

Case # 4

Stage IV NSCLC: Choice & Sequence of Systemic Therapy

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Established Key Points in 2008

- Chemotherapy prolongs survival in any stage of NSCLC (except stage I).
- Platinum-based doublets with 3rd generation cytotoxics (Gemcitabine, Taxanes, and Vinorelbine) are the reference regimens.
- Elderly patients may benefit from chemotherapy in terms of survival but patients with poor KPS may not.
- Classical cytotoxic chemotherapies have already reached an “efficacy plateau”.
- Further improvements anticipated through integration of targeted therapies.

Determinants of Treatment Choices in Advanced NSCLC

- Age
- Performance Status
- Co-morbidity
- Ethnicity
- Gender
- Smoking history
- Histology
- Pharmacogenomic markers?

Elderly



- Definition: ≥ 65 or 70 years
- Decreased drug clearance
- Decreased marrow reserve
- Higher degree of co-morbidities

Chemotherapy Options

- Single Agent Therapy
 - Vinorelbine or Gemcitabine
 - Paclitaxel or Docetaxel
 - Molecular Targeted Agents
- Combination Chemotherapy
 - Cisplatin – based
 - Carboplatin – based
 - Non-platinum combinations
- Platinum – based Chemotherapy + Targeted Agent

Performance Status (PS) Predicts Chemotherapy Outcome in Advanced Stage NSCLC*

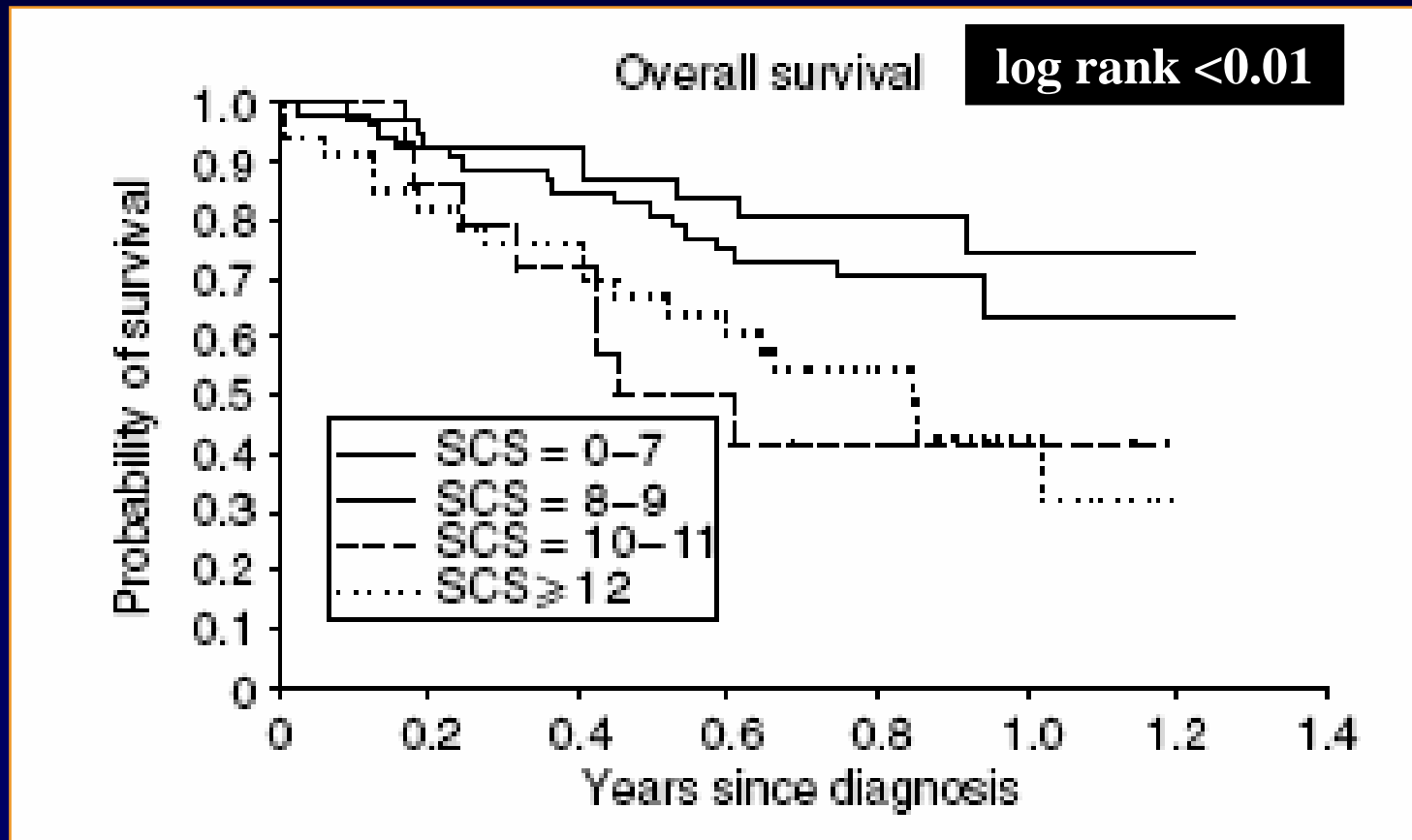
Zubrod PS	Median Survival (months)	Fatal Toxicity
0	12 +	3%
1	8-10	2%
2	3-4	10%
3	2	NA

* ECOG 1581 (Ruckdeschel: JCO, 1986)

ECOG 1594: PS 2 Subanalysis

- 68 of 1207 patients enrolled had PS 2
- Accrual suspended b/o untoward inc. of Gr 4/5 AEs
- Overall toxicity rate, however, did not differ significantly from that observed in PS 0-1 pts
- 5 deaths (7.35% Grade 5 AE), but only two were directly attributable to Tx
- MST of 4.1 mo and 1-yr survival rate 19.1% likely secondary to disease process rather than toxicity

NSCLC Treatment Choices Impact of Co-morbidity



“Efficacy Plateau” of Cytotoxic Chemotherapy in NSCLC

Study	Drugs	# Pts	%, St. IV	%, ORR	MST	%, 1-YS
Kelly,2001 SWOG 9503	Vnr/Cis	202	88	28	8	33
	Tax225/Cb	208	89	25	8	36
Schiller,2002 ECOG 1594	Tax135/Cis	292	89	21.3	8.1	31
	Gem/Cis	288	86	21	8.1	36
	Txt/Cis	293	86	17.3	7.4	31
	Tax225/Cb	290	86	15.3	8.3	35
Scagliotti,2002 ILCP	Vnr/Cis	201	81	30	9.5	37
	Gem/Cis	205	81	30	9.8	37
	Tax225/Cb	201	82	32	9.9	43
Belani,2002 TAX 326	Vnr/Cis	404	67	25	10.1	41
	Txt/Cis	408	67	32	11.3	46
	TxT/Cb	402	67	24	9.4	38

CISCA - IPD Meta-analysis

- Overall (9 studies/2.968 pts) Cis > Carbo in terms of RR, but not of survival
- Subgroup analyses suggest that Cis > Carbo in terms of survival when combined with third generation agents (80% of the overall study population) and in non-squamous tumors
- Grade 3-4 PLT toxicity worse with Carbo, while grade 3-4 nausea/vomiting and renal toxicity worse with Cis
- The slight increase in response rate in the overall population and in survival in the subgroup of patients treated with III generation CT regimens may support the preference of Cis over Carbo in the treatment of selected NSCLC patients

