97%) than adjuvant chemo (66%), there was no difference in resectability rates, surgical procedures, and post-operative mortality in stage IB and II patients
- Preoperative chemo had a non-significant trend towards improved DFS when compared to surgery alone
- **Issues:**
 - Early stage of these patients may prevent significant benefit from chemotherapy to be seen. Usually recommend adjuvant chemotherapy in stage II and III patients. Sometimes in IB tumors greater than 4 cm.
 - Would not recommend neoadjuvant chemo in stage IB or II
 - The use of carboplatin – CALGB 9633 was also negative in IB patients (except in tumors > 4 cm). Recommend cisplatin in a curative intent population

Abstract #7501 JBR.10 Updated



April 1994 – April 2001

Median F/U 5.1 years

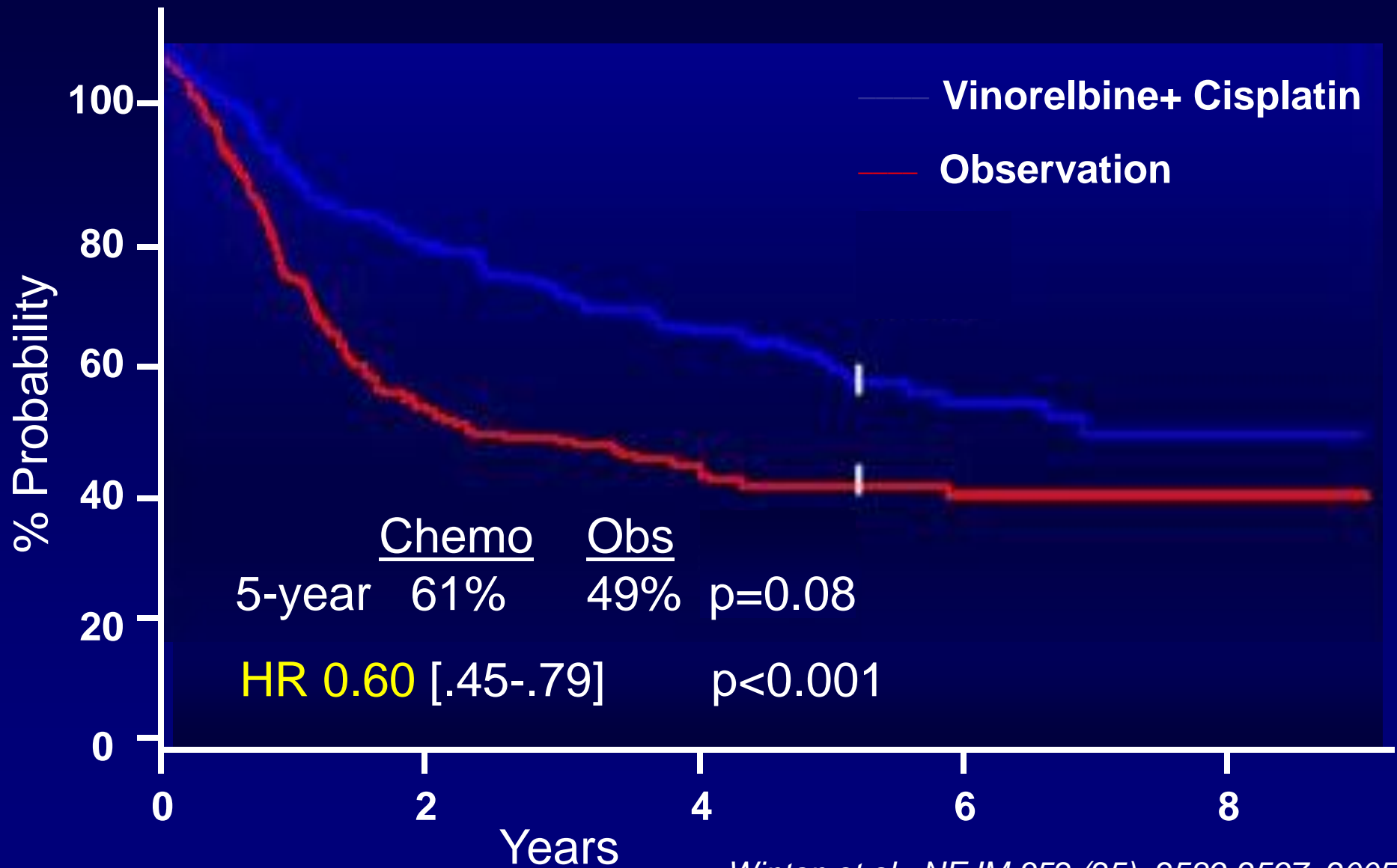
Cisplatin 50 mg/m² on D1 and 8 every 4 weeks for 4 cycles
Vinorelbine* 25 mg/m²/weekly for 16 weeks
*originally 30 mg/m²/wk but was changed after 30 patients

JBR.10 Patient Characteristics (n=482)

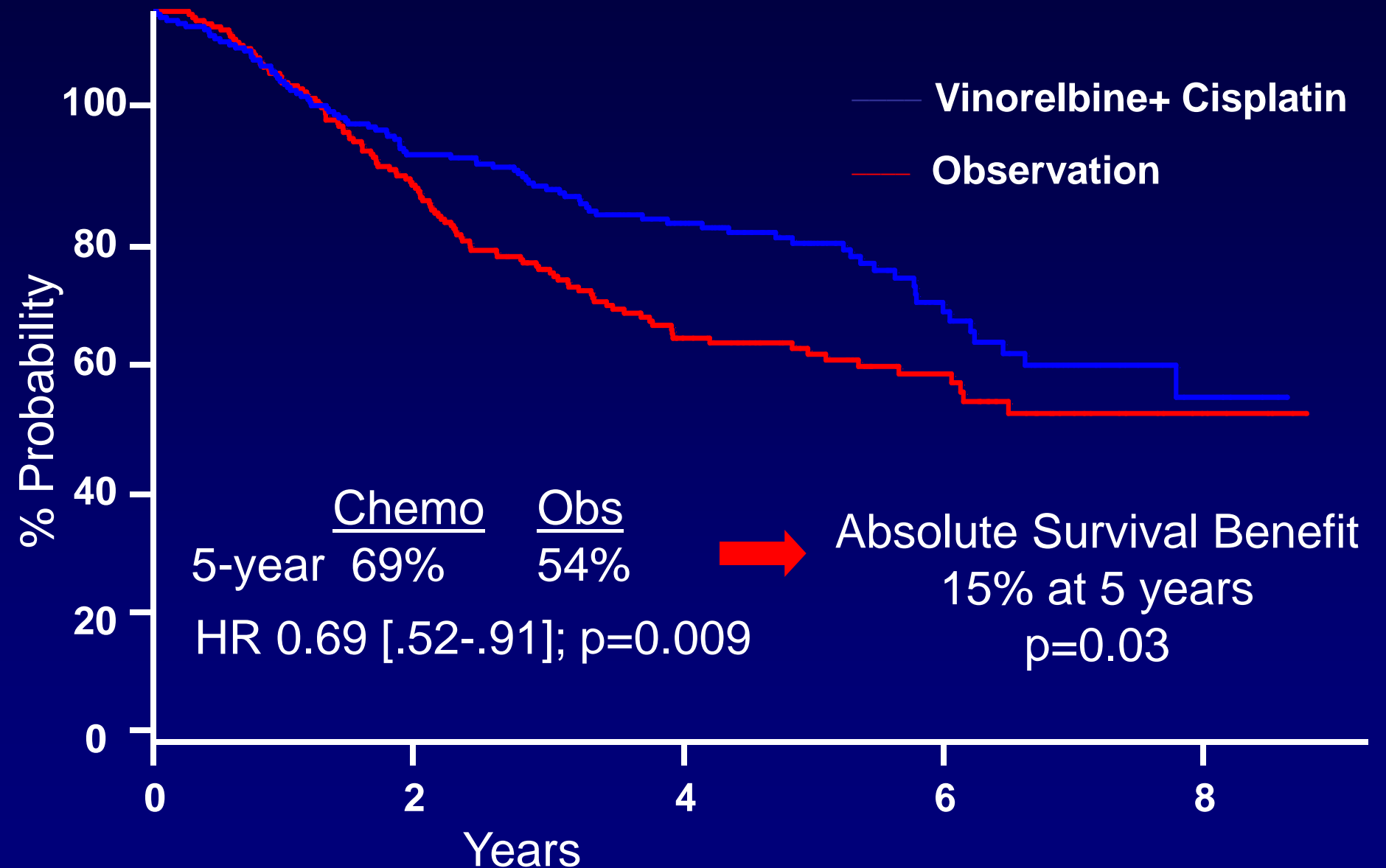
Cisplatin+Vinorelbine
(n=242) Observation
(n=240)

Men	66%	64%
Median Age	61	61
Stage IB	46%	45%
Stage IIA	16%	13%
Stage IIB	38%	42%
Squamous Cell	37%	38%
Adenocarcinoma	53%	53%
Ras mutation (+)	24%	24%
Ras mutation (?)	8%	6%

JBR.10 Recurrence-Free Survival



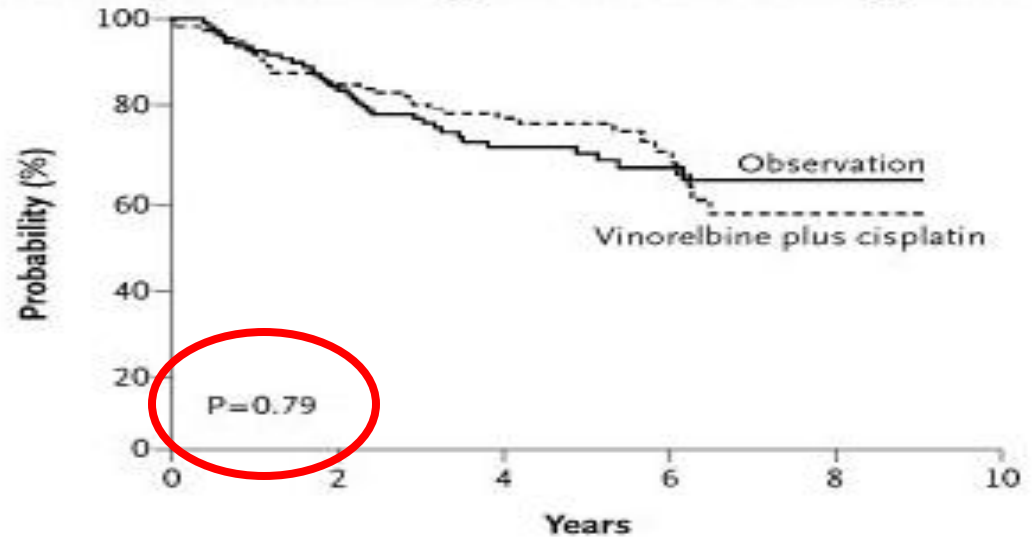
JBR.10 Overall Survival



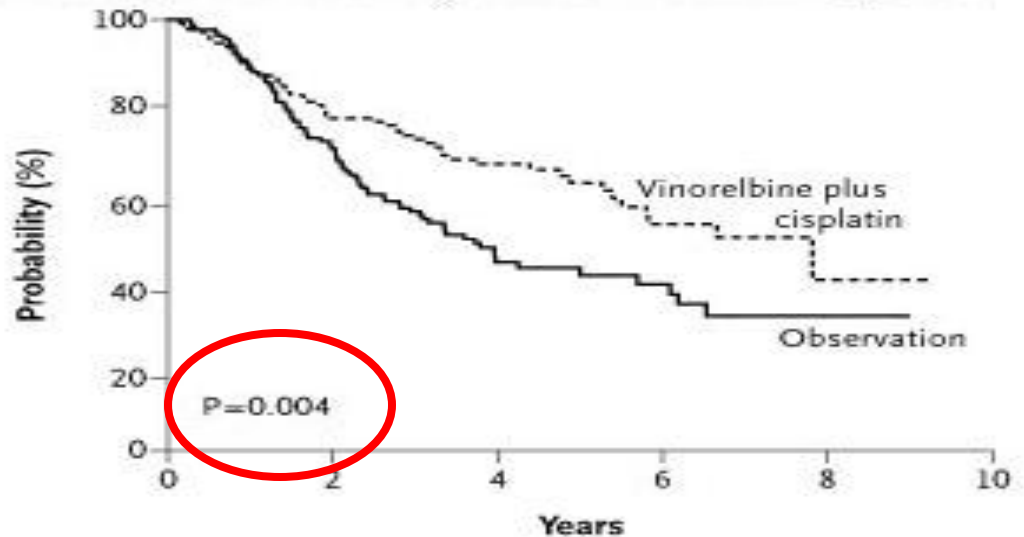
2005 JBR.10 Overall Survival by Stage

The OS benefit in stage IB was not statistically significant as in Stage II.

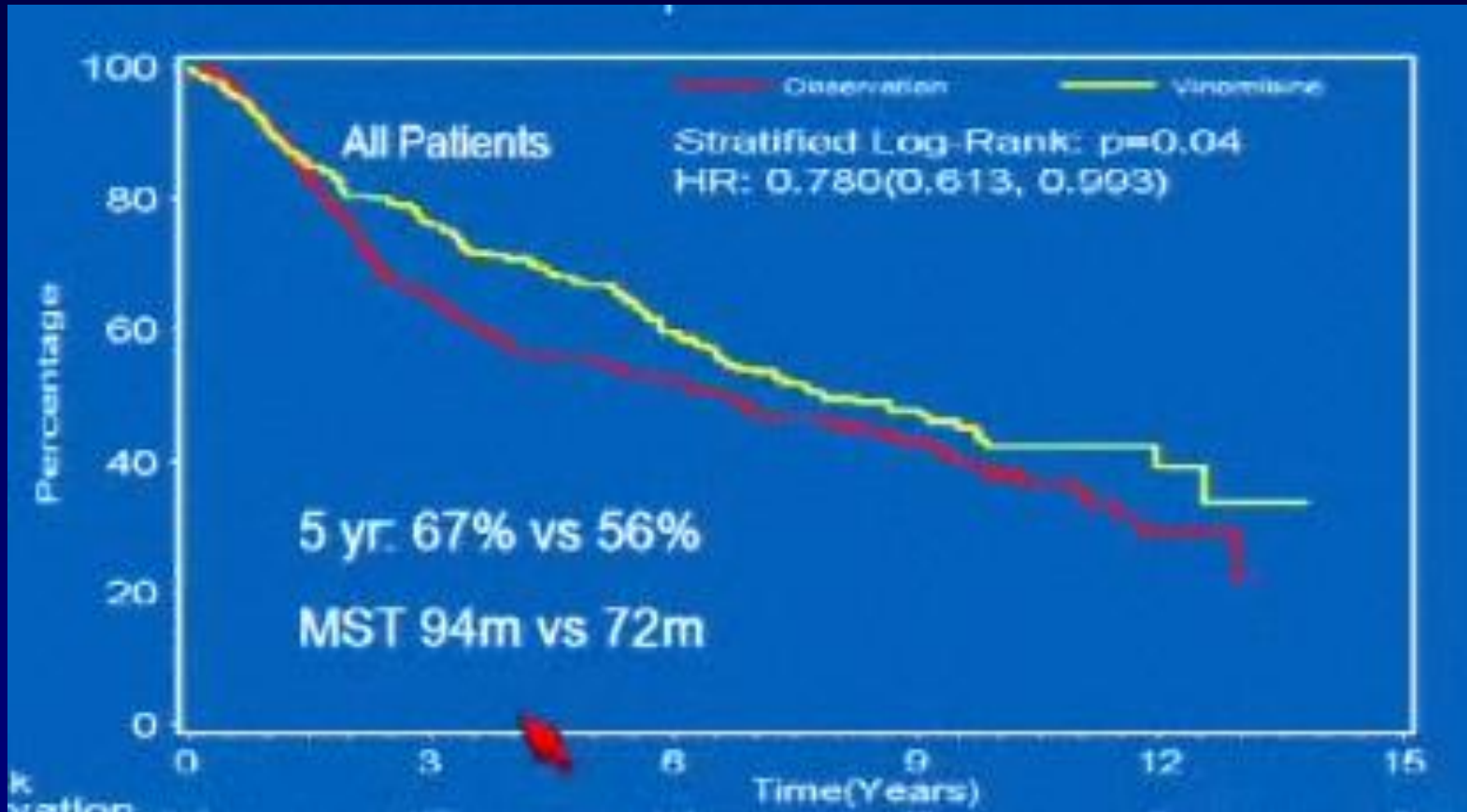
Overall Survival, Patients with Stage IB Non-Small-Cell Lung Cancer



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



2009 Updated Overall Survival

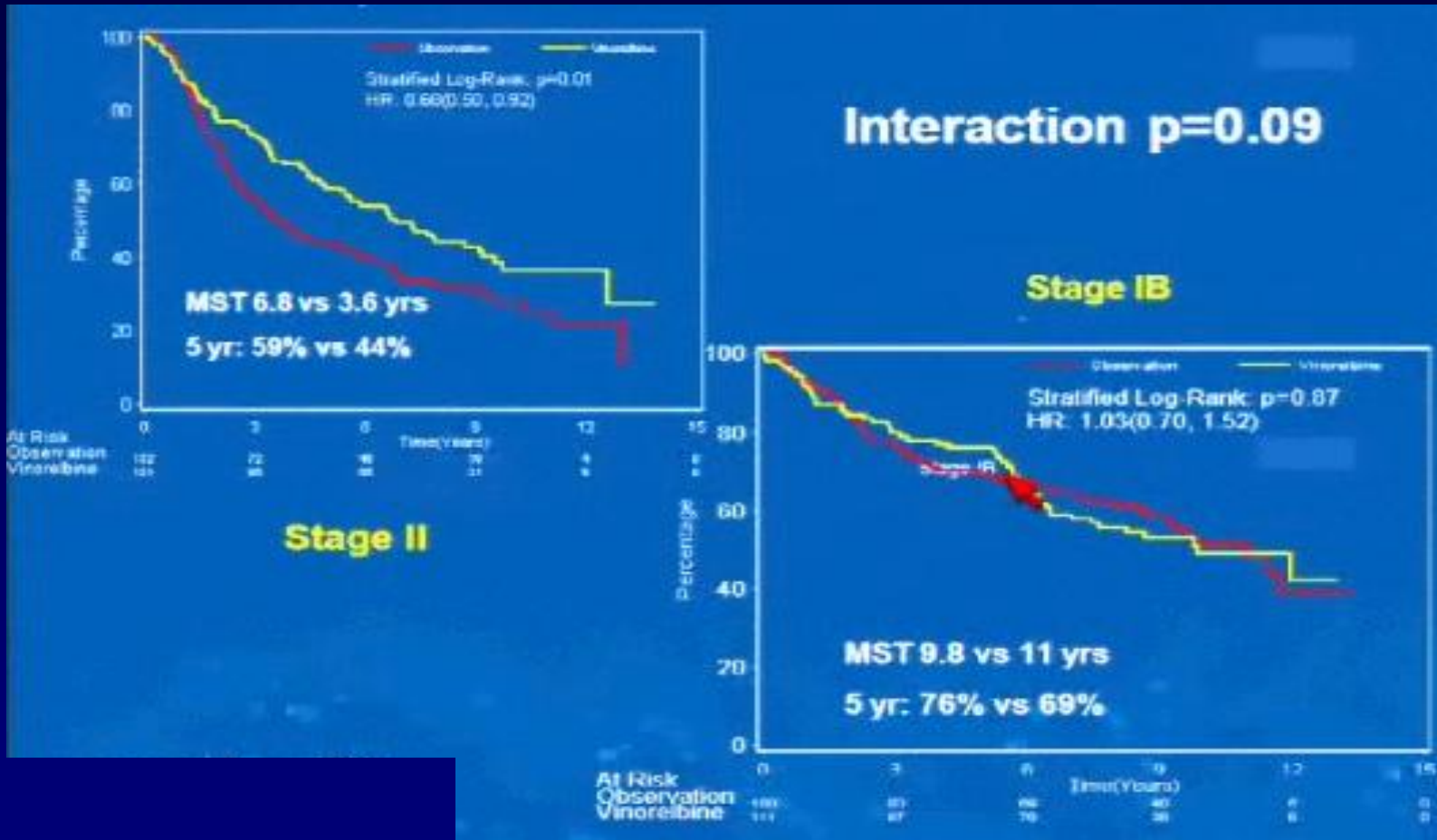


Absolute improvement in 5-yr OS 11%

HR 0.78, $p=0.04$

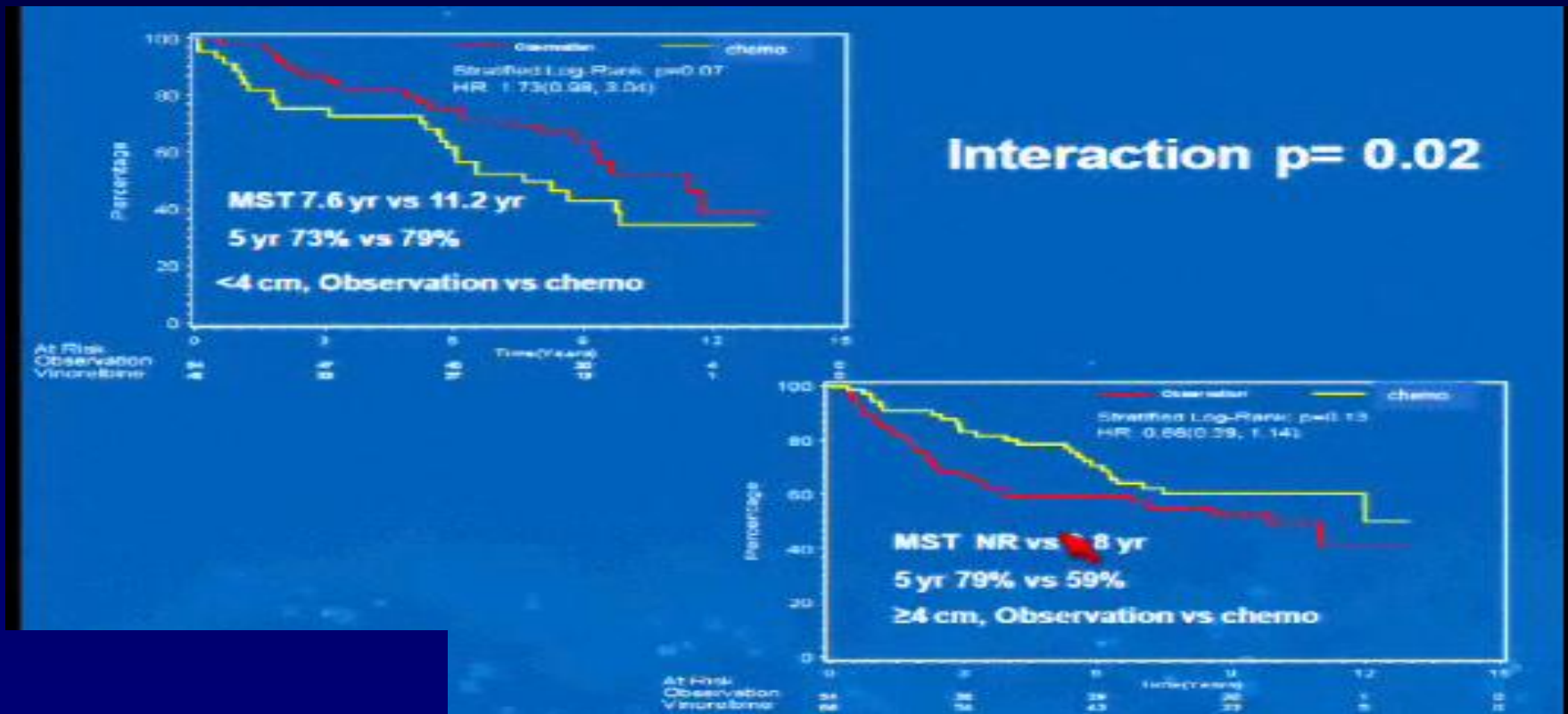
Vincent et al. ASCO abstract #7501

2009 Updated OS by Stage



Adjuvant chemo improves survival in stage II disease but not significantly in stage I ($p=0.07$)

2009 Updated OS by T-size



Adjuvant chemo improves survival in stage IB tumors ≥ 4 cm ($p=0.02$)

Causes of Death

Characteristic	Observation (n=240)	Adjuvant chemo (n=242)
Deaths	59.6%	52.3%
Disease-related	43.4%	36.4%
Other primary cancer	3.8%	2.5%
Other cause of death	10.8%	12.8%
COPD/Respiratory	4	5
Cardiac	7	8
Vascular	7	2
Misc	8	16

There is no difference in non-disease related death.

Summary Abstract #7501

- JBR.10 update (>9 years) shows survival benefit to adjuvant chemotherapy over observation.
- No difference in non-disease related deaths
- Stage II and Stage 1B (N0 and T size ≥ 4 cm) have survival benefit from adjuvant chemotherapy

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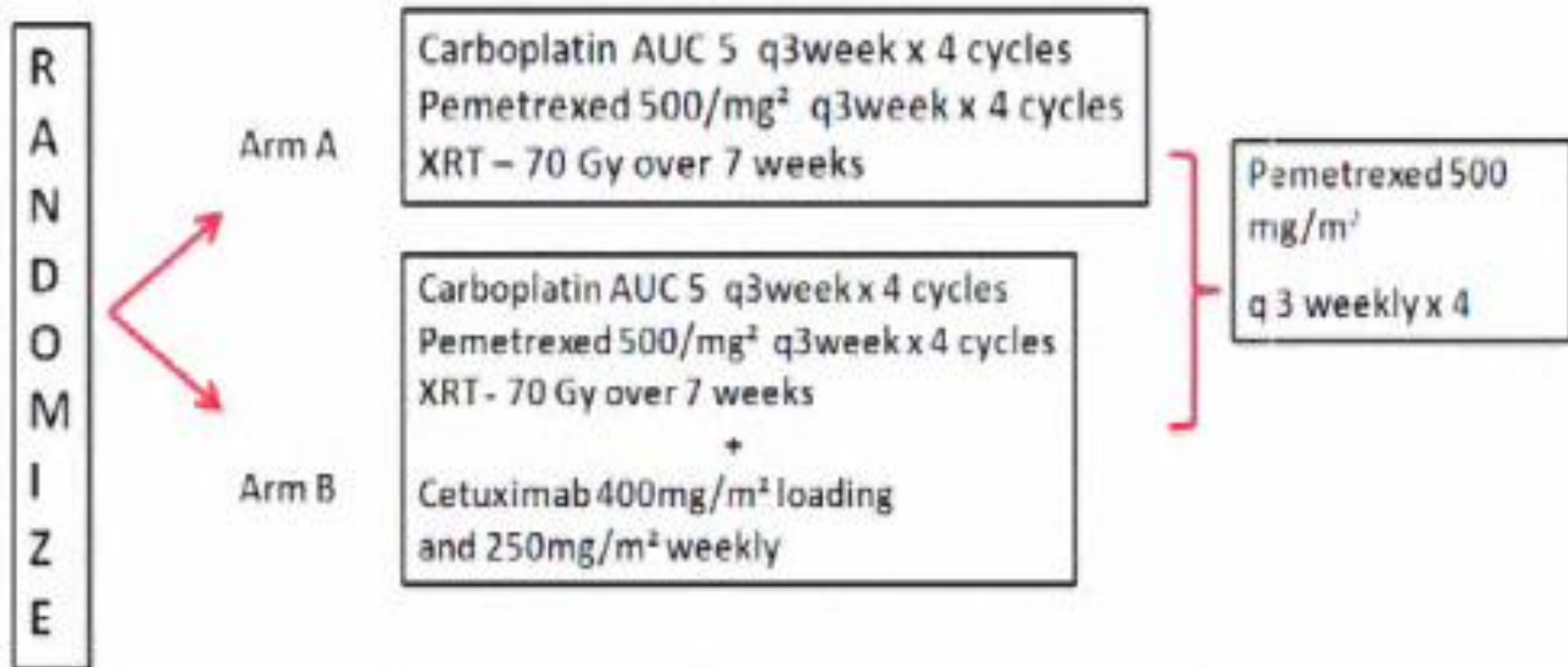
Biomarkers



