elcc European Lung Cancer Conference

Chemotherapeutic or targeted agents as maintenance treatment: Efficacy and toxicity issues

Jesús Corral, MD
Replaced by Luis Paz-Ares
University Hospital Virgen del Rocio
Seville, Spain

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Disclosure

- J Corral:

No conflicts of interest to declare.

- Luis Paz-Ares:

Scientific advise and lectures for Lilly and Roche

Outline

- **Types and data**
  - Supportive evidence
- **Arguments against**
  - Trial design
  - Cost
- **Patient Selection**

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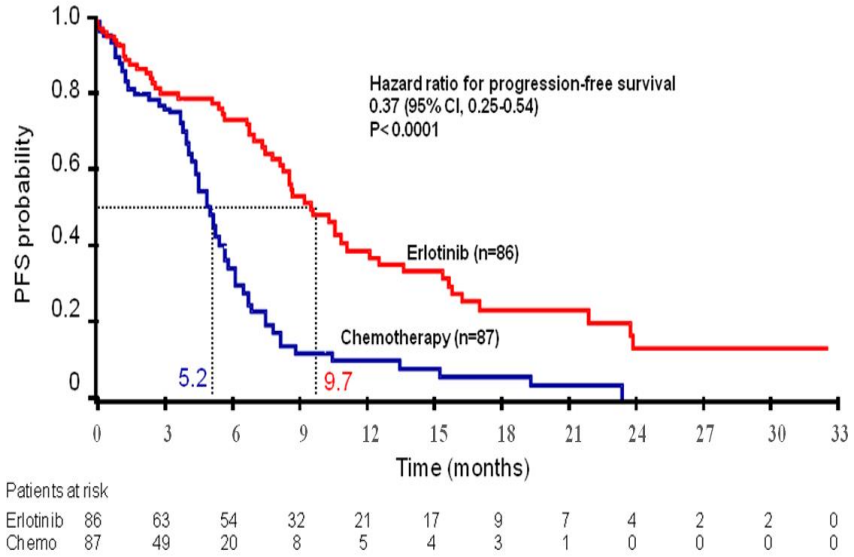
Maintenance Therapy Rationale

- **Objective: to keep disease (and symptoms) under control**
- **Rationale**
  - More may be better !!!; Goldman H, Sequential therapy (Norton H)
  - We do maintenance treatment in other tumor types and respiratory diseases
  - We do continuous treatment in oncoge addicted lung cancer

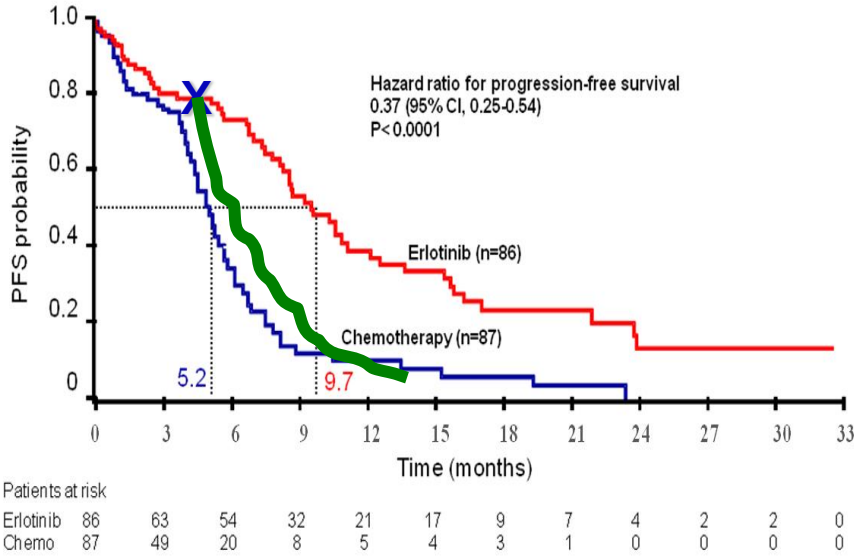
Maintenance in Lung Cancer "Oncogene Addicted"

Erlotinib in EGFR m+ NSCLC EURTAC Trial



Rosell R et al., Lancet Oncol 2012

Simulation- EURTAC Trial 4 months treatment



Rosell R et al., Lancet Oncol 2012

Types of Maintenance

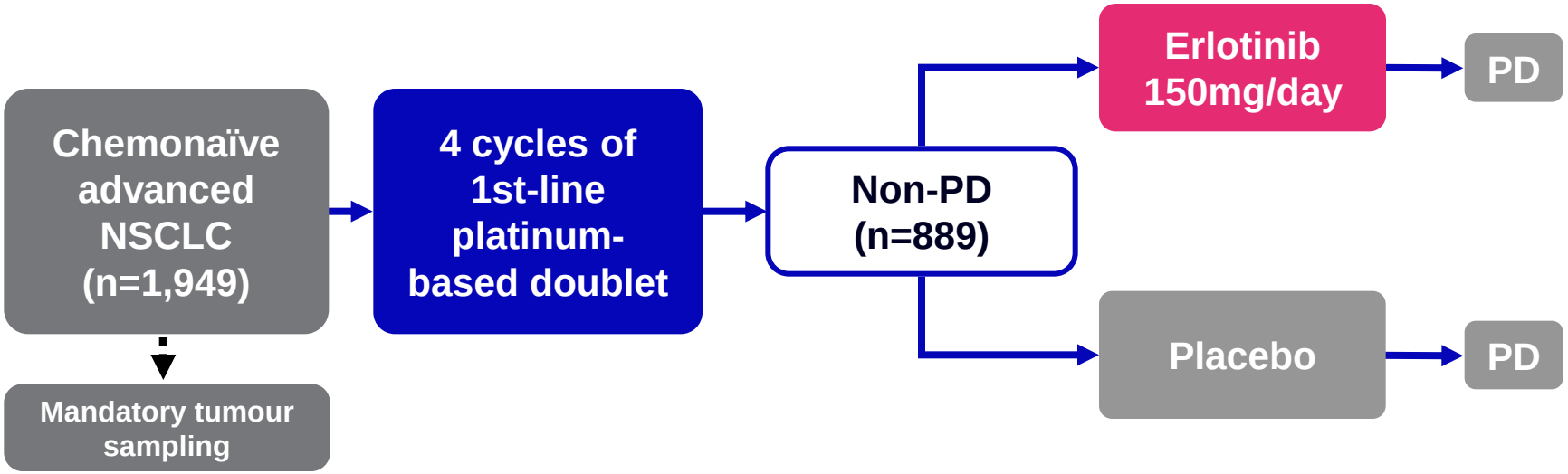
- **Continuation therapy: Prolonged platinum doublet chemotherapy**

- **Continuation Maintenance: Continuation of non-platinum agent used in doublet chemotherapy**
  - e.g. paclitaxel, gemcitabine, pemetrexed
- **Switch Maintenance: Introduction of a new cytotoxic agent**
  - e.g. docetaxel, pemetrexed, erlotinib

- **Targeted Maintenance: Triplet induction therapy followed of maintenance with the same targeted agent**
  - e.g. bevacizumab (EGOC 4599), cetuximab (Flex)

Stinchcombe, TE et al. J Thoracic Oncol 2009;4:243–50

SATURN Trial
Erlotinib Switch Maintenance



Co-primary endpoints

PFS in all patients

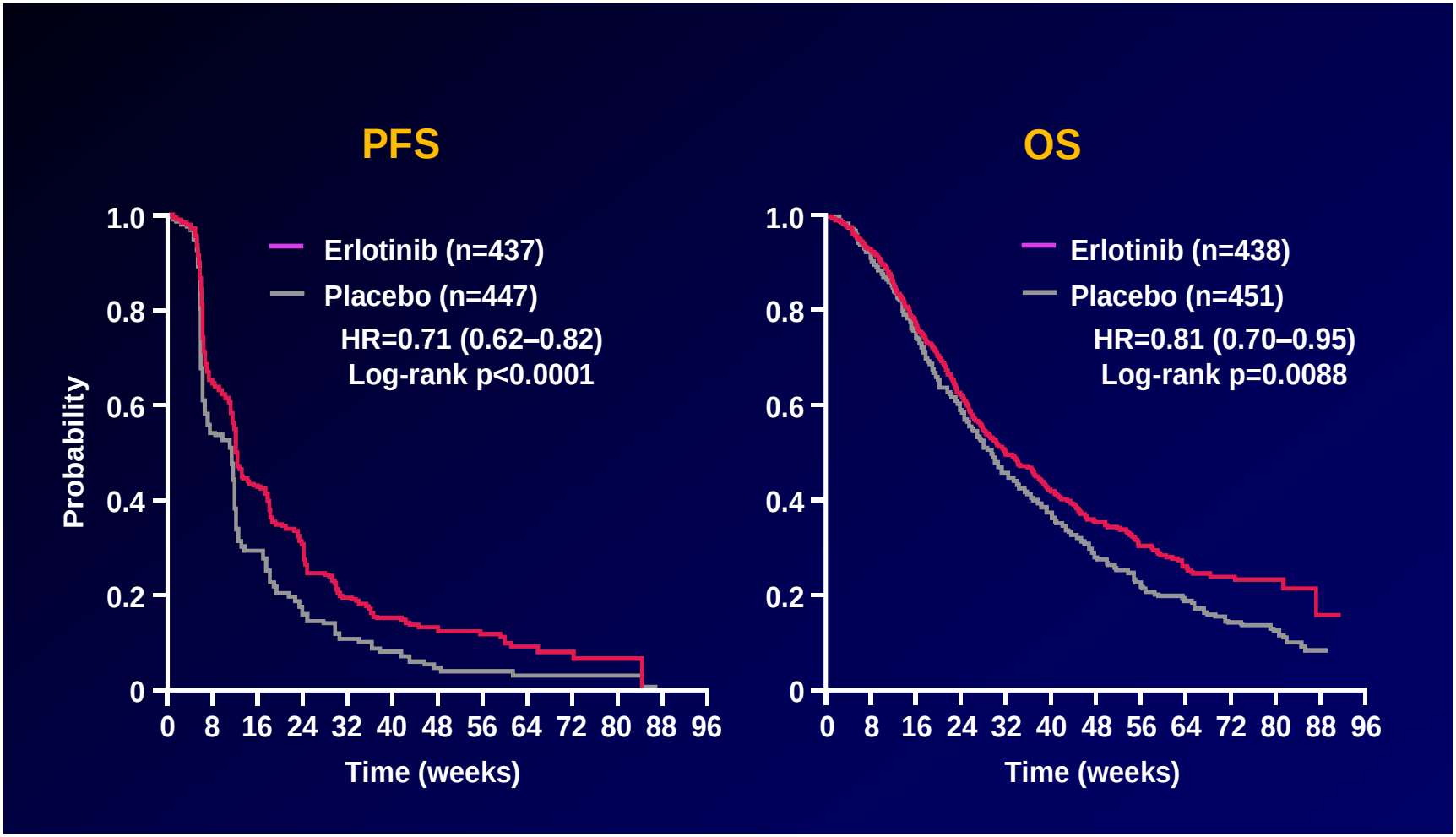
PFS in IHC+ tumours

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; quality of life (QoL)