Many Targeted Therapies Failed When Combined with Platinum-based Chemotherapy

	Agent	CT	N	Median OS (months)		OS benefit?
				CT	CT + Agent	
INTACT-1	Gefitinib (250/500mg)	Cis/Gem	1093	10.9	9.9/9.9	No
INTACT-2	Gefitinib (250/500mg)	Cis/Pac	1037	9.9	9.8/8.7	No
TRIBUTE	Erlotinib	Cis/Pac	1059	10.5	10.6	No
TALENT	Erlotinib	Cis/Gem	1172	10.0	10.3	No
	Lonafarnib	Cb/Pac	800	-	-	No
SPIRIT-1	Bexarotene	Cis/Vino	623	9.9	8.7	No
SPIRIT-2	Bexarotene	Cis/Pac	612	9.2	8.5	No
	Aprinocarsen (PKC-a)	Cis/Gem	670	10.4	10.0	No
	Aprinocarsen (PKC-a)	Cis/Pac	600	9.7	10.0	No
	Prinomastat	Cb/Pac	678	10.2	9.7	no
	Prinomastat	Cis/Gem	362	10.8	11.5	No
BR.18	BMS-275291	Cis/Gem	774	9.2	8.6	No
	Panitumumab	Cis/Pac	175	8.0	8.5	No
ESCAPE	Sorafenib	Cb/Pac	926	Phase III study stopped due to high mortality		No
BR.24	Cediranib (AZD2171)	Cb/Pac	n.a.	Phase II/III study stopped due to high toxicities		No
	PF-676	Cb/Pac	828	Both Phase III studies stopped due to lack of efficacy and high toxicities		No
	PF-676	Cis/Gem	839			No
AVAiL	Bevacizumab (7.5/15mg)	Cis/Gem	986	ESMO 2008		No

Overview: Bevacizumab in Non-squamous NSCLC

	Regimen	RR (%)	PFS (months)	OS (months)
ECOG 4599	Carbo/Pac	15	4.5	10.3 *
	Carbo/Pac + Bev	35	6.5	12.3 *
AVAIL	Cis/Gem	20	6.1 *	OS Endpoint not met**
	Cis/Gem + Bev 7.5 mg	34	6.5 *	
	Cis/Gem + Bev 15 mg	30	6.7 *	

- **No survival benefit in combination with Cisplatin/Gemcitabin**
- **Exclusion criteria:**
squamous cell, hemoptysis, brain metastases, uncontrolled hypertension
- **High risk of pulmonary bleeding**

* Primary Endpoint

** Manegold et al., ESMO 2008, oral presentation

Sandler et al., *NEJM* 2006, 355, 2542-2550

Manegold et al., *JCO* 2007, 25, 18 (Suppl), 967 (abstr. 7514)

Cisplatin/Vinorelbine+/- Cetuximab Efficacy Results

	CT + Cetuximab	CT		p-value**
OS	11.3	10.1	HR 0.871 [0.762–0.996]	0.044
RR	36 %	29 %		0.012
PFS	4.8 m	4.8 m	HR 0.943 [0.825–1.077]	ns
TTF*	4.2 m	3.6 m	HR 0.859 [0.760–0.970]	0.015

* post-hoc analysis

** RR: Cochran-Mantel-Haenszel Test

OS, PFS, TTF: stratified log-rank test (2-sided)



FLEX Overall Survival Across All Histologies

Major treatment group: Caucasians (n=946)

pre-specified analysis

	Median OS (months)		HR
	CT + Cetuximab	CT	
Caucasian (n=946)	10.5	9.1	0.80
Adeno (n=413)	12.0	10.3	0.82
Squamous cell (n=347)	10.2	8.9	0.79
Other (n=185)	9.0	8.2	0.80

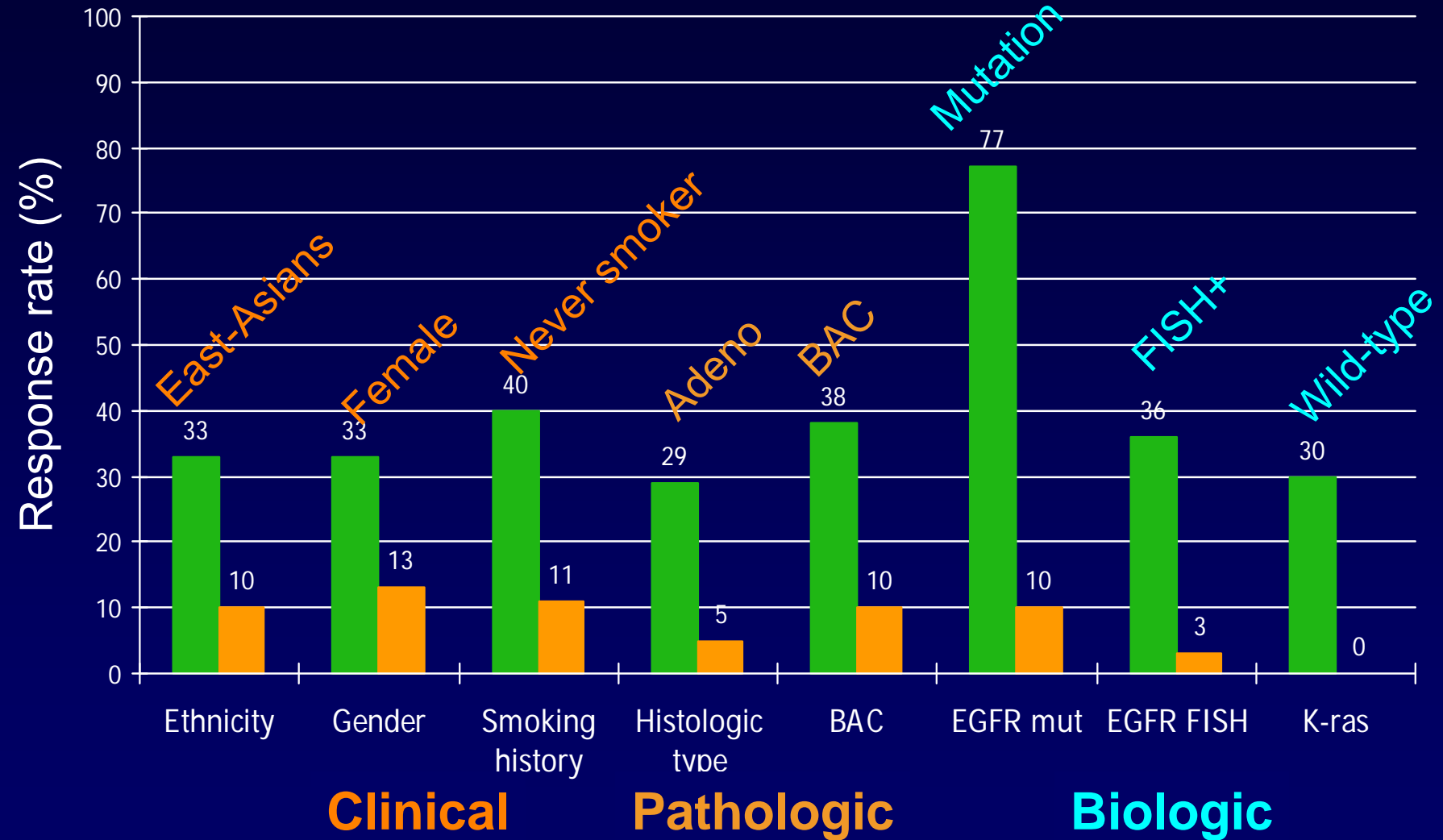
Other: includes large cell, adenosquamous, undifferentiated



Additional Determinants of Treatment Choices in Advanced NSCLC

- Ethnicity
- Gender
- Smoking history
- Histology
- Pharmacogenomic markers?

EGFR TKIs are Effective in Patients with Distinct Clinico-Pathological Features



Compiled from the literature (N=1974)

Miller, 2005 (N=671)

Cappuzzo, 2005 (N=246)

