

Maintenance Therapy for Advanced NSCLC A New Treatment Paradigm

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Maintenance / Consolidation / Sequencing

- **Maintenance Therapy (defined as immediate therapy after 4-6 cycles of standard first line treatment) is one of many strategies to optimize first line treatment for advanced NSCLC and an area of active investigation for decades**
- **A recently published meta-analysis of 13 trials from 1989-2008 demonstrated a substantial improvement in PFS (HR 0.75; $p < .00001$) and a modest prolongation in OS (HR 0.92; $P = .03$)**

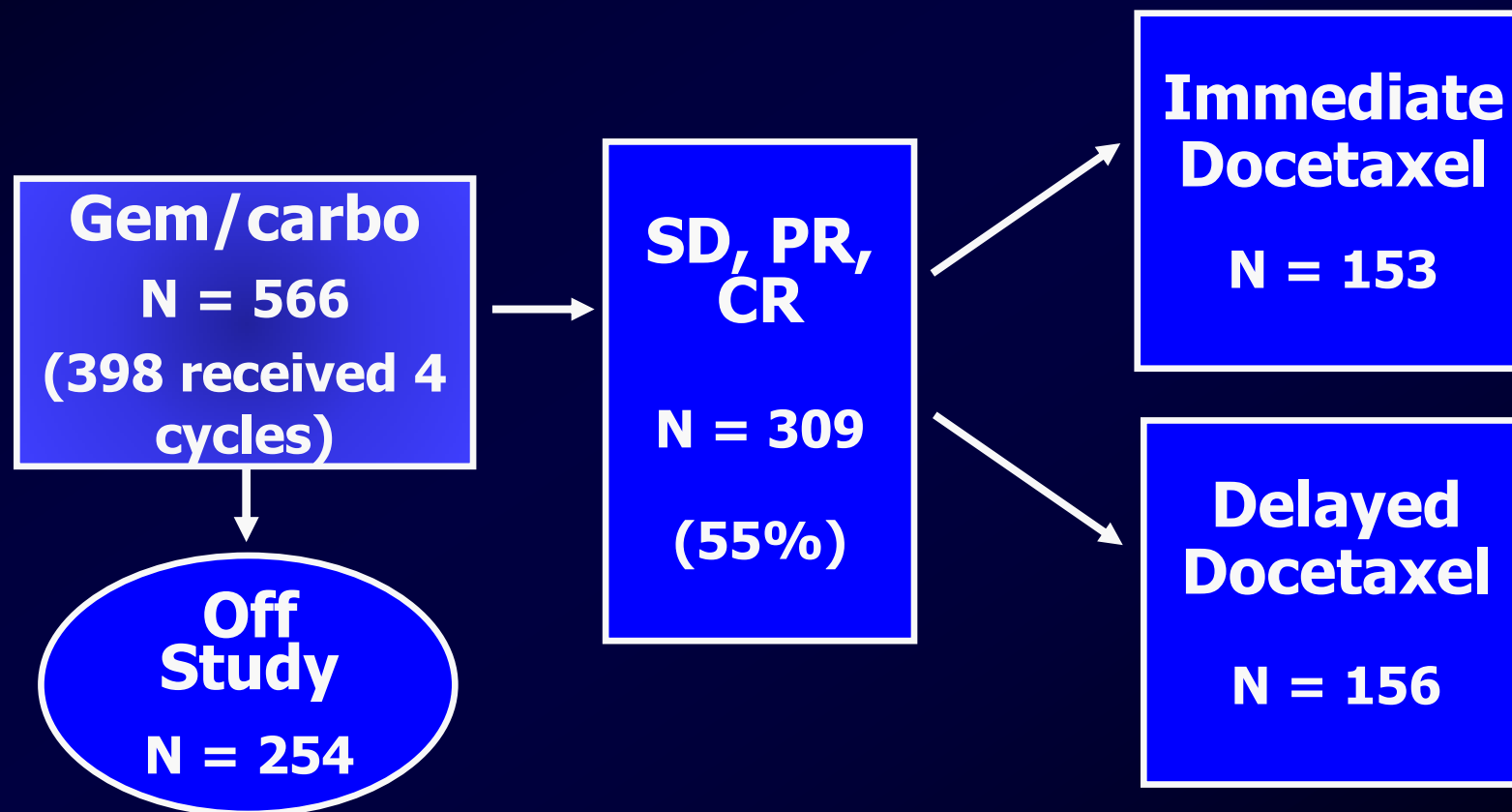
Treatment Paradigm in the Pre-maintenance ERA

- **First line platinum based chemotherapy given for 4-6 cycles**
- **Treatment break for all patients with either response or stable disease**
- **Second-line therapy for patients at the time of documented radiologic progression or symptom worsening**

Should Patients Receive Maintenance Therapy OR Wait Until Their Tumor Progresses?

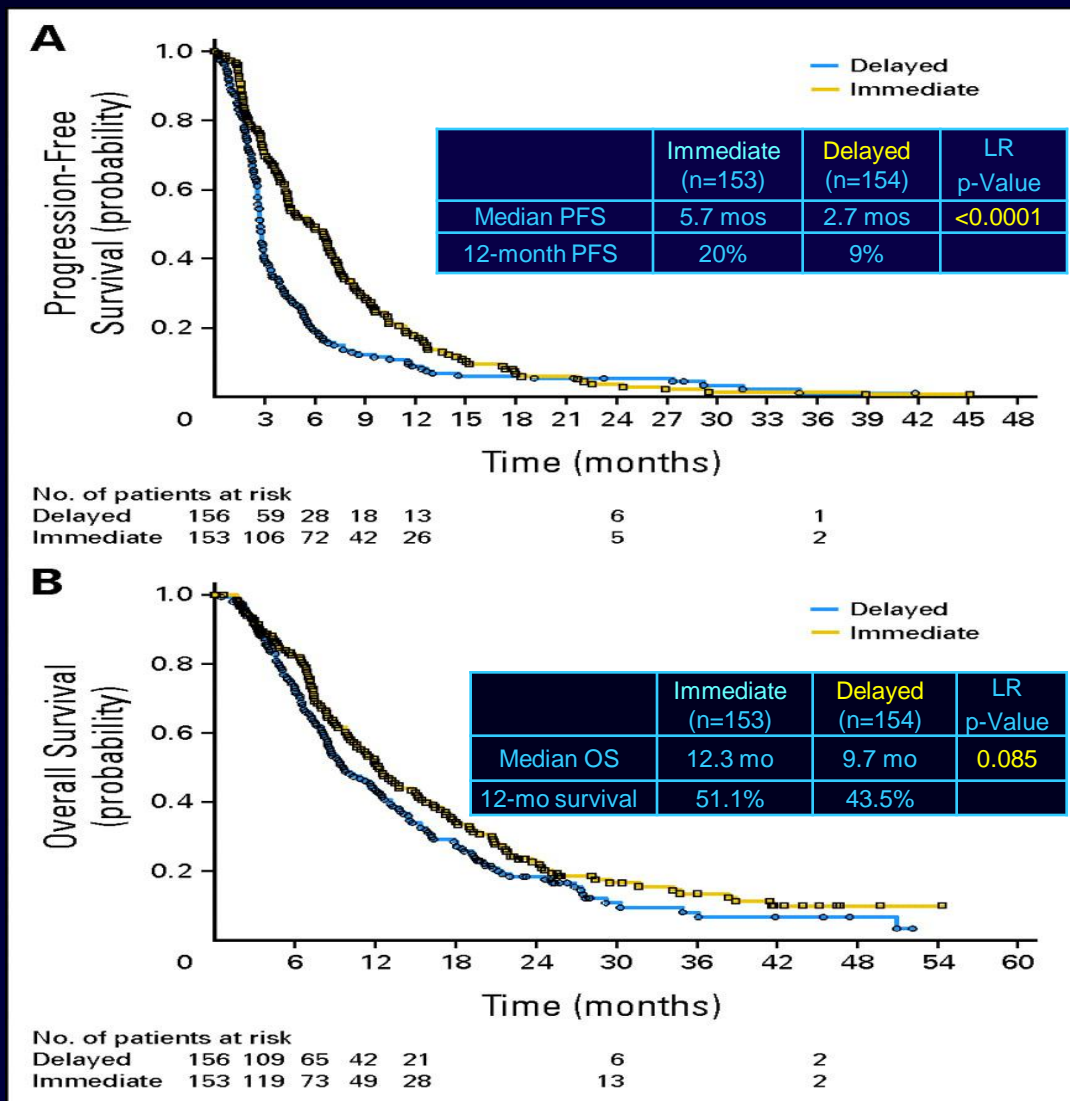
True Maintenance *vs.* Second -line

Immediate vs. Delayed Docetaxel After First Line Gemcitabine/Carboplatin in Advanced NSCLC



Primary endpoint: Overall Survival

Immediate vs. Delayed Docetaxel After First Line Gemcitabine/Carboplatin in Advanced NSCLC



Advantages of Maintenance Therapy

- **All patients with advanced NSCLC experience progression despite extent of response to first line therapy**
- **Maintenance therapy has the potential to delay progression and potentially improve survival**
- **Patients are in a better overall condition to tolerate additional therapy than in the second-line setting**
- **Ability to administer the same or a mechanistically distinct agent after first-line therapy**

Key Questions

- **Is there an improvement in survival?**
- **Is the treatment tolerated well?**
- **Are patient selection methods available?**

Maintenance Therapy: Strategies

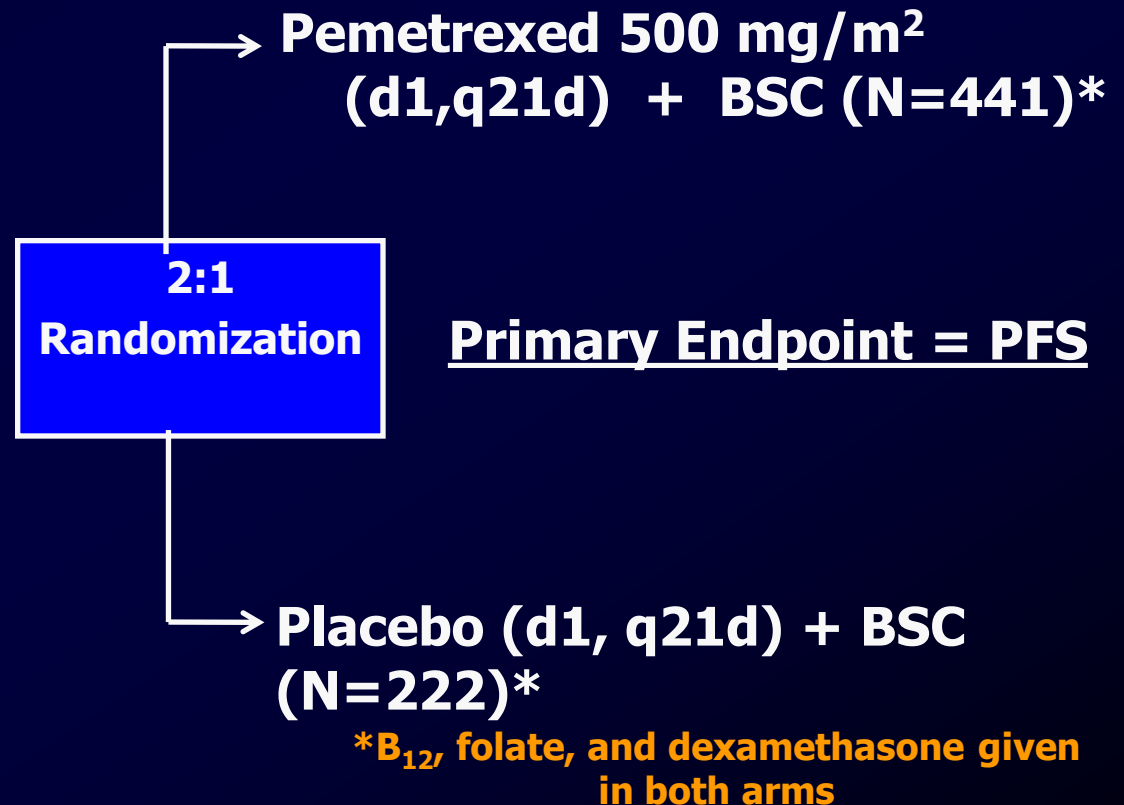
- **Initiating a new agent (“switch”)**
 - **Carboplatin and paclitaxel followed by pemetrexed**
- **Continuation of a targeted agent**
 - **Carboplatin, paclitaxel and bevacizumab followed by bevacizumab**
- **Continuing one of the same agents from the original combination**
 - **Cisplatin and pemetrexed followed by pemetrexed as maintenance**

