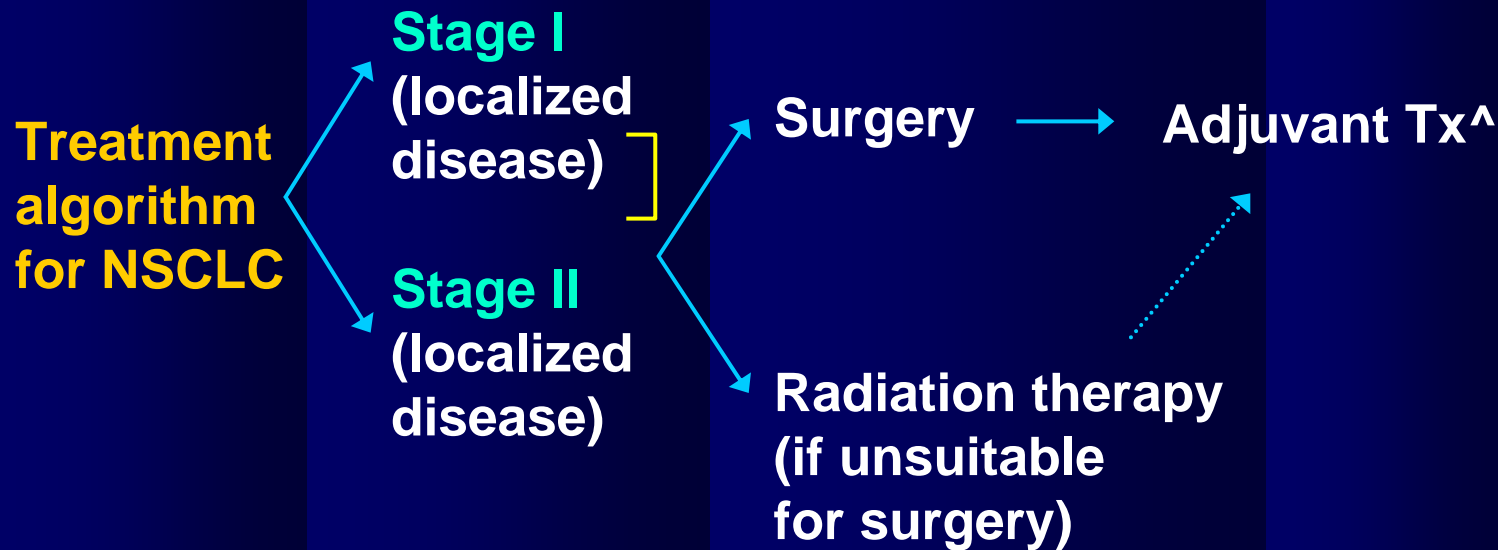


State-of-the-Art in the Treatment of Advanced Non- Small Cell Lung Cancer: 2011

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Current Systemic Treatment NSCLC – ASCO and NCCN Guidelines

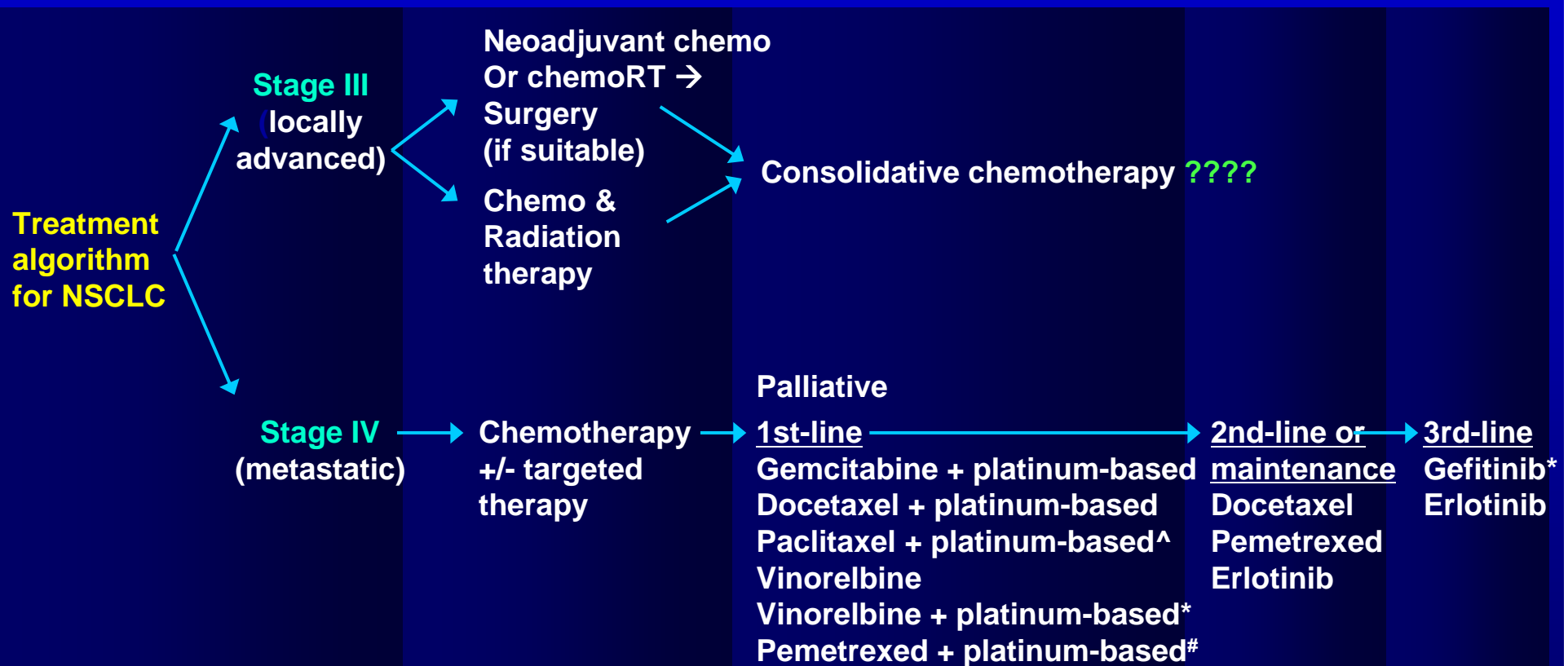


[^]Emerging, albeit controversial data for IB \geq 4cm and stage II/III

Pfister et al. *J Clin Oncol*. 2004;22:330;

Ginsberg et al. Non-small cell lung cancer. In: *Cancer: Principles & Practice of Oncology*. 2001:925.

Current Treatment Options for NSCLC (cont'd)



Pfister et al. *J Clin Oncol*. 2004;22:330;

Ginsberg et al. Non-small cell lung cancer. In: *Cancer: Principles & Practice of Oncology*. 2001:925.

