UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

Treatment Choices of Advanced NSCLC Patients without Driver Mutations

Maintenance

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UNIVERSITÀ DEGLI STUDI DI TORINO

Why Maintenance?

- Goal :
  - To extend progression-free and overall survival of patients with advanced NSCLC already treated with induction chemotherapy
  - To extend symptom-free survival of advanced NSCLC patients
- Therapeutic Action
  - Continuous administration of single agents/combos of cytotoxic agents and/or targeted agents
- Which target population?
  - Those with CR, PR or SD following induction and minimal cumulative toxicity

Maintenance Therapy: Strategies

- Continuation of a doublet beyond 4 cycles
- Initiating a new agent ("switch")
  - *Carboplatin and paclitaxel followed by pemetrexed*
  - *Carboplatin and gemcitabine followed by docetaxel*
  - *Platinum-based doublets followed by erlotinib*
- Continuation of a targeted agent
  - *Carboplatin, paclitaxel and bevacizumab followed by bevacizumab*
- Continuing one (or two) of the same agents from the original combination
  - *Cisplatin and pemetrexed followed by pemetrexed as maintenance or carboplatin and gemcitabine followed by gemcitabine*

Early Studies of Maintenance Therapy in Advanced NSCLC

Study	Ph.	Induction Treatment Regimen	Length of Induction	Maintenance Agent Under Investigation	Endpoint: Improved OS	Endpoint: Improved PFS
Smith et al 2001[1]	III	MVP (mitomycin + vinblastine + cisplatin)	3 cycles	3 more cycles	No	No
Socinski et al 2002[2]	III	Carboplatin + paclitaxel	4 cycles	Continuous treatment	No	No
Belani et al 2003[3]	II	Carboplatin + paclitaxel	2-4 cycles	Paclitaxel	No	No
Westeel et al 2005[4]	III	MIC (mitomycin + ifosfamide + cisplatin	2-4 cycles	Vinorelbine	No	No
Brodowicz et al 2006[5]	III	Gemcitabine + cisplatin	4 cycles	Gemcitabine	No	TTP: Yes

All studies had Observation as comparator arm with the exclusion of the study of Brodowicz et al. in which BSC was the comparator

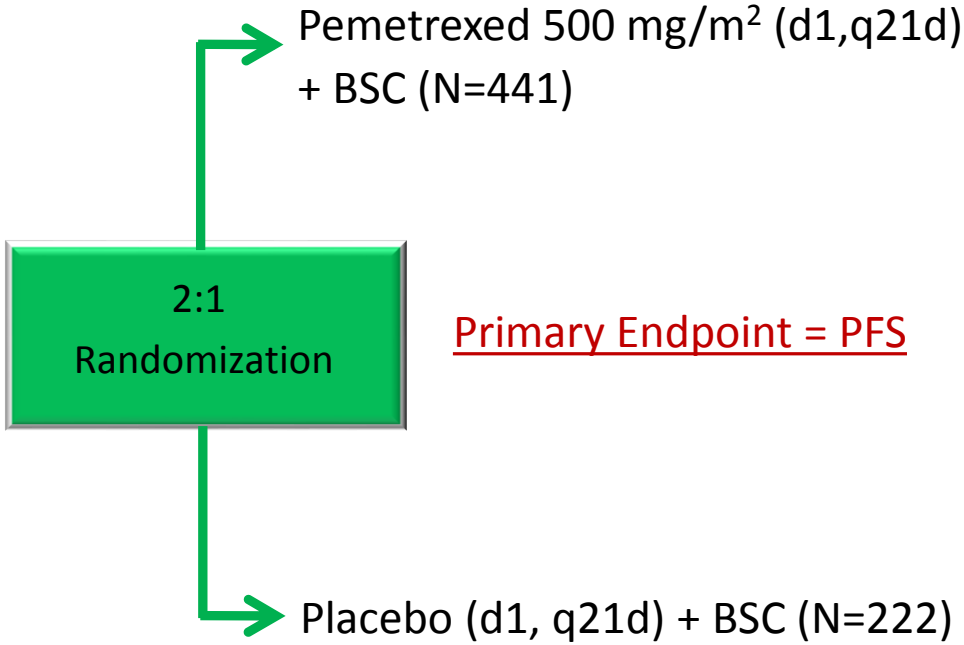
PFS: progression-free survival; OS: overall survival; TTP: time to progression; BSC: best supportive care

Smith IE, et al. *J Clin Oncol*. 2001;19:1336-1343. ; Socinski MA, et al. *J Clin Oncol*. 2002;20:1335-1343.
Belani CP, et al. *J Clin Oncol*. 2003;21:2933-2939; Westeel V, et al. *J Natl Cancer Inst*. 2005;97:499-506.
Brodowicz T, et al. *Lung Cancer*. 2006;52:155-163.

A Prototype of Switch Maintenance.....

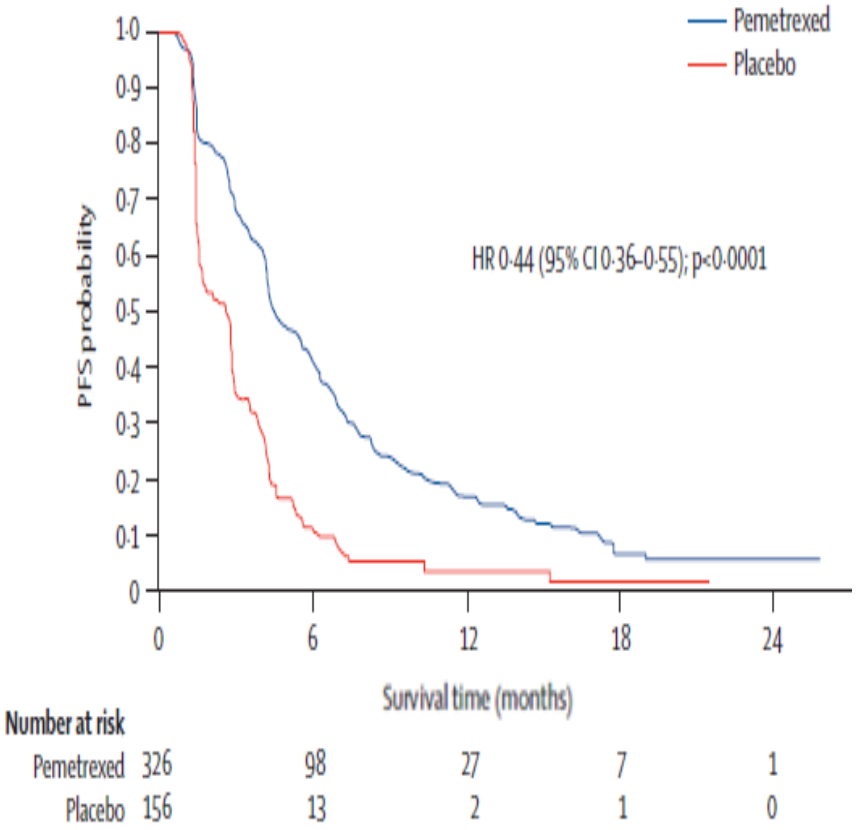
Maintenance Pemetrexed Versus Placebo in Advanced NSCLC

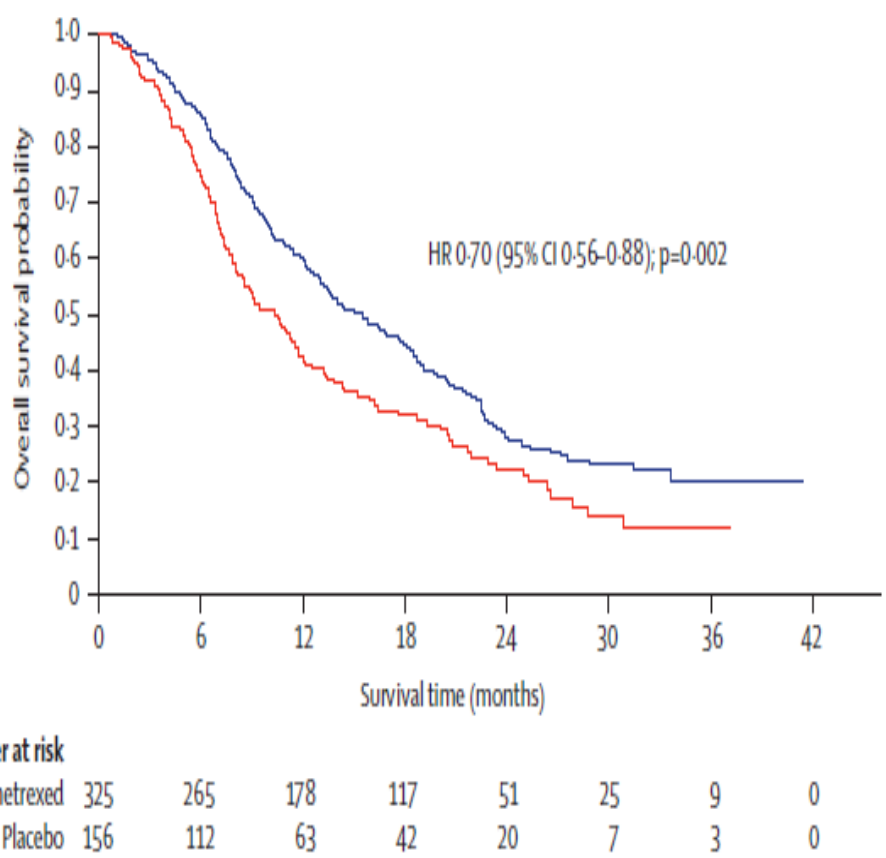
- Stage IIIB/IV NSCLC
- ECOG PS 0-1
- 4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD
- Randomization factors:
  - Gender
  - PS
  - Stage
  - Best tumor response
  - Non-platinum drug
  - Brain mets