Maintenance Therapy: Strategies

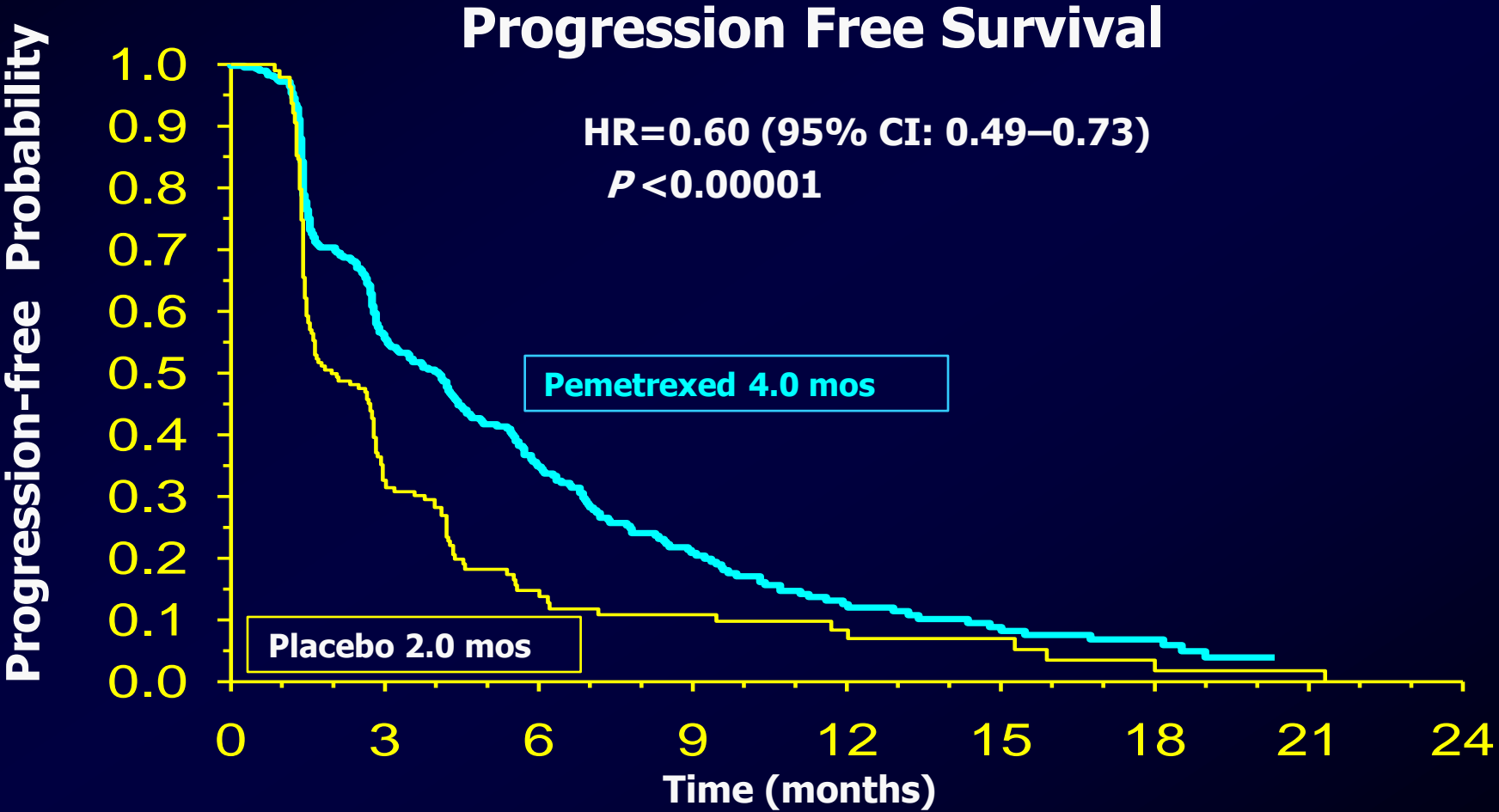
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Maintenance Pemetrexed Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Advanced NSCLC

- 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



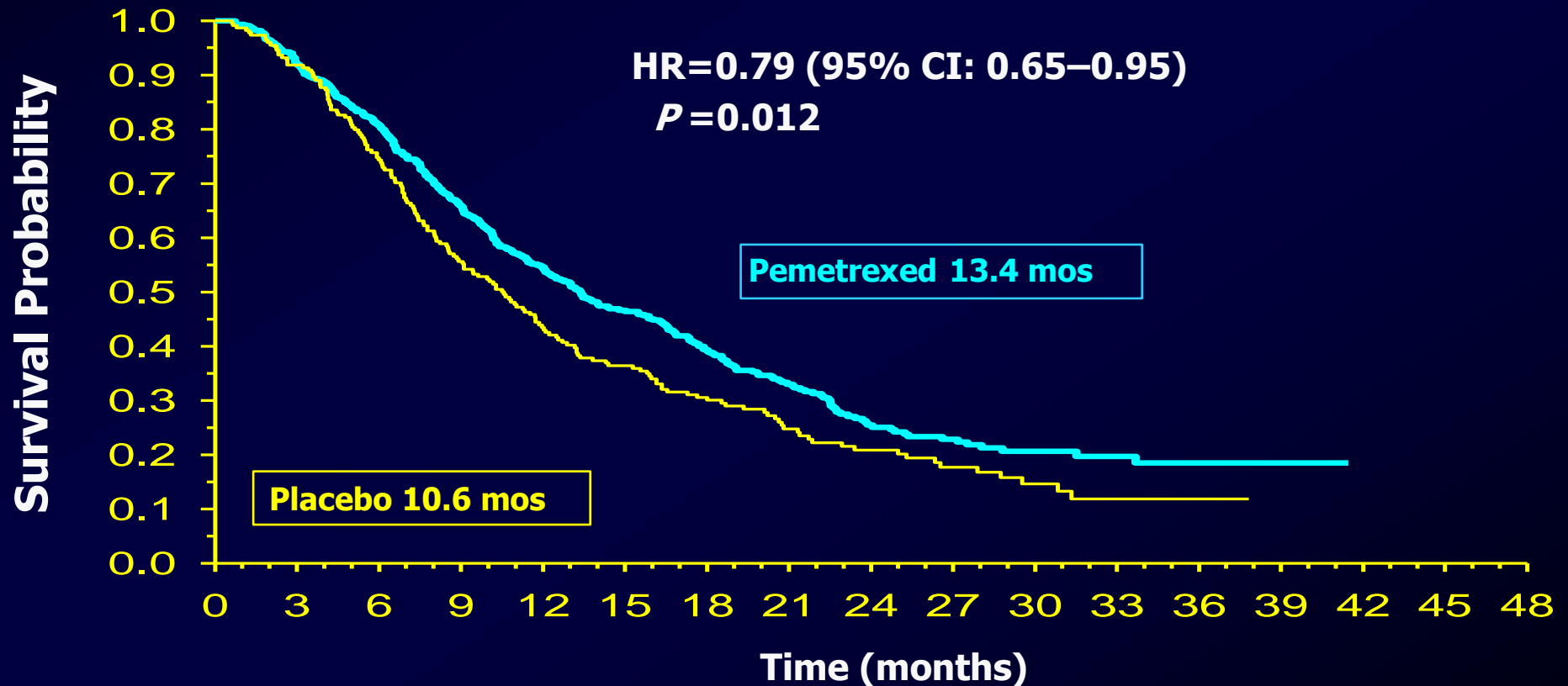
Maintenance Pemetrexed Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Advanced NSCLC



Ciuleanu...Belani, Lancet 374(9699):1432-40, 2009
Belani et al, J Clin Oncol 28:15s, 2010 (suppl; abstr 7506)

Maintenance Pemetrexed Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Advanced NSCLC

Overall Survival



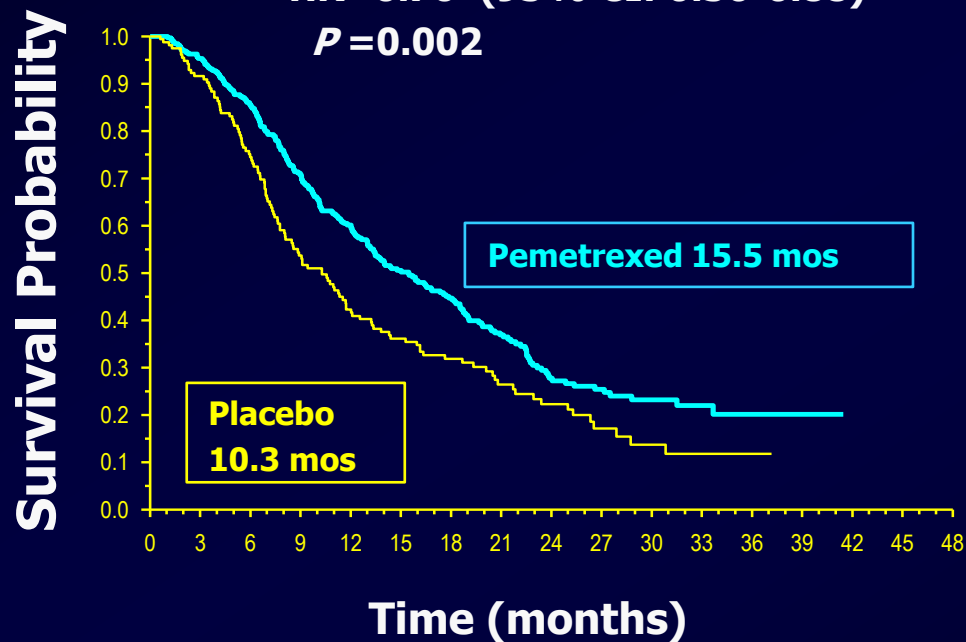
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Overall Survival by Histology

Non-squamous (n=481)