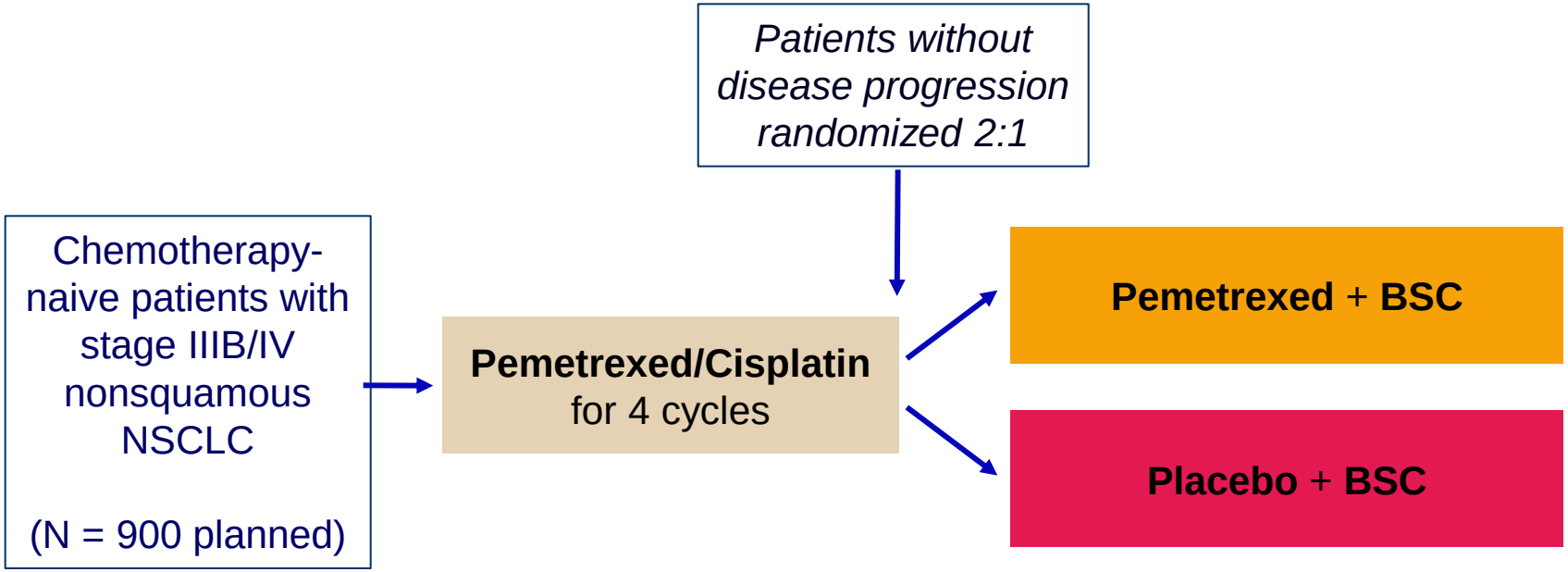
Cappuzzo et al., Lancet Oncol 2011

SATURN Trial
Erlotinib Switch Maintenance



Cappuzzo F et al., Lancet Oncol 2010

Paramount Trial
Pemetrexed Continuation Maintenance

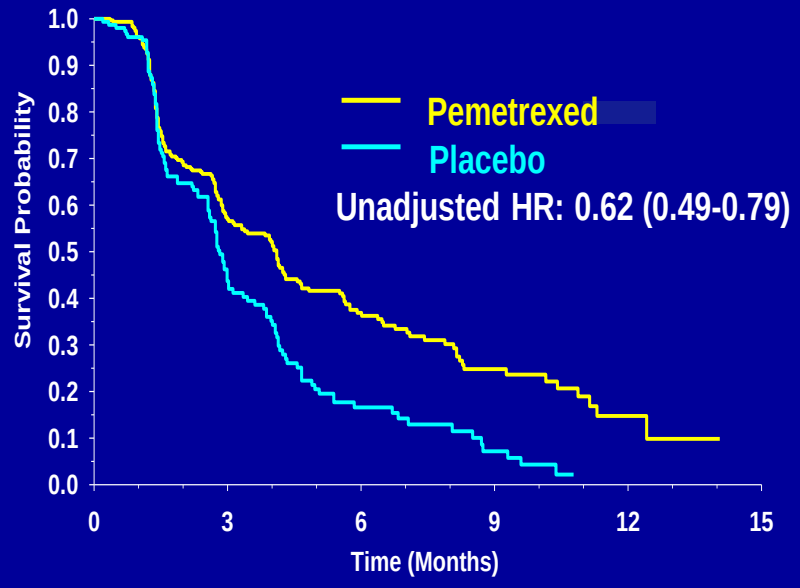


- **Primary endpoint: PFS**
- **Other endpoints: OS, ORR, safety, patient-reported outcomes, resource utilization,**

Paz-Ares LG, et al. BMC Cancer. 2010;10:85.

Paramount Trial
Pemetrexed Continuation Maintenance

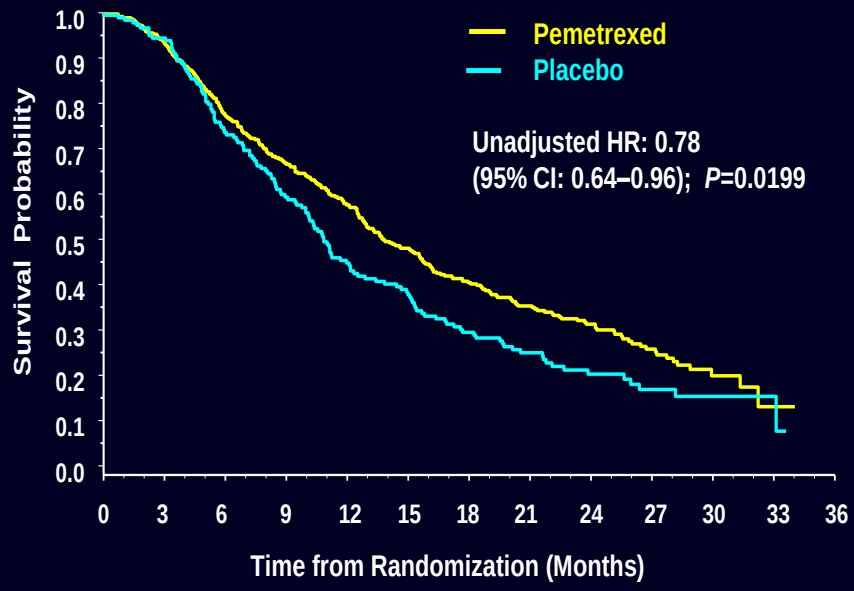
PFS: Primary Efficacy Endpoint



Patients at Risk

Pem + BSC	359	132	57	21	4	0
Plac+ BSC	180	52	15	5	0	0

PARAMOUNT: Final OS



Paz-Ares L et al., Lancet Oncol 2012
Paz-Ares L, et al., J Clin Oncol 2013

Maintenance Efficacy
PFS & OS

Trial	N	Maintenance drug	PFS HR (95% CI)	OS HR (95% CI)
Switch Maintenance				
Westeel et al.	181	Vinorelbine	0.77 (0.56-1.07)	1.08 (0.79-1.47)
Fidias et al.	309	Docetaxel	0.71 (0.55-0.92)	0.84 (0.65-1.08)
Capuzzo	889	Erlotinib	0.71 (0.62–0.82)	0.81 (0.70-0.95)
Ciuleanu et al.	663	Pemetrexed	0.60 (0.49-0.73)	0.79 (0.65-0.95)
Continuation Maintenance				
Paz-Ares et al	539	Pemetrexed	0.62 (0.49-0.79)	0.78 (0.64-0.96)
Brodowicz et al.	206	Gemcitabine	0.69 (0.56-0.86)	0.84 (0.52-1.30)
Belani et al.	255	Gemcitabine	1.09 (0.81-1.45)	0.97 (0.72-1.30)
Perol et al.	309	Gemcitabine	0.56 (0.44-0.72)	0.89 (0.67-1.15)

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Arguments Against

- **Trial Design**
  - Patient Selection
  - Number of induction courses
  - Post-study treatment
  - Other end-points
- **Cost**