Ciuleanu T et al. Lancet 374:1432-1440, 2009

Maintenance Pemetrexed: PFS & OS Non-squamous NSCLC



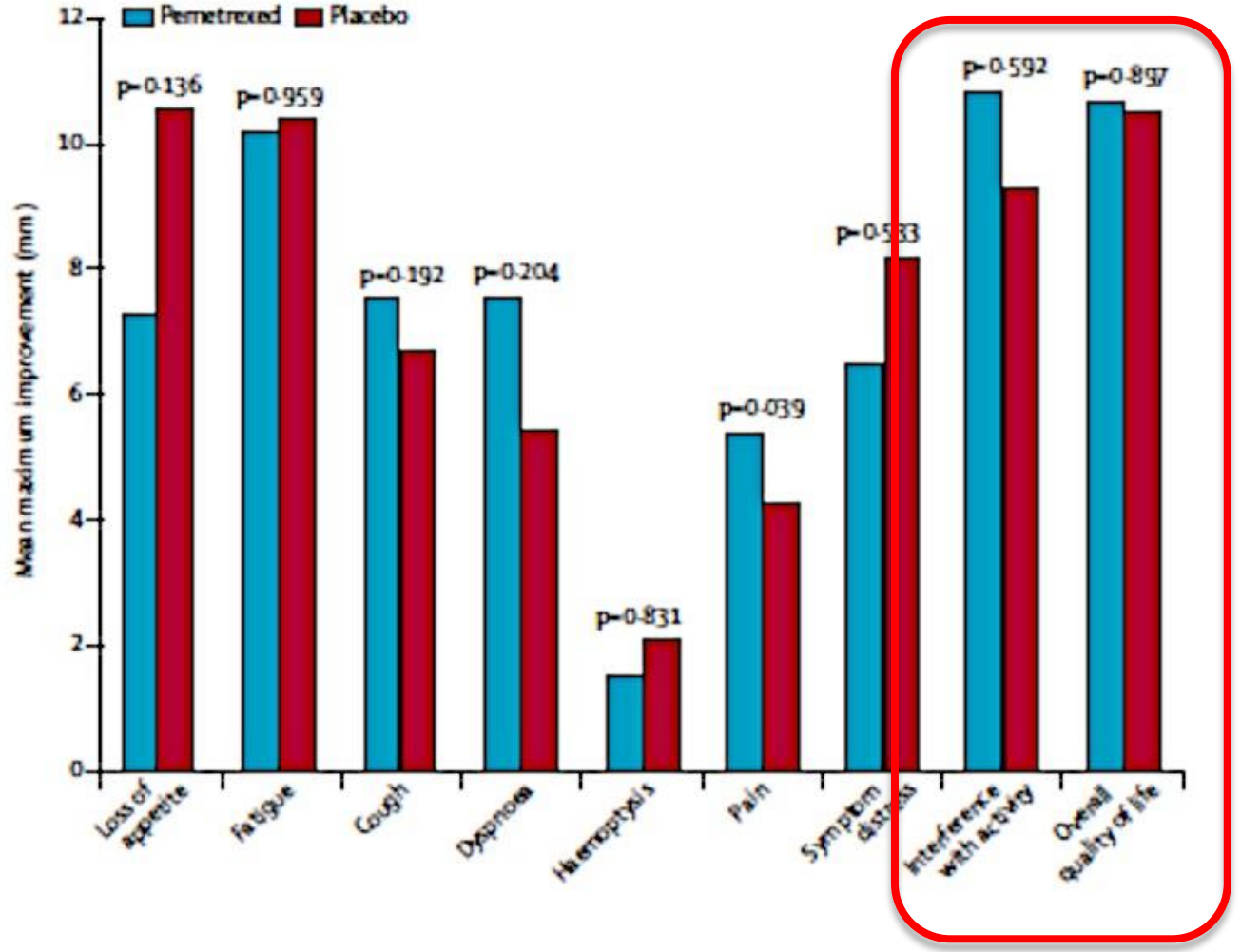


(Investigator assessed)

Ciuleanu et al Lancet 2009; 374(9699):1432-40.

QoL and Pemetrexed Maintenance

Mean Maximum Improvement in LCSS items



Belani CP et al. Lancet 2012; 13;292-99

Immediate *versus* Delayed 2nd-Line Docetaxel in Advanced NSCLC

- Chemo-naïve
- Stage IIIB/IV NSCLC

↓

- Gemcitabine 1,000 mg/m^2 d1, 8
- Carboplatin (AUC=5), day 1, every 21 days
- 4 cycles

R

Immediate Docetaxel

75 mg/m^2 day 1, every 21 days until PD or maximum 6 cycles (N=153)

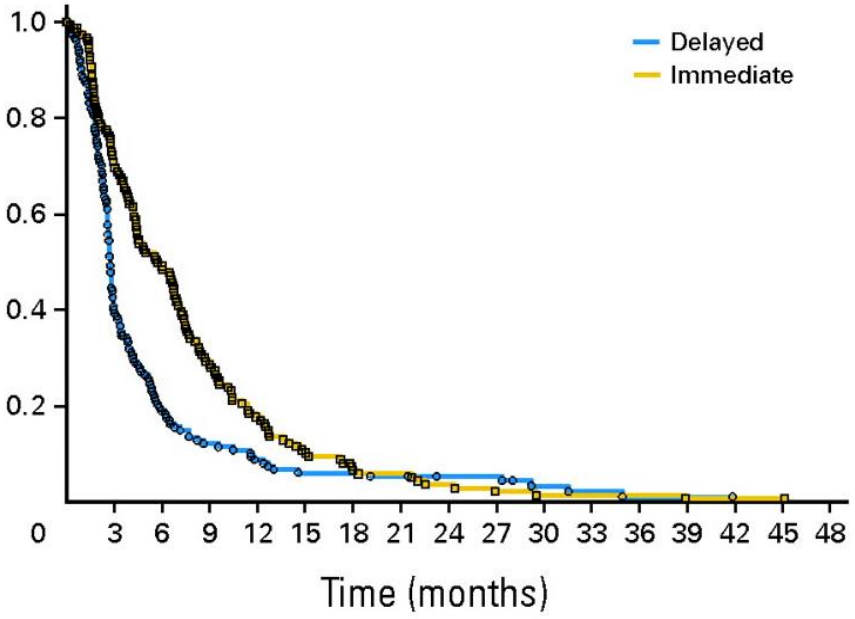
Delayed Docetaxel

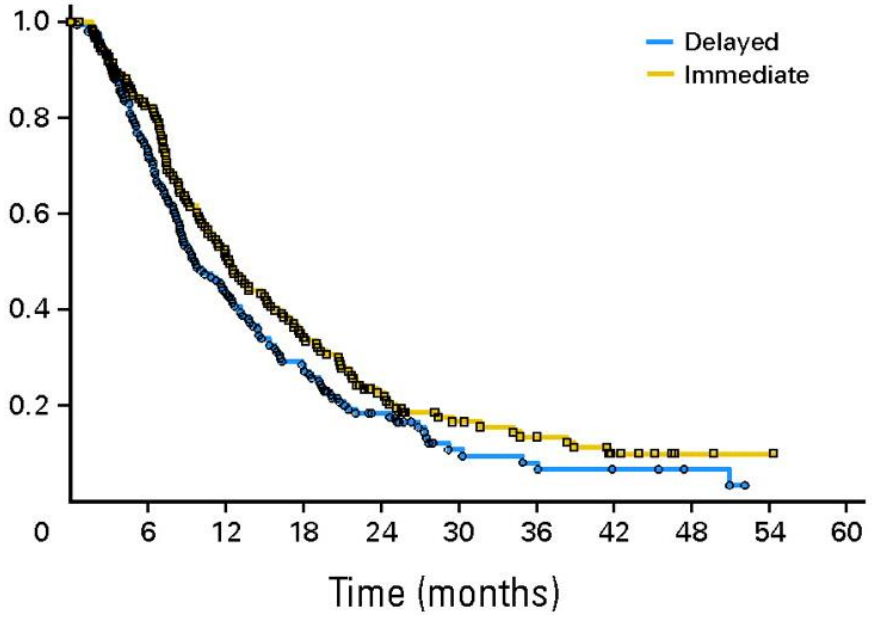
Best supportive care until PD, then 75 mg/m2 day 1, every 21 days until PD or maximum 6 cycles (N=154)

Primary endpoint: OS measured from date of randomization until death
Secondary endpoints: tumor response rate, PFS, toxicity, quality of life

Fidias P, et al. *J. Clin. Oncol.* 2009;27:591.

Immediate vs Delayed 2nd-Line Docetaxel in Advanced NSCLC: Results



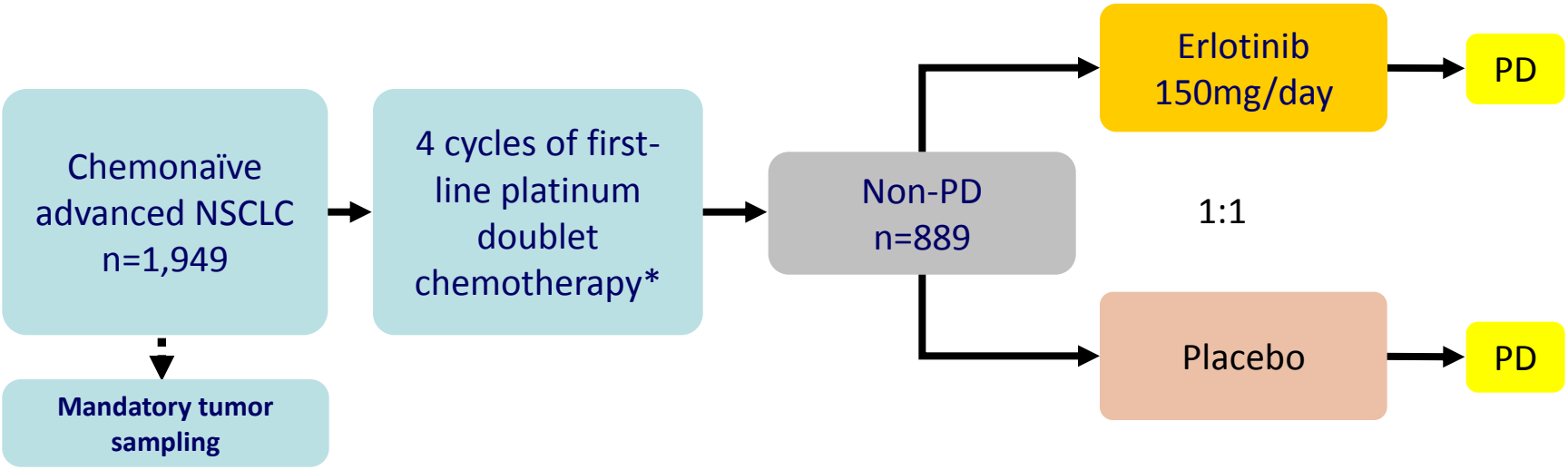


Results	Immediate Docetaxel	Delayed Docetaxel	*P*-Value
ORR, %	12% (36*)	11	NR
Median OS, mos; HR (95% CI)	12.3 (10.4-15.2)	9.7 (8.4-12.5)	.085
Median PFS, mos (95% CI)	5.7 (4.4-6.9)	2.7 (2.6-2.9)	0.0001

% of patients had a CR or PR from gemcitabine/carboplatin phase. PR=partial response.