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

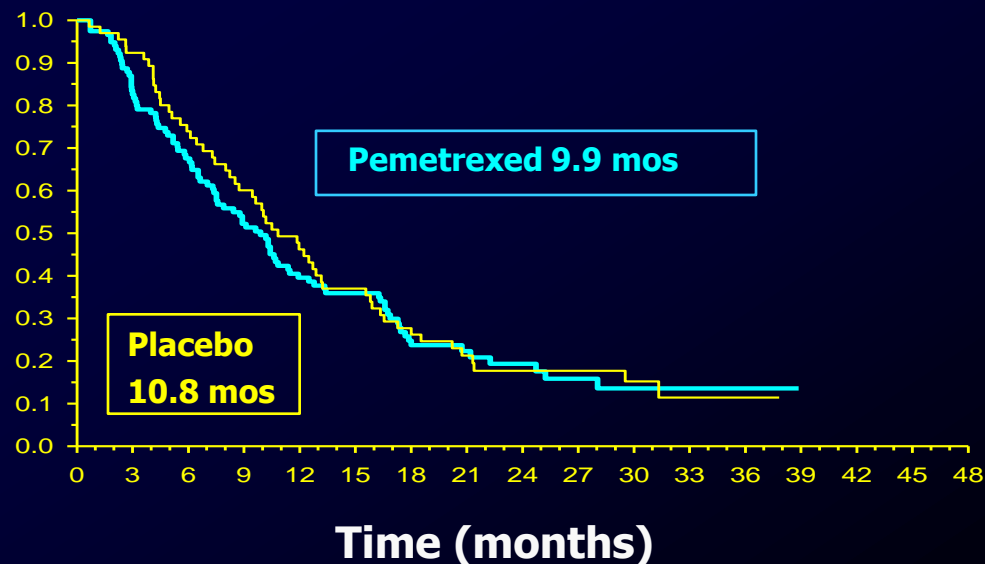
P=0.002



Squamous (n=182)

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

P=0.678



Ciuleanu...Belani, Lancet 374(9699):1432-40, 2009

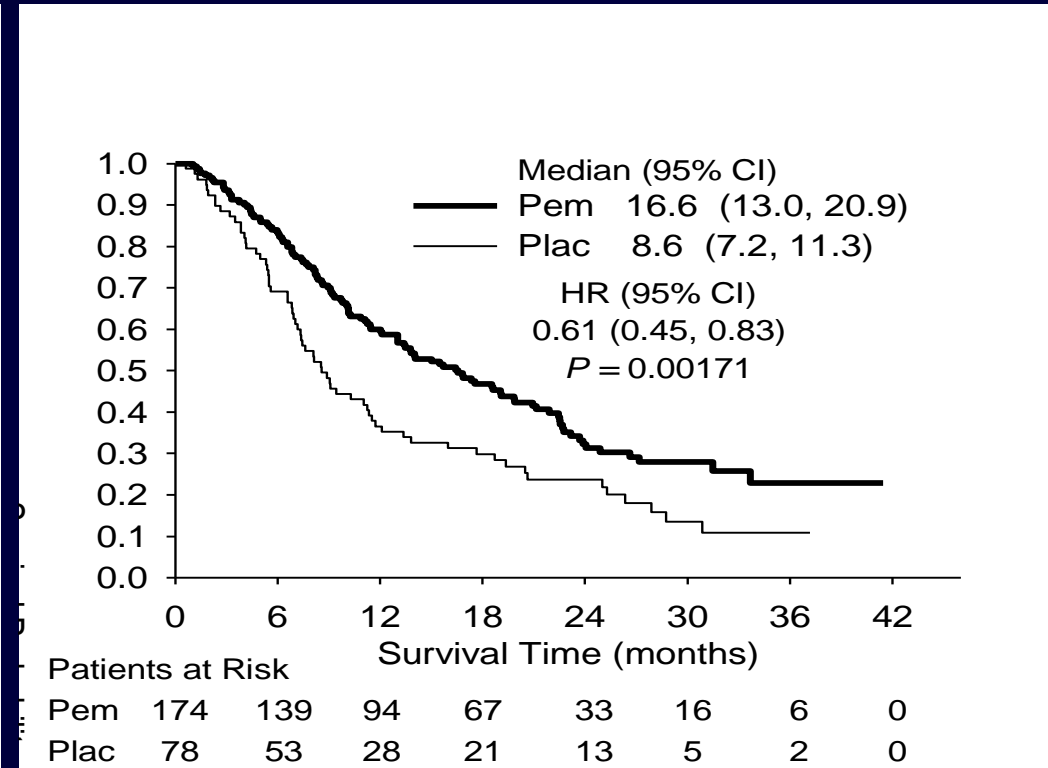
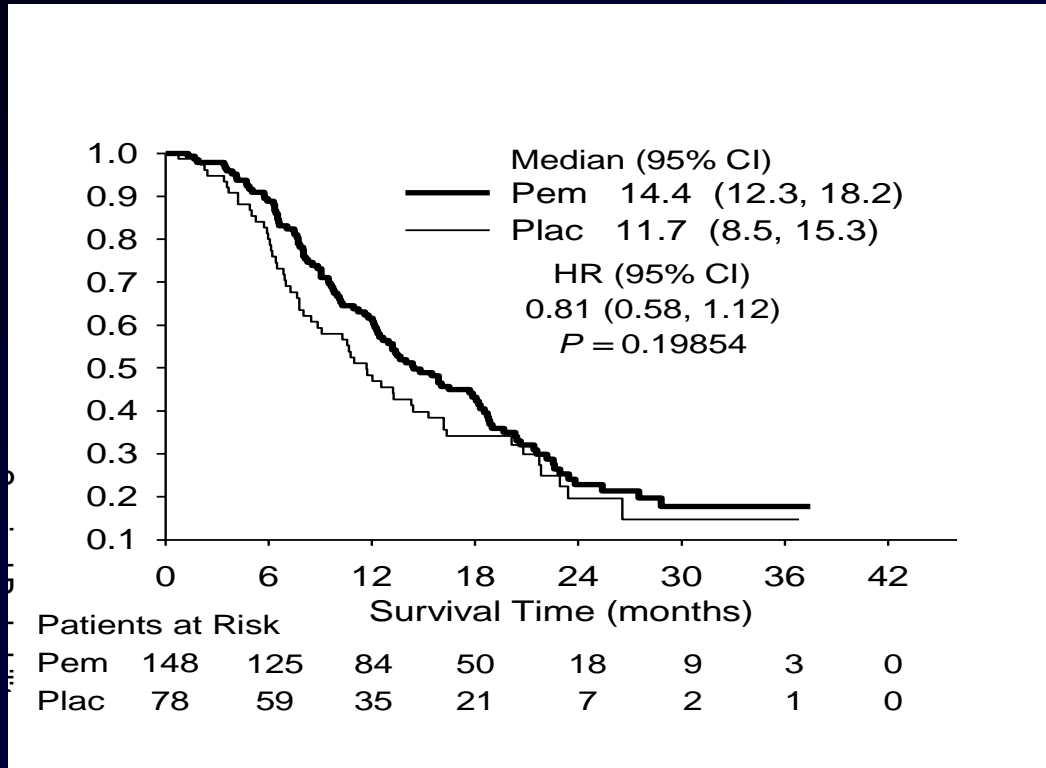
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Efficacy by Histology in Pemetrexed Studies

NSCLC Histologic Group	Second-line Pem vs. Docetaxel		First-line Pem/Cis vs. Gem/Cis		Maintenance Pem vs. Placebo	
	Pem	Doc	Cis/Pem	Cis/Gem	Pem	Placebo
Non-squamous	n=205	n=194	n=618	n=634	n=325	n=156
Median OS, months	9.3	8.0	11.0	10.1	15.5	10.3
Adjusted HR (95% CI) P value	0.78 (0.61–1.00) 0.048		0.84 (0.74–0.96) 0.011		0.70 (0.56–0.88) 0.002	
Squamous	n=78	n=94	n=244	n=229	n=116	n=66
Median OS, months	6.2	7.4	9.4	10.8	9.9	10.8
Adjusted HR (95% CI) P value	1.56 (1.08–2.26) 0.018		1.23 (1.00–1.51) 0.050		1.07 (0.77–1.50) 0.678	

Non-squamous = adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology

Effect of Response to Induction on OS in JMEN



Non-Squamous Patients with CR/PR prior to randomization to pem/placeholder

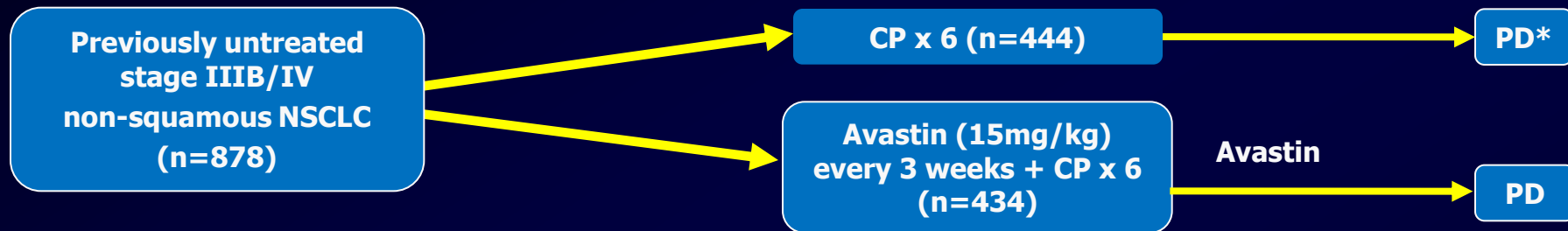
Non-Squamous Patients with SD prior to randomization to pem/placeholder

Maintenance Therapy: Strategies

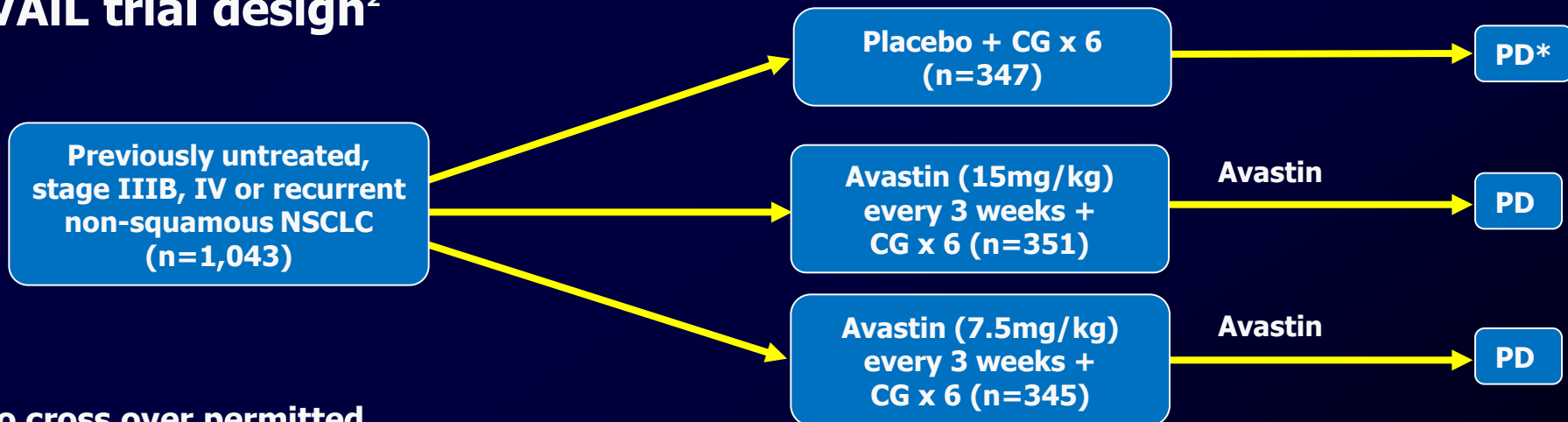
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Bevacizumab in NSCLC

