



Hospital Universitario  
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# Maintenance treatment: chemo, targeted agents or both?

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# Disclosures

- **Scientific advise:**
  - Lilly, Roche, Pfizer, BMS, MSD, AZD, Boehringer, Clovis

# Outline

- **Rationale**
- **Supportive Evidence**
  - According to strategy
- **Pitfalls and Arguments against**
  - Trial design
  - Cost
- **Patient Selection**
- **Future perspectives**

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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 oncogene addicted lung cancer

# Maintenance in Other Chronic Diseases

## Other Cancers

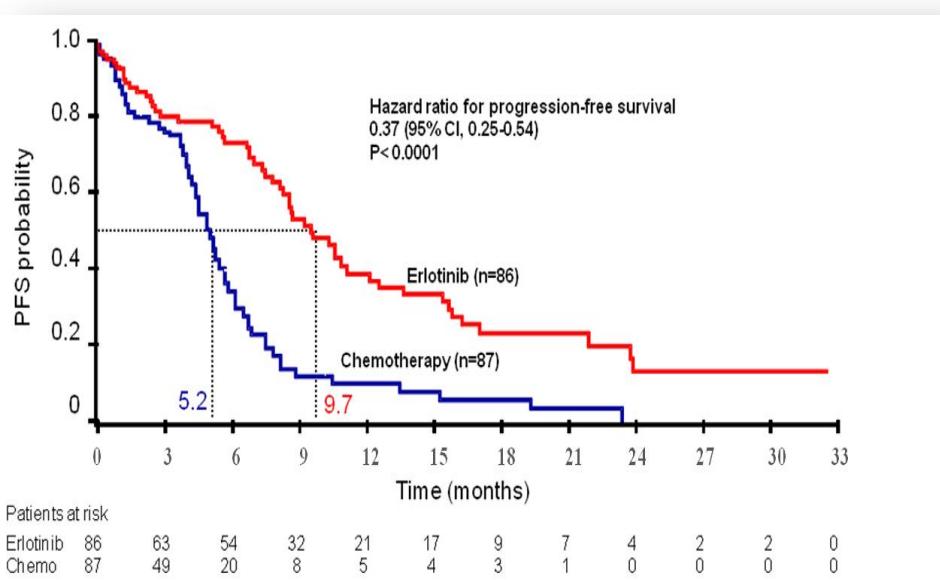
- Breast
- Colorectal
- Prostate
- Mesothelioma ?
- ...

## Respiratory Diseases

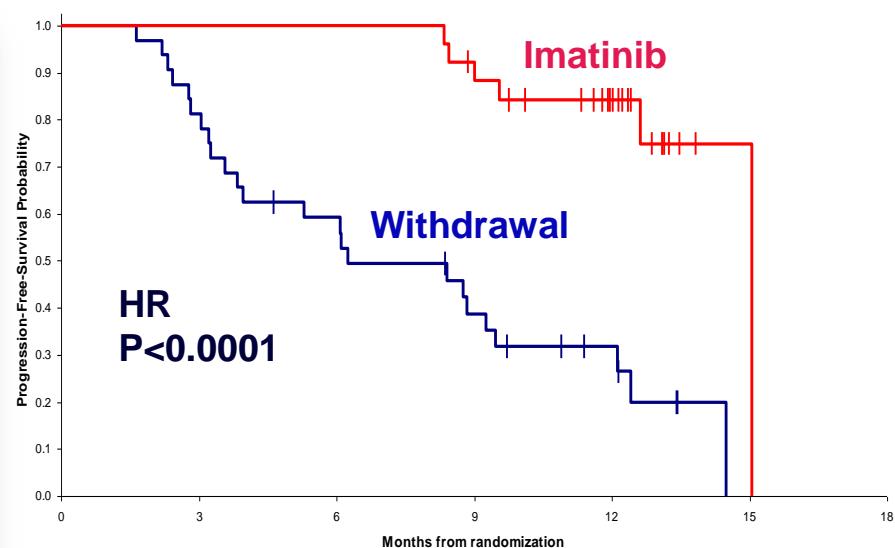
- COPD
- Granulomatosis
- Lupus
- Fibrosis
- ...

# Maintenance in Lung Cancer “Oncogene Addicted”

## Erlotinib in EGFR m+ NSCLC EURTAC Trial



## Imatinib Withdrawal in GIST BFR 14 Trial

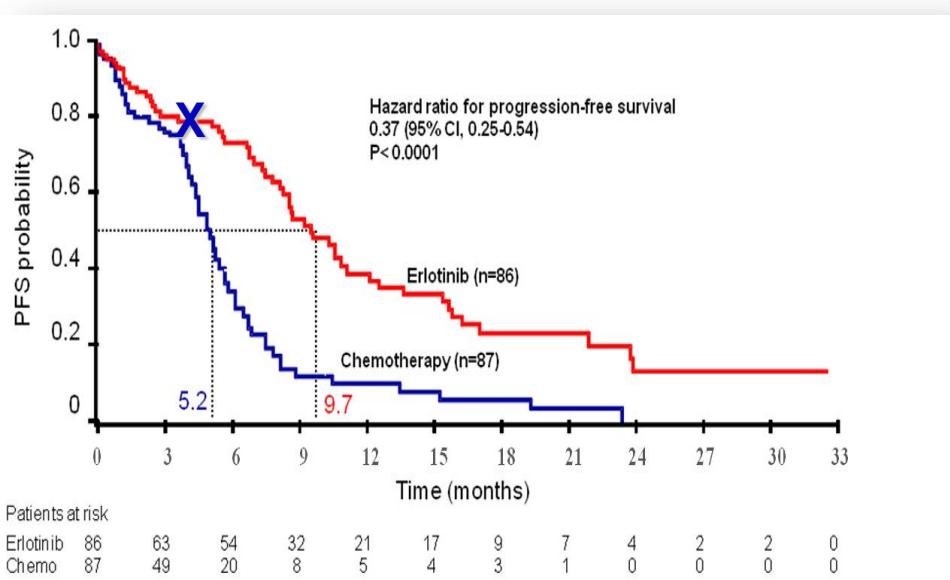


Rosell R et al., Lancet Oncol 2012

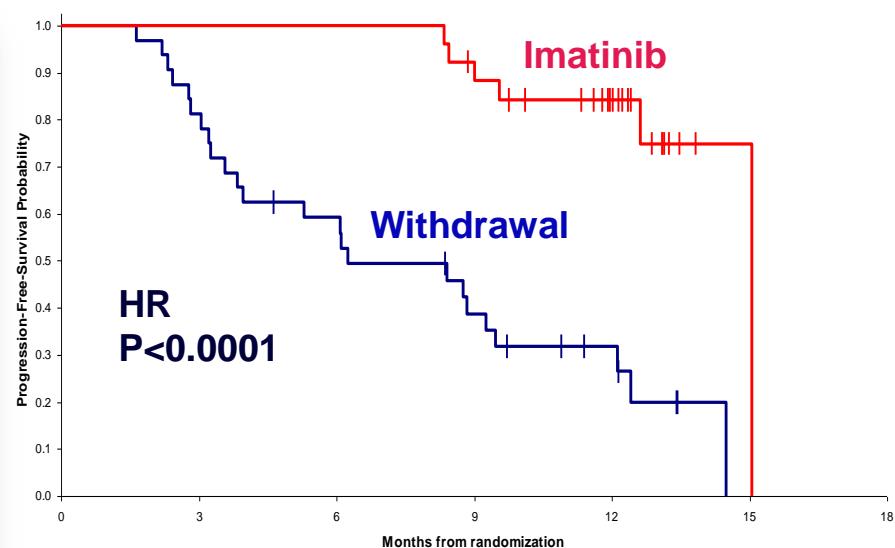
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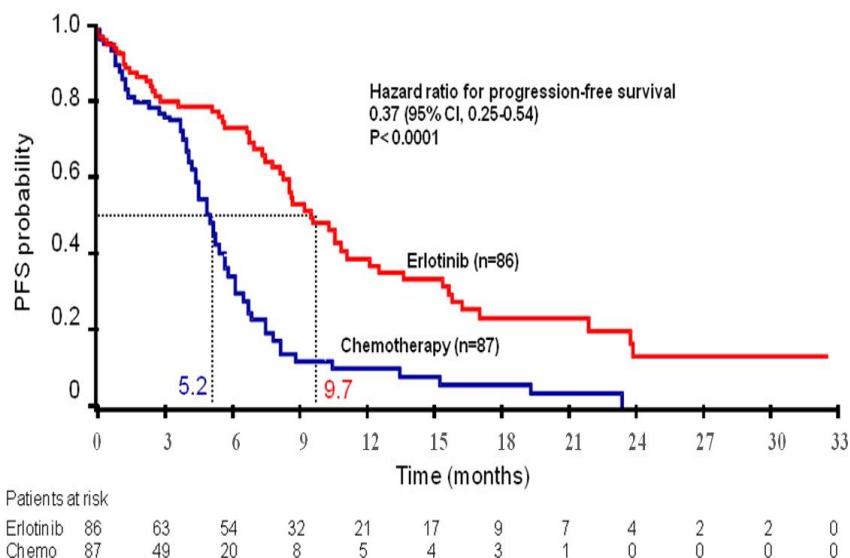


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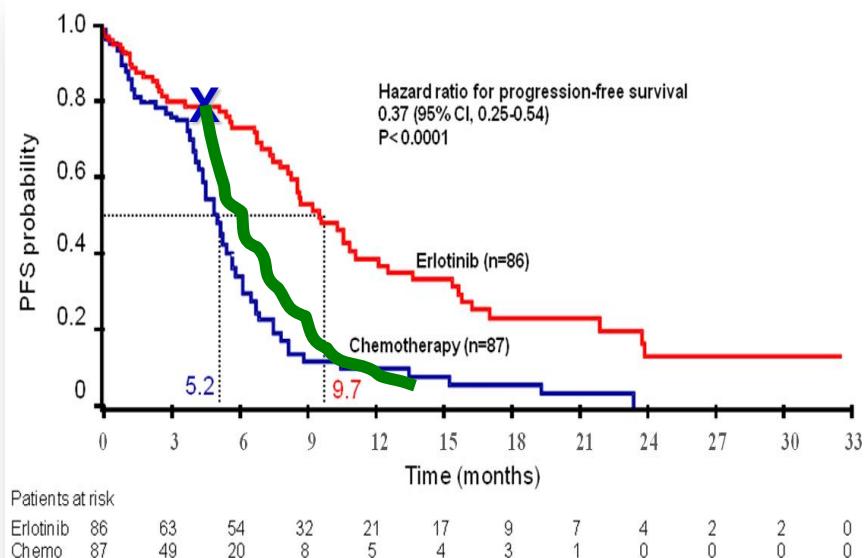
Le Cesne A et al., Lancet Oncol 2010

# Maintenance in Lung Cancer “Oncogene Addicted”

## Erlotinib in EGFR m+ NSCLC EURTAC Trial



## Simulation- EURTAC Trial 4 months treatment



Rosell R et al., Lancet Oncol 2012

Rosell R et al., Lancet Oncol 2012

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# Types of Maintenance

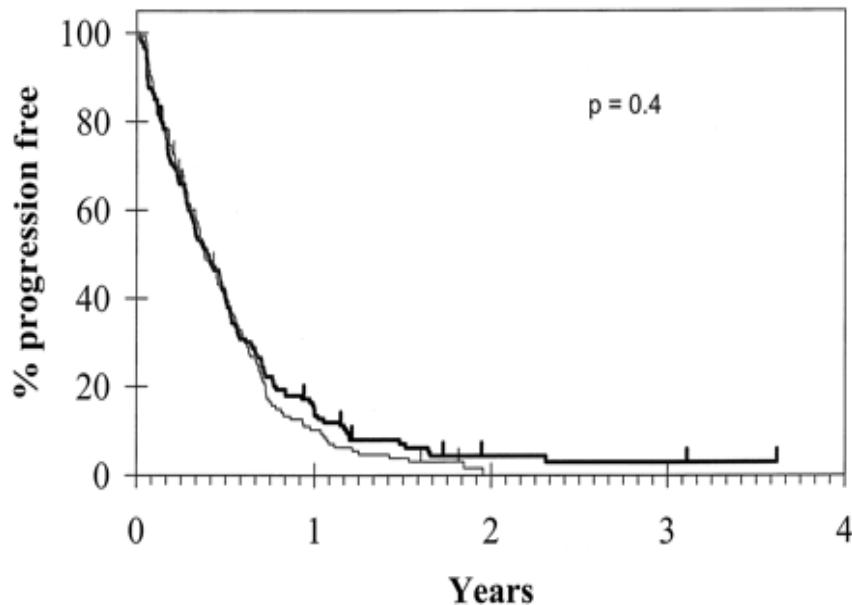
- **Continuation therapy:** Prolonged platinum doublet chemotherapy
- **Continuation Maintenance:** Continuation of non-platinum agent used in doublet chemotherapy
  - e.g. paclitaxel, gemcitabine, pemetrexed
- **Switch Maintenance:** Introduction of a new cytotoxic agent
  - e.g. docetaxel, pemetrexed, erlotinib
- **Targeted Maintenance:** Triplet induction therapy followed of maintenance with the same targeted agent
  - e.g. bevacizumab (EGOC 4599), cetuximab (Flex), Necitumumab (Squire)

# Types of Maintenance

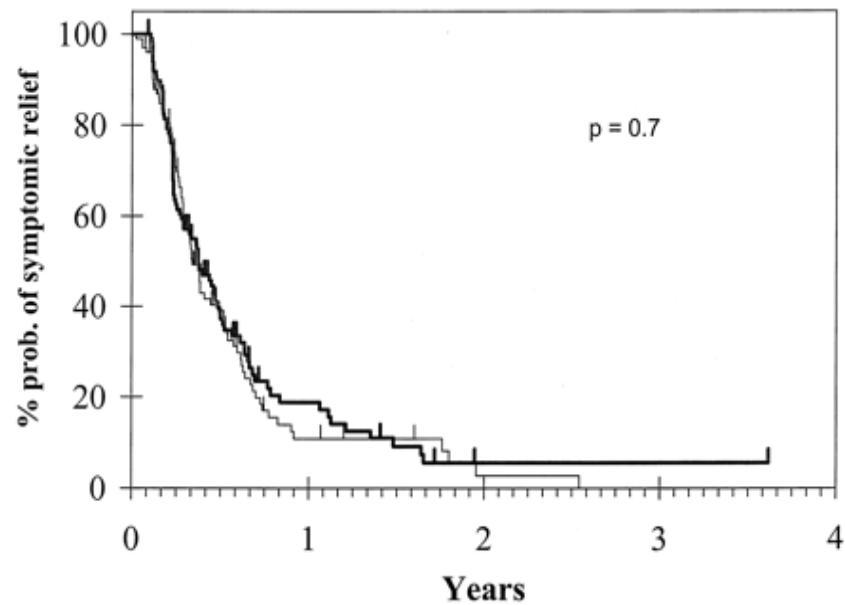
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# Optimal Chemo Duration UK Trial: MIC\* x 3 v MIC x 6

