Recent Advances in Chemo and Targeted therapy of NSCLC

Tarun Puri MD,DNB,ECMO

Disclosure

- Medical Advisor Oncology - Eli Lilly
- Opinion expressed in this presentation is of the speaker and not reflective of recommendations of “Eli Lilly and company”

Worldwide incidence for lung cancer

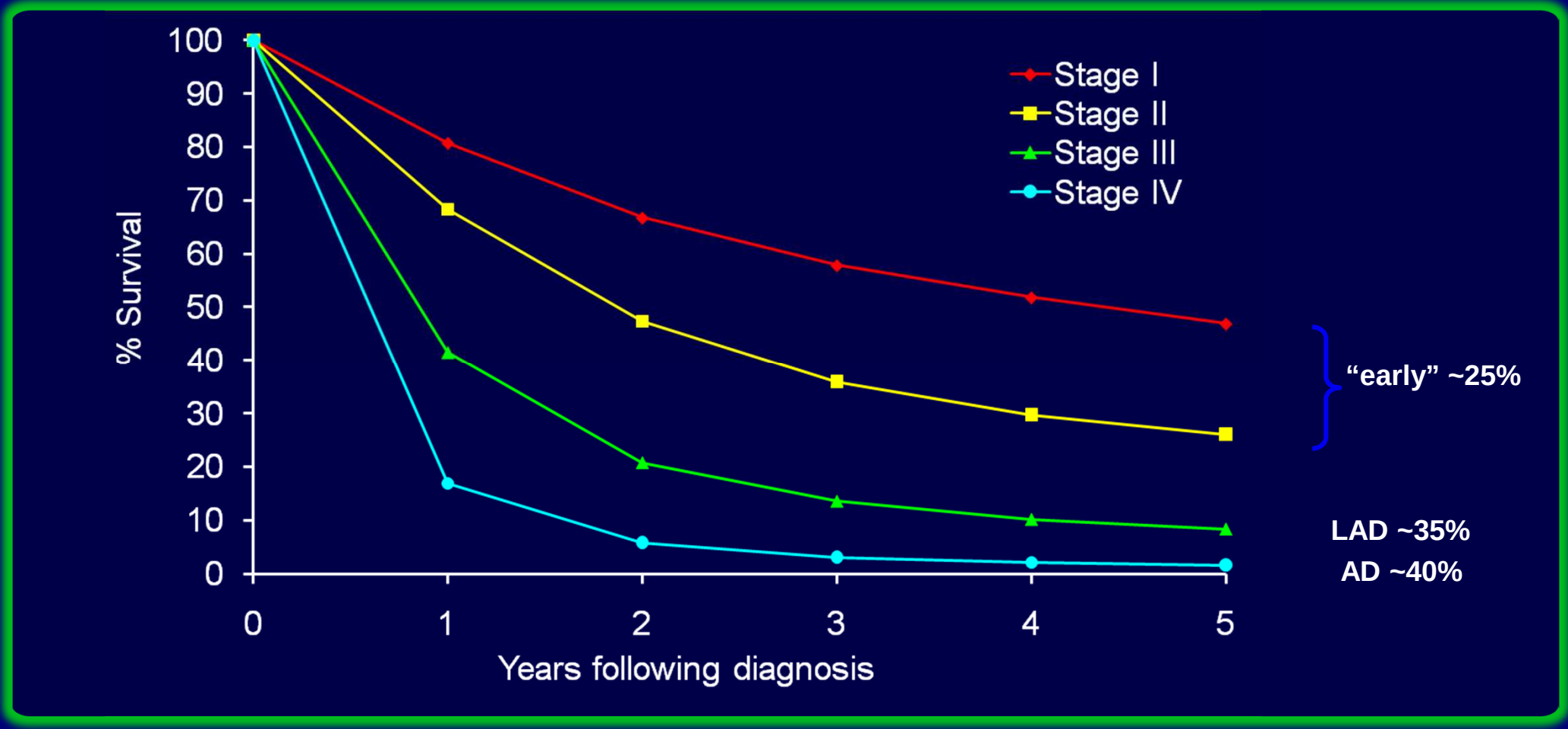
- **Lung cancer is the most common cancer in the world**

Lung Cancer	Incidence
World	>1.3 million
Continent	% of World
Asia	49
Europe	28
North America	17
Central/South America	4
Africa	1

- Lung cancer is the most common cause of cancer deaths in the world

Kamangar et al. J Clin Oncol. 2006;24:2137-2150.

NSCLC:
Survival by stage at diagnosis*



*Historical data; recent developments and increases in survival not reflected
Adapted from Greene FL, et al (eds). *AJCC Cancer Staging Manual*. 6th ed. 2002.

Why Are The Survival Rates So Low?

- Majority present with late-stage disease
  - Effective and efficient screening tools needed
- Older patients with significant co-morbidities
  - 80% are current or former smokers
- Chemotherapy (and radiation) only somewhat effective
  - Why? How are cells resistant?
  - Who should we target? What drugs should we use?

Standard Therapy for NSCLC

- "Early stage" – surgical resection
  - Benefit of adjuvant chemotherapy for appropriate patients
- "Locally advanced" – combined radiation and chemotherapy
  - Sometimes surgery
- "Advanced" or metastatic – palliative chemotherapy and/or radiation
  - Combinations of chemotherapy agents
  - Newer targeted drugs

Systemic Treatments for advanced NSCLC patients

- Chemotherapy

  Cisplatin, carboplatin, gemcitabine, paclitaxel, docetaxel, vinorelbine, pemetrexed, irinotecan, etoposide etc.

- Targeted therapy

  Gefitinib, erlotinib, bevacizumab, cetuximab etc.

Selecting treatments for patients

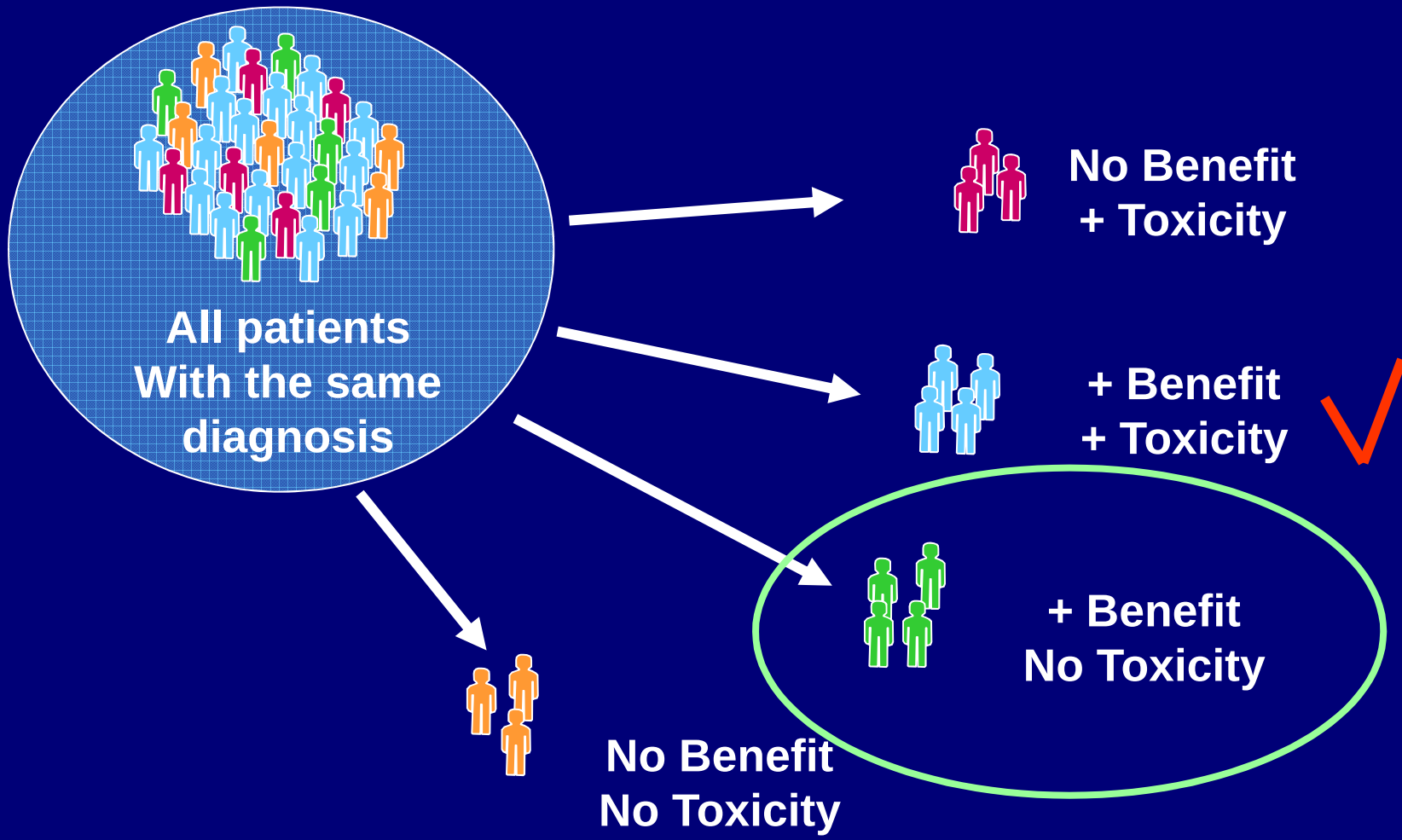
- Clinical selection

  Stage, Performance Status, Age, Pathology, Gender, Smoking status, Ethnicity

- Molecular selection

  EGFR mutation / FISH, k-ras mutation, Thymidylate synthase etc.

Individualized treatment for NSCLC



Walgren, R. A. et al. J Clin Oncol 2005 ; 23:7342-7349

Definition of a “Biomarker”

“Indicator signaling an event or condition in a biological system or sample and giving a measure of exposure, effect, or susceptibility*.”

- Nordberg M, et al. *Pure Appl Chem 2004;*76:1033-1082.

- **Blood, bodily fluids and/or tissue**
- **Reproducible**
- **Affordable**
- **Technically feasible**
- **Results in something clinically meaningful**

*** Note: Such an indicator may be a measurable chemical, biochemical, physiological, behavioral or other alteration within an organism.**

Biomarkers

Predictive marker:

- Characteristic of a patient or a tumor that identifies a subgroup within which the effect of a treatment will be different from those who do not have this feature

Prognostic marker:

- Characteristic that identifies a subgroup who will have a different outcome regardless of treatment effects

Biomarkers in NSCLC: Simple histology

- Within NSCLC are subcategories of squamous, adeno, BAC, and large cell:
  - Squamous (Sq) histology is associated with:
    - High level of thymidylate synthase (TS)
    - EGFR expression but not mutations
    - Rare K-ras mutations
  - Adenocarcinoma histology is associated with:
    - EGFR mutations
    - K-ras mutations
- Histology now plays an important role in treatment selection:
  - "not otherwise specified" is no longer an acceptable distinction

Biomarkers in NSCLC: EGFR pathway

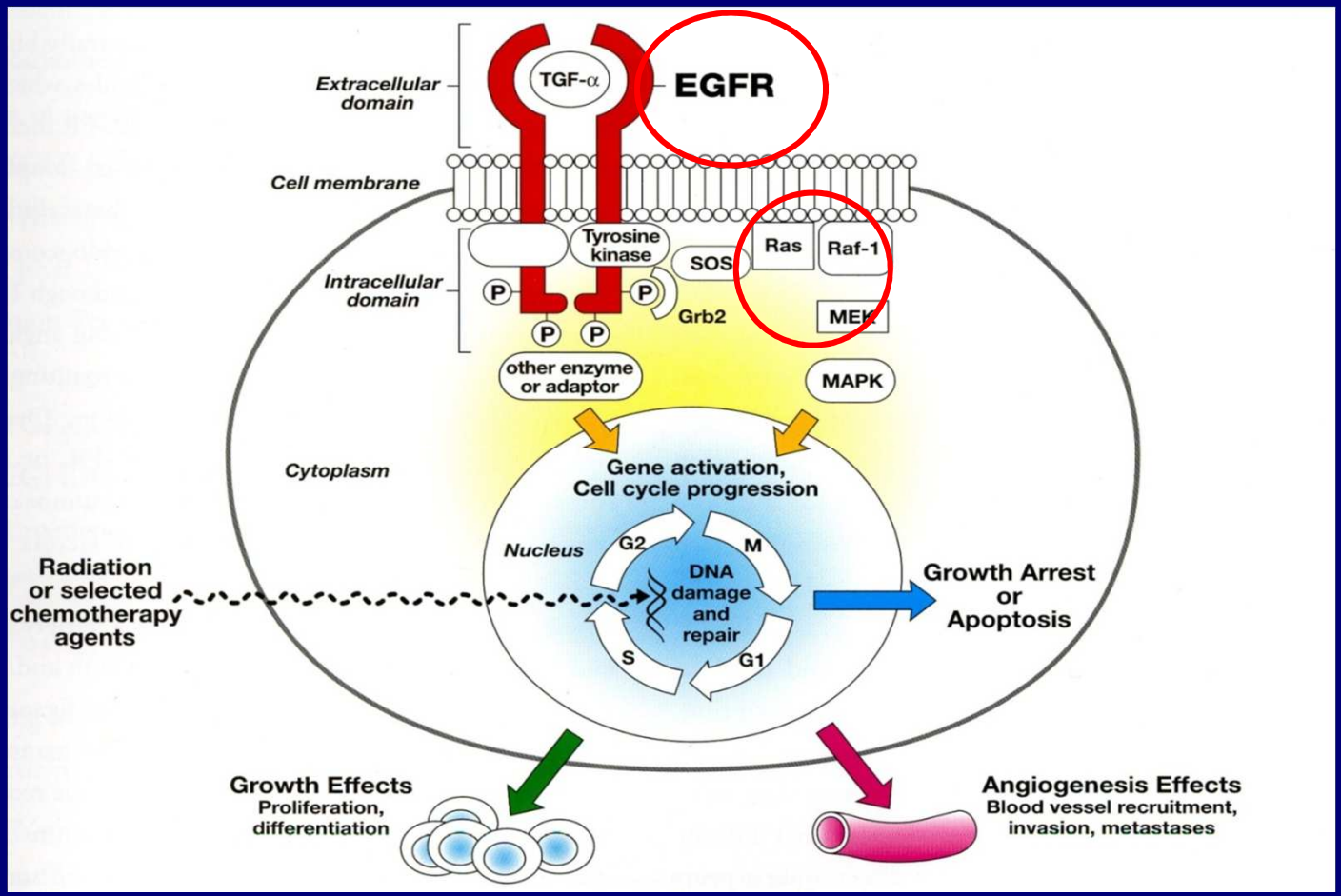


Figure reproduced with permission from Huang SM, Harari PM. *Investig New Drugs* 2000;17:259-69.

Biomarkers in NSCLC: EGFR pathway

- Quantification of EGFR
  - IHC intensity of staining
  - FISH overexpression
- Function of EGFR
  - Activating mutations
  - Resistance mutations

Biomarkers in NSCLC: Downstream in the EGFR pathway

- 3 genes H-ras, K-ras, N-ras
- Ras mutations are detectable in ~20% of lung cancers, usually in smokers
  - 90% of mutations are due to K-ras
- K-ras mutations appear to be important for:
  - EGFR TKI therapy as a negative predictor of response
  - Lack of responses to adjuvant cisplatin-vinorelbine chemotherapy

Huncharek M, et al. *Carcinogenesis* 1999;20:1507–10.
Pao, W, et al. *PLoS Med* 2005;2:e17.