E4599 trial design¹



AVAiL trial design²

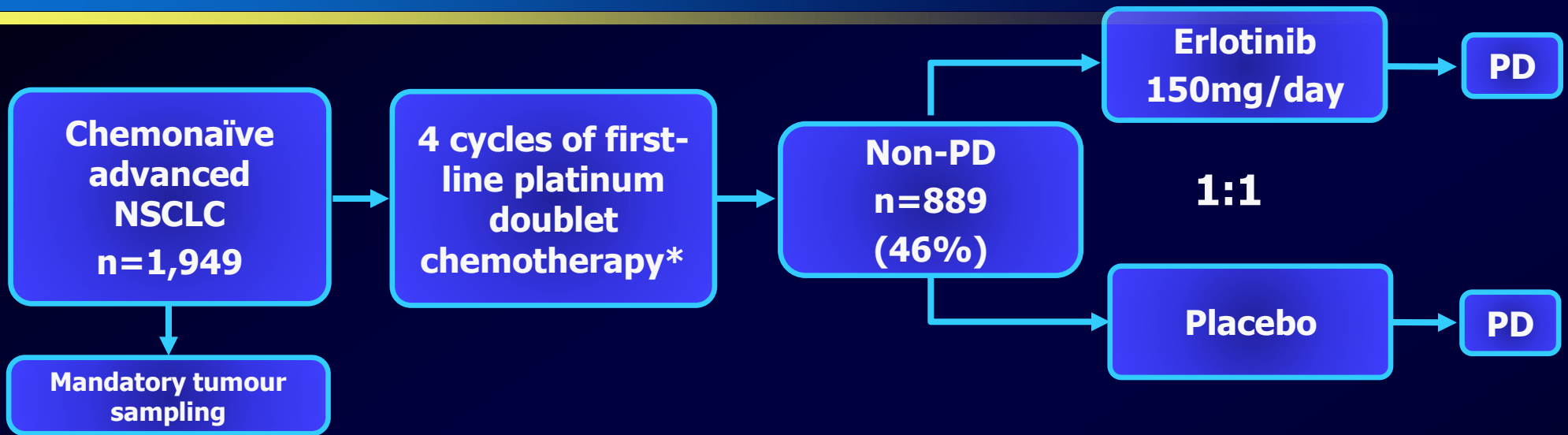


*No cross over permitted
CP=carboplatin + paclitaxel
CG=cisplatin + gemcitabine
PD=progression of disease

1. Sandler, et al. N Engl J Med 2006;355:2542-2550.

2. Reck, et al. J Clin Oncol 2009;27:1227-1234.

SATURN Study Design



Stratification Factors:

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

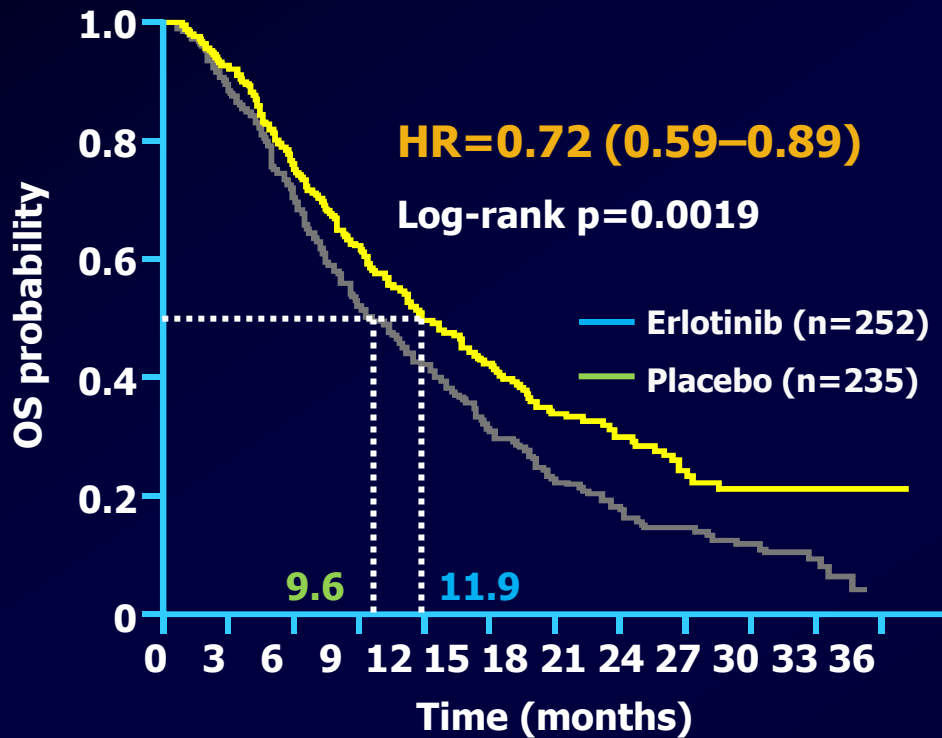
Co-Primary Endpoints:

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

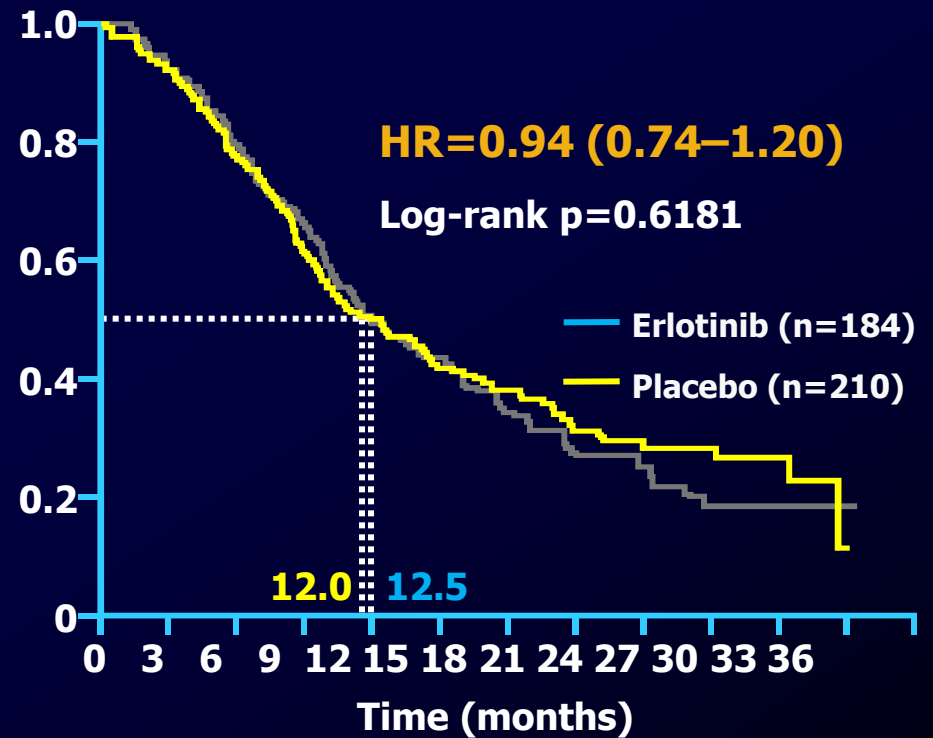
*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel carboplatin/paclitaxel

SATURN Trial: OS According to Response to First-line CT (ITT Population)

SD



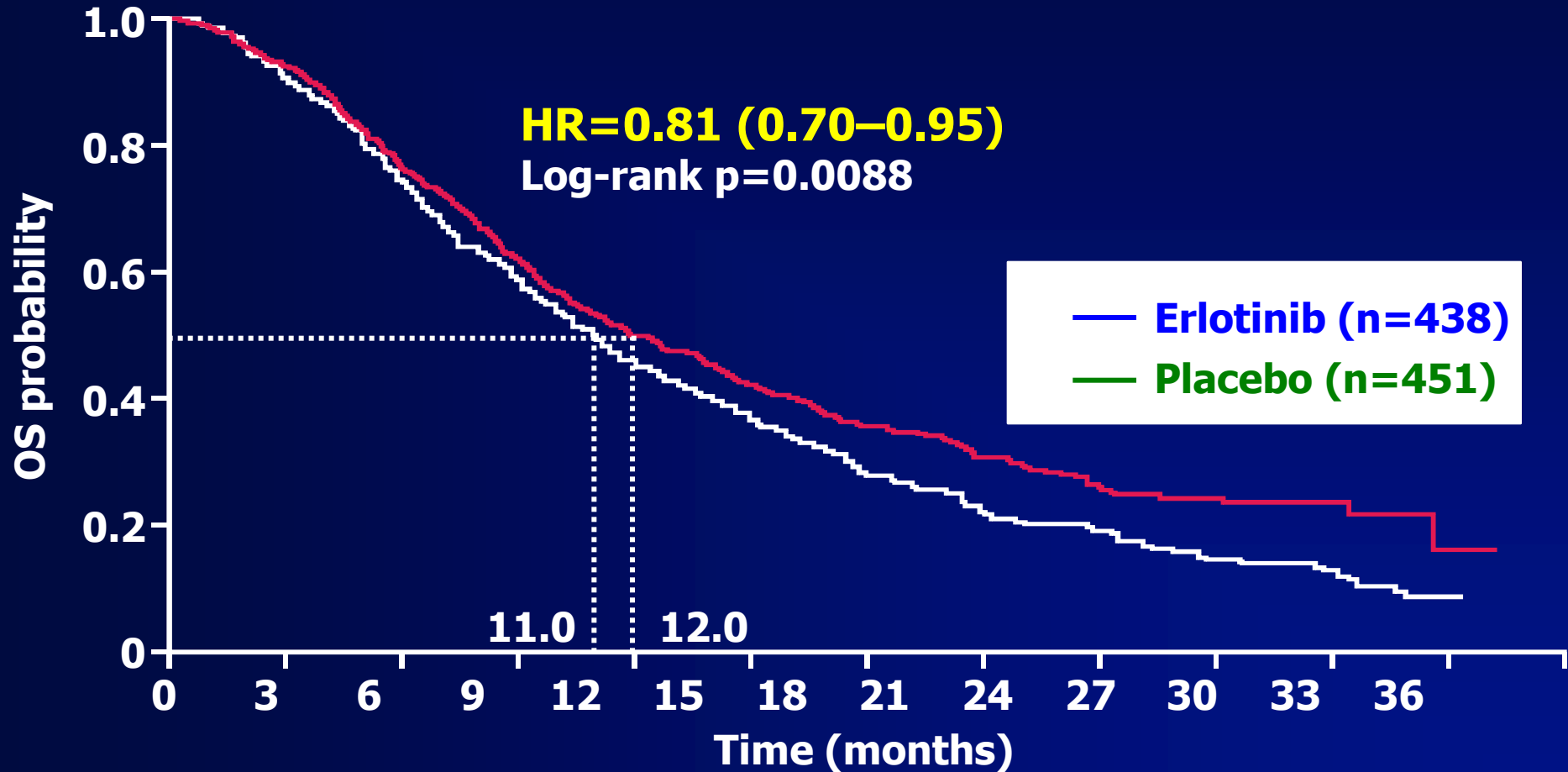
CR/PR



Multivariate HR for OS in SD population
0.71, p=0.0019

SATURN Survival*

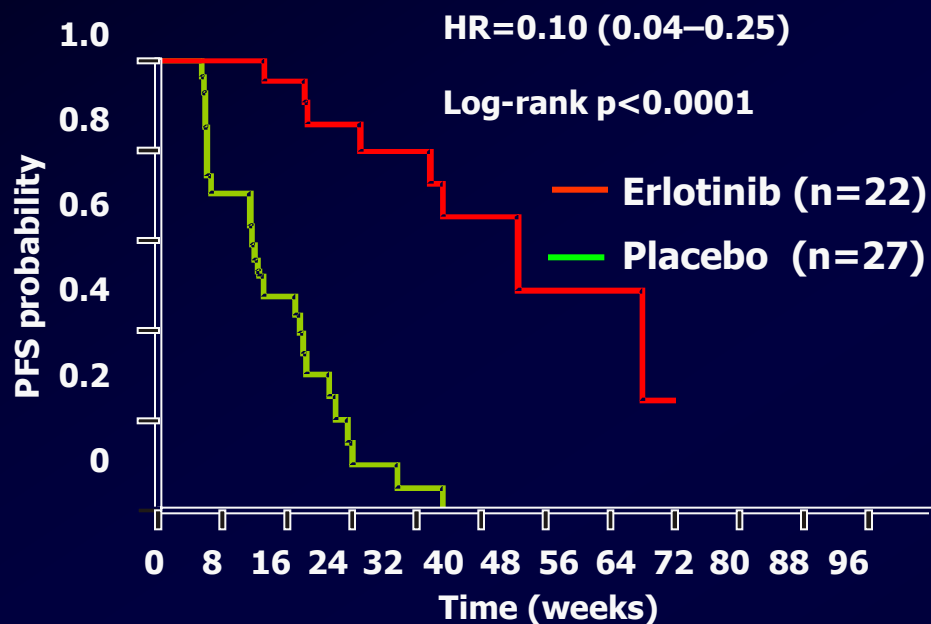
All Patients (ITT)