- Similar or better QoL ( $\downarrow$  asthenia ( $p=0.03$ );  $\downarrow$  N/V ( $p=0.06$ ))

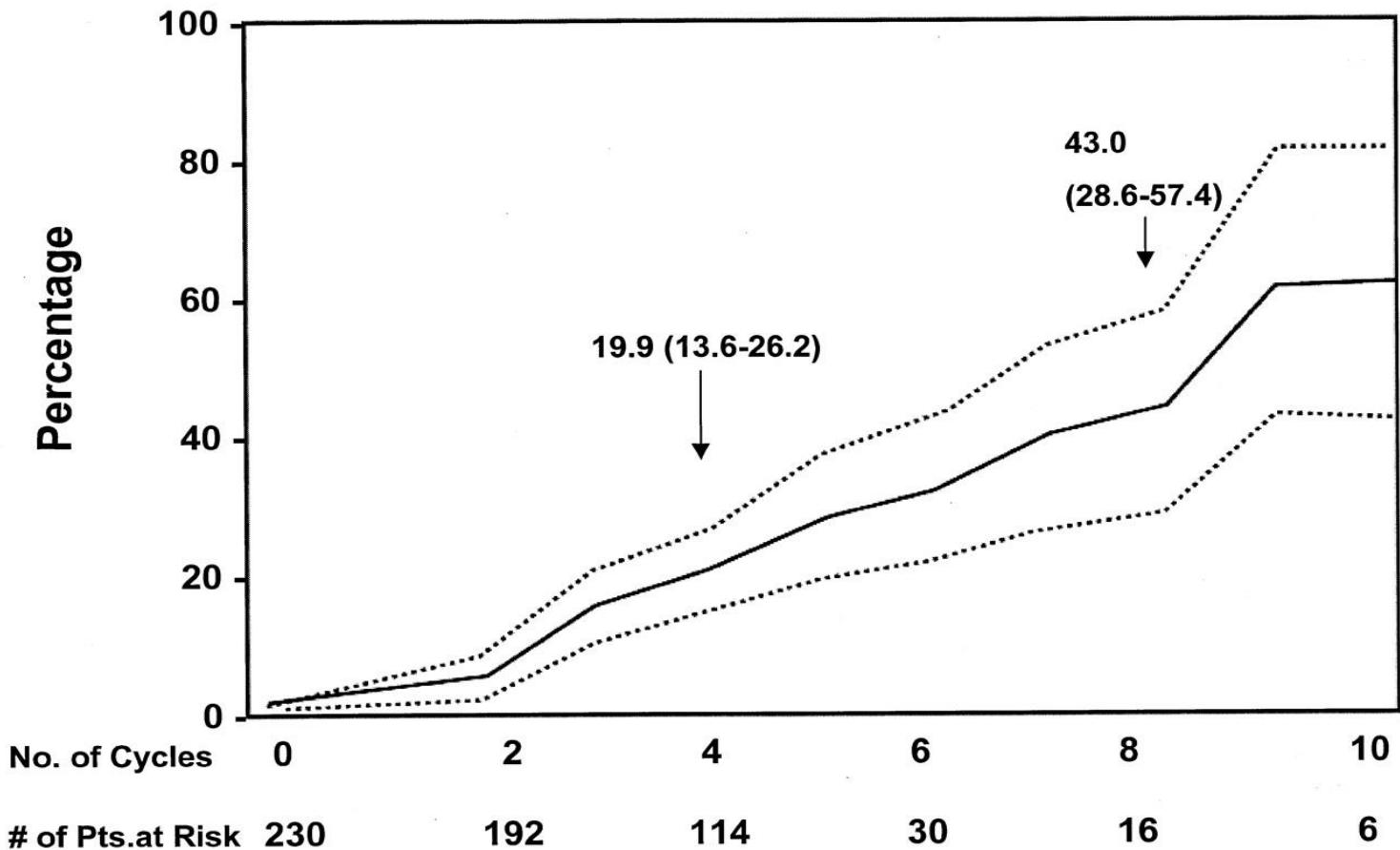


PFS



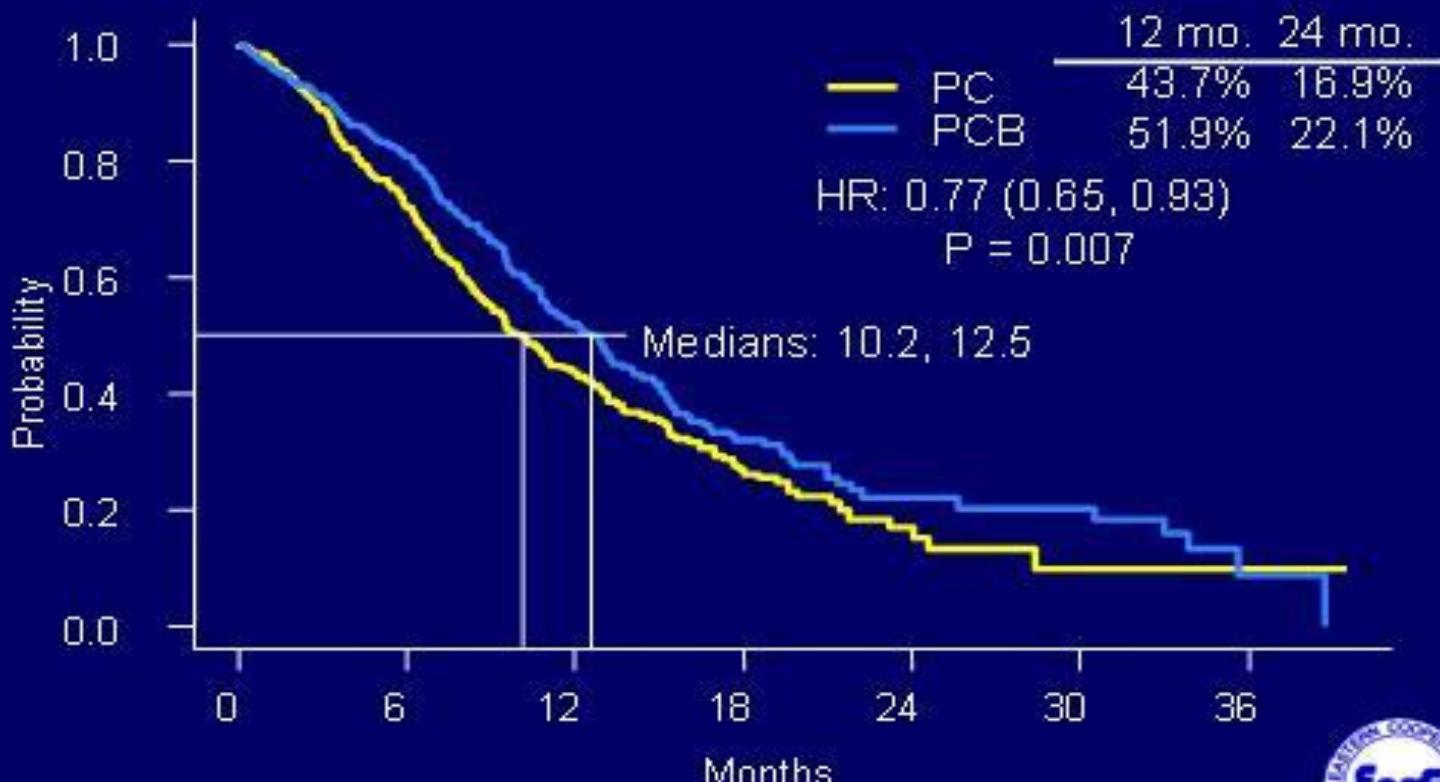
Symptoms Relief

# Optimal Chemo Duration PC\* x 4 v Prolonged PC \*



# Targeted Maintenance Bevacizumab

## Survival by Treatment

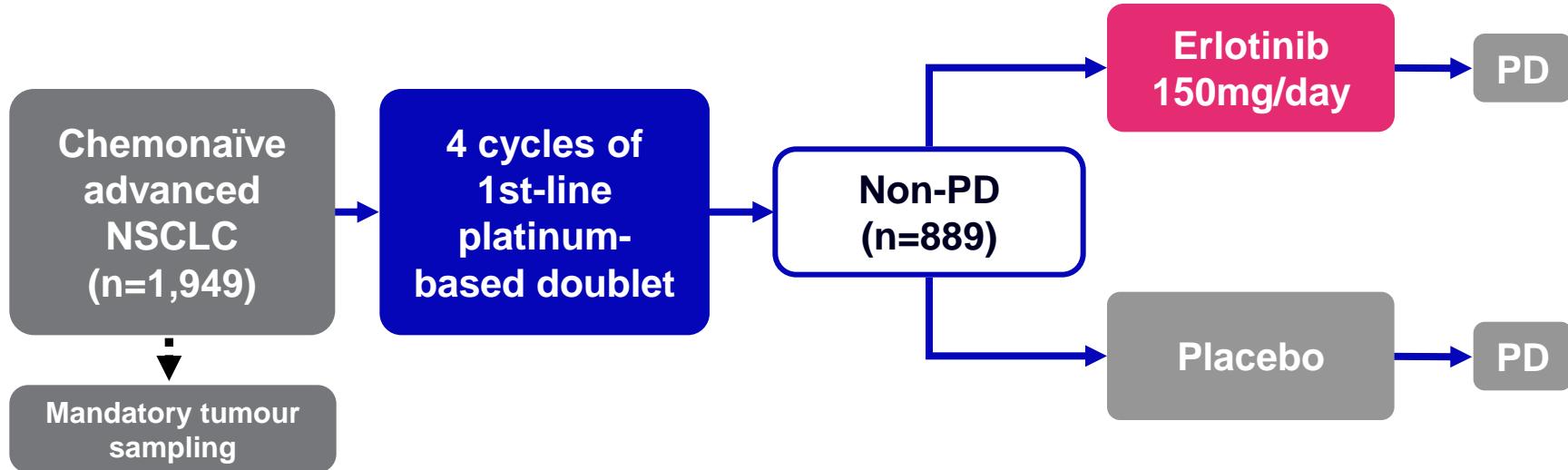


Sandler A et al., New Eng J Med 2006

# Types of Maintenance

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# SATURN Trial Erlotinib Switch Maintenance