• Indicated only for those who have already demonstrated a therapeutic benefit on gefitinib

^ Bevacizumab indicated in non-sq, NSCLC with no Hx of antecedent hemoptysis

• Compendia listing for C225 in combination with Vinorelbine and Cisplatin

Pemetrexed approval restricted to non-squamous histology

Agents with Activity in NSCLC*

Older Agents

- Carboplatin
- Cisplatin
- Etoposide
- Ifosfamide
- Mitomycin C
- Vinblastine
- Vindesine

Newer Agents

- Docetaxel
- Gemcitabine
- Irinotecan
- Paclitaxel
- Topotecan
- Vinorelbine
- Pemetrexed
- Gefitinib
- Erlotinib
- Bevacizumab
- Cetuximab

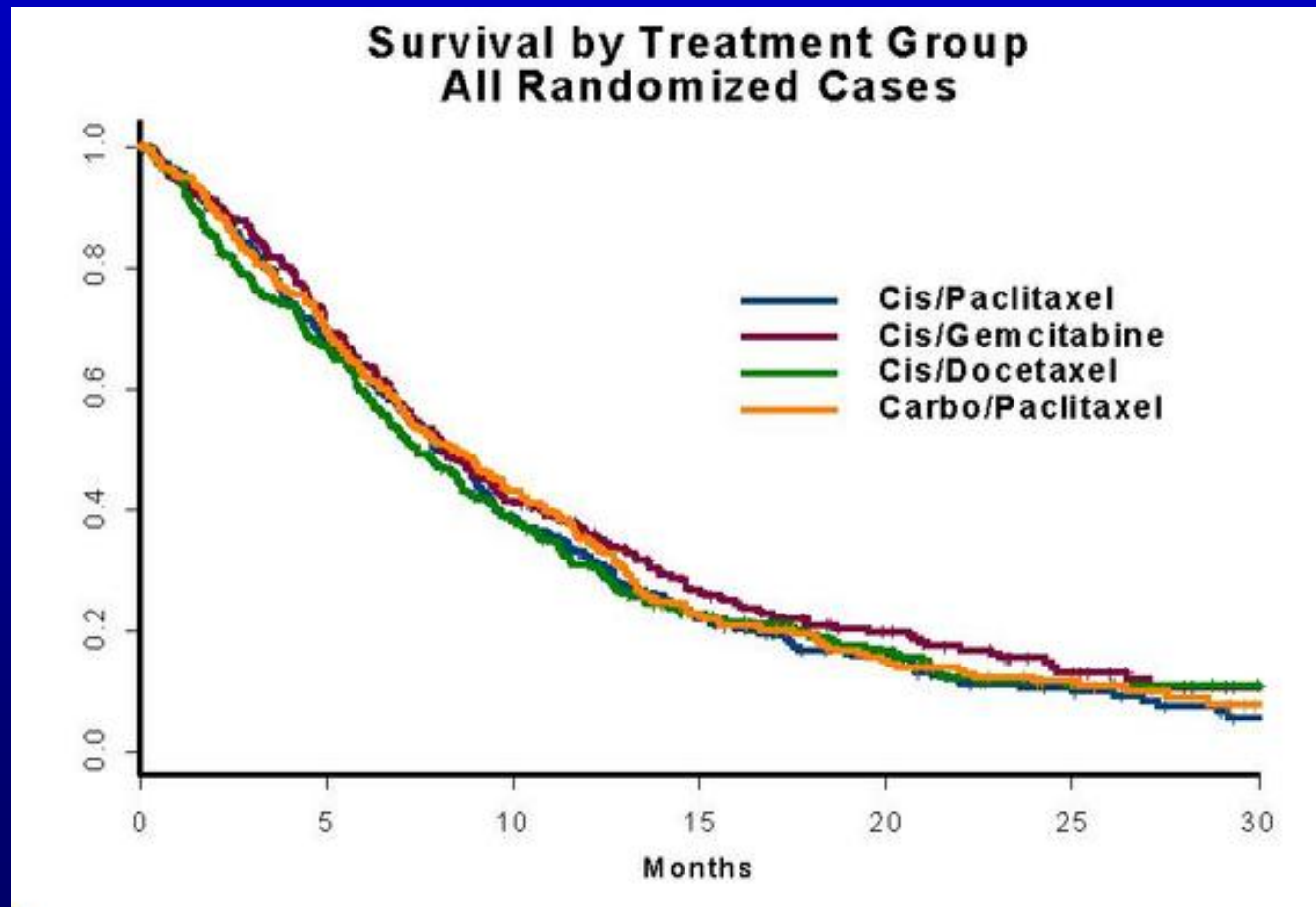
*Since
1990*

*Since
2000*

* Not all of these agents are indicated for use as a single agent or in combination for the treatment of NSCLC.

ECOG 1594: Overall Survival by Treatment Group

- 1207 patients, stage IIIB/IV :(15/85%), PS 0–2; Median age 63, M/F (64/36%)



Personalized Therapy: in evolution

- Previous “one size fits all” approach
- Eclipsed by “personalized” or “patient-specific” treatment
 - Histology
 - Molecular markers

Emergence of Histology as Determinants of Therapy

E4599: Paclitaxel-Carboplatin +/- Bevacizumab
Scagliotti: Gemcitabine-DDP vs
Pemetrexed-DDP

ECOG 4599: Phase 3 Trial of Bevacizumab in Nonsquamous NSCLC

Eligibility

- Nonsquamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

PC
Paclitaxel 200 mg/m²
Carboplatin AUC 6 mg/m² q3wk

No crossover to
bevacizumab
permitted

PCB
Paclitaxel x 6 cycles
+
bevacizumab
(15 mg/kg q3wk) to PD

Stratification variables

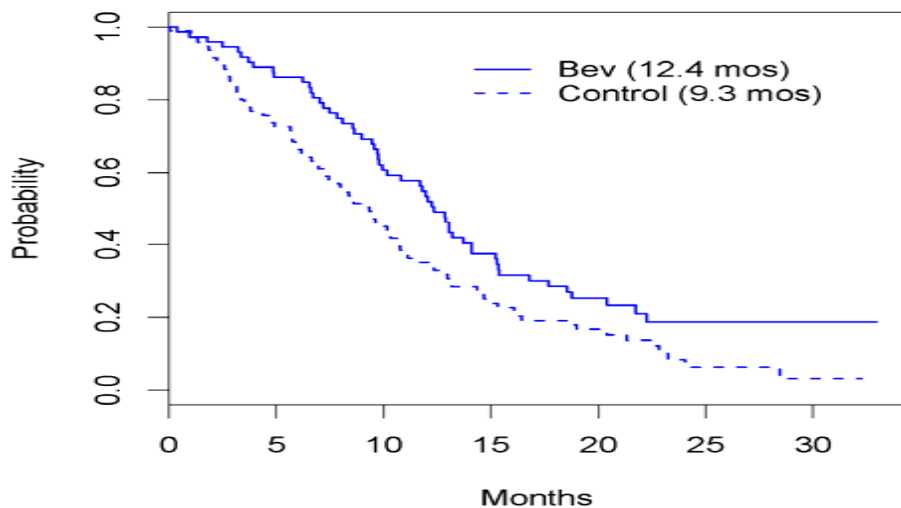
- RT vs no RT
- Stage IIIB or IV vs recurrent
- Wt loss <5% vs ≥5%
- Measurable vs nonmeasurable

Parameter	PC	PCB	P value
RR (%)	15	35	<0.001
PFS (mo)	4.5	6.2	<0.001
Median survival (months)	10.3	12.3	<i>P</i> = 0.003
1-year survival (%)	44	51	
2-year survival (%)	15	23	

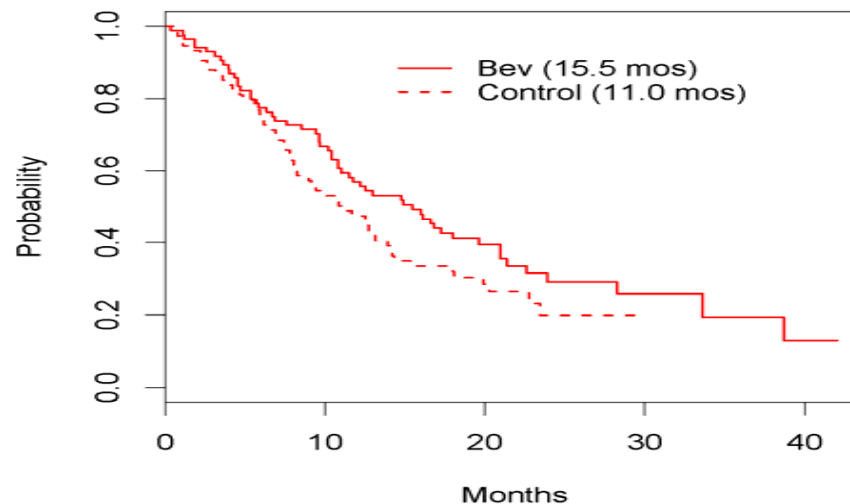
RT = radiotherapy; PD = progressive disease; PC = paclitaxel/carboplatin; PCB = paclitaxel/carboplatin/bevacizumab. Sandler A et al. N Engl J Med. 2006;355:2542-2550.