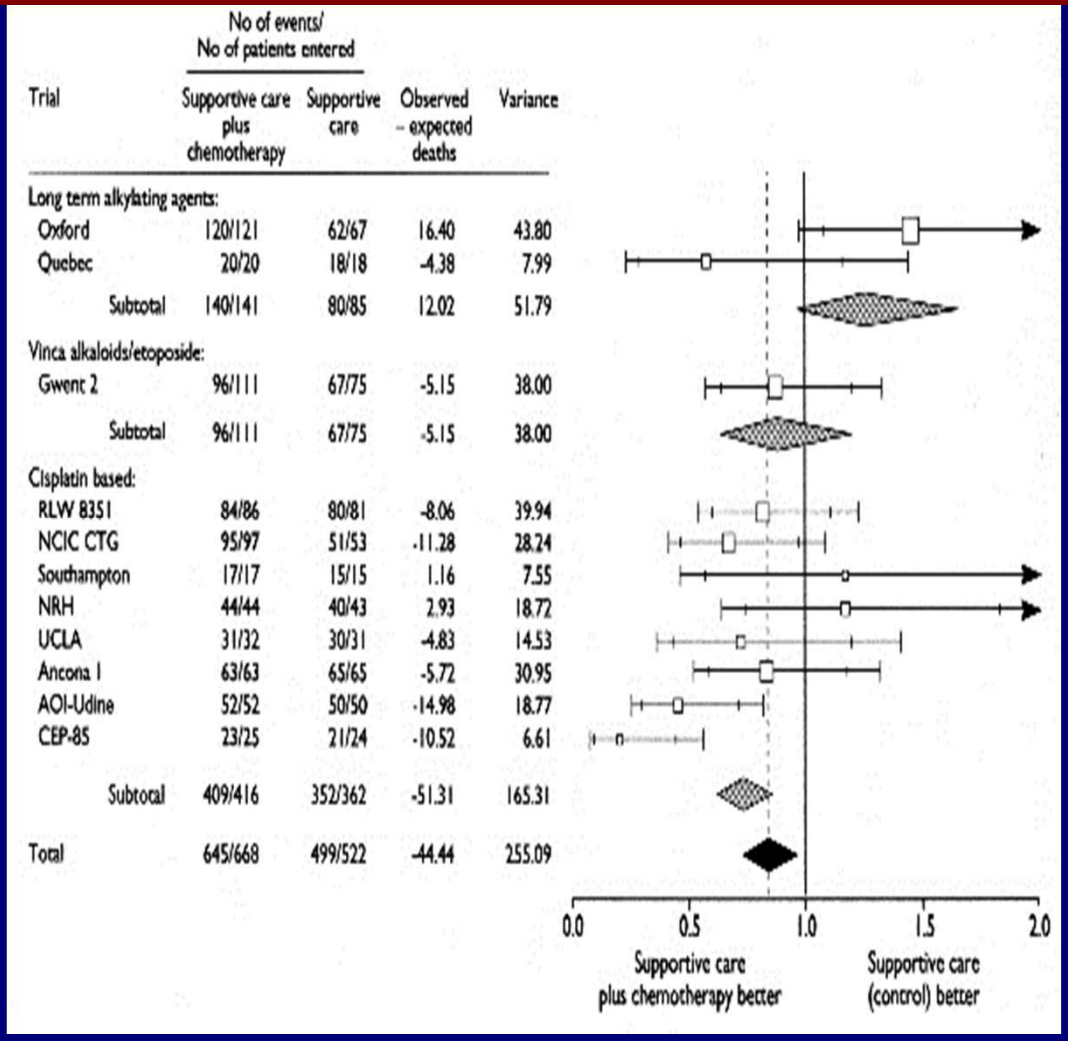
Biological Correlates: What goes in…

Quality of any biomarker study will depend on what goes into it:

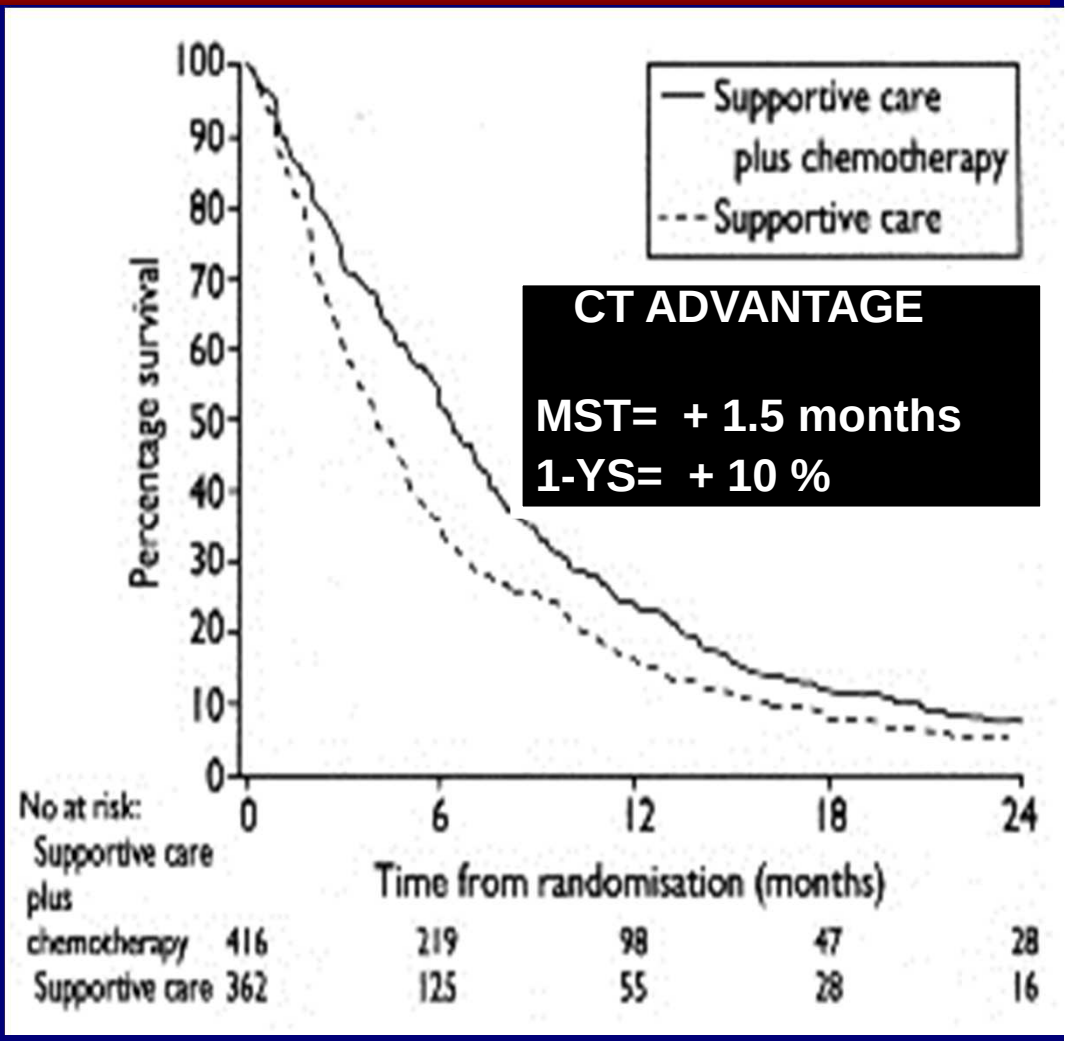
- Characteristics of the disease
- Characteristics of the individual patient
- Characteristics of the actual sample:
  - How many patients participate?
  - Quality of the samples?
    - blocks vs. slides
  - Consistency and reproducibility of testing?

ADVANCED-NSCLC TREATMENT

"Old" CT Cis-based > BSC

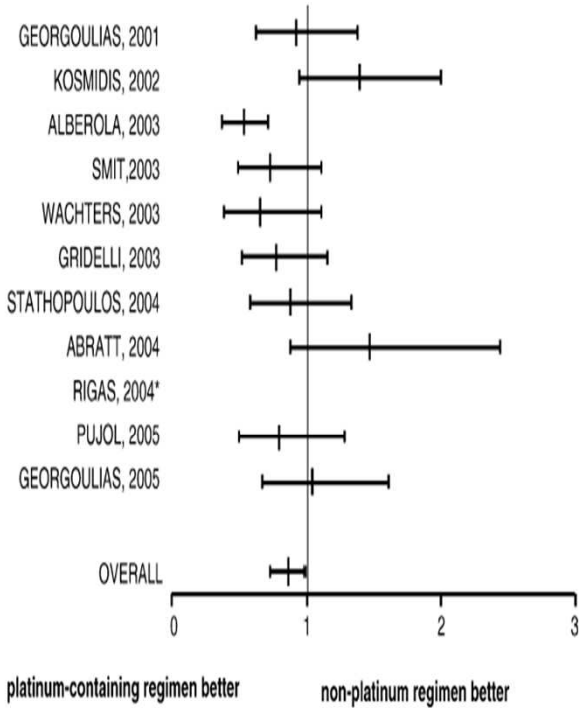


Trial	No of events/ No of patients entered: Supportive care plus chemotherapy	Supportive care	Observed – expected deaths	Variance
Long term alkylating agents:				
Oxford	120/121	62/67	16.40	43.80
Quebec	20/20	18/18	-4.38	7.99
Subtotal	140/141	80/85	12.02	51.79
Vinca alkaloids/etoposide:				
Gwent 2	96/111	67/75	-5.15	38.00
Subtotal	96/111	67/75	-5.15	38.00
Cisplatin based:				
RLW 8351	84/86	80/81	-8.06	39.94
NCIC CTG	95/97	51/53	-11.28	28.24
Southampton	17/17	15/15	1.16	7.55
NRH	44/44	40/43	2.93	18.72
UCLA	31/32	30/31	-4.83	14.53
Ancona I	63/63	65/65	-5.72	30.95
AOI-Udine	52/52	50/50	-14.98	18.77
CEP-85	23/25	21/24	-10.52	6.61
Subtotal	409/416	352/362	-51.31	165.31
Total	645/668	499/522	-44.44	255.09



Meta-Analysis, BMJ 1995

Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials



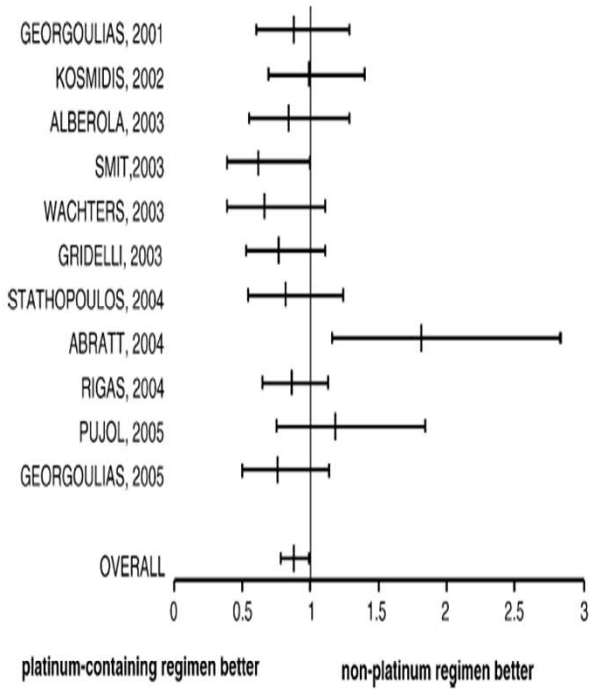


Fig. 3 Overall response rate with platinum-based vs. non-platinum chemotherapy regimens. The summary odds ratio for the risk of being non responder to chemotherapy was 0.87 (95% CI, 0.73–0.99, $p = 0.049$) indicating a 2.5% benefit for response for patients treated with a platinum-based chemotherapy doublet (*, data non available).

ng regimens
iction in the
latinum-free

with platinum-based vs. non-platinum chemotherapy regimens. The summary odds ratio
/ear was 0.88 (95% CI, 0.78–0.99, $p = 0.044$) indicating a 2.94% survival benefit at 1 year
atinum-based chemotherapy doublet.

chemotherapy without a perceptible increase in risk of toxic-death.

JL Pujol et al, Lung Cancer 2006

ECOG 1594: Treatment Schema

Stage IIIB or IV NSCLC patients

Stratified by:

- Extent of disease
- PS
- Weight loss
- Brain metastases

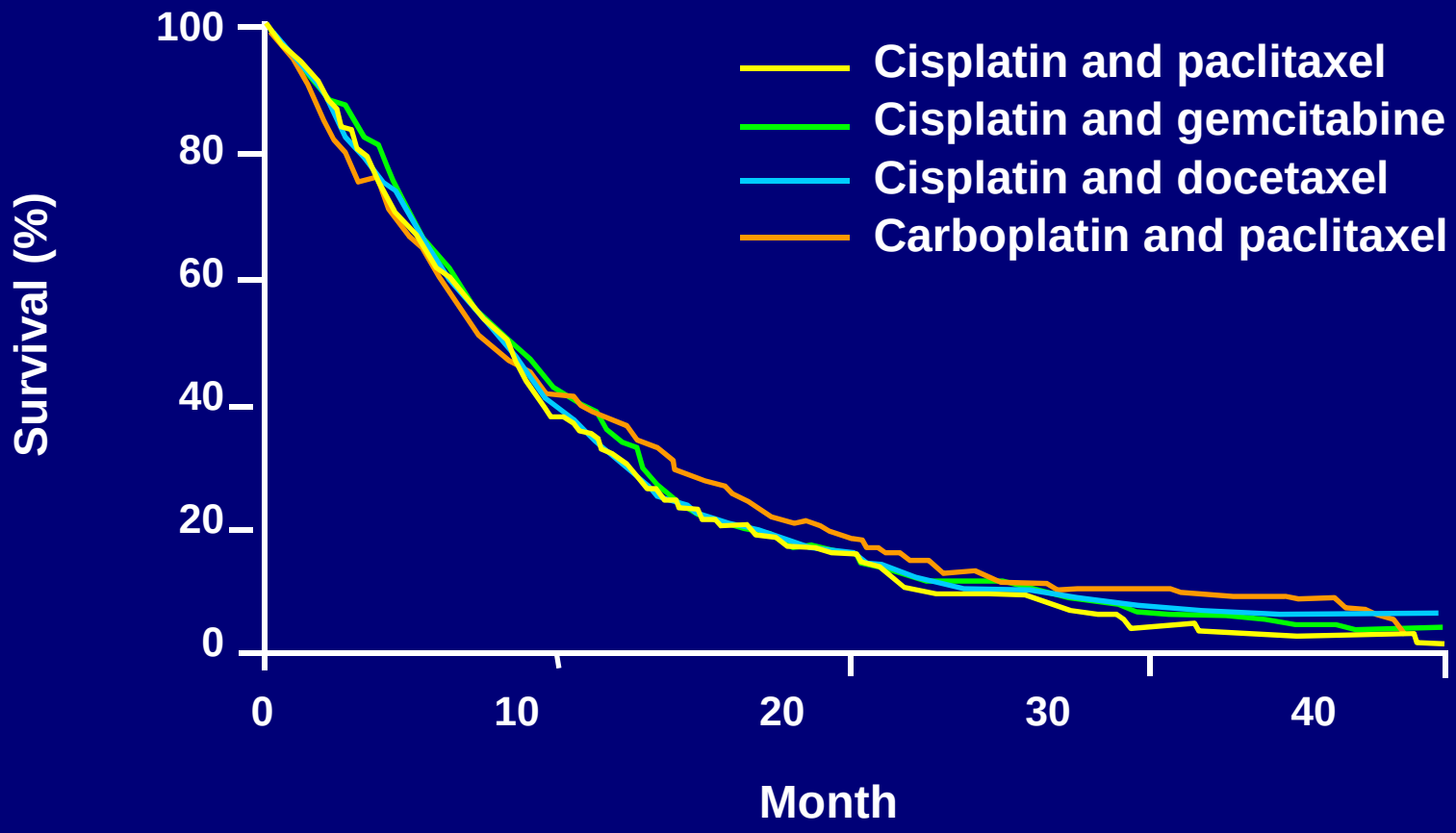
RANDOMIZE

Arm A*	q 3 wk	Paclitaxel: 135 mg/m^2, day 1 Cisplatin: 75 mg/m^2, day 2
Arm B	q 4 wk	Cisplatin: 100 mg/m^2, day 1 Gemcitabine: 1000 mg/m^2, days 1, 8, 15
Arm C	q 3 wk	Docetaxel: 75 mg/m^2, day 1 Cisplatin: 75 mg/m^2, day 1
Arm D	q 3 wk	Paclitaxel: 225 mg/m^2, day 1 Carboplatin: AUC=6, day 1

*Control arm.

Schiller JH, et al. *J Clin Oncol* 2002;346:92-98

ECOG 1594: Kaplan-Meier Estimates of Overall Survival



Schiller et al. *N Eng J Med* 2002; 346:92-98

Challenge in 2000 : Which drug to choose?