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

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+ tumors

Secondary endpoints:

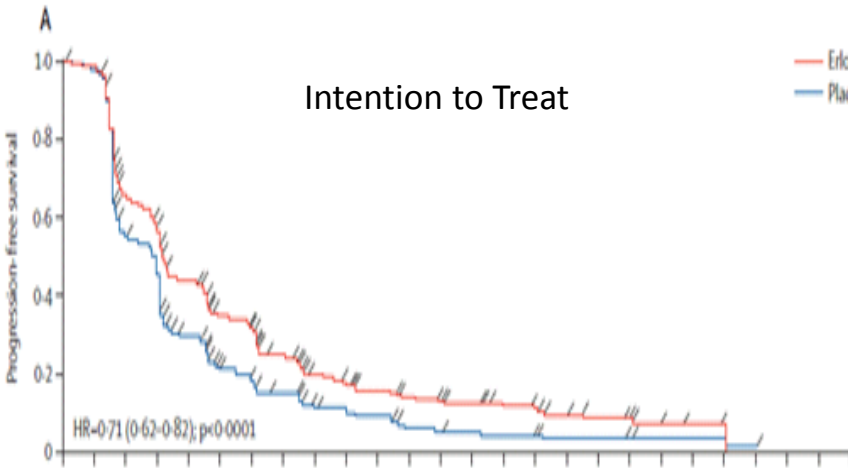
- OS in all patients and those with EGFR IHC+ tumors, OS and PFS in EGFR IHC– tumors; biomarker analyses; safety; time to symptom progression; QoL

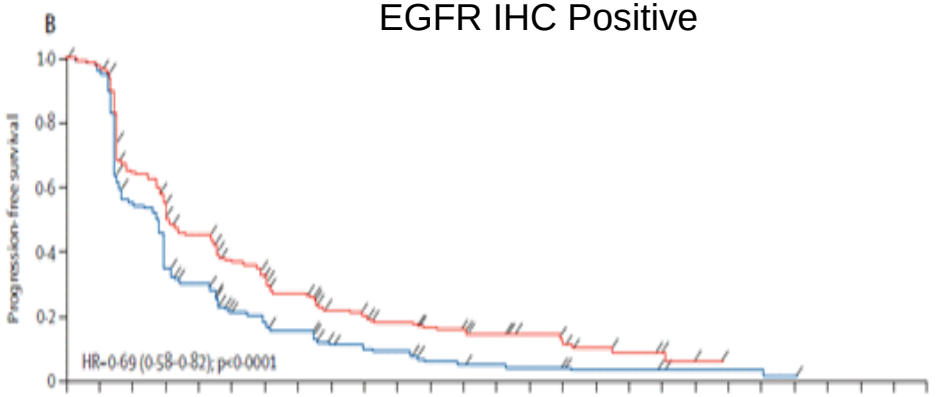
*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel carboplatin/paclitaxel

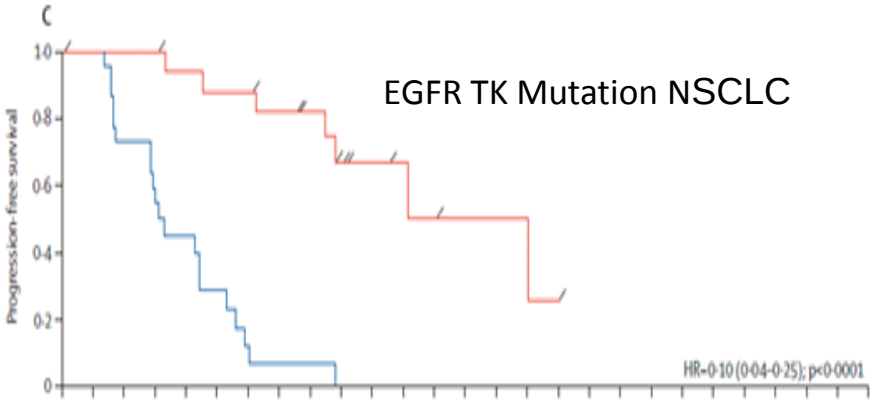
Cappuzzo F. WCLC 2009 (Abstract A2.1).

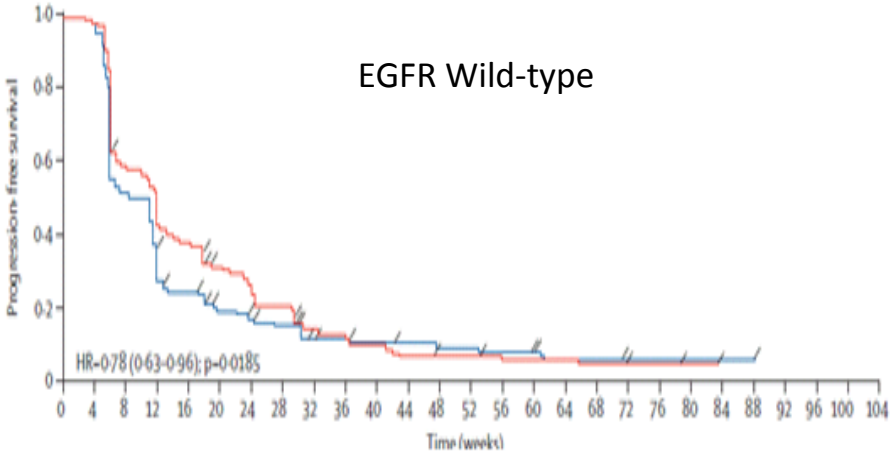
Maintenance Erlotinib

Progression Free Survival



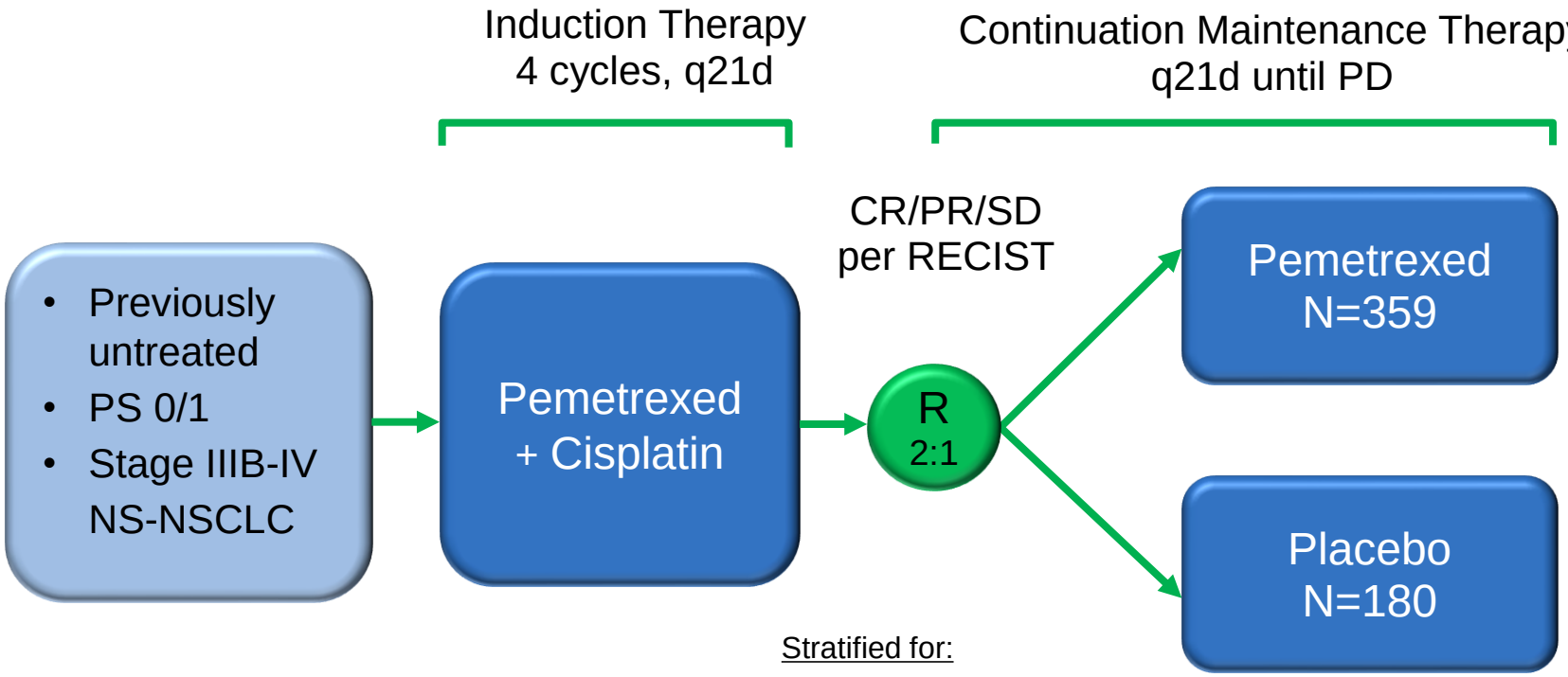






Cappuzzo et al. Lancet Oncol.2010; 11:521-29.