EGFR-TKI

Never Smoker -Adeno-Female

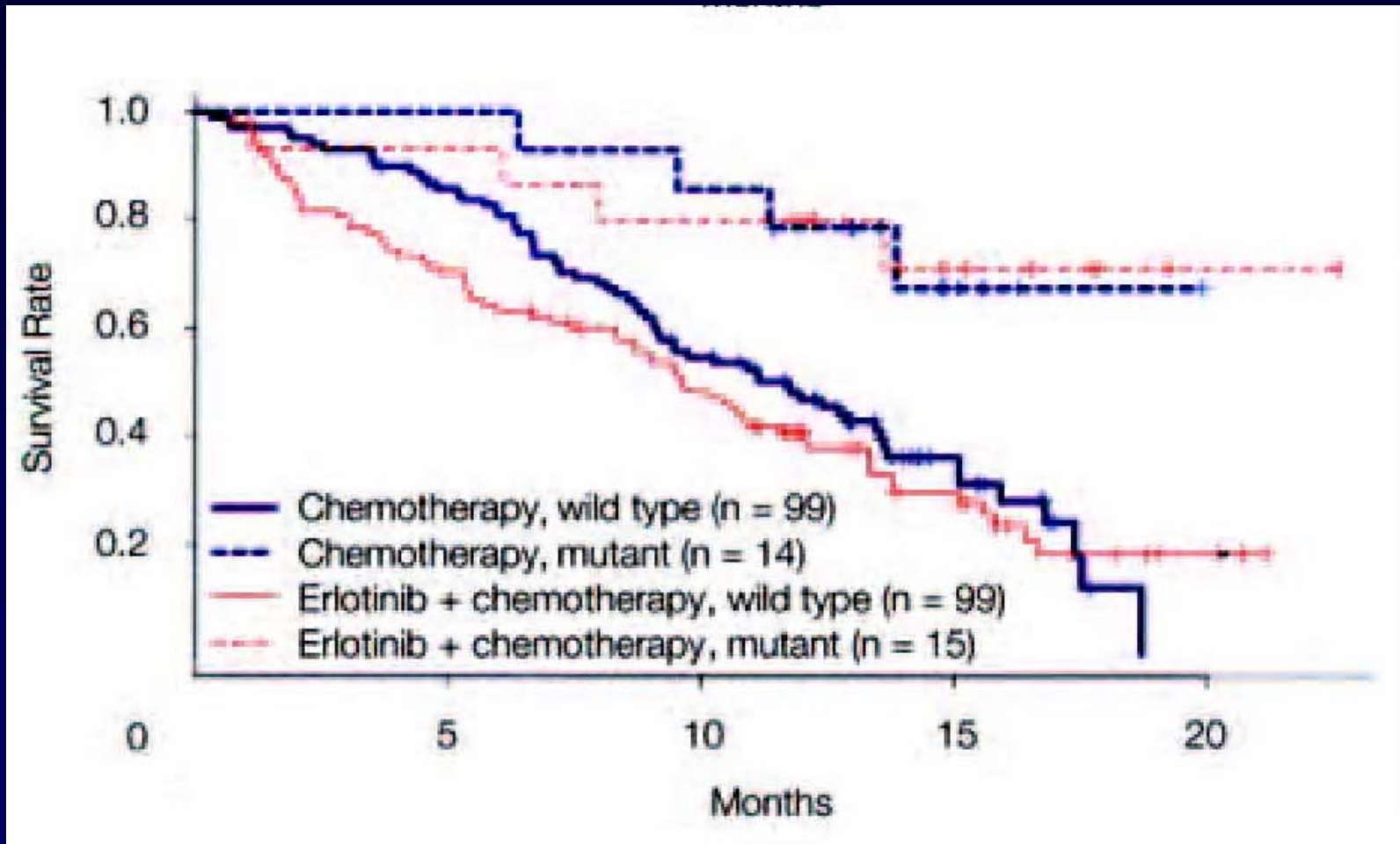
Number of Clinical Factors	Response Rate	MST (months)
3	56%	14+ mo
2	30%	12 mo
1	9%	5 mo
0	3%	3 mo

Survival of Never-Smokers with NSCLC on EGFR-Based Therapies

	<u>BR.21</u> Erlotinib Monotherapy 2nd/3rd	<u>TRIBUTE</u> Erlotinib + Carbo/Pac 1st Line	<u>TALENT</u> Erlotinib + CDDP/Gem 1st Line	<u>ISEL</u> Gefitinib Monotherapy 2nd/3rd Line
N	731	1079	1172	1692
Never-smokers	146 (20%)	116 (10.8%)	18/175 (10%)	375 (22%)
HR for Overall Survival (95% CI)				
All Subjects	0.73 (0.61-0.86)	1.00 (0.86-1.16)	1.06 (0.90-1.23)	0.89 (0.77-1.02)
Never-smokers	0.42 (0.28-0.64)	0.49 (0.28-0.85)	0.39 (0.08-2.04) (n=18)	0.67 (0.49-0.92)
Current/Former Smokers	0.67 (0.71-1.05)	1.11 (0.94-1.29)	1.05 (0.62-1.75) (n=121)	0.92 (0.79-1.06)

Prognostic vs Predictive Biomarkers

The Tale of EGFR Mutations in NSCLC



Molecular analysis of TRIBUTE trial (CT vs. CT + erlotinib)

Pem/Cis vs Gem/Cis Subgroups Analyses : Gender, Smoking Status

	Medians (95% CI)		Adjusted HR (95% CI)
	Pem/Cis	Gem/Cis	
Females (n=515)	13.3 (12.3, 15.0)	11.4 (10.2, 12.7)	0.84 (0.68, 1.03)
Males (n=1210)	9.6 (8.8, 10.2)	9.9 (9.1, 10.6)	0.98 (0.86, 1.11)
Ever/Former smoker (n=1266)	10.0 (9.4, 11.1)	10.3 (9.5, 10.9)	0.93 (0.81, 1.05)
Never smoker (n=250)	15.9 (13.8, 20.2)	15.3 (12.1, 22.9)	1.00 (0.71, 1.41)

Prognostic Variables

- From separate Cox models, controlling for treatment, disease stage, ECOG PS, gender, and basis of diagnosis:

Subgroup	HR (95% CI)	P-value
Females vs Males	0.76 (0.67, 0.86)	<0.001
Ever/Former vs Never-smoker	1.74 (1.44, 2.09)	<0.001
Age (continuous)	1.00 (0.99, 1.00)	0.656
Caucasian vs Others	1.36 (1.18, 1.57)	<0.001
E/SE Asian vs Others	0.65 (0.54, 0.78)	<0.001
ECOG PS 0 vs 1	0.65 (0.58, 0.73)	<0.001
Stage IIIB vs IV	0.82 (0.71, 0.93)	0.003
Histo vs Cyto Dx	1.02 (0.91, 1.15)	0.693
Adeno vs Others	0.75 (0.67, 0.84)	<0.001
Squamous Cell vs Others	1.12 (0.98, 1.27)	0.088
Large Cell vs Others	1.29 (1.07, 1.54)	0.007

Pem vs Doc in Second Line Survival Analysis

Characteristic	Med. Survival	Uni p-value	Multi p-value
Age < vs ≥ 70	7.9 vs 8.8	0.809	NA
Male vs Female	7.2 vs 9.4	0.001	0.03
Stage III vs IV	9.5 vs 7.8	0.036	0.012
Adeno vs Scca	9.1 vs 6.5	0.004	0.054
PS 0/1/2	12.7 vs 8.3 vs 2.6	<0.001	<0.001
Response 1 st line: PR/SD/PD	15.8 vs 10.5 vs 4.6	<0.001	<0.001
Time since 1 st line: ≤3 vs 3-6 vs ≥ 6 mos	6.9 vs 9.2 vs 9.3	0.001	0.183

NSCLC Treatment Choices

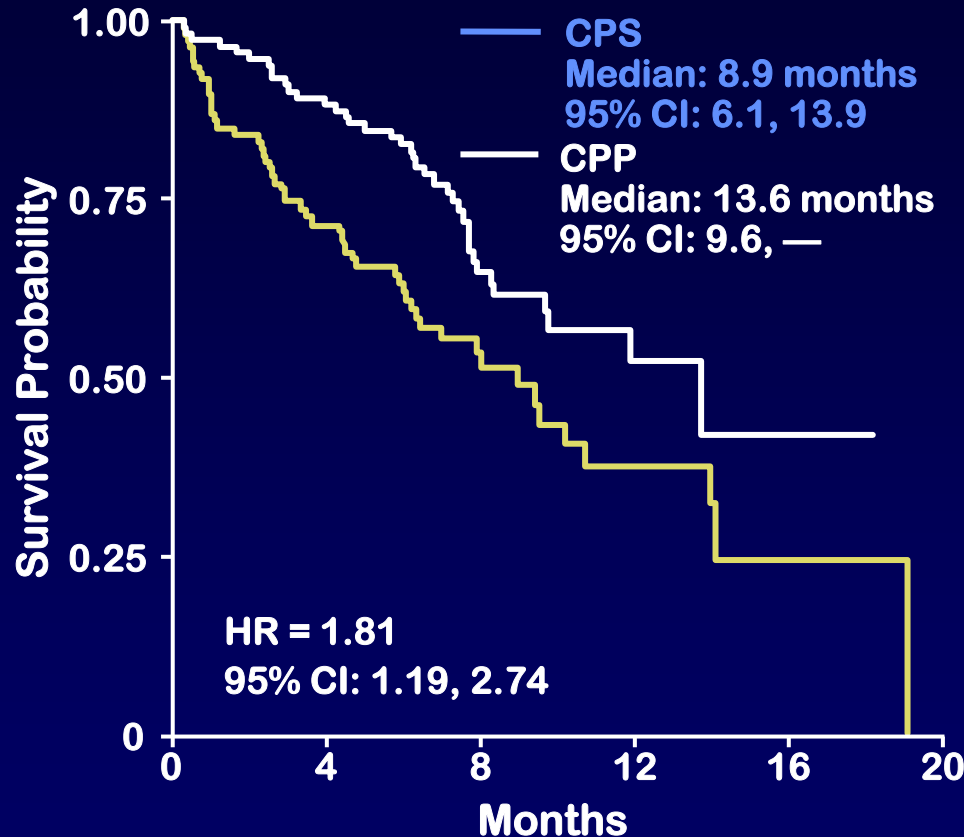
Histology Matters for Bevacizumab Toxicity