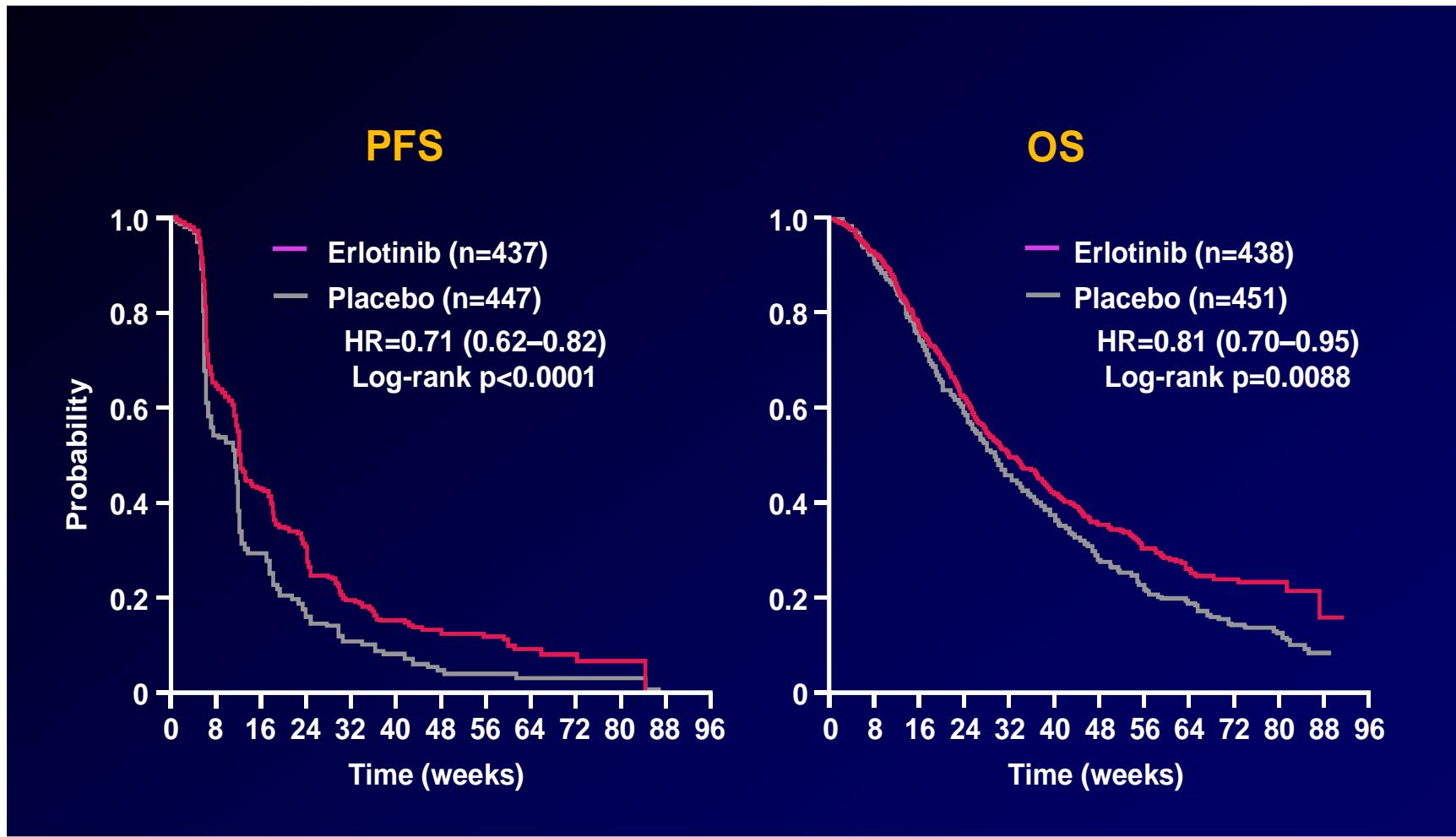


**Co-primary endpoints**  
PFS in all patients  
PFS in IHC+ tumours

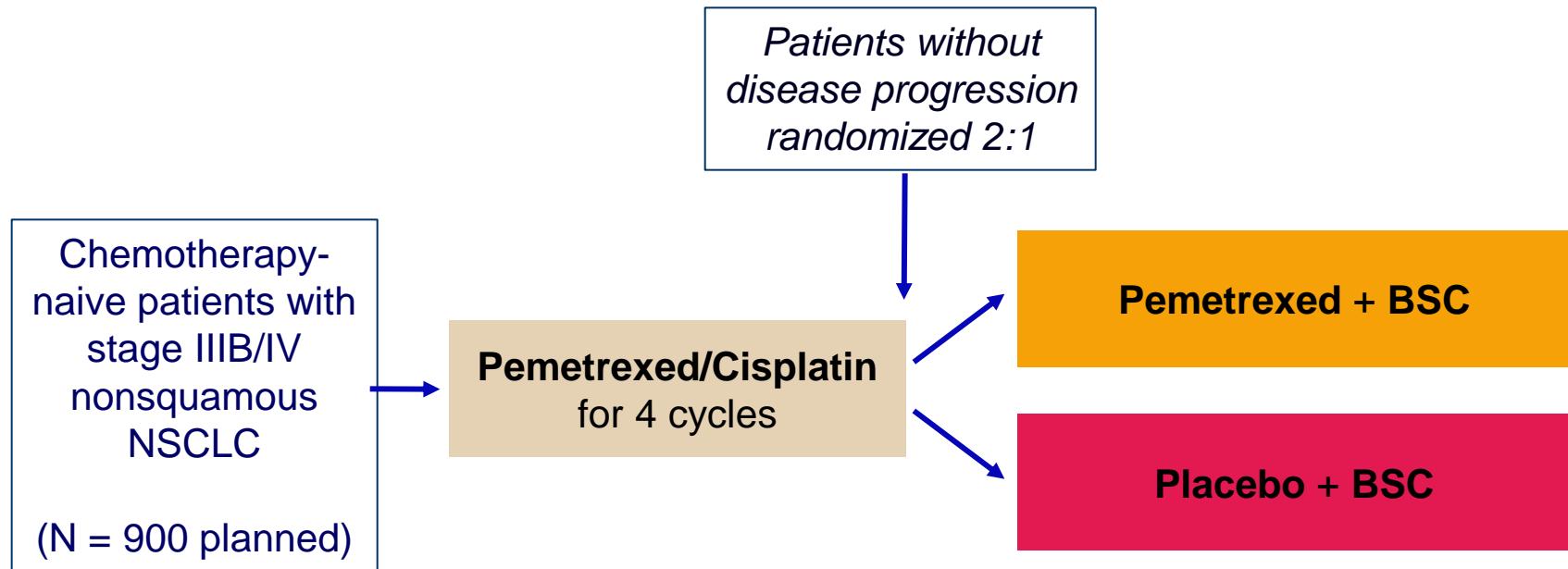
## Secondary endpoints

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)

# SATURN Trial Erlotinib Switch Maintenance



# Paramount Trial Pemetrexed Continuation Maintenance

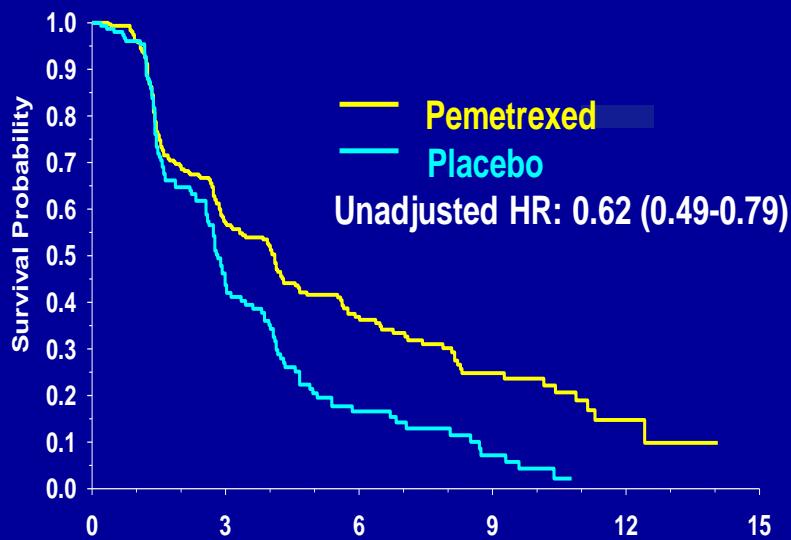


- Primary endpoint: PFS
- Other endpoints: OS, ORR, safety, patient-reported outcomes, resource utilization,

# Paramount Trial

## Pemetrexed Continuation Maintenance

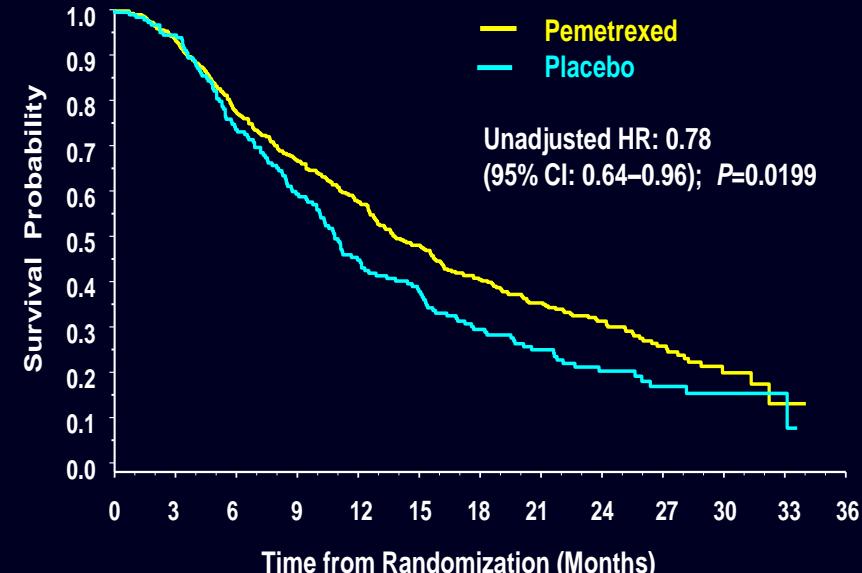
### PFS: Primary Efficacy Endpoint



Patients at Risk

	0	3	6	9	12	15
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)
<b>Switch Maintenance</b>				
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)
<b>Continuation Maintenance</b>				
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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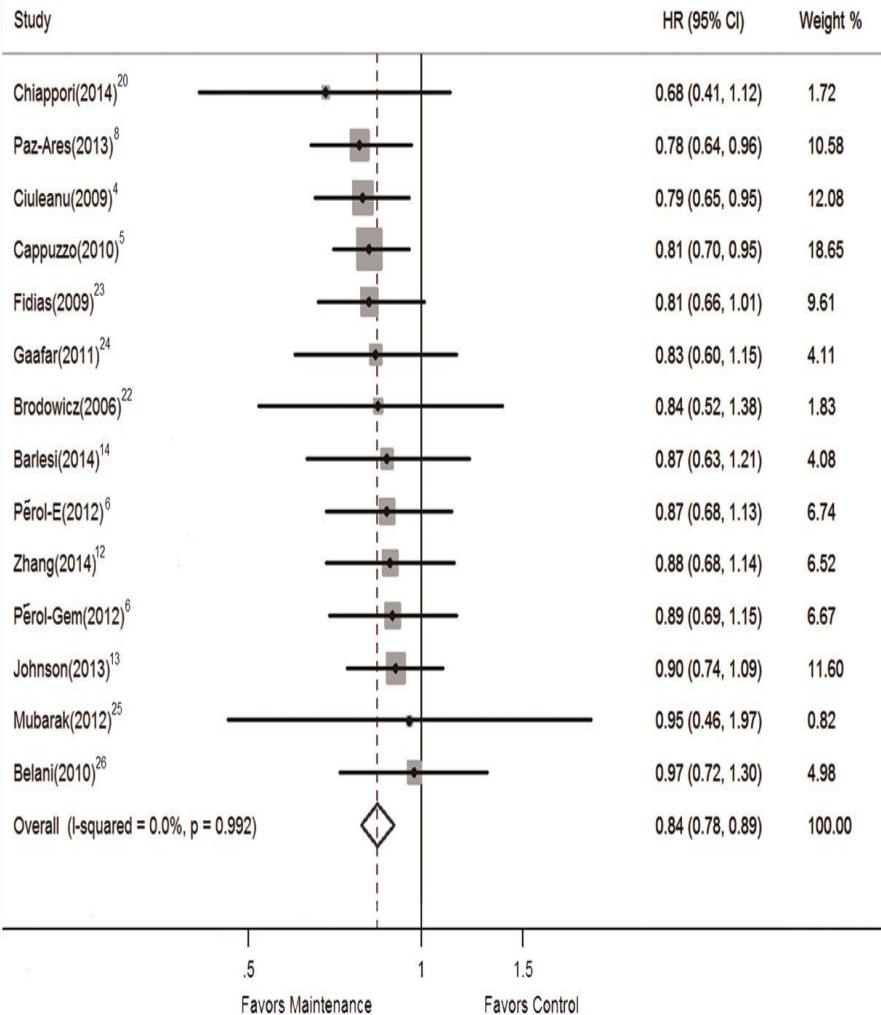
# Maintenance Efficacy

## PFS & OS

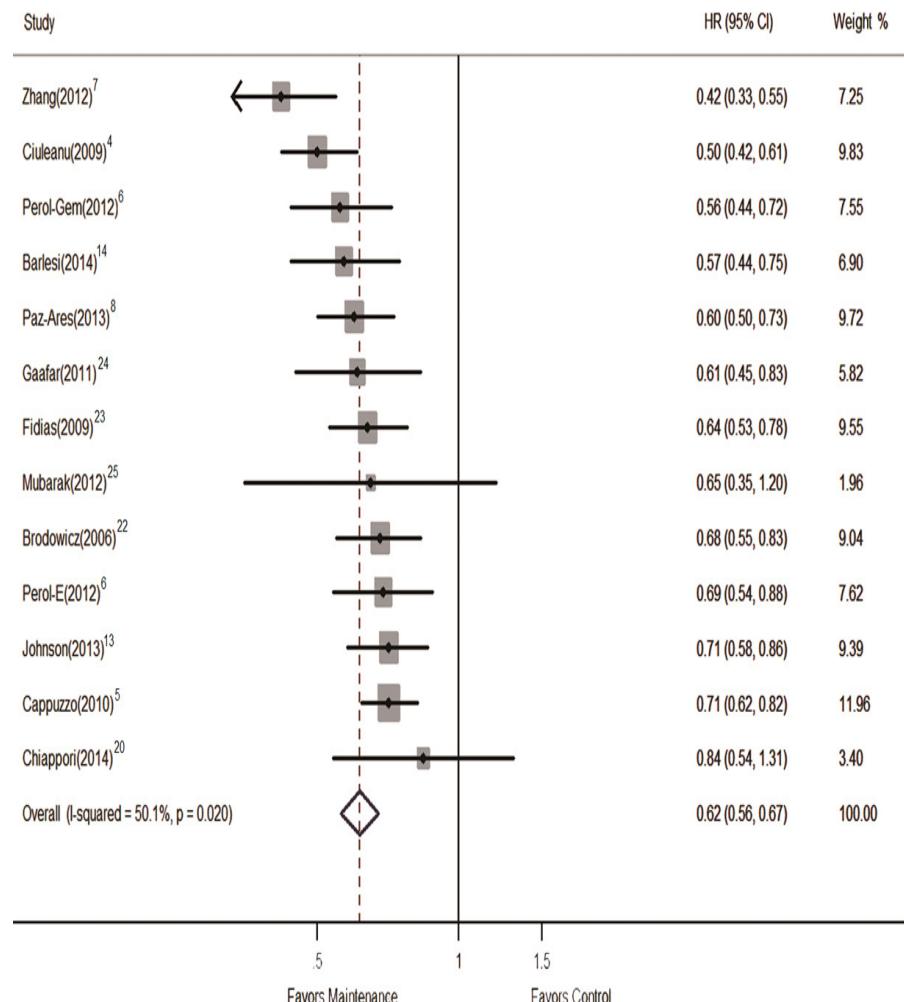
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# Maintenance Meta-analysis

## Overall Survival

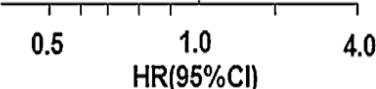


## Progression-free Survival



# Maintenance Meta-analysis OS by Subgroups

Subgroup	No. of Comparisons	Test of association		Favors Maintenance	Favors Control	Test of heterogeneity			Interaction P
		HR (95% CI)	P			Q	I <sup>2</sup> %	P	
<b>Maintenance strategy</b>									
Continuation maintenance <sup>6, 8, 14, 22, 25, 26</sup>	6	0.86(0.76-0.97)	0.013	■		1.68	0.0	0.891	0.631
Switch maintenance <sup>4-6, 12, 13, 20, 23, 24</sup>	8	0.83(0.77-0.90)	<0.001	■		2.01	0.0	0.959	
<b>No. of maintenance agent used</b>									
Single agent <sup>4-6, 8, 12, 20, 22-26</sup>	12	0.83(0.77-0.89)	<0.001	■		3.19	0.0	0.988	0.439
Double agents <sup>13, 14</sup>	2	0.89(0.76-1.05)	0.179	■		0.03	0.0	0.861	
<b>Maintenance regimen</b>									
Cytotoxic agent <sup>6, 22, 23, 26</sup> (excluding pemetrexed)	4	0.87(0.76-1.00)	0.043	■		1.00	0.0	0.800	0.375
Pemetrexed <sup>4, 8, 14, 25</sup>	4	0.80(0.71-0.91)	0.001	■		0.54	0.0	0.909	
<b>Maintenance regimen</b>									
Cytotoxic agent <sup>6, 22, 23, 26</sup> (excluding pemetrexed)	4	0.87(0.76-1.00)	0.043	■		1.00	0.0	0.800	0.788
Molecular-targeted therapy <sup>5, 6, 12, 13, 24</sup>	5	0.85(0.77-0.94)	0.001	■		0.84	0.0	0.933	
<b>Maintenance regimen</b>									
Pemetrexed <sup>4, 8, 14, 25</sup>	4	0.80(0.71-0.91)	0.001	■		0.54	0.0	0.909	0.455
Molecular-targeted therapy <sup>5, 6, 12, 13, 24</sup>	5	0.85(0.77-0.94)	0.001	■		0.84	0.0	0.933	



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# Pitfalls and Arguments Against