Cisplatin / Carboplatin

+ **Gemcitabine Docetaxel Vinorelbine Paclitaxel**

Treatment selection based on clinical parameters

Pathology
Gender
Smoking status
Performance status
Age
Response/reaction to therapy

European Consensus Panel on Treatment of Advanced NSCLC Patients with Performance Status 2

Annals of Oncology 15: 419–426, 2004
DOI: 10.1093/annonc/mdh087

Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel

C. Gridelli[1]*, A. Ardizzoni[2], T. Le Chevalier[3], C. Manegold[4], F. Perrone[5], N. Thatcher[6], N. van Zandwijk[7], M. Di Maio[5], O. Martelli[8] & F. De Marinis[8]

[1]Division of Medical Oncology, 'S.G.Moscati' Hospital, Avellino; [2]Department of Medical Oncology, National Institute for Cancer Research, Genoa, Italy; [3]Department of Medicine, Institute Gustave Roussy, Villejuif, France; [4]Department of Medical Oncology, Thoraxklinik, Heidelberg, Germany; [5]Clinical Trials Unit, National Cancer Institute, Naples, Italy; [6]Department of Medical Oncology, Christie Hospital, Manchester, UK; [7]Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands; [8]Fifth Pulmonary-Oncology Unit, Lung Disease Department, Forlanini Hospital, Rome, Italy

Received 1 July 2003; revised 7 October 2003; accepted 27 October 2003

Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel

Table 4. Consensus on treatment of patients with advanced NSCLC and ECOG PS2 in clinical practice

Preferred option
Single-agent chemotherapy with a third generation drug (e.g. gemcitabine, vinorelbine, taxanes)
Alternative options
Carboplatin-based doublets
Cisplatin-based doublets with attenuated doses of cisplatin

C Gridelli et al, Ann Oncol 2004

INTERNATIONAL CONSENSUS EXPERTS PANEL

April 19 th, 2004

"Treatment of advanced non small cell lung cancer in the elderly"

Istituto Piccole Ancelle di Cristo Re - Posillipo (Italy)

VOLUME 23 · NUMBER 13 · MAY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Treatment of Advanced Non–Small-Cell Lung Cancer in the Elderly: Results of an International Expert Panel

Cesare Gridelli, Matti Aapro, Andrea Ardizzoni, Lodovico Balducci, Filippo De Marinis, Karen Kelly, Thierry Le Chevalier, Christian Manegold, Francesco Perrone, Rafael Rosell, Frances Shepherd, Luigi De Petris, Massimo Di Maio, and Corey Langer

Treatment of Advanced Non–Small-Cell Lung Cancer in the Elderly: Results of an International Expert Panel

Table 5. Treatment Options for Elderly Patients With Advanced NSCLC in Clinical Practice

Single-agent chemotherapy with a third-generation drug (eg, vinorelbine, gemcitabine, taxanes) in PS 0-2 patients
Platinum-based (cisplatin or carboplatin) doublets in fit patients (PS 0-1) selected for adequate organ function
Best supportive care (in addition to chemotherapy or as exclusive therapeutic option for those patients unsuitable for active treatment)

C Gridelli et al, JCO 2005

NSCLC: 2003 ASCO treatment recommendations for advanced disease

- Chemotherapy prolongs survival and is most appropriate for individuals with good performance status (PS 0 or 1, and possibly 2)
- Chemotherapy should be a platinum-based two-drug combination regimen
- Non-platinum containing regimens may be used as alternatives to platinum-based regimens. For elderly patients, or patients with PS 2, available data support the use of single-agent chemotherapy
- Chemotherapy should be stopped at 4 cycles in patients who are not responding to treatment, and should be administered for no more than six cycles
- If chemotherapy is to be given it should be initiated while the patient still has good PS

Pfister, et al. J Clin Oncol, 22:330–353, 2004

Treatment selection based on clinical parameters

Pathology

Gender

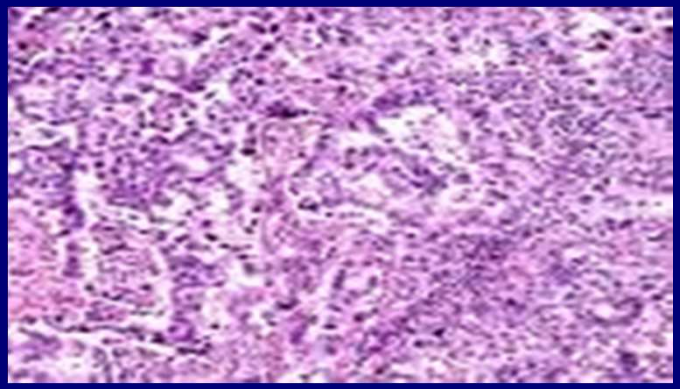
Smoking status

Performance status

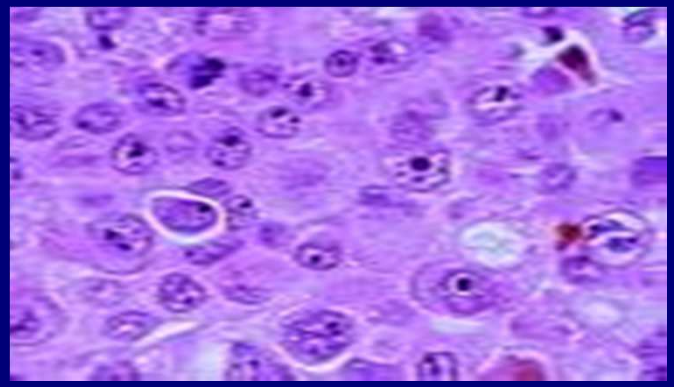
Age

Response/reaction to therapy

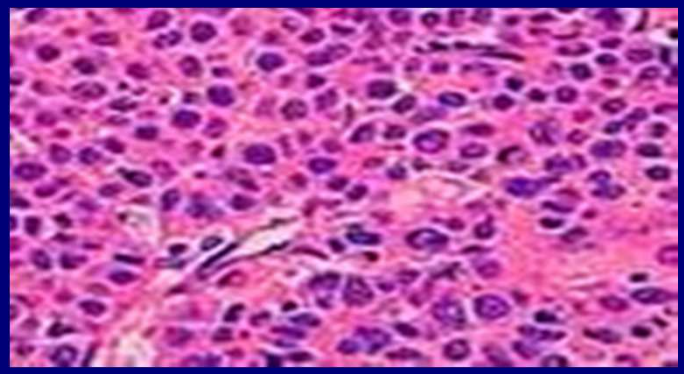
Lung Cancer - Histology



Adenocarcinoma



Squamous cell Carcinoma



Large cell Carcinoma

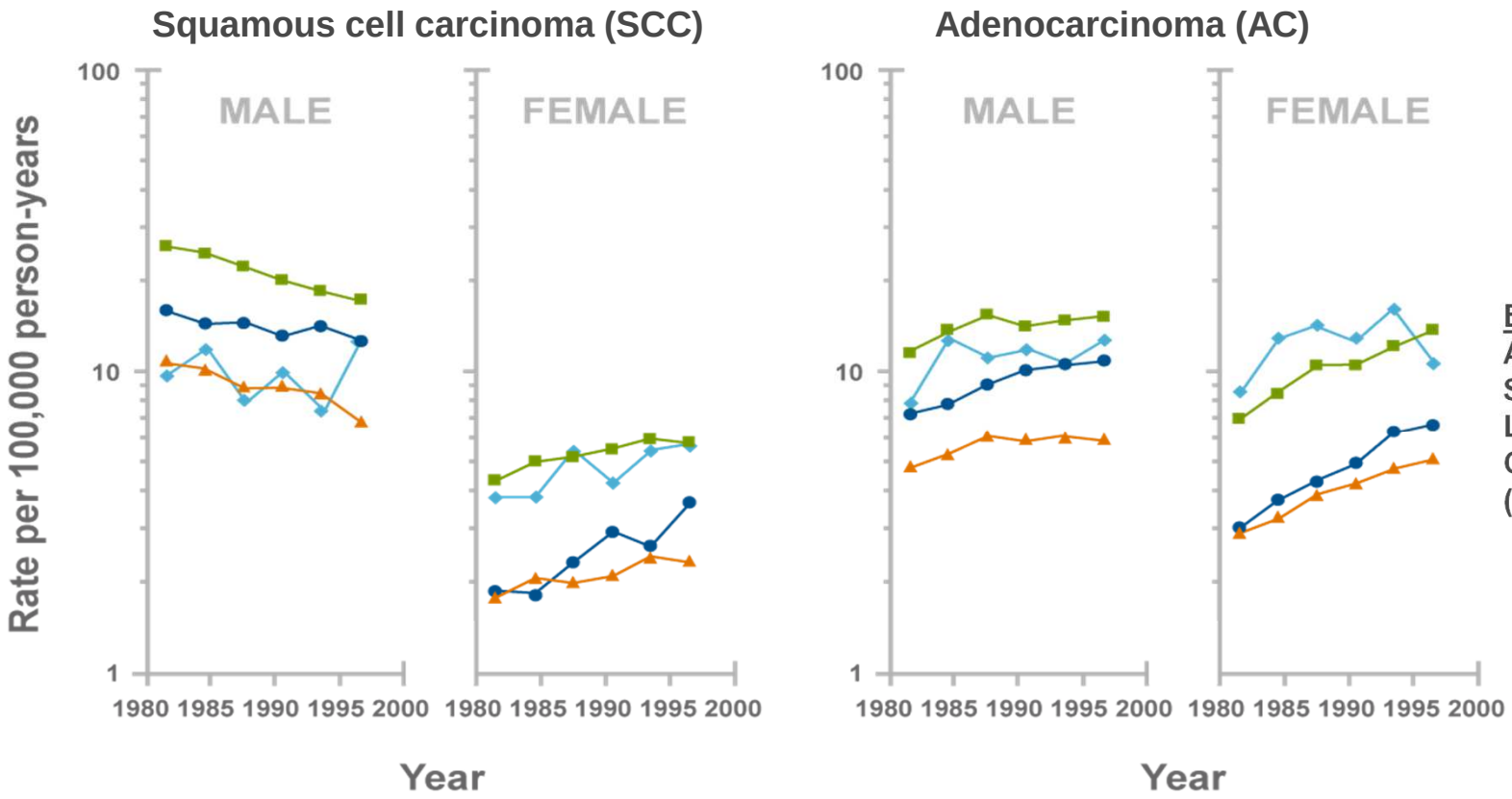
Adenocarcinoma

- Cancer arising out of glandular tissues
- Most frequent type diagnosed in lung cancer (30 – 40%)
- Common in smokers and non-smokers
- More common in women than in men
- Usually arise in the peripheral areas of lung and metastasize quickly
- Bronchoalveolar carcinoma (BAC) is a subtype of adenocarcinoma and is found more in women and is associated with scars of tuberculosis
- Early diagnosis is rare and prognosis is poor

Squamous cell carcinoma

- Accounts for 30% of lung cancers
- Strongly associated with smoking
- Tend to be more centrally located
- Forms necrotic cavities, that can be seen on X-rays
- Cell doubling rate is slow and surgical resection leads to a 30% 5 year survival rate
- 5 year survival rate of all SCC is 5 – 7%

Trends in squamous cell carcinoma and adenocarcinoma incidence rates in Europe[1]



European incidence rates[2]

AC:	34%
SC:	44%
LCC:	13%
Other**:	8%

(LCC=large-cell carcinoma)

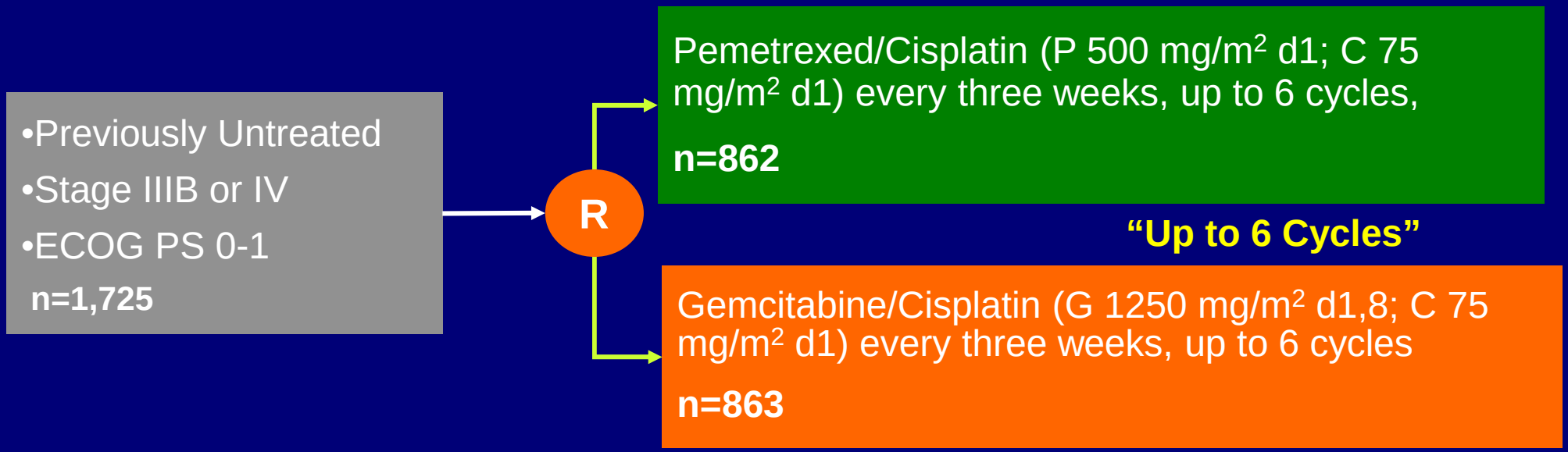
* Generally similar trends were observed in other European countries (Eindhoven Netherlands, Varese Italy, Slovenia, France, Spain, and Switzerland)

**Other includes histology types that are not clearly AC, SCC, or LCC, and may include mixed histology types

Histology may be used to determine treatment approach and may also be prognostic

1. Devesa SS, et al. Int J Cancer. 2005;117:294-299.
2. Cancer Research UK (www.cancerresearchuk.org).

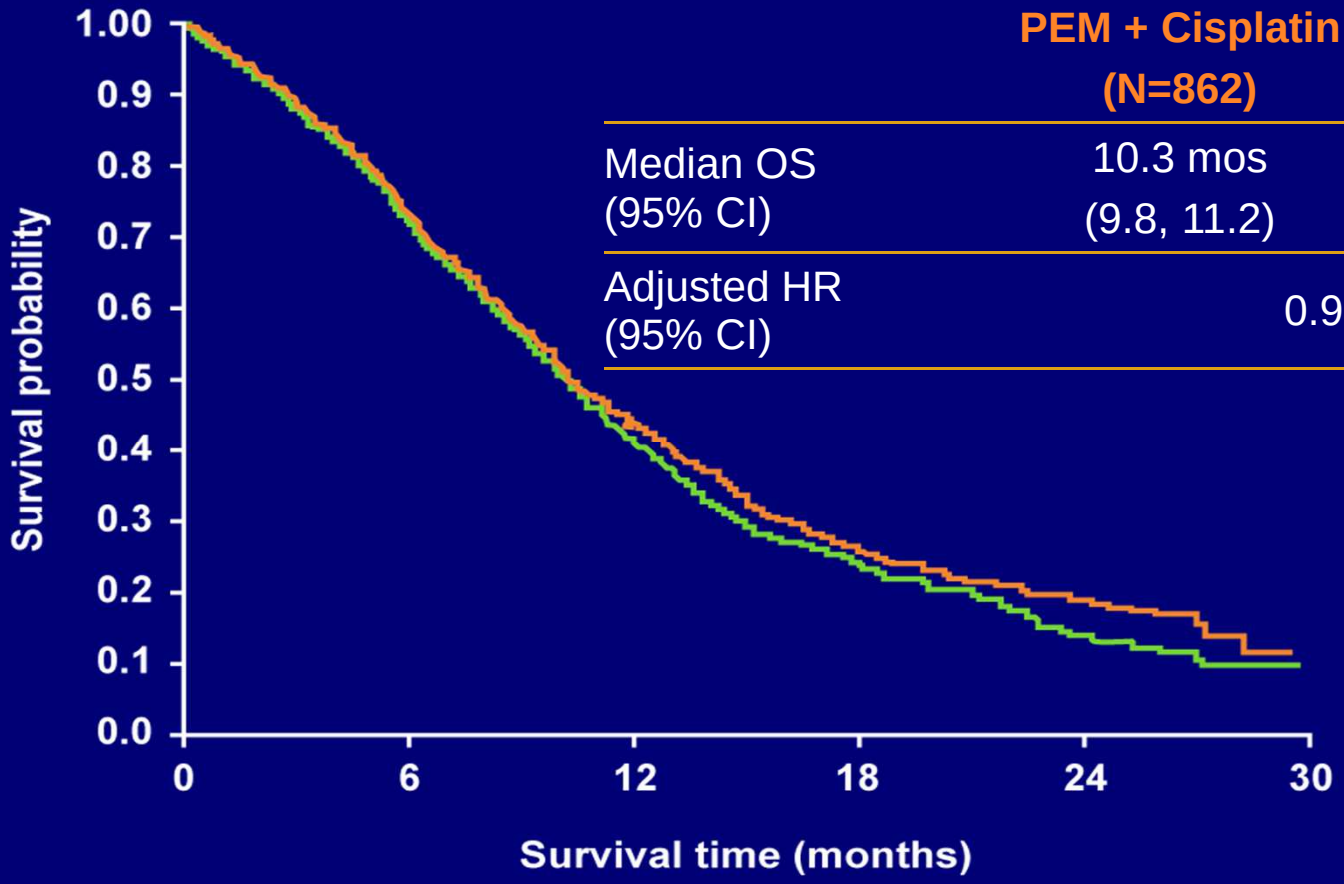
H3E-MC-JMDB Schema



- The primary endpoint: **non-inferiority, overall survival.**
- The Largest trial ever reported in this setting with 1,725 patients from 177 sites in 26 countries*