ECOG 4599: Outcome by Gender and Age

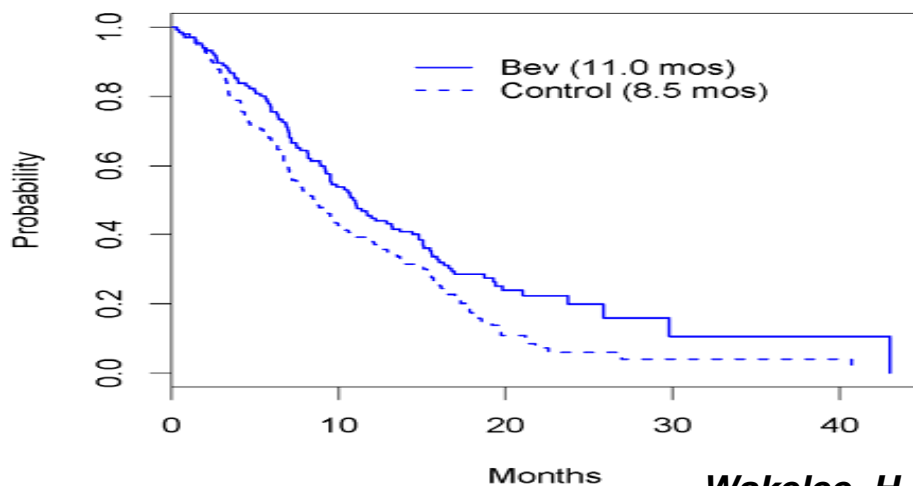
Overall Survival, Males < 60



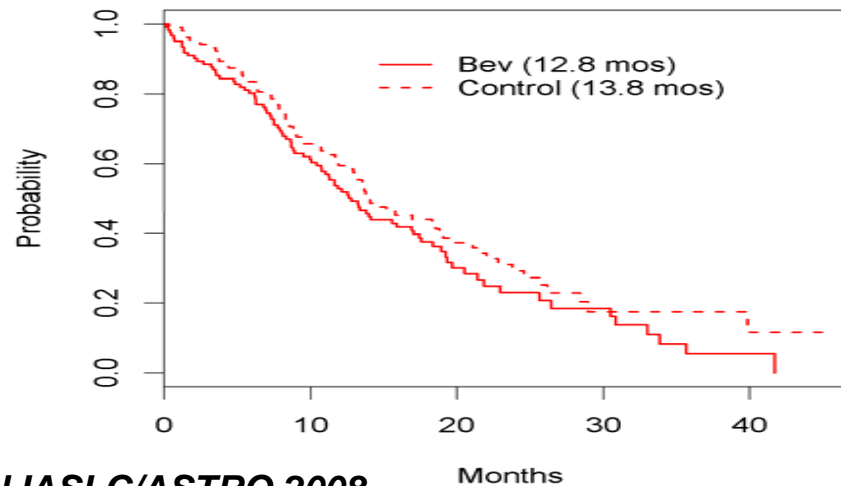
Overall Survival, Females < 60



Overall Survival, Males 60 +



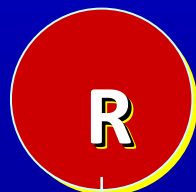
Overall Survival, Females 60 +



Wakelee, H et al IASLC/ASTRO 2008

Study Design

- Stage IIIB/IV NSCLC
 - PS 0 - 1
- No prior chemo
- Randomization: gender, PS, stage, histo vs cyto dx, brain mets



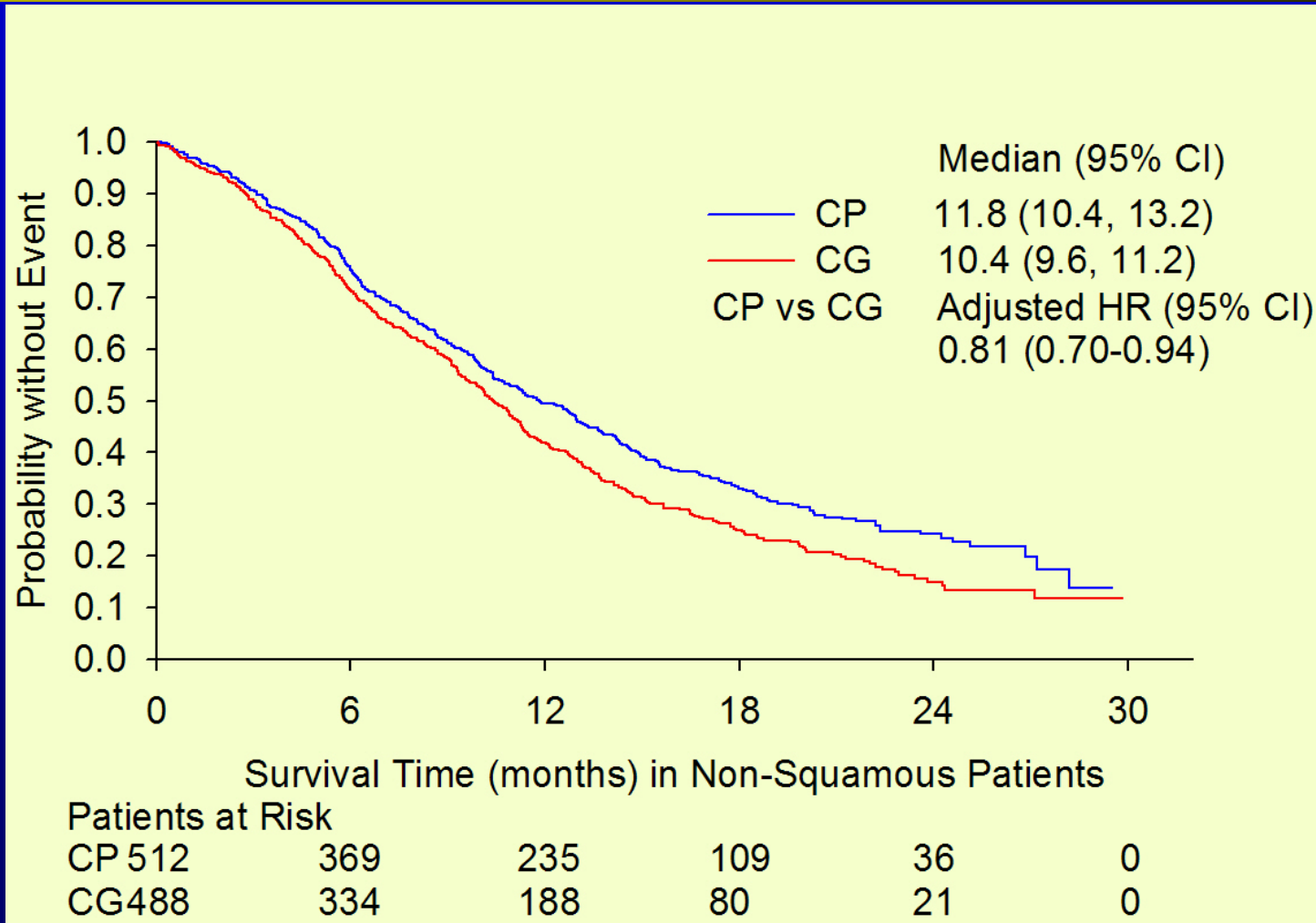
**Pemetrexed 500 mg/m² +
Cisplatin 75 mg/m² day 1**