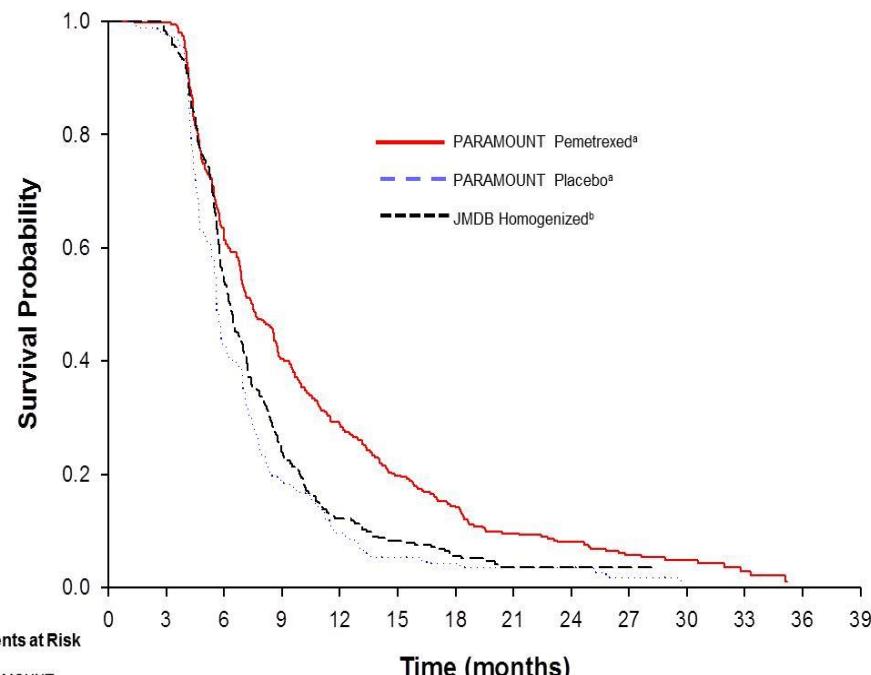
- **Trial Design**
  - Patient Selection
  - Number of induction courses
  - Post-study treatment
  - Other end-points
- **Cost**

# Induction: 4 v 6 courses Paramount v JMDB

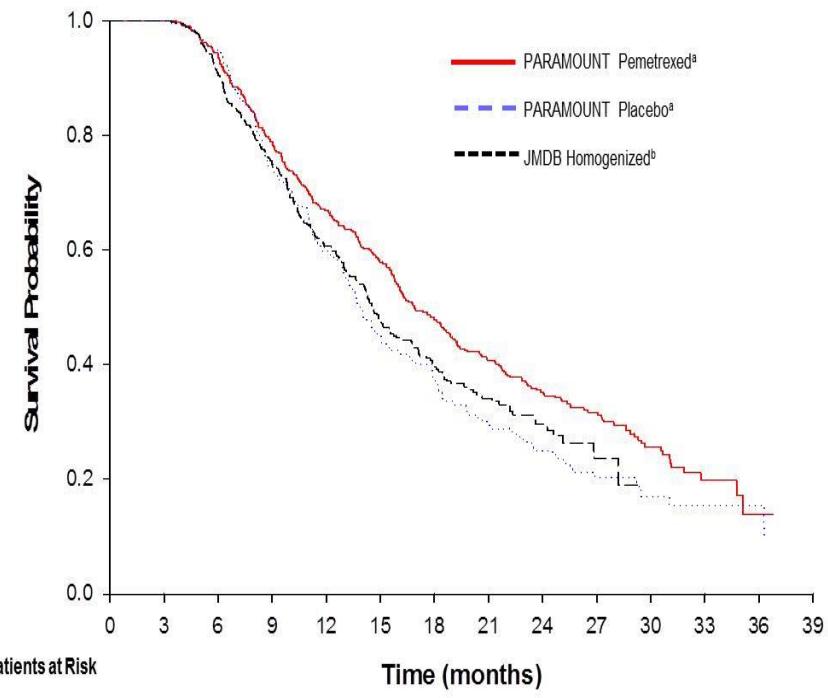
	PARAMOUNT Induction	JMDB
Median number of induction cycles	4 cycles then pemetrexed maintenance	1 <sup>st</sup> -line treatment with 6 cycles
<b>Response:</b>		
• Response Rate (CR/PR)	30.1%	28.6%
• Disease control rates (CR/PR/SD)	74.5%	63.8%
<b>Toxicity</b>		
• Laboratory toxicities	13.7%	21.4%
• Nonlaboratory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

# Induction: 4 v 6 courses Paramount v JMDB

PFS



Overall Survival



G Scagliotti et al, WCLC 2013

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%

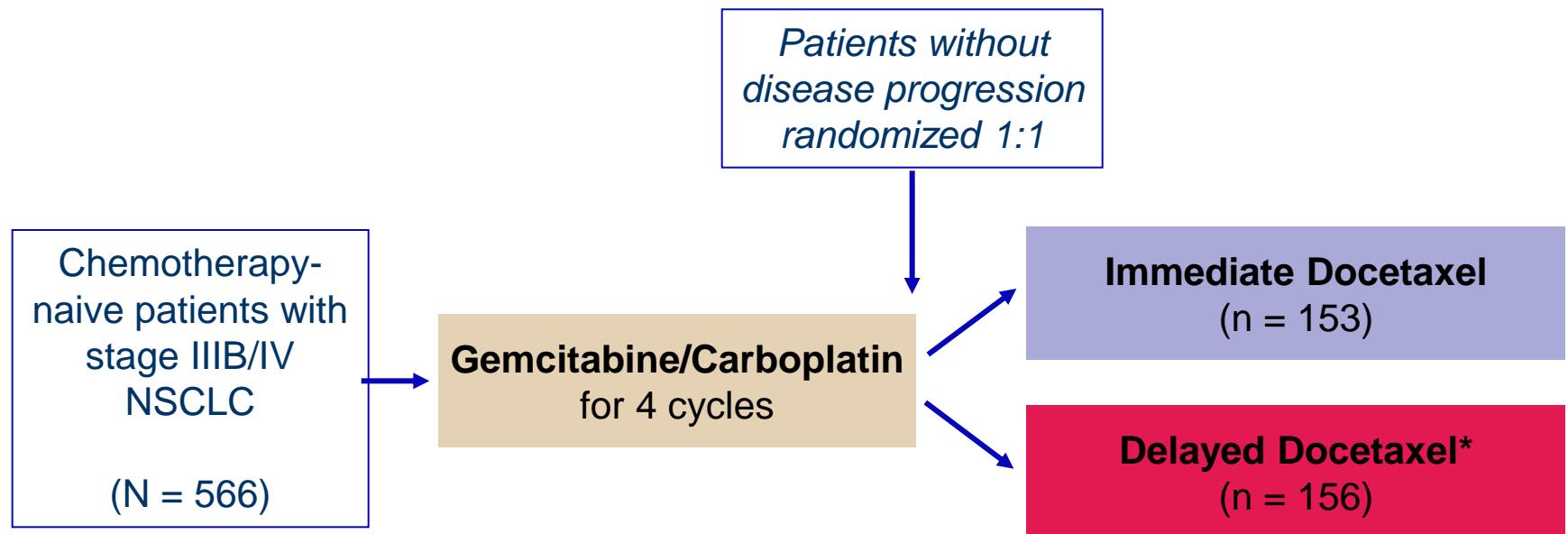
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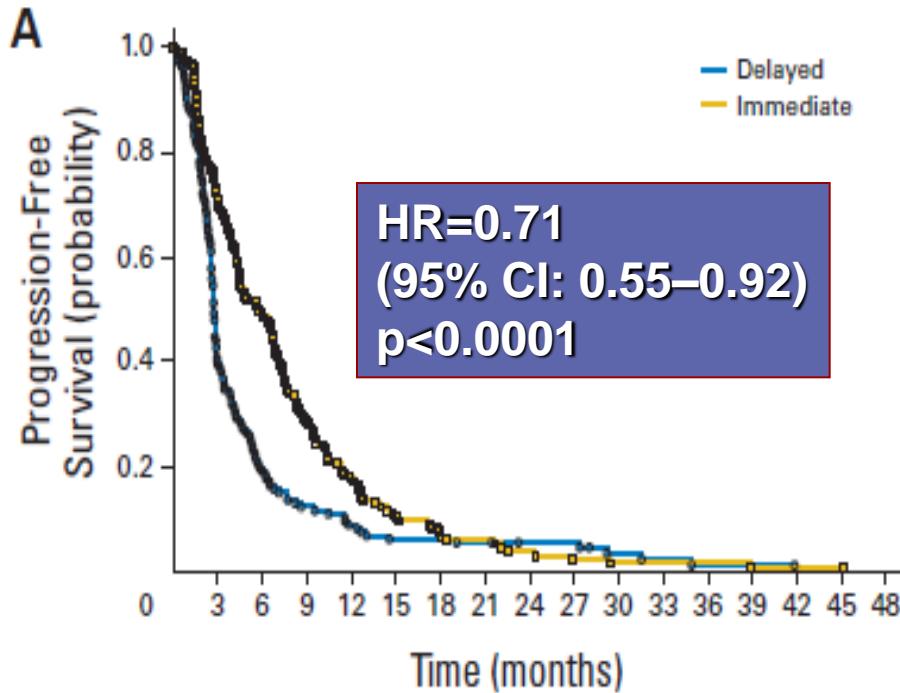
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# Switch Maintenance With Docetaxel

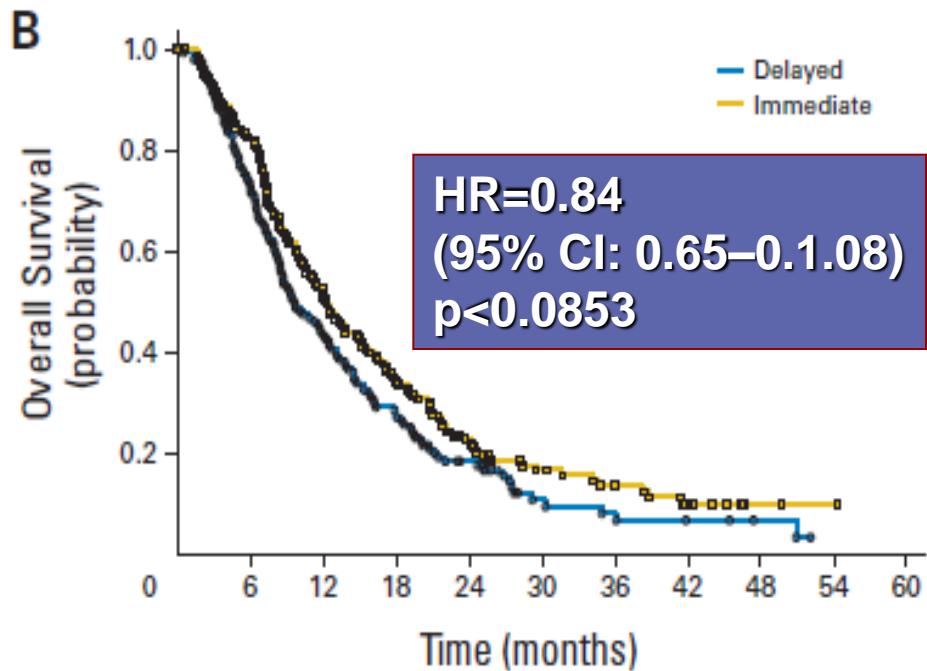


- Primary endpoint: OS
- Other endpoints: PFS, ORR, safety, QOL

# Docetaxel Switch Maintenance PFS & OS



No. of patients at risk						
Delayed	156	59	28	18	13	6
Immediate	153	106	72	42	26	5

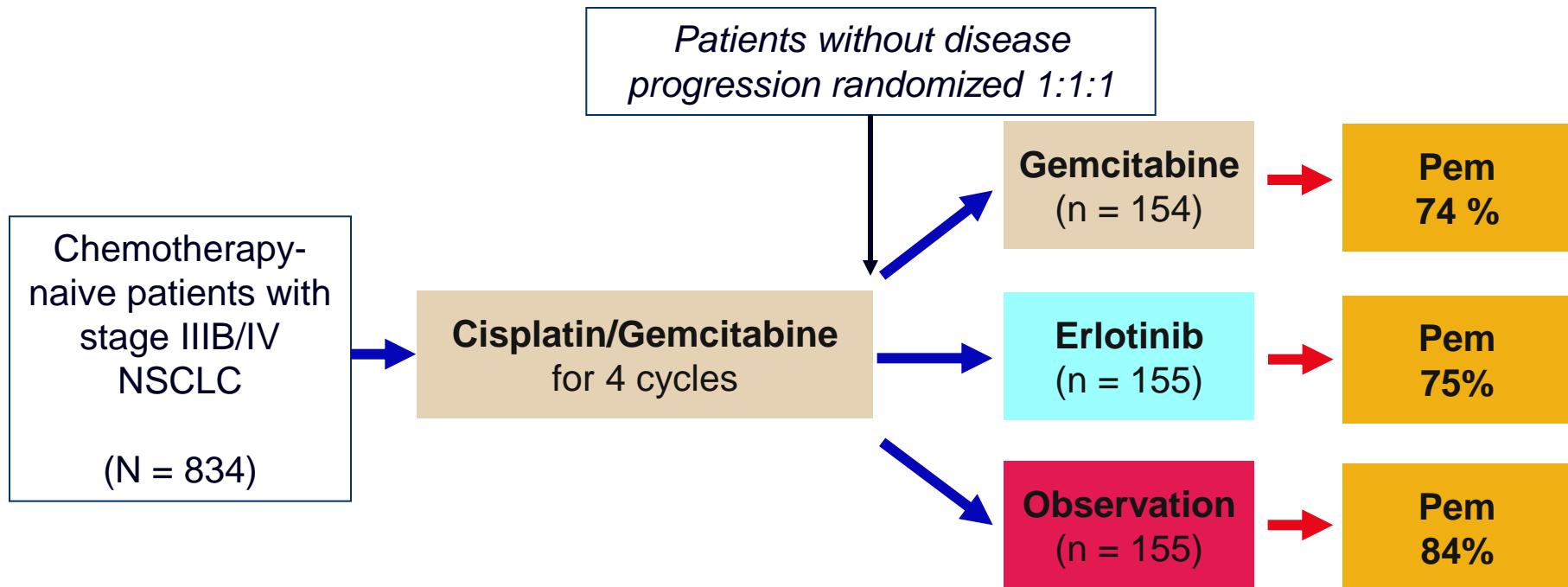


No. of patients at risk						
Delayed	156	109	65	42	21	6
Immediate	153	119	73	49	28	13