Phase II trial:

- 6/66 (9%) life-threatening pulmonary haemorrhages in patients with carboplatin-paclitaxel plus bevacizumab
- Majority were squamous cell histology (n=4) and centrally located or cavitory lesions (n=5)
- In a multivariate analysis, independent factors were bevacizumab treatment and squamous cell histology (20% had important bleeding)

Phase III Study of C/P ± Sorafanib Overall Survival by Histology

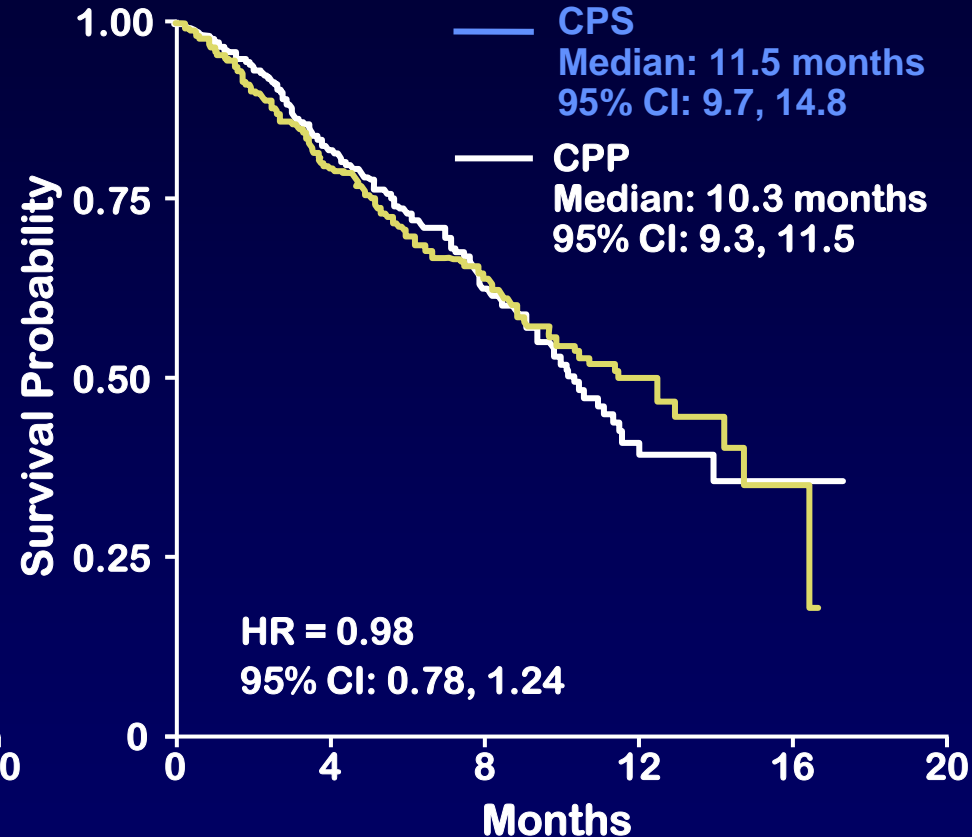
Squamous Cell



Patients at Risk

CPS	107	73	24	9	2
CPP	112	97	41	12	3

Non-Squamous Cell



Patients at Risk

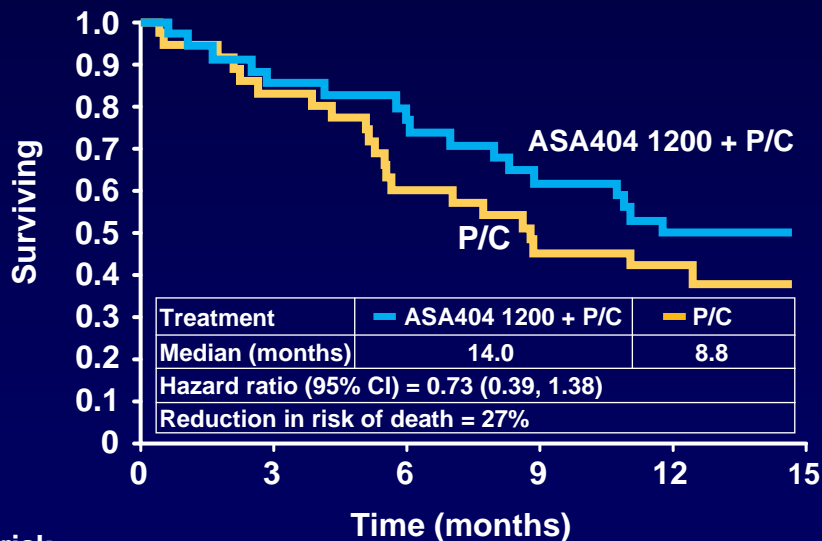
CPS	357	281	173	38	5
CPP	350	280	168	22	2

Tumor-Vascular Disrupting Agents (Tumor-VDAs)

- **Novel class of anticancer agents that primarily target established tumor blood vessels**
- **Rationale**
 - All solid tumors rely on functioning vasculature for oxygen and nutrients
 - Tumor vasculature differs morphologically and molecularly from vasculature of normal organs
 - Tumor-VDAs selectively target vascular endothelial cells in established tumor blood vessels, causing widespread necrosis in the central part of the tumor

ASA404 + Paclitaxel/Carboplatin (P/C) in First-Line Therapy of Advanced NSCLC

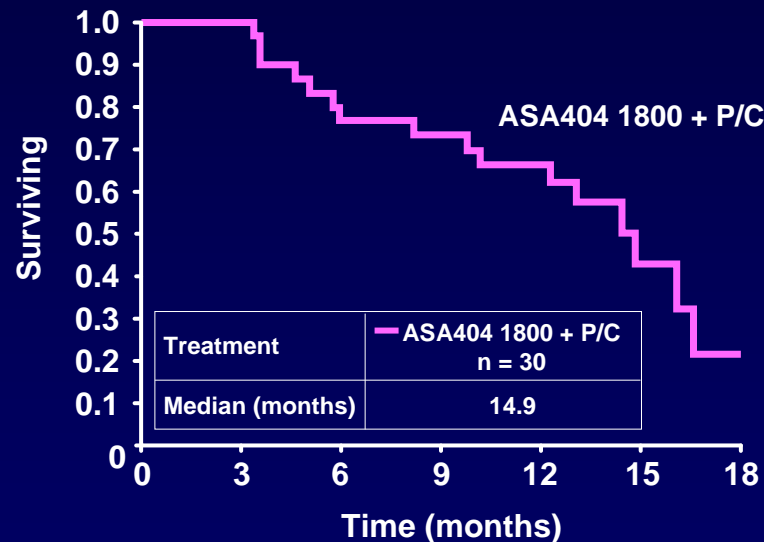
ASA404 1200 mg/m² increases median overall survival by > 5 months