**Abstract 8006 I-PASS (EGFR mutation)
Abstract 8007 FLEX (EGFR FISH)**

Abstract #7505 Phase II CALGB 30407

Eligible Patients: Untreated stage III, PS 0-1, No pleural effusions



Primary endpoint: Overall Survival

Secondary endpoint: FFS, RR, toxicity, tissue EGFR expression and mutation

Stats: 90% power to detect whether median survival is 20.9 months or more

compared to historical control (CALGB 39801) 13.9 months

Govindan et al. ASCO abstract #7505

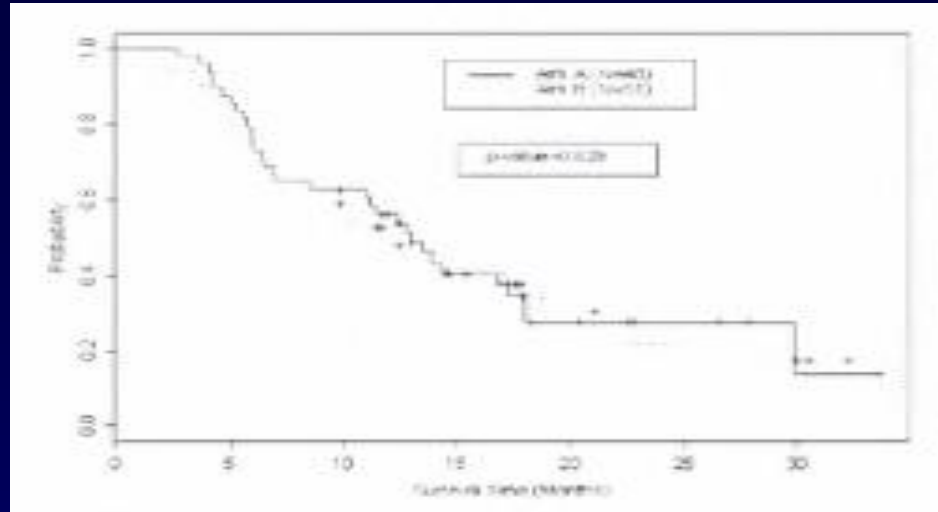
Patient Demographics

Characteristic	Carbo-Pem (n=48)	Carbo-Pem-C225 (n=51)
Median age	62	65
Proportion over 70 yrs	25%	20%
Male	58%	65%
Caucasians	77%	94%
Stage IIIA/IIIB	58%/40%	55%/45%
Histology: Adeno	46%	41%
SCC	33%	35%
Poorly differentiated	19%	18%

Compliance CALGB 30407

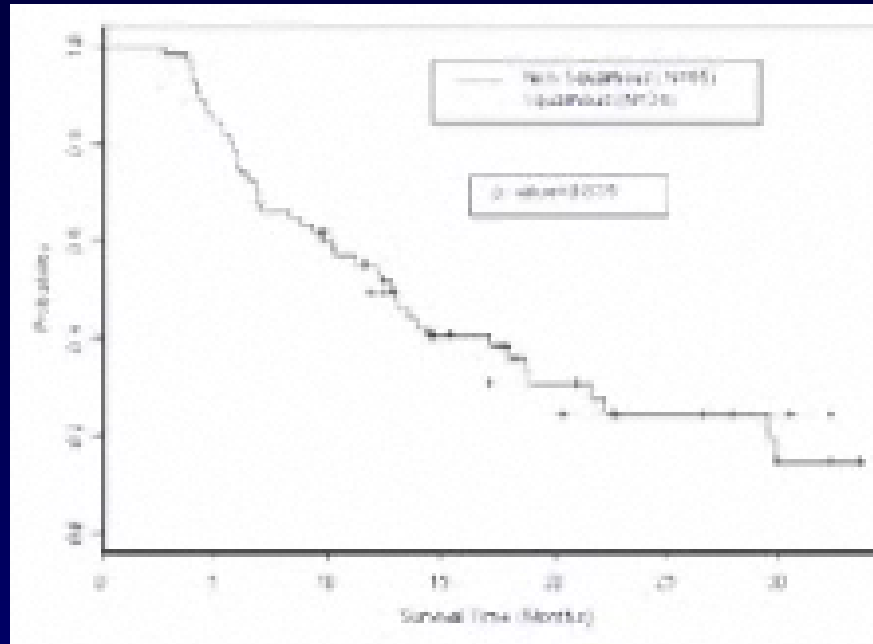
Treatment Delivery	Carbo-Pem (n=48)	Carbo-Pem-C225 (n=51)
% failed to complete systemic therapy	46%	51%
Adverse event	19%	18%
Disease progression	8%	10%
Death	2%	6%
Patient refusal	13%	10%
Treatment during chemoradiation	Carbo-Pem (n=48)	Carbo-Pem-C225 (n=51)
All 4 cycles	90%	80%
3 cycles	2%	4%
2 cycles	4%	10%
1 cycle	4%	4%

CALGB 30407 RR and FFS



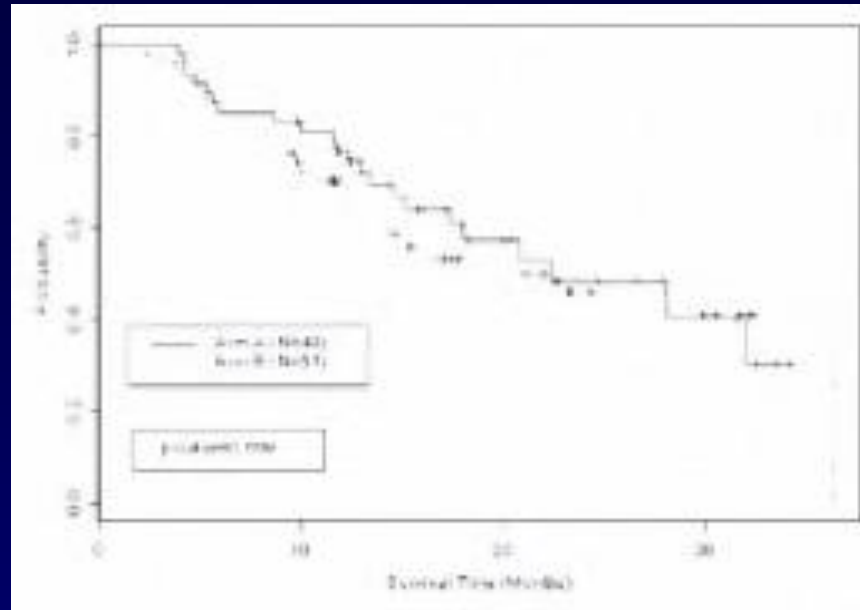
	Carbo-Pem (n=48)	Carbo-Pem-C225 (n=51)
CR/PR	6%/64%	2%/68%
SD	25%	24%
ORR	73%	71%
Median FFS	13 months	12 months
18 month FFS	28%	34%

FFS by Histology



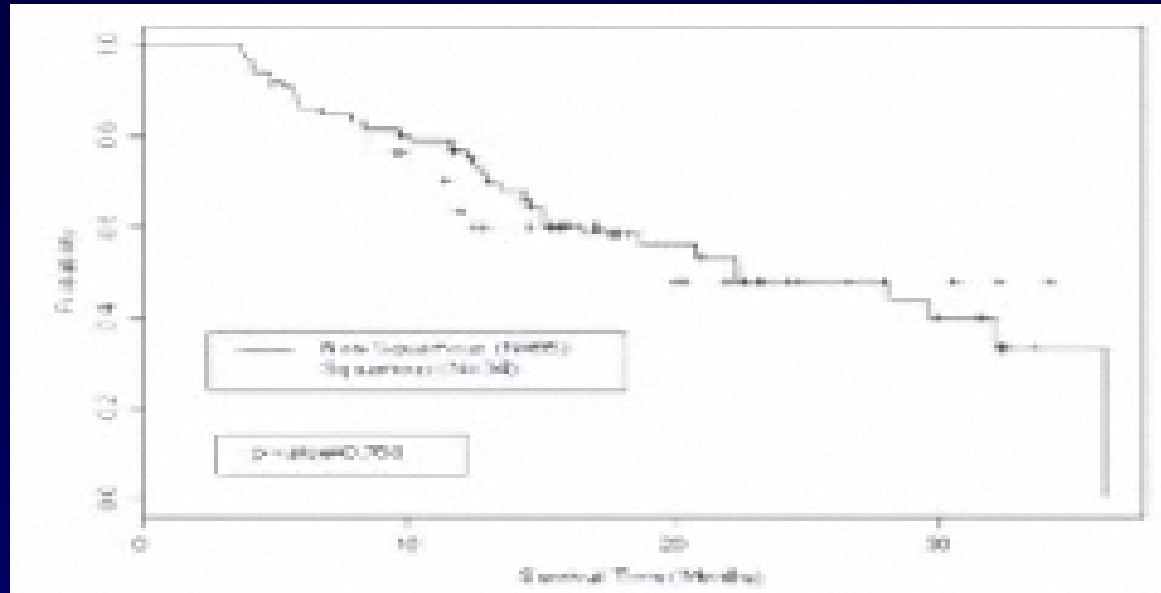
	Median FFS	18-month FFS
SCC	12 months	25%
Non-SCC	13 months	36%

CALGB 30407 by OS



	Carbo-Pem (n=48)	Carbo-Pem-C225 (n=51)
Median OS (months)	22	22
18-month OS	57%	50%

CALGB 30407 OS by Histology



	Median OS	18-month OS
SCC	18 months	48%
Non-SCC	22 months	56%

CALGB 30407 Grade 3/4 Toxicity

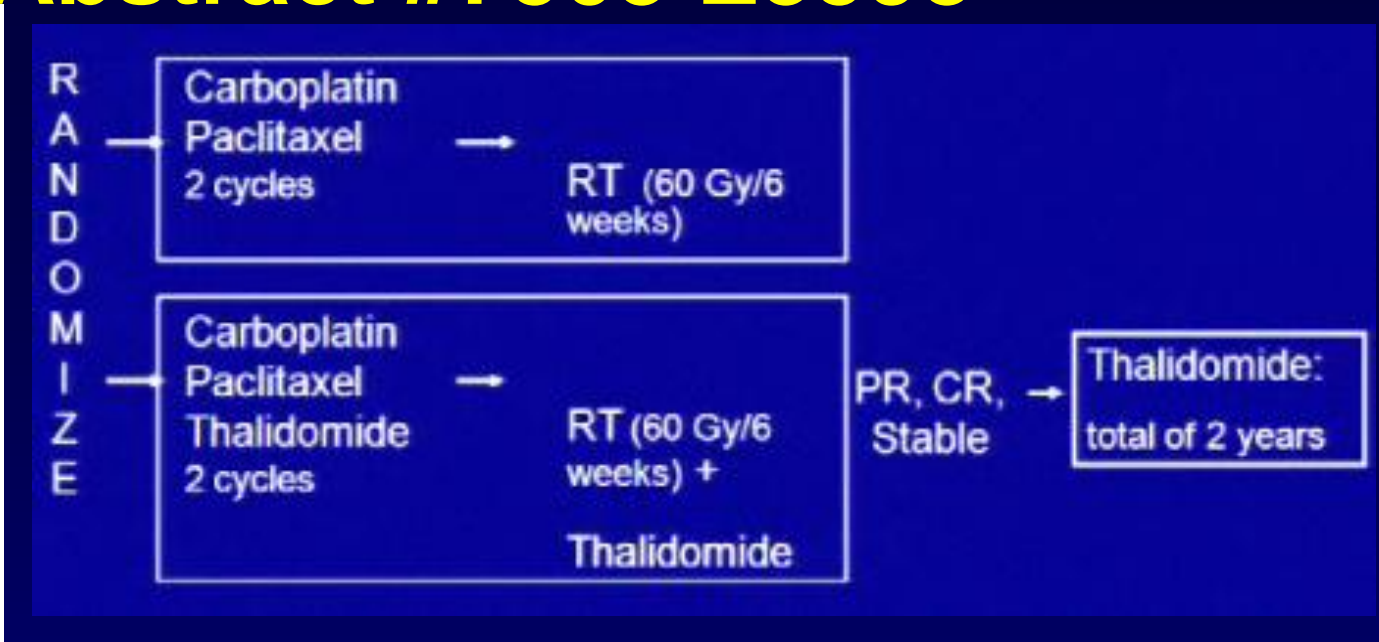
Adverse Event	Carbo-Pem (n=48)	Carbo-Pem- C225 (n=51)
Neutropenia	50%	59%
Anemia	18%	14%
Thrombocytopenia	36%	34%
Febrile neutropenia	8%	6%

Abstract #7505 Summary

- Carboplatin-pemetrexed \pm cetuximab given with thoracic XRT yielded median survival of 22 months.
 - No difference between the 2 arms in RR, FFS, OS
- Non-SCC had a trend towards better survival in the trial.
- No new safety signals.
- Phase III trial (PROCLAIM) is underway comparing cisplatin-etoposide-XRT to cisplatin-pemetrexed-XRT for non-SCC NSCLC and RTOG 0617 is evaluating role of cetuximab with carboplatin-paclitaxel and thoracic XRT.

Abstract #7503 E3598

Unresectable
IIIA/IIIB
Without pleural
effusion
IIIA – mediastinal
nodes > 2 cm
Nodes 1-2 cm:
mediastinoscopy
PS 0-1



Primary endpoint: Overall Survival
Secondary endpoint: TTP, RR, toxicity, lab correlates
Stats: 83% power to detect a 30% improvement in median survival (14 months to 18 months)

Induction: carbo (AUC 6) + paclitaxel 225 mg/m²

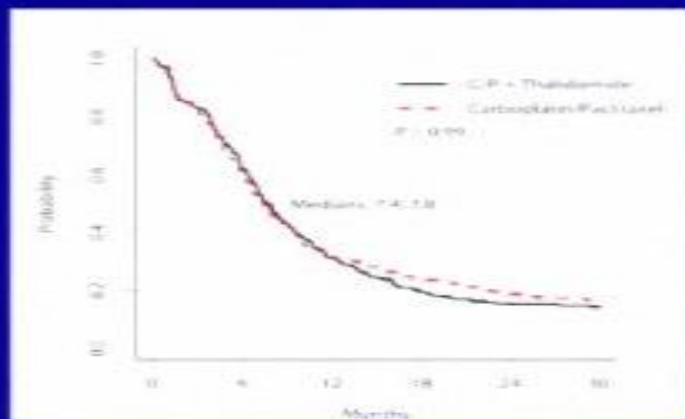
Study stopped early for futility

Weekly concurrent chemo: carbo (AUC 2) + paclitaxel 45 mg/m²

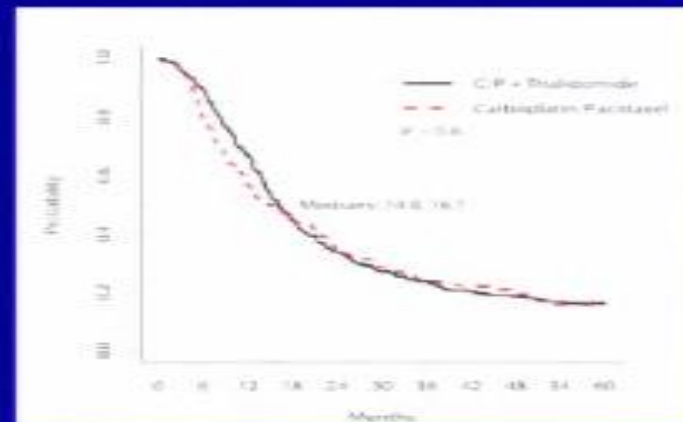
Thalidomide 200 mg/day – dose escalate or de-escalate by 100 mg/day per tolerance.
Max 1000 mg/day

E3598 Efficacy

Progression Free Survival



Survival



Efficacy	Chemo	Chemo+ thalidomide	p-value
RR	35%	39%	0.36
Median TTP	7.4 months	7.8 months	HR 1; p=0.99
Median OS	14.9 months	16.1 months	HR 0.98; p=0.84
1-yr OS	57%	67%	--

No clinical subsets had any benefit to thalidomide with chemo

Grade 3+ Toxicity

Adverse Event	Chemo (n=288)	Chemo + thalidomide (n=288)
Neutropenia	50.3%	55.9%
Infection	5.1%	8%
Febrile neutropenia	2.4%	2.4%
Anemia	3.1%	1.3%
Thrombocytopenia	3.5%	2.1%
Neuropathy-motor	1.7%	3.1%
Neuropathy-sensory	5.5%	11.1%
Constipation	1.3%	8.7%
Rash	1%	6.9%

Patients on thalidomide had increase thrombotic events 11% vs 3% compared to chemo alone and all patients thereafter (amendment 6) were started on aspirin (81 mg/day) where the incidence of thrombotic events then dropped down to 9%

Summary Abstract #7503

- Thalidomide does not improve survival when combined with carboplatin-paclitaxel and thoracic XRT
- Thalidomide is associated with thrombotic events even when low-dose aspirin is initiated.

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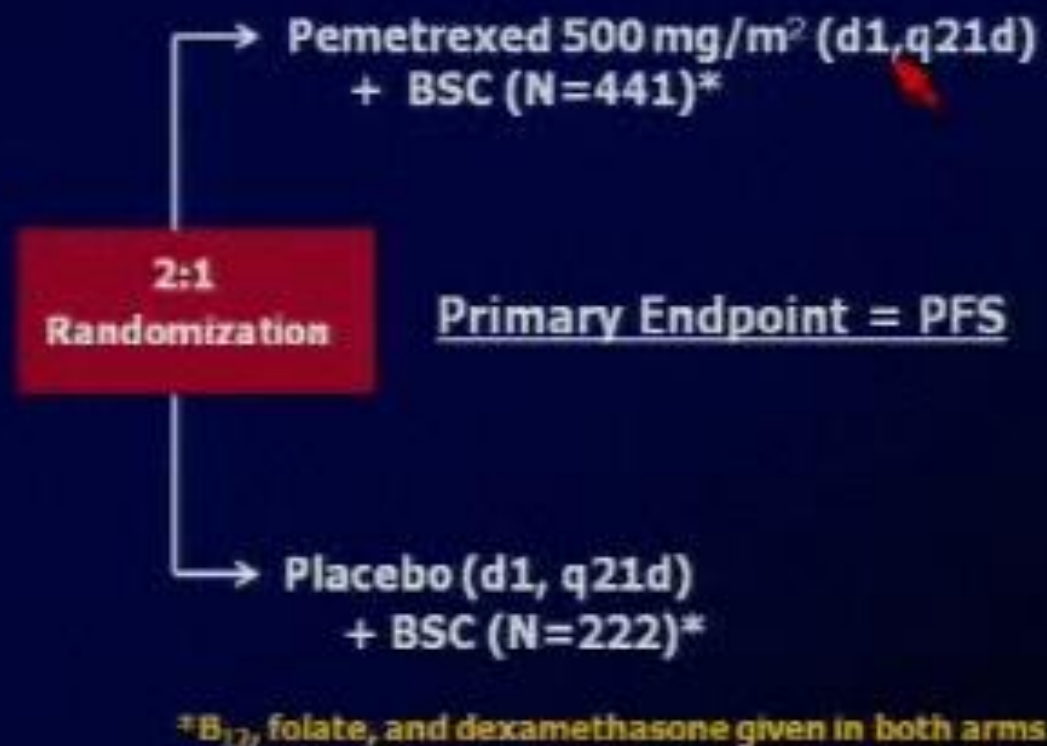
**Abstract 8006 I-PASS (EGFR mutation)
Abstract 8007 FLEX (EGFR FISH)**

Abstract #8000 Phase III Maintenance pemetrexed

- 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



Primary endpoint: PFS

Secondary endpoint: RR, OS, DCR, safety

Patient Demographics

Characteristic	Pemetrexed (n=441)	Placebo (n=222)
Median age	60.6	60.4
Male	73%	73%
Caucasian/Asian	63%/32%	67%/30%
Stage IIIB/IV	18%/82%	21%/79%
PS 0/1	40%/60%	38%/62%
Smoking: Never	26%	28%
Histology: Adeno	50%	48%
Large cell	2%	5%
Other	21%	18%
SCC	26%	30%

Initial Chemotherapy

Chemo	Pemetrexed (n=441)	Placebo (n=222)
Docetaxel-carboplatin	5%	3%
Docetaxel-cisplatin	2%	2%
Paclitaxel-carboplatin	30%	27%
Paclitaxel-cisplatin	6%	9%
Gemcitabine-carboplatin	24%	22%
Gemcitabine-cisplatin	33%	38%
Best response to initial chemo:		
CR + PR	48%	52%
SD	52%	48%

Maintenance Treatment Compliance

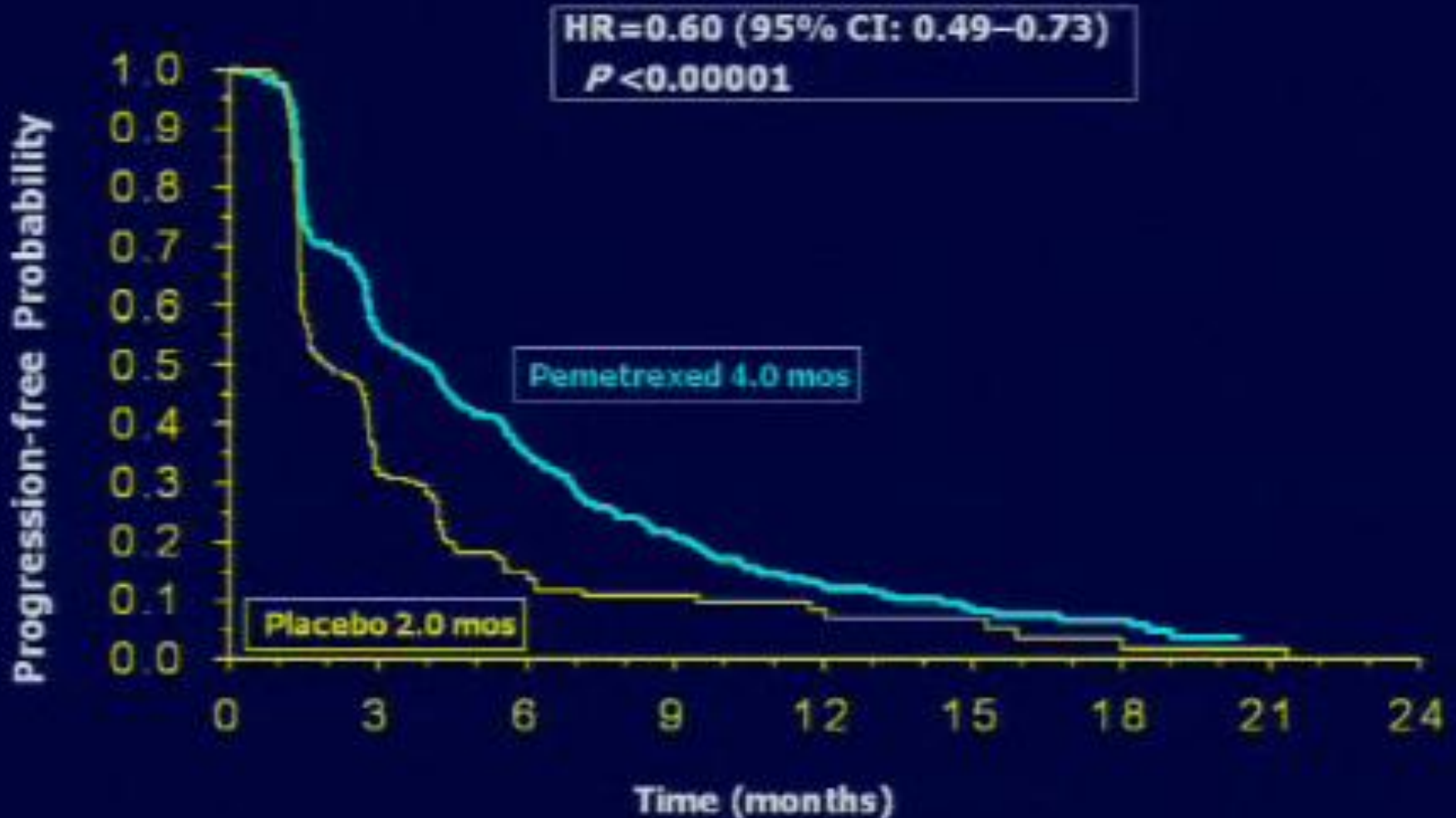
Maintenance Chemo	Pemetrexed (n=441)	Placebo (n=222)
# pts treated	434	222
Median # cycles	5 (1-34)	3.5 (1-30)
Dose reductions	5%	1%
Discontinuation due to toxicity	5%	1%
Pts completing ≥ 6 cycles	48%	28%
Pts completing ≥ 10 cycles	23%	9%
Dose intensity	96%	-
Median F/U time (mo)	12.0	10.1

Efficacy

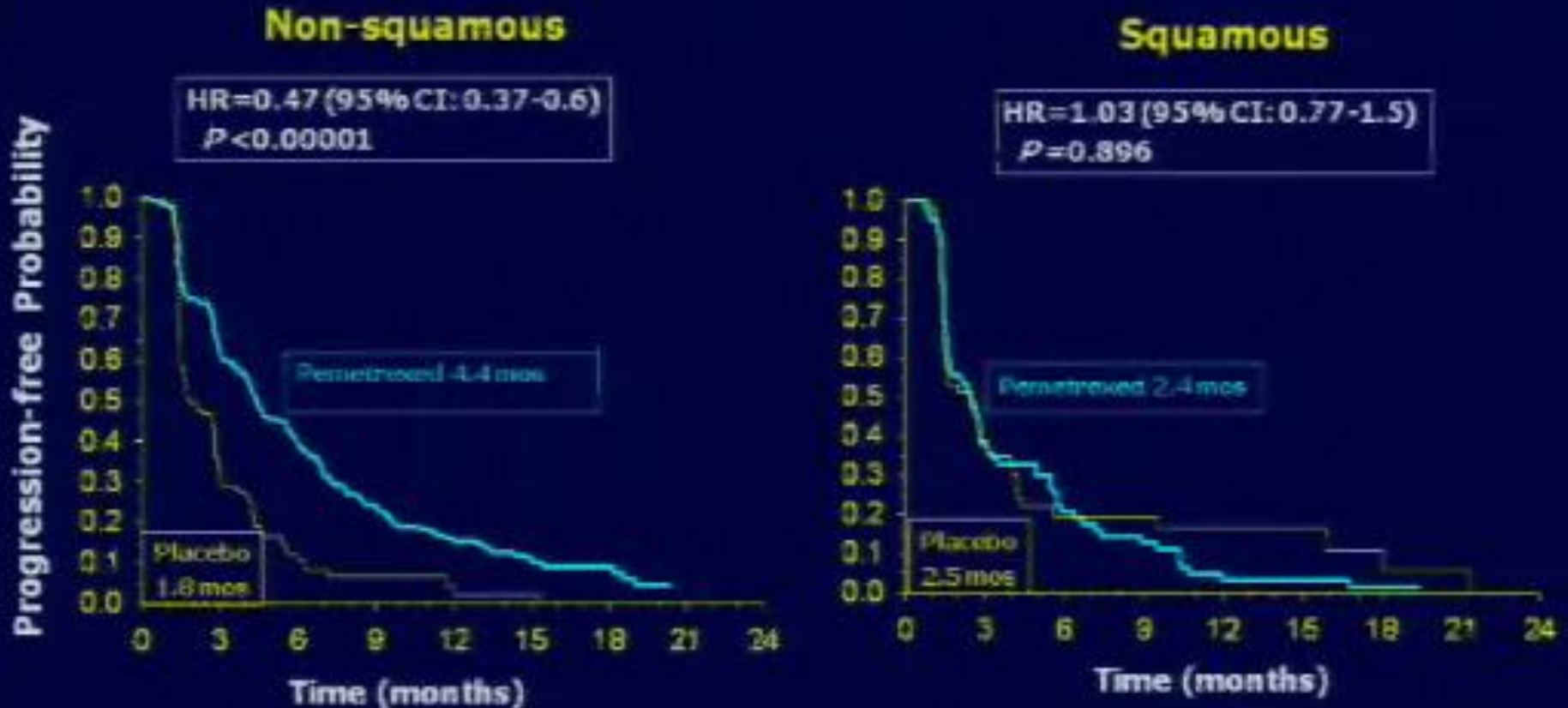
	CR + PR			CR + PR + SD		
	Pemetrexed	Placebo	P-value	Pemetrexed	Placebo	P-value
ITT (N=663)	3.4%	0.5%	0.042	49.1%	28.9%	<0.001

Response based on independent review (n=581)

Progression-free Survival



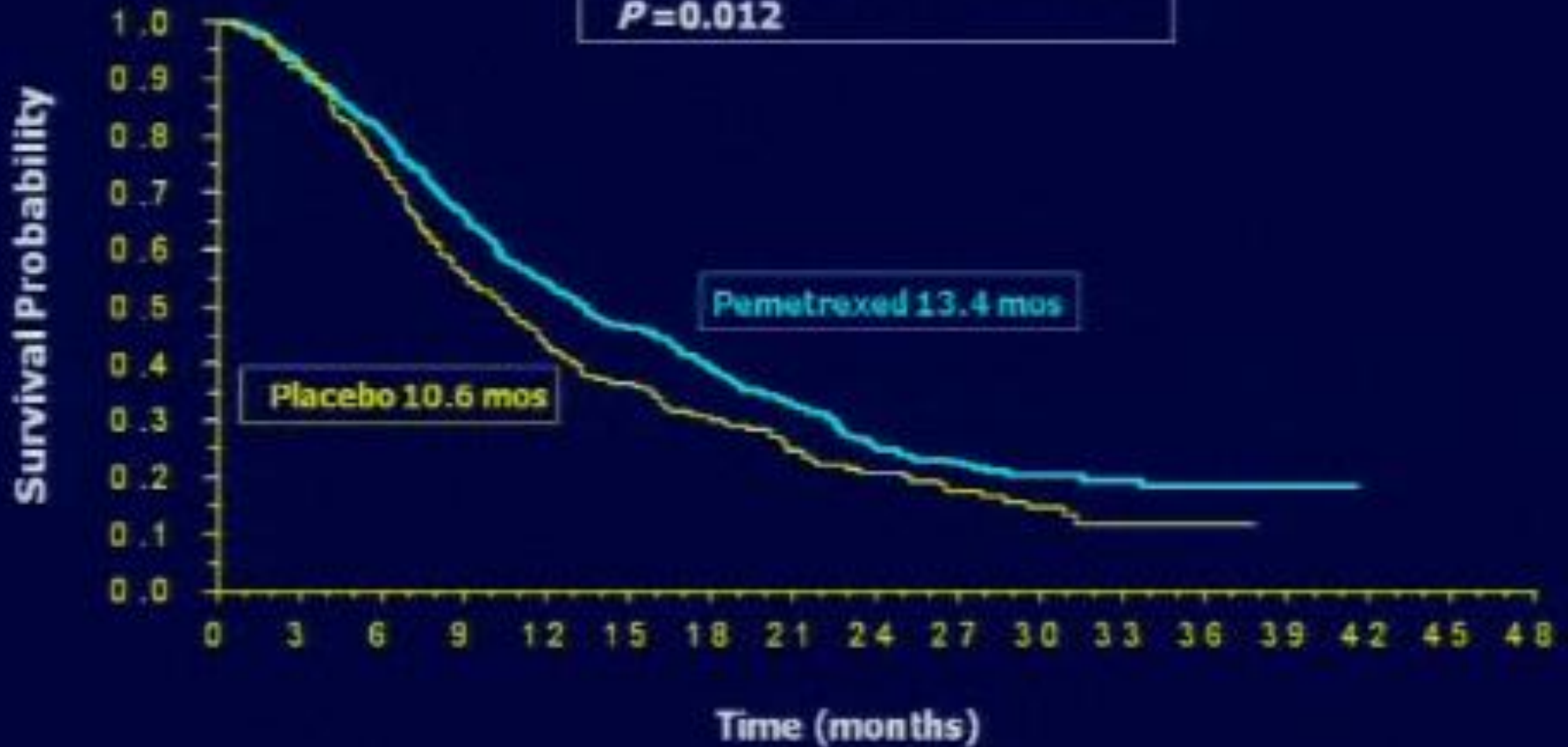
PFS by Histology



SCC have elevated thymidylate synthase levels and this may lead to drug resistance to pemetrexed. Pemetrexed is now only indicated for non-SCC NSCLC.