# IFCT-GFPC 0502

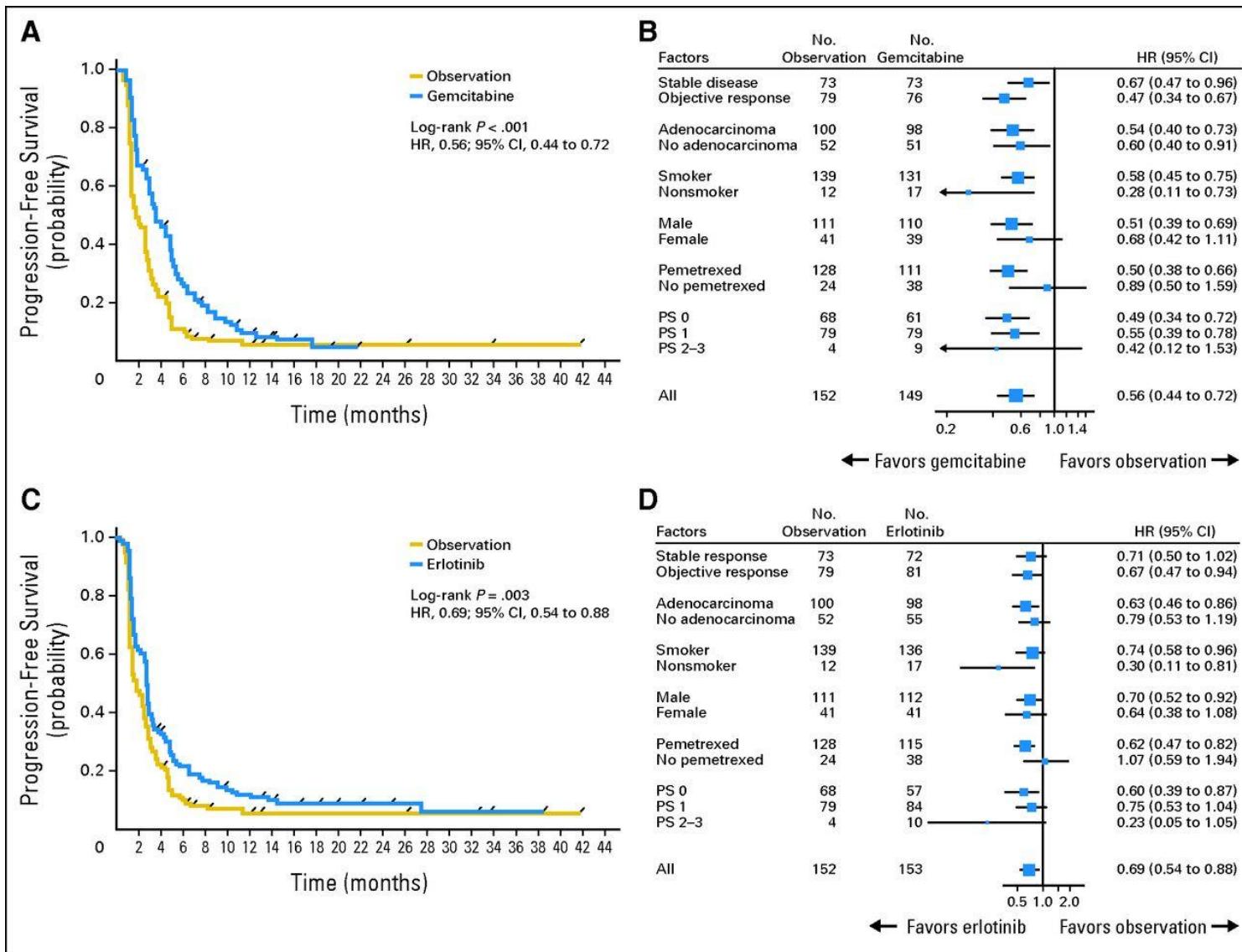
## Gemcitabine v Erlotinib v Observation

- 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



# IFCT-GFPC 0502

## Gemcitabine v Erlotinib v Observation



# Post-discontinuation Therapy Paramount Trial

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

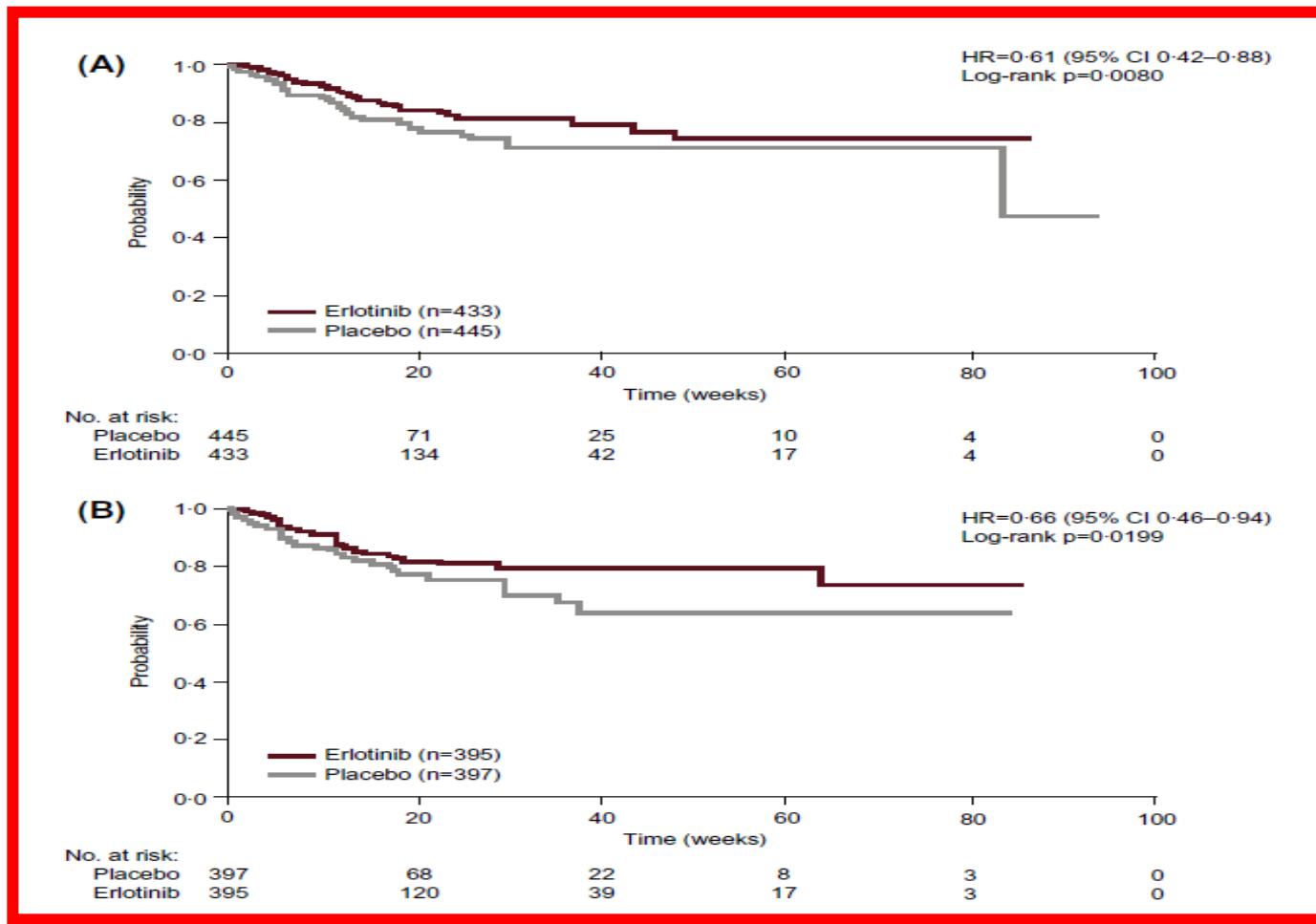
# Pitfalls and Arguments Against

- **Trial Design**
  - Patient Selection
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# Maintenance Efficacy QoL

Trial	N	Maintenance drug	QoL & Symptom Control
<b>Switch Chemotherapy Maintenance</b>			
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 hemoptysis control
<b>Continuation Chemotherapy Maintenance</b>			
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



# 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

# Toxicity: Paramount Trial

## Possible Drug-related CTCAEs\*

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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

# Pitfalls and Arguments Against

- **Trial Design**
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# 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

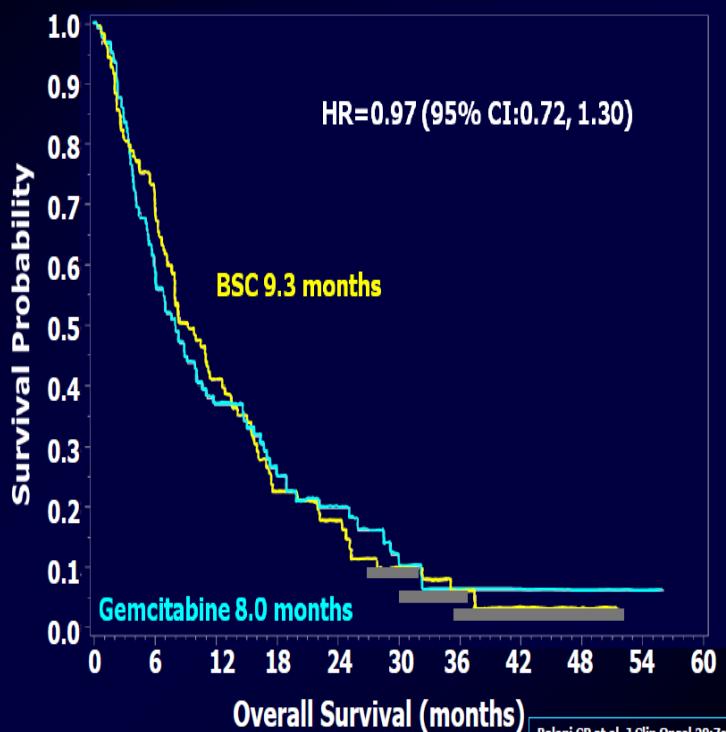
# Outline

- **Rationale**
- **Supportive Evidence**
  - According to strategy
- **Pitfalls and Arguments against**
  - Trial design
  - Cost
- **Patient Selection**
- **Future perspectives**

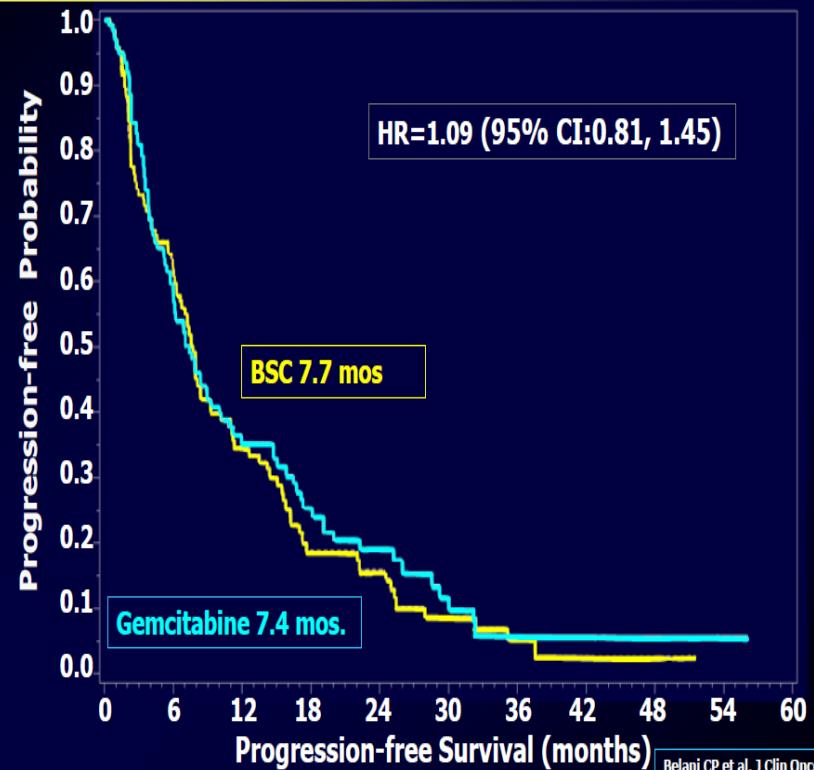
# Patient Selection

## Gemcitabine Maintenance Therapy – PS 2

Overall Survival  
(Intent-to-treat Population)



Progression-free Survival  
(Intent-to-treat Population)



# Patient Selection Tumor Histology

## JMEN Trial: Overall Survival by Histology

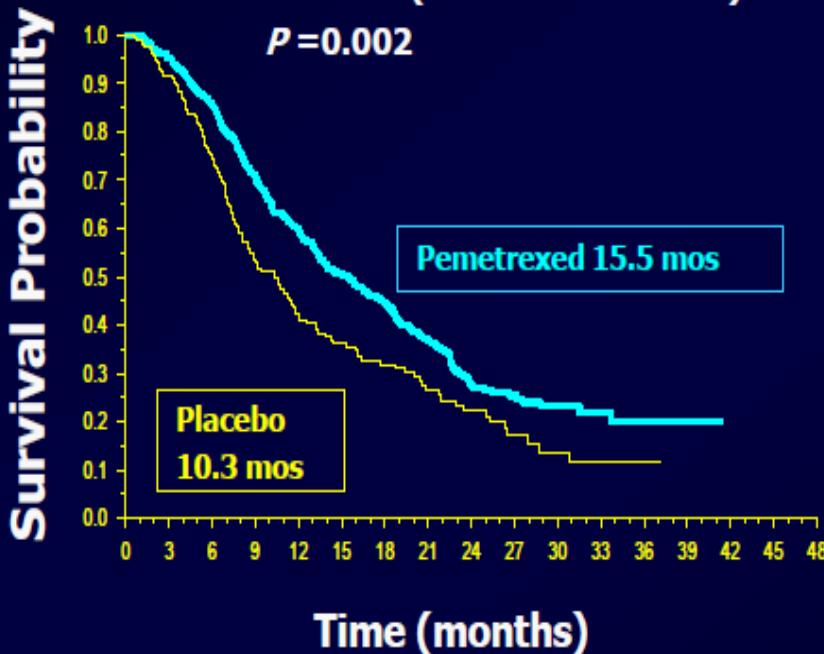
### Non-squamous (n=481)