Scagliotti GV et al, J Clin Oncol 2008 20;3543-51

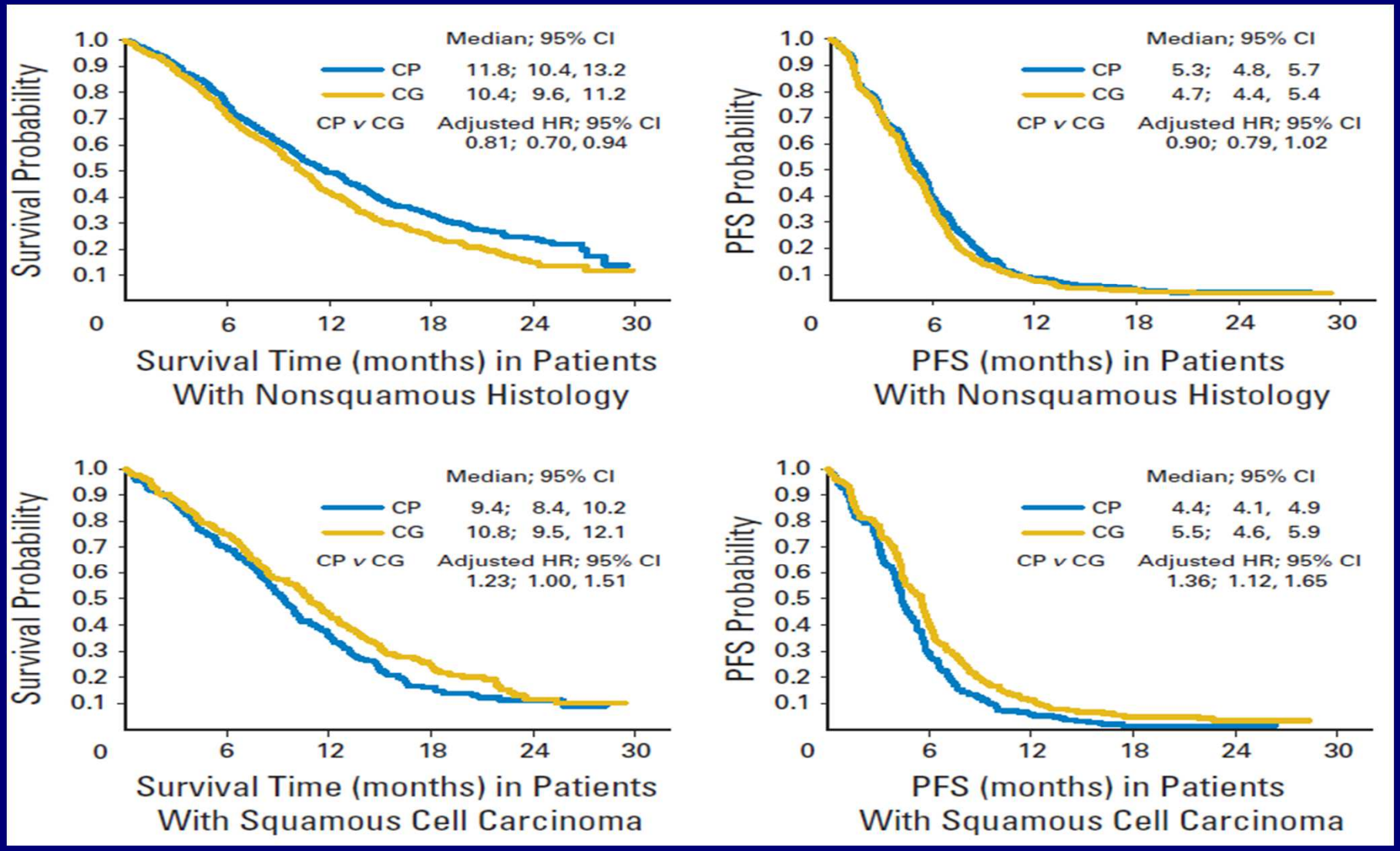
Pem/cisplatin is similar to Gem/cisplatin: Overall survival (overall population)



	PEM + Cisplatin (N=862)	Gemc + Cisplatin (N=863)
Median OS (95% CI)	10.3 mos (9.8, 11.2)	10.3 mos (9.6, 10.9)
Adjusted HR (95% CI)	0.94 (0.84, 1.05)	

Scagliotti GV et al, J Clin Oncol 2008 20;3543-51

Pem/Cis vs. Gem/Cis



Scagliotti GV et al, J Clin Oncol 2008 20;3543-51

Is the toxicity profile different among the histology groups examined in this study?

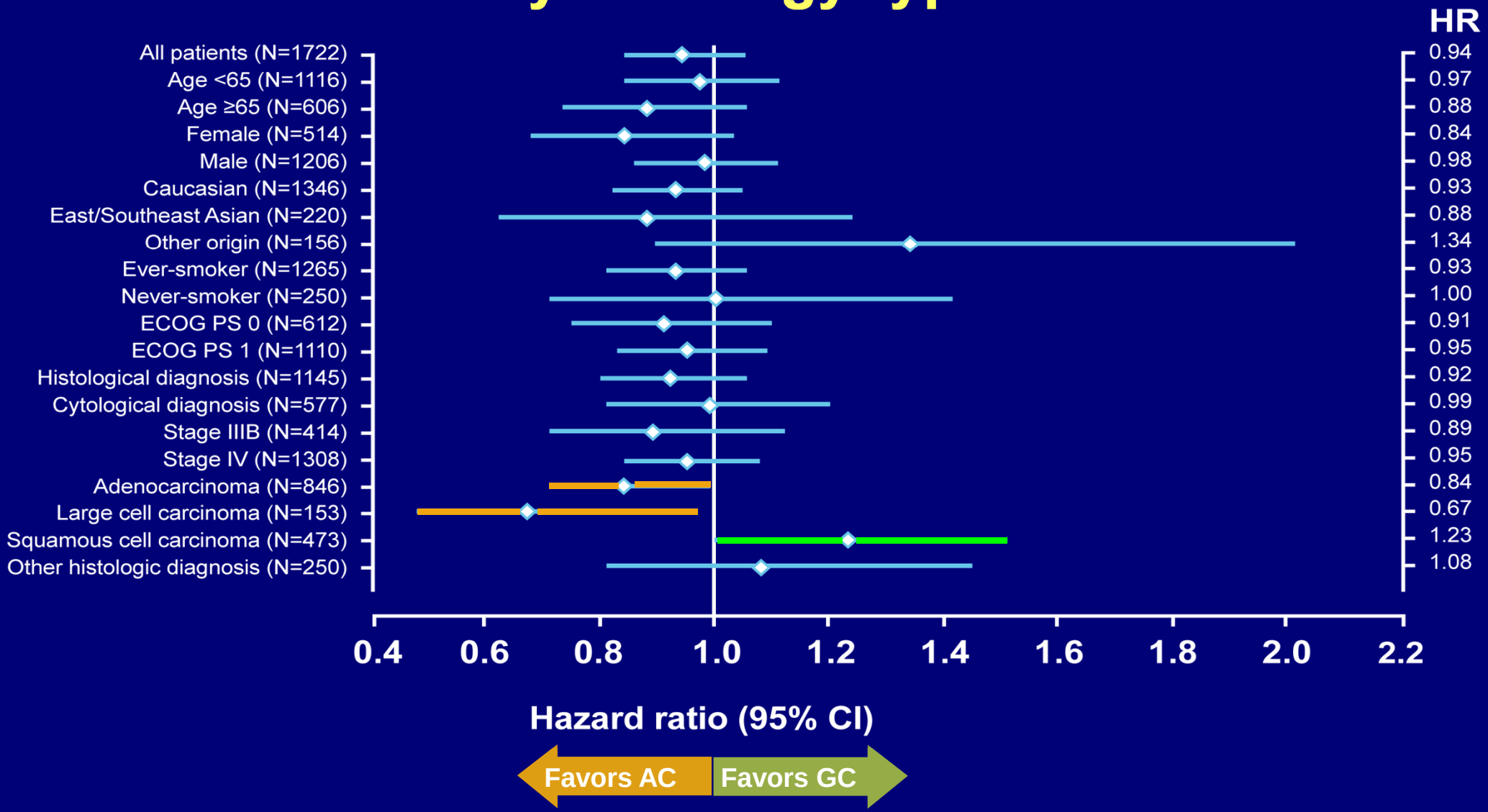
Grade 3 or 4 Toxicity: Pemetrexed + Cisplatin

G 3/4 Toxicity	Adenocarcinoma (n=425)	Large Cell Carcinoma (n=76)	Other Histology (n=103)	Squamous Carcinoma (n=235)
Neutropenia	15.5%	14.5%	12.6%	15.7%
Anemia	4.0%	3.9%	9.7%	7.2%
Thrombocytopenia	3.1%	2.6%	6.8%	5.1%
Leukopenia	4.0%	3.9%	4.9%	6.4%
Febrile neutropenia	1.4%	0.0%	1.9%	1.3%
Alopecia (all grades)	14.1%	11.8%	4.9%	11.1%
Nausea	7.3%	11.8%	7.8%	5.1%
Vomiting	5.4%	6.6%	9.7%	5.5%
Dehydration (all grades)	4.0%	3.9%	4.9%	2.1%
Fatigue	6.4%	7.9%	6.8%	6.8%

- **No clinically relevant differences were observed for the safety profile of pemetrexed + cisplatin within the histology subgroups[2]**

1. Data on file. Eli Lilly and Company
2. ALIMTA [Summary of Product Characteristics]. Eli Lilly and Co; Approved 08 April 2008.

Significant treatment-related differences observed by histology type



Scagliotti GV et al, J Clin Oncol 2008 20;3543-51

Gender, Smoking, PS, ethnics are prognostic factors

Characteristic	No. of Patients	Survival (months)				Adjusted Hazard Ratio
		Cisplatin/Pemetrexed		Cisplatin/Gemcitabine		
		Median	95% CI	Median	95% CI	
Age						
< 65 years	1,118	10.3	9.6 to 11.3	10.3	9.6 to 11.3	0.97
≥ 65 years	607	10.1	9.2 to 12.0	10.2	8.5 to 11.2	0.88
Sex						
Males	1,210	9.6	8.8 to 10.2	9.9	9.1 to 10.6	0.98
Females	515	13.3	12.3 to 15.0	11.4	10.2 to 12.7	0.84
Race						
White	1,349	10.0	9.3 to 10.8	10.1	9.3 to 10.8	0.93
East/South East Asian	220	13.8	10.2 to 17.1	11.9	9.0 to 14.7	0.88
All other	156	9.9	8.6 to 12.8	11.5	9.6 to 14.1	1.34
Smoking status*						
Former/current smoker	1,266	10.0	9.4 to 11.1	10.3	9.5 to 10.9	0.93
Never-smoker	250	15.9	13.8 to 20.2	15.3	12.1 to 22.9	1.00
Disease stage						
IIIB	415	11.9	10.0 to 14.2	11.3	9.6 to 13.1	0.89
IV	1,310	10.0	9.3 to 10.8	10.1	9.3 to 10.8	0.95
Performance status†						
0	612	13.4	11.9 to 14.9	12.2	11.3 to 13.4	0.91
1	1,110	9.1	8.1 to 9.9	9.0	8.3 to 9.8	0.95

Scagliotti GV et al, J Clin Oncol 2008 20;3543-51

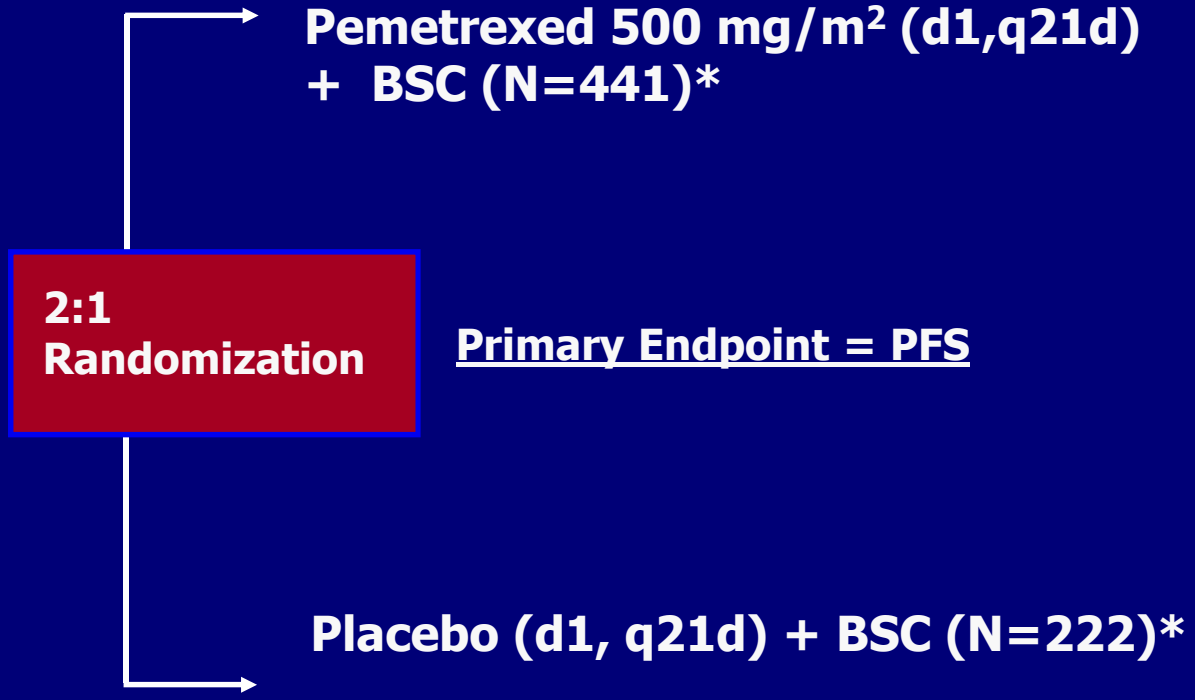
Phase III Trial of Maintenance Pemetrexed in Advanced NSCLC

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

- Stage IIIB/IV NSCLC
- 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 to induction
- non-platinum induction drug
- brain mets