PARAMOUNT
Continuation Maintenance



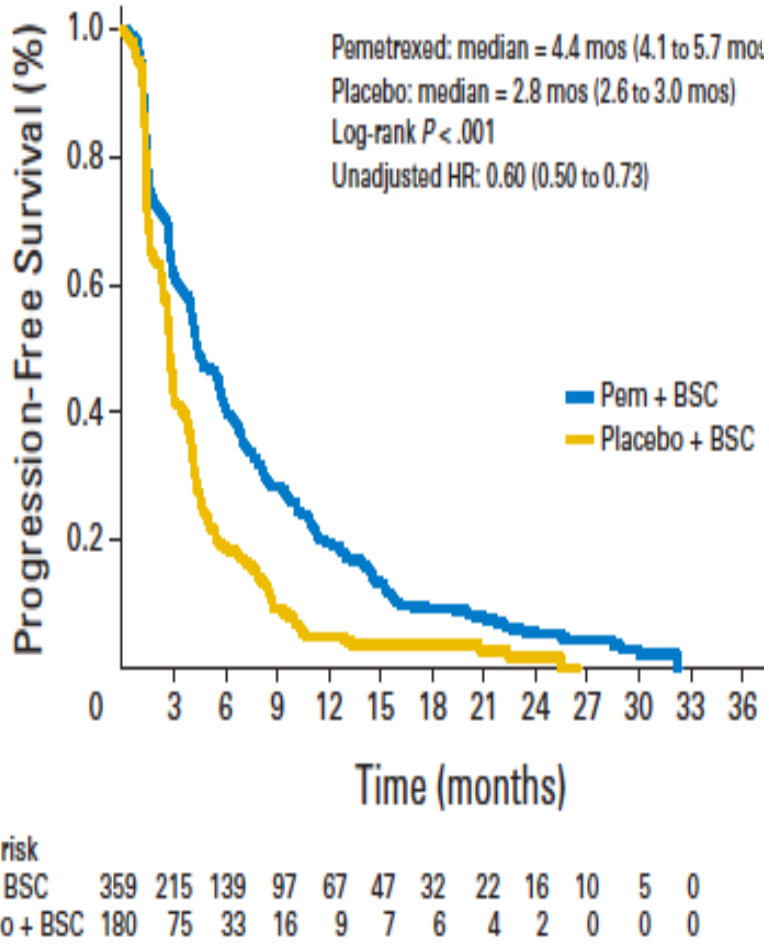
Primary Endpoint: PFS

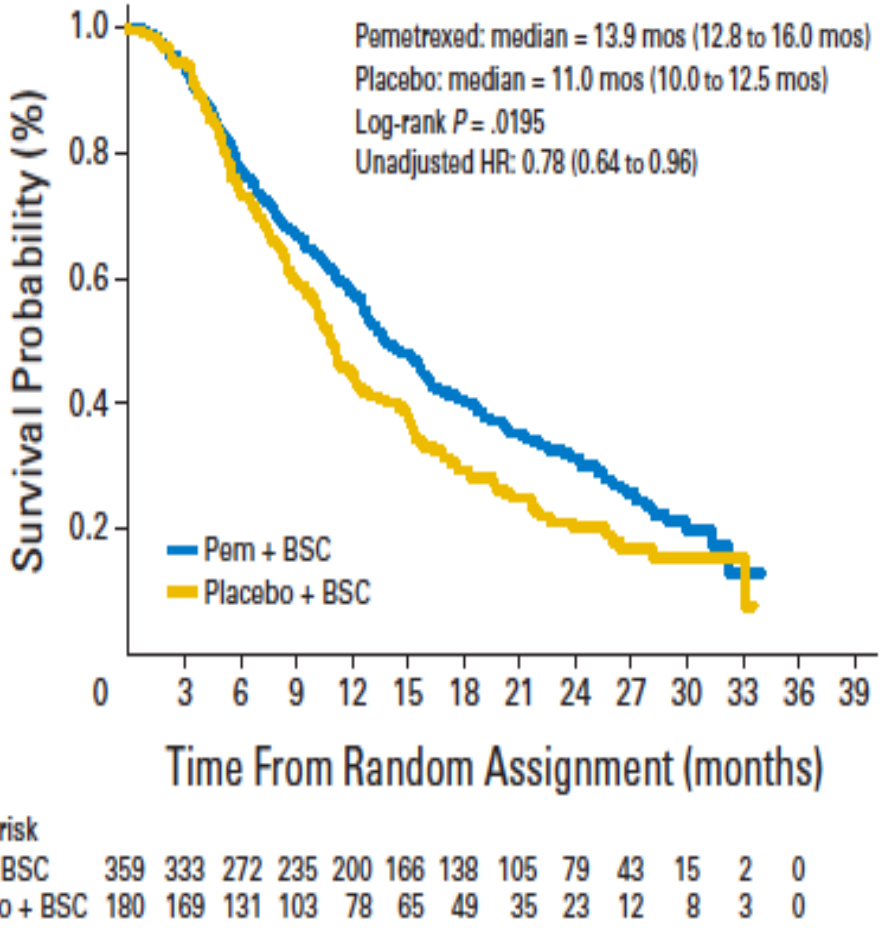
Stratified for:

- PS (0 vs. 1)
- Disease stage (IIIB vs. IV) prior to induction
- Response to induction (CR/PR vs. SD)

Paz-Ares LG et al. Lancet Oncol 13: 247-255,2012
Paz-Ares LG, et al J Clin Oncol 31, July 8,2013 [epub ahead of print]

PARAMOUNT: PFS & OS From Randomization





Paz-Ares LG et al. Lancet Oncol 13: 247-255,2012
Paz-Ares LG, et al J Clin Oncol 31, July 8,2013 [epub ahead of print]

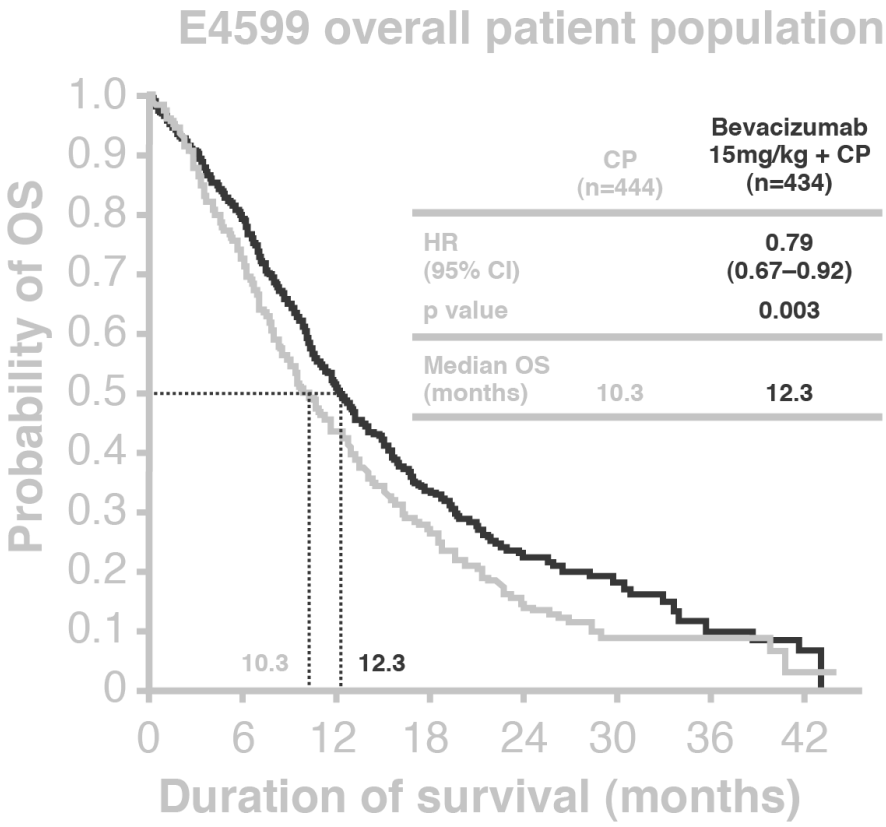
Induction: 4 *v* 6 courses
Paramount *v* JMDB

	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**

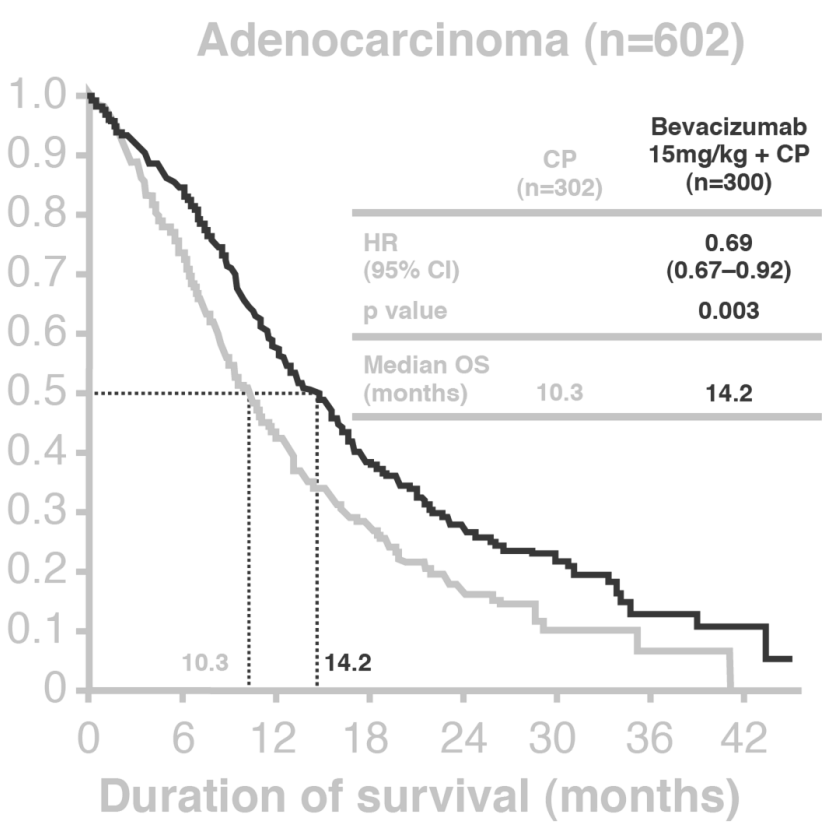
Scagliotti G. et al, abstr 203. WCLC 2011
Paz-Ares LG, et al. Lancet Oncol 2012