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

P=0.002

Placebo  
10.3 mos

Pemetrexed 15.5 mos



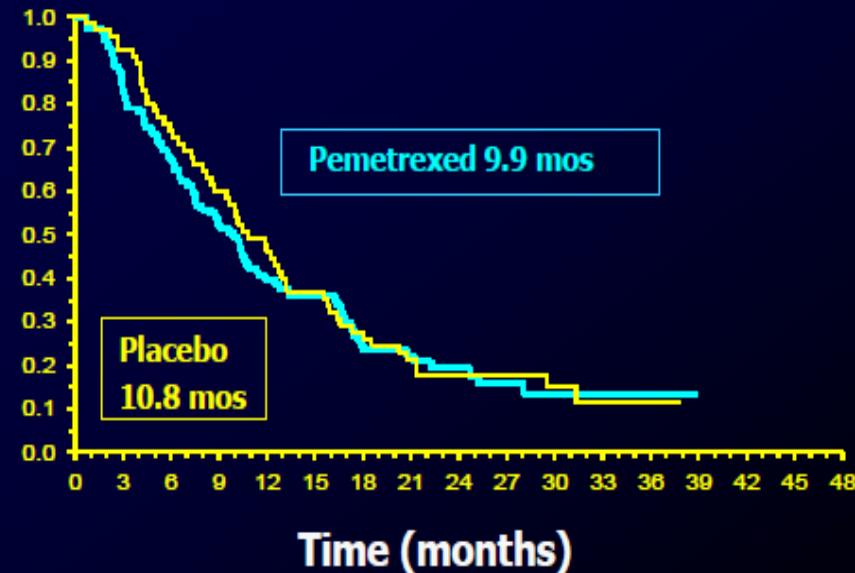
### Squamous (n=182)

HR=1.07 (95% CI: 0.49–1.73)

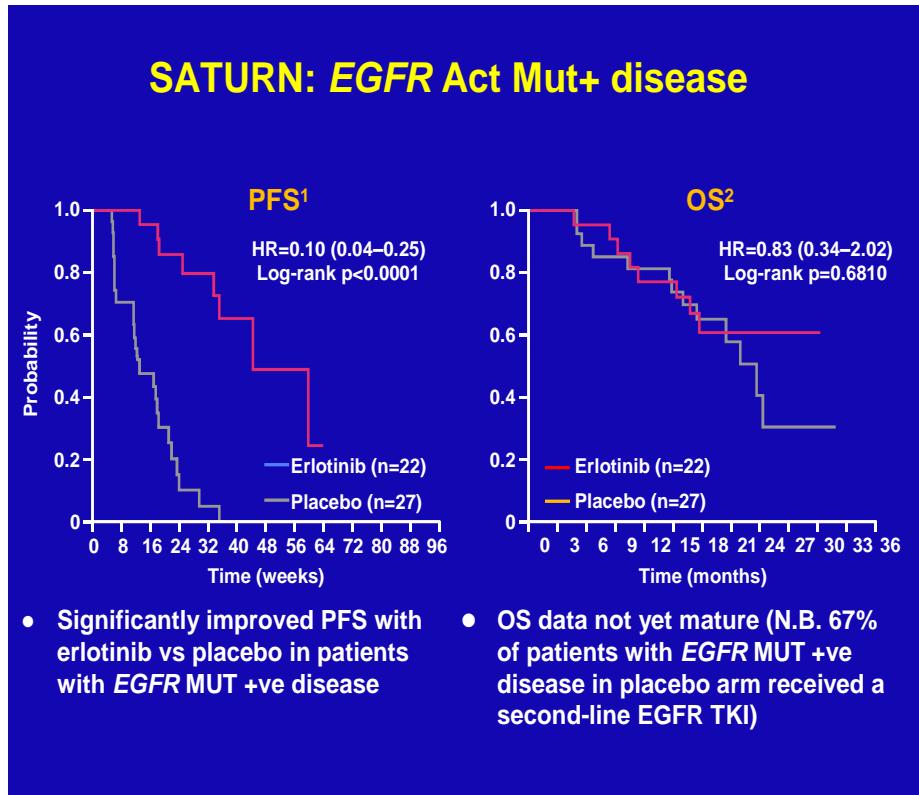
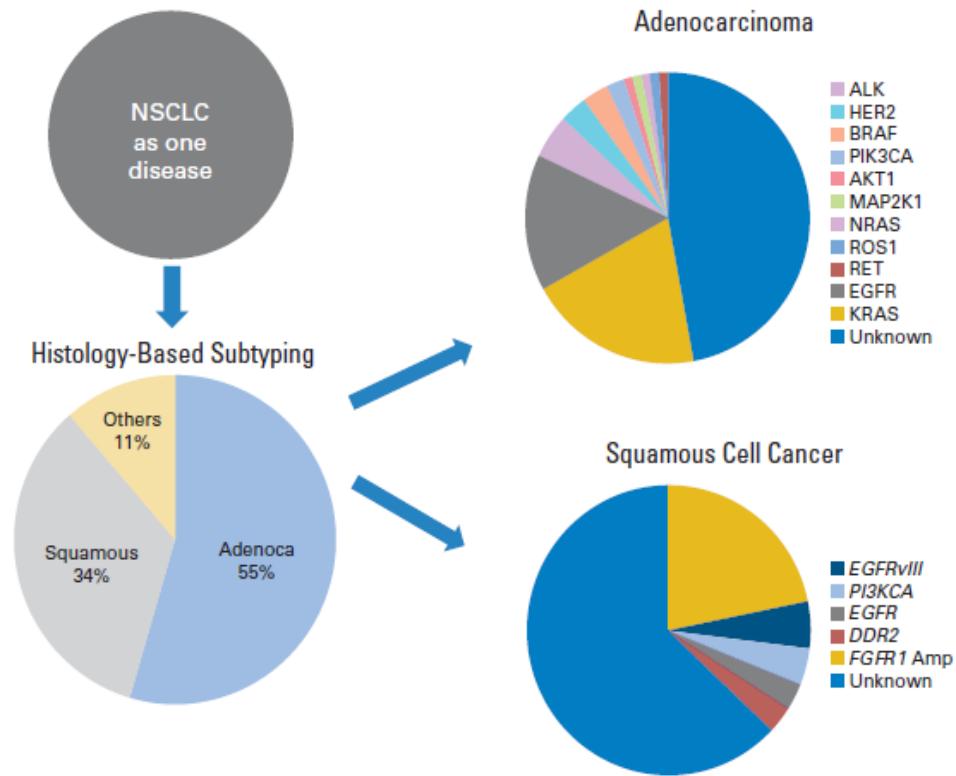
P=0.678

Placebo  
10.8 mos

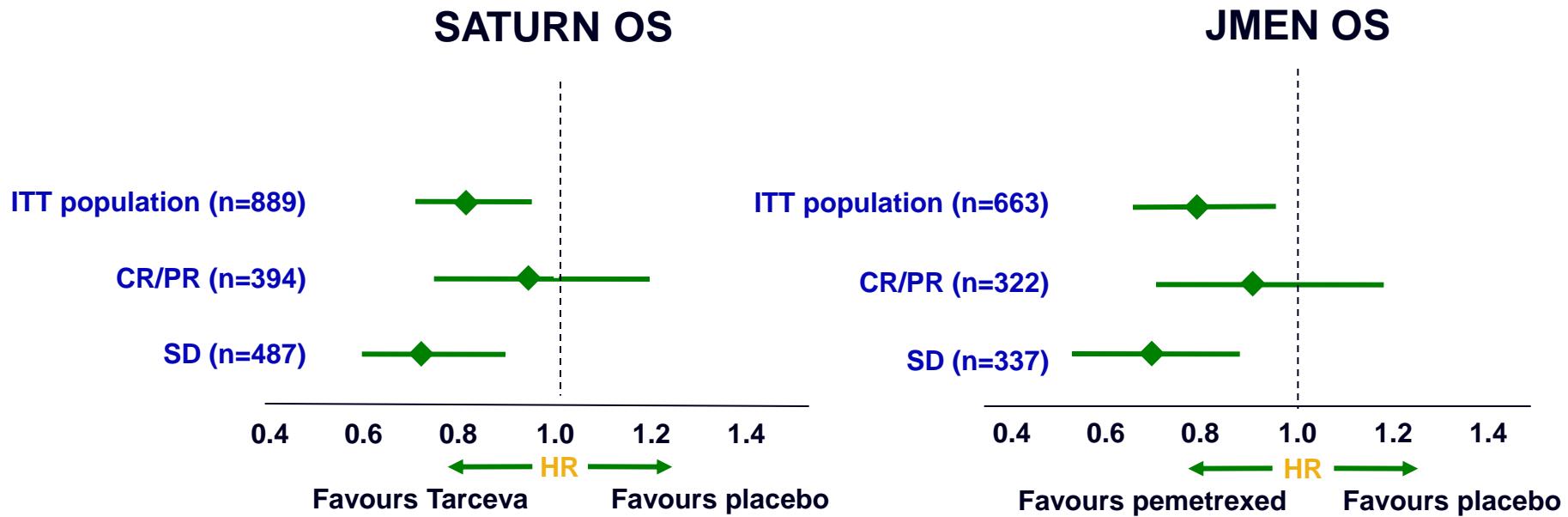
Pemetrexed 9.9 mos



# Patients Selection Tumor Genotype

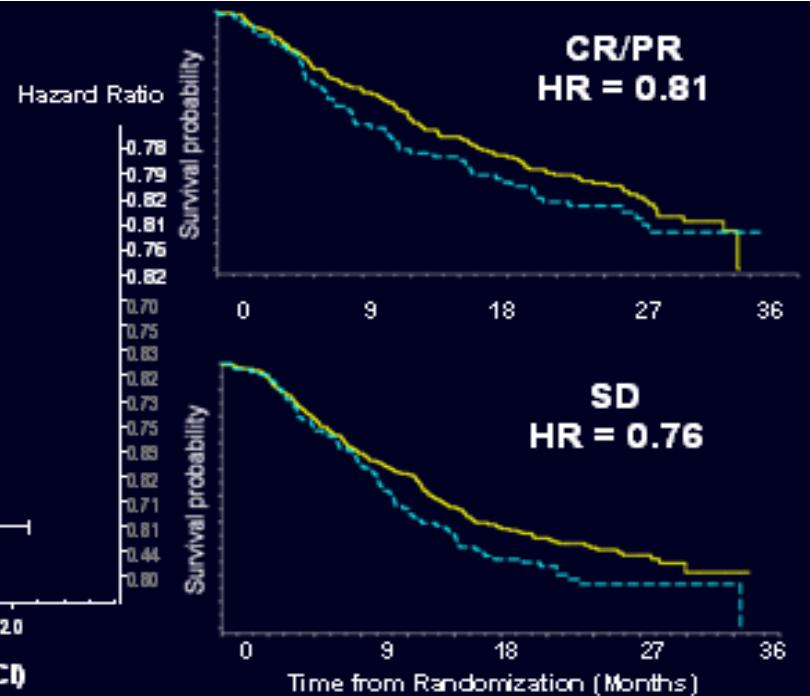
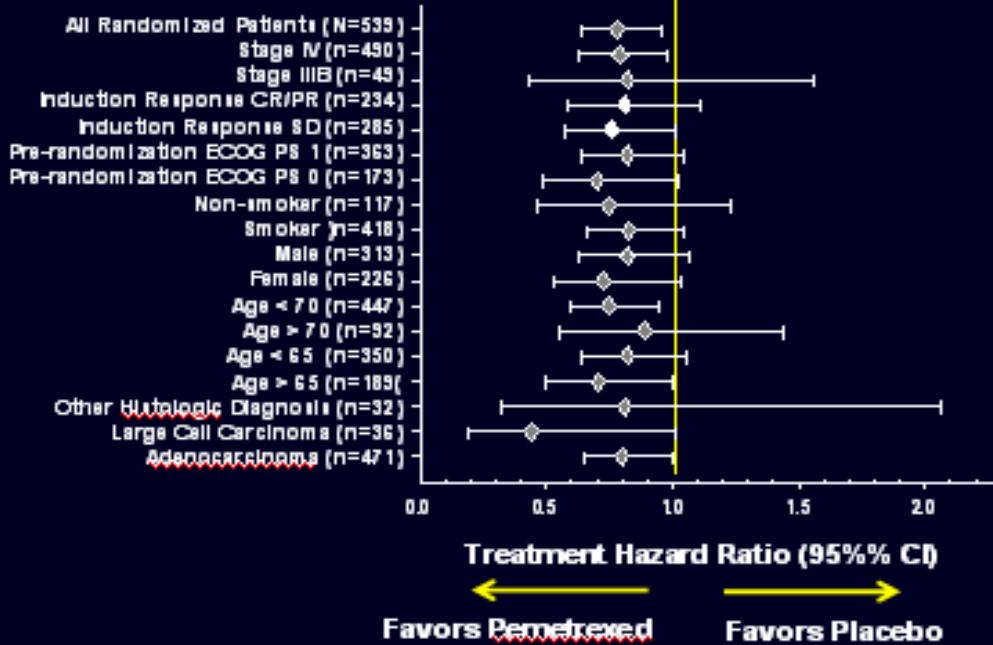