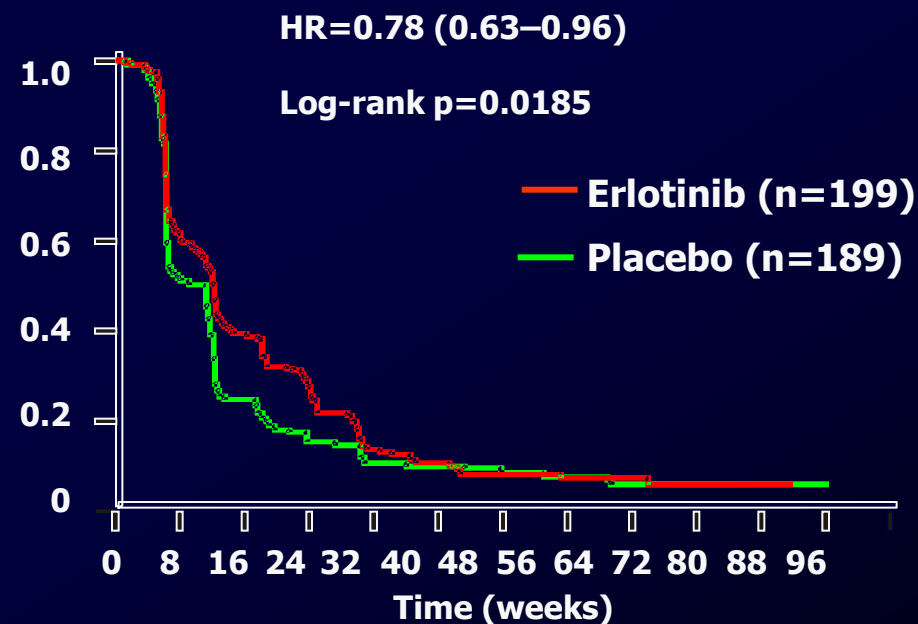
*OS is measured from time of randomisation into the maintenance phase;
ITT = intent-to-treat population

SATURN : Largest PFS Benefit with Erlotinib in Patients with *EGFR* Mutated Tumours

EGFR mutation+



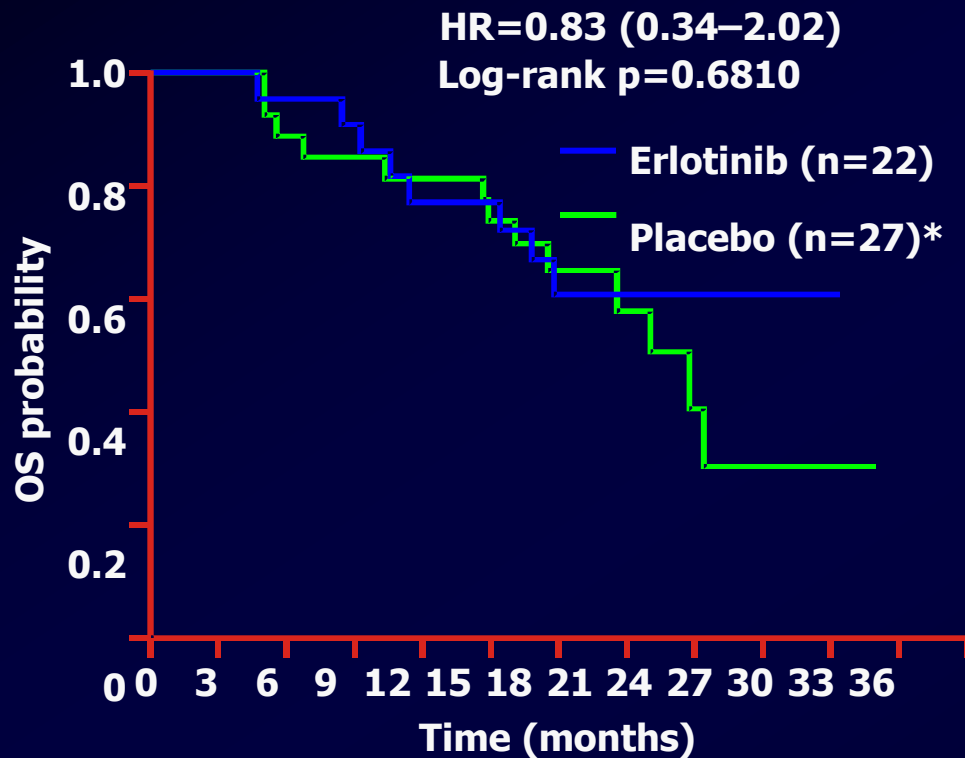
EGFR wild-type



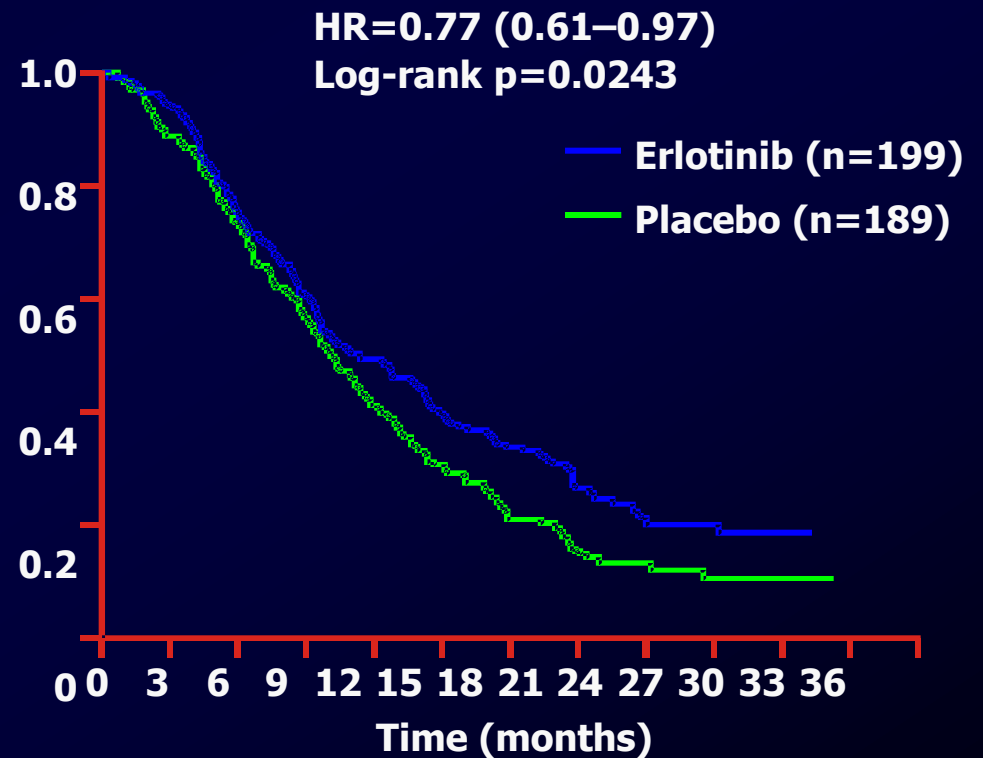
Interaction p<0.001

OS According to *EGFR* Mutation Status

EGFR mutation+

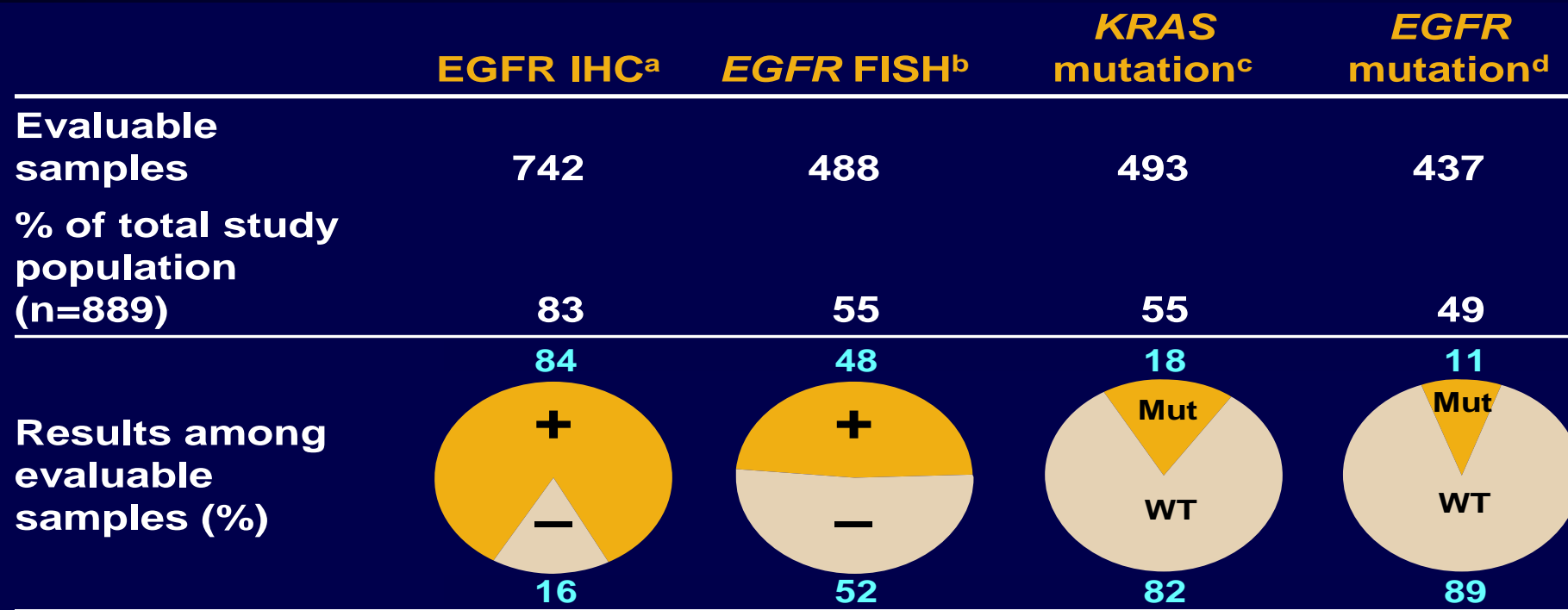


EGFR wild-type



*Note that 67% of patients with *EGFR* mutation+ disease in the placebo arm received a second-line *EGFR* TKI