Induction: 4 *v* 6 courses
Paramount *v* JMDB

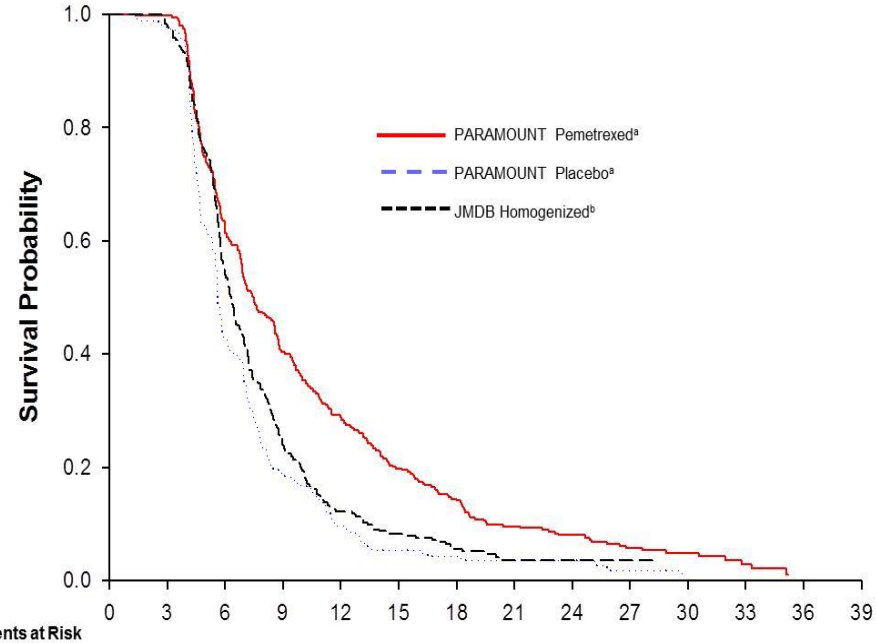
	PARAMOUNT Induction	JMDB
Median number of induction cycles	4 cycles then pemetrexed maintenance	1st-line treatment with 6 cycles
Response:		
• Response Rate (CR/PR)	30.1%	28.6%
• Disease control rates (CR/PR/SD)	74.5%	63.8%
Toxicity		
• Laboratory toxicities	13.7%	21.4%
• Nonlaboratory toxicities	14.8%	21.9%
• Possibletreatment-related deaths	1.2%	1.0%
• Serious adverse events	14.2%	16.4%
Supportive care	More colony-stimulating factors in PARAMOUNT	More anti-emetics use in JMDB

G Scagliotti et al, WCLC 2013

Paz-Ares LG, et al. J Clin Oncol 2013

Induction: 4 *v* 6 courses
Paramount *v* JMDB

PFS

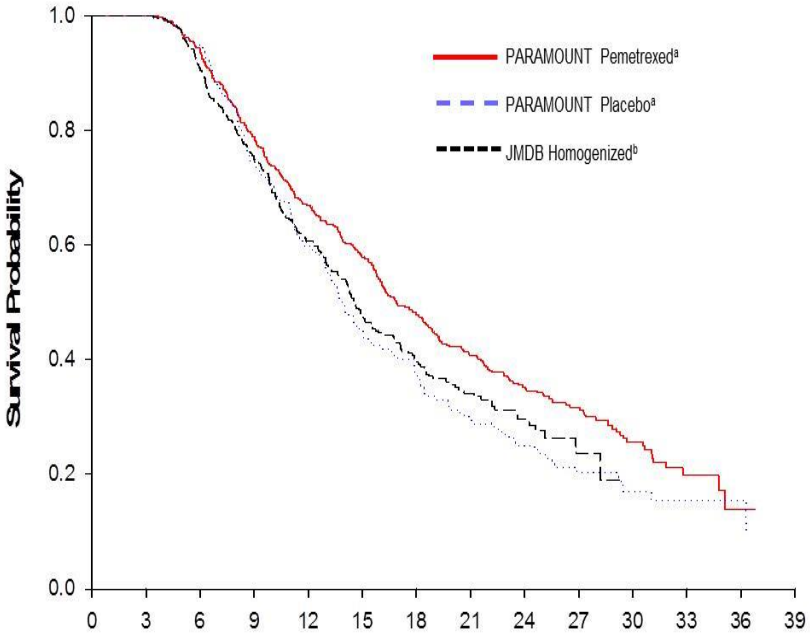


Patients at Risk

PARAMOUNT Pemetrexed, n	359	356	218	138	98	67	48	32	21	14	10	4	0	0
PARAMOUNT Placebo, n	180	174	75	33	16	9	7	6	4	2	0	0	0	0
JMDB,[b] n	346	339	184	76	34	19	10	4	1	0	0	0	0	0

G Scagliotti et al, WCLC 2013

Overall Survival



Patients at Risk

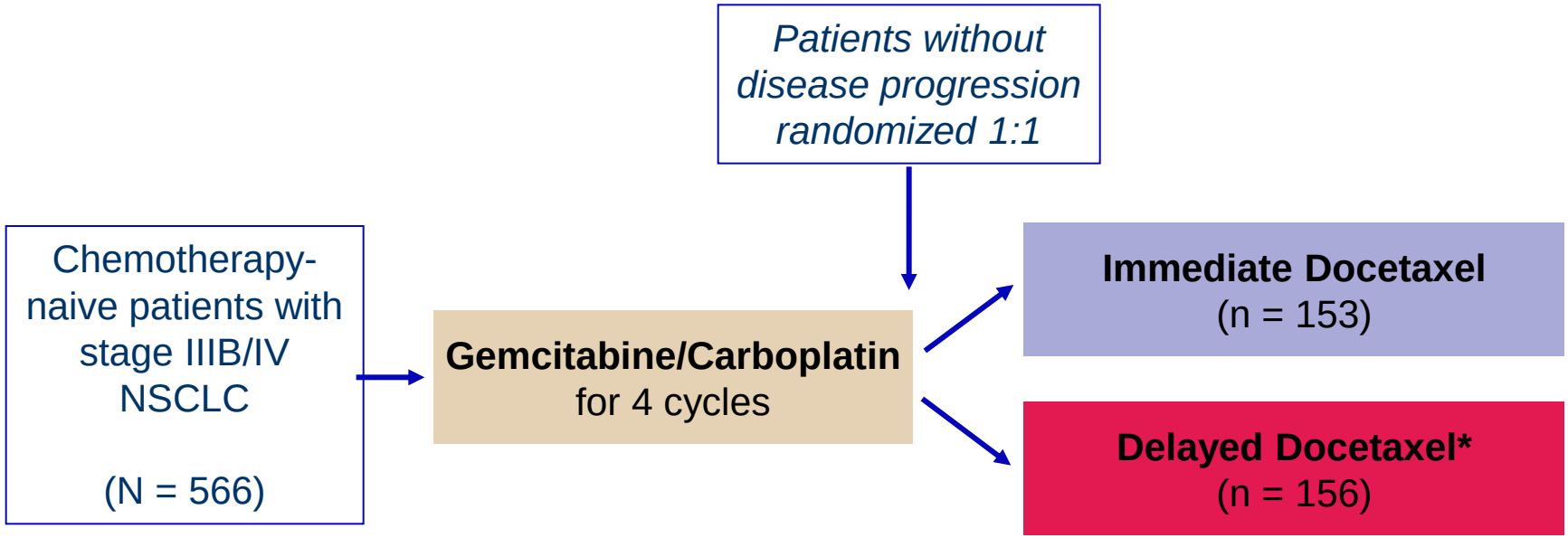
PARAMOUNT Pemetrexed, n	359	359	335	276	234	200	164	138	106	77	42	15	2	0
PARAMOUNT Placebo, n	180	180	168	132	103	78	63	49	35	23	12	8	3	0
JMDB,[b] n	346	346	308	245	195	135	83	49	23	4	0	0	0	0

Paz-Ares LG, et al. J Clin Oncol 2013

Post-discontinuation Therapy Switch Maintenance Trials

Trial	N	Maintenance drug	Second Line Rate	Maintenance Drug Second Line
Fidias et al.	309	Docetaxel Delayed Docetaxel	?? 63%	?? 63%
Capuzzo et al.	889	Erlotinib Placebo	71% 72%	5% 21%
Ciuleanu et al.	663	Pemetrexed Observation	51% 67%	<1 19%
Perol et al.	309	Erlotinib Observation	67% 91%	2% 50%