Targeting angiogenesis/VEGF can improve survival

E4599: 1st line paclitaxel/carboplatin +/- bevacizumab in nonsquamous

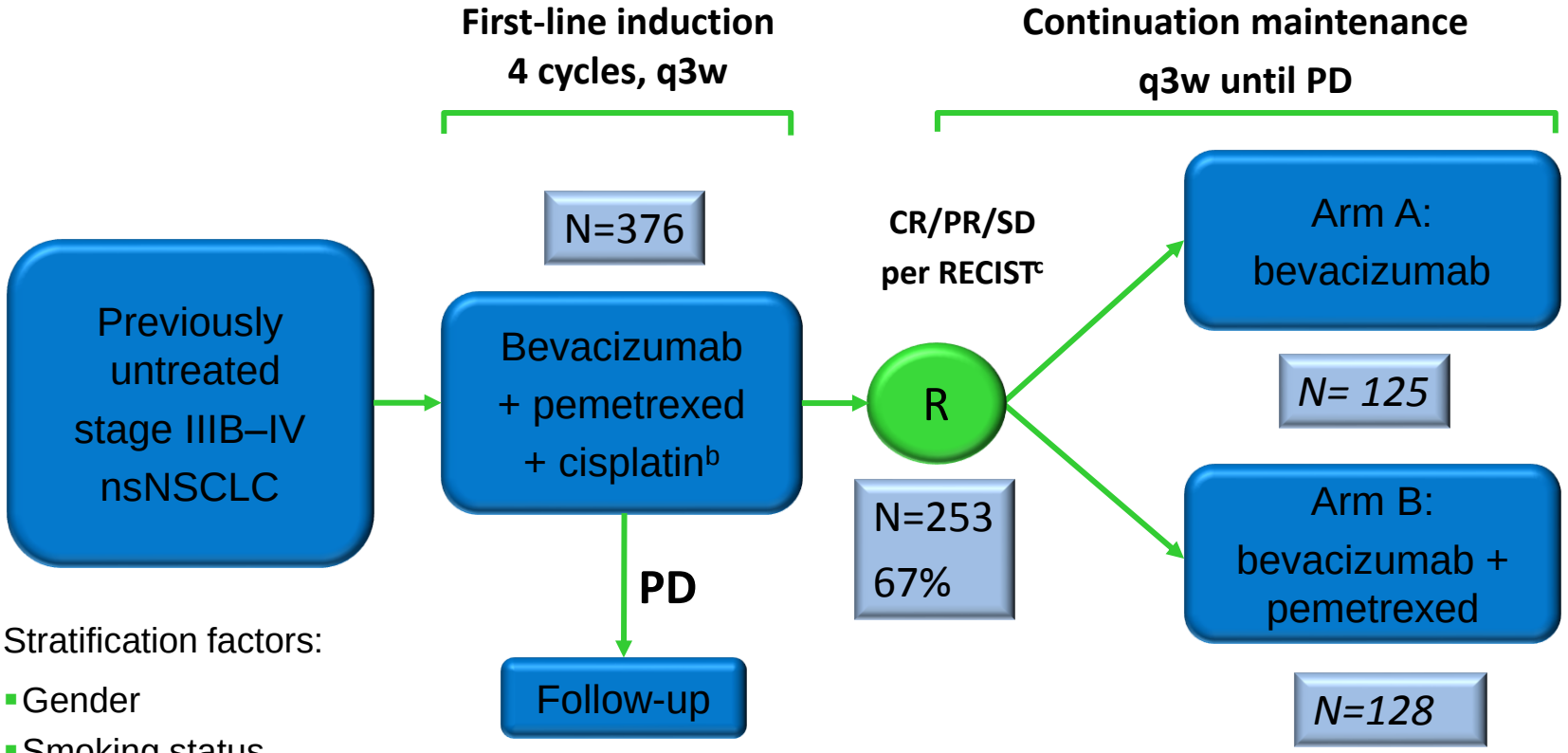


E4599: adenocarcinoma subset



Sandler, et al. N Engl J Med 2006; Sandler, et al. J Thorac Oncol 2010.

AVAPERL



Stratification factors:

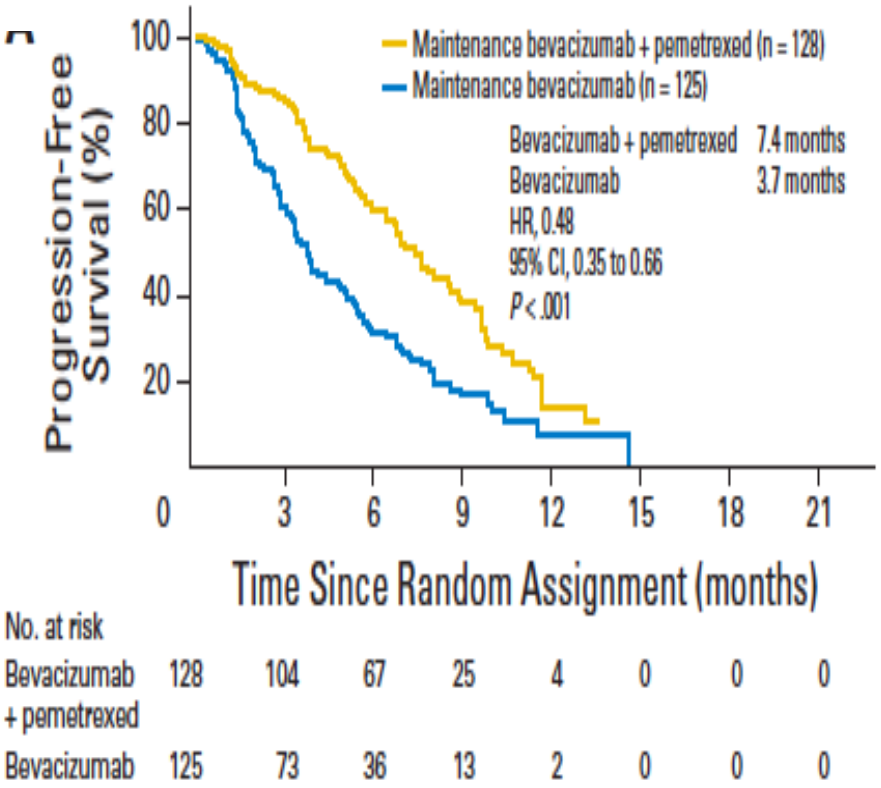
- Gender
- Smoking status
- Response at randomization

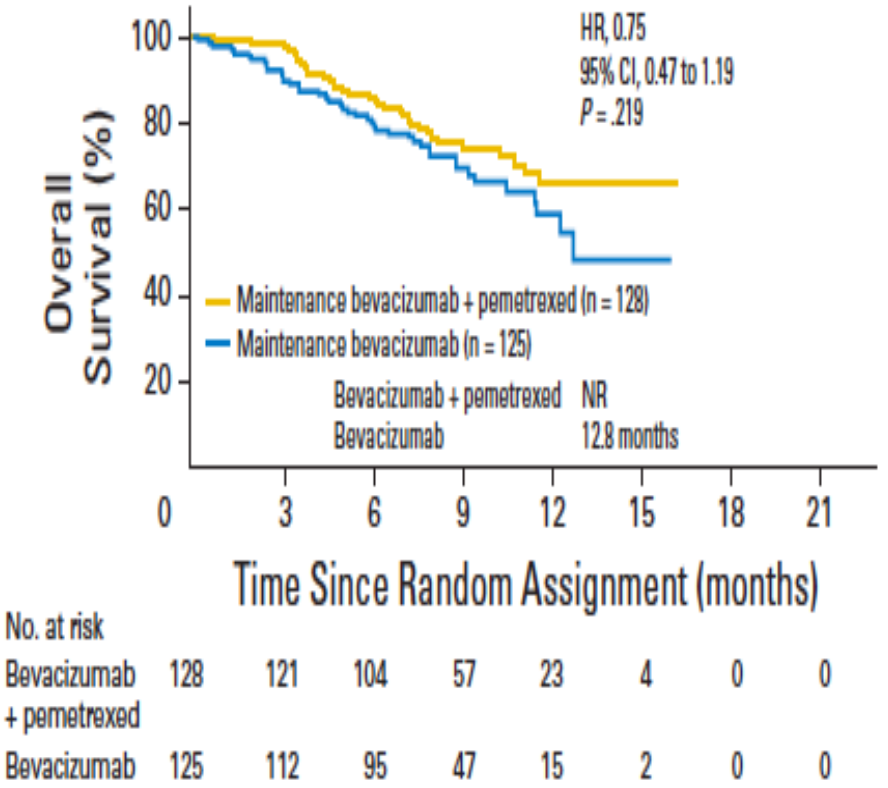
Primary objective: progression-free survival

Secondary objectives: Overall survival, response rate, disease control rate, duration of response, duration disease control, safety, QOL

Barlesi F, et al. J Clin Oncol 30 July 8, 2013 [epub ahead of print]