Patients at risk

ASA404 1200 + P/C	34	29	27	21	17	3
P/C	36	29	21	15	14	1

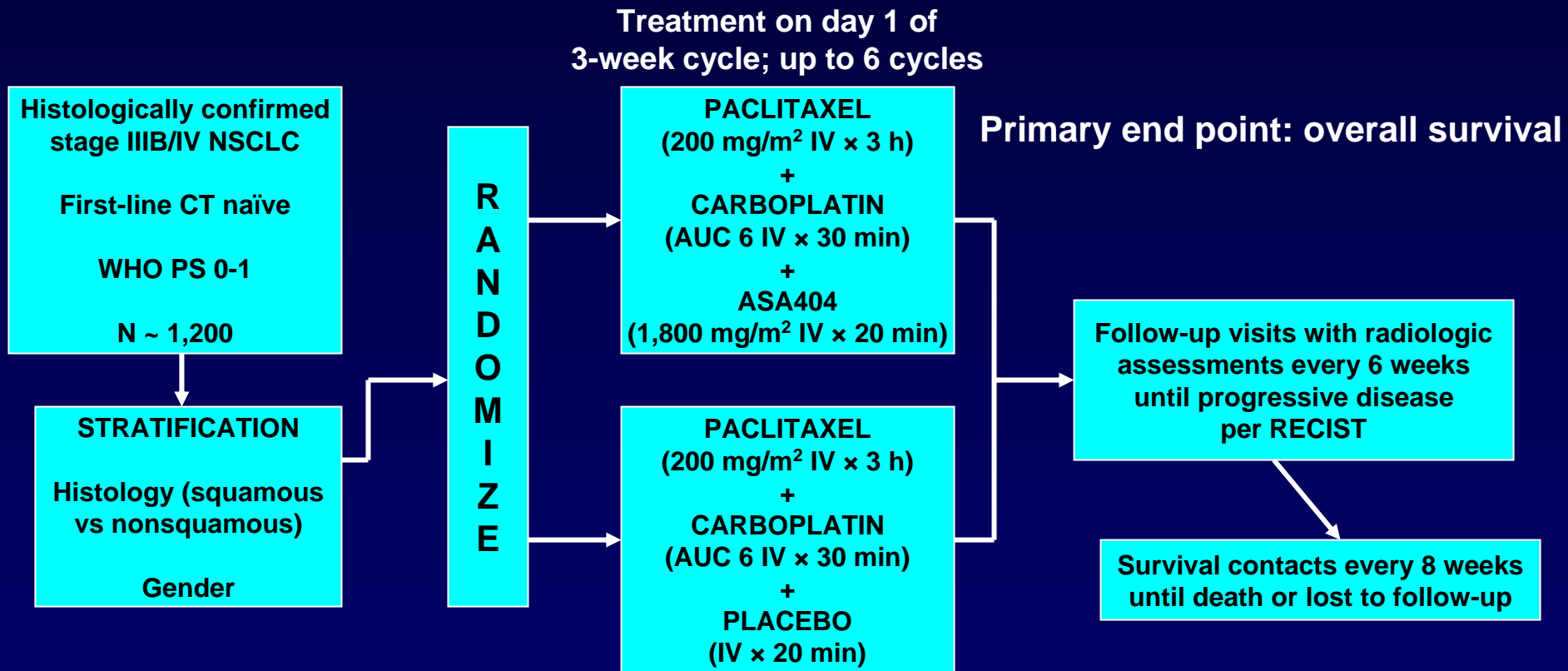
ASA404 1800 mg/m² confirmed the effect of ASA404 on survival



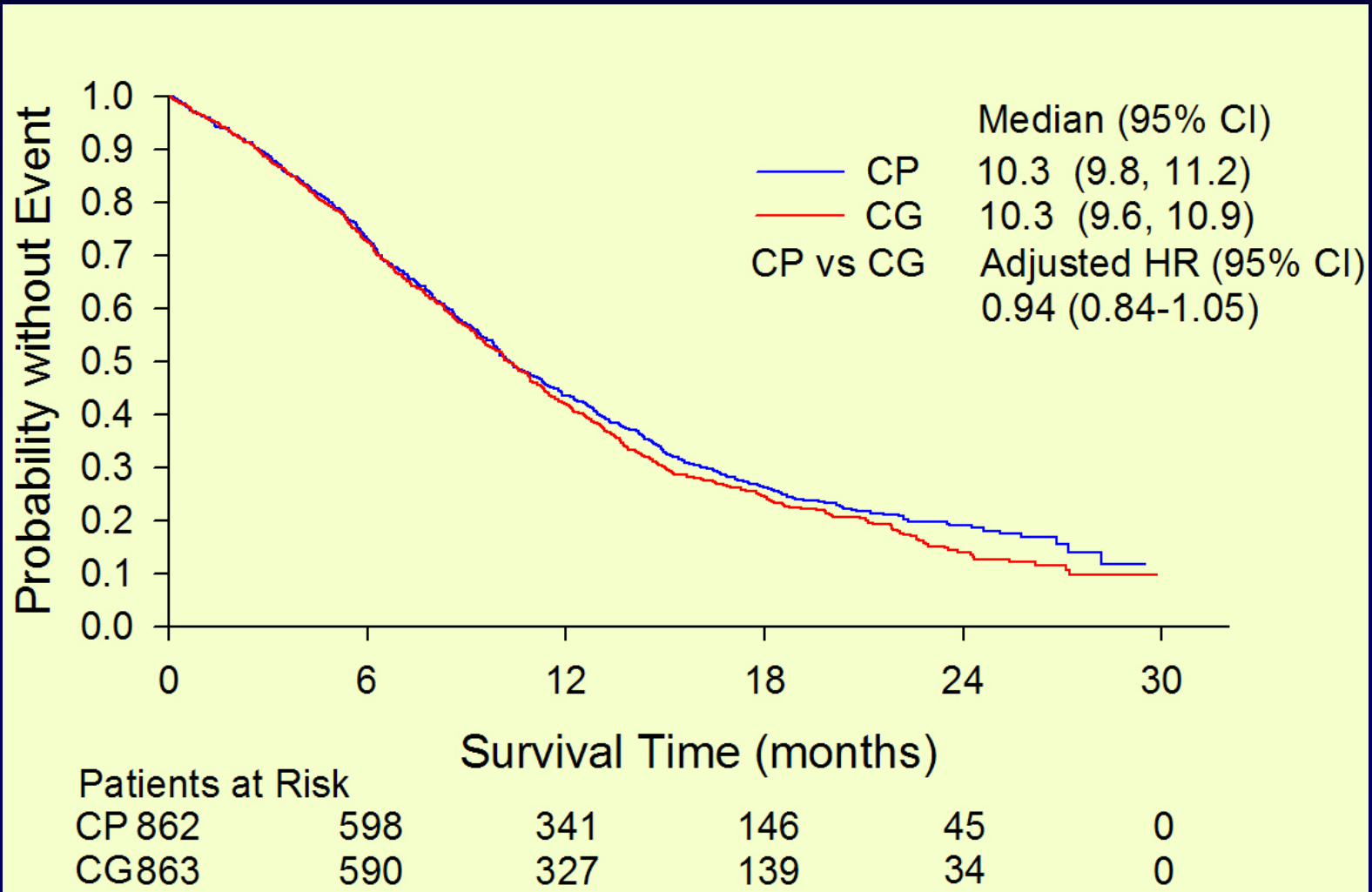
McKeage et al. IASLC 2007.

Von Pawel et al. EORTC-NCI-AACR 2006.