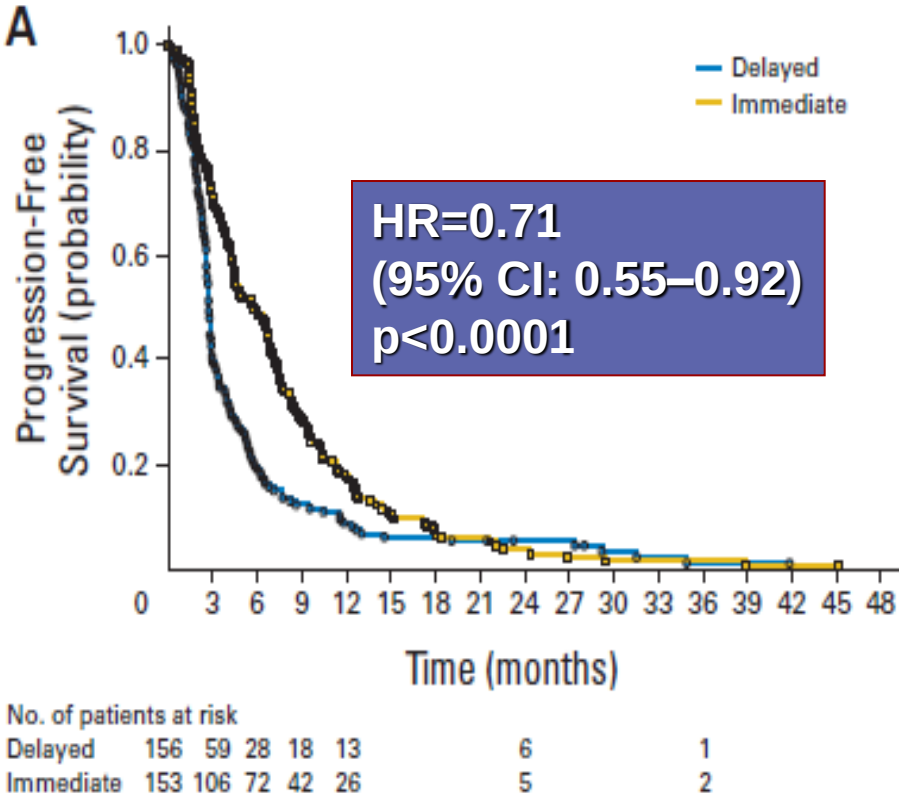
Switch Maintenance With Docetaxel

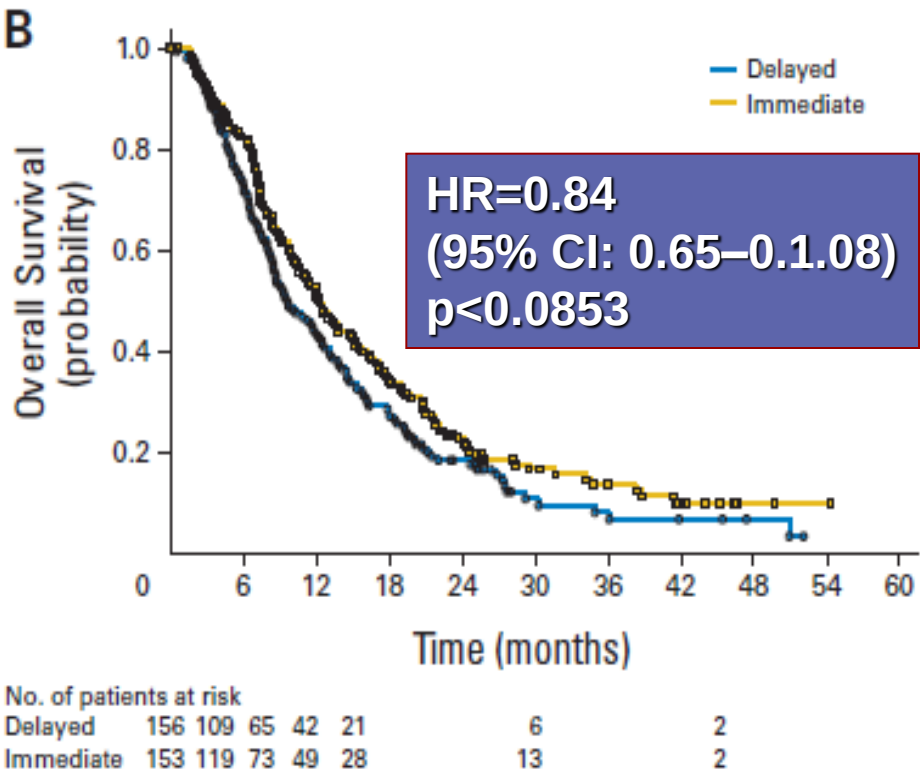


- **Primary endpoint: OS**
- **Other endpoints: PFS, ORR, safety, QOL**

Fidias PM, et al. J Clin Oncol. 2009;27:591-598.

Docetaxel Switch Maintenance
PFS & OS

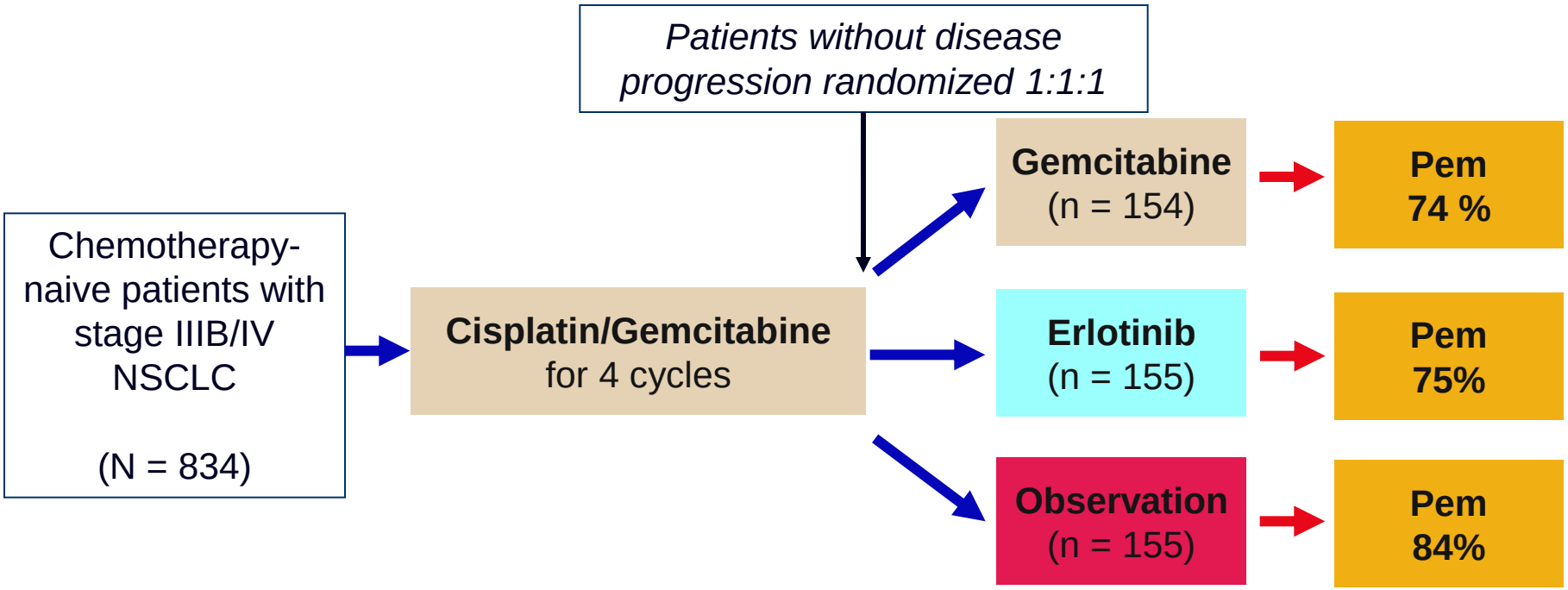




Fidias PM, et al. J Clin Oncol. 2009;27:591-598.

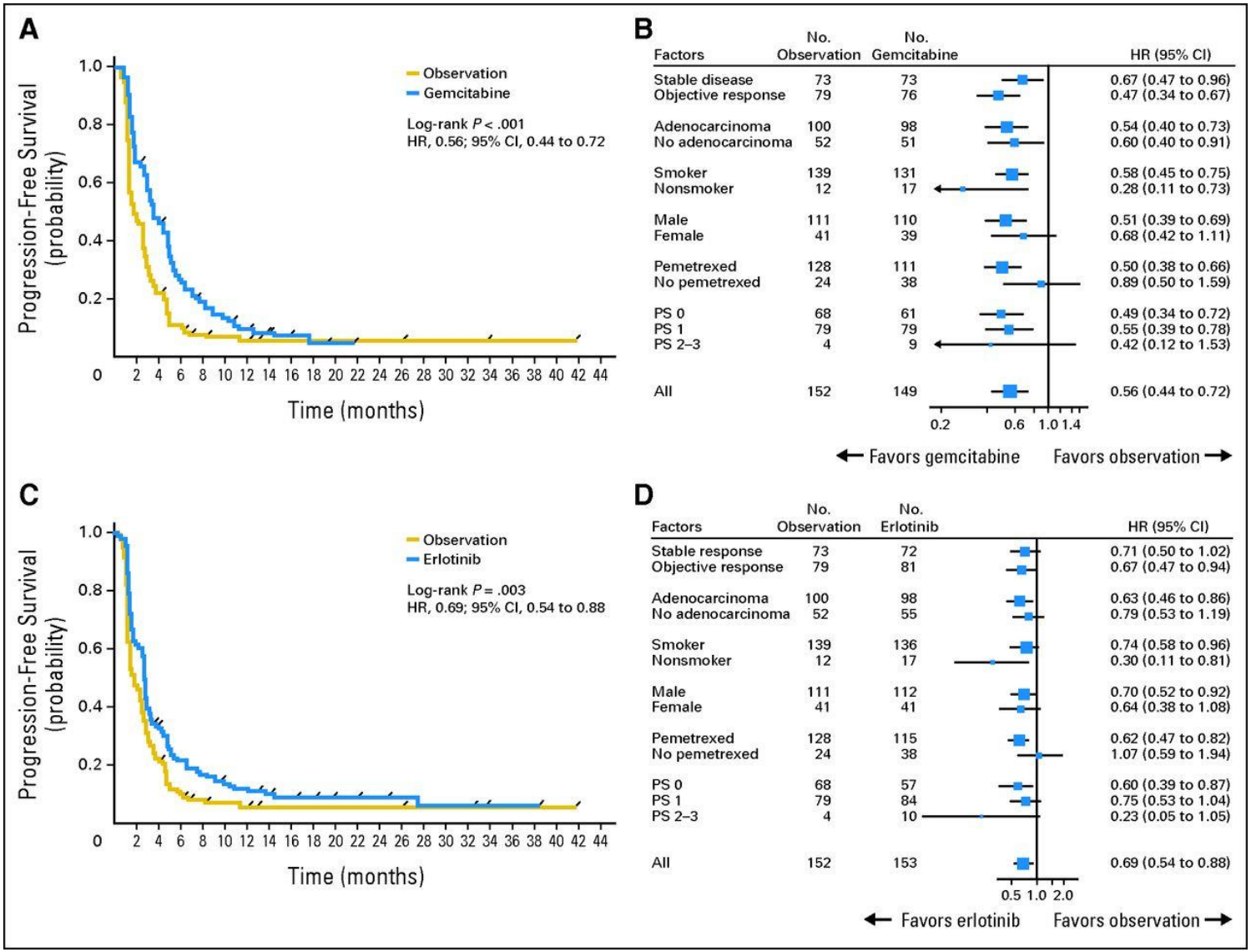
IFCT-GFPC 0502
Gemcitabine *v* Erlotinib *v* Observation