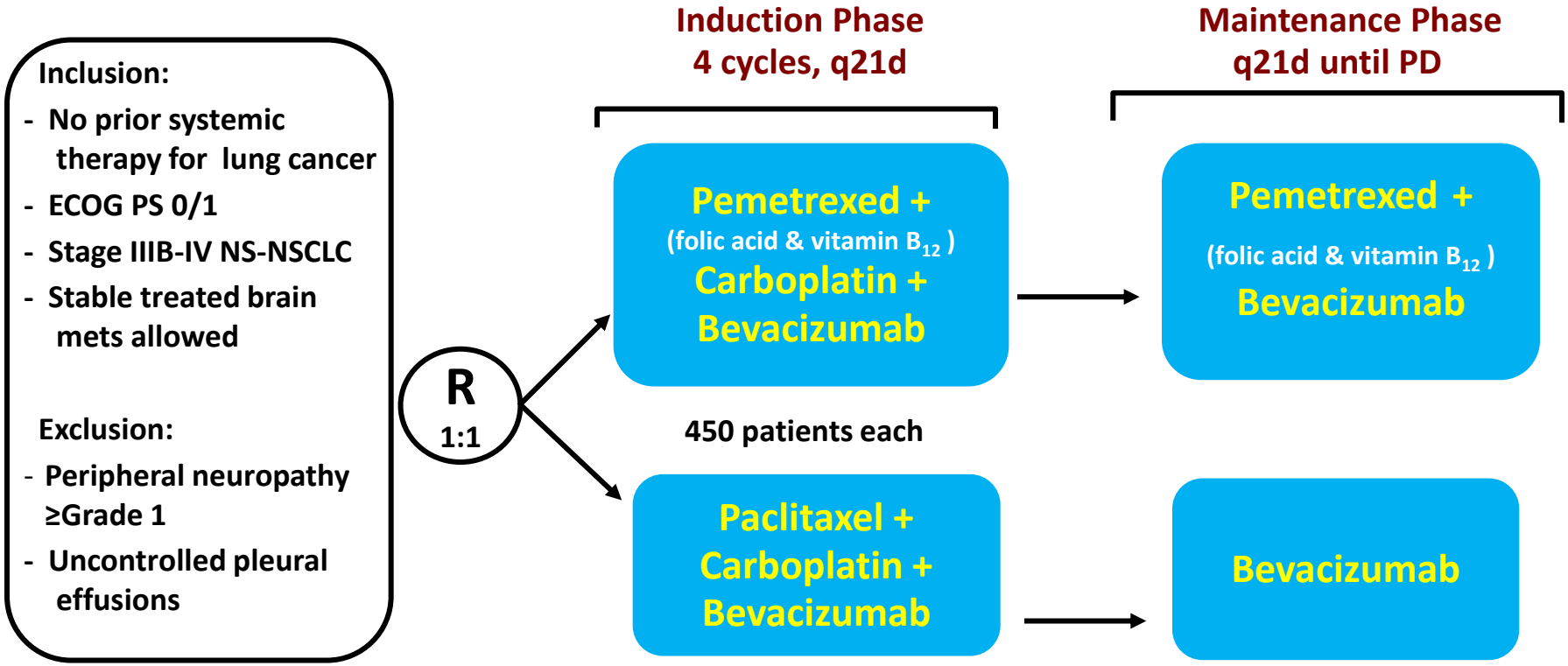
AVAPERL





Barlesi F, et al. J Clin Oncol 30 July 8, 2013 [epub ahead of print]

PointBreak
Study Design



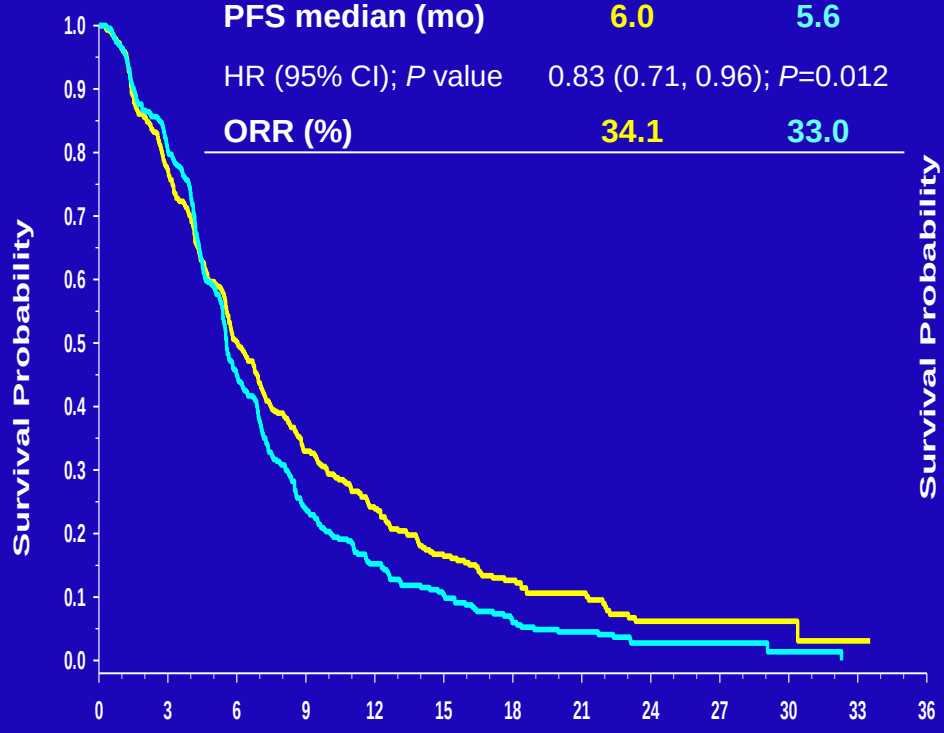
Stratified for:

PS (0 vs. 1) ; sex (M vs. F); disease stage (IIIB vs. IV); measurable vs. nonmeasurable disease

Socinski MA et al. Proc. ASCO 2013

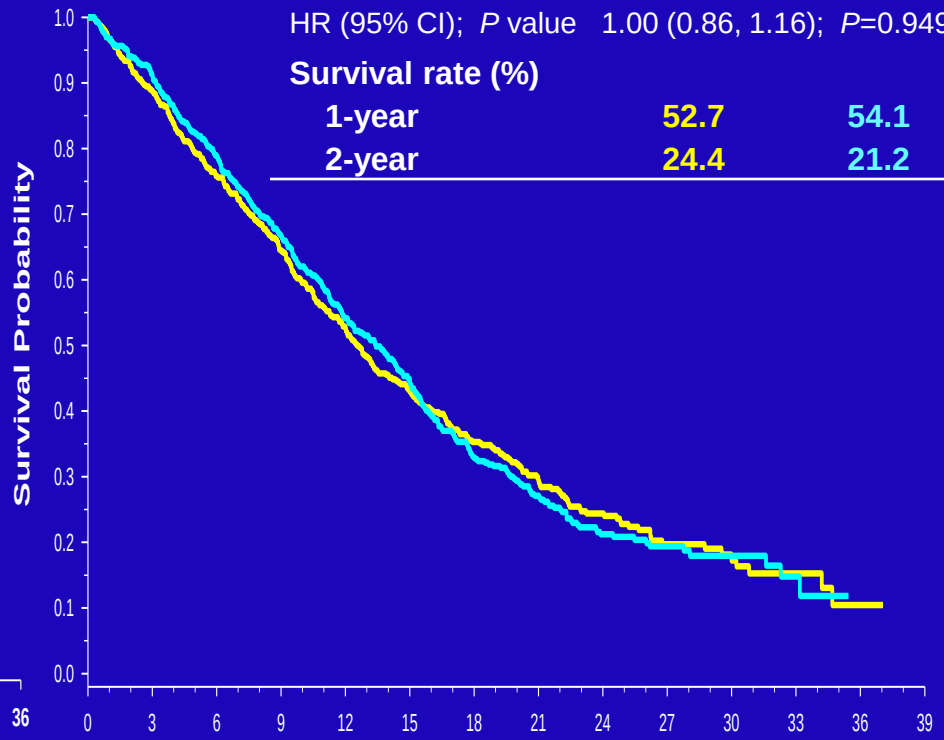
Pointbreak Trial
PFS & OS – ITT Population

	Pem+ Cb+Bev	Pac+ Cb+Bev
PFS median (mo)	**6.0**	**5.6**
HR (95% CI); *P* value	0.83 (0.71, 0.96); *P*=0.012	
ORR (%)	**34.1**	**33.0**



Time from Induction (months)

	Pem+ Cb+Bev	Pac+ Cb+Bev
OS median (mo)	**12.6**	**13.4**
HR (95% CI); *P* value	1.00 (0.86, 1.16); *P*=0.949	
Survival rate (%)		
1-year	**52.7**	**54.1**
2-year	**24.4**	**21.2**



Time from Induction (months)