SATURN: Summary of Tumor Biomarker Analyses



Mut = mutation positive; WT = wild-type

a. IHC+ status: ≥10% tumour cells with any membranous staining

b. Scored according to Cappuzzo et al. (J Natl Cancer Inst 2005;97:643)

c. Codons 12, 13 and/or 61 versus confirmed wild-type

d. Exon 19 deletion and/or L858R versus confirmed wild-type

Maintenance with Targeted Therapy: WJTOG 0203 Trial

NSCLC

Stage III B/IV

Dynamic

Balancing

• histology

• stage

• gender

• Chemotherapy
regimen

R

A

N

D

O

M

I

Z

E

Arm A: Chemotherapy alone

≥ 3 cycles (up to 6 cycles)

Arm B: Chemotherapy followed
by gefitinib

3 cycles → gefitinib 250 mg until PD

Chemotherapy regimens

Carboplatin + paclitaxel

Cisplatin + irinotecan

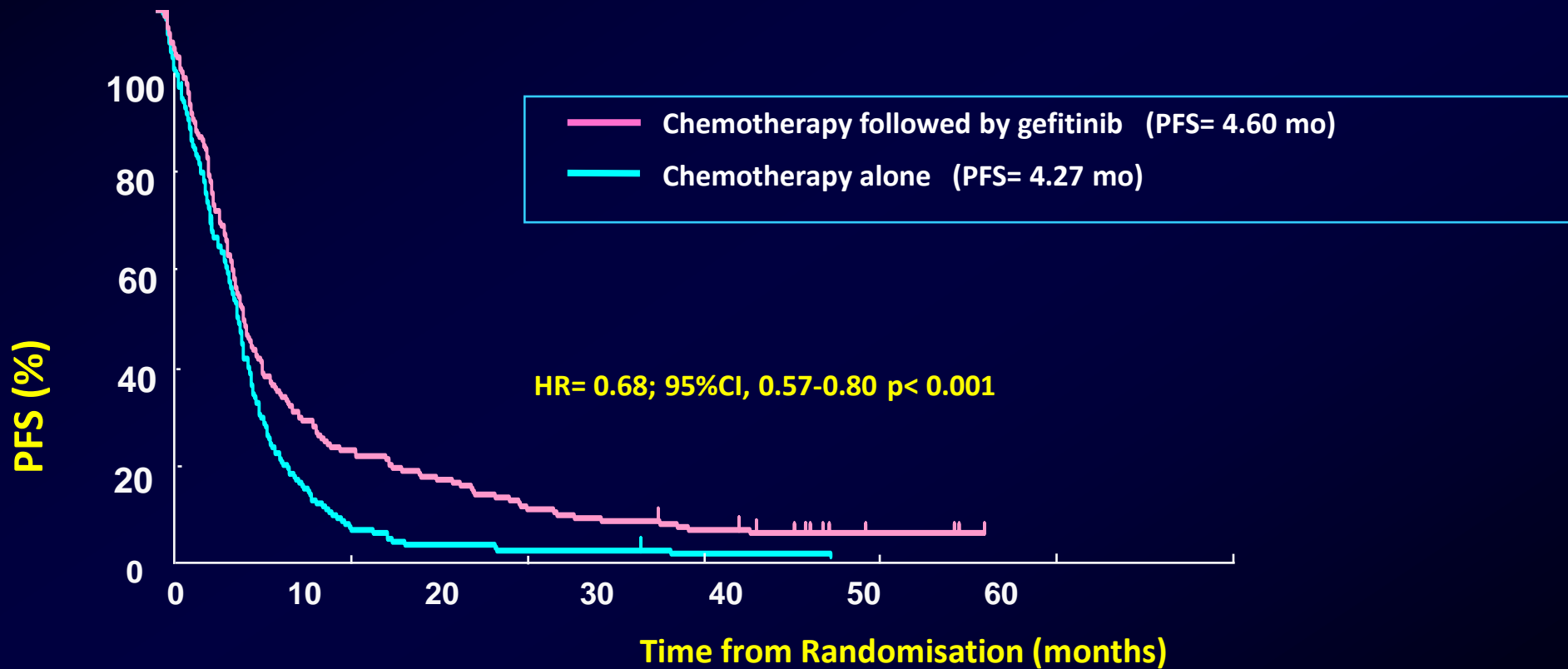
Cisplatin + vinorelbine

Cisplatin + gemcitabine

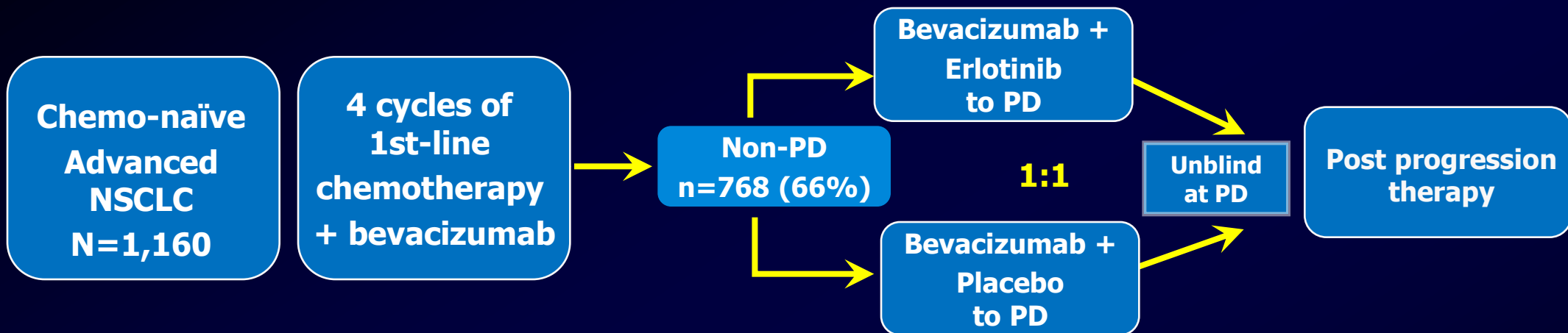
Cisplatin + docetaxel

Sample size n = 600
(n = 300 per arm)

Maintenance with Targeted Therapy: WJTOG 0203 Trial



ATLAS Study



Eligibility

Stage III/IV NSCLC

ECOG performance status 0-1

Stratification factors

Gender

Smoking history (never vs former/current)

ECOG performance status (0 v \geq 1)

Chemotherapy regimen

Primary endpoint

PFS in all randomized pts

Secondary endpoints

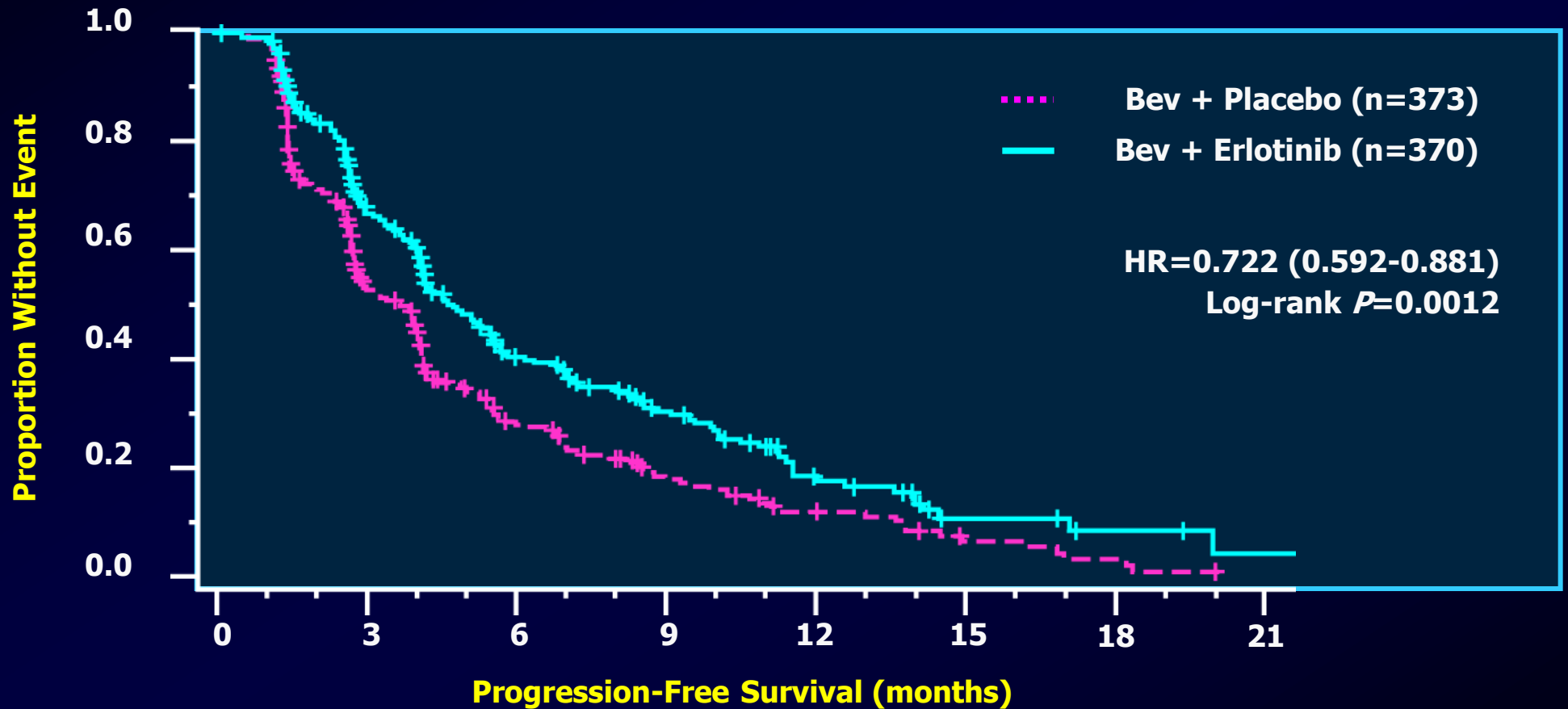
Overall survival

Safety

Exploratory endpoints

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

ATLAS: Progression Free Survival (ITT Population Investigator Assessment)



No. of patients at risk:

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

ATLAS : OS RESULTS

Evaluate Bev 15mg/kg + Erl 150mg vs Bev + Placebo following Bev + Platinum-based chemotherapy

Data cut-off	Patients with events, n/N (%)	Median OS (months) Bev+Erl vs Bev	HR (95% CI)	p-value
July 18, 2008 (pre-specified)	228/743 (31)	14.4 vs 13.3	0.92 (0.70-1.21)	0.5604
Jan 28, 2009	357/768 (46)	14.4 vs 13.6	0.90 (0.73-1.12)	0.3574
Jun 19, 2009	439/768 (57)	15.9 vs 13.9	0.90 (0.74-1.09)	0.2686

Comparison of the Recent Maintenance Studies

	JMEN pemetrexed vs. placebo	SATURN erlotinib vs. placebo	ATLAS bev/placebo vs. bev/erlotinib
Type of trial	Consolidation	Consolidation	Consolidation
Cross over design?	No	No	No
Endpoint?	Survival	PFS	PFS
Second line therapy?	Reported	Reported	Reported
PFS (mos.)	4.0 vs. 2.0	3.0 vs. 2.7	4.8 vs. 3.8
HR (p)	0.6 (p< 0.001)	0.71 (p=0.0001)	0.71 (p=0.0012)
Survival (mos.)	13.4 vs. 10.6	12.0 vs. 11.0	15.9 vs 13.9
HR (p)	0.79 (p=0.012)	0.81	0.90

The Numbers Matter !