**Primary objective: Overall Survival
15% Non-inferiority margin (HR 1.17)
N = 1700 Patients , Power 80%**

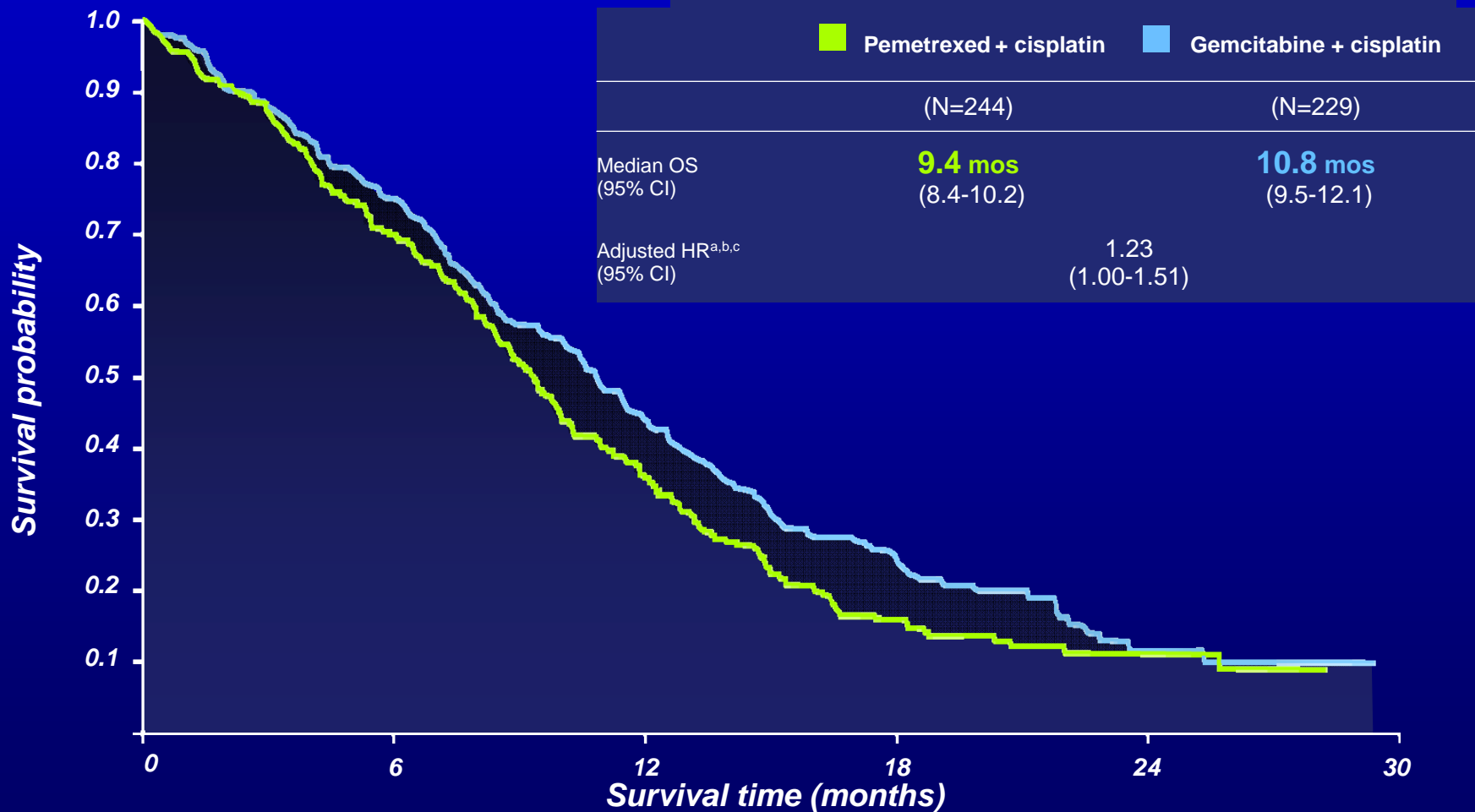
**Gemcitabine 1250 mg/m² days 1 + 8
Cisplatin 75 mg/m² day 1;**

B12, folate, and dexamethasone given in both arms

Overall Survival in Patients with Nonsquamous Histology



Pemetrexed Plus Cisplatin in 1st-line: Survival with Gemcitabine/Cisplatin for Patients with Squamous Cell Carcinoma