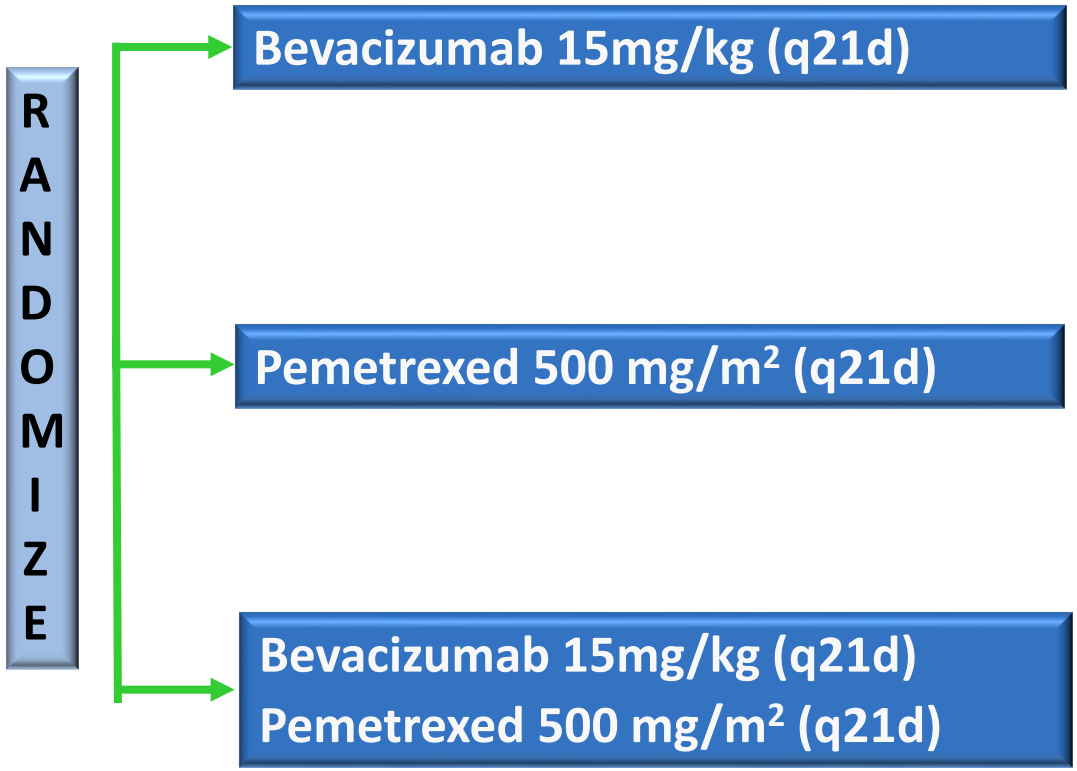
Socinski MA et al. Proc. ASCO 2013

ECOG 5508
Phase III Study Design

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

Randomization factors:
- Gender
- PS
- Stage
- Best tumor response to induction

Primary Endpoint = OS



B_{12}, folate, and dexamethasone given in Pem. arms

Total 1236 patients with 864 randomized (288/arm)

Control Arm Therapy at Progression

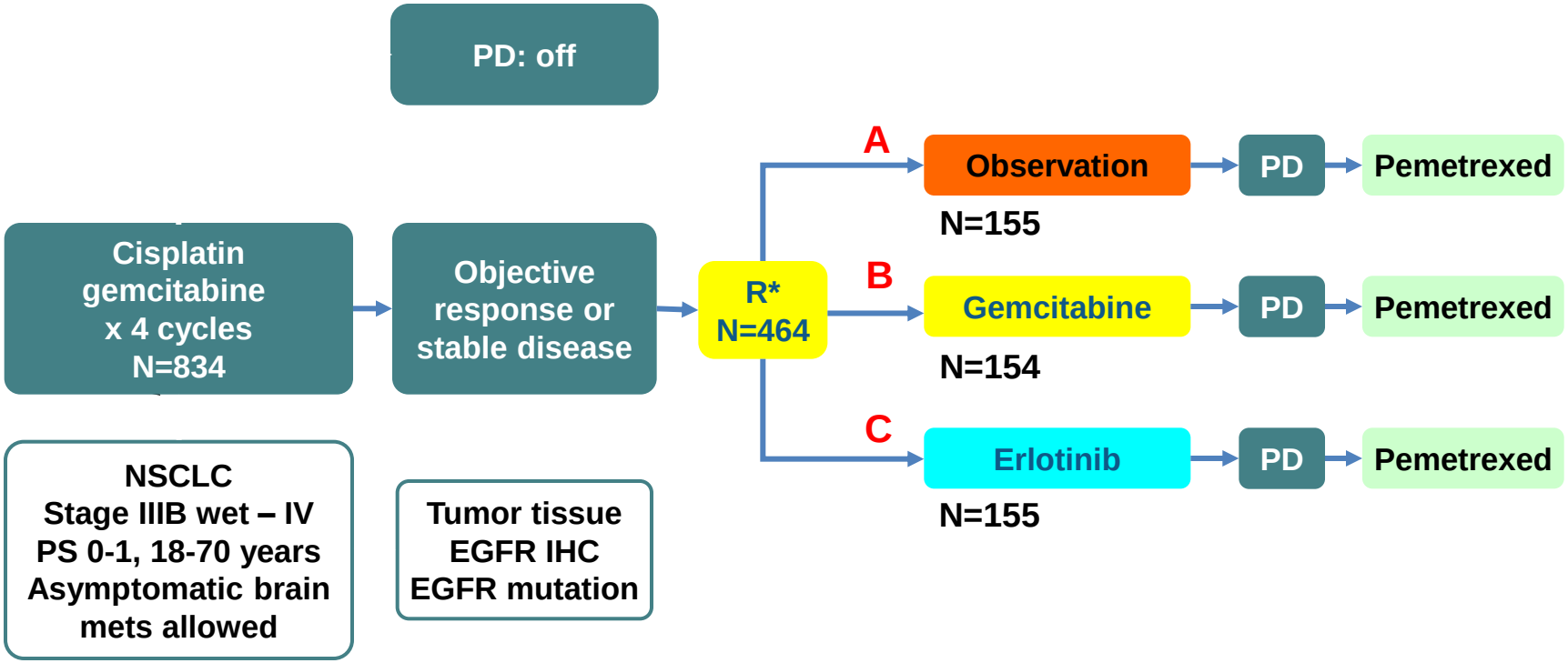
Study	Agent	Any Agent (%)	Cross-over (%)
Fidias	Docetaxel	62	62
JMEN	Pemetrexed	67	18
SATURN	Erlotinib	72	21
ATLAS	Erlotinib	56	40
Belani	Gemcitabine	17	n/a
IFCT-GFPC	Gemcitabine/Erlotinib	na	84*
PARAMOUNT	Pemetrexed	72	3.9**
INFORM	Gefitinib	67	30

Effective Treatment vs Suboptimal Treatment in the Control Arm?

* 2nd line pemetrexed mandated ** induction including pemetrexed

Adapted from : Edelman MJ et al, J Thoracic Oncol 2012; 7(9): 1331

IFCT-GFPC 0502 study design



Induction chemo: cisplatin 80mg/m^2 d1

+ gemcitabine 1,250mg/m^2 d1, d8

Arm B: gemcitabine 1,250mg/m^2 d1, d8 /3 wks

Arm C: erlotinib 150mg daily

*Stratification factors:

- gender
- histology: adenocarcinoma vs other histology
- smoking status: non-smokers vs current/former smokers
- center
- response vs stabilization to induction chemotherapy

EGFR = epidermal growth factor receptor
IHC = immunohistochemistry; PD = progressive disease