- **Patients stratified by sex, histology, smoking status, treatment center, and response/stabilization following first-line therapy**
- **Primary endpoint: PFS**
- **Other endpoints: OS, safety, symptom control, effect of EGFR status**



Perol M et al, J Clin Oncol 2012; Bylicki o et al., JTO 2013

IFCT-GFPC 0502
Gemcitabine *v* Erlotinib *v* Observation



Perol M et al, J Clin Oncol 2012

Post-discontinuation Therapy Paramount Trial

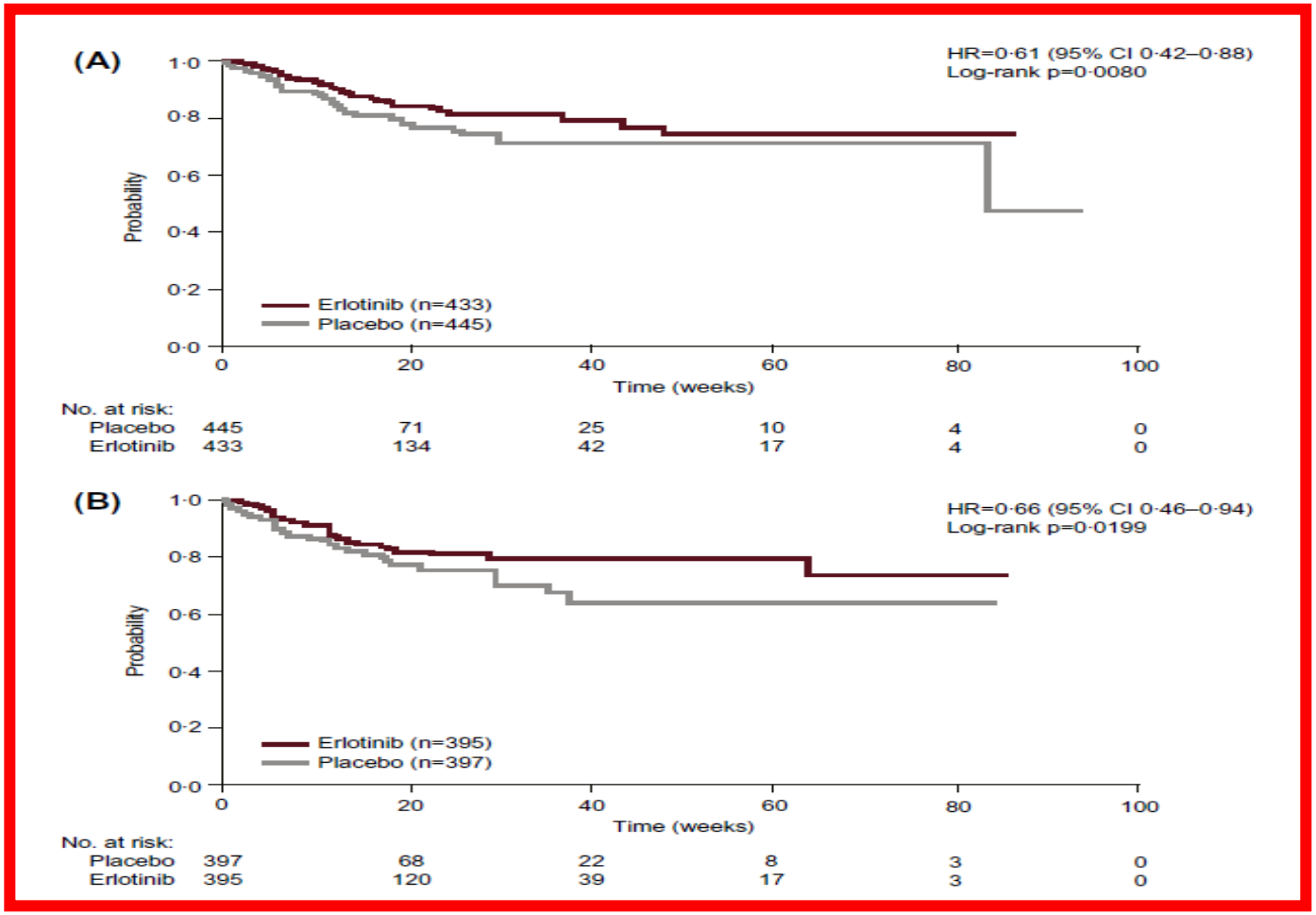
	Pemetrexed (N=359) %*	Placebo (N=180) %*
Patients Receiving Post Discontinuation Therapy	64	72
Erlotinib	40	43
Docetaxel†	32	43
Gemcitabine	10	8
Vinorelbine	8	6
Investigational drug	6	4
Carboplatin	5	4
Paclitaxel	3	3
Pemetrexed	2	4
Cisplatin	1	2

Paz-Ares L., et al. J Clin Oncol 2013 (in press)

Maintenance Efficacy QoL

Trial	N	Maintenance drug	QoL & Symptom Control
Switch Chemotherapy Maintenance			
Westeel et al.	181	Vinorelbine	NR
Fidias et al.	309	Docetaxel	No differences
Capuzzo	889	Erlotinib	Better pain control
Cieleanu et al.	663	Pemetrexed	Better pain and hemoptisis control
Continuation Chemotherapy Maintenance			
Paz-Ares et al	539	Pemetrexed	No detrimental effect
Brodowicz et al.	206	Gemcitabine	NR
Belani et al.	255	Gemcitabine	NR
Perol et al.	309	Gemcitabine	NR

Saturn Trial
QoL



Juhasz E, et al. Eur J Cancer 2013

Toxicity: Paramount Trial
Possible Drug-related CTCAEs*

	Pemetrexed (N=359)		Placebo (N=180)	
	Grade 1/2 %	Grade 3/4 %	Grade 1/2 %	Grade 3/4 %
Fatigue†	17.5	4.7	10.6	1.1
Nausea	13.4	0.6	2.2	0
Anemia†	11.7	6.4	4.4	0.6
Vomiting	7.5	0.3	1.1	0
Mucositis/stomatitis‡	5.8	0.6	2.2	0
Neuropathy/sensory	5.3	0.3	6.1	0.6
Neutropenia†	5.0	5.8	0.6	0
Leukopenia	2.8	2.2	0	0
ALT (SGPT)	2.5	0.3	0.6	0

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Leukopenia	2.8	2.2	0	0
ALT (SGPT)	2.5	0.3	0.6	0

Maintenance Treatment Expenses by Improvement

	Erlotinib		Pemetrexed (NSC)	
Setting	**Second line**	**Maintenance**	**First Line**	**Maintenance**
Median courses	**2.2**	**4**	**5**	**4**
HR	**0.73**	**0.81**	**0.82**	**0.78**

Shepherd F et al., NEJM 2006; Capuzzo F et al., Lancet Oncol 2010
Scagliotti GV et al, J Clin Oncol 2008; Paz-Ares et al JCO 2013 (in press)