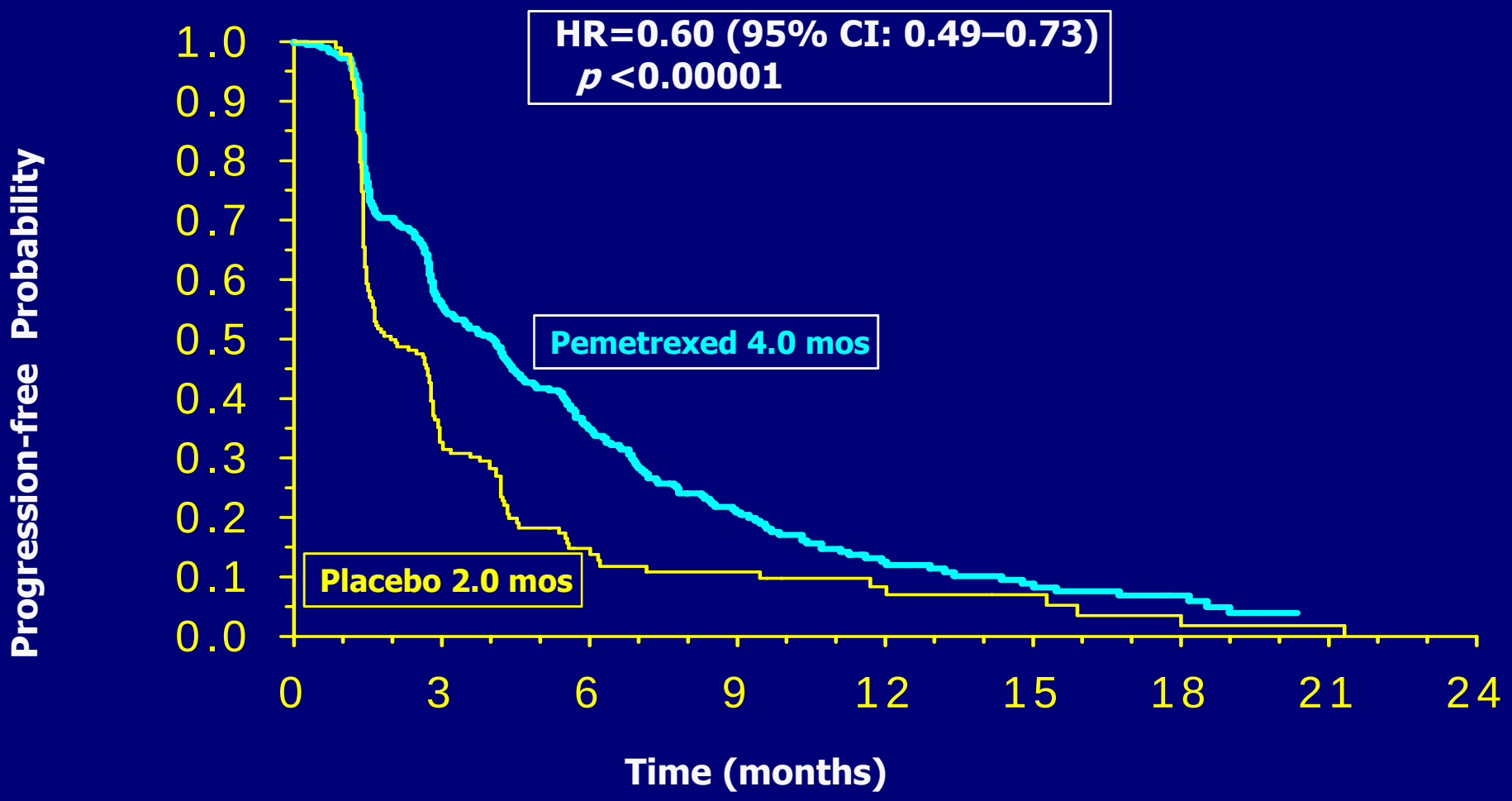


Primary Endpoint = PFS

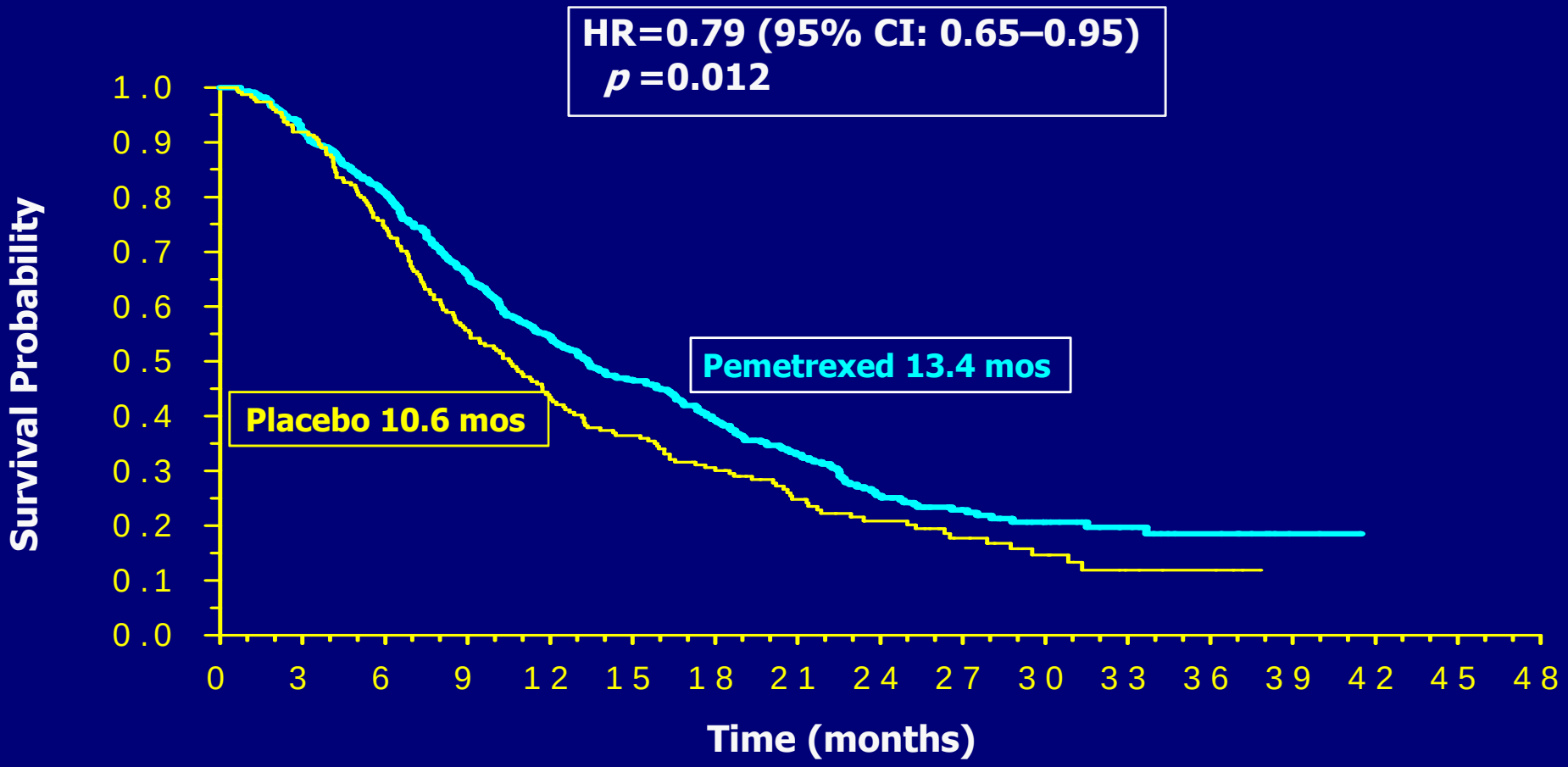
*B_{12}, folate, and dexamethasone given in both arms

Ciuleanu. *ASCO*. 2008 (abstr 8011)

Progression-free Survival



Overall Survival (Intent-to-treat Population)

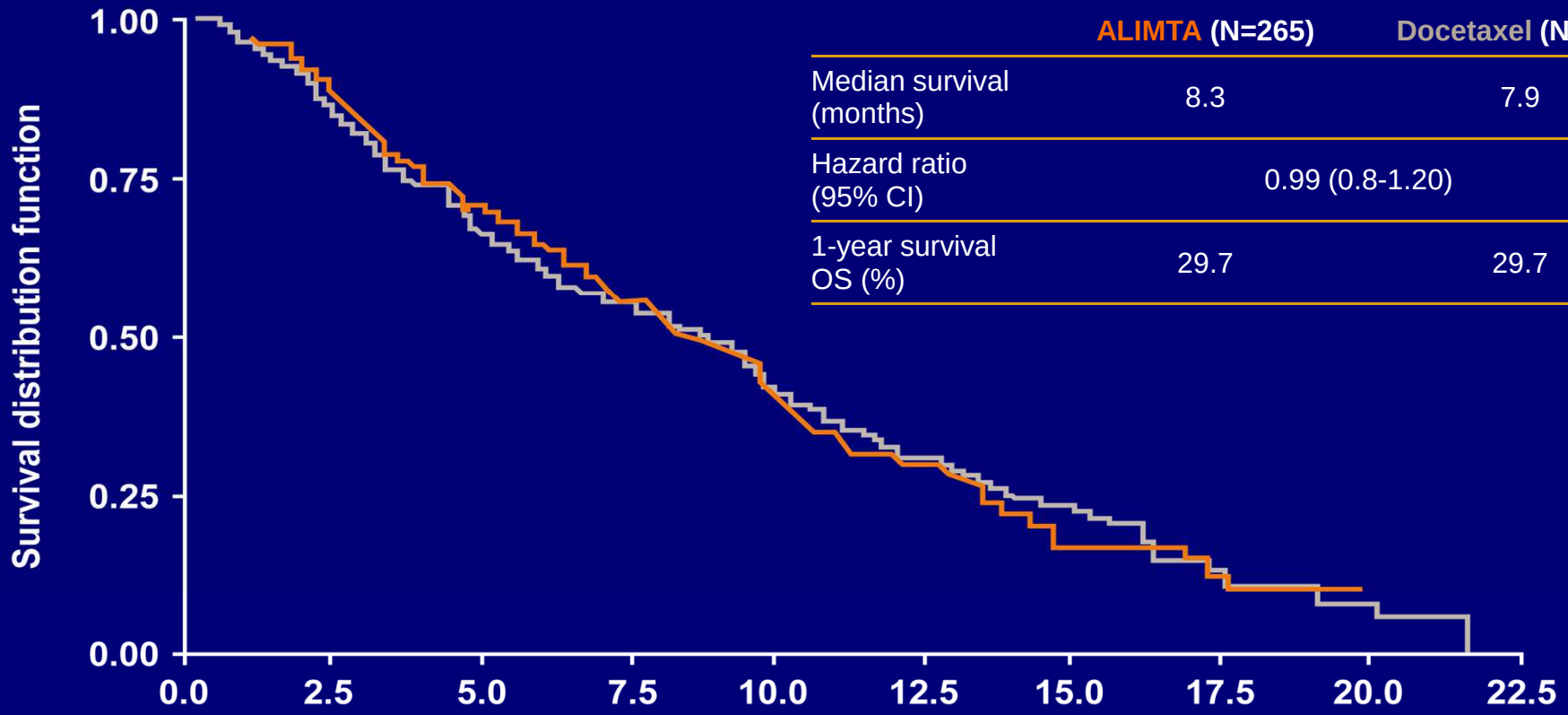


Efficacy by Histologic Groups

Histology Groups	Median OS, mos			Median PFS, mos		
	Pem	Plac	*P*-value (HR)	Pem	Plac	*P*-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*=0·033).

Survival with ALIMTA is comparable to docetaxel for second-line treatment of advanced NSCLC



	ALIMTA (N=265)	Docetaxel (N=276)
Median survival (months)	8.3	7.9
Hazard ratio (95% CI)	0.99 (0.8-1.20)	
1-year survival OS (%)	29.7	29.7

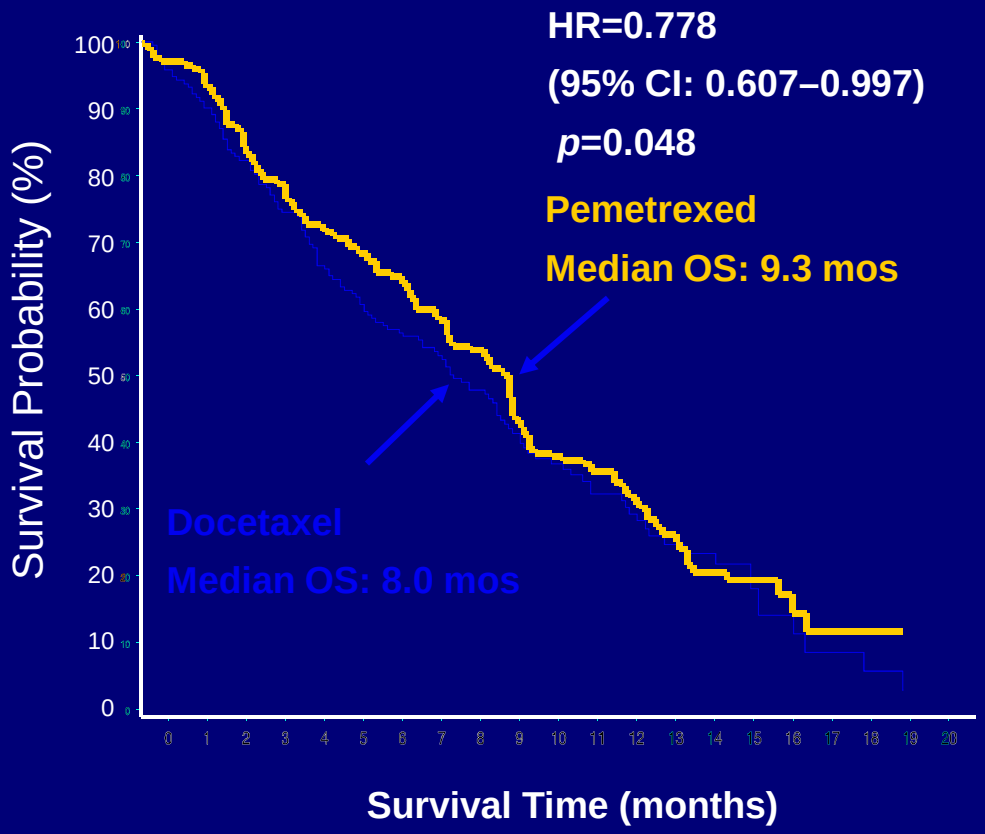
Pts at risk

ALIMTA	283	189	78	16	0
Docetaxel	288	177	78	19	1

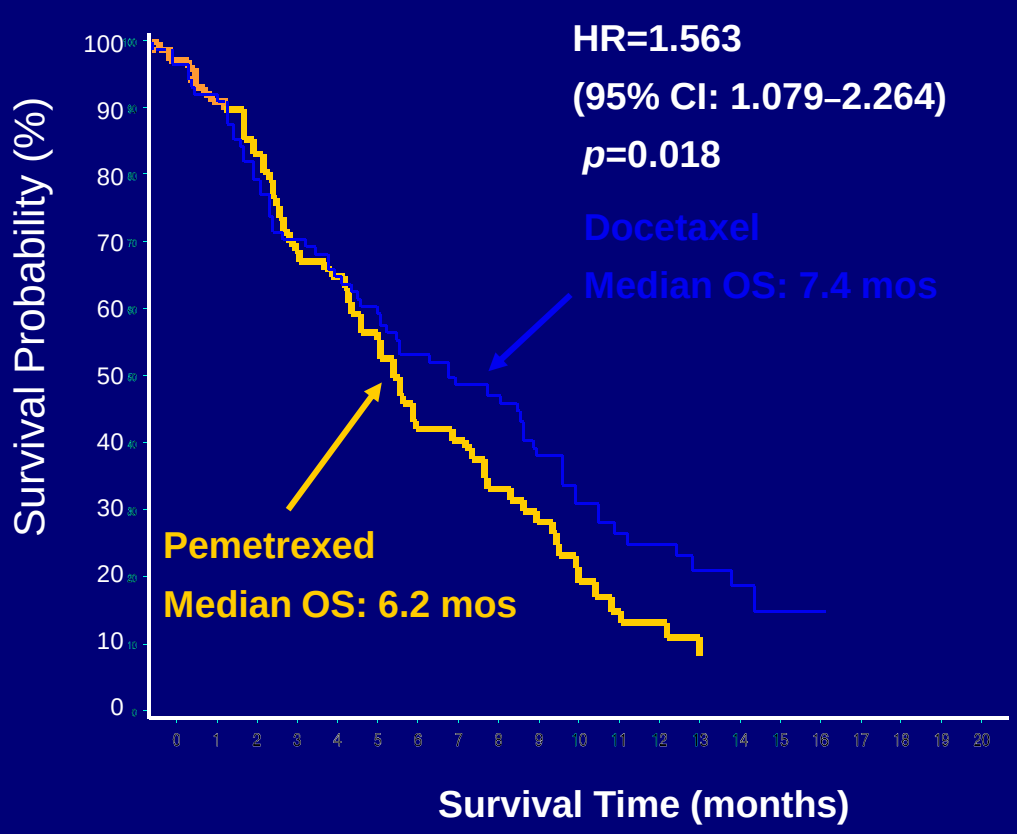
Hanna N, et al. *J Clin Oncol*. 2004;22:1589-1597.

JMEI: Retrospective Analysis of Histology and Survival

Nonsquamous* (n=399)

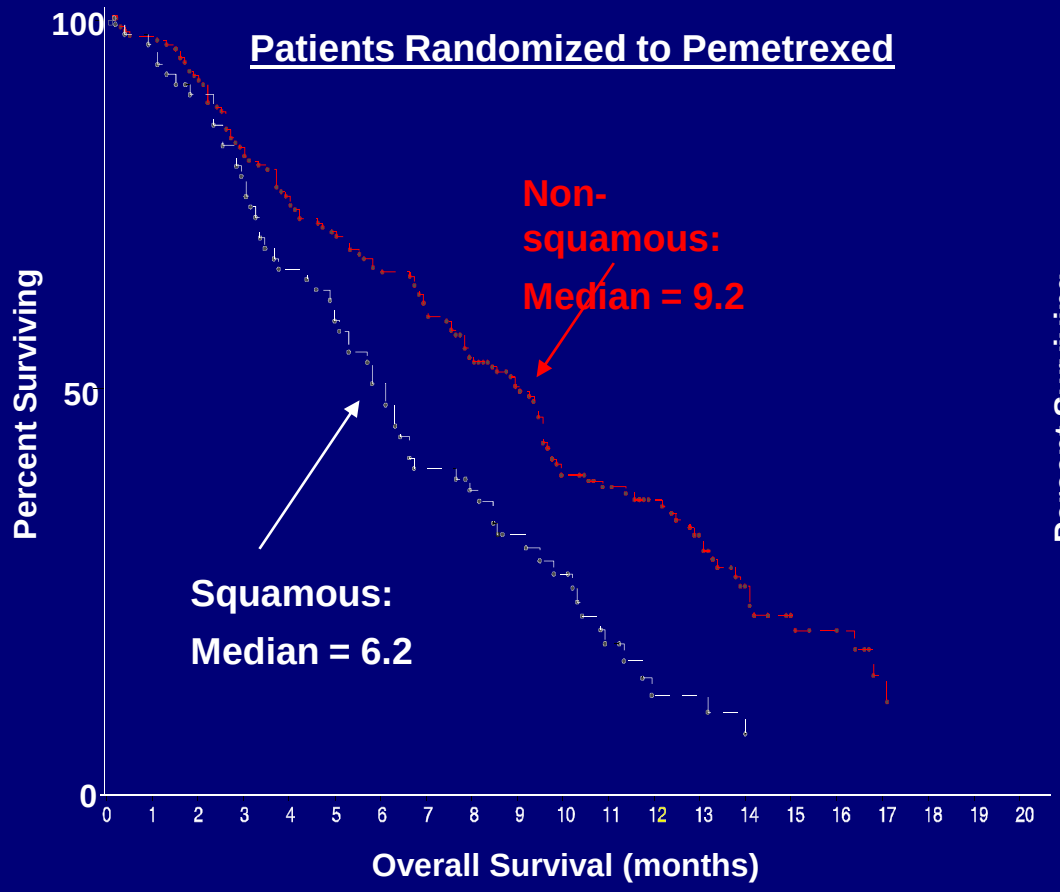


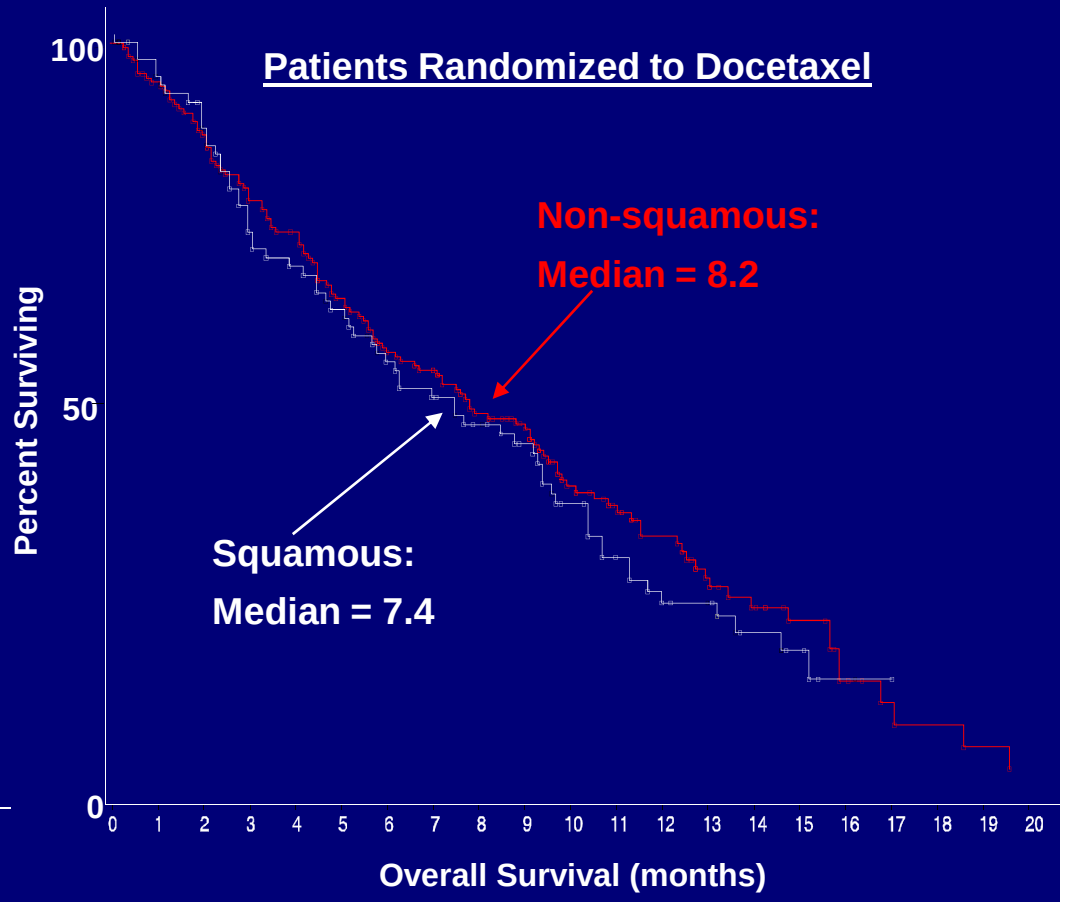
Squamous (n=172)