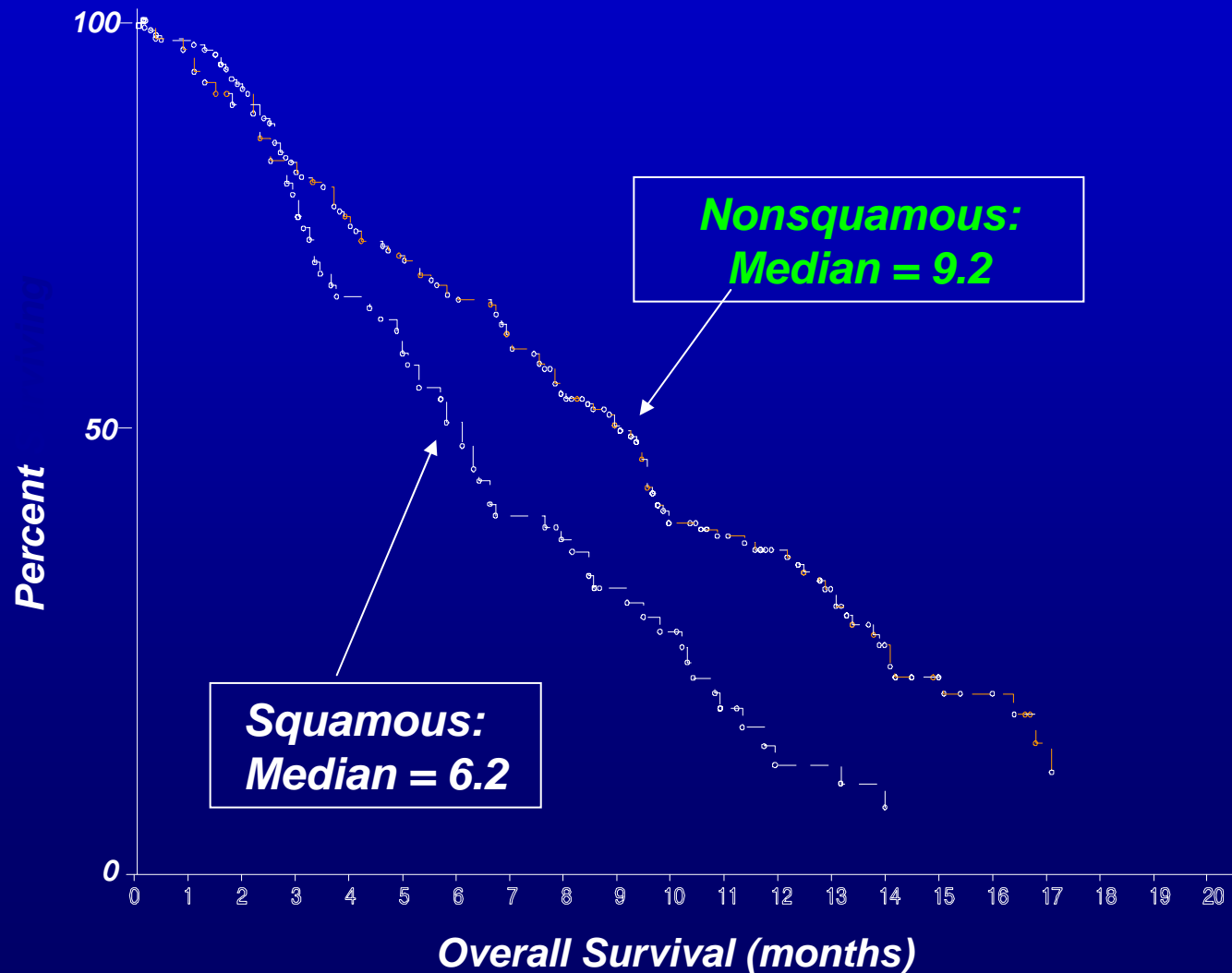


Second-Line Study of Pemetrexed vs Docetaxel: Efficacy by Histology

	Nonsquamous group		Squamous group	
	Pemetrexed (n=205)	Docetaxel (n=194)	Pemetrexed (n=78)	Docetaxel (n=94)
% ECOG PS 2	12.5	10.1	8.3	17.4
% TSPC <3 months	51.0	51.0	48.7	41.9
% Stage IV	81.5	78.9	57.7	66.0
% Male	60.5	69.1	89.7	88.3
Median OS, months	9.3	8.0	6.2	7.4
Adjusted OS HR (95% CI)	0.778 (0.607, 0.997)		1.563 (1.079, 2.264)	
Median PFS, months	3.1	3.0	2.3	2.7
Adjusted PFS HR (95% CI)	0.823 (0.664, 1.020)		1.403 (1.006, 1.957)	

Treatment by Histology Interaction: Survival Adjusted for Cofactors (p=0.001)

Pemetrexed in Second-line NSCLC



Conclusions Regarding Histology

- Based on E4599 and Scagliotti trials, use of pemetrexed and bevacizumab is limited to NON-squamous histology
- Standard cytotoxic platform for Adenocarcinoma:
 - Platinum plus either pemetrexed or taxane
- Standard platform for squamous cell carcinoma:
 - Platinum plus either gemcitabine or taxane

Emergence of Maintenance Therapy as a Viable Option in Advanced NSCLC

- FIDIAS
- JMEN
- SATURN
- ATLAS

Summary of Efficacy Results: Maintenance Treatment (2009)

Study	N	PFS (HR)	P value	Adeno (PFS HR)	Squamous (PFS HR)	OS (HR)
Docetaxel	153	NR	P=.0001 Median PFS	NR	NR	P=.0853 Median OS
Pemetrexed	441	.60	P<0.00001	.51	1.03	.79 P=0.012
Erlotinib (Saturn)	437	.71	P<0.0001	.60	.76	.81
Erlotinib (ATLAS)	370	.72	P=0.0012	.64	1.21*	NS

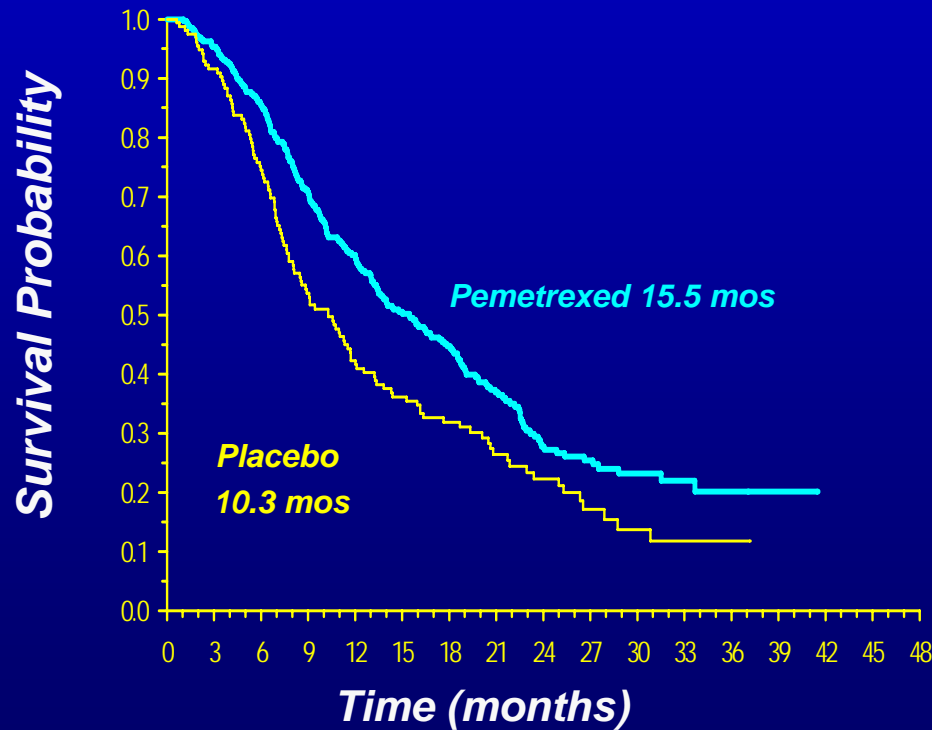
* 6 patients

- **Maintenance therapy significantly prolonged PFS in all studies,with relatively greater benefit in adenoca.**
- **Overall survival to date also favors maintenance therapy.**

Overall Survival by Histology

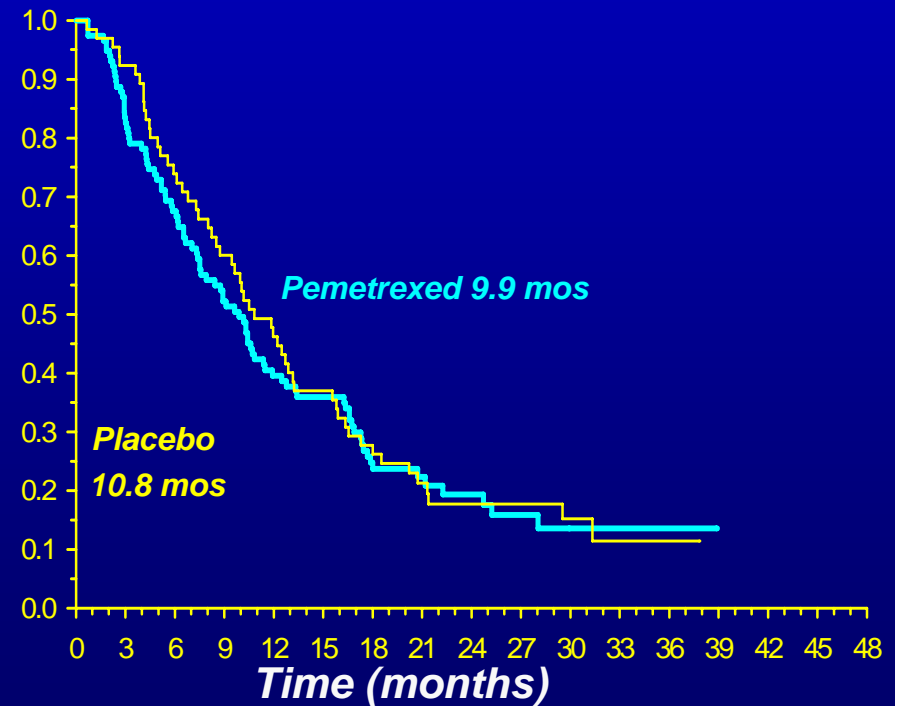
Nonsquamous (n=481)