ATTRACT-1 Study Design

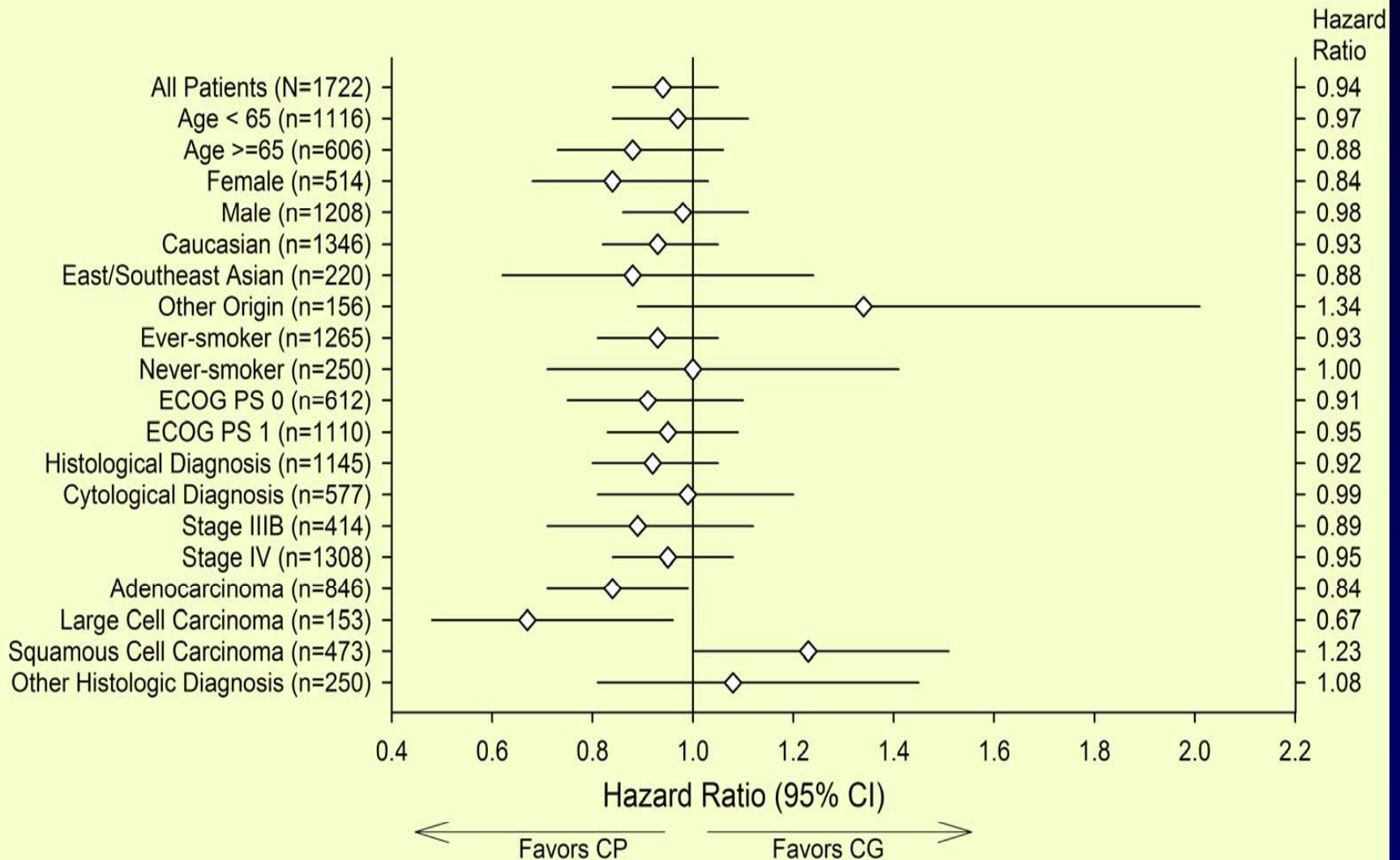


Pem/Cis vs Gem/Cis in NSCLC



Pem/Cis vs Gem/Cis in NSCLC

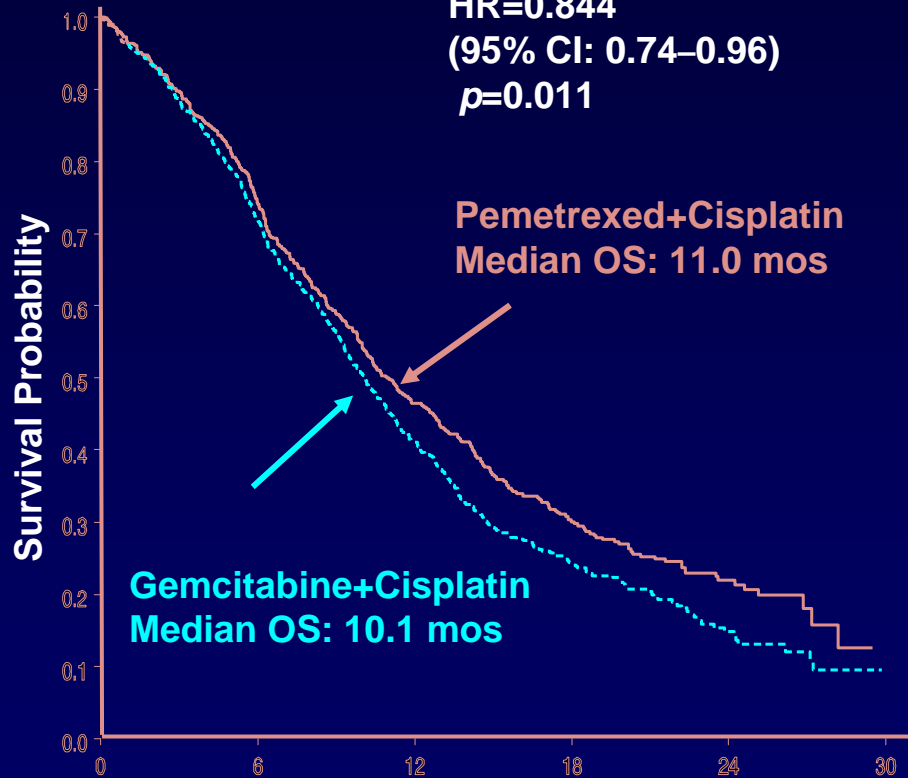
Subgroup Analyses Forest Plot



Pem/Cis vs Gem/Cis in NSCLC: Prospective Analysis

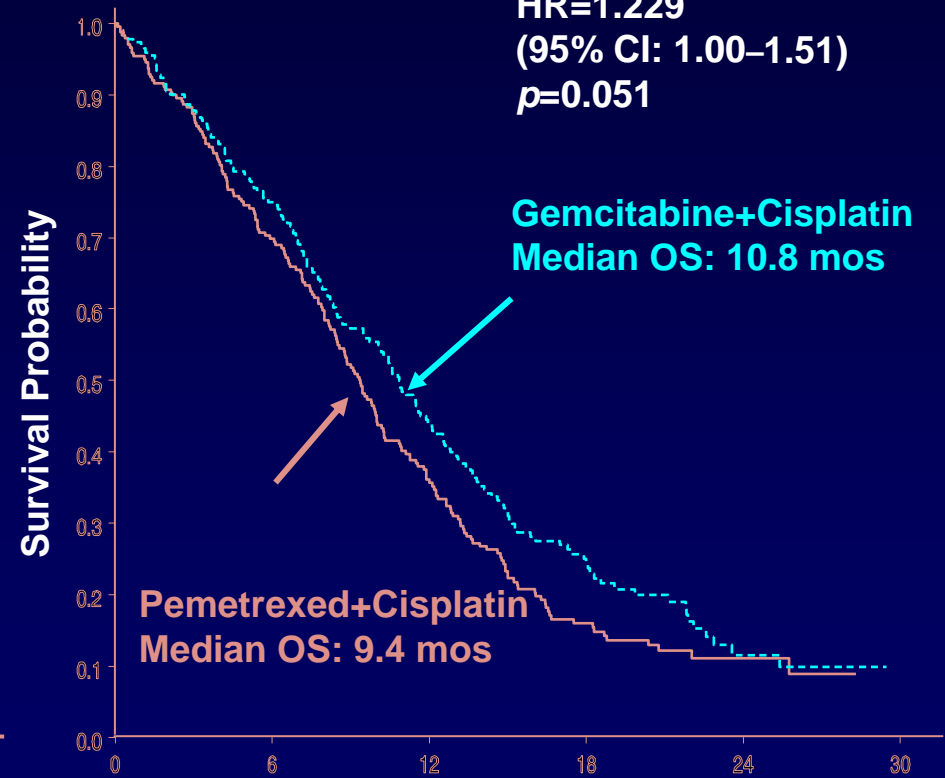
Nonsquamous* (n=1252)

HR=0.844
(95% CI: 0.74–0.96)
 $p=0.011$



Squamous (n=473)