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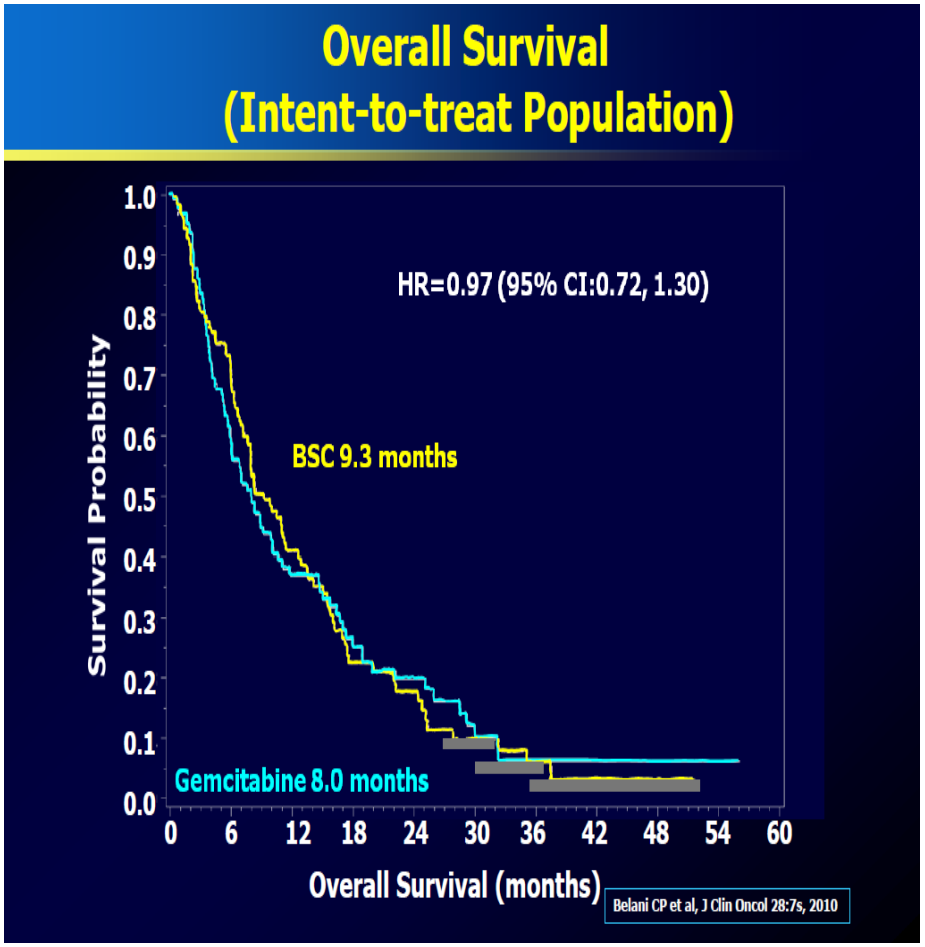
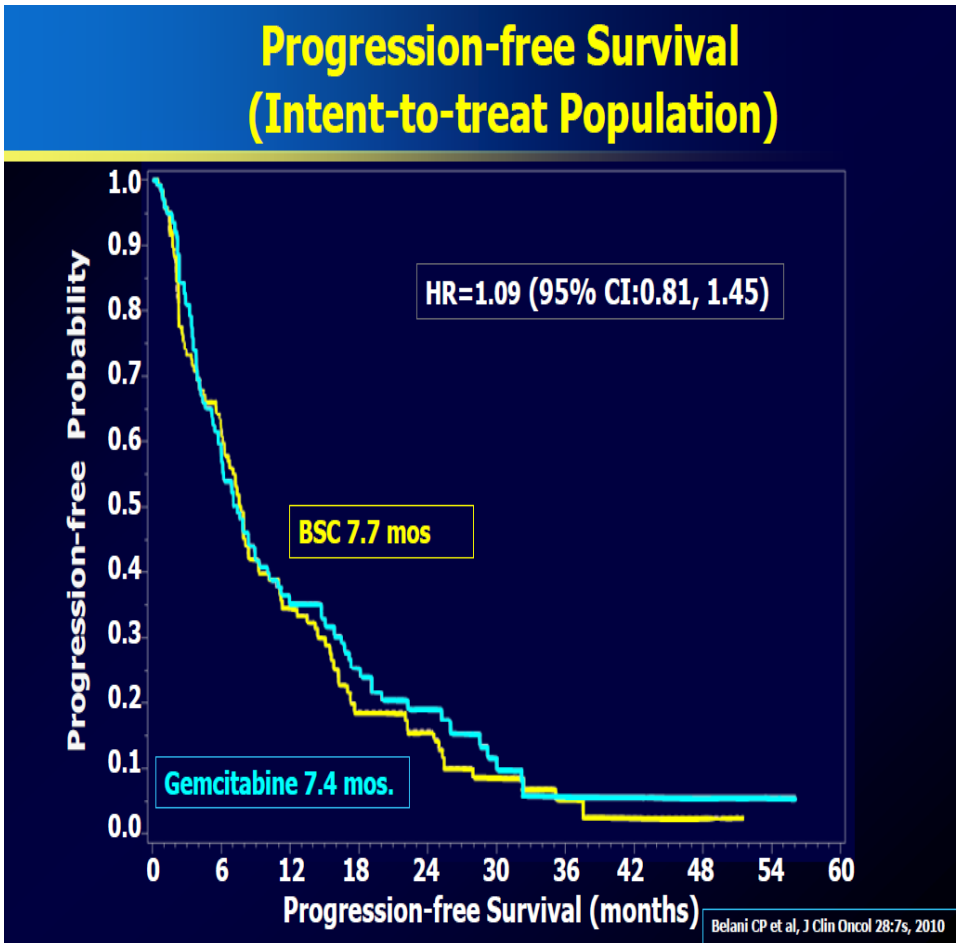
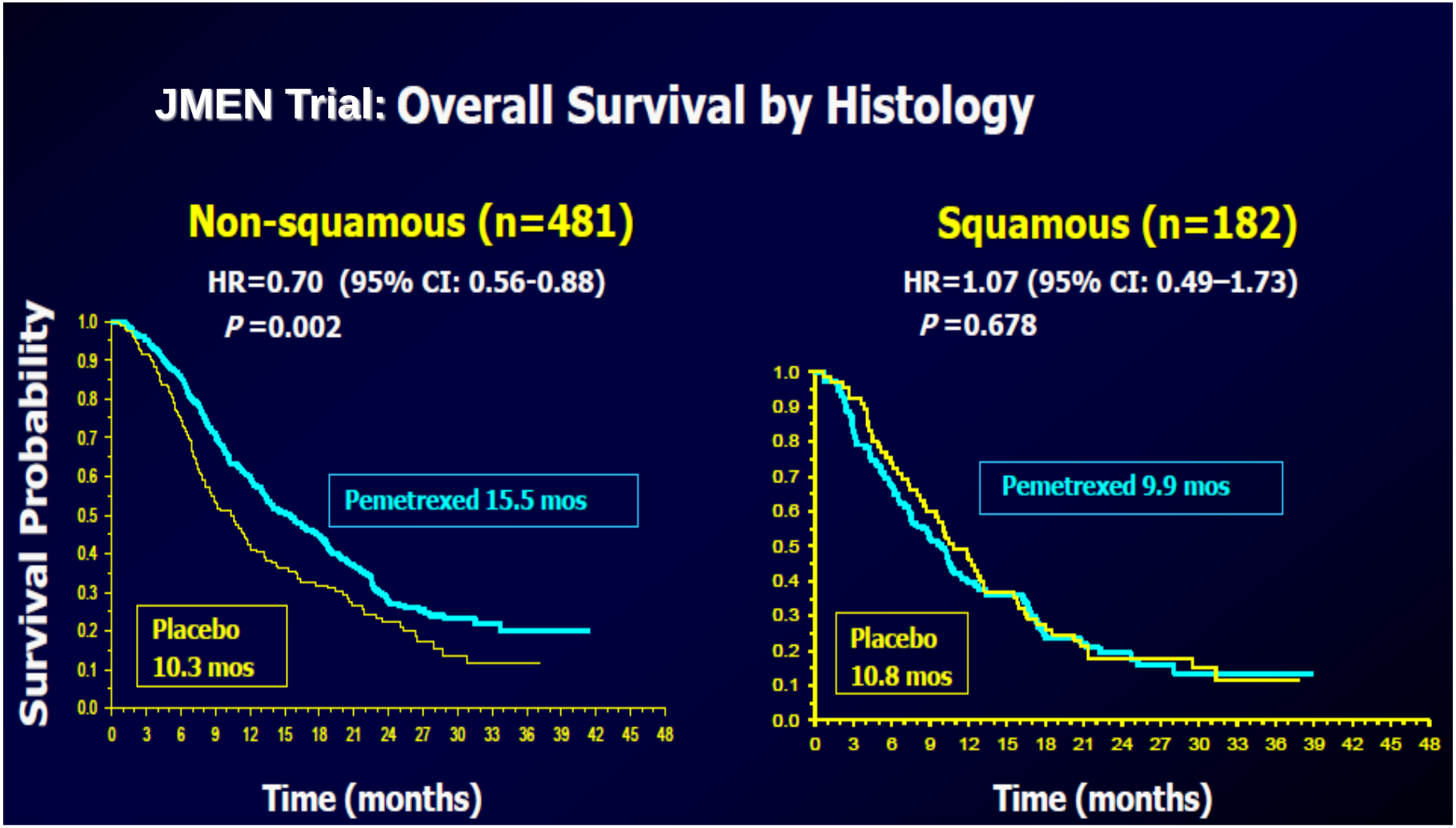
Patient Selection
Gemcitabine Maintenance Therapy – PS 2





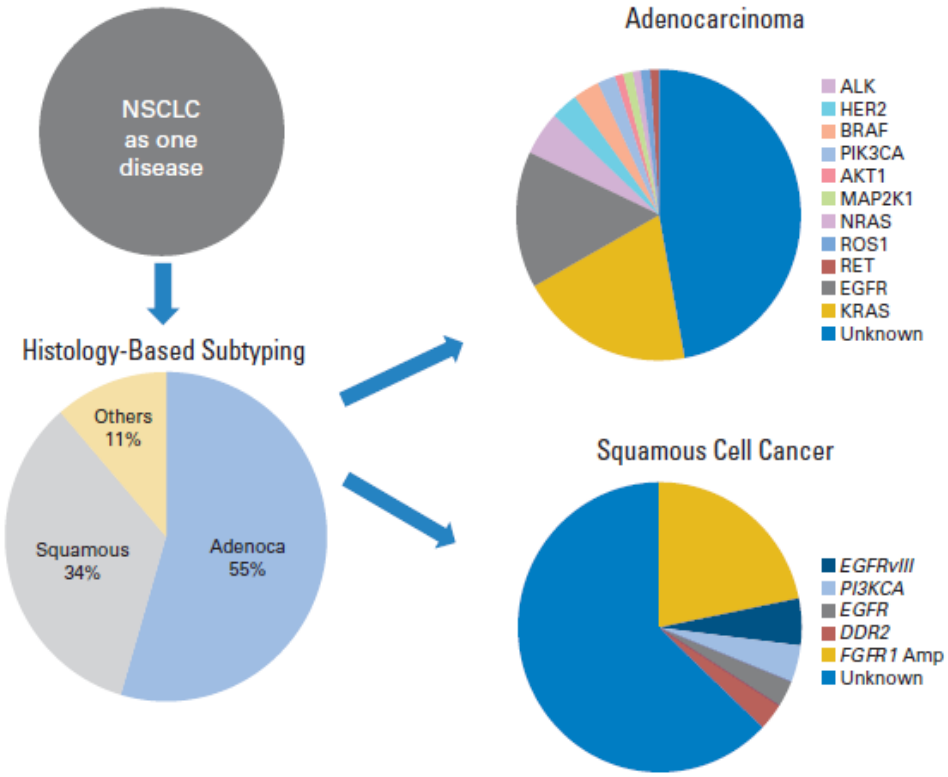
Belani CP, et al. ASCO 2010. Abstract 7506.