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



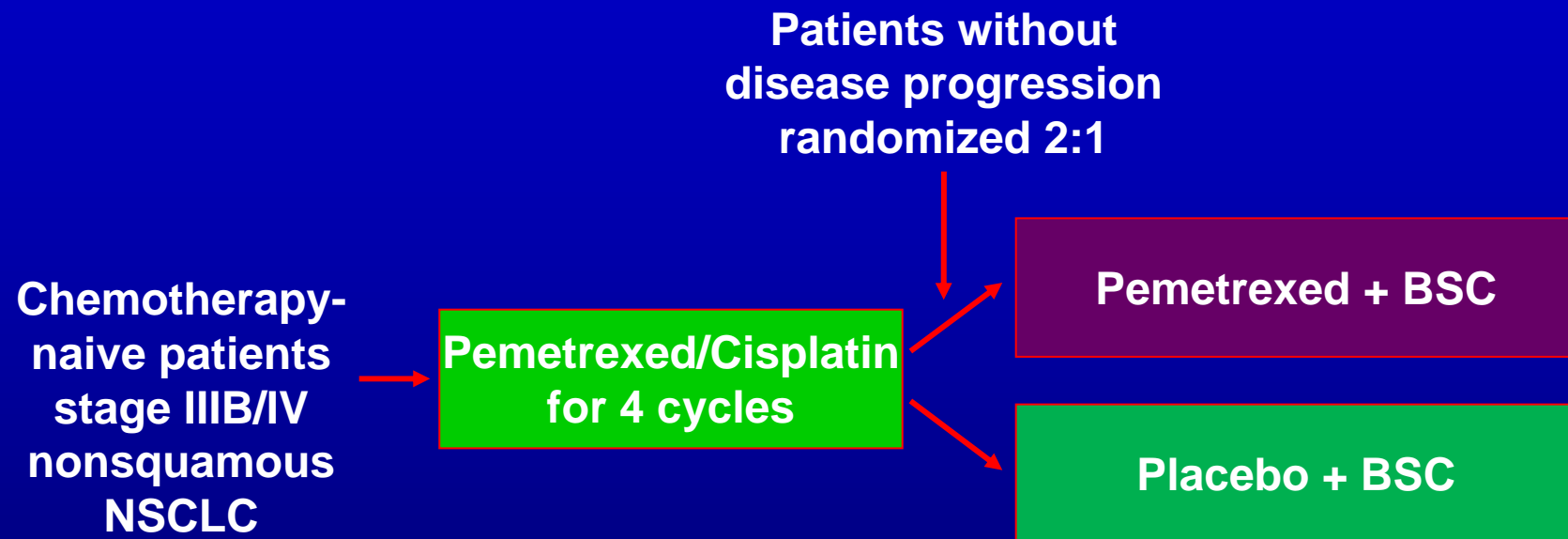
Squamous (n=182)

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



Ciuleanu TE, et al. J Clin Oncol . 2008; 26(May 20 suppl; abstr 8011).

Pemetrexed Maintenance vs Placebo in Nonsquamous NSCLC



N = 900 (planned)

Primary endpoint: PFS

Other endpoints: OS, ORR, patient-reported outcomes, resource utilization, toxicity

1. Paz-Ares LG, et al. BMC Cancer. 2010;10:85. 2. ClinicalTrials.gov. NCT00789373.

Pemetrexed Maintenance vs Placebo in Nonsquamous NSCLC

Patients without
disease progression
randomized

Chemotherapy-
naive patients
stage IIIB/IV
nonsquamous
NSCLC

Pemetrexed + BSC

Placebo + BSC

Placebo + BSC

Results Available
2011 at ASCO

N = 900 (planned)

Primary endpoint: PFS

Other endpoints: OS, ORR, patient-reported outcomes, resource utilization, toxicity

1. Paz-Ares LG, et al. BMC Cancer. 2010;10:85. 2. ClinicalTrials.gov. NCT00789373.

Can we Combine Platinum and Pemetrexed with Bevacizumab Frontline?

- ❖ Are there clinical insights?
- ❖ Should both bevacizumab and pemetrexed be continued beyond 6 cycles?