Maintenance Therapy: Grade 3/4 Toxicity by Study

Agent	Neutropenia	Fatigue	Rash	Diarrhea
Docetaxel [^]	28%	10%	NR	1%
Pemetrexed [†]	3%	5%	1%	<1%
Gefitinib	0%	2%	2%	0%
Erlotinib [*]	0%	<1%	6%	2%

***No Grade 4**

[^]All patients received decadron and anti-emetics; 28% had Grade 3/4 thromobcytopenia

[†]10% received an RBC transfusion; 6% received epo and 4% were hospitalized for Grade 3/4 toxicity; all patients received oral decadron, anti-emetics, B12 injections and daily folic acid supplementation

Maintenance Therapy

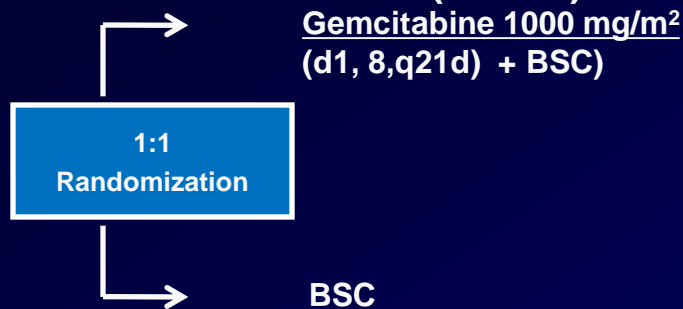
- **Advanced non-squamous cell cancer patients whose disease is stable or responding to first-line chemotherapy should generally be offered maintenance pemetrexed**
- **Absolutely agree, provided they do not have**
 - **Evidence of EGFR mutation**
 - **Declining PS**

Maintenance therapy with pemetrexed till progression was approved by FDA for patients with non-squamous cell histology and has become the new treatment paradigm

FIRST-LINE THERAPY (N=519)*

- Stage IIIB/IV NSCLC
- ECOG PS 0-2
- 4 cycles of carbo-gem with CR, PR, or SD

MAINTENANCE THERAPY (N=255)*



No survival benefit for maintenance Gemcitabine following G-Cb for patients with advanced NSCLC

Cox Regression Analysis

Variable	Reference level	Hazard Ratio*	P value
PS ≥ 2	PS=1	1.50	0.009

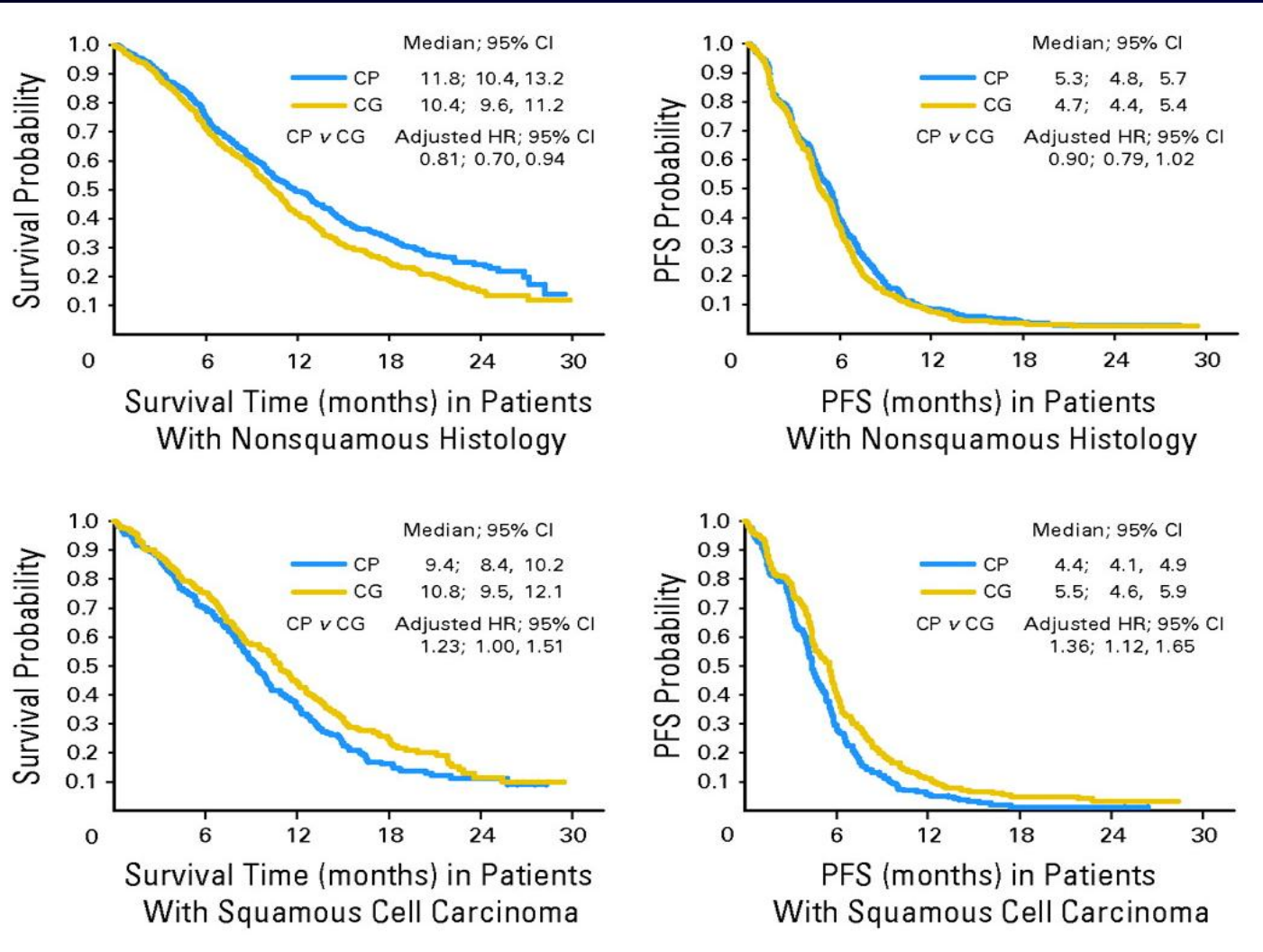
*Modeling hazard ratio associated with worsened survival

IMPACT : Though maintenance therapy is a new treatment paradigm for advanced NSCLC, it is not beneficial in PS ≥ 2 patients

Maintenance Therapy: Strategies

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Cis/Pem vs. Cis/Gem in Advanced NSCLC



S124 - PARAMOUNT: Study Design

**Induction treatment period (unblinded):
Four cycles of pemetrexed (500 mg/m², Day 1) +
cisplatin (75 mg/m², Day 1)*
(approximately 900 patients)**

**Patients who have a documented response
of CR, PR, or SD and have an
ECOG PS of 0 or 1**

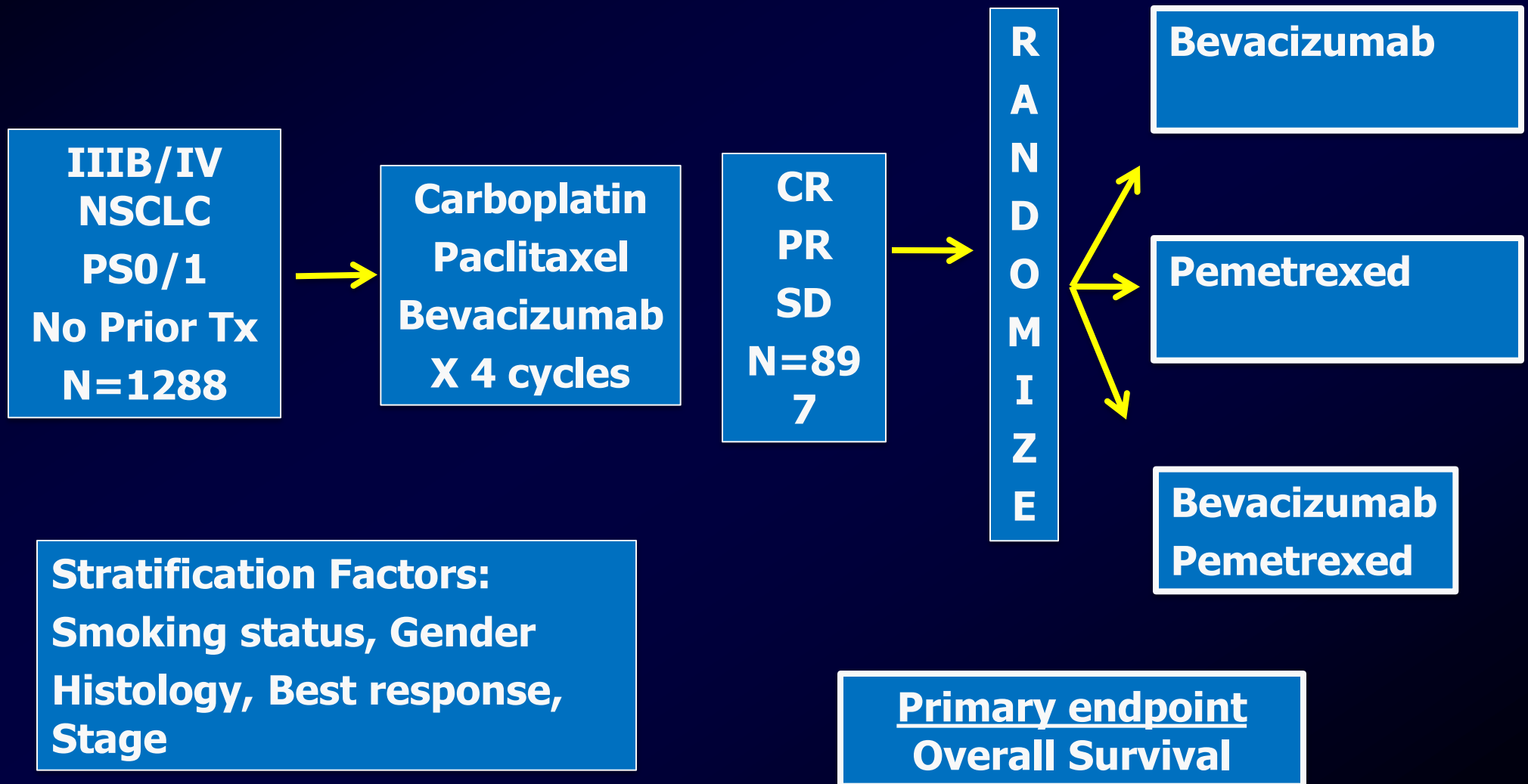
**Pemetrexed 500 mg/m²
+ BSC* (D1, q21d)
until disease progression
(approximately 372
patients)**