# Patient Selection Response to Induction Treatment



# Patient Selection Response to Induction Treatment

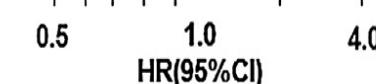
## Paramount Trial



# Maintenance Meta-analysis

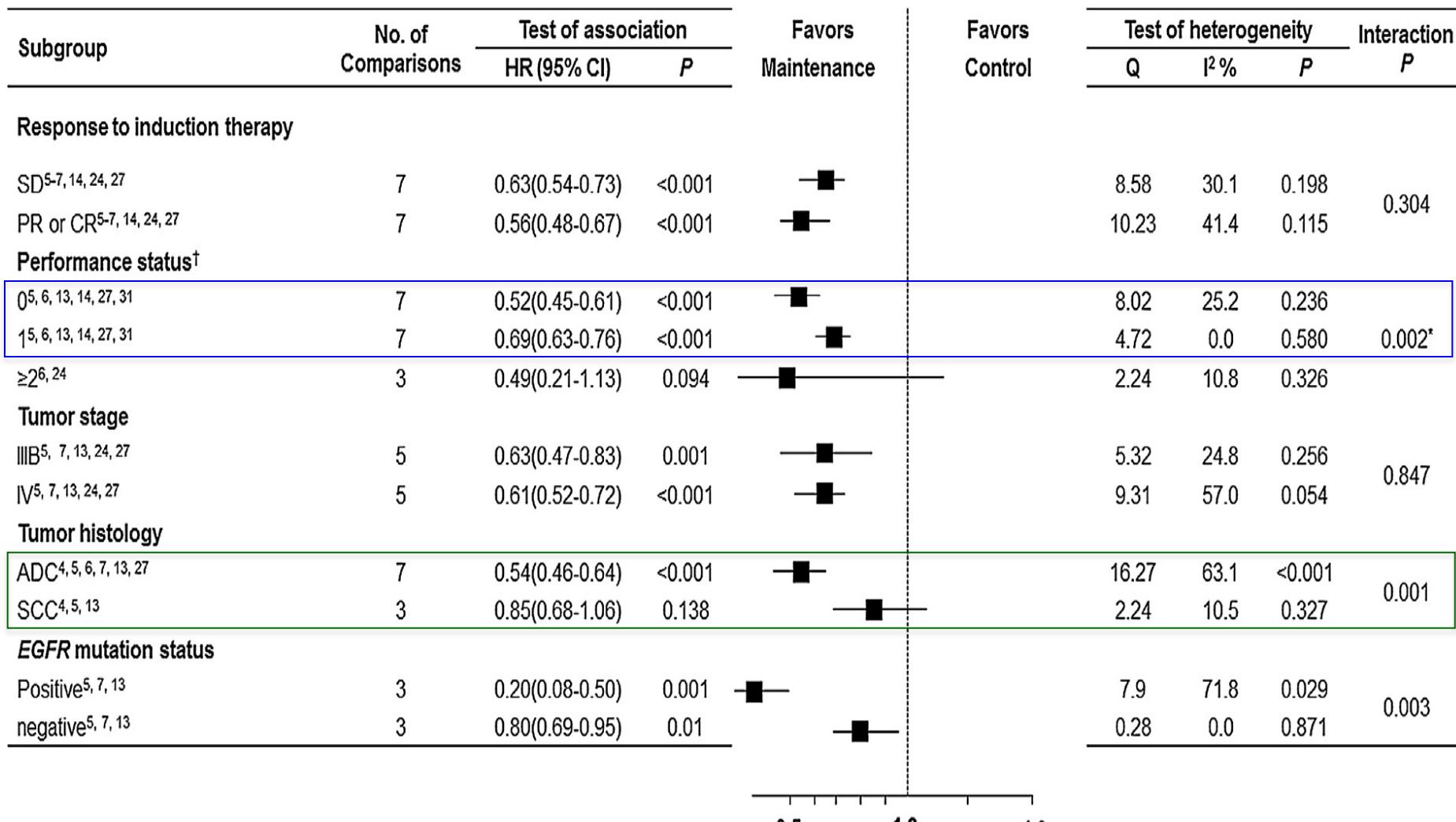
## PFS by Subgroups

Subgroup	No. of Comparisons	Test of association		Favors Maintenance	Favors Control	Test of heterogeneity		Interaction P
		HR (95% CI)	P			Q	I <sup>2</sup> %	
<b>Response to induction therapy</b>								
SD <sup>5, 14, 24, 27</sup>	7	0.63(0.54-0.73)	<0.001	■		8.58	30.1	0.198
PR or CR <sup>5, 14, 24, 27</sup>	7	0.56(0.48-0.67)	<0.001	■		10.23	41.4	0.115
<b>Performance status<sup>†</sup></b>								
0 <sup>5, 6, 13, 14, 27, 31</sup>	7	0.52(0.45-0.61)	<0.001	■		8.02	25.2	0.236
1 <sup>5, 6, 13, 14, 27, 31</sup>	7	0.69(0.63-0.76)	<0.001	■		4.72	0.0	0.580
≥2 <sup>6, 24</sup>	3	0.49(0.21-1.13)	0.094	■		2.24	10.8	0.326
<b>Tumor stage</b>								
IIIB <sup>5, 7, 13, 24, 27</sup>	5	0.63(0.47-0.83)	0.001	■		5.32	24.8	0.256
IV <sup>5, 7, 13, 24, 27</sup>	5	0.61(0.52-0.72)	<0.001	■		9.31	57.0	0.054
<b>Tumor histology</b>								
ADC <sup>4, 5, 6, 7, 13, 27</sup>	7	0.54(0.46-0.64)	<0.001	■		16.27	63.1	<0.001
SCC <sup>4, 5, 13</sup>	3	0.85(0.68-1.06)	0.138	■		2.24	10.5	0.327
<b>EGFR mutation status</b>								
Positive <sup>5, 7, 13</sup>	3	0.20(0.08-0.50)	0.001	■		7.9	71.8	0.029
negative <sup>5, 7, 13</sup>	3	0.80(0.69-0.95)	0.01	■		0.28	0.0	0.871



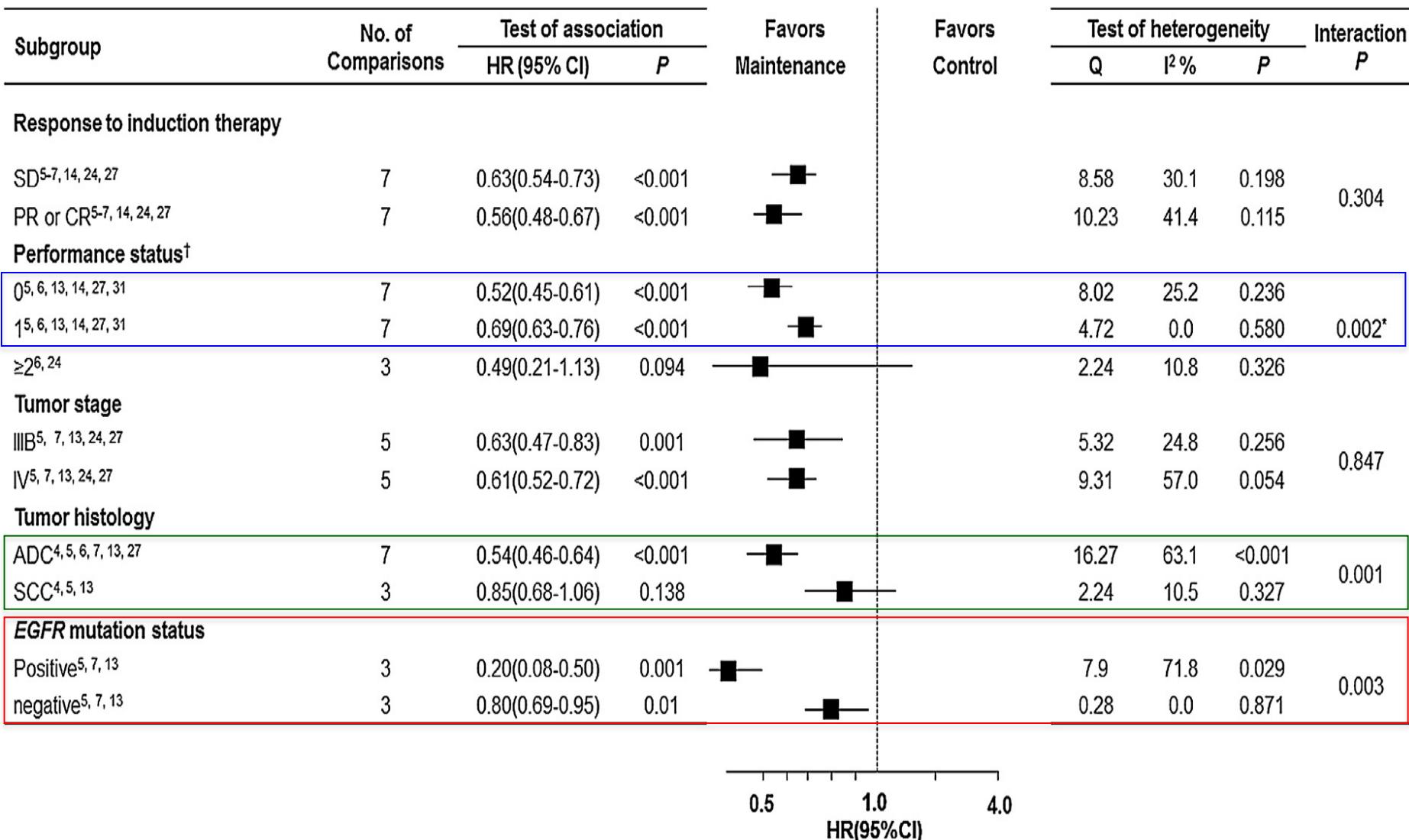
# Maintenance Meta-analysis

## PFS by Subgroups



# Maintenance Meta-analysis

## PFS by Subgroups

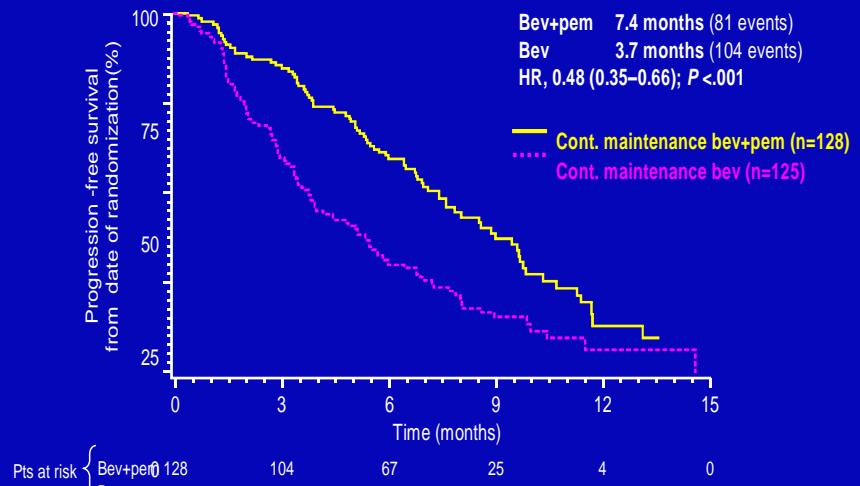


# Outline

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# Recent Developments Bevacizumab + Pemetrexed

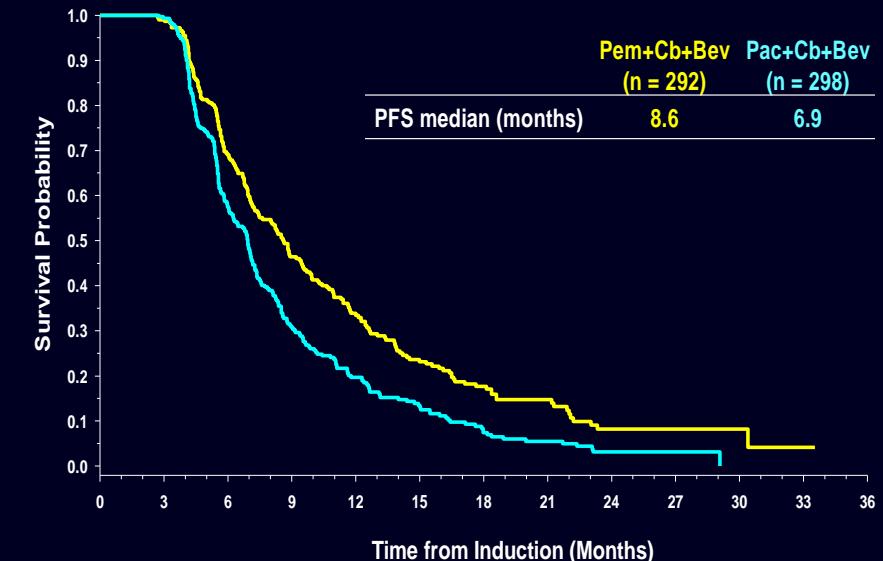
## AVAPERL: PFS From Randomization<sup>a</sup>



<sup>a</sup> 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

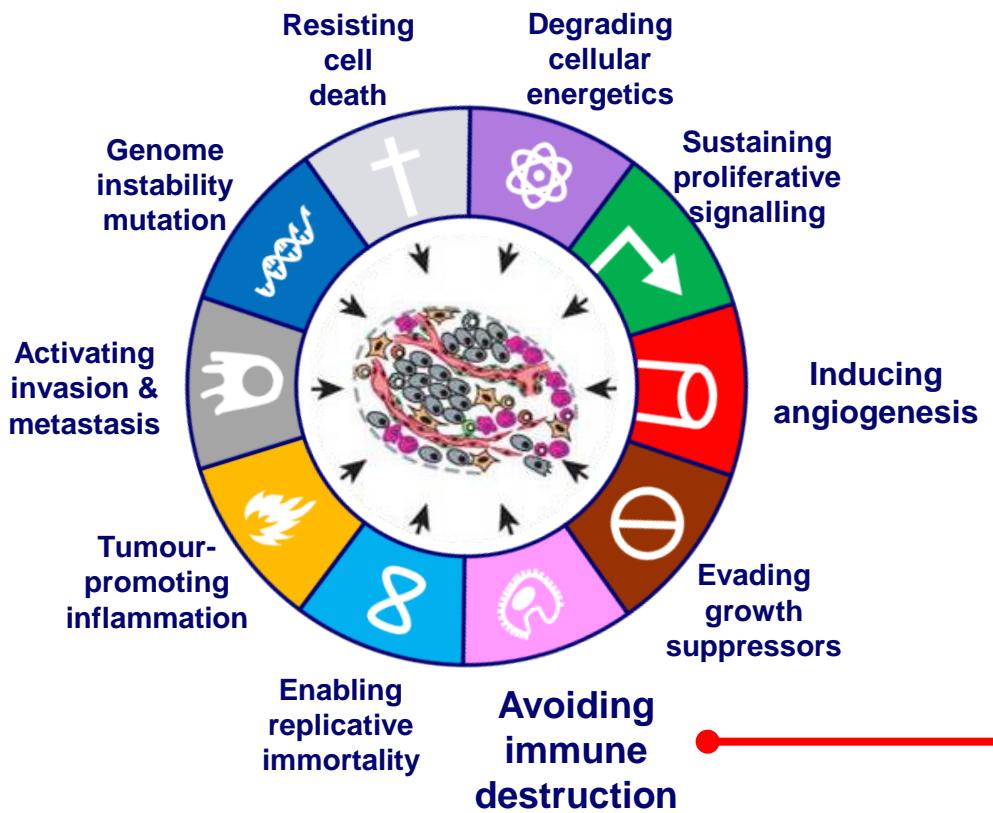
## PointBreak: Prespecified Analysis of KM PFS from Randomization (Maintenance Population)