Phase 2 Study of Carboplatin + Pemetrexed + Bevacizumab

Chemotherapy-naïve

Stage IIIB/IV

ECOG PS 0-1

Non-squamous histology

No CNS mets

Carboplatin AUC 6 i.v. day 1

Pemetrexed 500 mg/m² i.v. day 1

Bevacizumab 15 mg/kg i.v. day 1

Cycles q3 weeks X 6

PD

Off Study

Non-PD

Pemetrexed 500 mg/m²

Bevacizumab 15 mg/kg

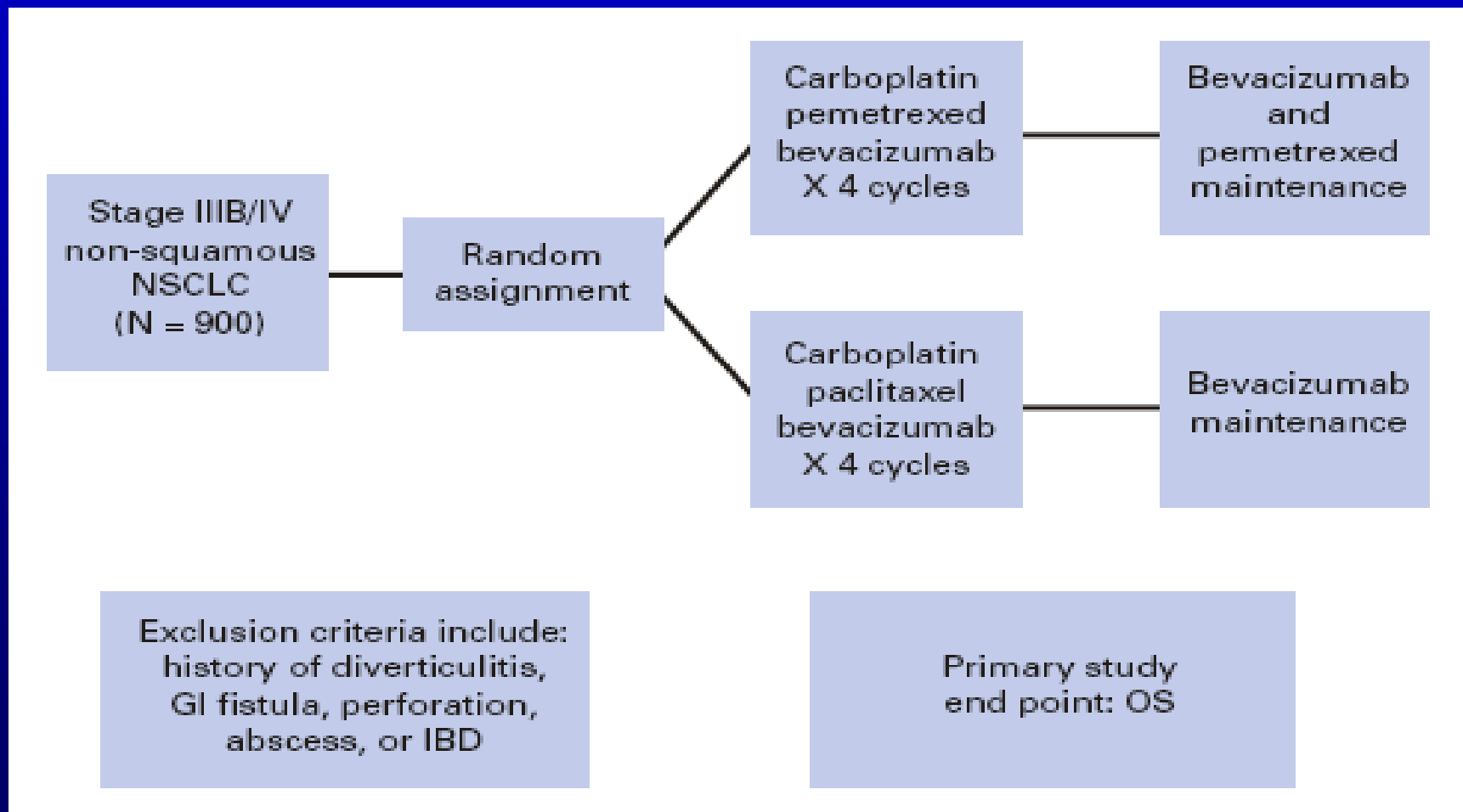
Cycles q3 weeks until PD

Phase 2 study of Carboplatin + Pemetrexed + Bevacizumab

- 51 patients enrolled
- ORR 55% (41-69%)
- MPFS 9.3 months (5.5-15)
- MST 14 months (10.8-19.6)
- 0% inc. of FN; 2% inc of TRDs

Phase 3 First-Line Pem/Carbo/ Bevacizumab in Advanced Nonsquamous NSCLC

POINT-BREAK



ECOG 5508 Phase 3: Maintenance Bevacizumab vs Pemetrexed vs Bevacizumab + Pemetrexed

Primary Endpoint = OS

Eligibility

- Stage IIIB/IV Bev eligible NSCLC
- PS 0-1
- 4 prior cycles of CarbTax +Bev (1236) with CR, PR, SD (864)

Randomization factors:

- Gender
- PS
- Stage
- Best tumor response to induction

**R
A
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→ Pemetrexed 500 mg/m² (q21d)

→ Bevacizumab 15mg/kg (q21d)

→ Pemetrexed 500 mg/m² (q21d)
Bevacizumab 15mg/kg (q21d)

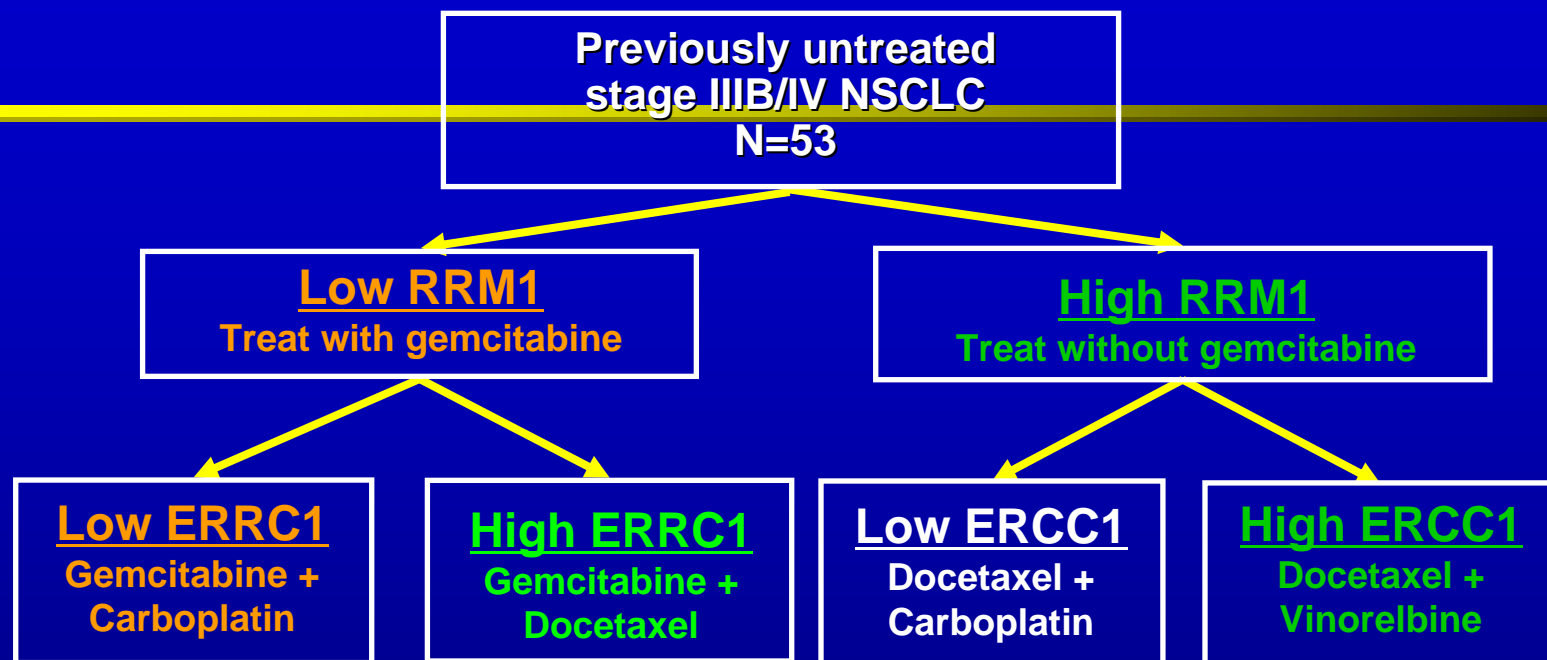
*B₁₂, folate, and dexamethasone given in Pem. arms

Total 1236 patients with 864 randomized (288/arm)

Other Chemotherapy Selection Strategies: Molecular Determinants Used for Selection

- **ERCC1**, a component of the nucleotide excision repair complex, is important for platinum-induced DNA adduct repair and therefore a determinant of **platinum** resistance
- **RRM1** is a crucial gene for nucleotide metabolism, and is the dominant molecular determinant of **gemcitabine** efficacy

Phase 2 Trial: MADeIT in NSCLC



	MCC-13208 MADeIT	MCC-12621 [Hx Control] Gemcitabine + Carboplatin → Docetaxel
Median OS	13.3 mos	6.7 mos
12-Month Survival	59%	38%
CR/PR	44%	24%
PFS	6.6 mos	4.9 mos