Peterson et al., JTO 2, 8 (suppl4), 851 (Abstr. P2-328), 2007

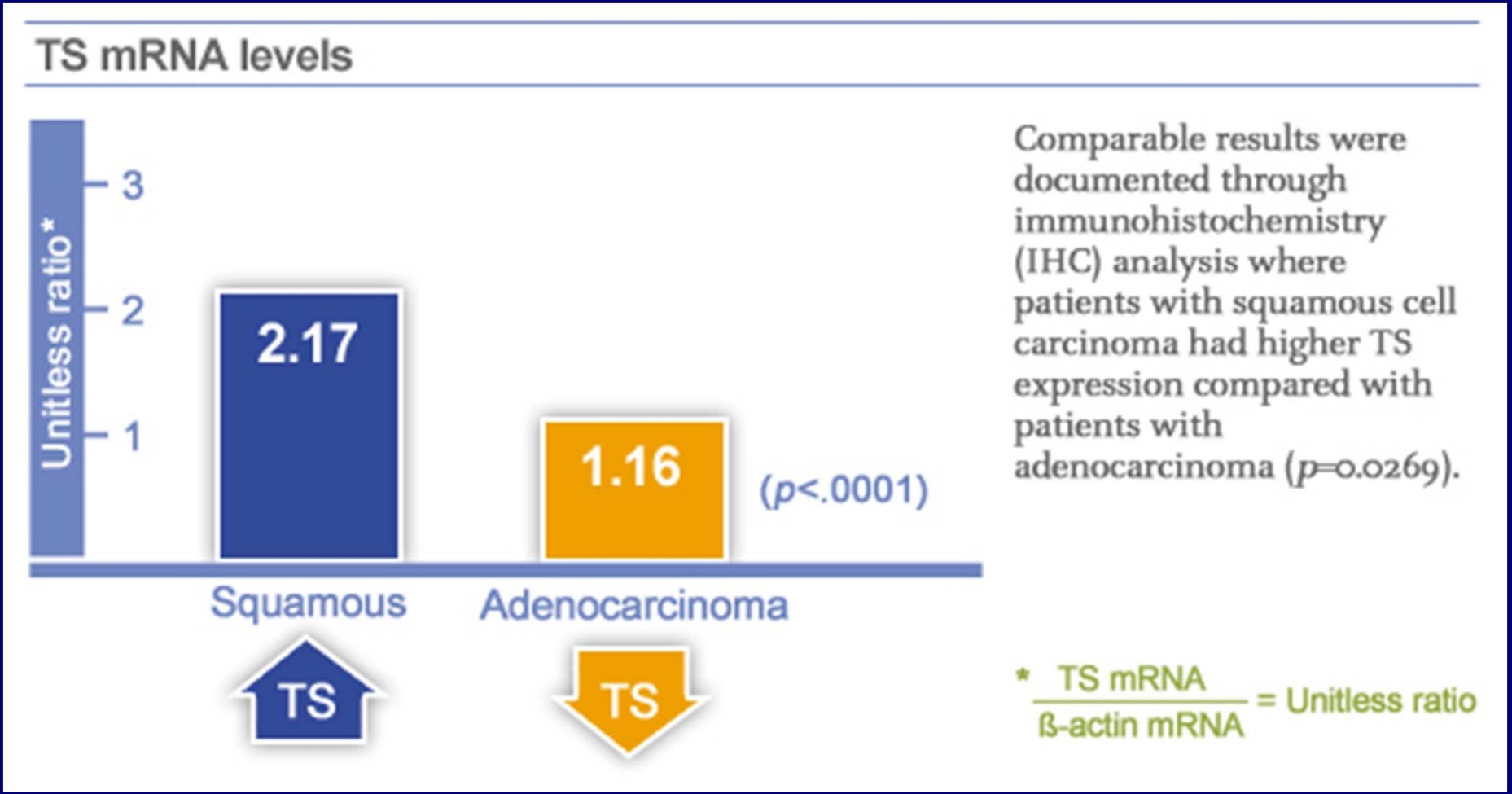
NSCLC: Pemetrexed is more effective in patients with non-squamous tumors





Peterson et al., JTO 2, 8 (suppl4), 851 (Abstr. P2-328), 2007

TS gene expression level is higher in Squamous NSCLC



TS: Thymidylate Synthase

Ceppi P et al. *Cancer* .2006;107:1589-1596.

Treatment selection based on clinical parameters

Pathology

Gender

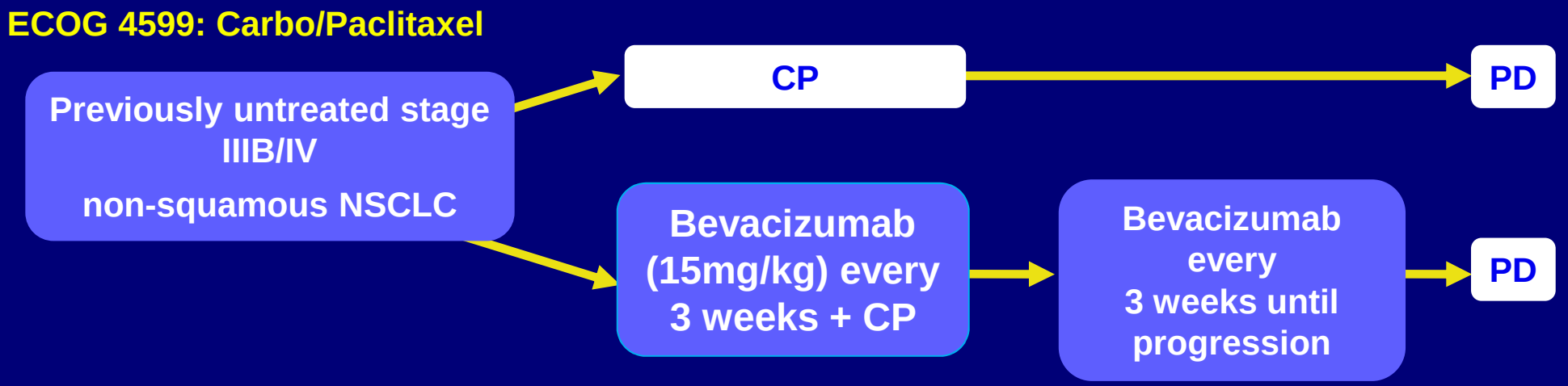
Smoking status

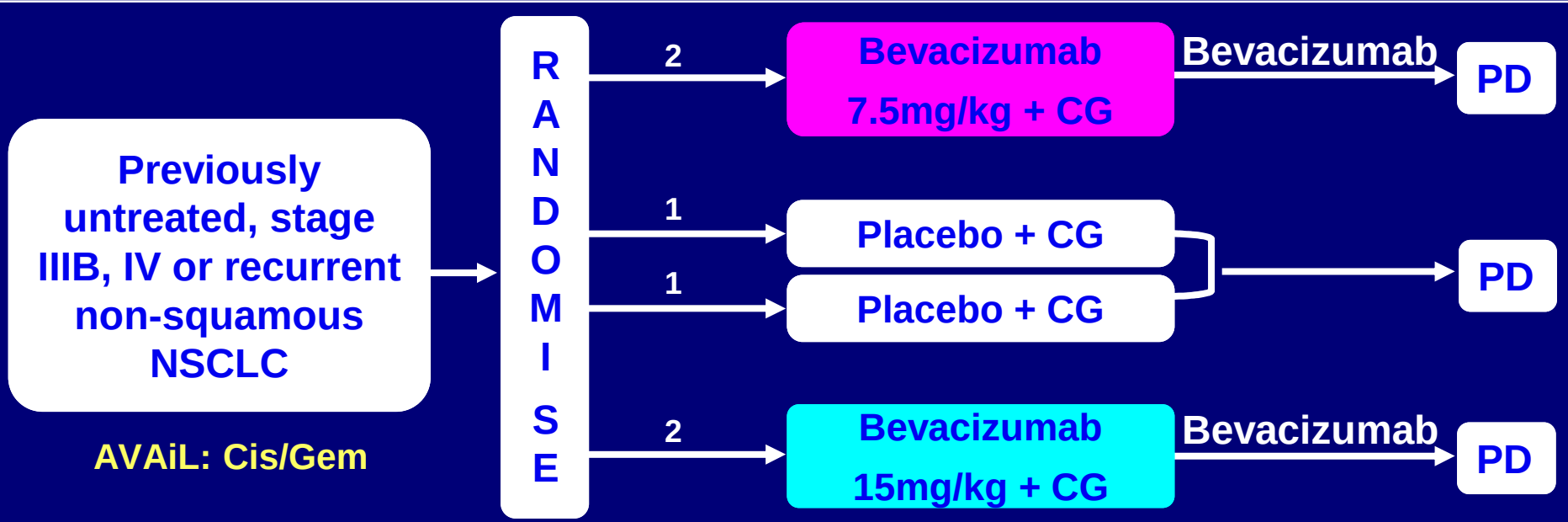
Performance status

Age

Response/reaction to therapy

NSCLC: Bevacizumab following Standard Triplet CT





Histology as a predictive factor – VEGF

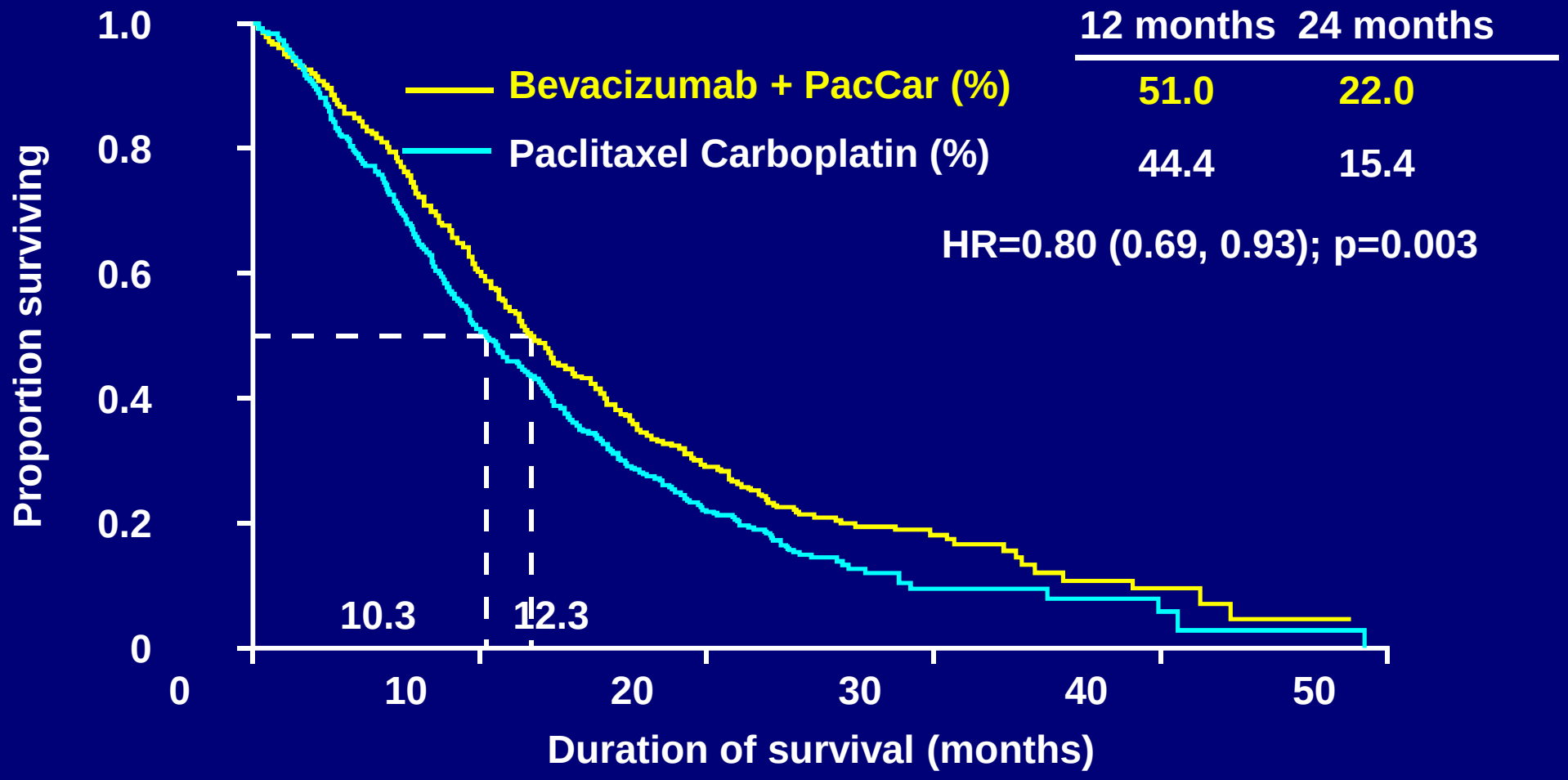
- Histology may also be useful in defining patient population based on safety

- Phase-2 trial of an anti-VEGF agent in 67 patients
  - Similar efficacy in squamous and adeno groups
  - Life threatening pulmonary haemorrhages in 6 patients
    - 4/13 patients (31%) had squamous carcinoma
    - 2/54 patients (4%) had adenocarcinomas

- Squamous cell tumours
  - more frequently centrally located
  - have a greater tendency to cavitate as compared to adenocarcinoma

Johnson, *et al.* J Clin Oncol 2004; 22: 2184-2191

Present Standard at USA: ECOG 4599 for Non-Squamous Cell Carcinoma



	12 months	24 months
Bevacizumab + PacCar (%)	51.0	22.0
Paclitaxel Carboplatin (%)	44.4	15.4

HR=0.80 (0.69, 0.93); p=0.003

HR = hazard ratio

Sandler NEJM 2006

Treatment selection based on clinical parameters

Pathology
Gender
Smoking status
Performance status
Age
Response/reaction to therapy

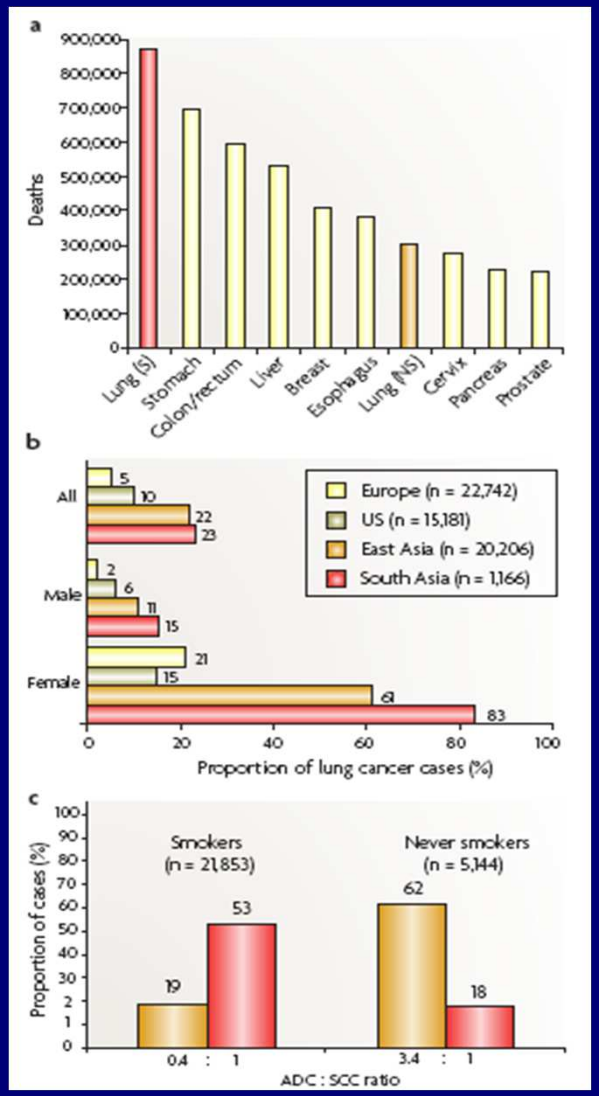
Lung Cancer in Never Smokers

At a glance

- About 25% of lung cancer cases worldwide are not attributable to tobacco smoking. Thus, lung cancer in never smokers is the seventh leading cause of cancer deaths in the world, killing more people every year than pancreatic or prostate cancers.
- Globally, lung cancer in never smokers demonstrates a marked gender bias, occuring more frequently among women. In particular, there is a high proportion of never smokers in Asian women diagnosed with lung cancer.
- Although smoking-related carcinogens act on both proximal and distal airways inducing all the major forms of lung cancer, cancers arising in never smokers target the distal airways and favour adenocarcinoma histology.
- Environmental tobacco smoke (ETS) is a relatively weak carcinogen and can only account for a minority of lung cancers arising in never smokers.
- Although multiple risk factors, including environmental, hormonal, genetic and viral factors, have been implicated in the pathogenesis of lung cancer in never smokers, no clear-cut dominant factor has emerged that can explain the relatively high incidence of lung cancer in never smokers and the marked geographic differences in gender proportions.
- Molecular epidemiology studies, in particular of the *TP53*, *KRAS* and epidermal growth factor receptor (*EGFR*) genes, demonstrate strikingly different mutation patterns and frequencies between lung cancers in never smokers and smokers.
- There are major clinical differences between lung cancers arising in never smokers and smokers and their response to targeted therapies. Indeed, non-smoking status is the strongest clinical predictor of benefit from the EGFR tyrosine kinase inhibitors.
- The above-mentioned facts strongly suggest that lung cancer arising in never smokers is a disease distinct from the more common tobacco-associated forms of lung cancer.
- Further efforts are needed to identify the major cause or causes of lung cancers arising in never smokers before successful strategies for prevention, early diagnosis and novel therapies can be implemented.