HR=1.229
(95% CI: 1.00–1.51)
 $p=0.051$



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

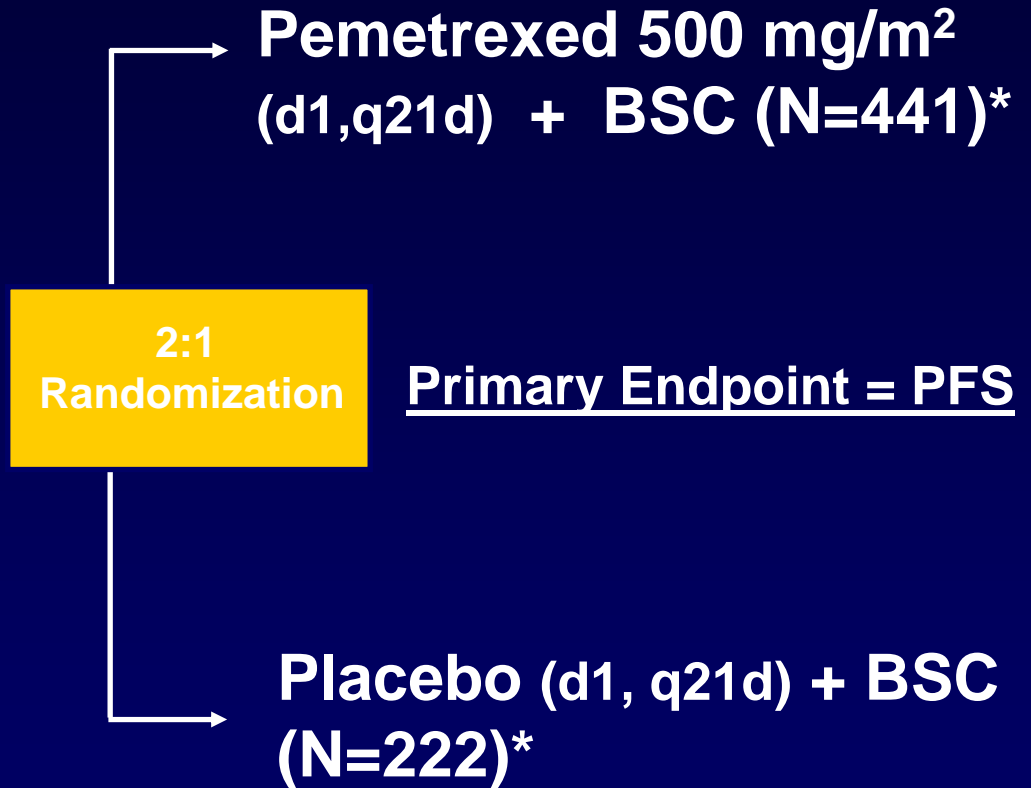
Study Design

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

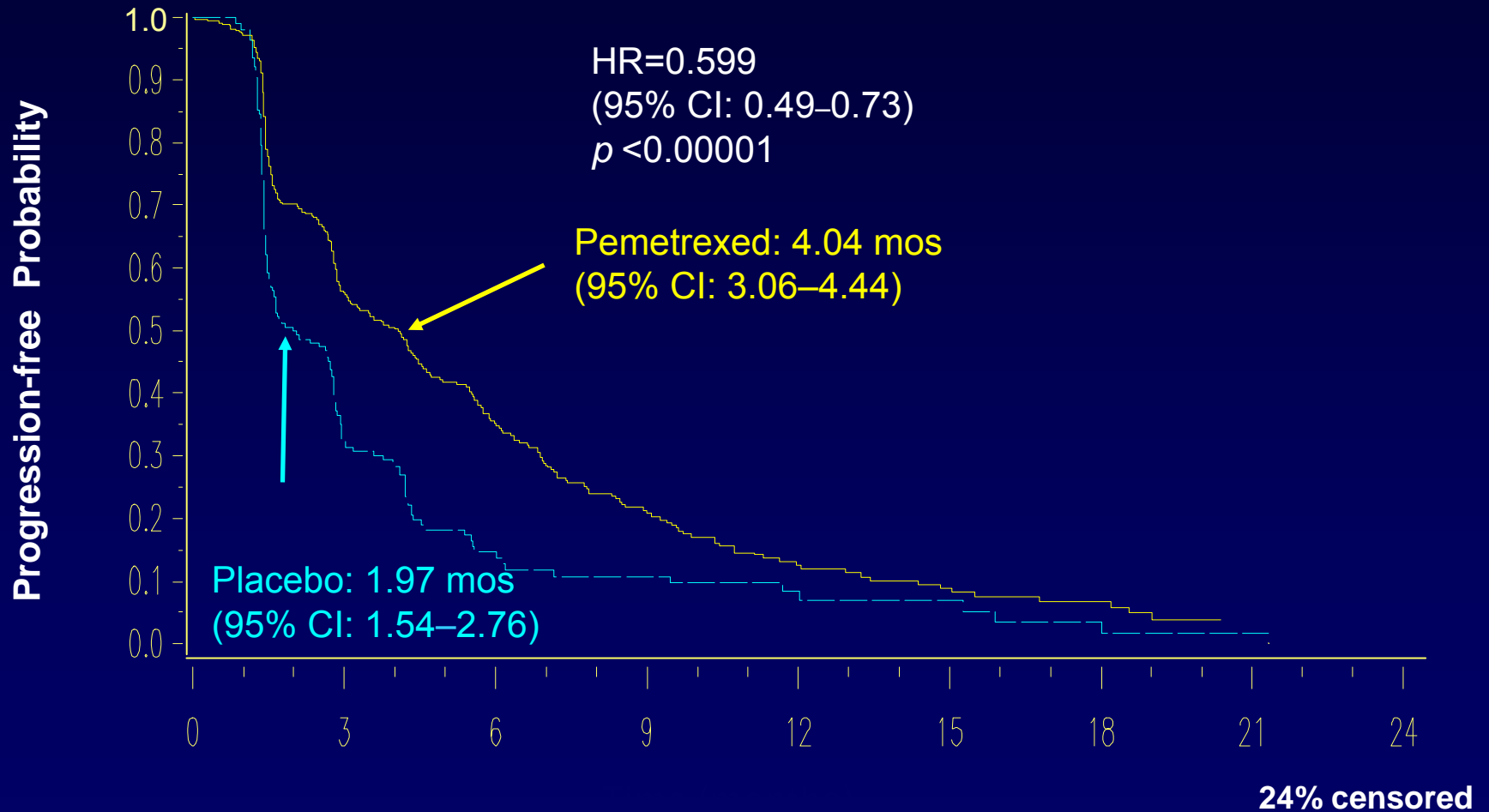
Randomization factors:

- ◆ Gender
- ◆ PS
- ◆ Stage
- ◆ Best tumor response to induction
- ◆ Non-platinum induction drug
- ◆ Brain mets



*B₁₂, folate, and dexamethasone given in both arms

Progression-Free Survival (n=581)



Efficacy by Histologic Groups








	Median PFS, mos			CR+PR+SD*, %			Prelim Median OS, mos		
	Pem	Plac	<i>p</i> -value	Pem	Plac	<i>p</i> -value	Pem	Plac	<i>p</i> -value
	Nonsquamous (n=482)	4.37	1.84	<0.00001	54.3	26.6	<0.001	14.4	9.4
Adeno (n=329)	4.60	2.66	<0.00001	58.2	29.6	<0.001	16.4	11.7	0.091
Large cell (n=20)	4.53	1.45	0.104	30.0	25.0	0.999	9.1	5.5	0.154
Other (n=133)	4.11	1.58	0.0001	47.5	18.9	0.004	11.3	7.0	0.005
Squamous (n=181)	2.43	2.50	0.896	33.3	34.5	0.999	9.6	11.9	0.231

* Clinical response (CR+PR+SD) was significantly improved with pemetrexed vs placebo in the intent-to-treat population (49% vs 29%, *p* <0.001).