Overall Survival (ITT)

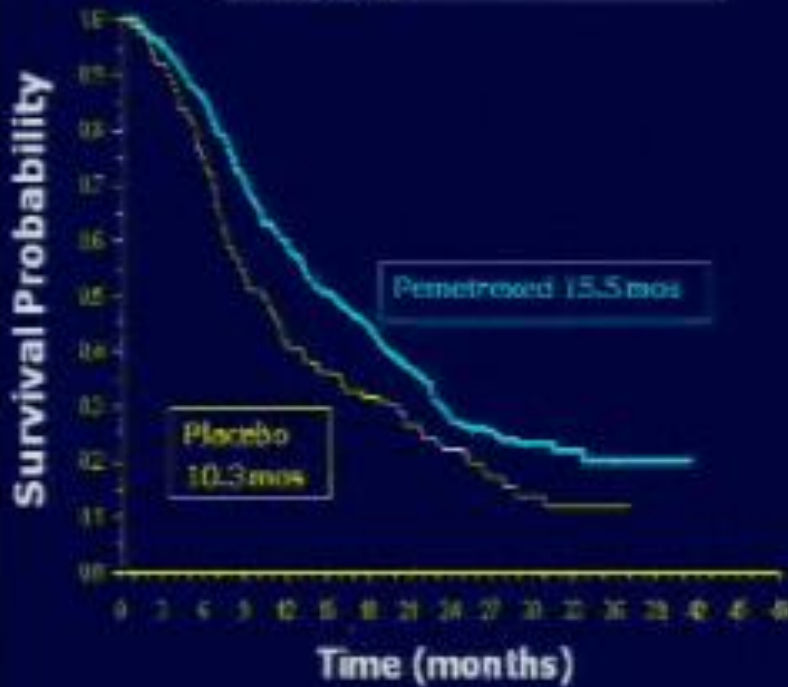
HR=0.79 (95% CI: 0.65–0.95)
P=0.012



OS by Histology

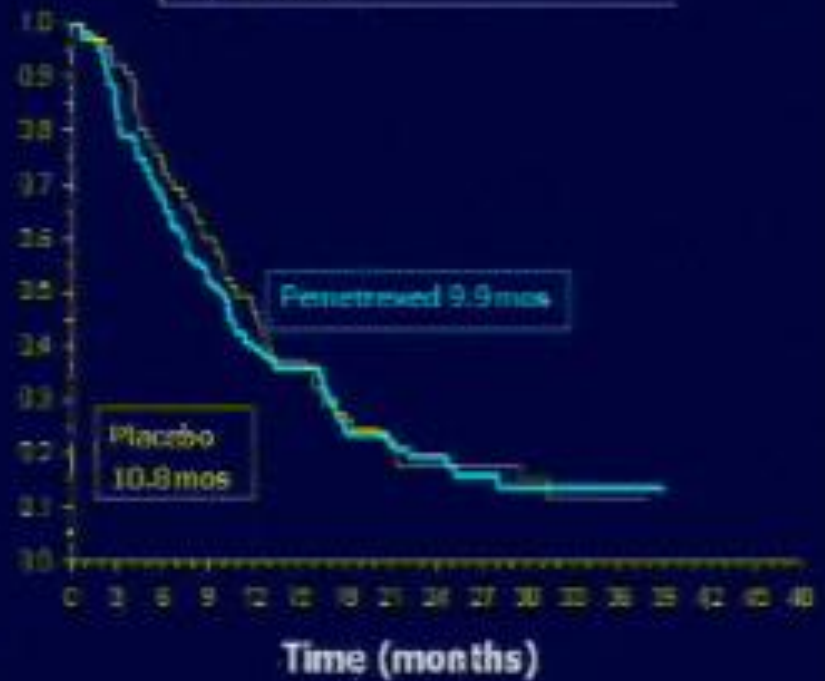
Non-squamous (n=481)

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



Squamous (n=182)

HR=1.07 (95% CI: 0.49-0.73)
P=0.678

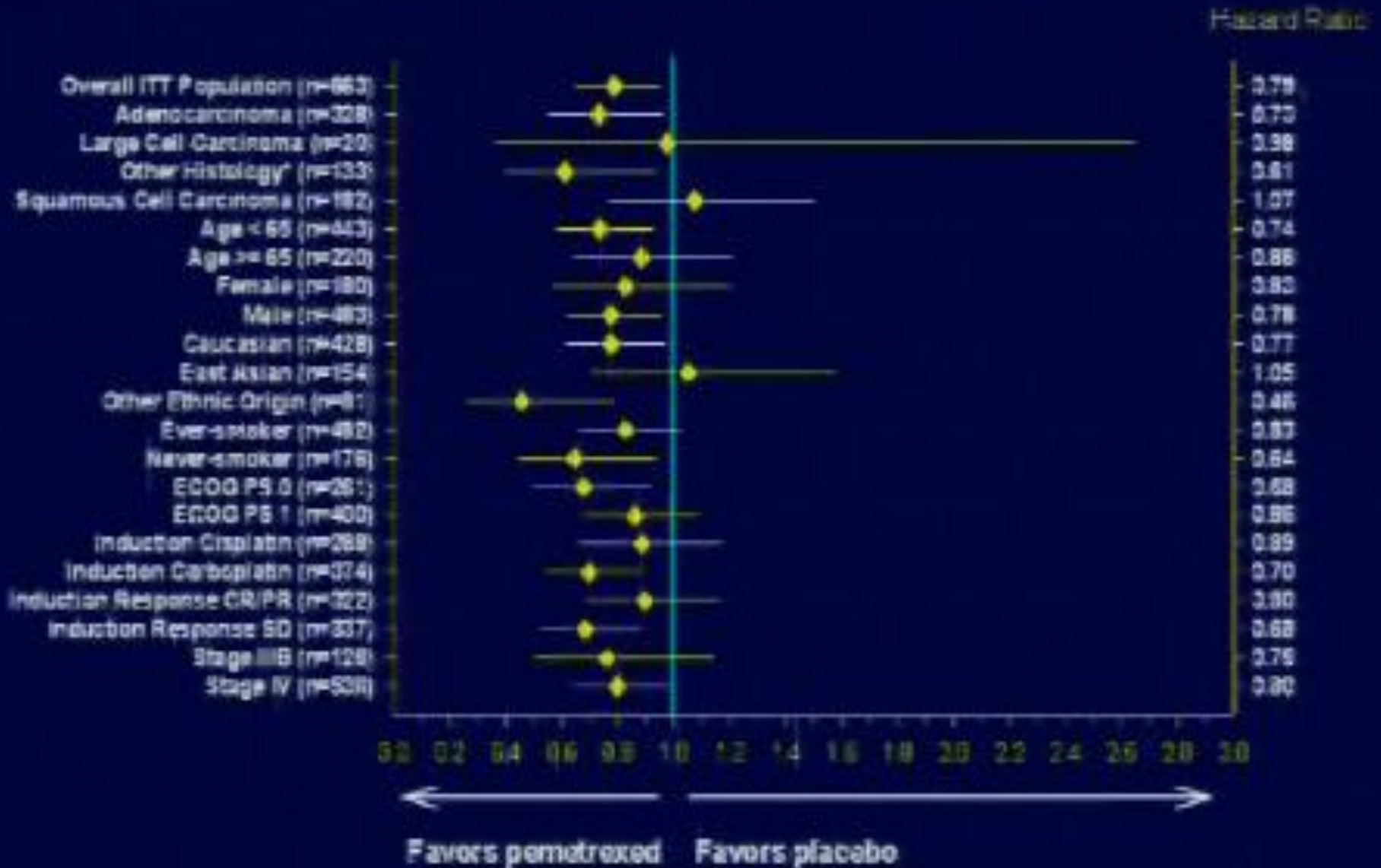


OS/PFS by Histology

Histology Groups	Median OS (months)			Median PFS (months)		
	Pemetrexed	Placebo	P-value	Pemetrexed	Placebo	P-value
Non-SCC (n=431)	15.5	10.3	0.002	4.4	1.8	<0.00001
Adeno (n=329)	16.8	11.5	0.026	4.6	2.7	<0.00001
Large cell (n=20)	8.4	7.9	0.964	4.5	1.5	0.104
Other (n=133)	11.3	7.7	0.025	4.1	1.6	0.0002
SCC (n=182)	9.9	10.8	0.678	2.4	2.5	0.896

Treatment by histology interaction by PFS (p=0.036) and OS (p=0.033)

OS – Subgroup analysis (ITT)



Post-study treatment

Treatment	Pemetrexed (n=441)	Placebo (n=222)
Post-study treatment	52%	67%
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%

Grade 3/4 Toxicity

Adverse Event	Pemetrexed (n=441)	Placebo (n=222)
Neutropenia	3%	0%
Anemia	3%	1%
Leukopenia	2%	1%
Fatigue	5%	1%
Anorexia	2%	0%
Infection	1%	0%
Diarrhea	1%	0%
Nausea	1%	1%
Vomiting	<1%	0%
Sensory neuropathy	1%	0%
Mucositis/stomatitis	1%	0%

Summary Abstract #8000

- Maintenance pemetrexed improves PFS and OS in patients with non-SCC NSCLC.
- This is the first phase III placebo-controlled maintenance trial to demonstrate this benefit.
- No new safety signals were seen.

Abstract LBA 8002: ATLAS

Chemotherapy* +
bevacizumab x 4
cycles
(N=1160)

Stratification: gender,
smoking history, PS,
chemo regimen

*Specified regimens:

Carbo or Cis / paclitaxel

Carbo or Cis / gemcitabine

Carbo or Cis / docetaxel

1:1 Randomization
non-PD patients
n=768 (66%)

Bevacizumab
(15 mg/kg) +
placebo

Bevacizumab +
erlotinib
(150 mg daily)

Unblinded
Post-progression
Therapy

1° End point: PFS

2° End points: OS; RR; safety

Exploratory: Biomarkers (IHC, FISH, K-ras & EGFR mutation)

Recently amended to include:

- Patients with previously treated intracranial metastases
- Peripheral and/or extrathoracic squamous NSCLC
- Therapeutic anticoagulation with low-molecular-weight heparins

ATLAS Patient Demographics

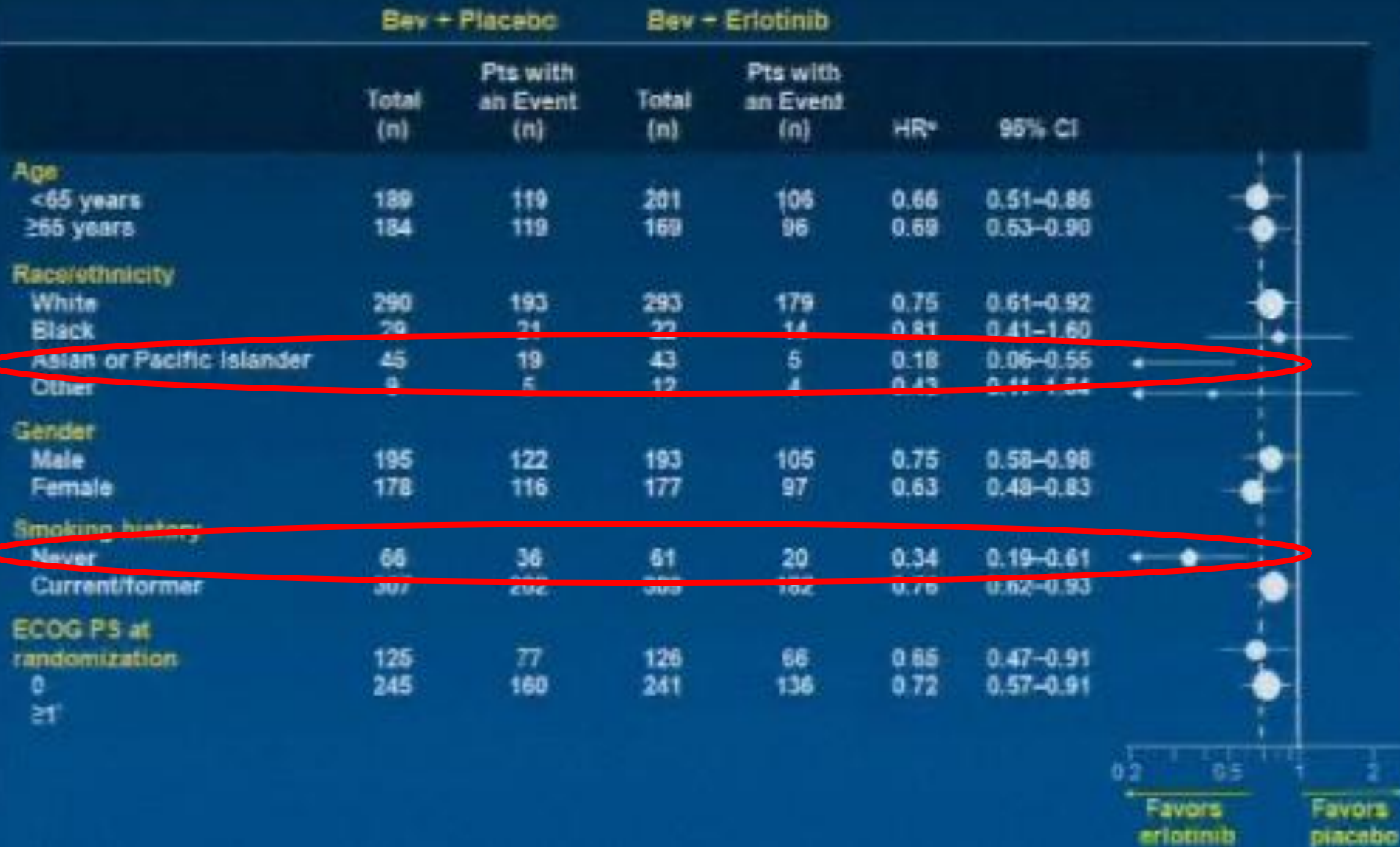
Characteristic	Bevacizumab + Placebo (n=373)	Bevacizumab + Erlotinib (n=370)
Median age	64	64
Male	52.3%	52.2%
Caucasian	77.7%	79.2%
Asian	12.1%	11.6%
Stage IIIB	10.2%	8.7%
IV	83.3%	85.6%
Recurrent	6.5%	5.7%
PS 0	46.1%	48.1%
Smoking: Never	17.7%	16.5%
Histology: Adeno	82.5%	81.3%
SCC	1.6%	3.0%
Prior XRT	15.3%	17.3%

ATLAS : PFS in ITT (assessed by investigators)

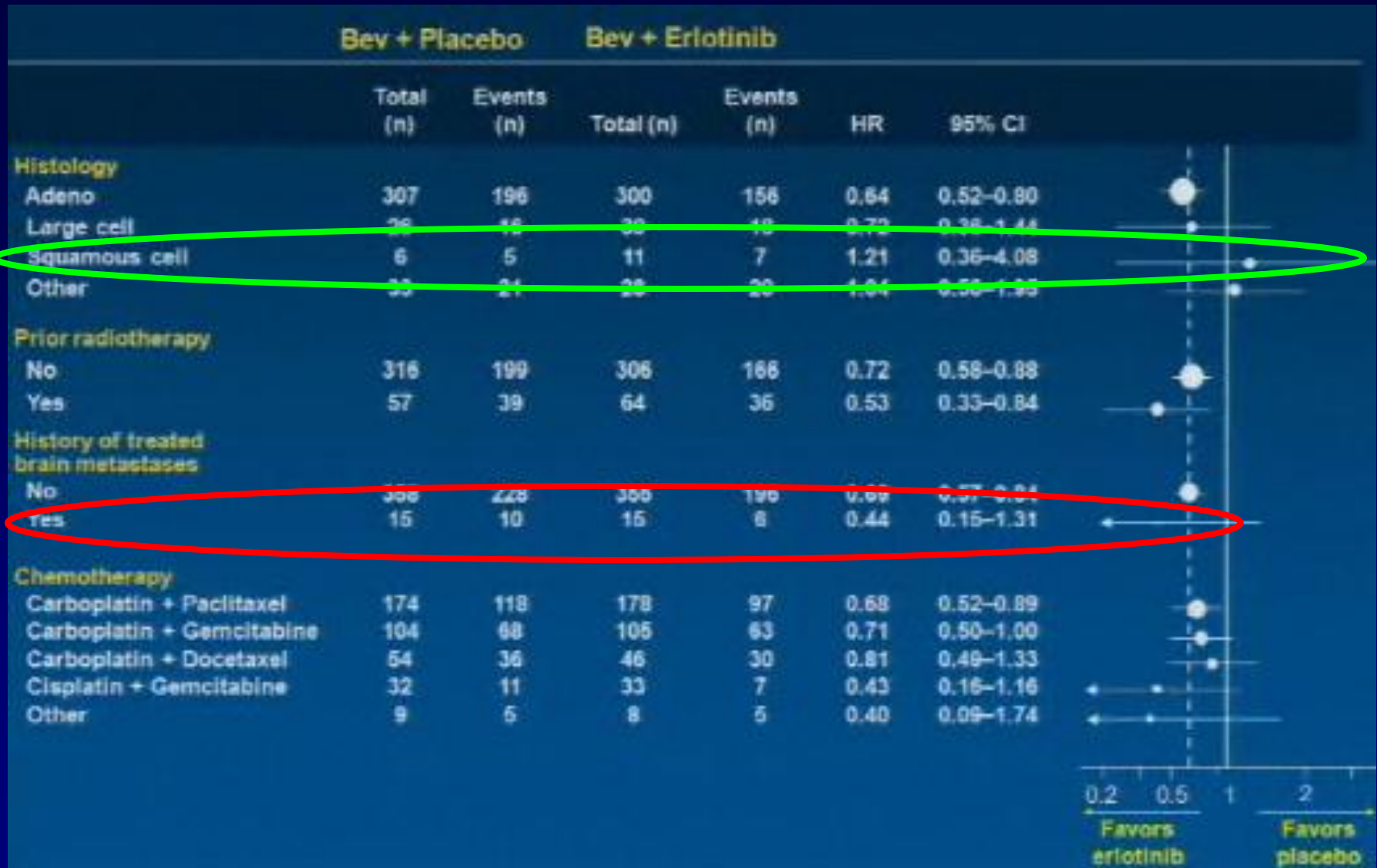


	Bev + P	Bev + Erlotinib
Median PFS	3.75 (2.83, 4.04)	4.76 (4.14, 5.52)
3 month PFS rate	53.4%	67.7%
6 month PFS rate	28.4%	40.3%

ATLAS PFS in Subgroups



ATLAS PFS in Subgroups



ATLAS: Subsequent Therapies

	Bev + Placebo (n=373)	Bev + Erlotinib (n=370)
Patients who received subsequent therapy	55.5%	50.3%
Anti-VEGF (bev)	39.9%	24.9%
EGFR-targeted (erlotinib)	39.7%	39.7%
Chemotherapy*	28.4%	33.2%
XRT	9.4%	6.8%
Investigational Therapy	4%	3.2%
Surgery/procedure	0.8%	0.3%

*pemetrexed was most commonly used

ATLAS Safety/Death after Chemotherapy

	Bev + Placebo (n=368)	Bev + Erlotinib (n=367)
Any Grade AE*	85.1%	95.1%
Grade 3-4 AE*	30.4%	44.1%
Grade 5 AE	1.1%	2.2%
Total number of deaths	30.4%	30.5%
<u>Cause of death:</u>		
Progression of cancer	29.3%	27%
Serious AE	1.1%	2.2%
Other	0%	1.4%

*Most common AE were rash and diarrhea

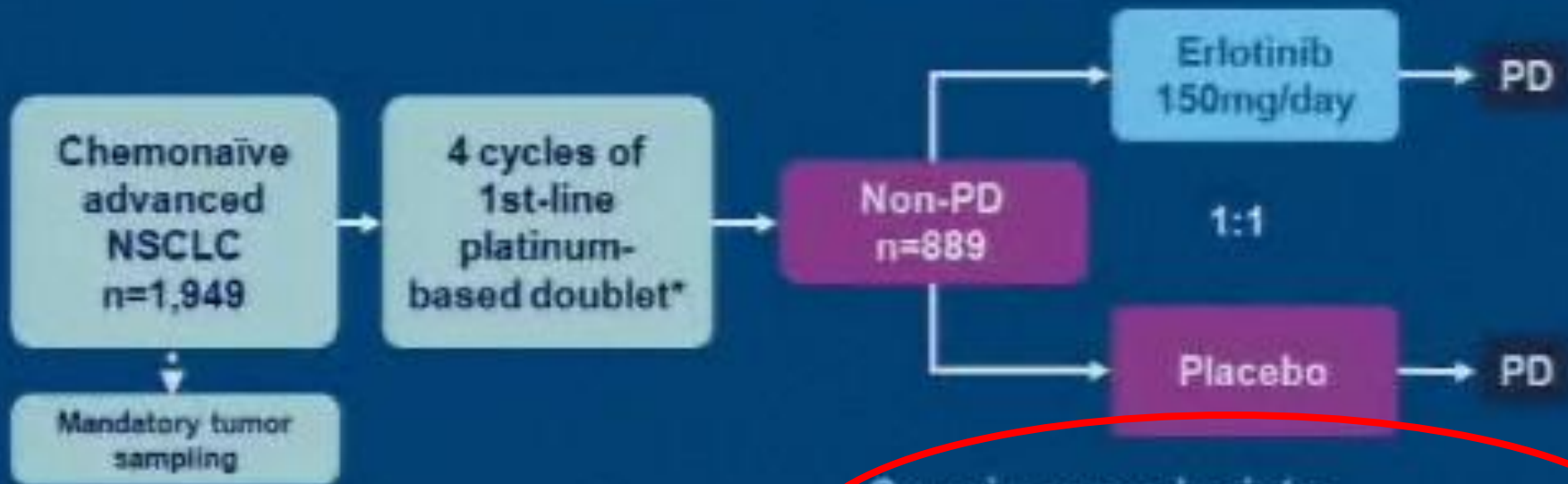
ATLAS Grade 3-4 Adverse Events

	Bev + Placebo (n=368)	Bev + Erlotinib (n=367)
Rash	0.5%	10.4%
Diarrhea	0.8%	9.3%
Infection	4.6%	4.1%
ILD-like event	0%	0.5%
Renal toxicity	0%	0.5%
Hepatic toxicity	0.3%	0.3%
Hemorrhage	1.4%	1.6%
Pulmonary hemorrhage	0.5%	0.8%
Proteinuria	1.9%	1.6%
Neutropenia	1.1%	0.5%
HTN	5.7%	5.4%
VTE	2.7%	1.1%
ATE	1.4%	2.2%

ATLAS Summary

- Erlotinib added to bevacizumab after 4 cycles of chemotherapy improved PFS (HR 0.722, $p=0.0012$)
 - Independent review of PFS underway
 - Await overall survival data later in 2009
 - Improvement in PFS was seen across multiple subgroups (especially Asians, never-smokers)
- No new safety signals
- Biomarker analysis are pending.