**Blinded maintenance
treatment period
2:1
randomization**

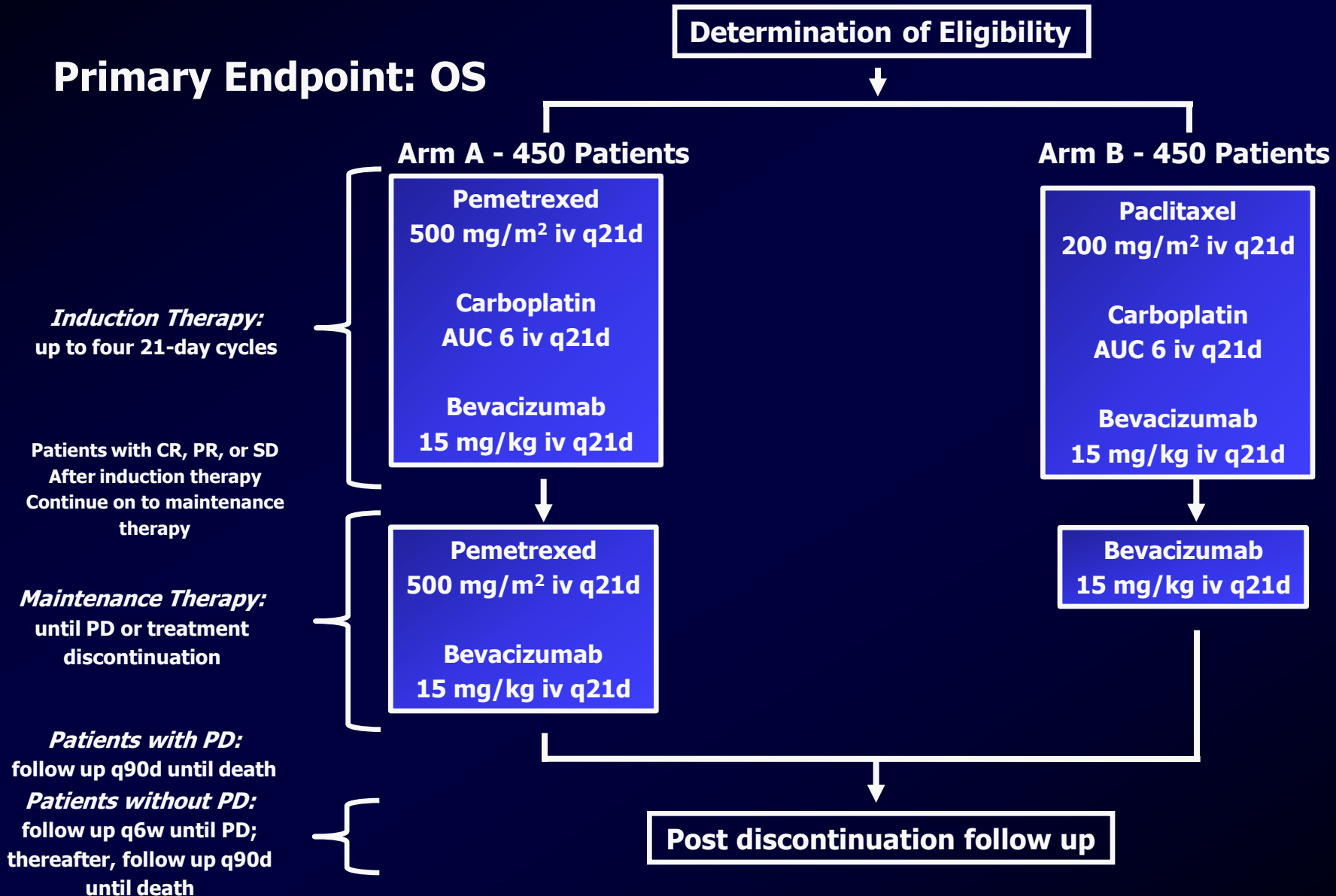
**Placebo + BSC*
(D1, q21d)
until disease progression
(approximately 186
patients)**

***Patients received folic acid, vitamin B₁₂, and dexamethasone.**

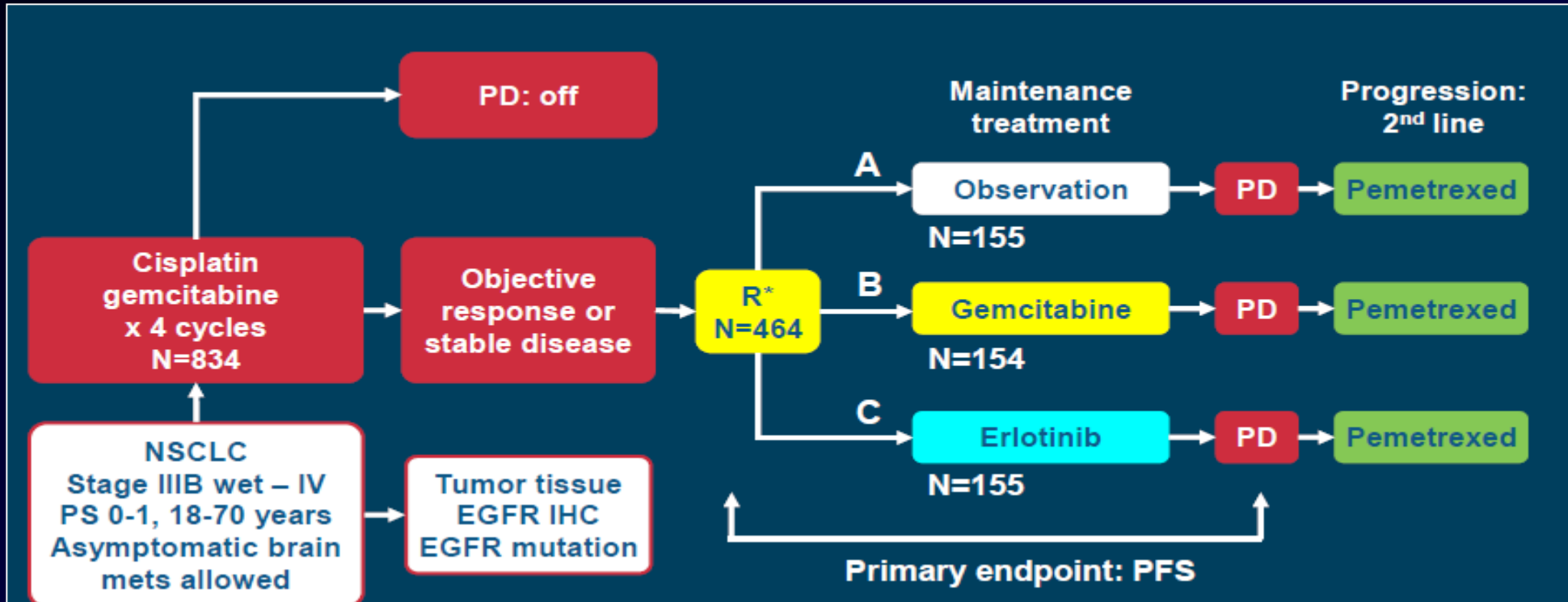
ECOG 5508: Schema



POINTBREAK STUDY



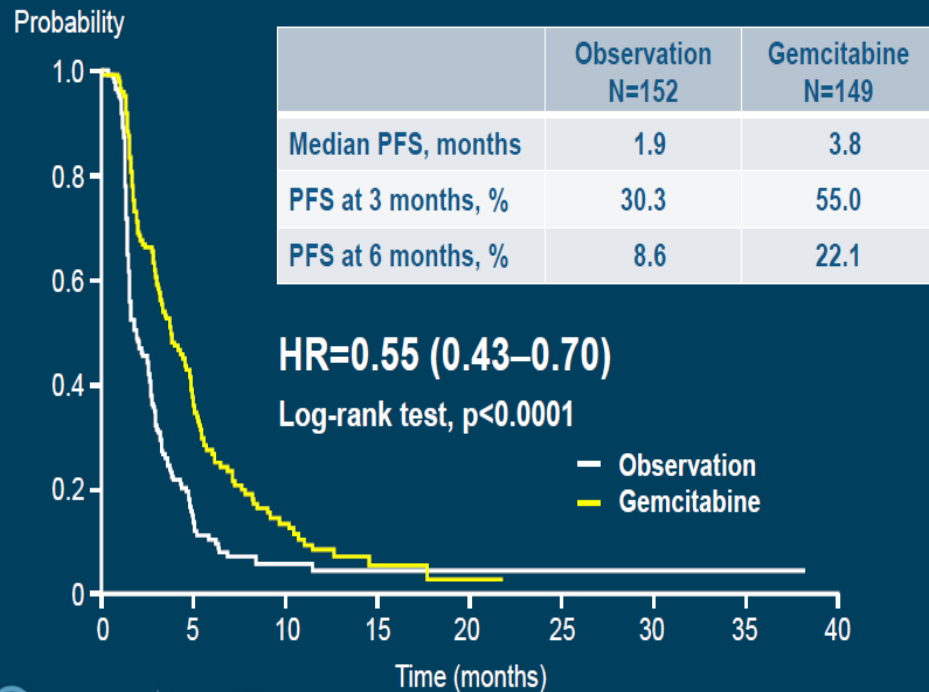
IFCT-GFPC 0502: Study Design



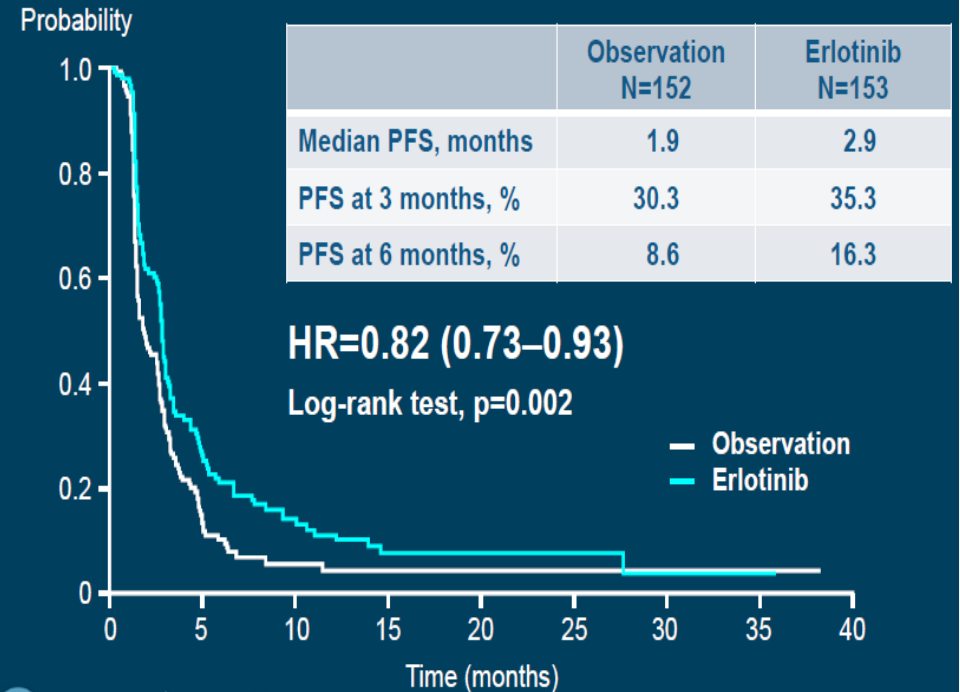
- **Primary endpoint** : independent review with 80% power to detect 50% improvement in median PFS: PFS by each comparison (Gem vs Obs and Erl vs Obs)
- **Secondary endpoints**: (OS, safety, symptom control, prognostic and predictive effect of tumor EGFR status (IHC, EGFR mut))

IFCT-GFPC 0502: Results

PFS by independent review Gemcitabine versus observation



PFS by independent review Erlotinib versus observation



- Patients who received 2nd-line pemetrexed: 73% (Obs), 55% (Gem), and 60% (Erl)
- Grade 3-4 treatment-related AEs were more common in Gem (27%) and Erl (14%) than in Obs (2%)

Maintenance Therapy

Reasons to Consider

- **Survival benefit has been noted in large phase III studies**
- **Approximately 30-40% of patients may be unable to receive second-line therapy**
- **If the goal of cancer therapy is to make lung cancer a chronic disease, then chronic therapy will be necessary**

Maintenance Therapy

Recommendations

- 1. Maintenance therapy with pemetrexed is a reasonable option in patients with tumors of non-squamous cell histology.**
- 2. Erlotinib maintenance after platinum-based chemotherapy is now approved by the FDA.**

Maintenance Therapy is The NEW TREATMENT PARADIGM

Fast Moving Paradigm