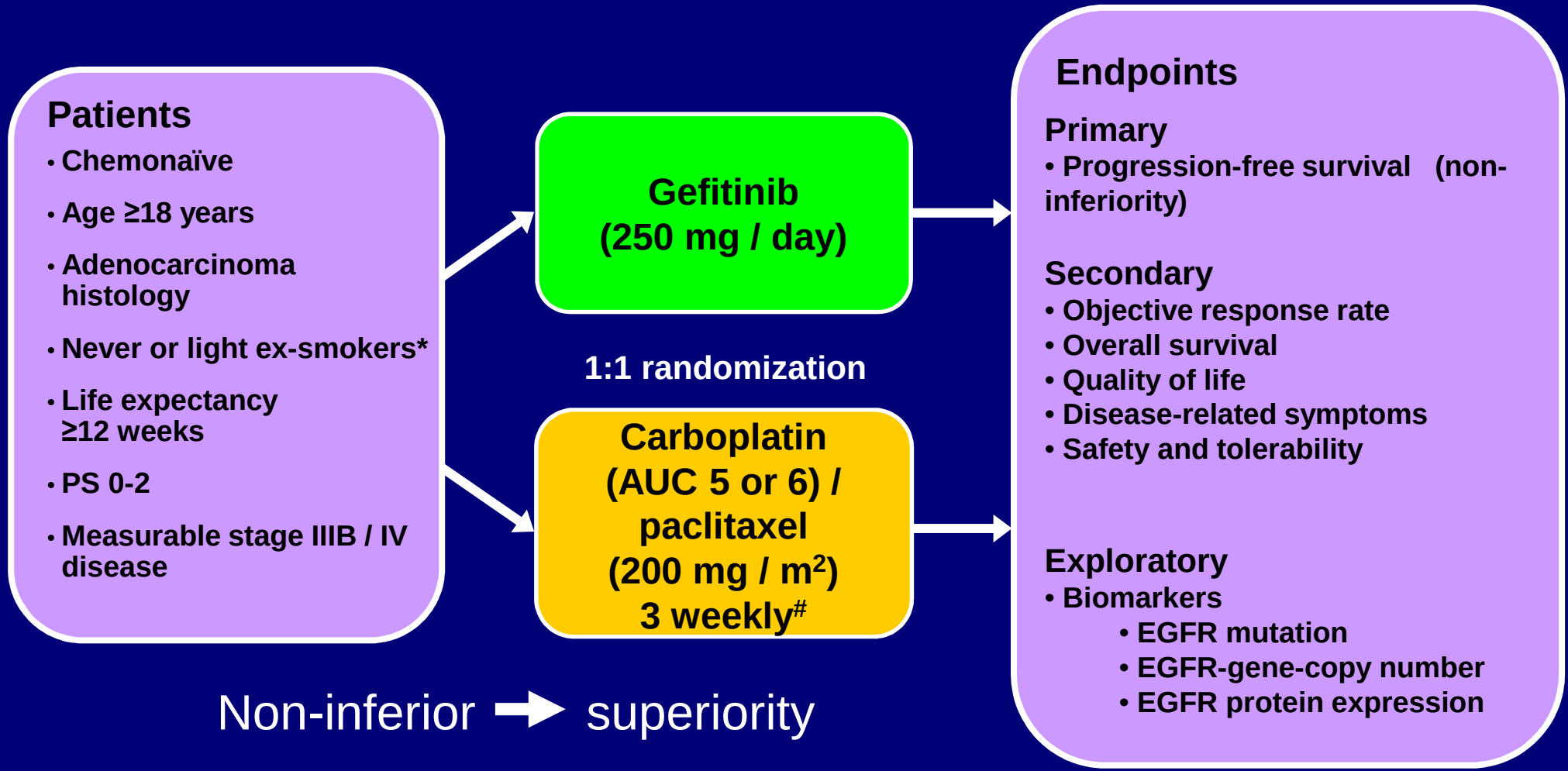
Sun et al. Nature 2007;7:778-790

Lung Cancer in Never Smokers



Sun et al. Nature 2007;7:778-790

iPASS - Study design



*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

Mok T et al. N Engl J Med 2009, 361

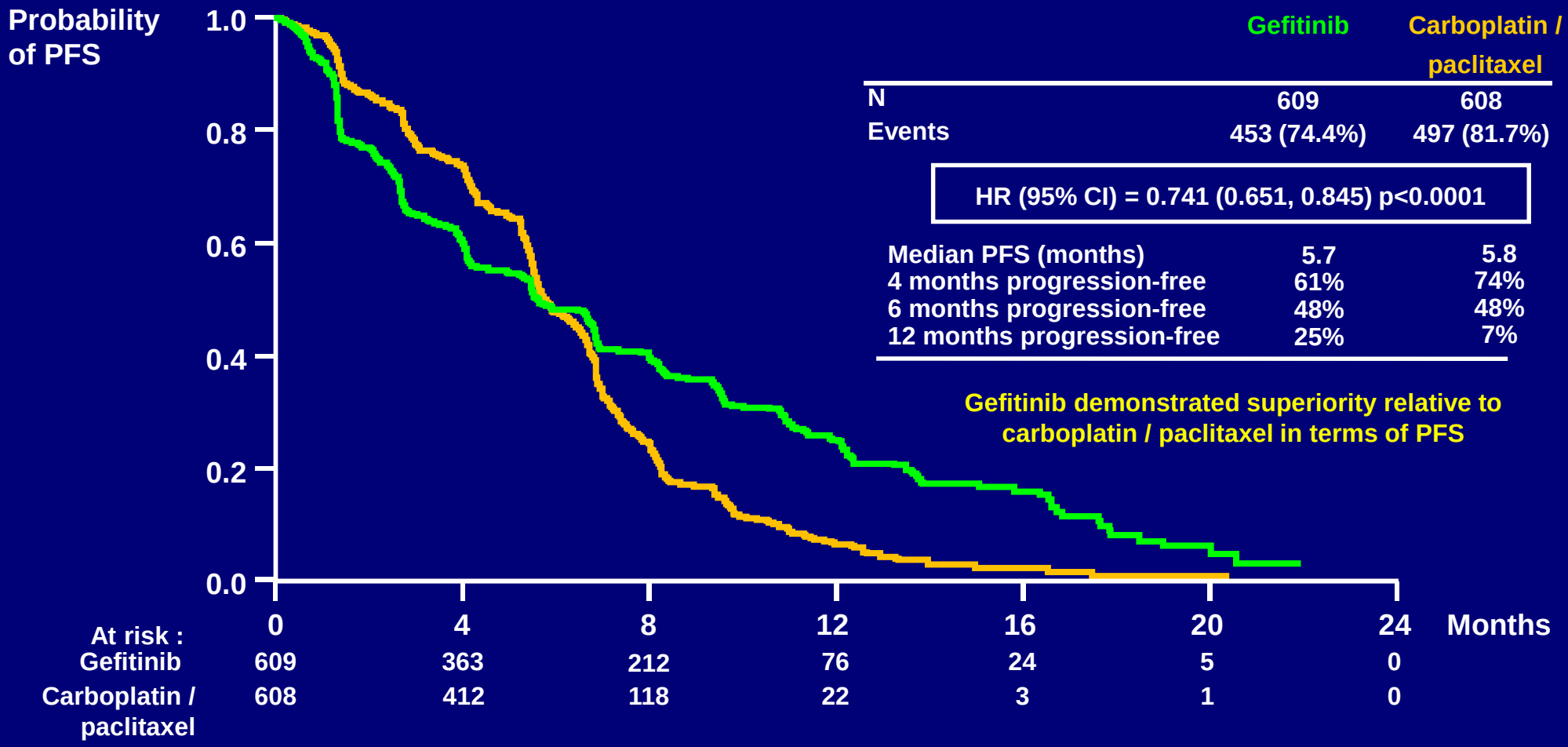
IPASS: Demography (ITT population)

	Gefitinib, % (N=609)	Carboplatin / paclitaxel, % (N=608)
Age <65 years	73	74
Median age (range), years	57 (24-84)	57 (25-84)
Female[a]	79	79
WHO PS 0 / 1 / 2[a]	26 / 64 / 10	26 / 63 / 11
Never smoker[a]	94	94
Light ex-smoker[a]	6	6
Mean smoking duration, years	11.5 (N=38)	14.5 (N=39)
Mean time since cessation, years	24.6 (N=38)	23.4 (N=39)
Metastatic disease	75	76
Time since diagnosis: <6 months	96	94
Chinese ethnicity[b]	52	50
Japanese ethnicity[b]	19	20

WHO, World Health Organization
[a]1 of the 3 stratification factors
[b]not the same as country of residence

Mok T et al. N Engl J Med 2009, 361

Progression-free survival in ITT population



	Gefitinib	Carboplatin / paclitaxel
N	609	608
Events	453 (74.4%)	497 (81.7%)

HR (95% CI) = 0.741 (0.651, 0.845) p<0.0001

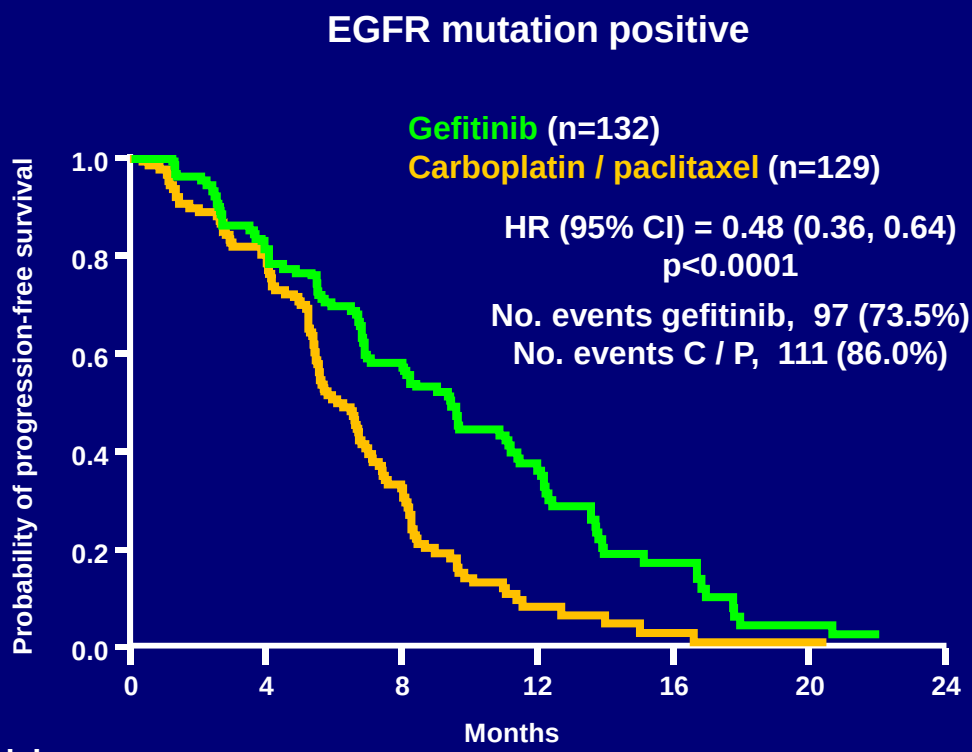
Median PFS (months)	5.7	5.8
4 months progression-free	61%	74%
6 months progression-free	48%	48%
12 months progression-free	25%	7%

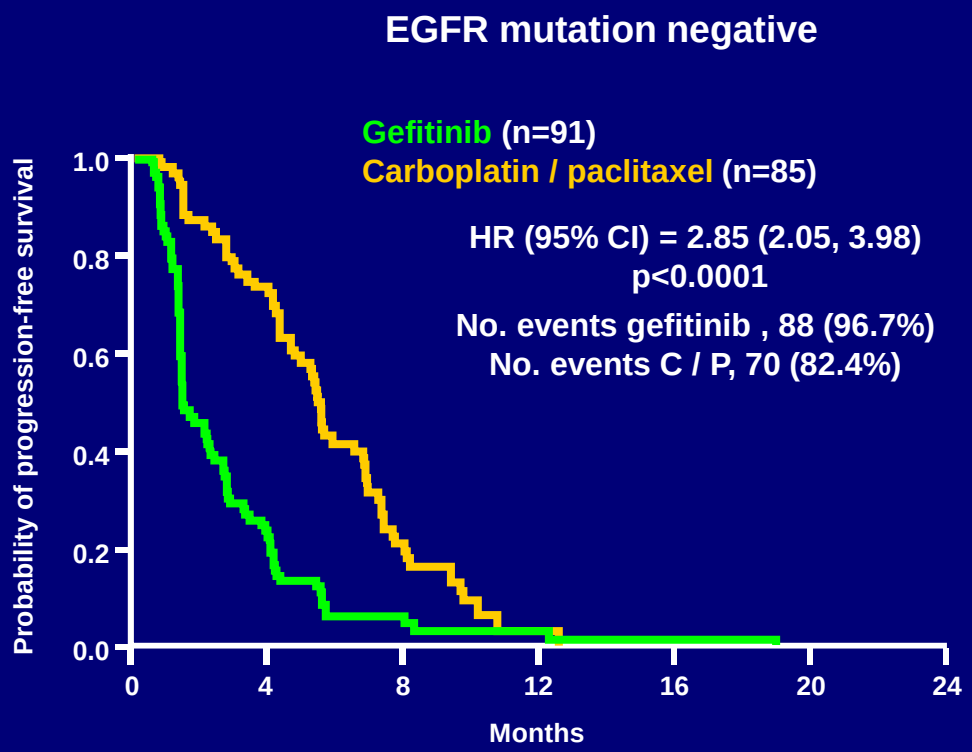
Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