SATURN



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+ tumors

Secondary endpoints:

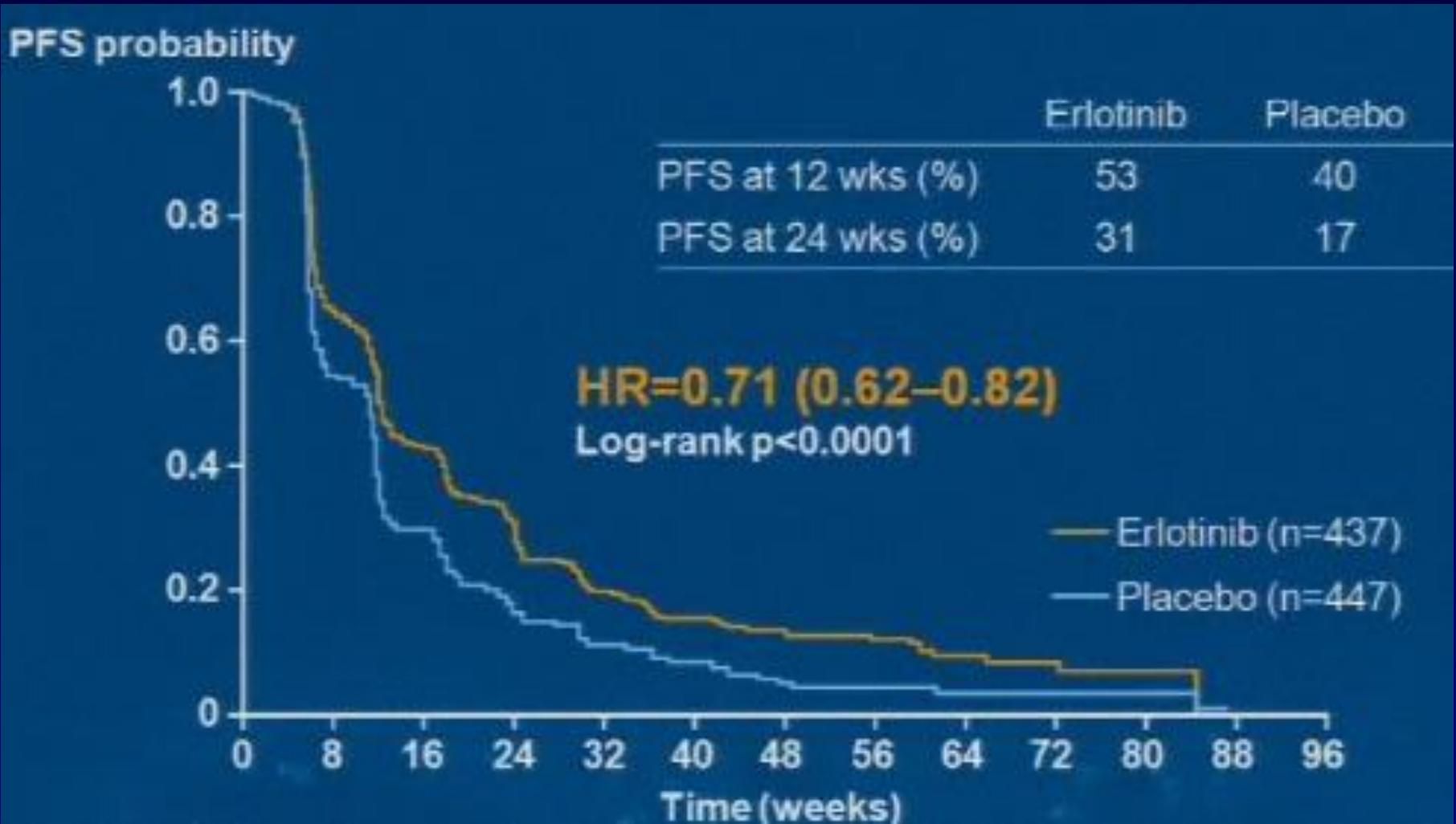
- Overall survival (OS) in all patients and those with EGFR IHC+ tumors; OS and PFS in EGFR IHC- tumors; biomarker analyses; safety; time to symptom progression; quality of life (QoL)

*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel; cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel; carboplatin/paclitaxel
EGFR = epidermal growth factor receptor; IHC = immunohistochemistry

SATURN Patient Demographics

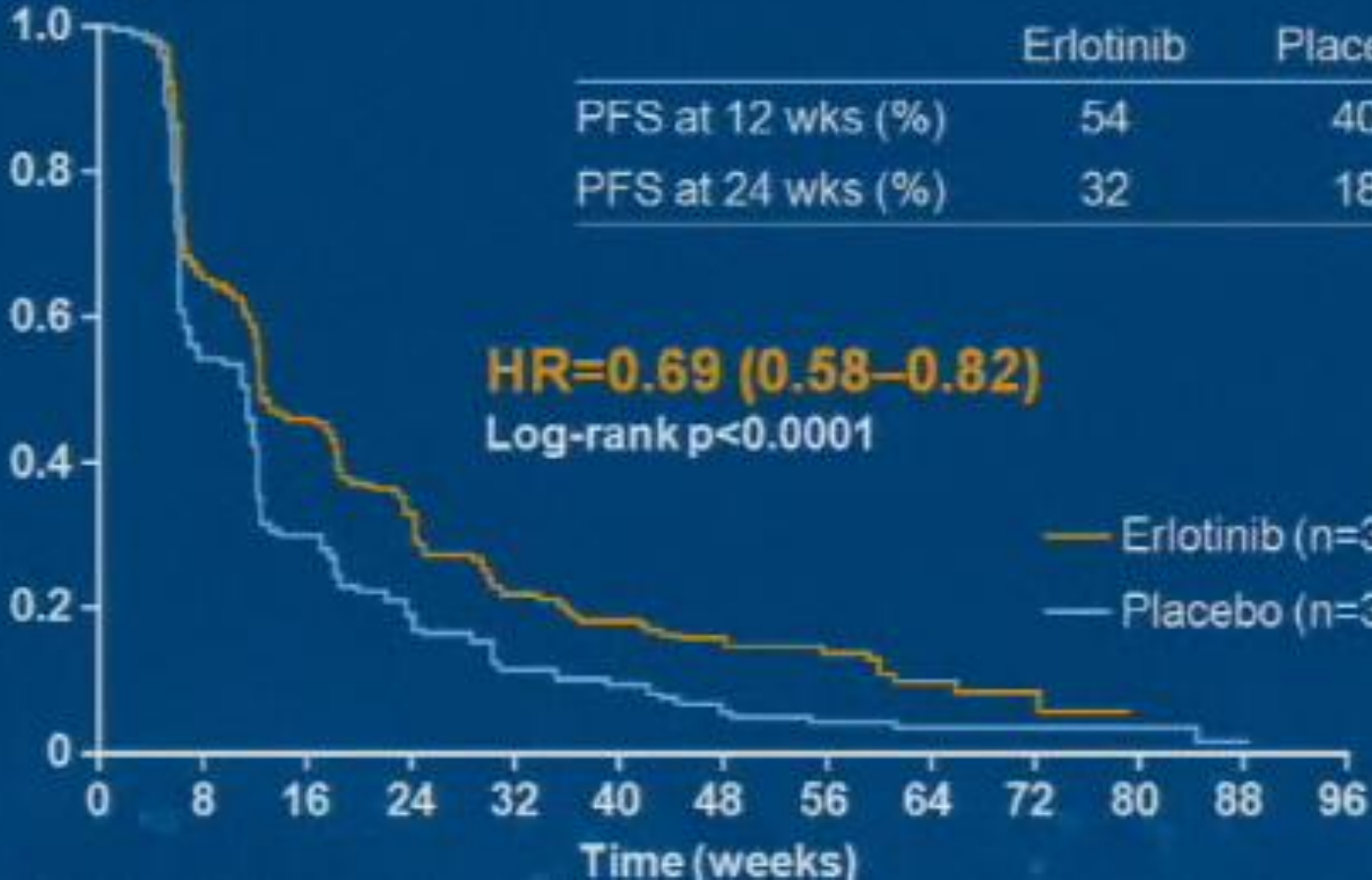
Characteristic	Erlotinib (n=438)	Placebo (n=451)
Median age	60	60
Male	73%	75%
Caucasian	84%	83%
Asian	14%	15%
Stage IIIB	26%	24%
IV	74%	76%
PS 0	31%	32%
Smoking: Never	18%	17%
Histology: Adeno	47%	44%
SCC	38%	43%
Chemo Response: CR	<1%	<1%
PR	42%	47%
SD	58%	52%

SATURN: PFS (ITT)



SATURN: PFS in EGFR IHC+ tumors

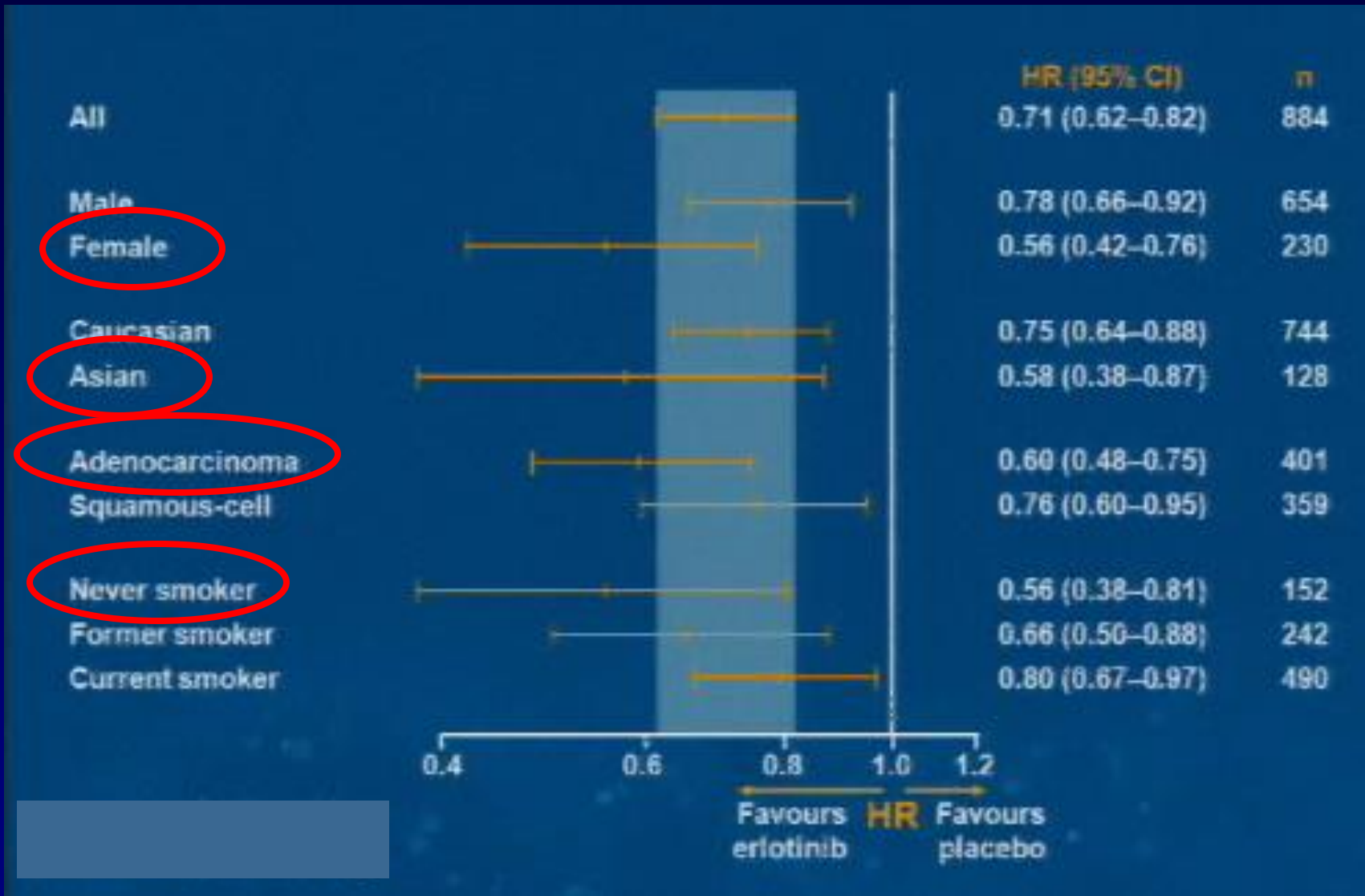
PFS probability



SATURN Efficacy

Efficacy	Erlotinib (n=438)	Placebo (n=445)	P-value
Response (CR/PR)	11.9%	5.4%	0.0006
Stable disease > 6 wks	48.6%	45.4%	NS
Disease control rate (CR+PR+SD)	60.6%	50.8%	0.0035
DCR \geq 12 wks	40.8%	27.4%	<0.0001

SATURN PFS Subgroup analysis

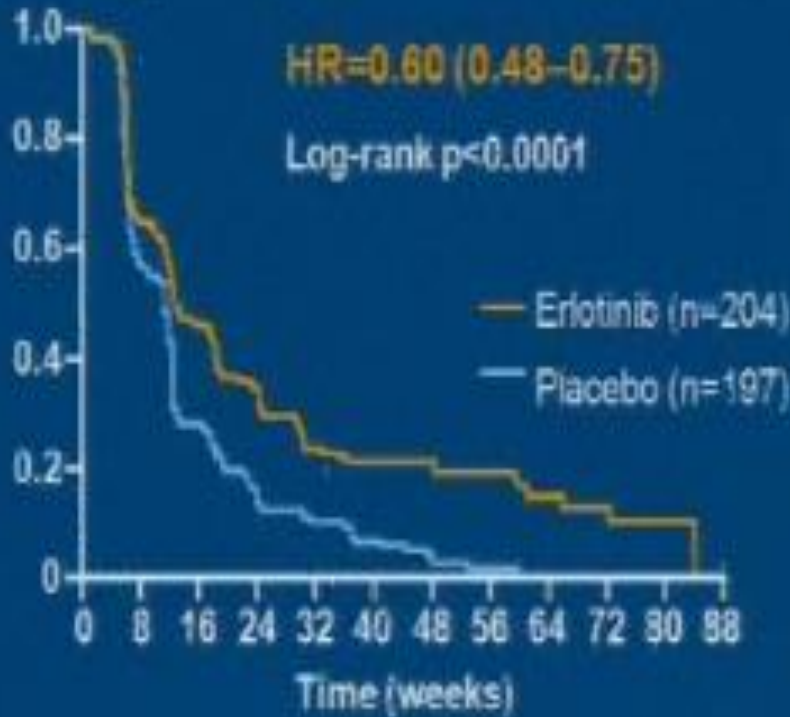


SATURN PFS by Histology

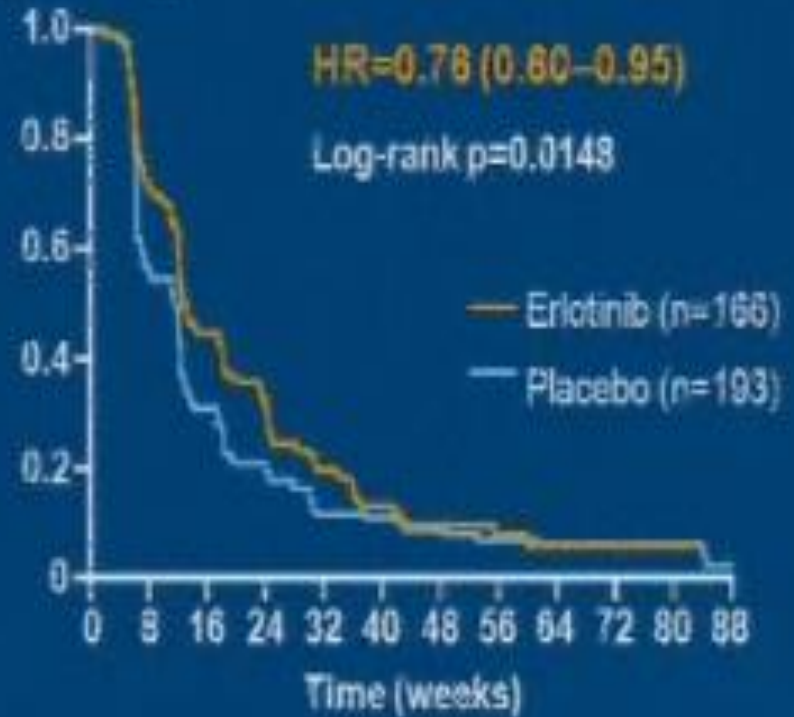
Adenocarcinoma

Squamous-cell carcinoma

PFS probability

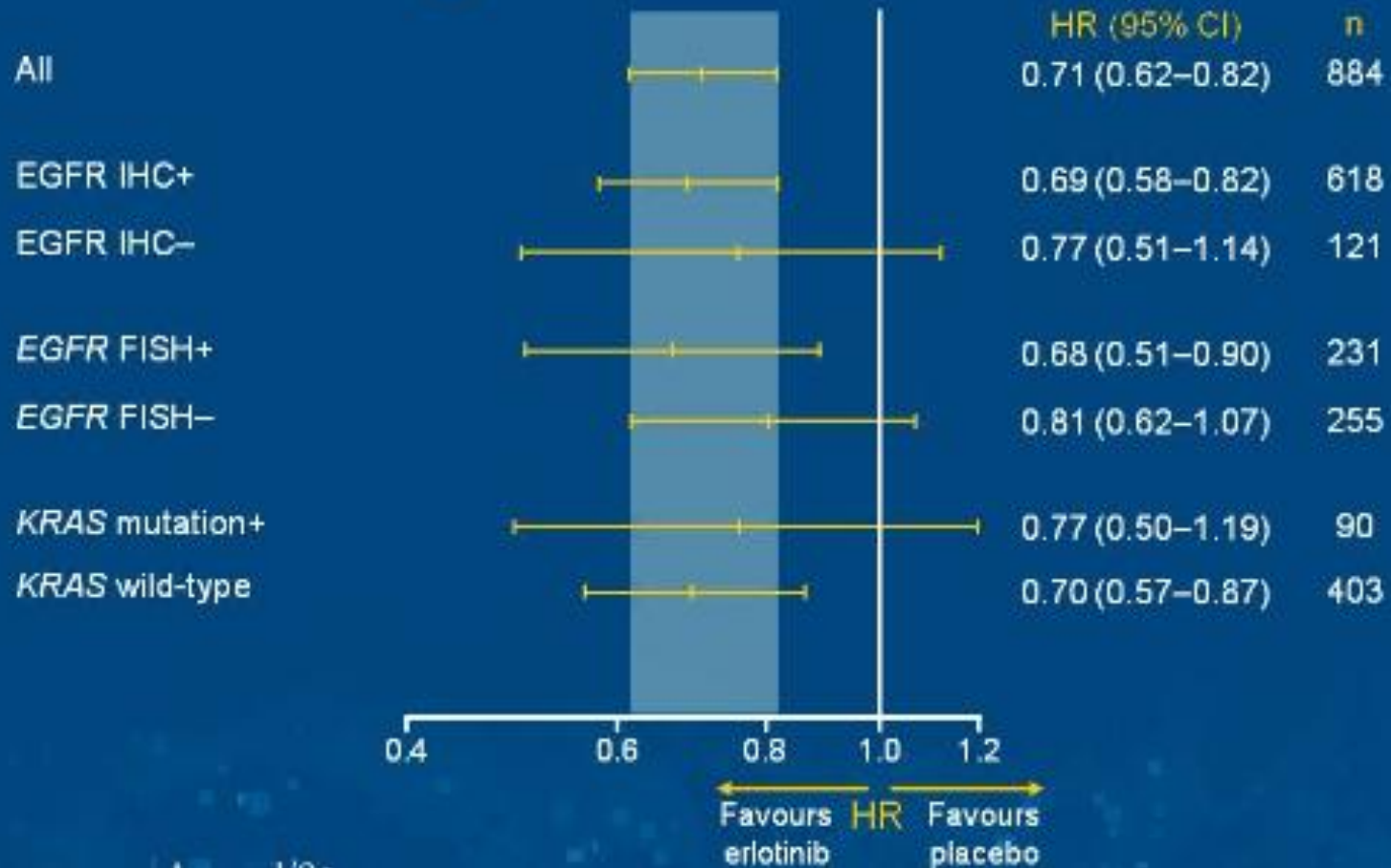


PFS probability



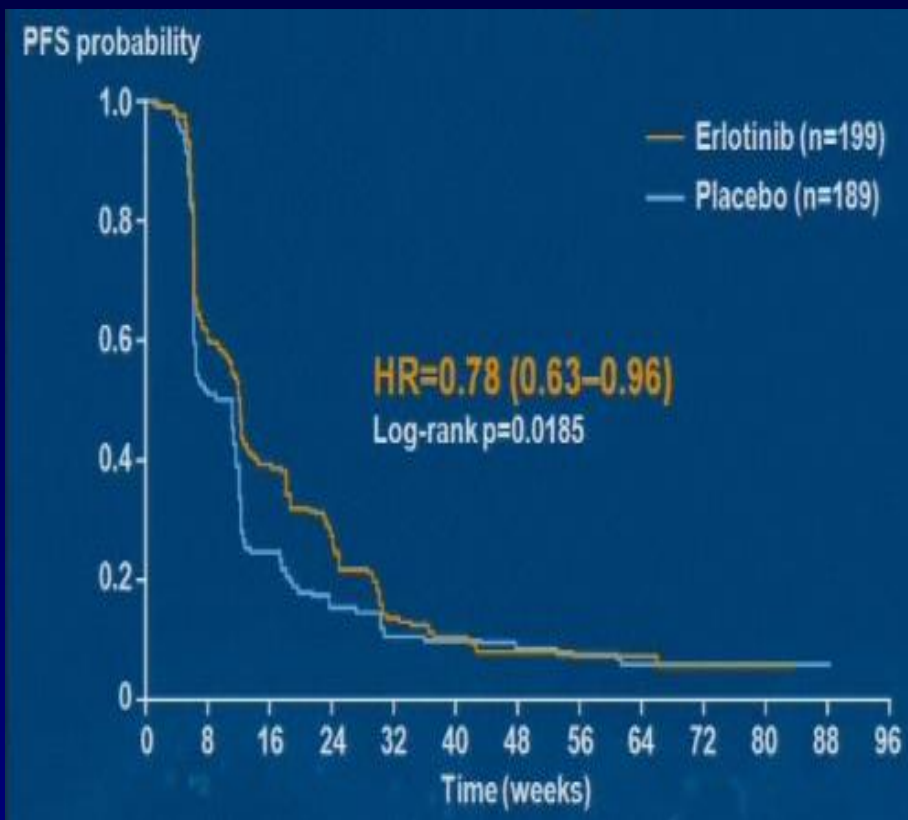
SATURN Biomarkers

PFS according to biomarker status

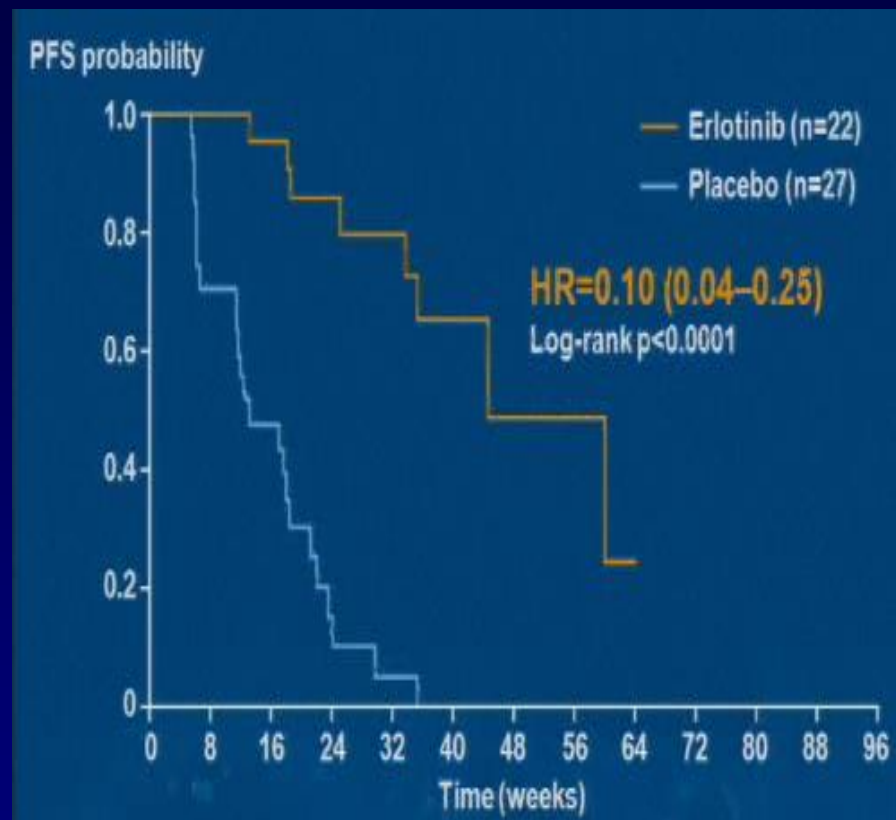


SATURN PFS by EGFR gene sequencing

EGFR Wild-Type Tumors



EGFR Mutation + Tumors



About 50% of all tumors were able to be sequenced for EGFR mutation.

SATURN Biomarkers

- EGFR IHC and FISH are not predictive for benefit from erlotinib
- Erlotinib yielded clinical benefit in both EGFR WT and EGFR mutation patients, although the mutant patients (n=22) had a low HR and thereby a greater magnitude of benefit.
- KRAS mutations are not predictive for treatment outcome to erlotinib therapy.

SATURN Toxicity

	Erlotinib (n=433)	Placebo (n=445)
Withdrawal due to any AE	5%	2%
Dose modification or interruption	16%	3%
Any Rash	60%	9%
Grade 3/4 Rash	9%	0%
Any Diarrhea	20%	4%
Grade 3/4 Diarrhea	2%	0%

No deterioration in QOL reported by FACT-L questionnaire.

No other AE occurring in $\geq 10\%$ of patients was reported.

SATURN Post-study treatment

	Erlotinib (n=438)	Placebo (n=451)
Any treatment	55%	64%
Taxanes	26%	27%
Antimetabolites (pemetrexed)	18%	20%
Antineoplastic agents	11%	15%
Tyrosine-kinase inhibitor	5%	16%
Platinum compounds	8%	11%

Summary Abstract #8001 SATURN

- SATURN met both co-primary endpoints of improved PFS with erlotinib maintenance over placebo in unselected patients (improved 41%) and in patients with EGFR IHC+ tumors
 - PFS benefit extends across most subgroups
- Current biomarker analysis are not informative for predictive benefit to erlotinib, although EGFR mutation patients may have a greater magnitude of benefit than EGFR WT patients.
- Await overall survival information
- No new safety signals

Summary Maintenance Therapy Trials NSCLC

Trial	Agent	PFS benefit	Overall OS benefit	Subgroup greater OS benefit
Ciuleanu et al.	Pemetrexed	Yes	Yes	Non-SCC
WJTOG	Gefitinib	Yes	No	AdenoCA
Fidias et al.	Docetaxel	Yes	No – but trend seen	NR
ATLAS	Bevacizumab + Erlotinib	Yes	?	?
SATURN	Erlotinib	Yes	?	?
Meta-analysis	Chemo	Yes	No	No

Maintenance Treatment

- **At this time, maintenance therapy after frontline chemo is not the standard practice. PFS appears to be improved but OS remains to be seen.**
- **Certain subgroups of patients may benefit: Japanese adenoCA (gefitinib), non-SCC (pemetrexed), EGFR mutation (erlotinib)**
- **For unselected NSCLC patients, regimens incorporating novel therapies already have maintenance with a targeted agent built in (i.e. E4599 - bevacizumab, FLEX – cetuximab, platinum-pemetrexed-bevacizumab).**
- **Future studies are needed to molecularly identify patients who will benefit from maintenance targeted therapy.**

July 2, 2009

FDA approves pemetrexed maintenance

- **On July 2, 2009, the U. S. Food and Drug Administration (FDA) approved pemetrexed injection for maintenance treatment of patients with locally advanced or metastatic non-SCC NSCLC whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy.**
- **This approval is the 3rd approved indication for pemetrexed in non-SCC NSCLC. Pemetrexed is not indicated for the treatment of patients with SCC NSCLC.**

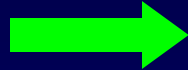
Outline

**Neoadjuvant
& Adjuvant
Chemo**



**Abstract 7500 NATCH trial
Abstract 7501 JBR.10 trial**

ChemoXRT



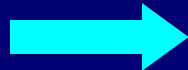
**Abstract 7505 CALGB 30407 (C225)
Abstract 7503 E3598 (thalidomide)**

Maintenance



**Abstract 8000 pemetrexed
Abstract 8001 SATURN (erlotinib)
Abstract 8002 ATLAS (bevacizumab \pm
erlotinib)**

**Metastatic
Salvage -
Vandetanib**



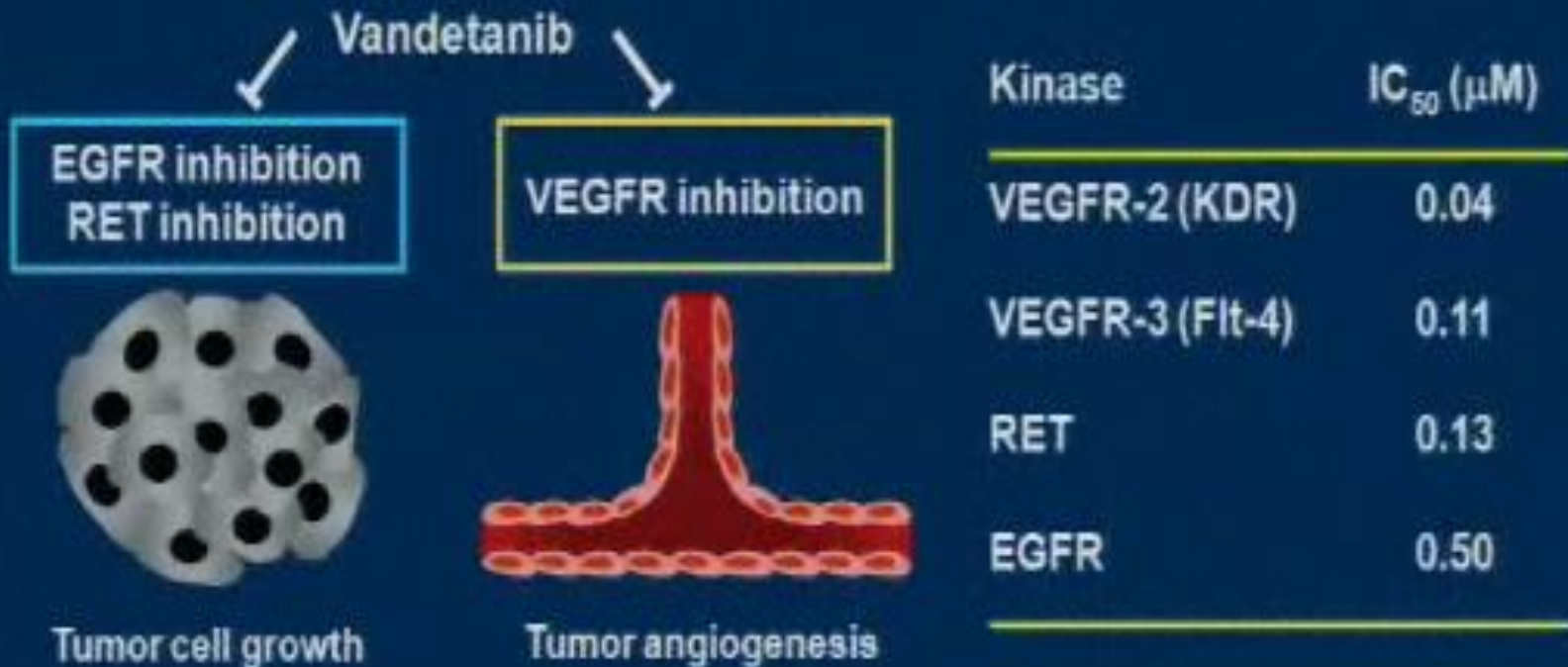
**Abstract CRA 8003 ZODIAC
Abstract 8009 ZEST
Abstract 8010 ZEAL**