Patient Selection
Tumor Histology

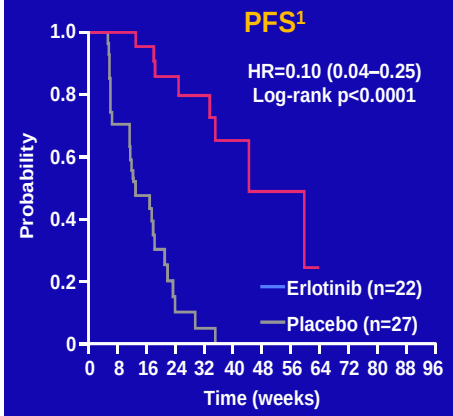


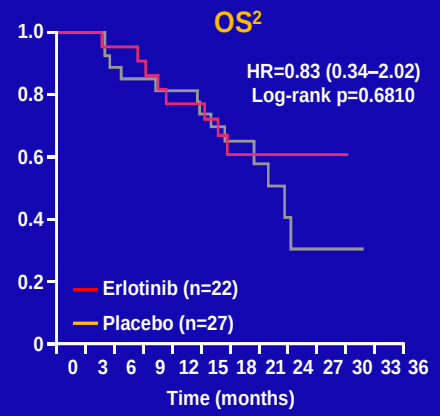
Ciuleanu et al., Lancet 2010

Patients Selection
Tumor Genotype



SATURN: *EGFR* Act Mut+ disease



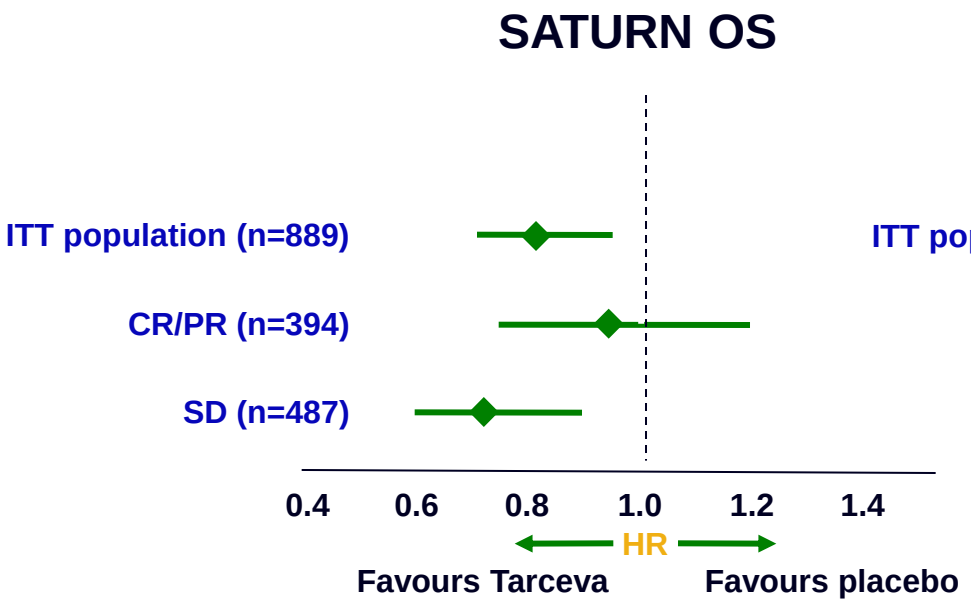


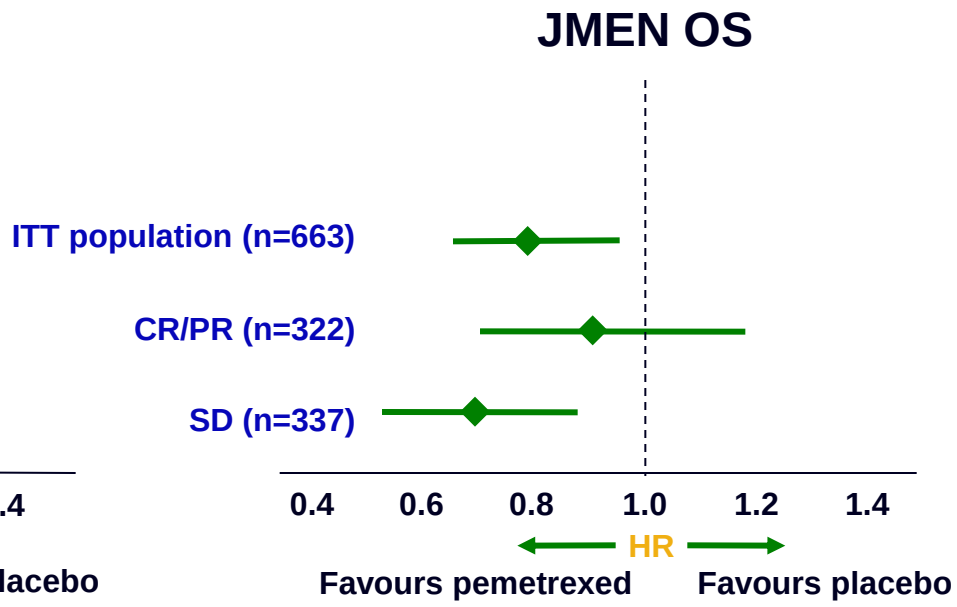
- Significantly improved PFS with erlotinib vs placebo in patients with *EGFR* MUT +ve disease
- OS data not yet mature (N.B. 67% of patients with *EGFR* MUT +ve disease in placebo arm received a second-line EGFR TKI)

Li et al. J Clin Oncol 2013

Brugger et et al., J Clin Oncol 2011

Patient Selection
Response to Induction Treatment





Cappuzzo F et al. 2010 Lancet Oncol 11:521–29

Ciuleanu et al., Lancet 2010

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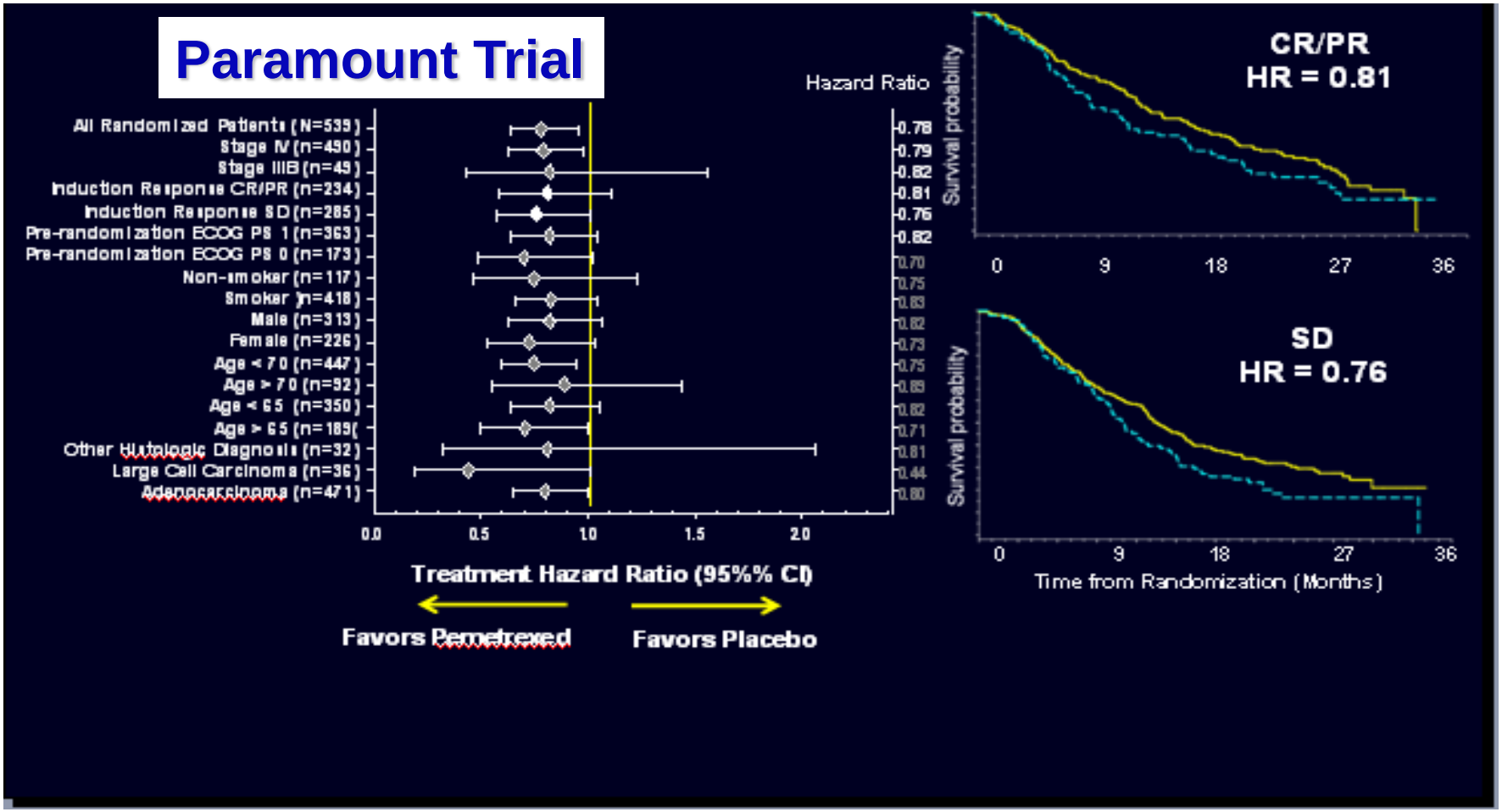
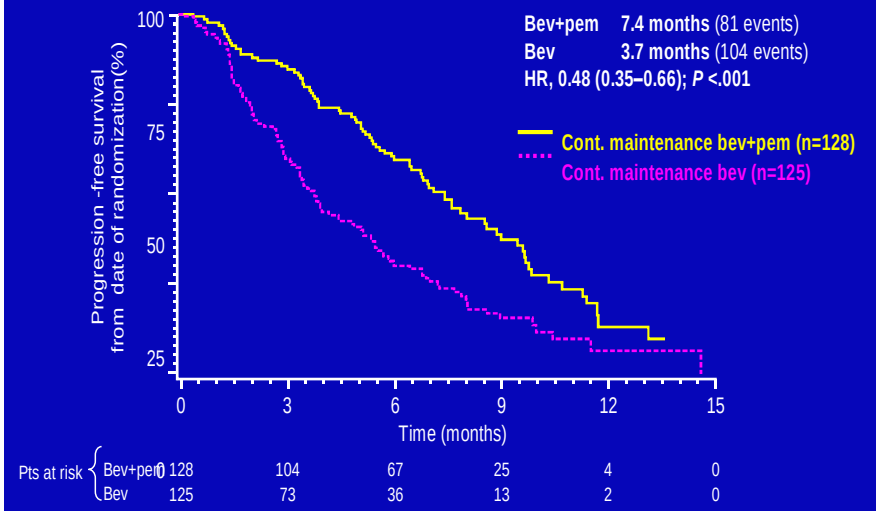