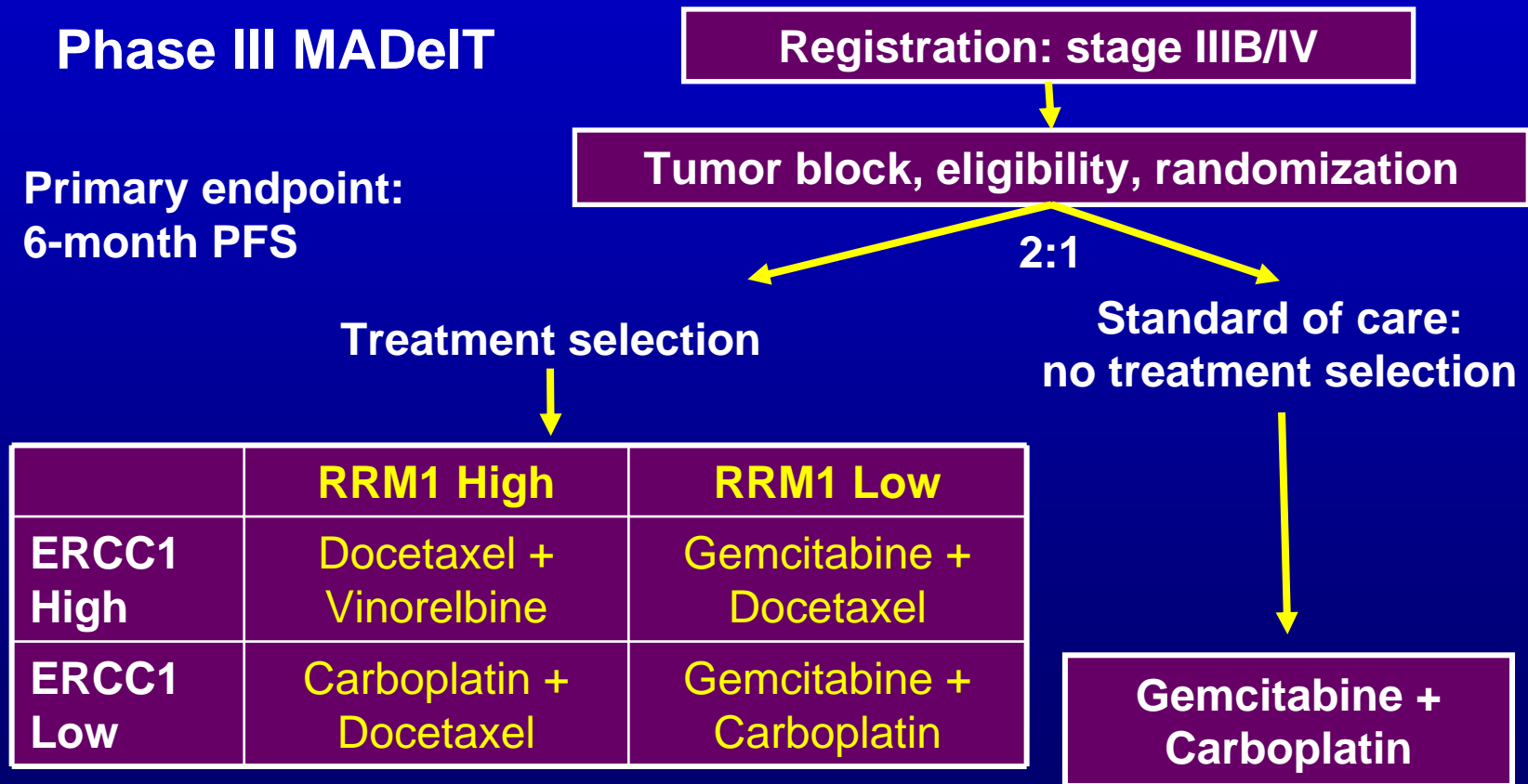
MADeIT=molecular analysis–directed individualized therapy.

Simon. J Clin Oncol. 2007;25:2741; Chiappori. Oncology. 2005;68:382.

Individualizing Therapy in NSCLC by RRM1 and ERCC1 Status: Trial in Advanced NSCLC

Phase III MADeIT

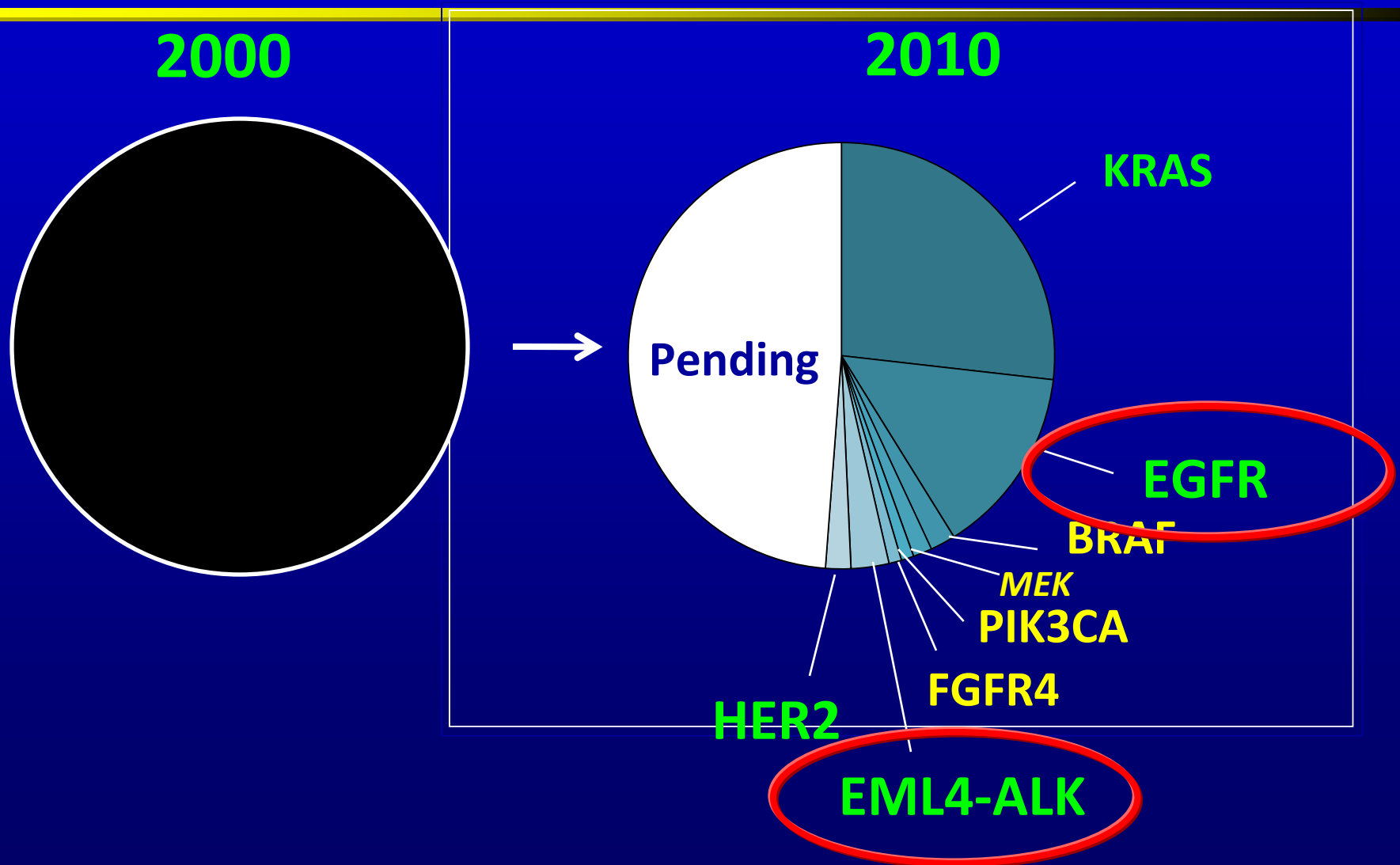
Primary endpoint:
6-month PFS



Bepler. Clin Lung Cancer. 2007;8:509; US National Institutes of Health website.
<http://clinicaltrials.gov/ct2/show/NCT00499109?id=NCT00499109&phase=2&rank=1>. Accessed 5/27/08.

An Evolving View of Adenocarcinoma

Emergence of Molecular Markers



EGFR, KRAS and EML4/ALK

Vince Miller's talk

Conclusions - NSCLC

- Histology now determines frontline therapy in advanced NSCLC
- Switch maintenance with pemetrexed or erlotinib confers survival advantage
- Clear role for first line EGFR TKI in pts harboring EGFR mutations [10-15%]
- Crizotinib highly active in pts with EML4/ALK translocation [4%]