Biomarkers



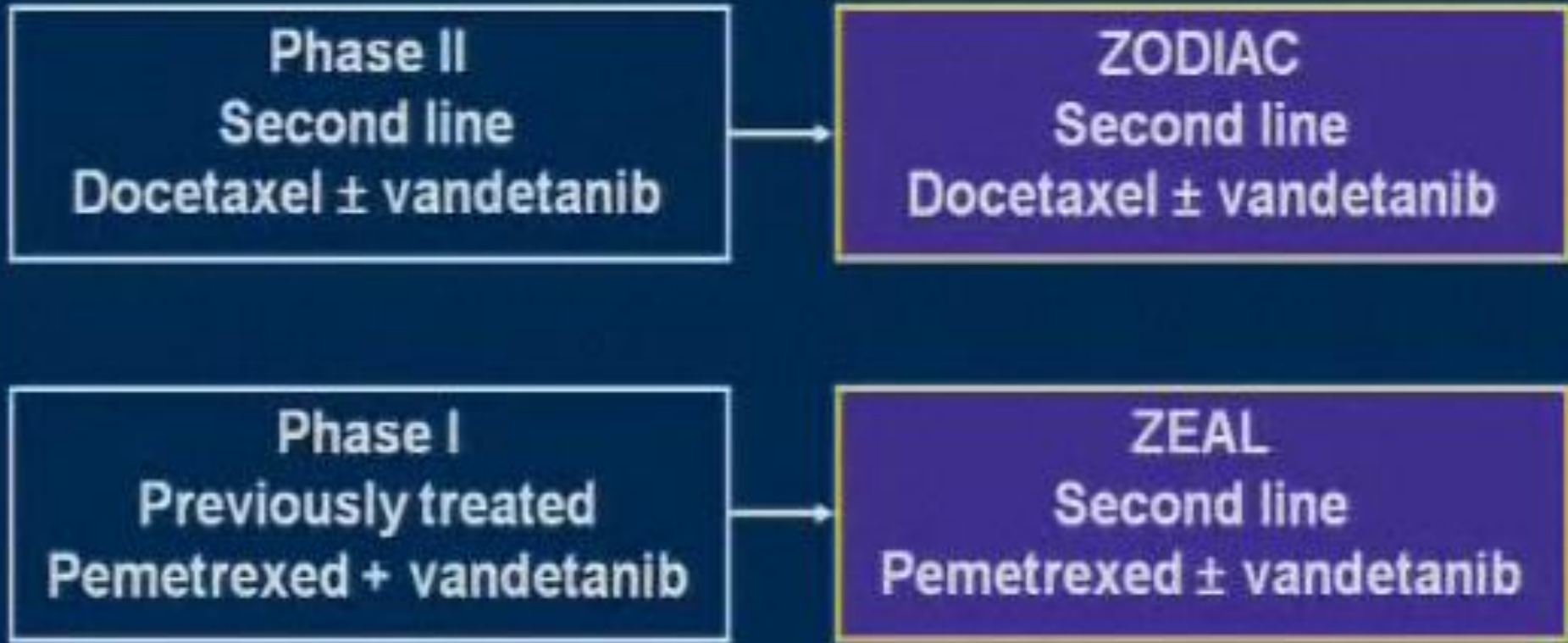
**Abstract 8006 I-PASS (EGFR mutation)
Abstract 8007 FLEX (EGFR FISH)**

Vandetanib



- A once-daily oral agent that targets VEGFR and EGFR signaling¹
- Preclinical data suggest vandetanib has potential to inhibit VEGFR and EGFR signaling in the clinic at doses of 100 mg/day²

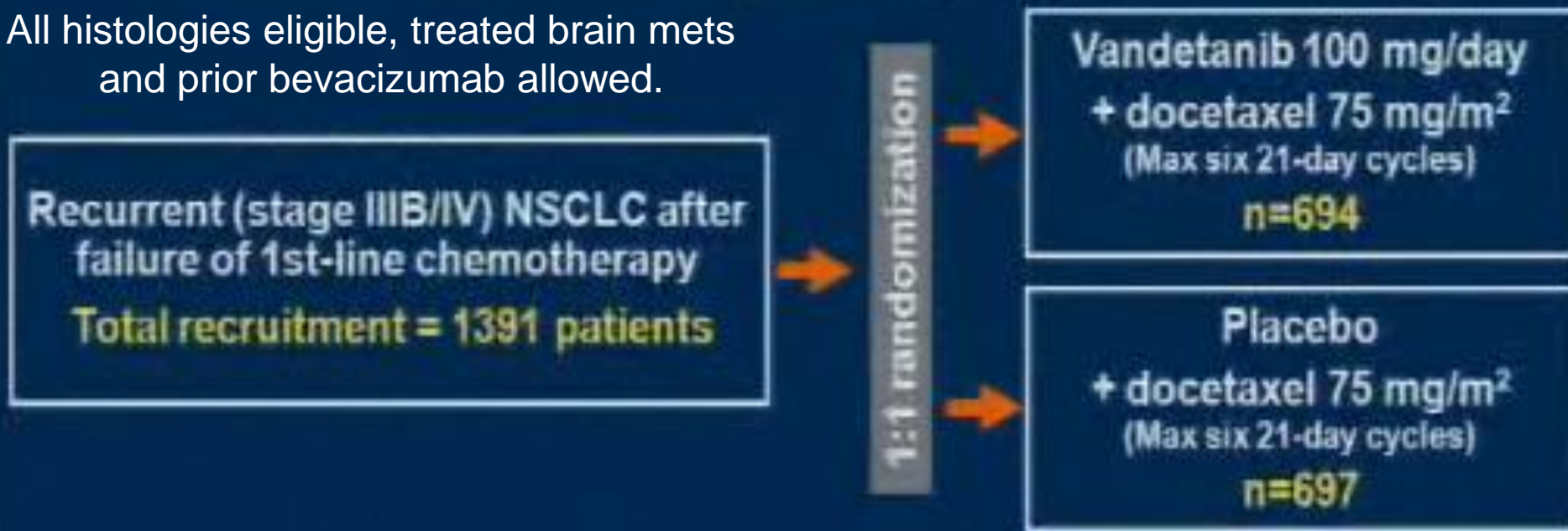
Phase III Vandetanib trials 100 mg



Abstract # 8003 ZODIAC

ZACTIMA in cOmbination with Docetaxel In non-smAll cell lung Cancer (ZODIAC)

All histologies eligible, treated brain mets and prior bevacizumab allowed.



Primary endpoint: PFS, efficacy/safety in women

Secondary endpoint: OS, RR, DCR \geq 6 wks, safety/toxicity, TDS

Stats: >90% power to detect 25% prolongation PFS (HR < 0.80)

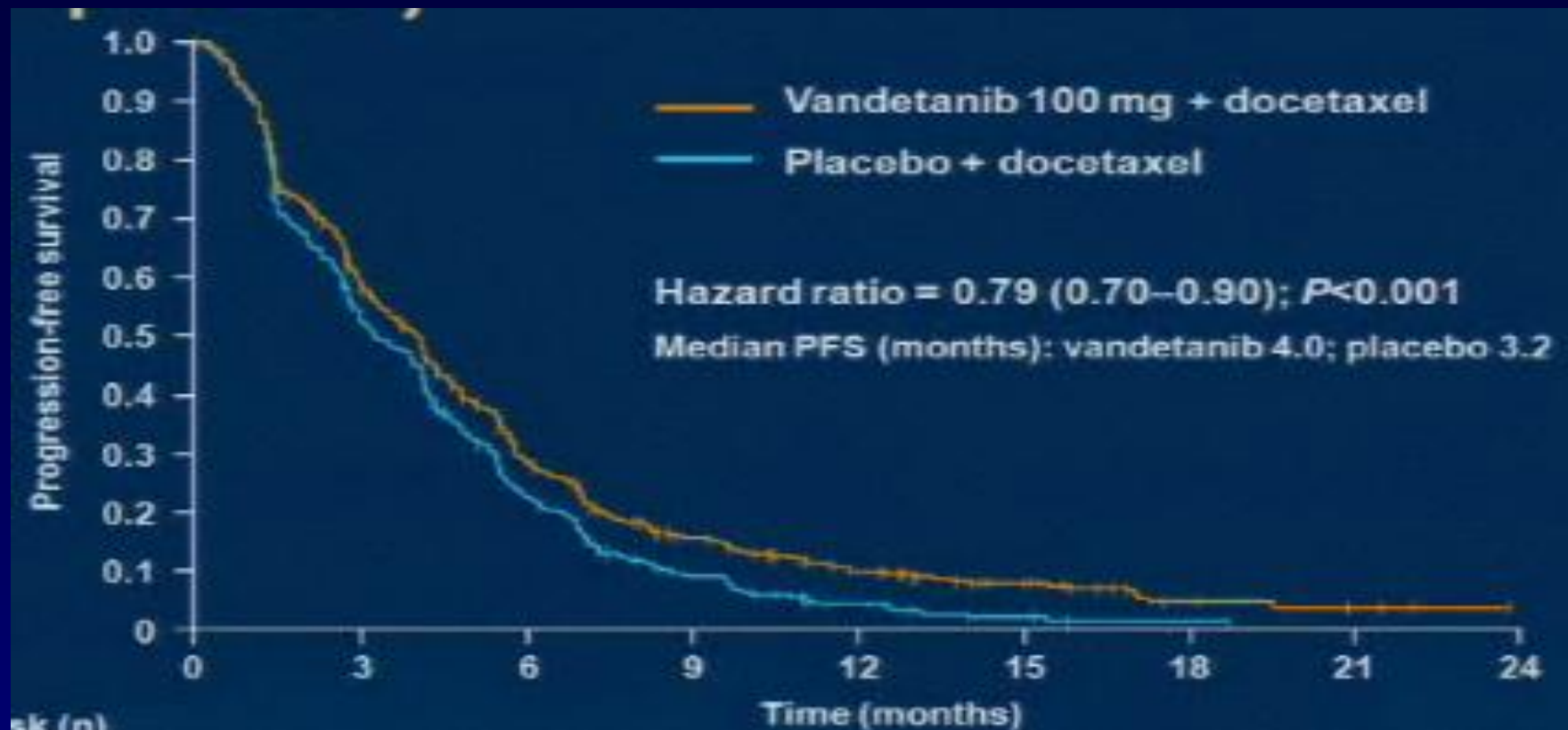
ZODIAC Patient Characteristics

Characteristic	Vandetanib + Docetaxel (n=694)	Docetaxel (n=697)
Median age	59	59
Male	72%	68%
Caucasian/Asian	59%/37%	60%/36%
Stage IIIB/IV	14%/86%	15%/85%
PS 0/1	36%/63%	34%/65%
Smoking: Never	23%	25%
Histology: Adeno	59%	60%
SCC	27%	23%
other	14%	17%
Brain mets	9%	11%
Prior bevacizumab	3%	3%

ZODIAC Efficacy

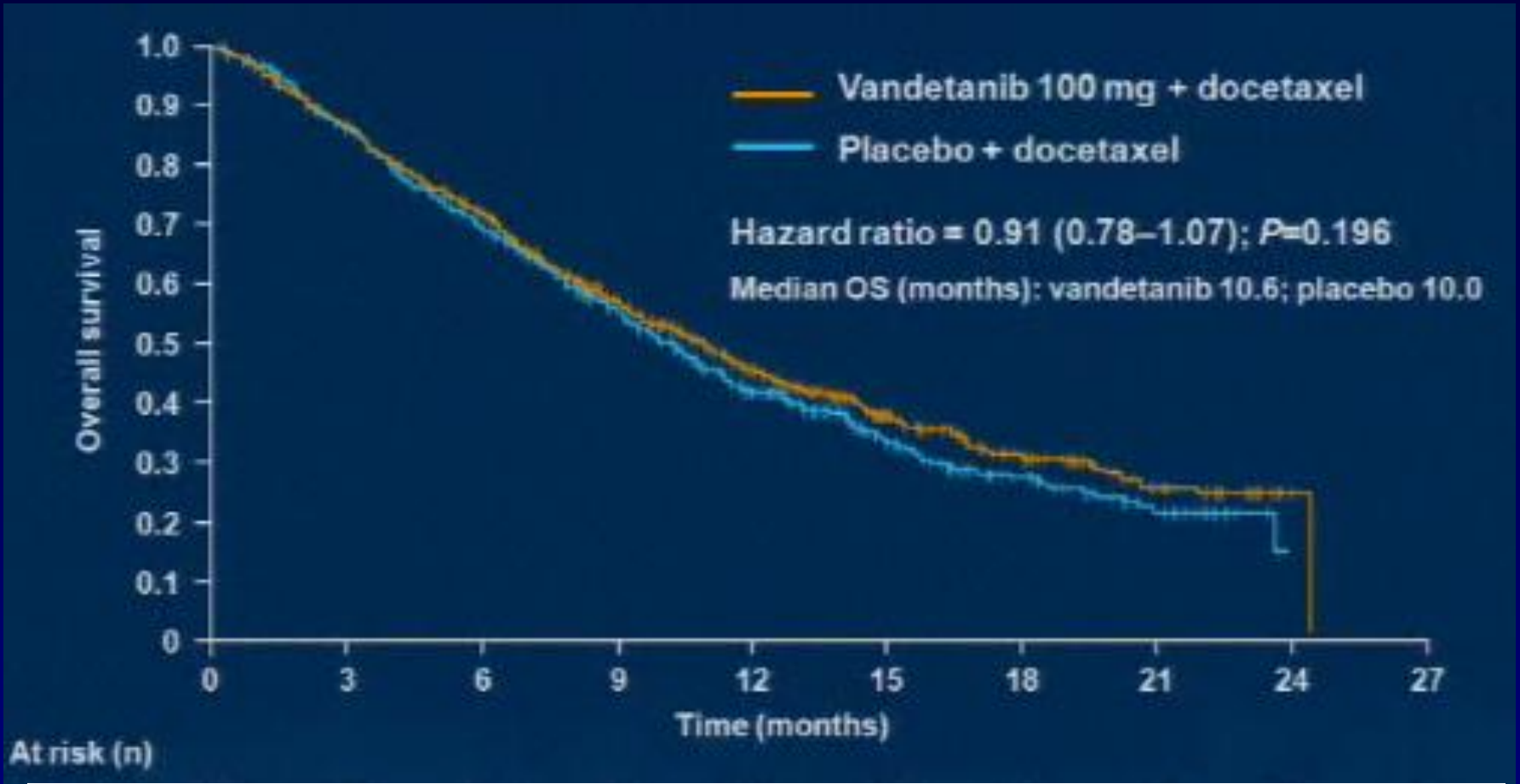
	Vandetanib + Docetaxel (n=694)	Docetaxel (n=697)	HR	P-value
RR	17%	10%	--	<0.001
DCR \geq 6 wks	60%	55%	--	0.06
Median PFS (months)	4	3.2	0.79	<0.001
% PFS at 6 months	28%	22.2%	--	--
Median OS (months)	10.6	10	0.91	0.196
%1 year survival	44.7%	41.2%	--	--

ZODIAC PFS



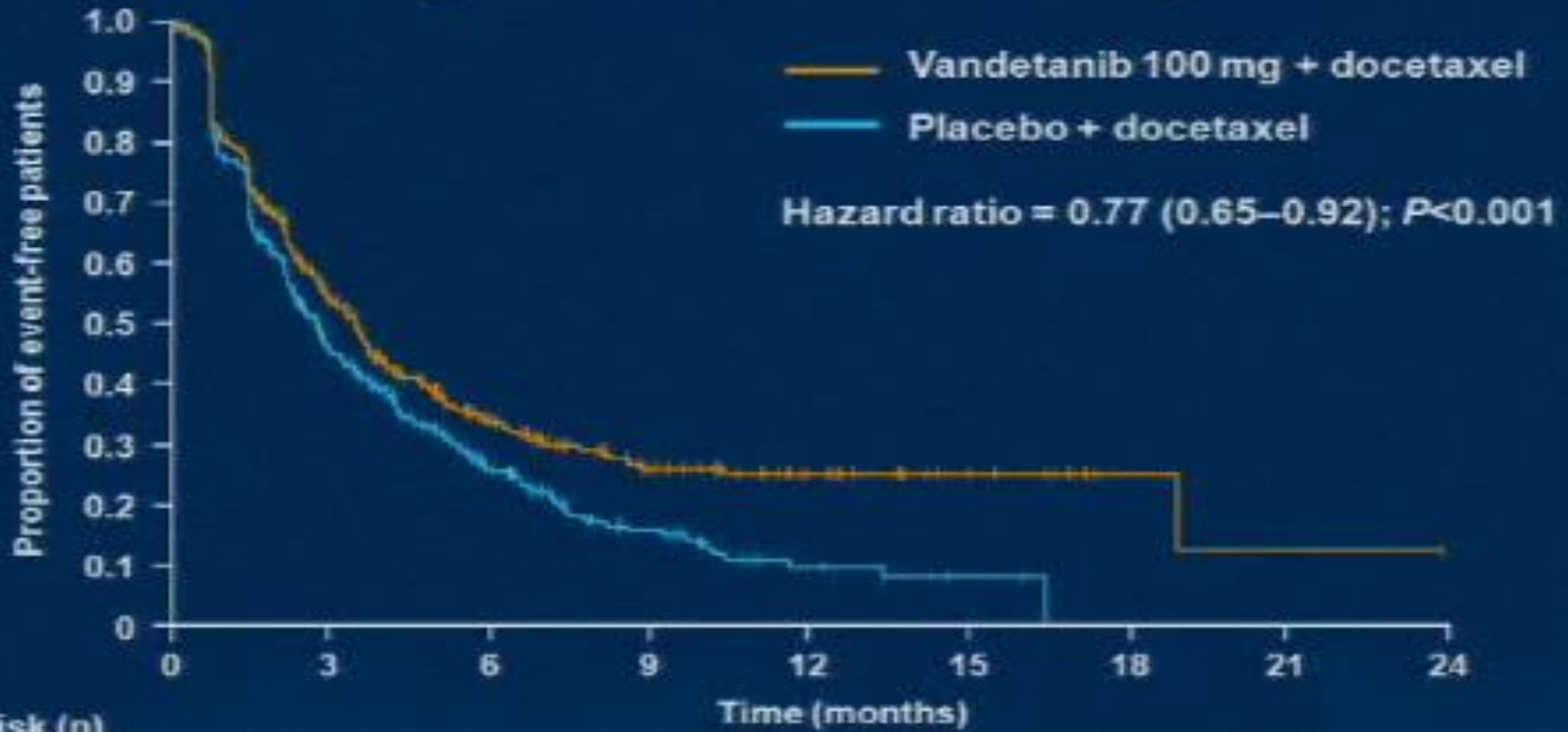
Women only (n=421)	Vandetanib +Docetaxel	Docetaxel	P-value
Median PFS (months)	4.6	4.2	HR 0.79; P=0.024
% PFS at 6 months	33.9%	29.6%	--

ZODIAC OS



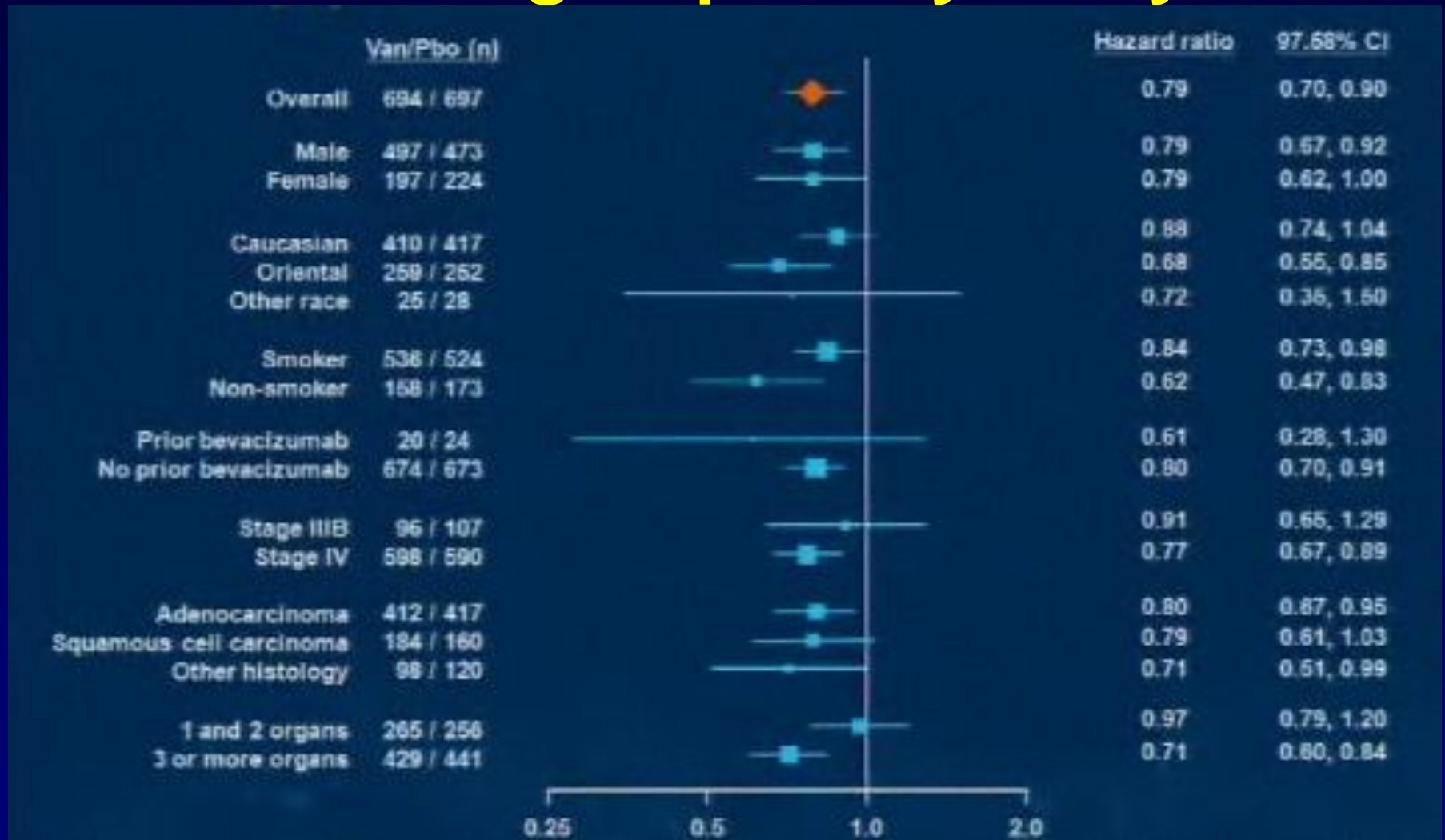
Women only (n=421)	Vandetanib +Docetaxel	Docetaxel	P-value
Median OS (months)	12.7	14.2	HR 0.96, p=0.759
1-year OS rate	33.9%	29.6%	--

ZODIAC Time to Deterioration of Symptoms (TDS) using FACT-L Lung Cancer Subscale



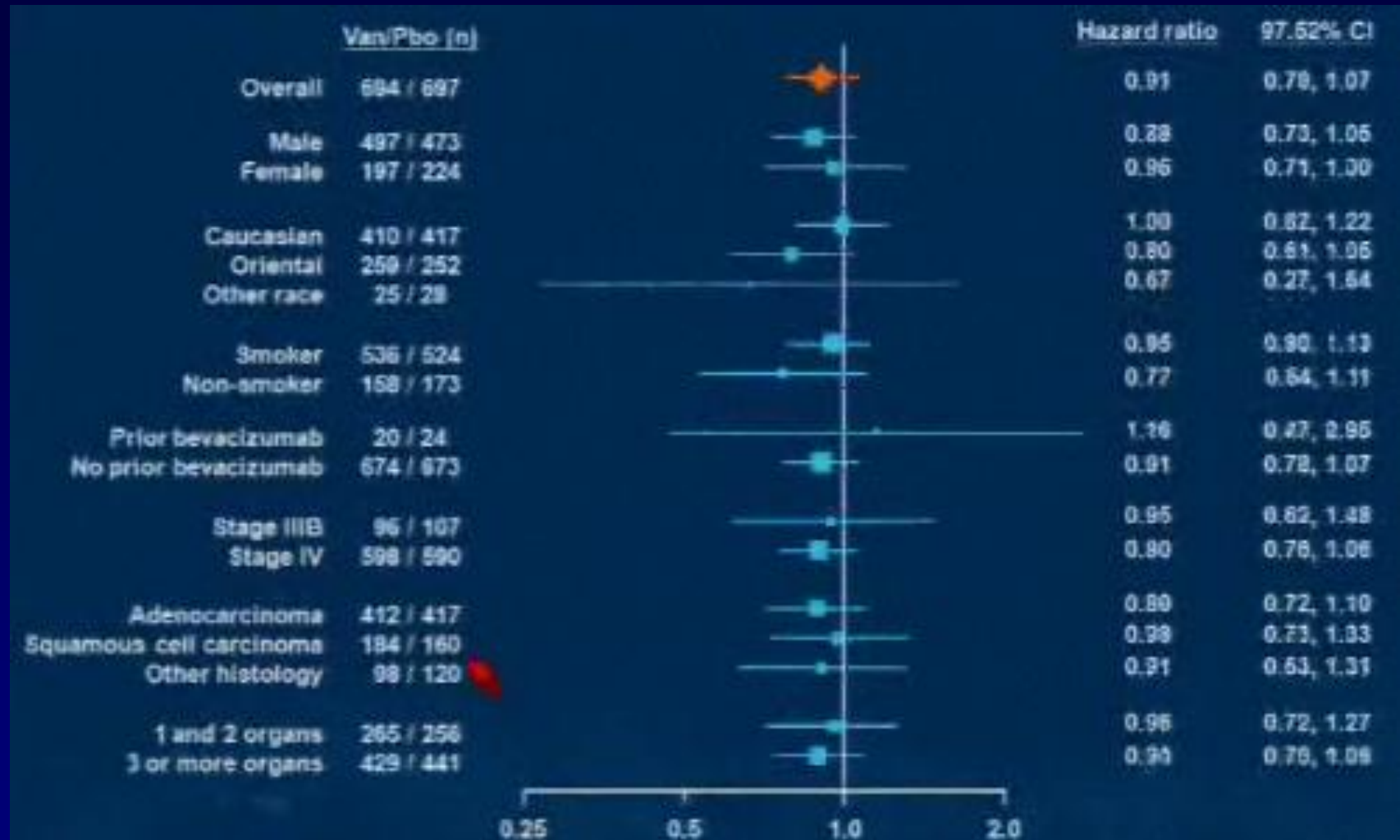
Vandetanib-docetaxel improved TDS over docetaxel alone.

ZODIAC Subgroup Analysis by PFS



Favors vandetanib

ZODIAC Subgroup Analysis by OS



Favors vandetanib

ZODIAC Grade 3+ Adverse Events

	Vandetanib + docetaxel (n=689)	Docetaxel (n=690)
Neutropenia	29%	24%
Leukopenia	14%	11%
Febrile neutropenia	9%	7%
Rash	9%	1%
Dyspnea	6%	7%
Fatigue	5%	5%
Diarrhea	5%	4%

For any grade toxicity :

vandetanib caused more **rash** (42% vs 24%), **diarrhea** (42% vs 33%), **neutropenia** (32% vs 27%), and **HTN** (6% vs 2%). There was a <2% rate of QTc prolongation with vandetanib. There was no increase in bleeding, thrombotic events, nor hemoptysis in the vandetanib arm.

There was **less nausea, vomiting, and anemia** in the vandetanib arm.

Summary Abstract #8003 ZODIAC

- ZODIAC was a positive study with the combination of vandetanib and docetaxel leading to improved RR, TDS, and PFS over docetaxel alone in a largely bevacizumab-naïve NSCLC population with ~25% never-smokers.
- No clinical subgroups were identified to have a greater magnitude of benefit, adenoCA and SCC both had similar PFS
- There was no OS benefit – a trend was seen but it was not statistically significant
- There was no increase in bleeding or thrombotic events in the vandetanib arm.
- Biomarker analysis were not conclusive.
- Subsequent therapy was not reported in this study.

Abstract #8010 ZEAL

All histologies eligible, treated brain mets and prior bevacizumab allowed.