Paz-Ares L., et al. J Clin Oncol 2013

Recent Developments
Bevacizumab + Pemetrexed

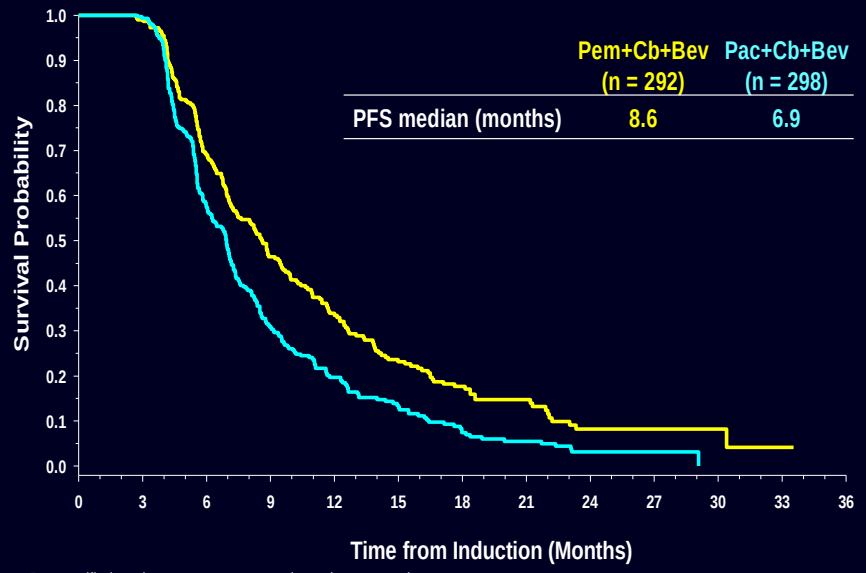
AVAPERL: PFS From Randomization[a]



[a] Median follow-up time in ITT population (excluding induction): 8.28 months (bev+pem arm), 7.95 months (bev arm)
bev, bevacizumab; cont., continuation; HR, hazard ratio; ITT, intent to treat; pem, pemetrexed; pts, patients.

Barlesi et al., ESMO 2011

PointBreak: Prespecified Analysis of KM PFS from Randomization (Maintenance Population)



Prespecified exploratory non-comparative subgroup analyses
Censoring rate for Pem+Cb+Bev was 24.7; for Pac+Cb+Bev was 14.1

Barlesi., et al. Ann Oncol 2014

Patel., et al. J Clin Oncol 2013

Summary

- **Maintenance therapy offers the possibility of continued active treatment to delay disease progression and improve survival**
- **Pros and cons of maintenance therapy, switch and continuation, should be discussed with the patient**
- **Further studies are warranted, in particular those evaluating tumor tailored strategies optimizing patient selection and treatment specificity**

JMEN Study Design

- Double-blind, multicenter, placebo-controlled, phase III trial

Randomized 2:1 according to sex, PS, stage, best response, nonplatinum drug, brain metastases

Patients with stage IIIB/IV NSCLC, ECOG PS 0-1, 4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD

(N = 663)

Pemetrexed 500 mg/m^2 (d1,q21d) + BSC

(n = 441)*

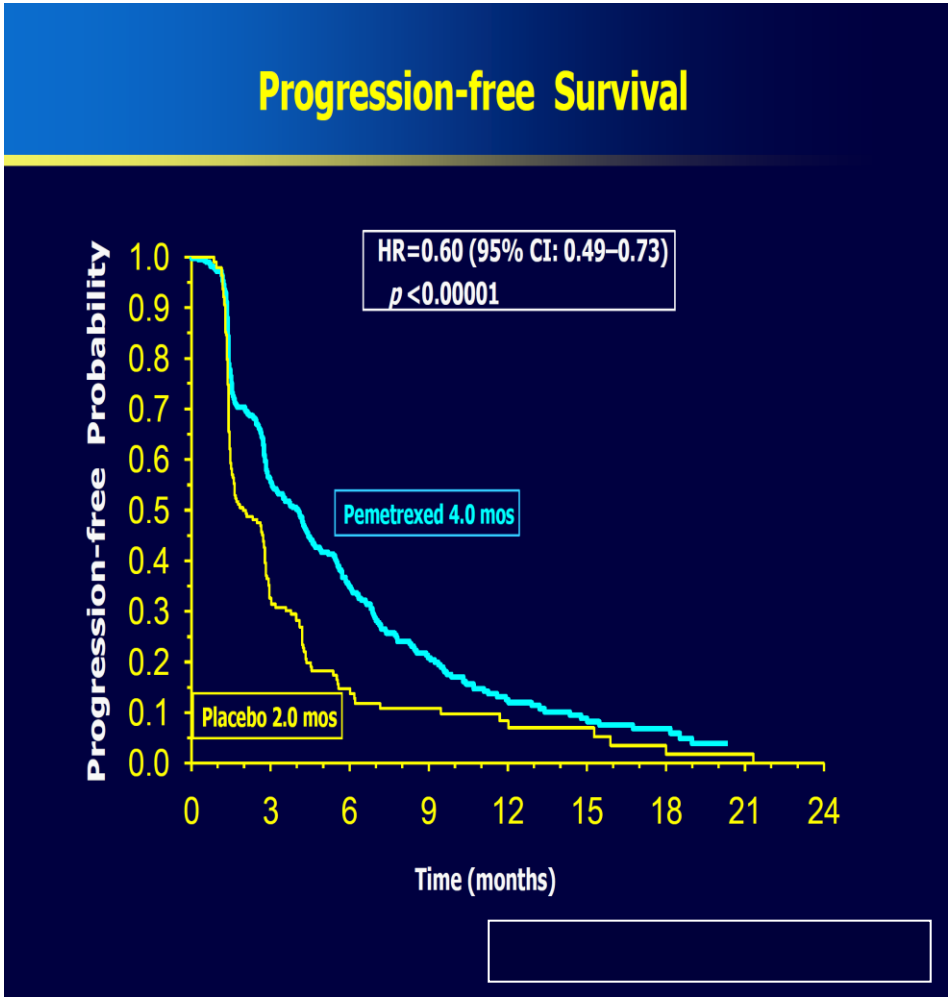
Placebo (d1, q21d) + BSC

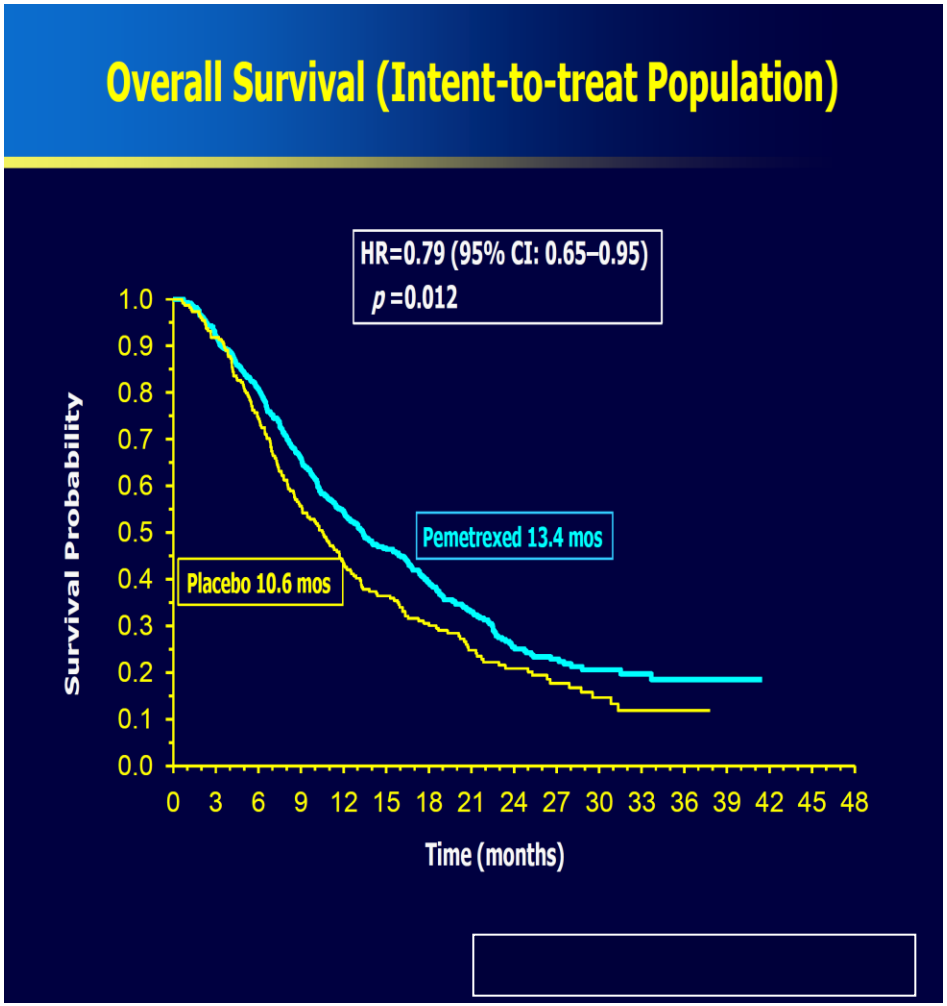
(n = 222)*

- **Primary endpoint: PFS**

Ciuleanu et al., Lancet 2010

JMEN Trial
Pemetrexed Switch Maintenance





Ciuleanu et al., Lancet 2010