Determinants of Treatment Choices in Advanced NSCLC

- Age
- Performance Status
- Co-morbidity
- Ethnicity
- Gender
- Smoking history
- Histology
- **Pharmacogenomic markers?**

Reported Predictive Molecular Markers in Tumor for Response to Chemotherapy in NSCLC

Gene	Abnormality	Drug	Response
p53	Mutation	Multiple	
K-ras	Mutation	Platinum	
β tubulin	Increased Isotype 3	Taxanes	
RRM1	Increased Expression	Gemcitabine	
ERCC 1	Increased Expression	Platinum	
TS	Increased Expression	Antifolates	
EGFR mutation	Present	Platinum	

Prognostic *versus* Predictive Markers

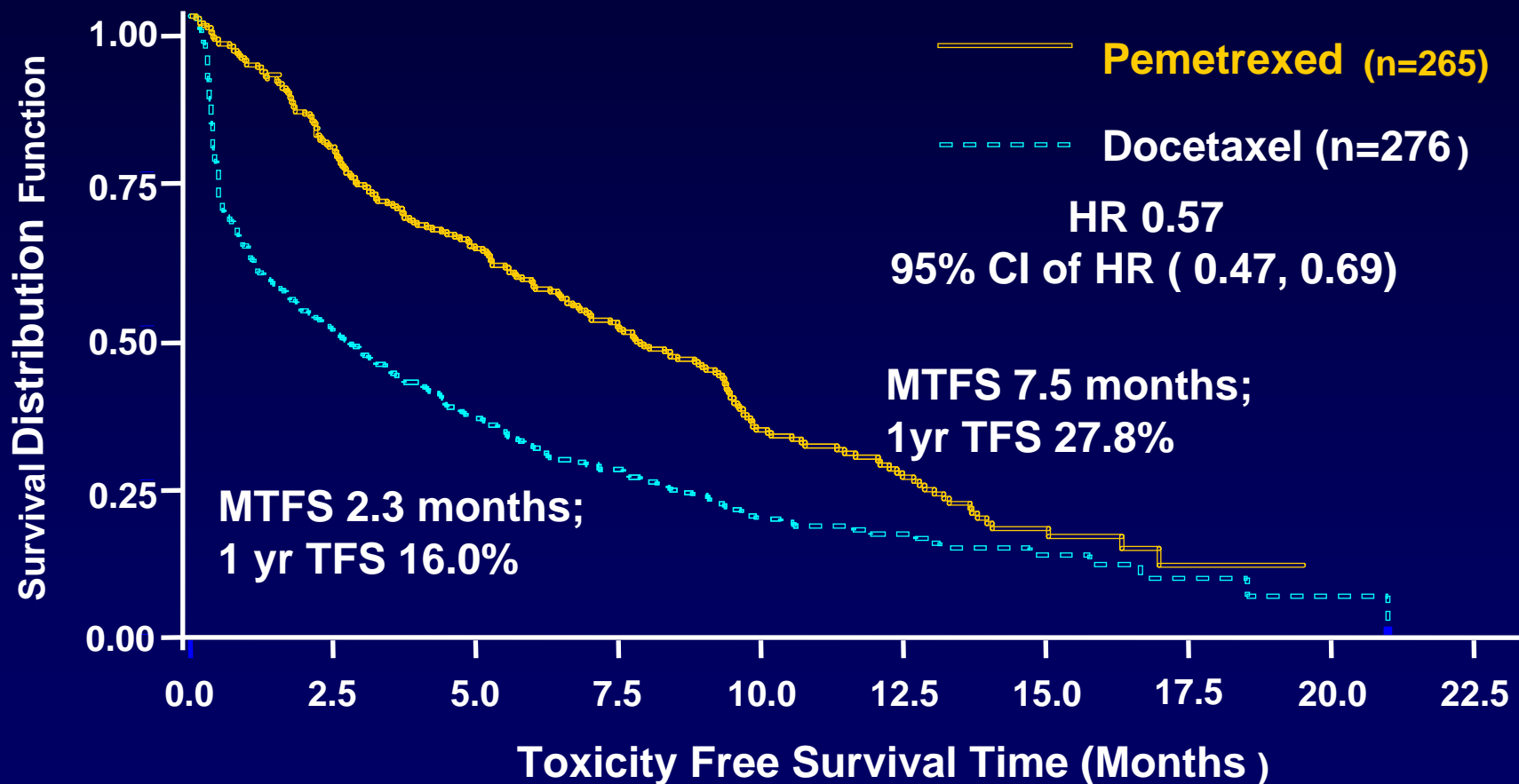
Two strategies :

- Candidate gene approach
 - RT-PCR
 - IHC (semi-quantitative & quantitative)
- Genome-wide approach

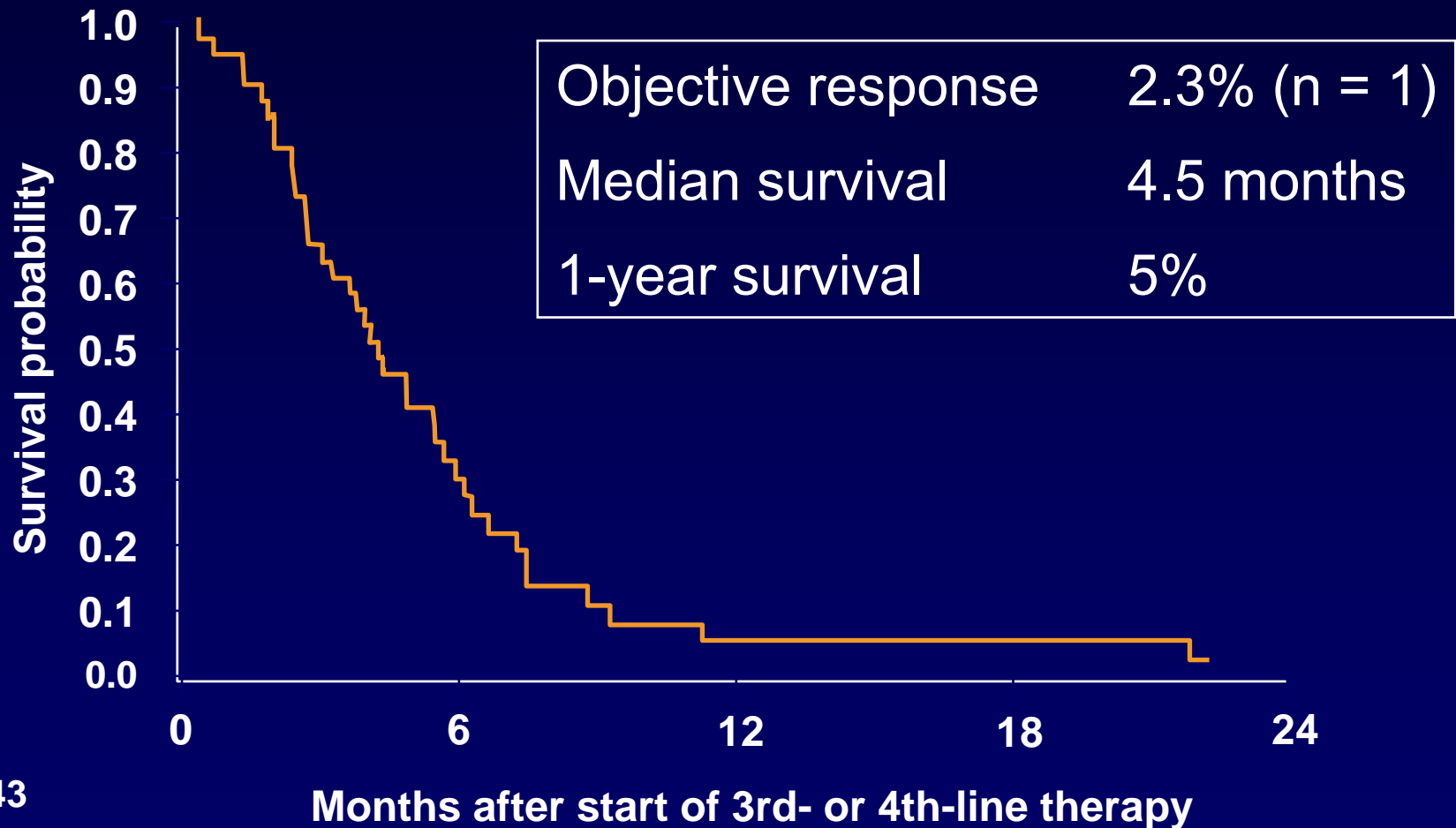
Opportunity for Second-Line Chemotherapy

- Changes in our perception of NSCLC and the effectiveness of chemotherapy following relapse
- Greater use of chemotherapy in early stage and locally advanced disease
- More patients are treated with CT in first line
- More good PS patients qualify for second line treatment
- Better supportive care

Pem vs Doc in 2nd Line : Toxicity Free Survival Curve



Outcomes in NSCLC Patients From Start of 3rd- and 4th-Line Therapy



3rd-Line Therapy for Non-Small Cell Lung Cancer: An Unmet Need

- Increasing numbers of patients with NSCLC for 3rd-line therapy
- Most of these patients have significant disease-related symptoms
- Only one agent approved in 3rd-line
- Standard chemotherapies a poor solution
- 3rd-line therapy for NSCLC represents an unmet medical need

Potential Second/Third Line Algorithm