Locally advanced or metastatic NSCLC (stage IIIB/IV) after failure of 1st-line anticancer therapy
Total recruitment = 534 patients

1:1 randomization

Vandetanib 100 mg/day
+
pemetrexed 500 mg/m²
(every 21 days)
n=256

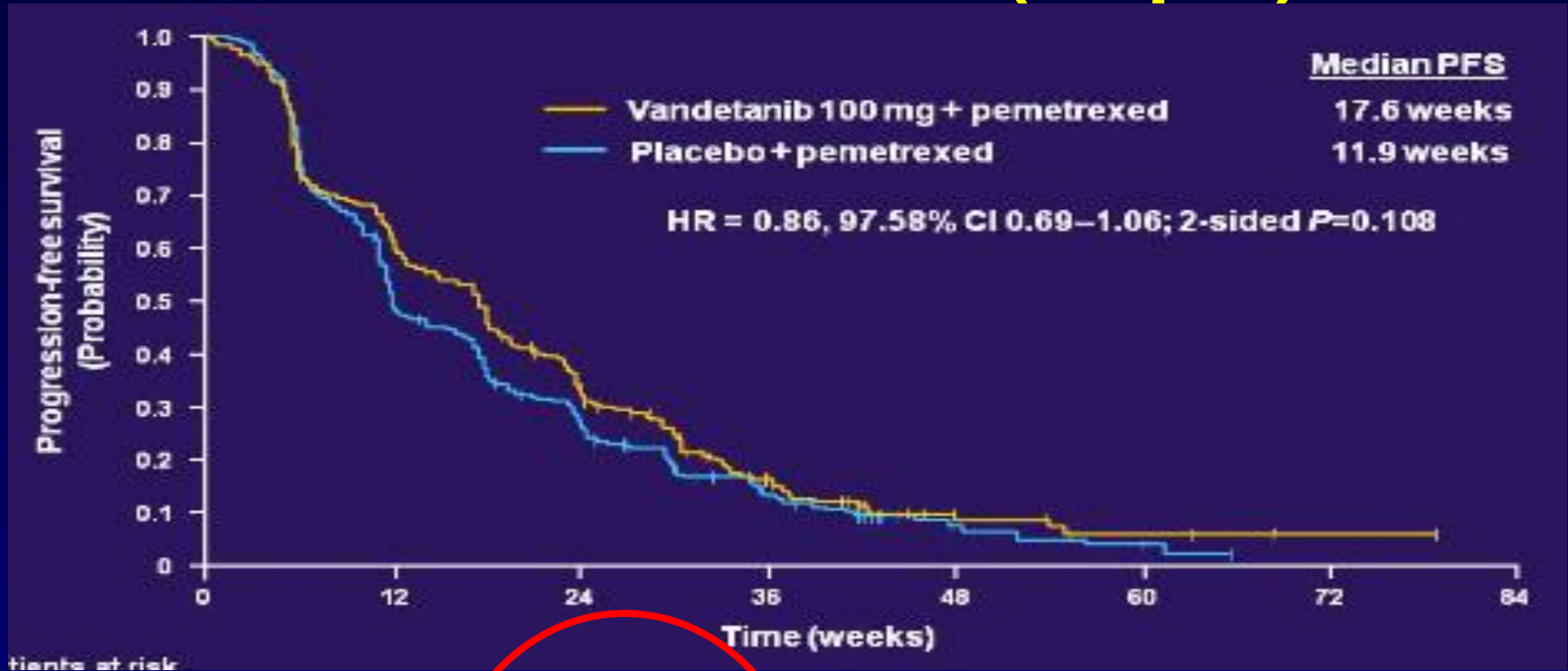
Placebo
+
pemetrexed 500 mg/m²
(every 21 days)
n=278

Primary endpoint: PFS, efficacy/safety in women

Secondary endpoint: OS, RR, DCR \geq 6 wks, safety/toxicity, TDS

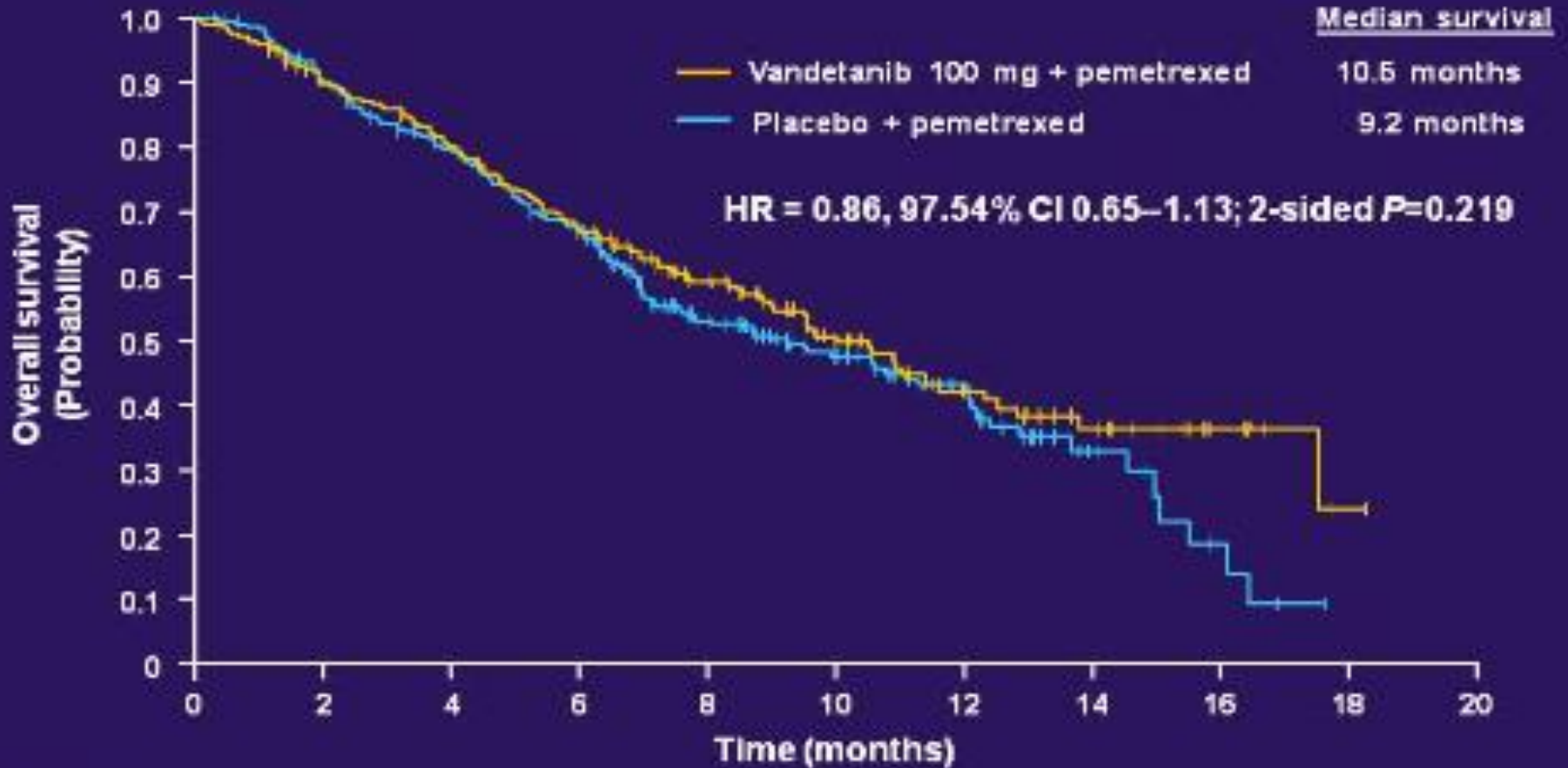
Stats: 80% power to detect 35% prolongation PFS (HR < 0.74)

ZEAL RR and PFS (all pts)



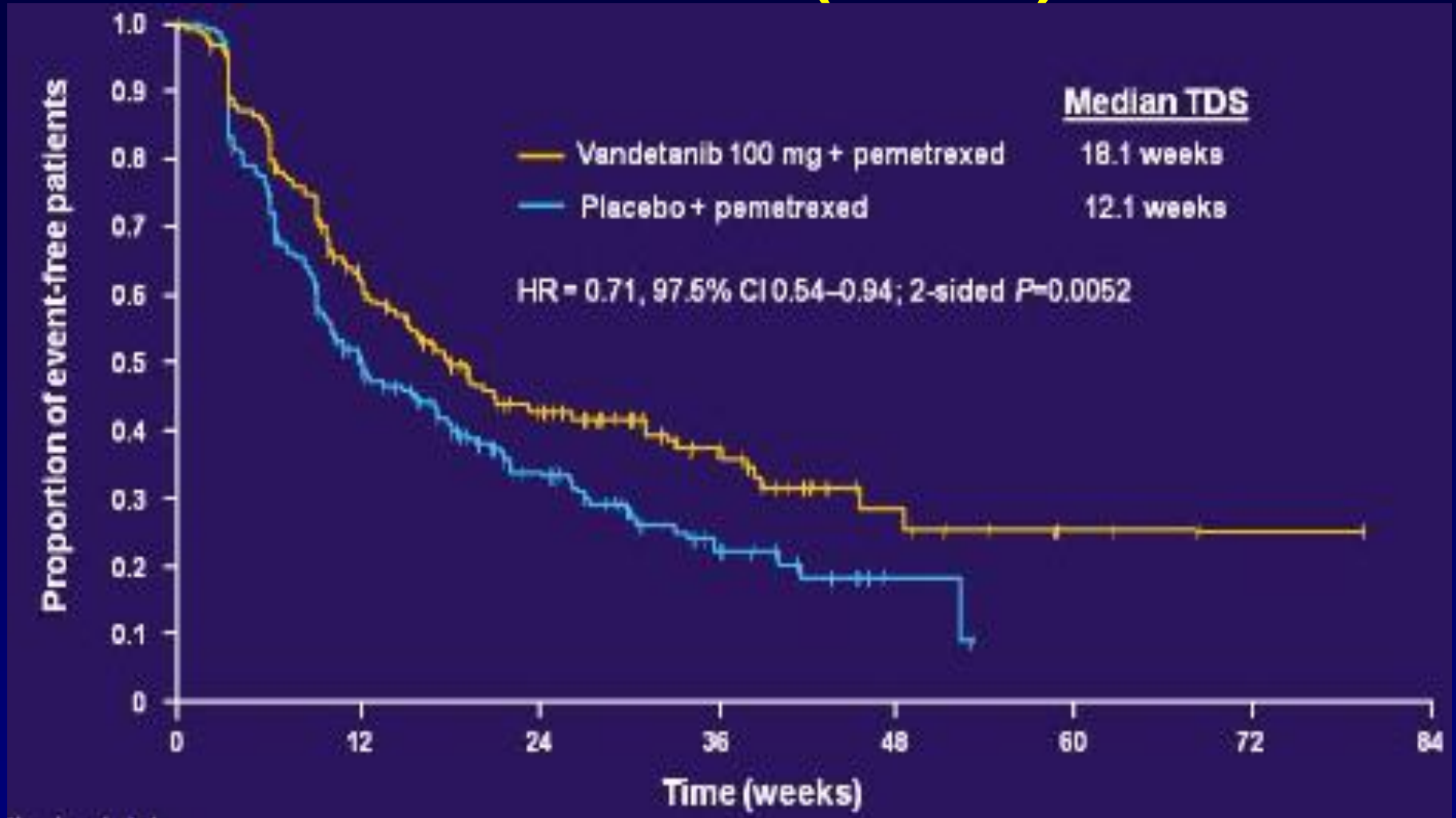
	Vandetanib Pemetrexed	Placebo Pemetrexed	P-value
RR	19.1%	7.9%	<0.001
DCR	56.6%	45.7%	0.0116
Median PFS (wks)	17.6	11.9	HR 0.86; p=0.108

ZEAL OS



	Vandetanib Pemetrexed	Pemetrexed	P-value
Median OS (mo)	10.5	9.2	HR 0.86, p=0.219

ZEAL TDS (LCSS)



Patient compliance was 82% vandetanib and 86% placebo

ZEAL : Grade 3+ toxicity

	Vandetanib + pemetrexed (n=260)	Pemetrexed (n=273)
Fatigue	5%	7%
Nausea	1%	2%
Rash	6%	3%
Cough	1%	1%
Anorexia	2%	2%
Dyspnea	6%	8%
Diarrhea	4%	2%
Constipation	1%	0.4%
Vomiting	2%	3%
Anemia	1%	6%

For any grade toxicity, vandetanib caused more **rash** (38% vs 26%), **diarrhea** (26% vs 18%) and **HTN** (12% vs 3%). There was **less anemia, N/V, fatigue and asthenia** in the vandetanib arm. There was no increase in bleeding or thrombotic events in the vandetanib arm.

Summary Abstract #8010 ZEAL

- Vandetanib + pemetrexed in pretreated NSCLC patients improved RR, DCR, and TDS (by LCSS) but did not reach statistical significance for improving PFS nor OS.
- There were no subgroups of patients that appeared to improve PFS nor OS – SCC did not have improvement with the addition of vandetanib to pemetrexed.

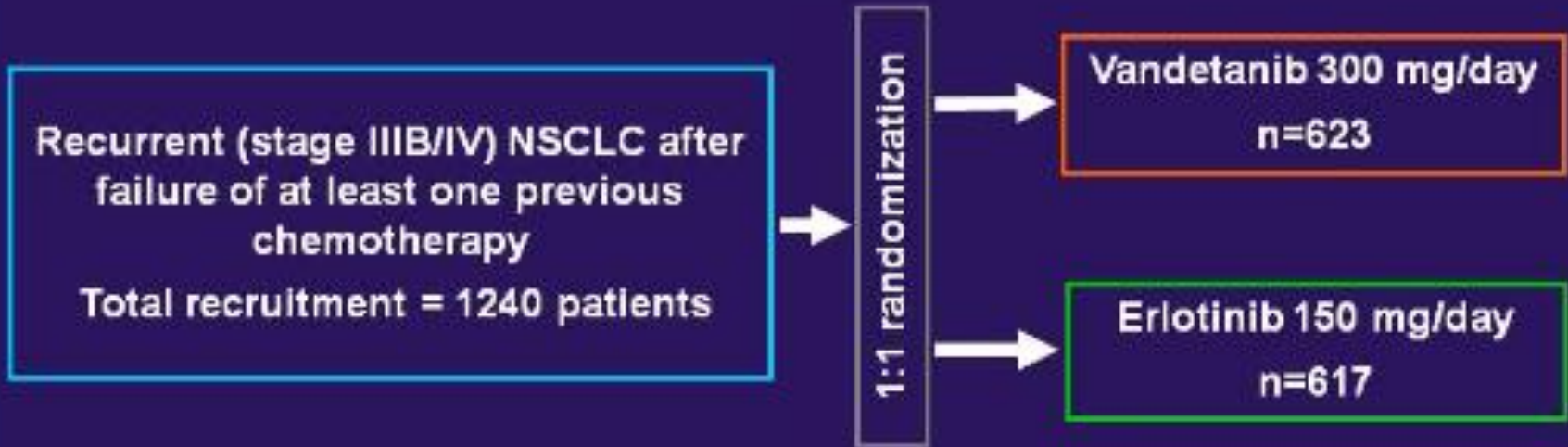
ZODIAC vs. ZEAL

	ZODIAC		ZEAL	
	Docetaxel Vandetanib	Docetaxel	Pemetrexed Vandetanib	Pemetrexed
RR	17%	10%	19.1%	7.9%
Median PFS (months)	4	3.2	4.4	2.97
Median OS (months)	10.6	10	10.5	9.2

The addition of vandetanib to chemotherapy improves RR and possibly PFS.

However, OS was not significantly improved.

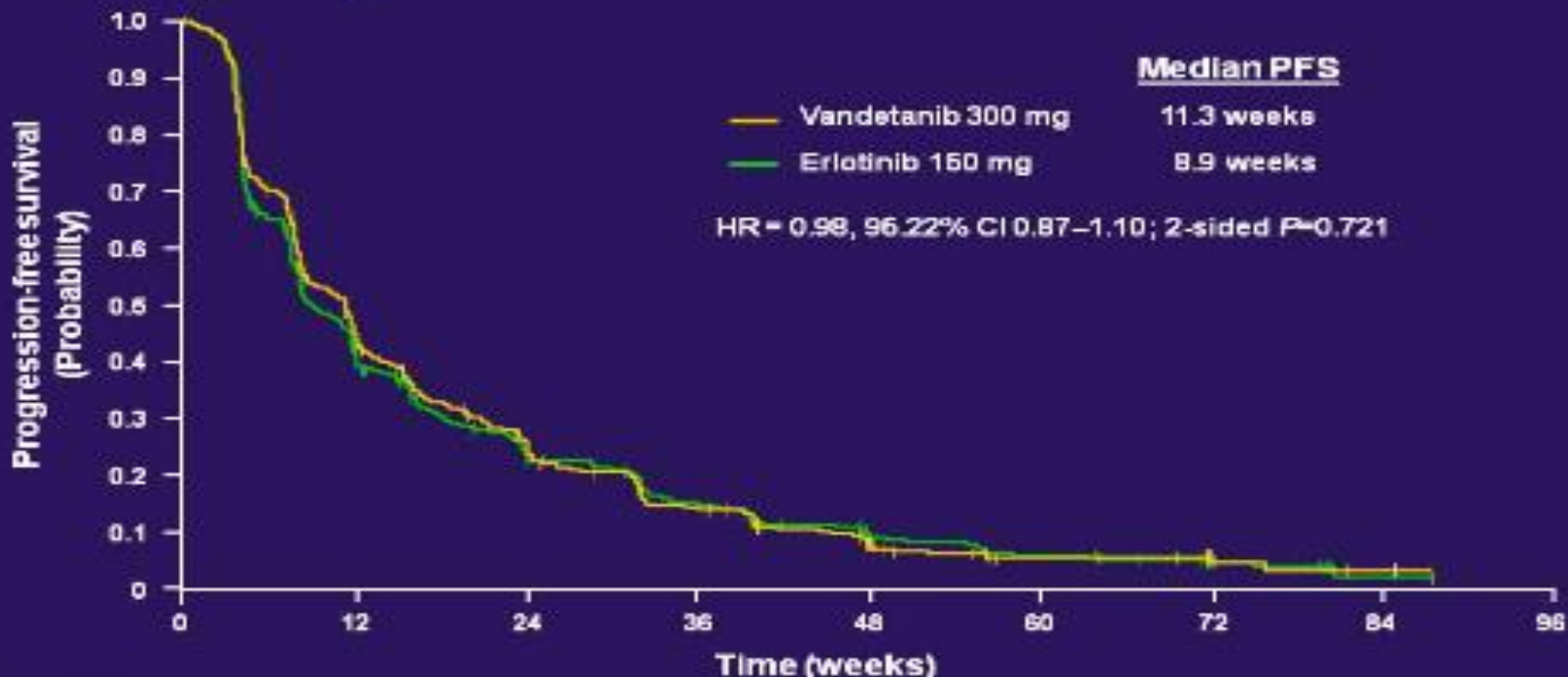
Abstract #8009 ZEST



- The primary objective was to show superiority in PFS for vandetanib versus erlotinib:
 - >90% power to detect a 25% prolongation of PFS (HR <0.80); a minimum of 1110 progression events were required
 - 2-sided significance level of 5% was adjusted to 4.78% to account for a single interim analysis
 - PFS determined from objective tumor assessments (RECIST)

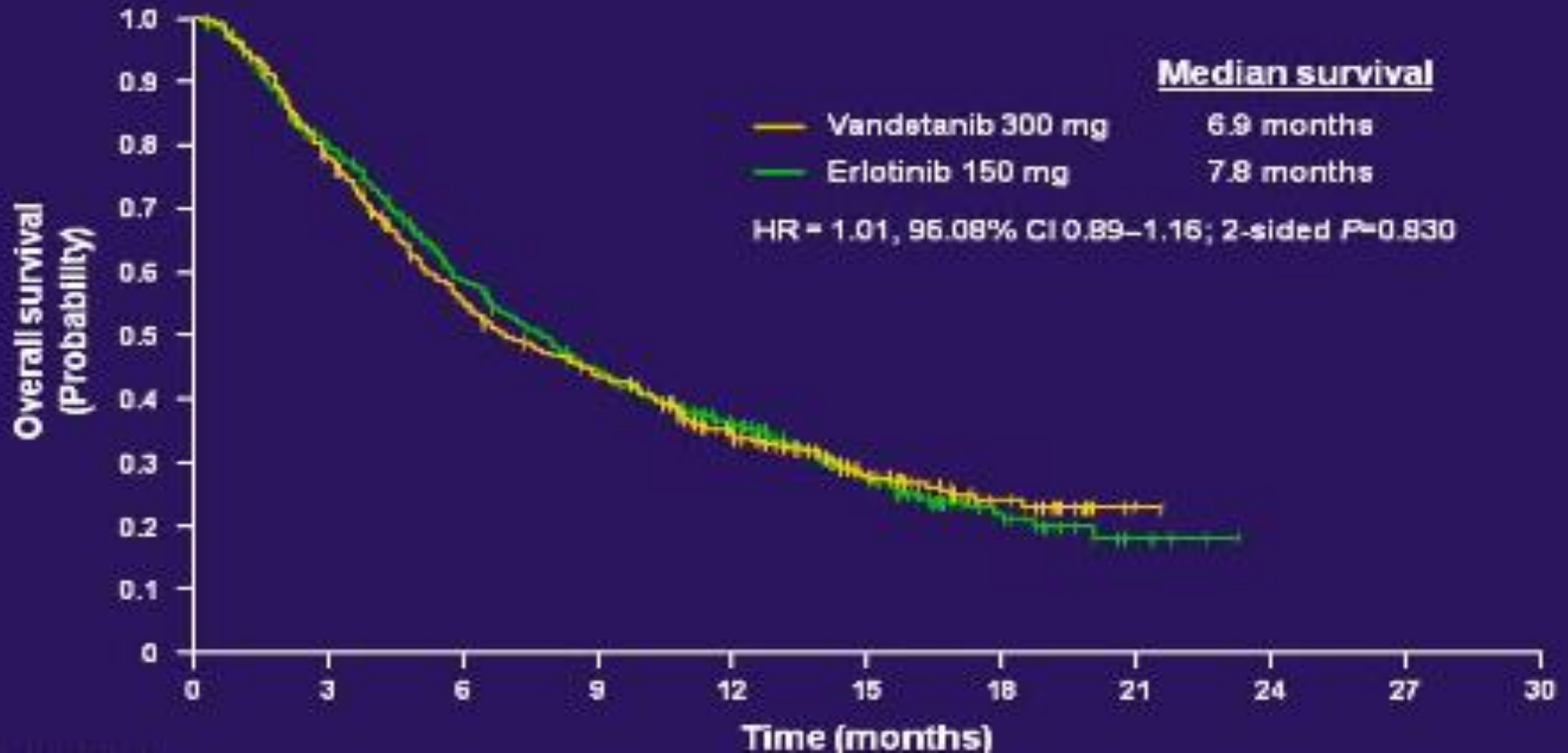
Secondary endpoint: OS, RR, TDS, safety

ZEST RR and PFS



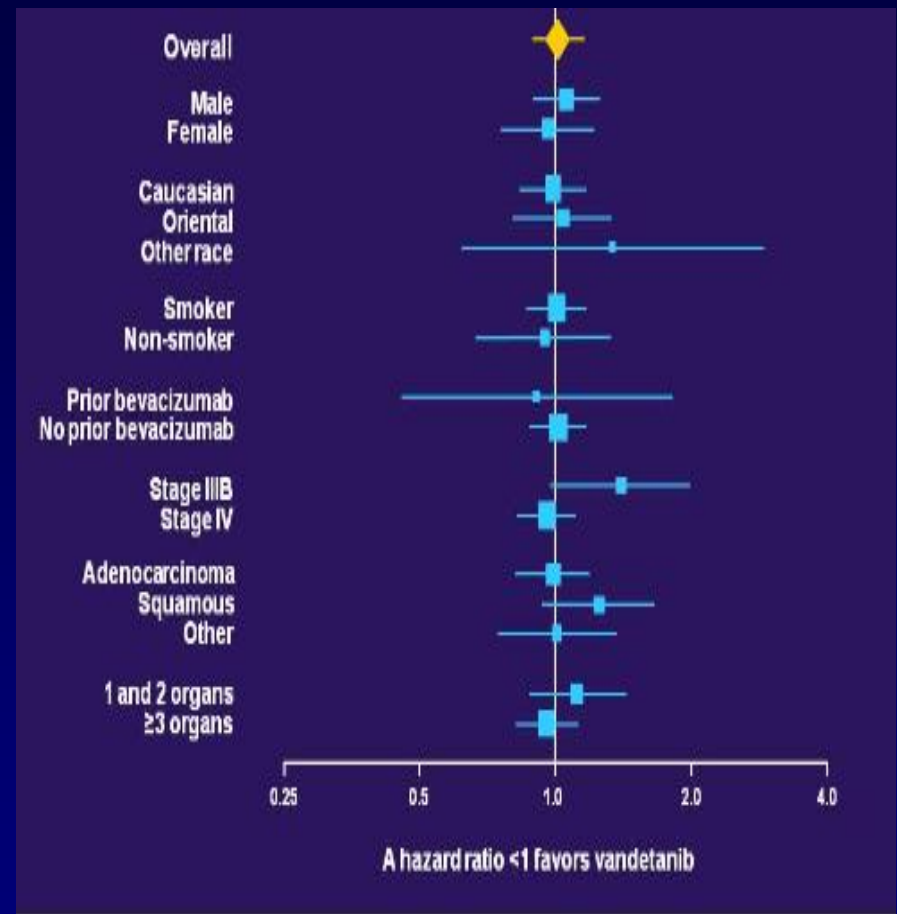
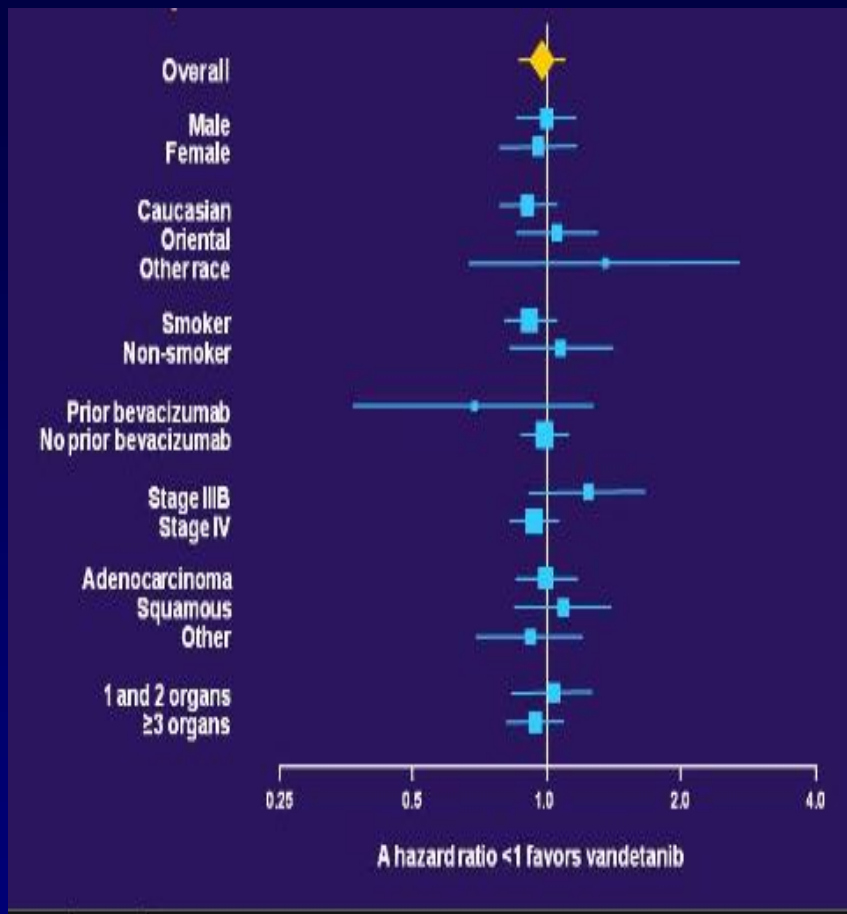
	Vandetanib (n=623)	Erlotinib (n=614)	P-value
RR	12%	12%	
Median PFS (wks)	11.3	8.9	HR 0.98, p=0.721

ZEST OS



	Vandetanib (n=623)	Erlotinib (n=614)	P-value
Median OS (months)	6.9	7.8	HR 1.01, p=0.830

ZEST PFS and OS by Subgroup Analysis



There were no clinical subgroups that had more benefit to vandetanib compared to erlotinib.

ZEST Time to Deterioration of symptoms (TDS)

- Patient compliance was similar 82% vandetanib and 80% erlotinib.
- There was no difference in TDS between the two arms.

	HR	P-value
Pain	0.96	0.582
Cough	0.94	0.402
Dyspnea	1.08	0.333

ZEST Toxicity Grade 3+

	Vandetanib (n=623)	Erlotinib (n=614)
Diarrhea	5%	3%
Rash	3%	4%
Nausea	1%	2%
Anorexia	2%	2%
Fatigue	4%	4%

For any grade toxicity

Vandetanib caused more diarrhea (50% vs 38%) and HTN (16% vs 2%).

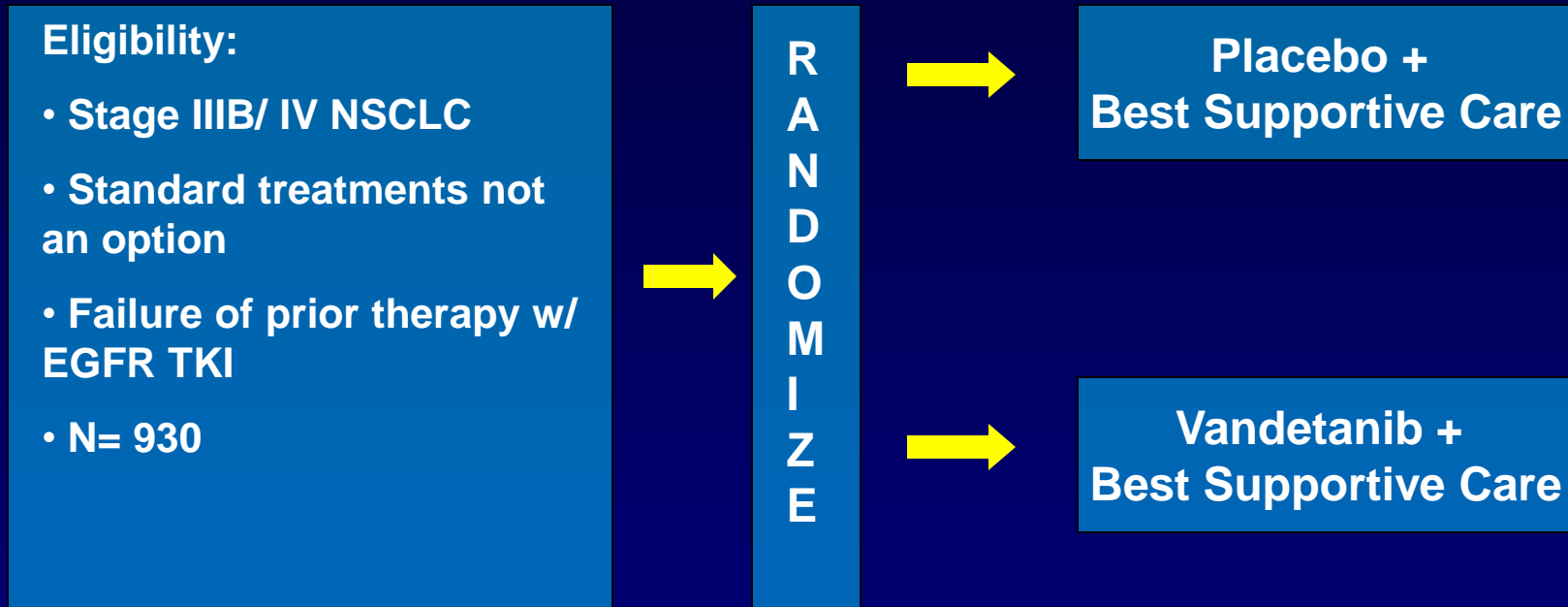
Erlotinib caused more rash (38% vs 28%).