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

Barlesi F et al., ESMO 2011; Patel J et al., IASLC 2011

# Therapeutic Intervention at Cancer Hallmarks

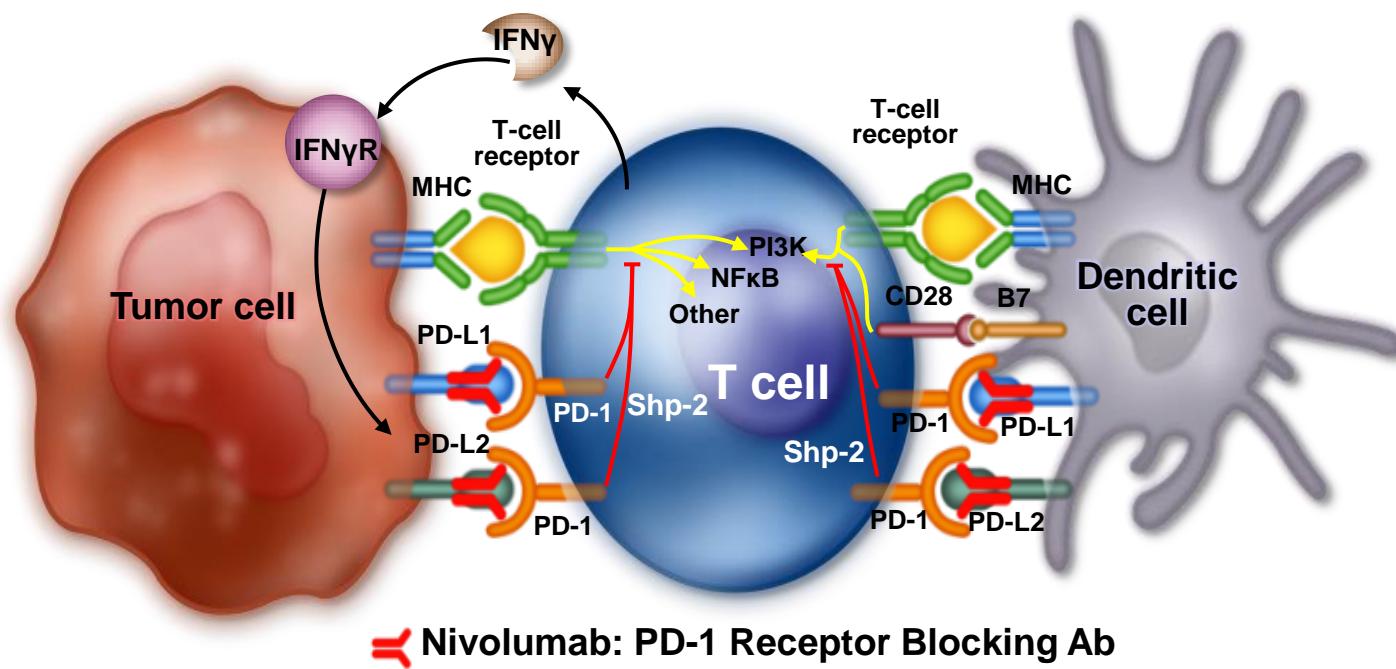


Vaccines

Immunomodulators

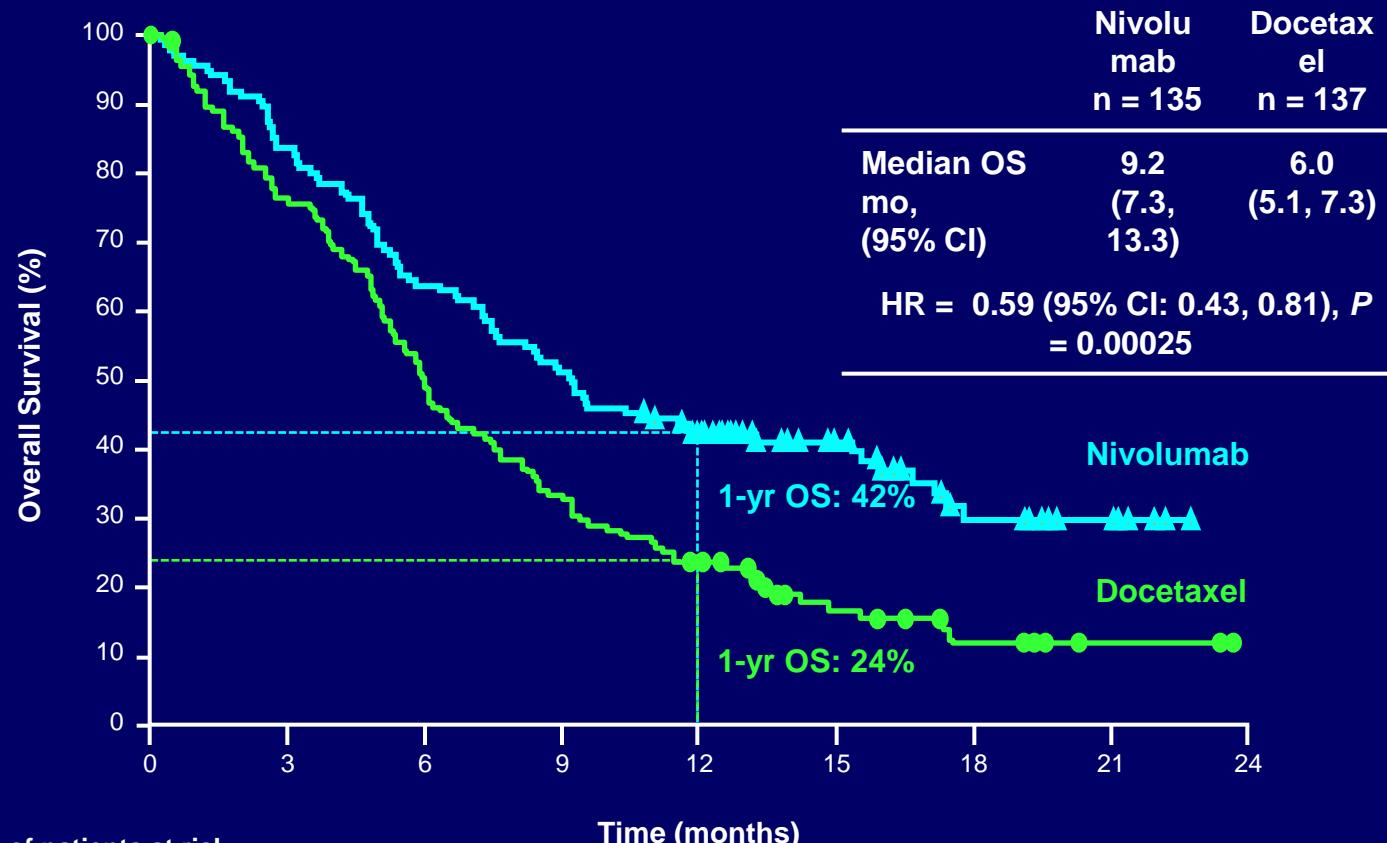
# PD-1/PD-L1 Inhibitors: Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function<sup>10</sup>
- Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function<sup>11–13</sup>



# CheckMate 017 Trial in SCC-NSCLC

## Nivolumab v Docetaxel

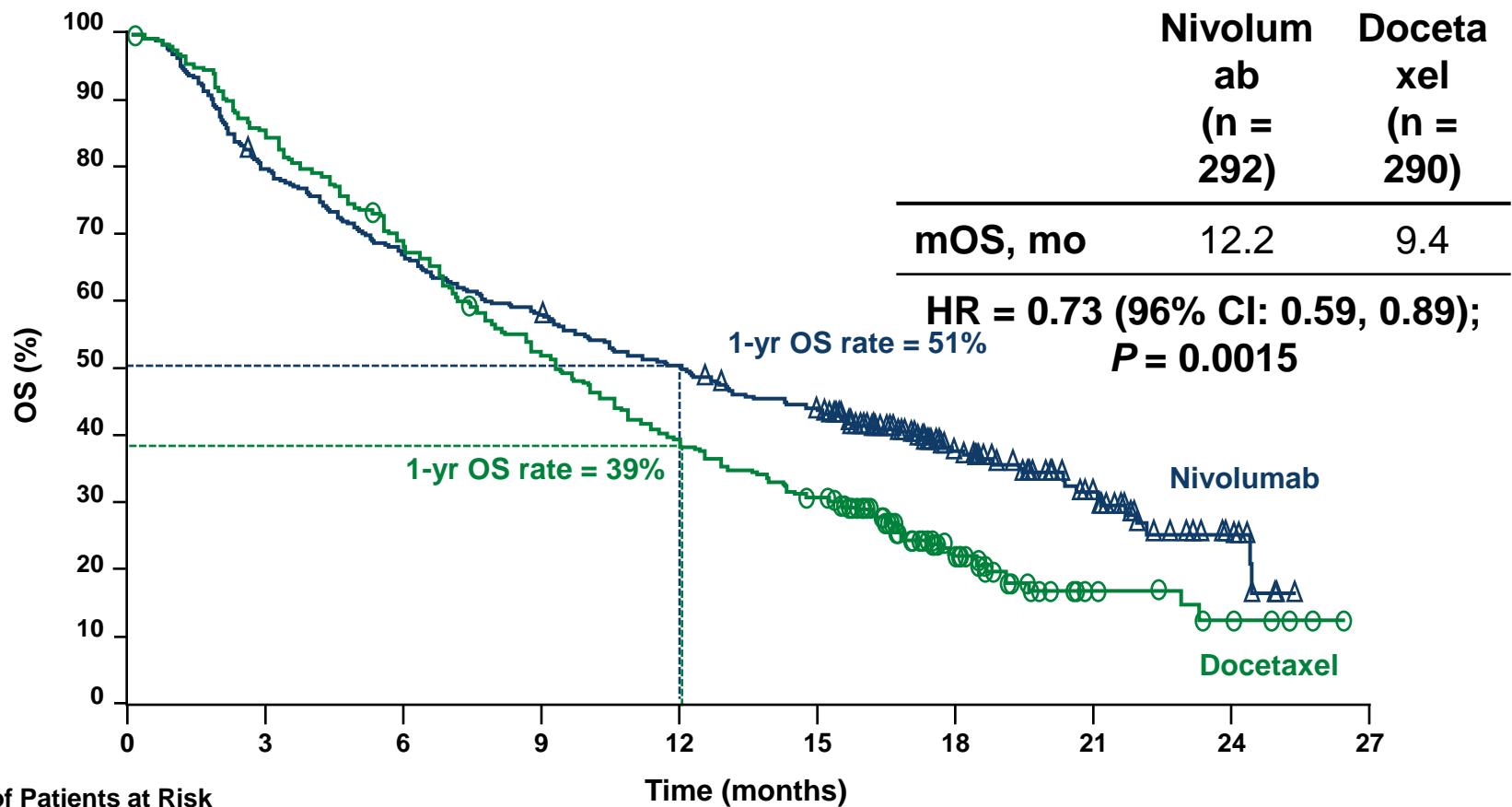


Number of patients at risk

	135	113	86	69	52	31	15	7	0
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Minimum follow-up of approximately 10.6 months

# CheckMate 057 Trial in Non SCC-NSCLC Nivolumab v Docetaxel



Symbols represent censored observations.

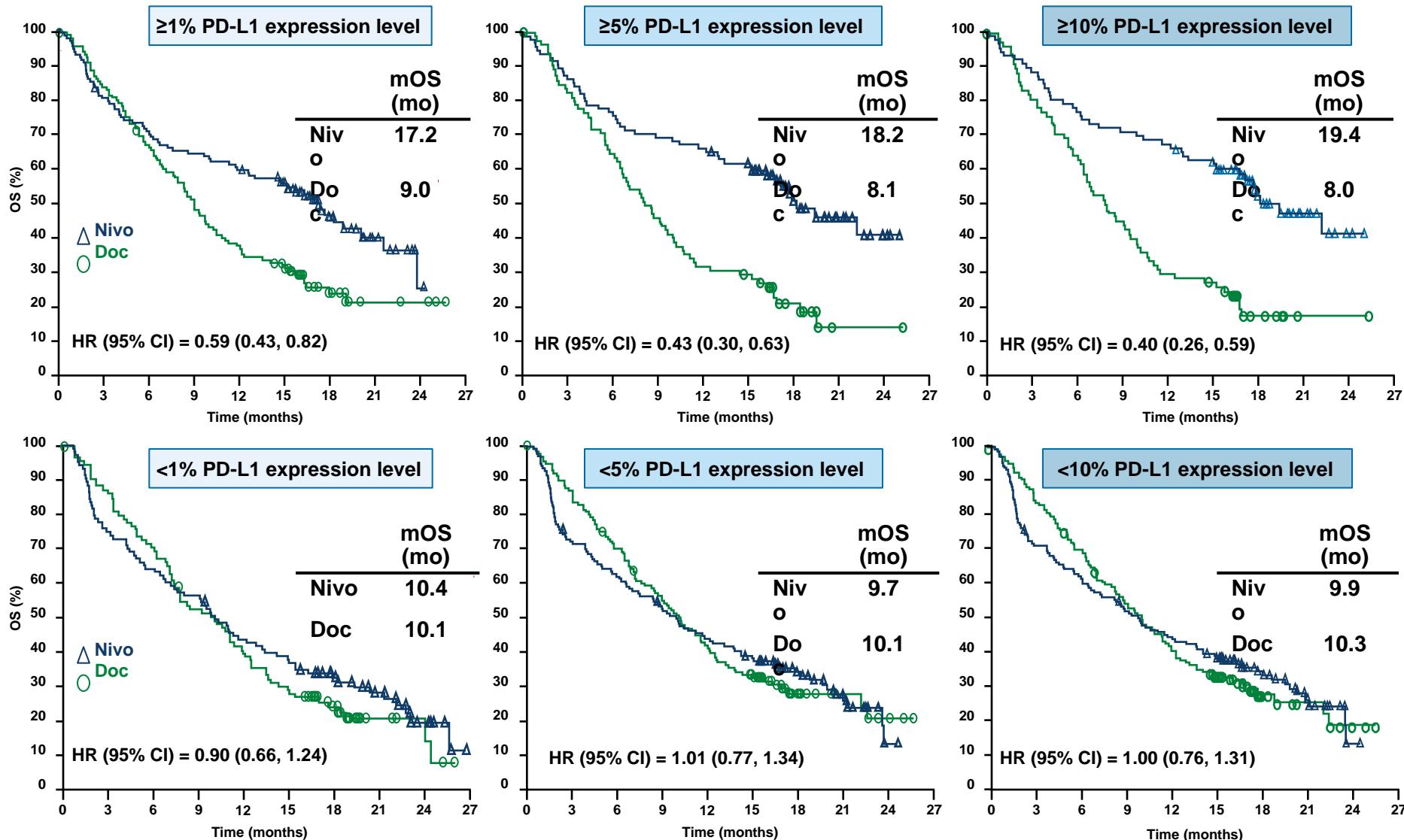
SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

Paz-Ares et al., ASCO 2015

PRESENTED AT:

ASCO Annual '15 Meeting

# CheckMate 057 Trial in Non SCC-NSCLC OS by PD-L1 Expression



Symbols represent censored observations.

# 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 candidate patients
- Further studies are warranted, in particular those evaluating tumor tailored strategies optimizing patient selection and treatment specificity