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

Mok T et al. N Engl J Med 2009, 361

Progression-free survival in EGFR mutation positive and negative patients



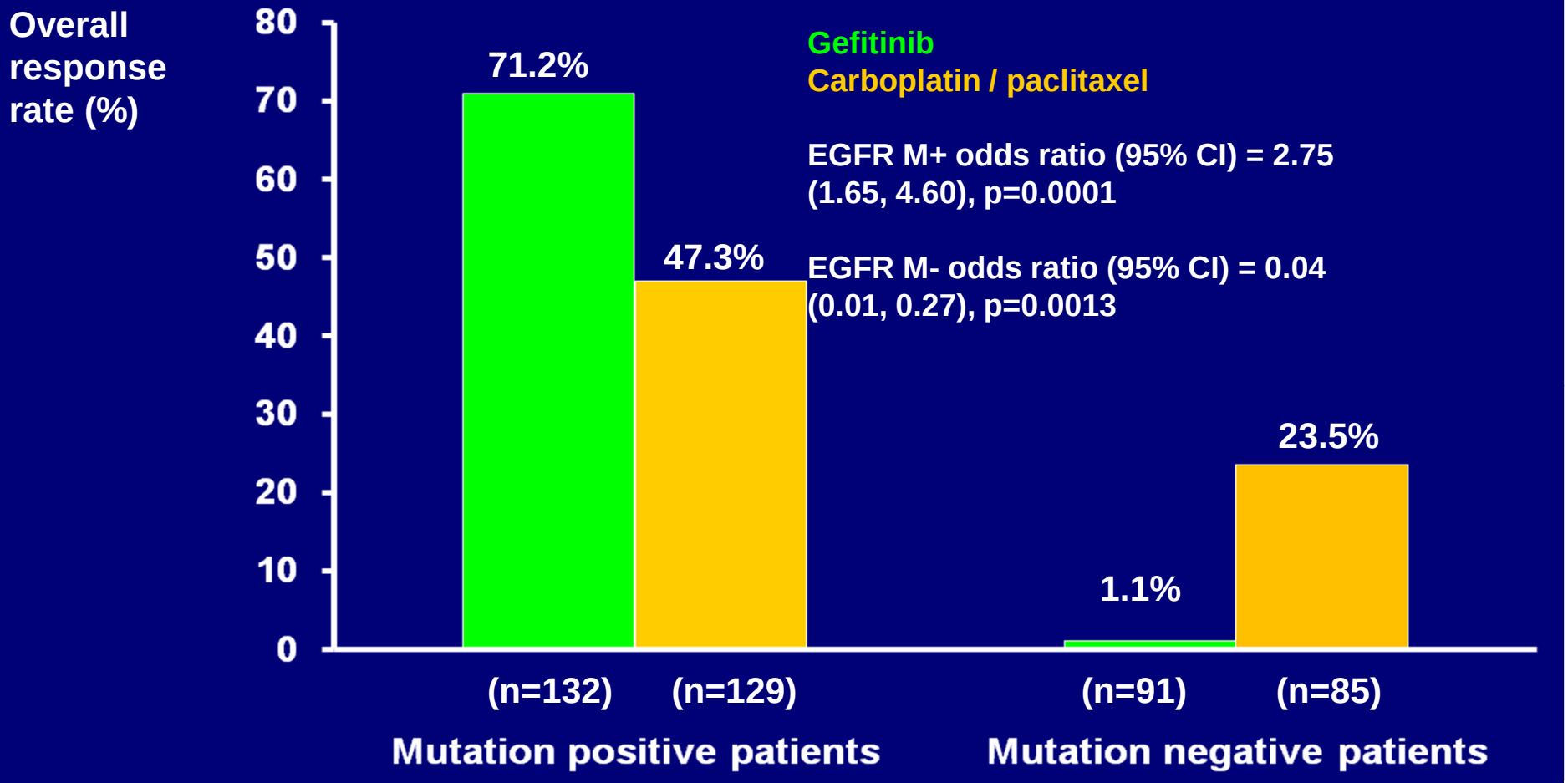


Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

Mok T et al. N Engl J Med 2009, 361

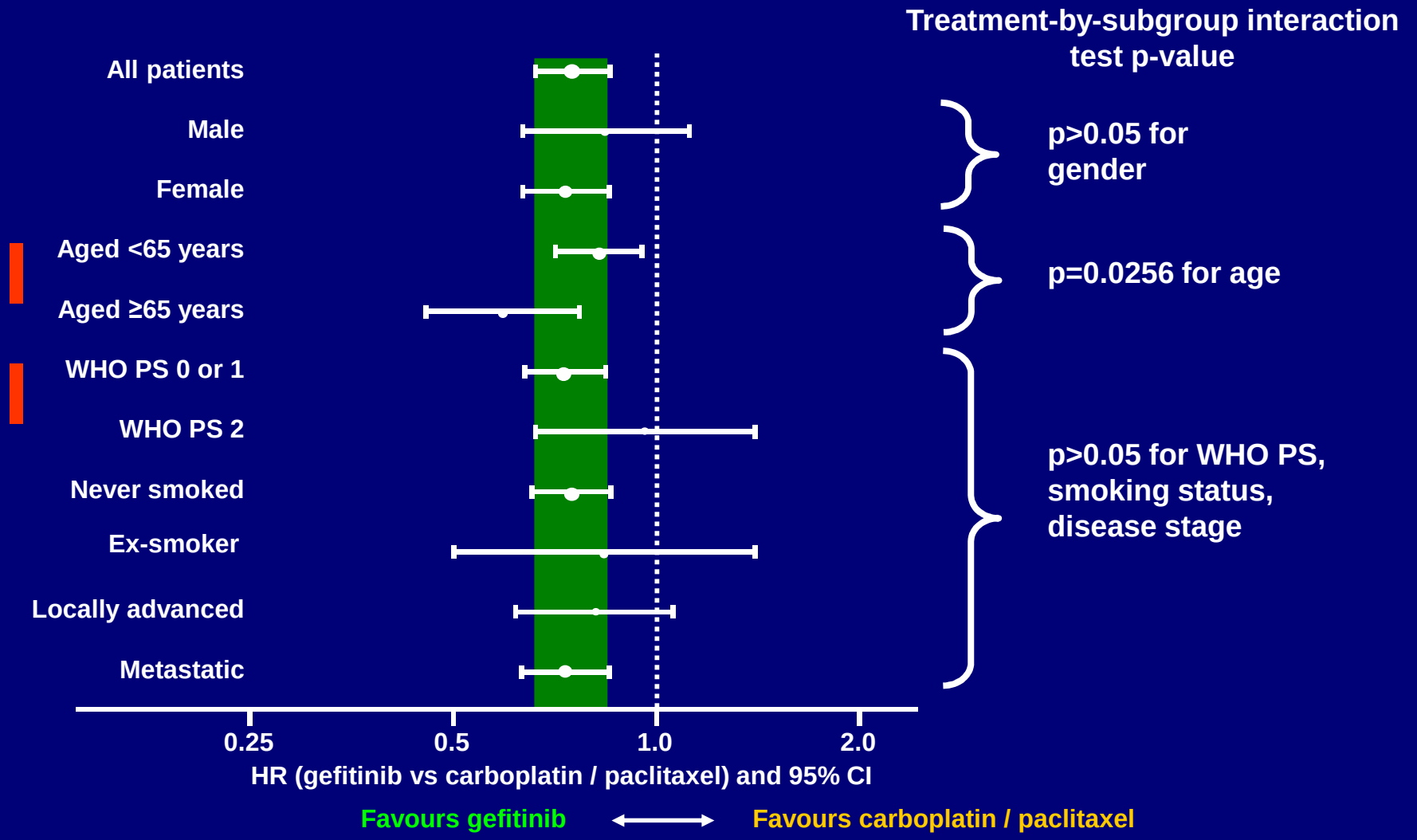
Objective response rate in EGFR mutation positive and negative patients



Odds ratio >1 implies greater chance of response on gefitinib

Mok T et al. N Engl J Med 2009, 361

PFS: Gefitinib vs. Paclitaxel/carbo in iPASS



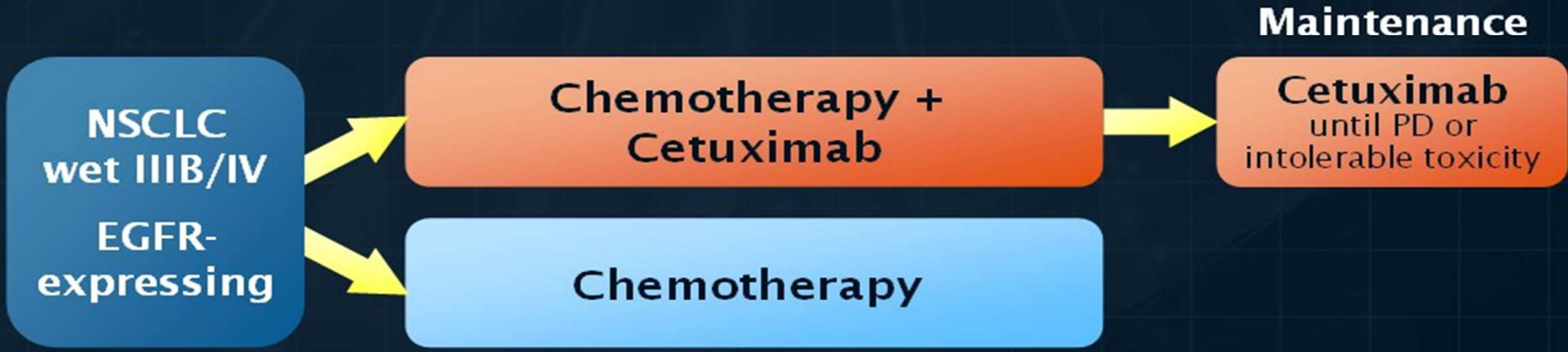
Cox analysis with covariates

Green band is the 95% CI for the HR for "all patients"

Treatment selection based on clinical parameters

Pathology
Gender
Smoking status
Performance status
Age
Response/reaction to therapy

FLEX
Study design

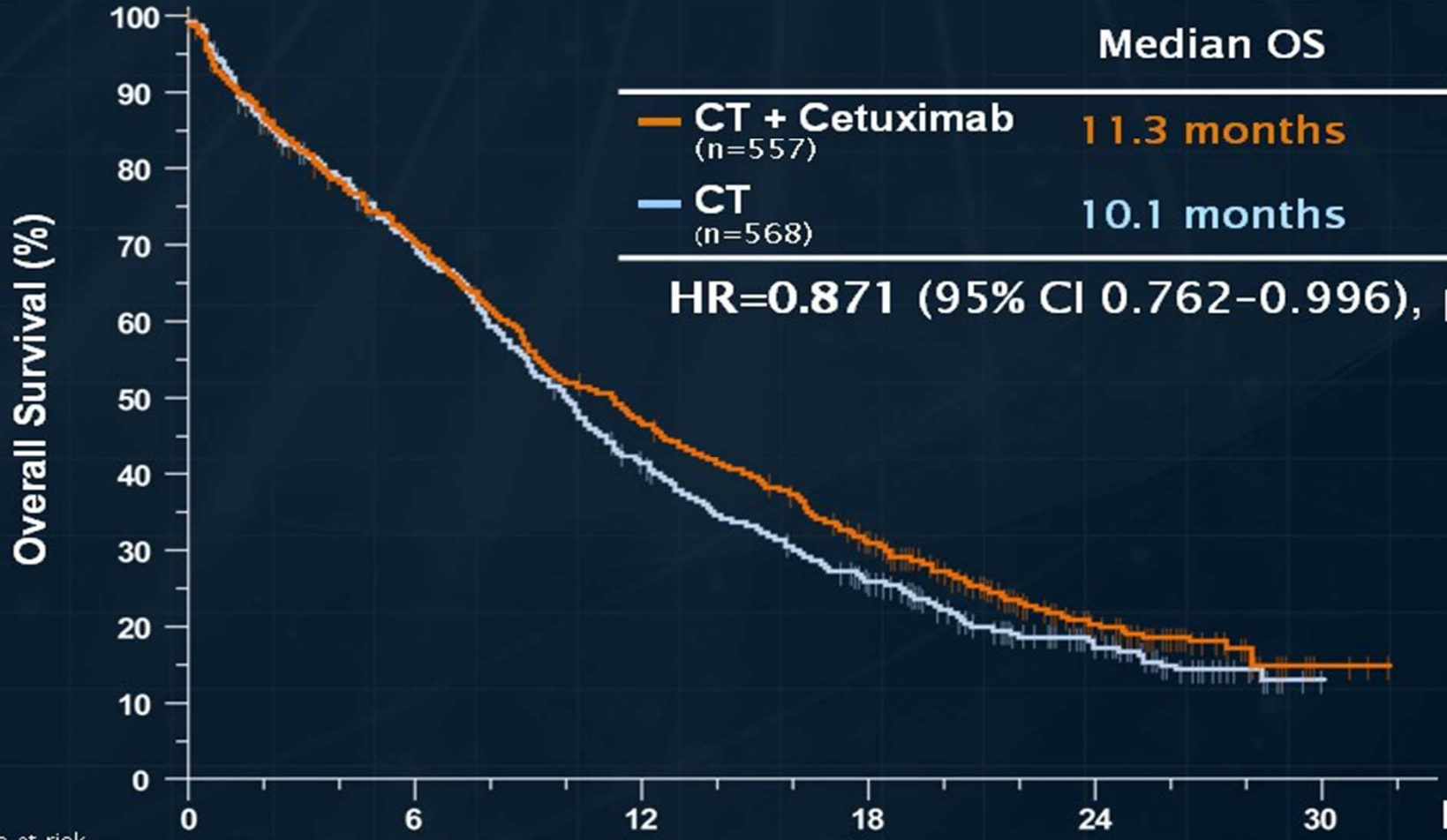


Chemotherapy (CT)	Cetuximab
Cisplatin 80 mg/m^2 day 1	initial dose 400 mg/m^2
Vinorelbine 25 (30) mg/m^2 days 1, 8	then 250 mg/m^2 weekly
Every 3 weeks, up to 6 cycles	

ASCO Annual '08 Meeting

Pirker et al, J Clin Oncol 2008, 18S (Abstract 3)

FLEX Overall survival



	Median OS	1-year survival
CT + Cetuximab (n=557)	11.3 months	47 %
CT (n=568)	10.1 months	42 %

HR=0.871 (95% CI 0.762–0.996), **p=0.044**

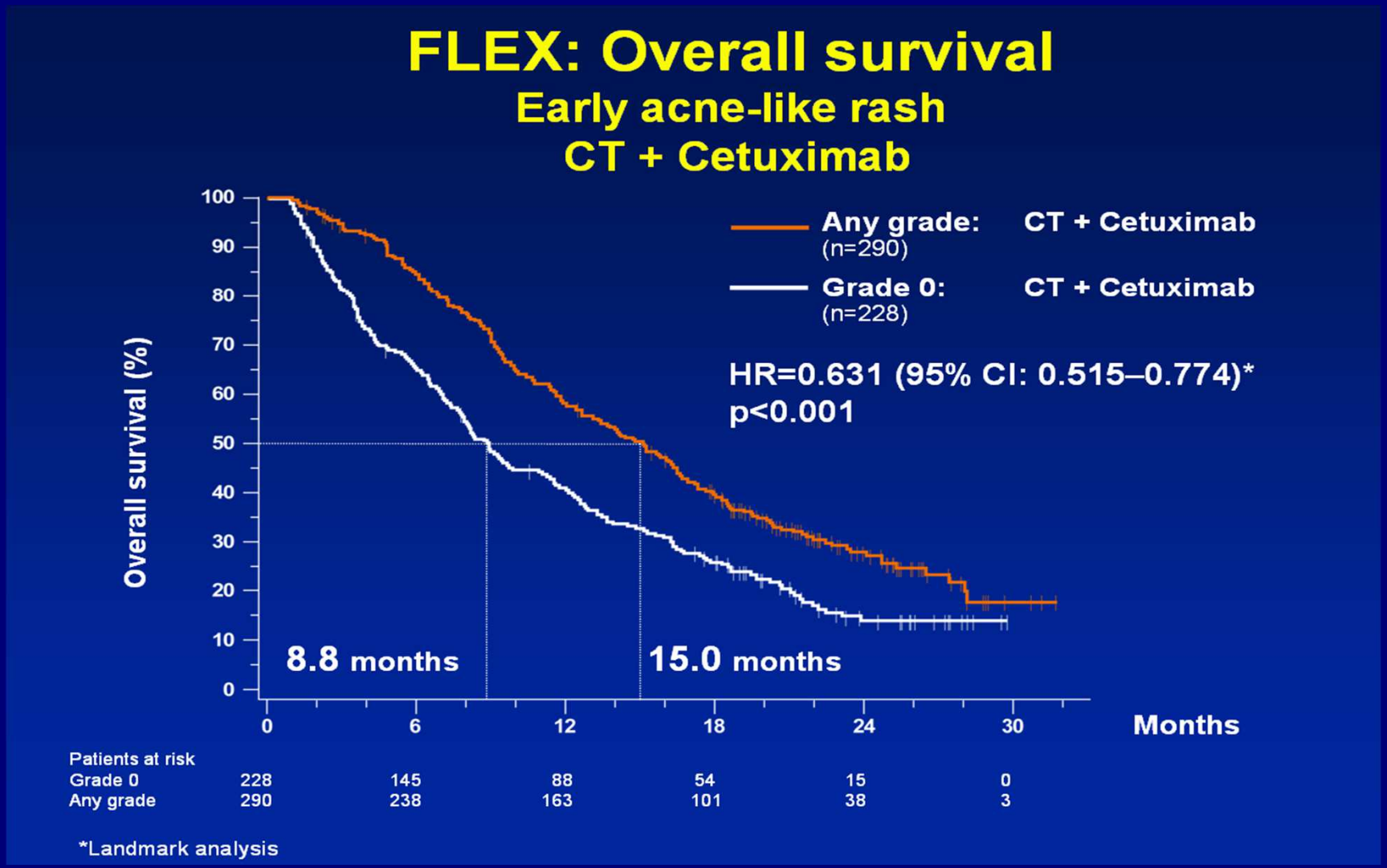
Patients at risk						
CT + Cetuximab	557	383	251	155	53	3
CT	568	383	225	134	48	0

ASCO | Annual '08 Meeting

p-value = stratified log-rank test (2-sided)

Pirker et al, J Clin Oncol 2008, 18S (Abstract 3)

FLEX: Overall survival and early acne-like rash



Gatzemeier et al. JTO 3, 11, 4, (Abstr. 8), 2008

Conclusions

- Need to individualize treatment for patients based on clinical characteristics and biomarkers
- Clinical parameters may be surrogate markers for target biomarkers
- Clinical parameters are still useful in most part of the world when biomarker analysis are not available
- The clinical applications of biomarkers need to be proven in well-designed trials