There was no difference in hemoptysis (5.1% vs 7.5%).

Summary Abstract #8009 ZEST

- There was no difference in RR, PFS, OS, nor TDS between vandetanib and erlotinib in previously treated NSCLC patients.
- There were no clinical subgroups that appeared to have more benefit to vandetanib compared to erlotinib.
- No new safety signals for vandetanib.
- A phase III trial ZEPHYR comparing vandetanib to placebo in previously treated patients with anti-EGFR therapy is underway

Phase III Vandetanib (ZD6474) Study in EGFR Failures (ZEPHYR)



Vandetanib 300 mg orally once daily

Primary Objective : OS

Secondary Objective: PFS; response duration; safety and tolerability; improvement of disease-related symptoms

Outline

**Neoadjuvant
& Adjuvant
Chemo**



**Abstract 7500 NATCH trial
Abstract 7501 JBR.10 trial**

ChemoXRT



**Abstract 7505 CALGB 30407 (C225)
Abstract 7503 E3598 (thalidomide)**

Maintenance



**Abstract 8000 pemetrexed
Abstract 8001 SATURN (erlotinib)
Abstract 8002 ATLAS (bevacizumab \pm
erlotinib)**

**Metastatic
Salvage -
Vandetanib**



**Abstract CRA 8003 ZODIAC
Abstract 8009 ZEST
Abstract 8010 ZEAL**

Biomarkers

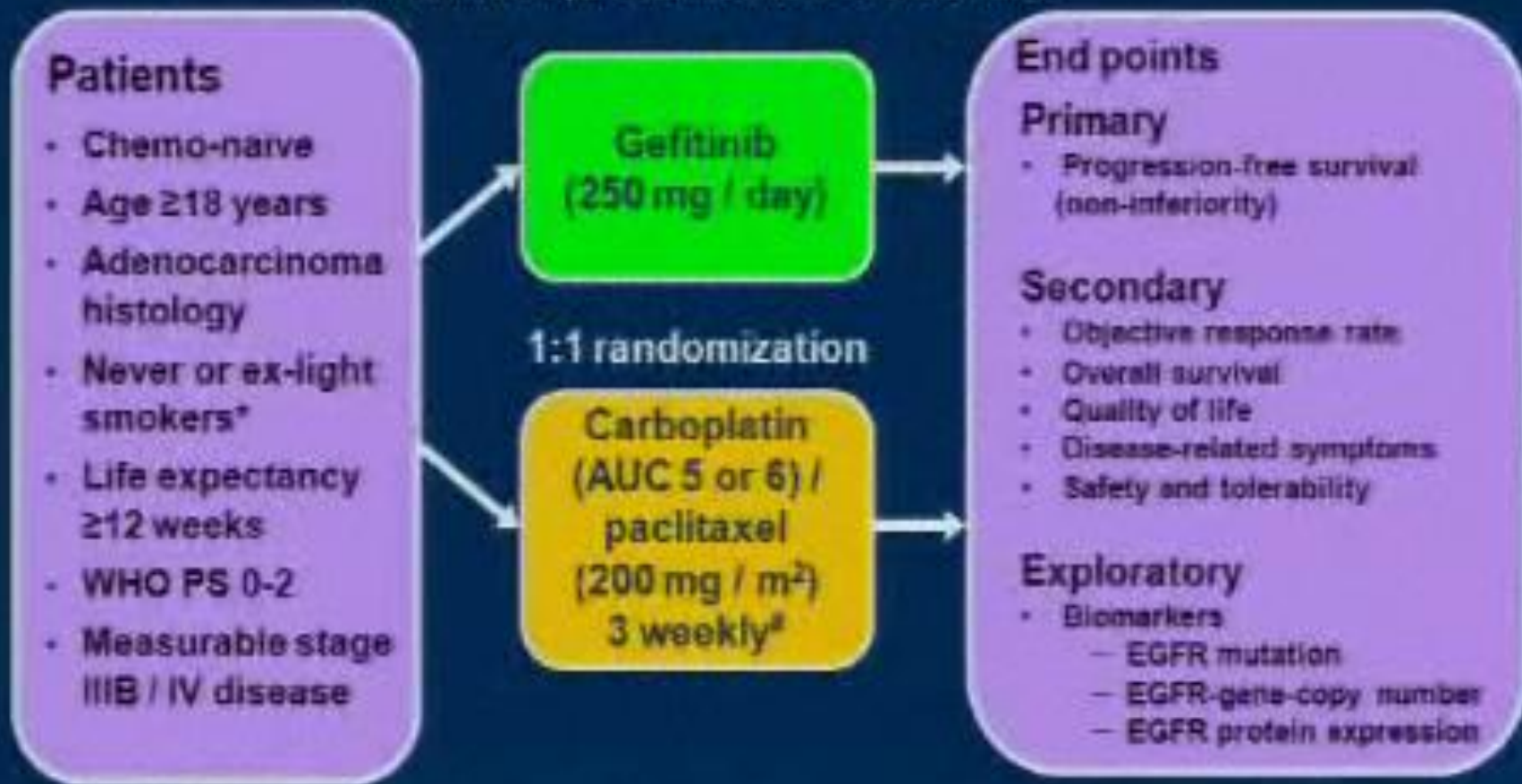


**Abstract 8006 I-PASS (EGFR mutation)
Abstract 8007 FLEX (EGFR FISH)**

Abstract #8006 I-PASS Biomarker Data

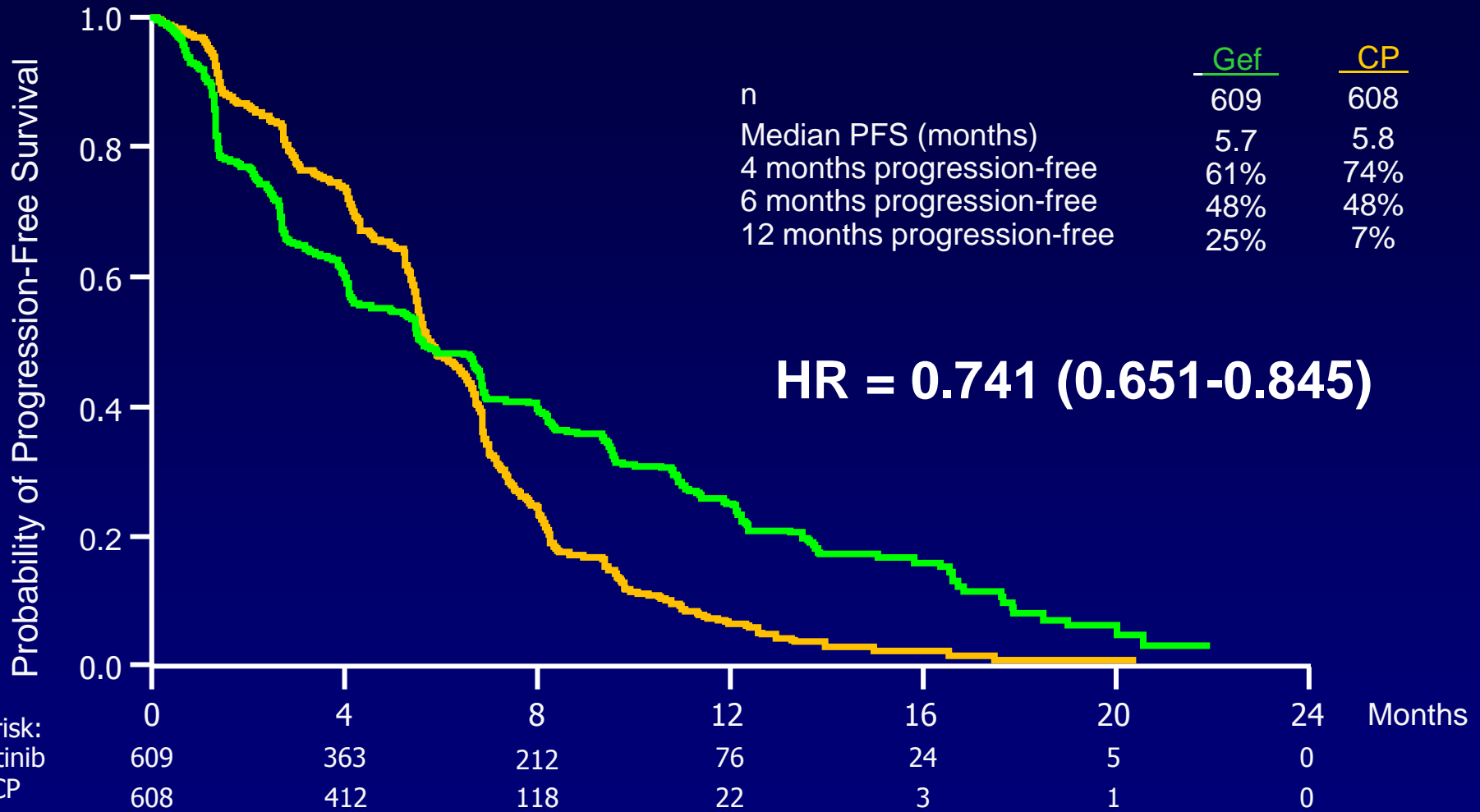
Conducted in China, Japan, Thailand, Taiwan, Indonesia, Malaysia, Philippines, Hong Kong and Singapore

Randomization period: March 2006 – October 2007



*Never smokers, <100 cigarettes in lifetime; ex-light smokers, stopped ≥15 years ago and smoked ≤10 pack years;
^alimited to a maximum of 6 cycles. Carboplatin/paclitaxel was offered to gefitinib patients upon progression.
WHO, World Health Organization; PS, performance status; AUC, area under the curve; EGFR, epidermal growth factor receptor

I-PASS PFS



EGFR Biomarkers by Treatment Arm

Biomarker	Status	Gefitinib	Chemo	Overall
EGFR mutation N=437 (36%)	Positive	132 (59%)	129 (60%)	261 (60%)
	Negative	91 (41%)	85 (40%)	176 (40%)
EGFR gene copy number N=406 (33%)	High	124 (60%)	125 (62%)	249 (61%)
	Low	81 (40%)	76 (38%)	157 (39%)
EGFR IHC expression N=365 (30%)	Positive	132 (71%)	134 (74%)	266 (73%)
	Negative	53 (29%)	46 (26%)	99 (27%)

1217 patients were randomized. 1038 (85%) consented for biomarker analysis. 683 (56%) provided samples. No correlation patient demographics and biomarkers.

High EGFR copy number = high polysomy (≥ 4 copies in $\geq 40\%$ of cells) or gene amplification (ratio gene/chromosome per cell ≥ 2 , or ≥ 15 copies of EGFR per cell in $\geq 10\%$ of cells).

Positive EGFR IHC defined as $\geq 10\%$ of cells stained for EGFR protein

EGFR Mutations

Mutation Status	Gefitinib (N=609)	Chemo (N=608)
EGFR mutation Negative	91 (14.9%)	85 (14%)
EGFR mutation Positive	132 (21.7%)	129 (21.2%)
Exon 19 deletions	66 (50%)	74 (57.4%)
Exon 21 L858R	64 (48.8%)	47 (36.4%)
Exon 20 T790M	5 (3.8%)	6 (4.7%)
Other	3 (2.3%)	7 (5.4%)
Unknown	386 (63.4%)	394 (64.8%)

EGFR mutations are not the same – Exon 20 T790 mutation is resistant to EGFR TKIs.

PFS by EGFR Mutations

EGFR mutation positive

Gefitinib (n=132)

Carboplatin/paclitaxel (n=129)

HR (95% CI) = 0.48 (0.36, 0.64)

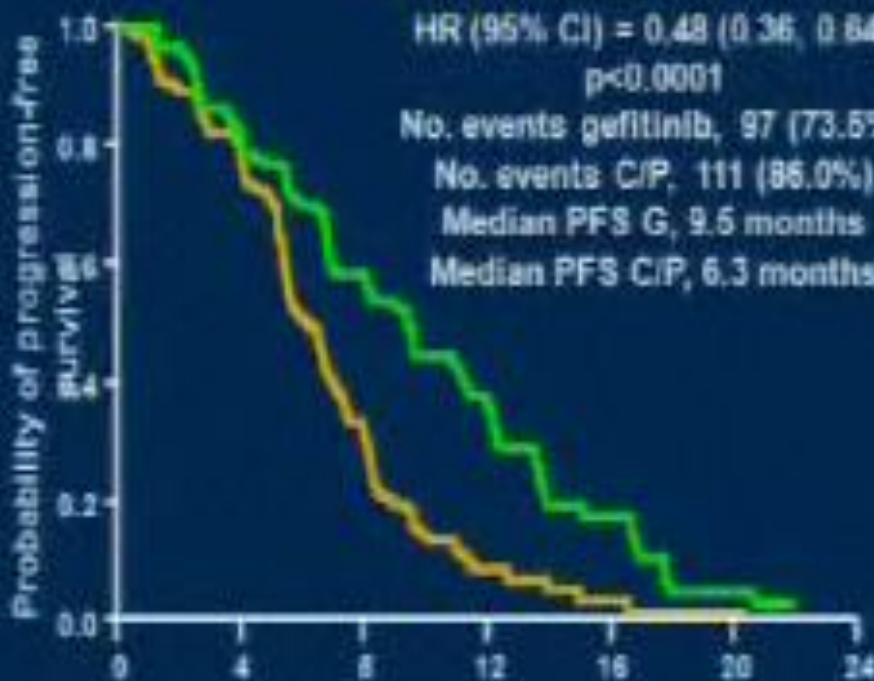
p<0.0001

No. events gefitinib, 97 (73.5%)

No. events C/P, 111 (86.0%)

Median PFS G, 9.5 months

Median PFS C/P, 6.3 months



EGFR mutation negative

Gefitinib (n=91)

Carboplatin/paclitaxel (n=85)

HR (95% CI) = 2.85 (2.05, 3.98)

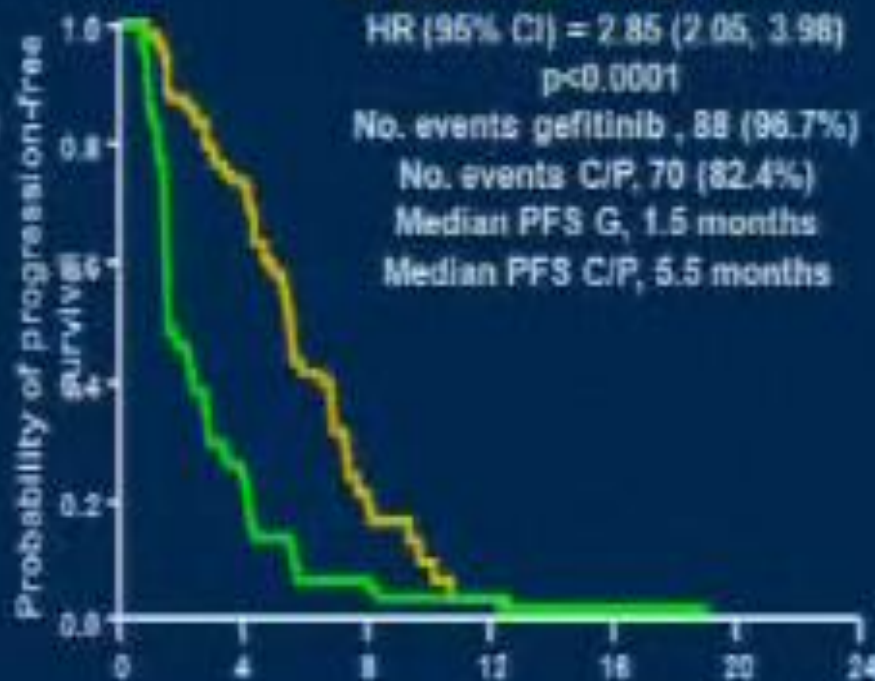
p<0.0001

No. events gefitinib, 88 (96.7%)

No. events C/P, 70 (82.4%)

Median PFS G, 1.5 months

Median PFS C/P, 5.5 months



Patients at risk:

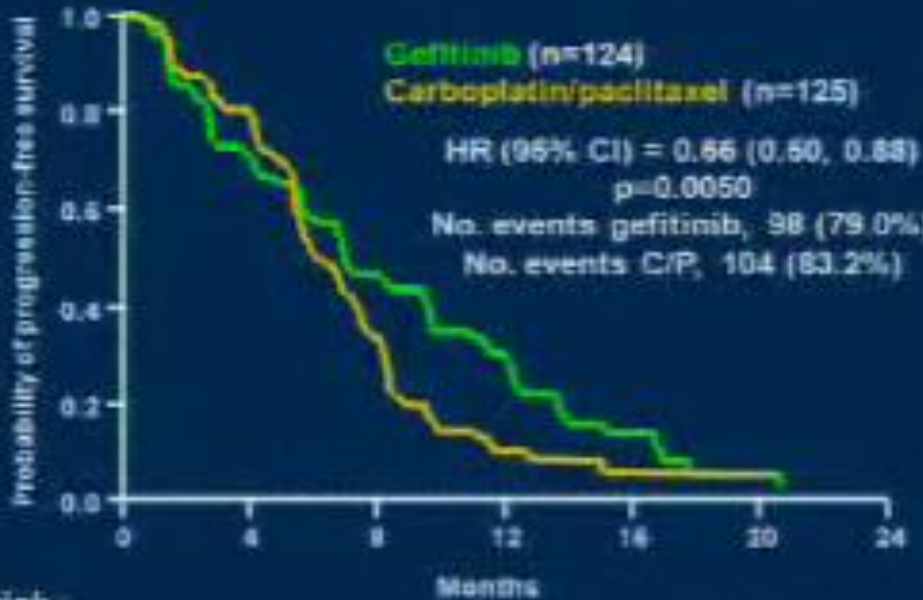
		0	4	8	12	16	20	24
Gefitinib	132	108	71	31	11	3	0	
C/P	129	103	37	7	2	1	0	

		0	4	8	12	16	20	24
Gefitinib	91	21	4	2	1	0	0	
C/P	85	58	14	1	0	0	0	

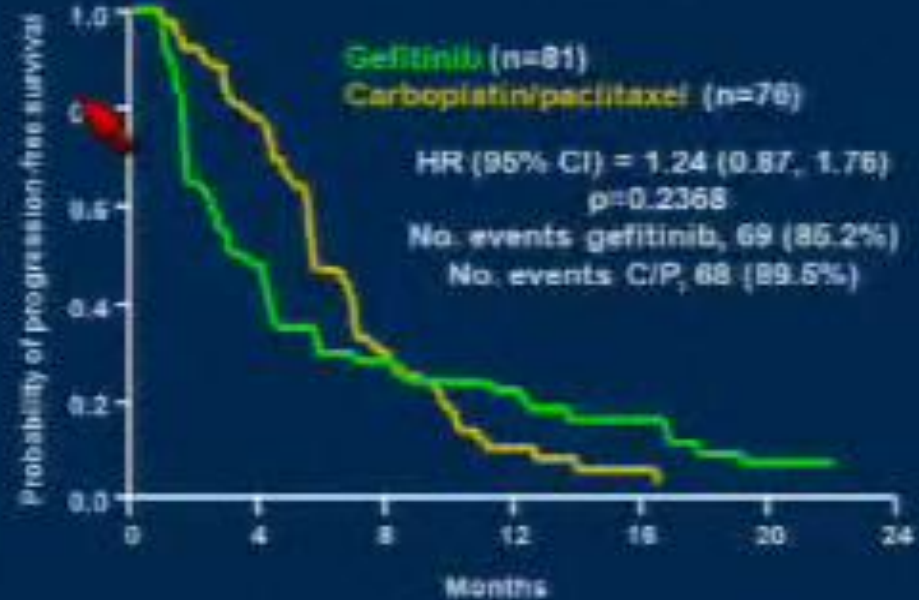
Treatment by EGFR mutation status interaction test, p<0.0001

EGFR Gene Copy Number and PFS

High EGFR-gene-copy number



Low EGFR-gene-copy number



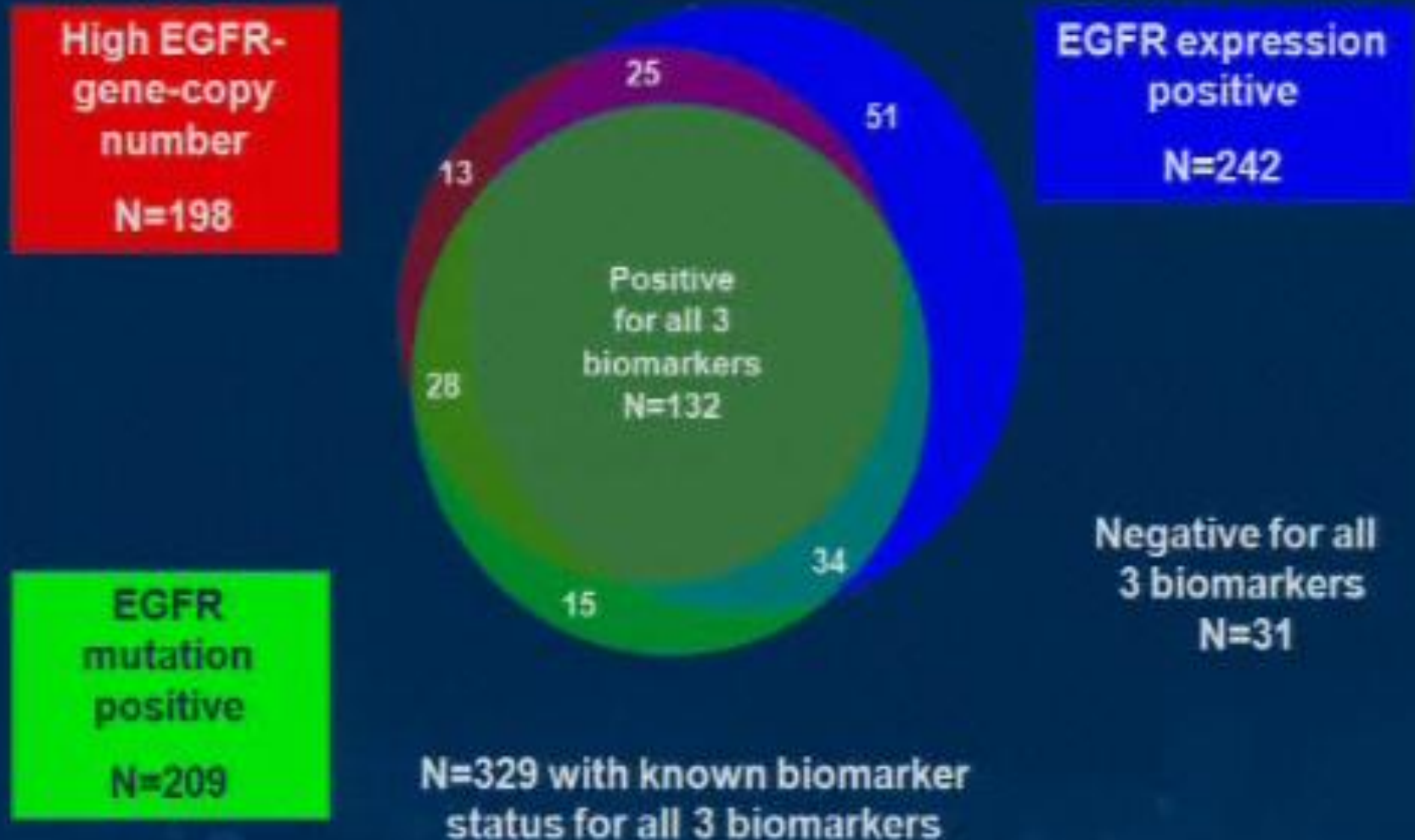
At risk	0	4	8	12	16	20	24
Gefitinib	124	87	53	20	5	1	0
C/P	125	95	32	5	1	1	0

At risk	0	4	8	12	16	20	24
Gefitinib	81	34	17	10	6	2	0
C/P	76	58	18	3	1	0	0

Treatment by EGFR-gene-copy number interaction test, p=0.0437

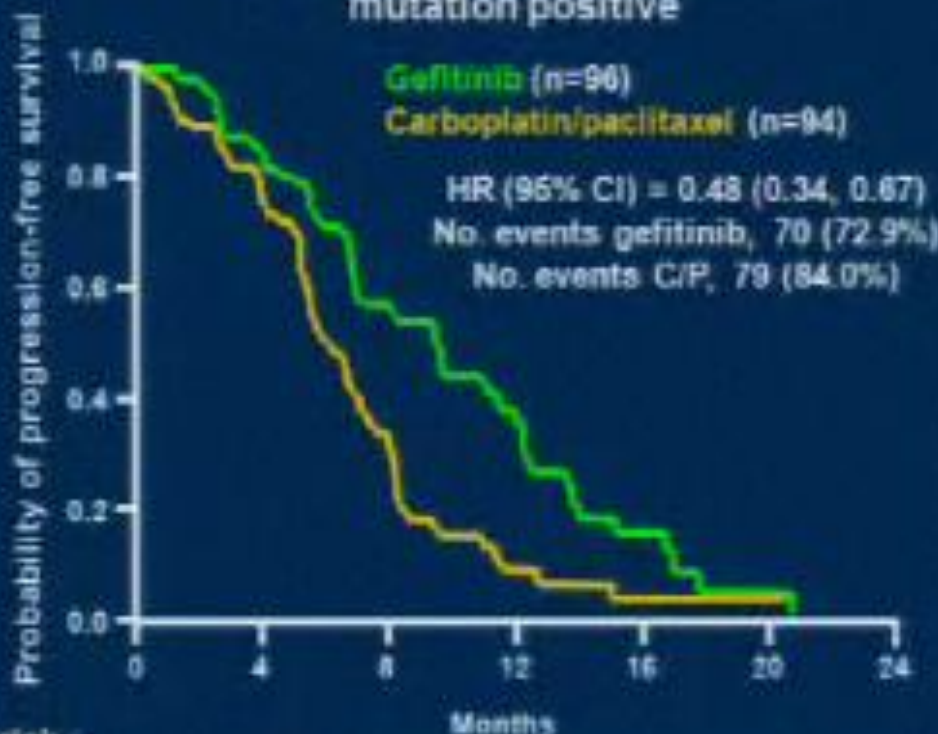
Having a higher EGFR gene copy number seemed to lead to an improved PFS when treated with gefitinib compared to patients with low EGFR gene copy numbers

Overlap of Biomarkers

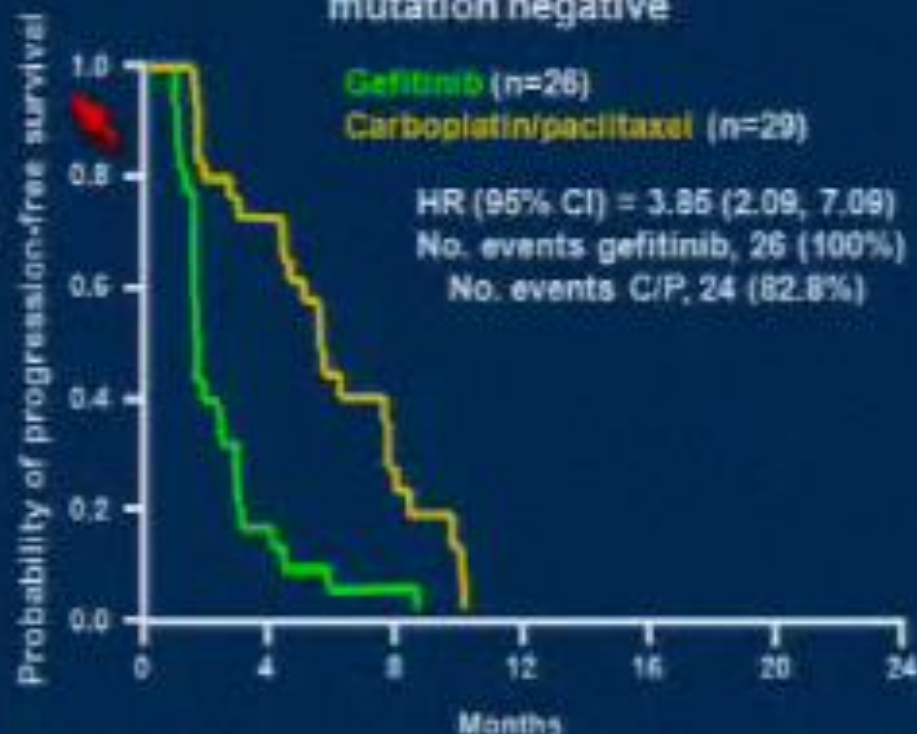


PFS by EGFR Gene Mutation Status and High Gene Copy Number

High EGFR-gene-copy number,
mutation positive



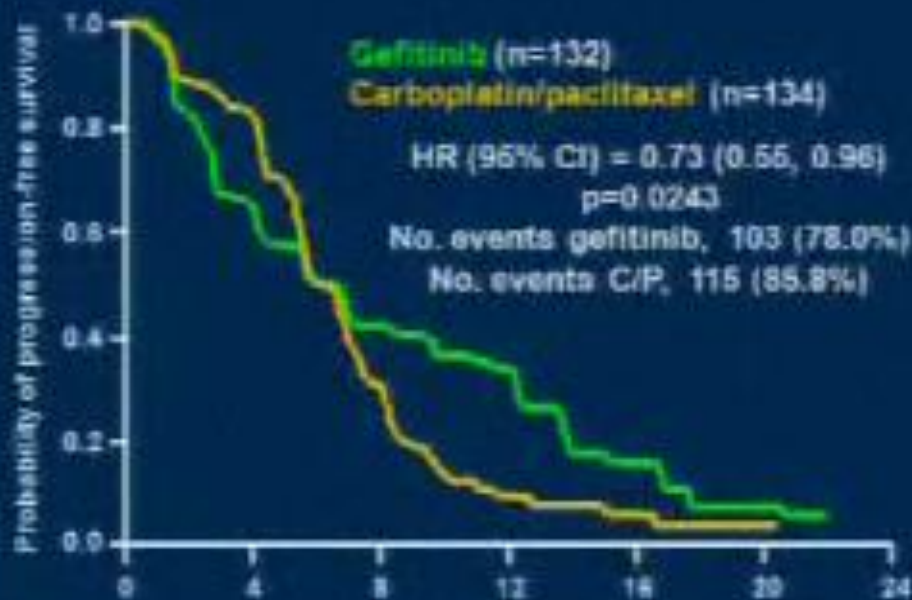
High EGFR-gene-copy number,
mutation negative



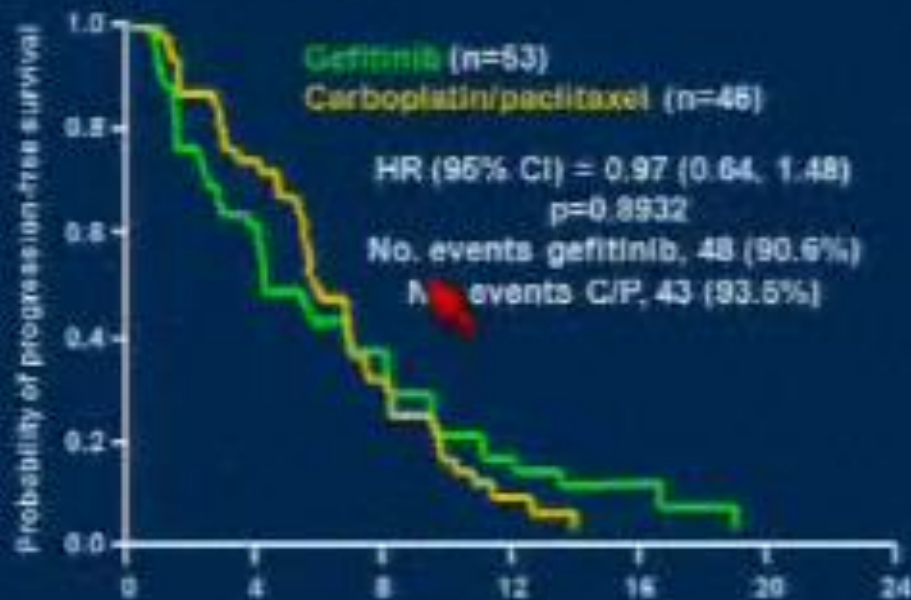
It is likely that EGFR gene copy number does not predict for response to gefitinib – having an EGFR gene mutation confers the survival benefit.

PFS by EGFR Protein expression (IHC)

EGFR protein expression positive



EGFR protein expression negative

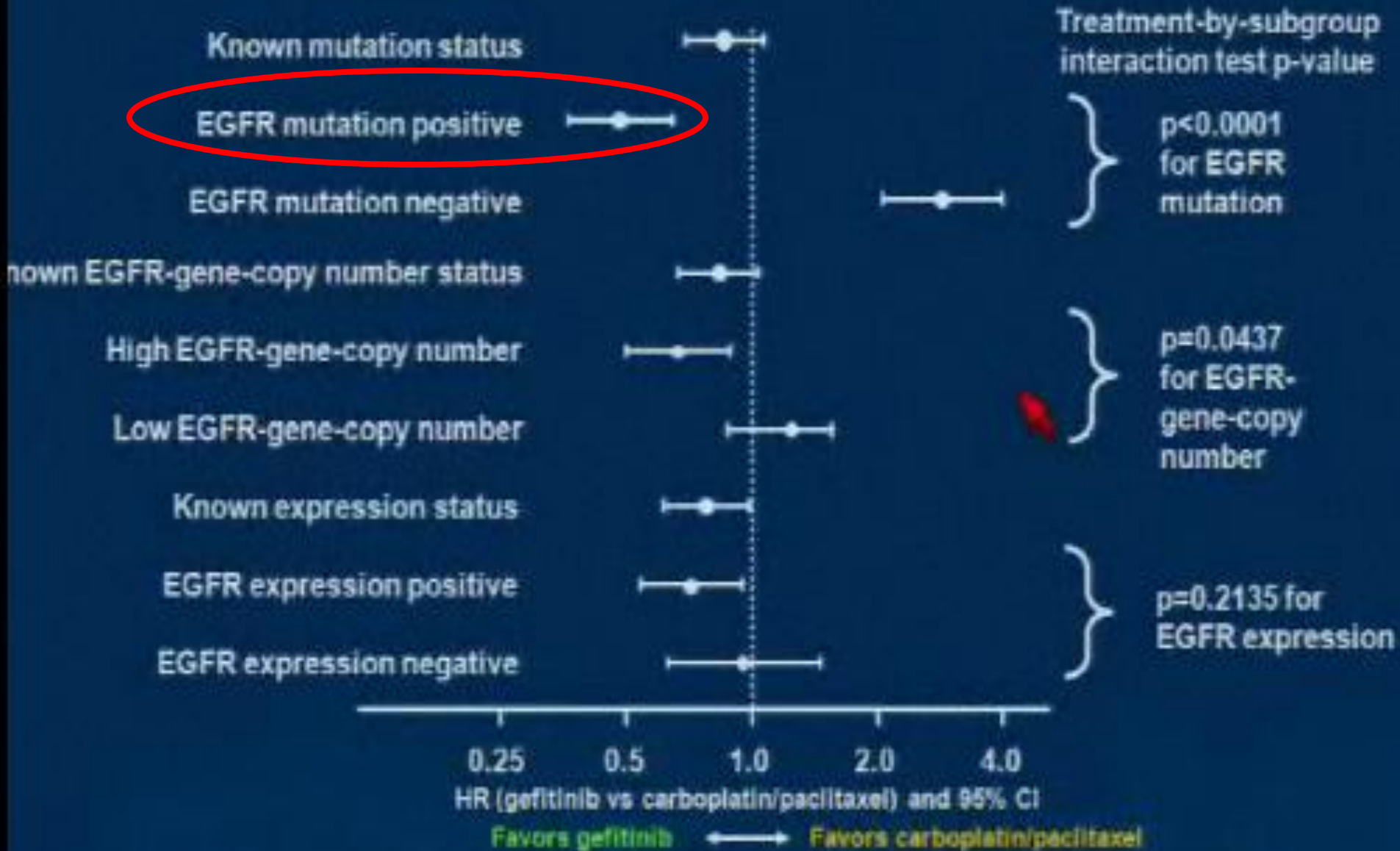


At risk:	0	4	8	12	16	20	24	0	4	8	12	16	20	24
Gefitinib	132	81	48	25	9	3	0	53	32	17	6	2	0	0
C/P	134	108	34	5	2	1	0	46	32	13	2	0	0	0

Treatment by EGFR protein expression status interaction test, $p=0.2135$

EGFR IHC does not predict for response to gefitinib.

PFS by Biomarkers



Summary Abstract #8006

- EGFR mutation positive patients had longer PFS with gefitinib than carboplatin-paclitaxel.
- EGFR mutation negative patients had a shorter PFS with gefitinib than with chemo.
- Neither EGFR gene copy number nor EGFR protein expression predict for benefit to gefitinib.
- Treating EGFR mutation patients with front-line EGFR tyrosine kinase inhibitors should be considered. EGFR mutation negative patients should receive frontline chemotherapy.

Abstract 8007 FLEX Trial

NSCLC

Any histology

ECOG PS 0-2

EGFR (+) IHC in

≤ one cell

No brain mets

Chemo-naïve

No prior anti-EGFR
therapy

Stratification: PS 0/1 or 2,
Stage wet IIIB or IV

R
A
N
D
O
M
I
Z
E

Cisplatin + Vinorelbine

Cisplatin 80 mg/m² day 1 every 3 wk

Vinorelbine 25 (30) mg/m² day 1, 8
every 3 wk

Chemo given for 6 cycles maximum

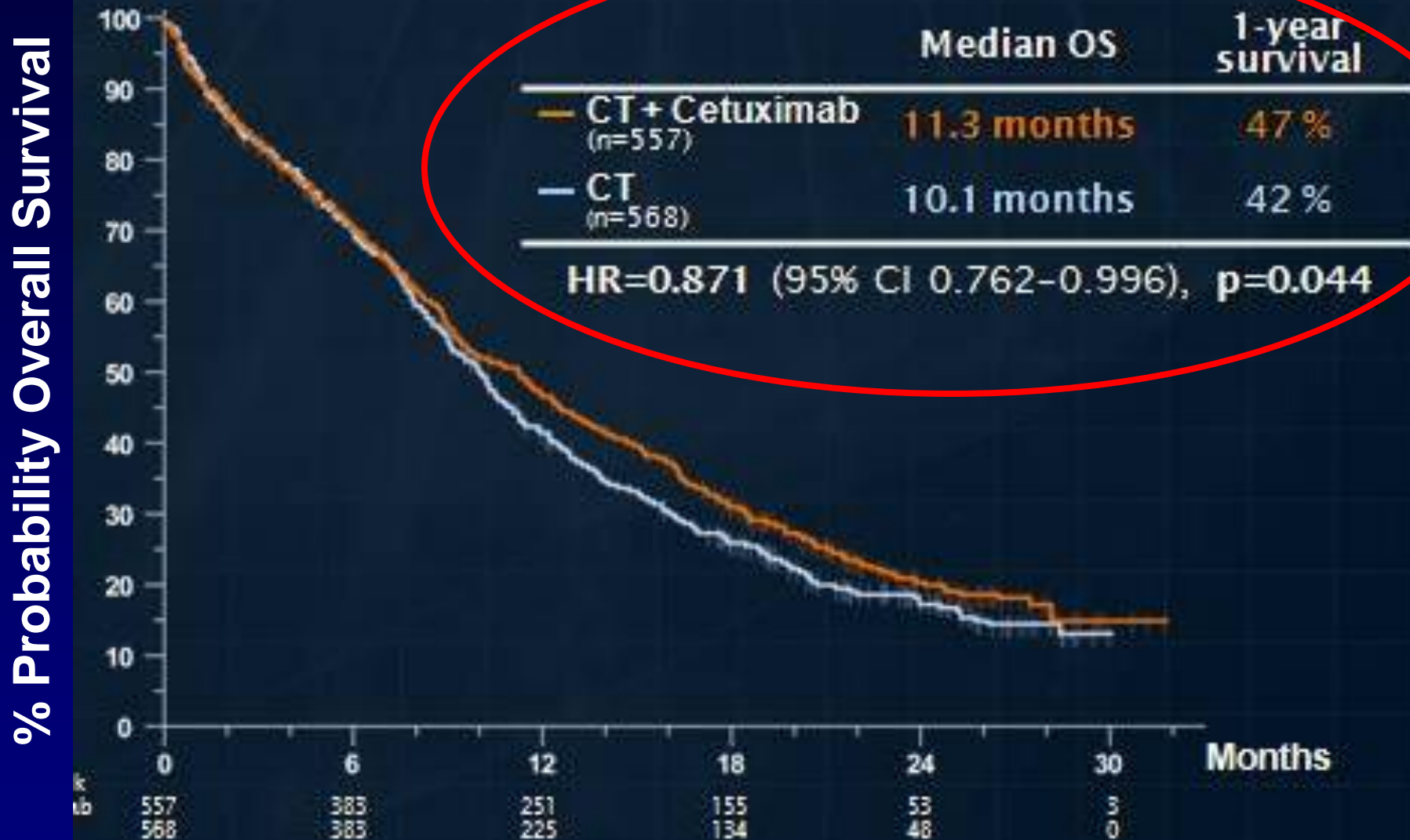
**Cisplatin + Vinorelbine
+ Cetuximab**

Cetuximab 400 mg/m² LD then 250 mg/m²
weekly. After 6 cycles of chemo, continued
as maintenance until PD or toxicity.

Primary endpoint: Overall Survival

Secondary: RR, PFS, disease control, QOL, safety

FLEX Overall Survival



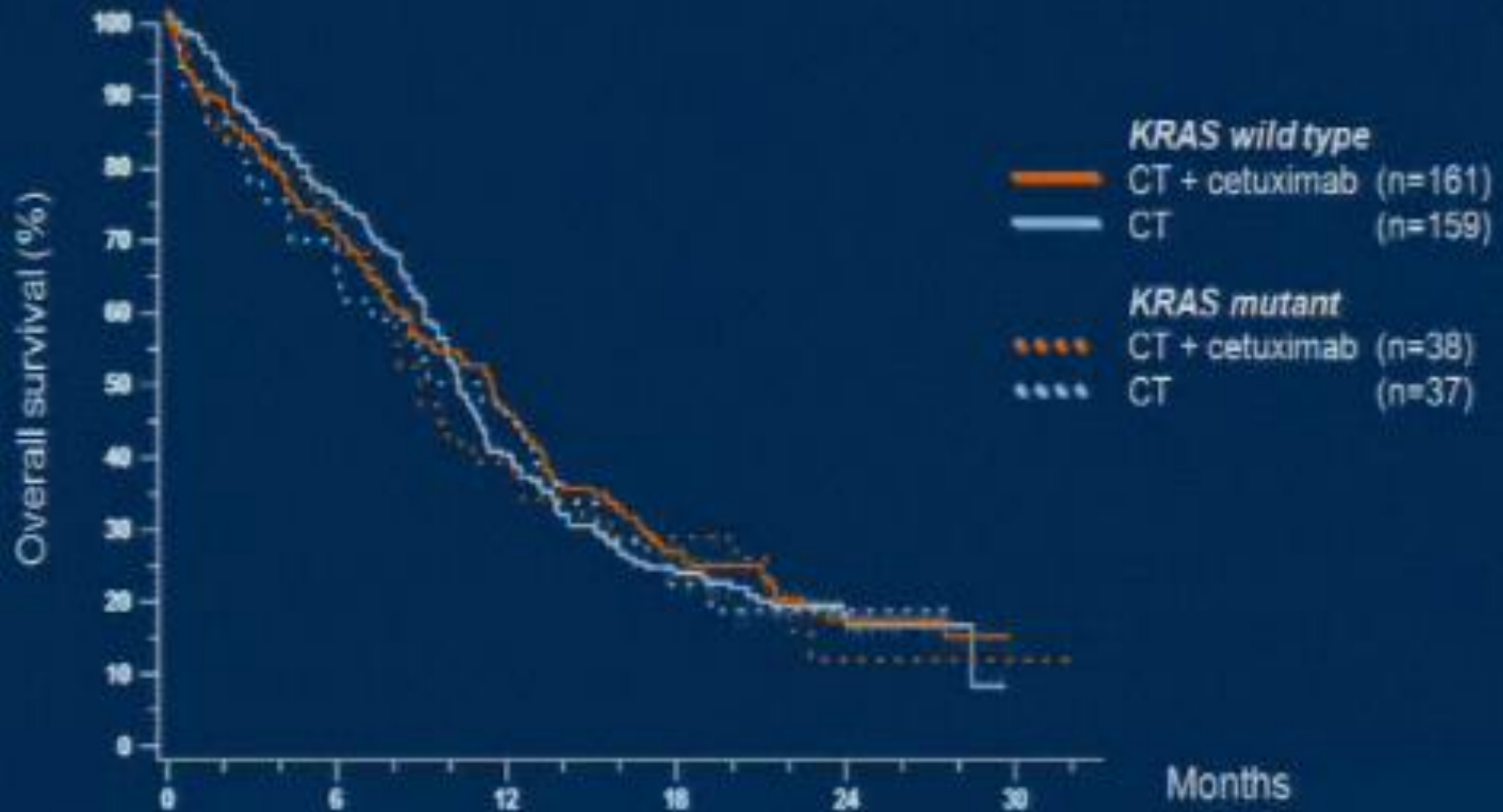
Abstract #8007 FLEX Biomarkers

- K-ras Mutation
 - Genomic DNA from formalin-fixed paraffin embedded tumor tissue. LBA-mediated qPCR clamping assay to detect codon 12 and 13 mutations.
- EGFR gene copy number by fluorescent in-situ hybridization (FISH)
 - FISH Colorado Scoring system

FLEX biomarkers

Biomarker	Status	C225 + chemo	Chemo	Total
KRAS mutation N=395 35% ITT	Wild-type	161 (81%)	159 (81%)	320 (81%)
	Mutant	38 (19%)	37 (19%)	75 (19%)
EGFR FISH N=279 25% ITT	Positive	49 (37%)	53 (36%)	102 (37%)
	Negative	82 (63%)	95 (64%)	177 (63%)

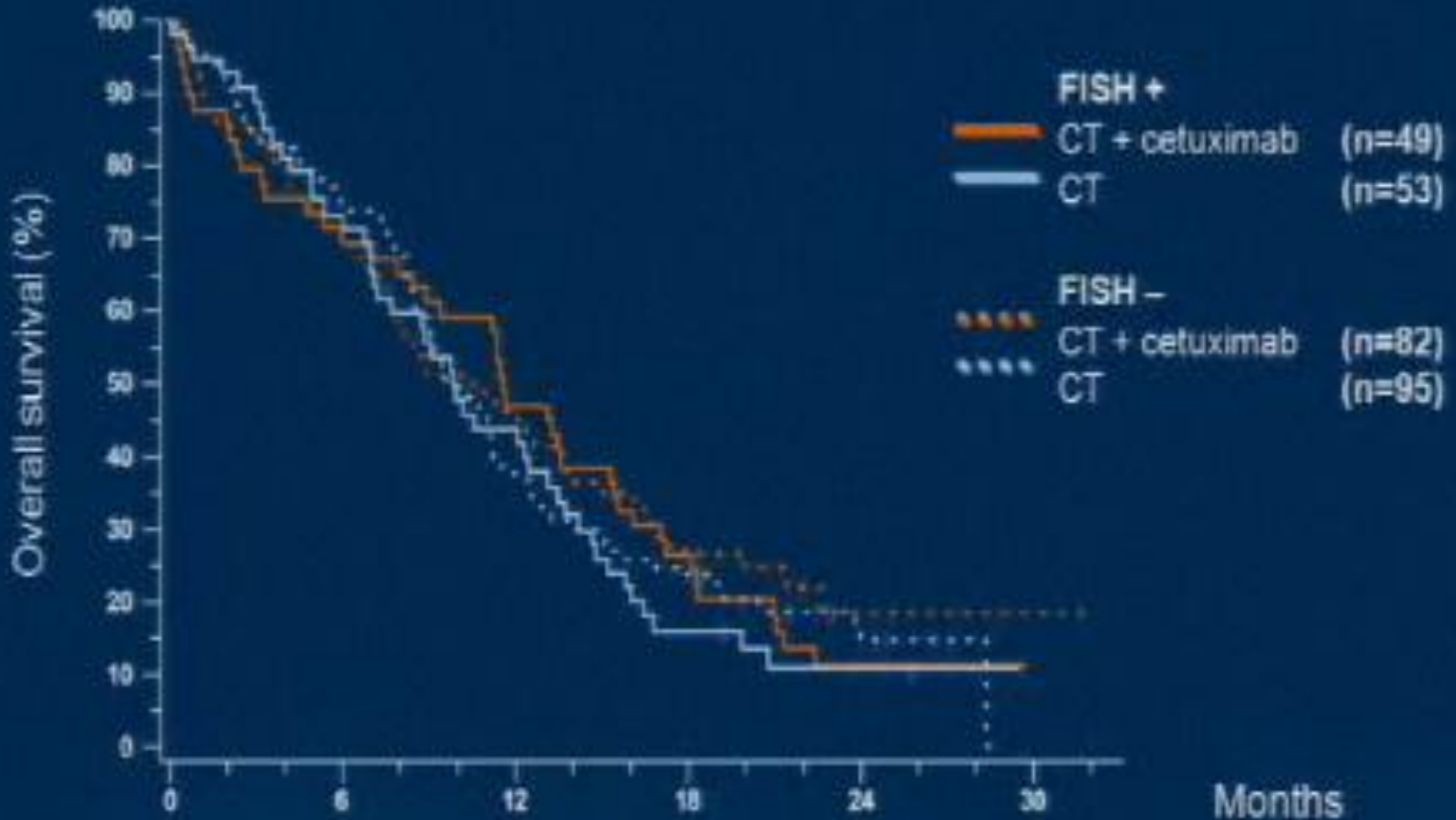
OS by KRAS mutation and Treatment Arm



KRAS mutation and efficacy

Biomarker	Status	C225 + chemo	Chemo	HR	P-value
Median OS (months)	Mutant	8.9	11.1	1	1
	Wild-type	11.4	10.3	0.96	0.75
Median PFS	Mutant	5.5	2.9	0.84	0.5
	Wild-type	4.4	4.8	0.97	0.8
RR	Mutant	36.8%	21.6%	-	0.15
	Wild-type	37.3%	28.3%	-	0.09

OS by FISH and Treatment Arms



EGFR FISH and Efficacy

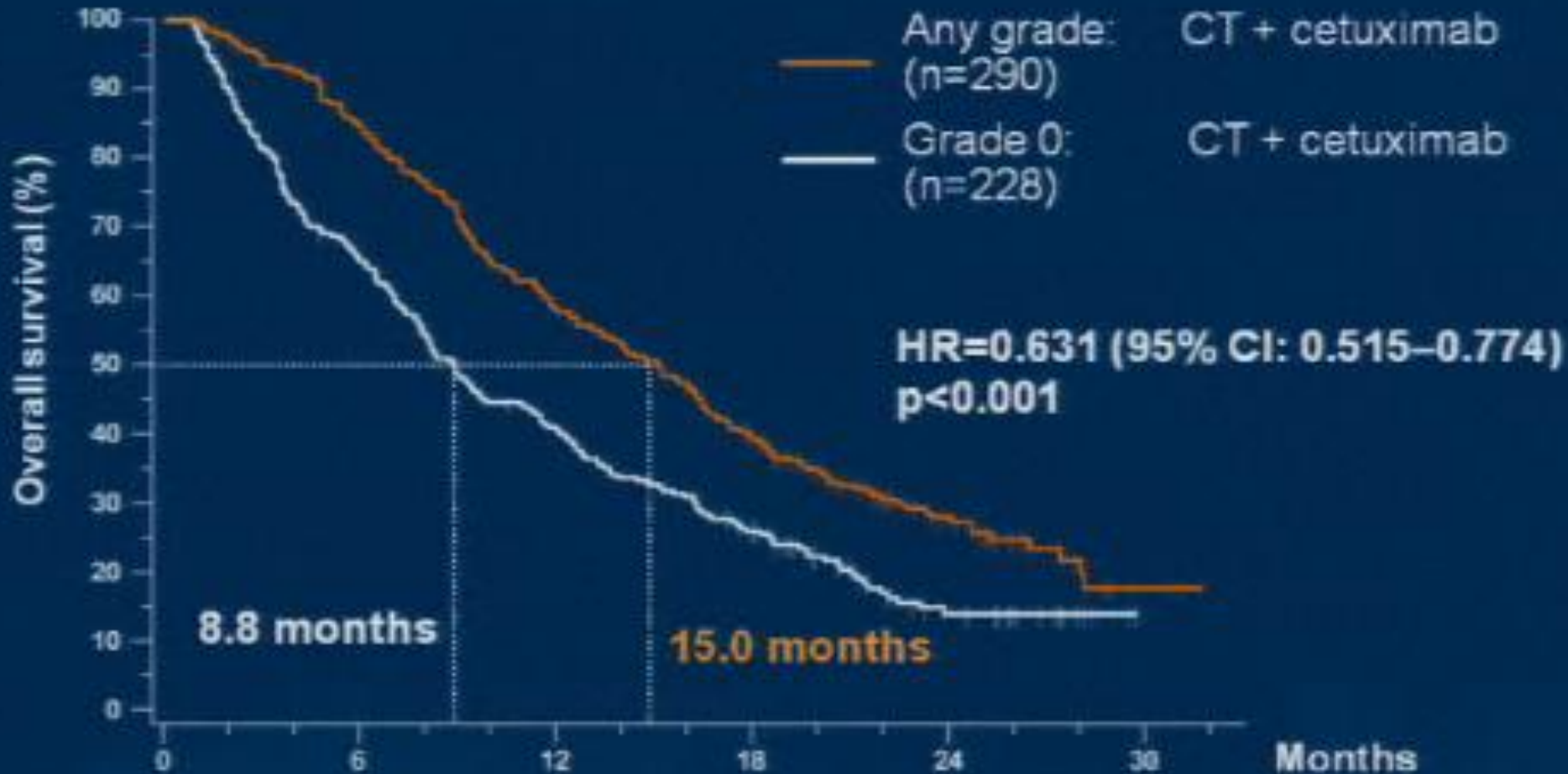
Biomarker	Status	C225 + chemo	Chemo	HR	P-value
Median OS (months)	FISH +	11.6	9.9	0.85	0.44
	FISH -	10.6	10	0.91	0.56
Median PFS	FISH +	4.2	4.4	0.8	0.33
	FISH -	4.2	5.2	1.05	0.77
RR	FISH +	36.7%	26.4%	-	0.26
	FISH -	32.9%	34.7%	-	0.8

FLEX Rash as a Clinical Biomarker

- Pre-planned analysis defined as acne-like rash between days 1-21
- Any grade 1-3 rash (56%) versus no rash (44%)

1 st cycle Rash (Grade) N=518	# patients
0	228 (44%)
1	170 (33%)
2	92 (18%)
3	28 (5%)
4	0

OS by 1st-cycle rash



Median OS

Grade 1-3 (n=290)

15 months

Grade 2-3 (n=120)

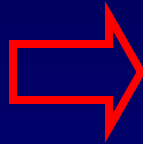
14.7 months

Summary Abstract #8007

- FLEX Trial biomarker analysis did not demonstrate any predictive value to KRAS mutation nor EGFR gene copy number by FISH.
- The only clinical biomarker that predicts for improved OS is the development of the 1st cycle rash.

Tsao's Conclusions: Neoadjuvant/Adjuvant Therapy

**Neoadjuvant
& Adjuvant
Chemo**



Adjuvant chemotherapy is still standard of care

Administer adjuvant chemo (cisplatin-doublet) in good PS

patients with stages II and III. Also consider in IB pts with tumors ≥ 4 cm

In stage IB/II patients, preop chemo does not downstage patients and alter resectability nor improve survival.

No significant difference in DFS or OS between preop or adjuvant chemo even though more chemotherapy was given preop than in the adjuvant setting in stage I/II patients.

Tsao's Conclusions: ChemoXRT

ChemoXRT

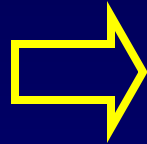


Thalidomide + chemoXRT does not work and increases thrombotic events.

Carbo-pemetrexed-cetuximab + XRT had similar outcomes to carbo-pem + XRT. Several trials underway to explore these pemetrexed and cetuximab concurrent regimens further.

Tsao's Conclusions: Maintenance

Maintenance



**Is not standard of care yet but
can be considered in specific
subpopulations of patients:**

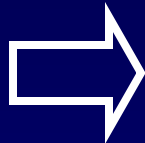
**Young, excellent PS, sensitive
EGFR mutations**

**However, need to weigh QOL
with PFS benefit to determine
if it is worth it.**

**Awaiting OS results from
additional maintenance trials.**

Tsao's Conclusions: Biomarkers

Biomarkers



Sensitive EGFR mutation patients should receive frontline EGFR TKI therapy. If they did not receive EGFR TKI frontline, they should receive it second line or as maintenance therapy.

No other biomarkers have predictive ability in NSCLC – Kras mutations are not reliable negative predictors and EGFR IHC is not predictive.

In large phase III trials, EGFR FISH does not predict for survival benefit in NSCLC patients treated with cetuximab.