IFCT-GFPC 0502

Overall 78% of patients received Pemetrexed

Observation – 83%

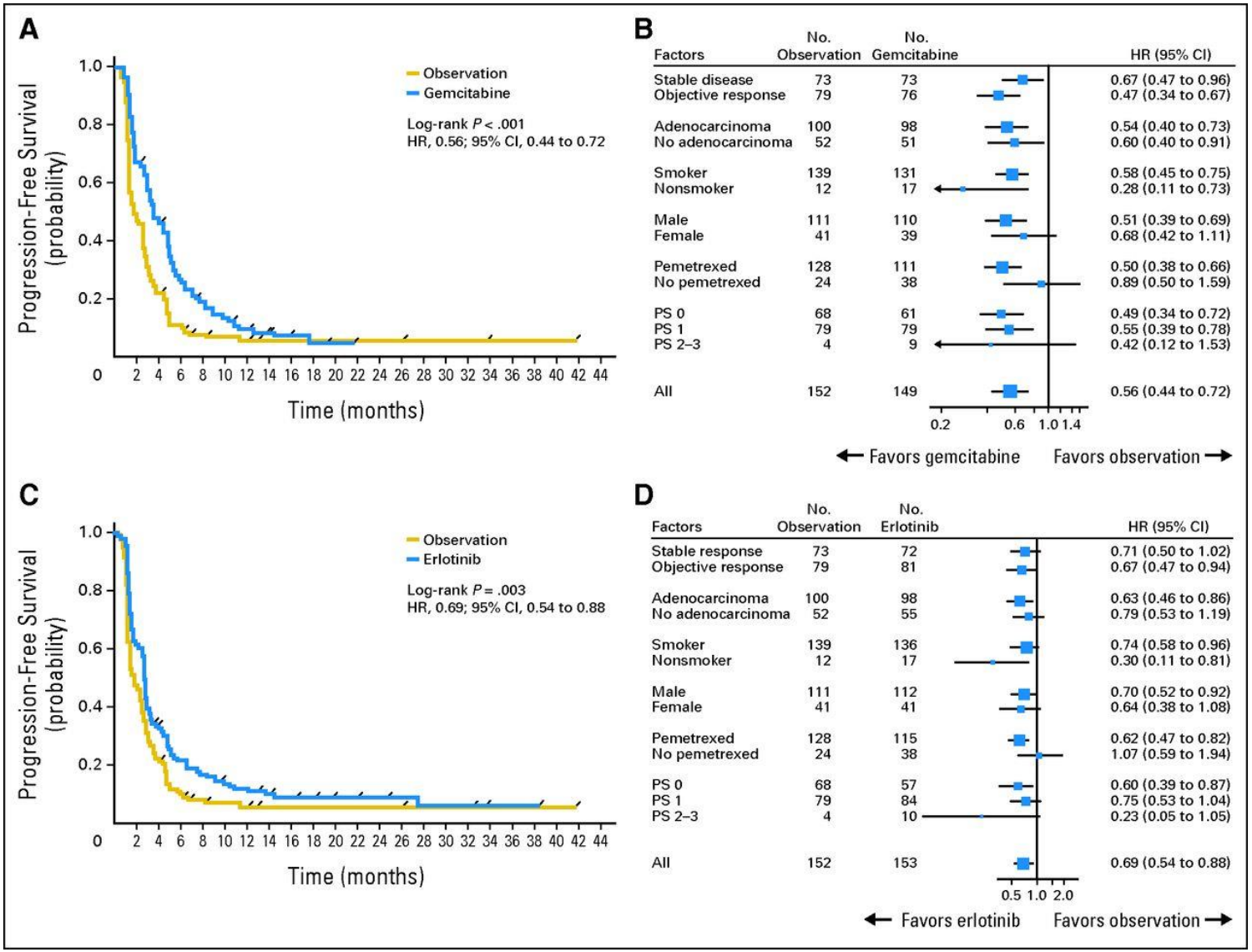
Gemcitabine – 74%

Erlotinib – 75%

94.5% of patients on the observation arm received subsequent therapy

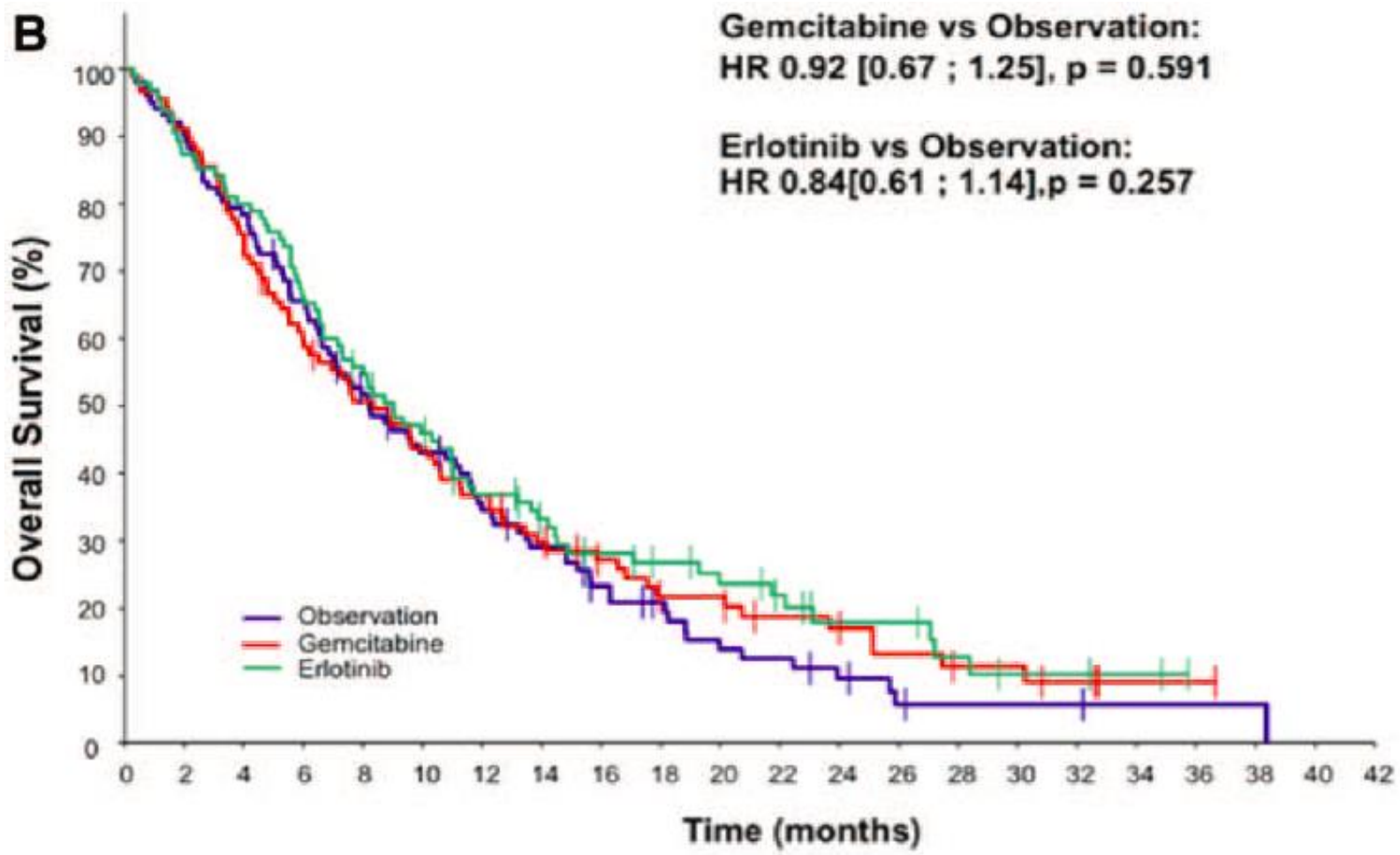
Bylicki O, et al. JTO 8 (7), July 2013

Gemcitabine or Erlotinib Maintenance – PFS



Pérol M et al. JCO 2012;30:3516-3524

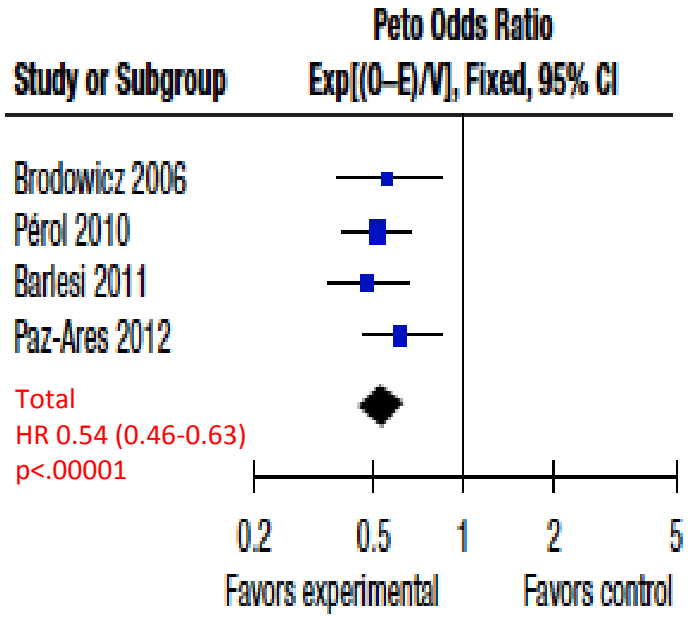
IFCT-GFPC 0502 – Overall Survival



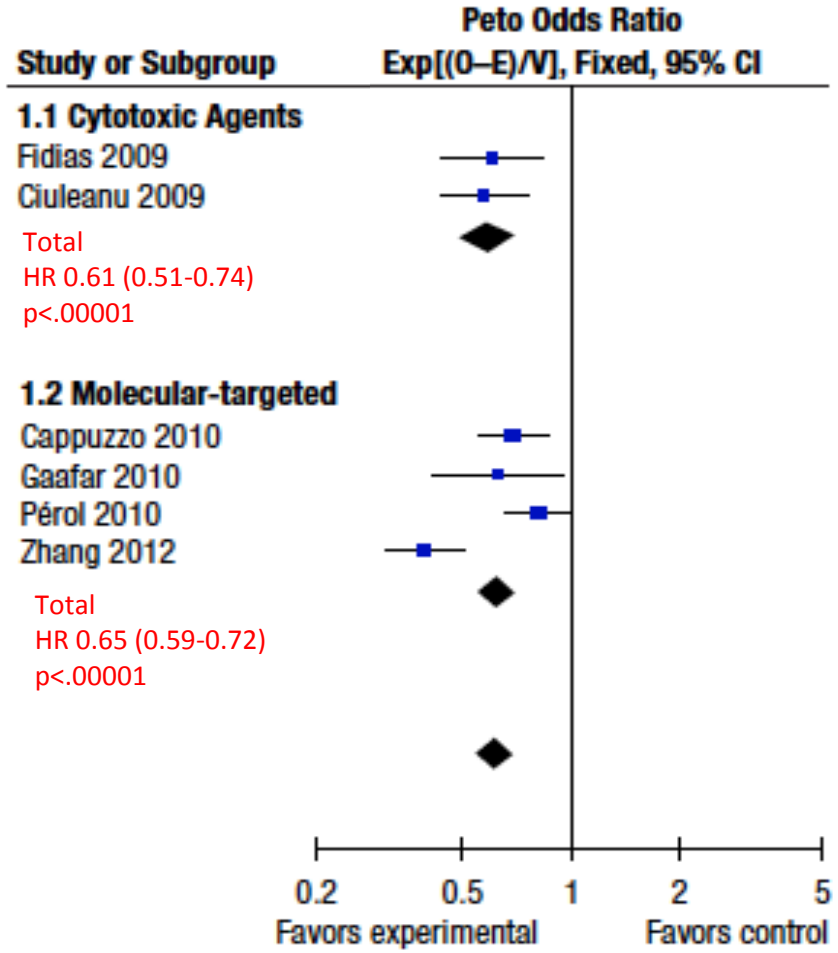
Bylicki O, et al. JTO 8 (7), July 2013

Meta-analysis of Maintenance Therapy : Progression Free Survival

Continuation Maintenance



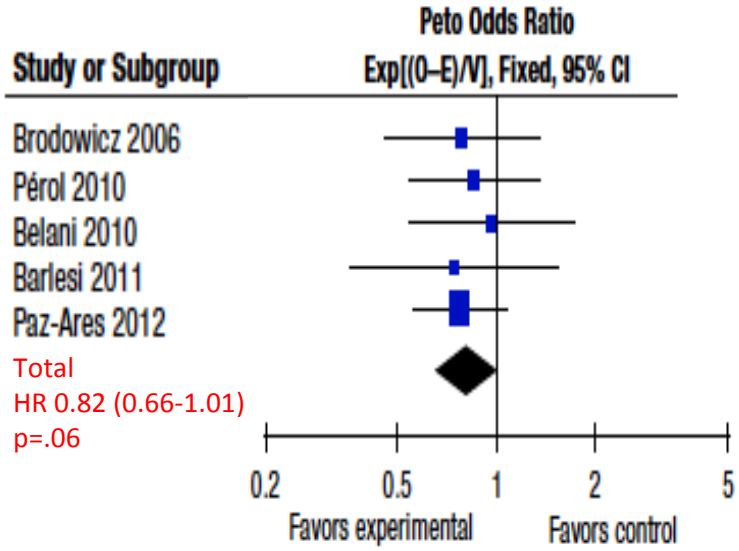
Switch Maintenance



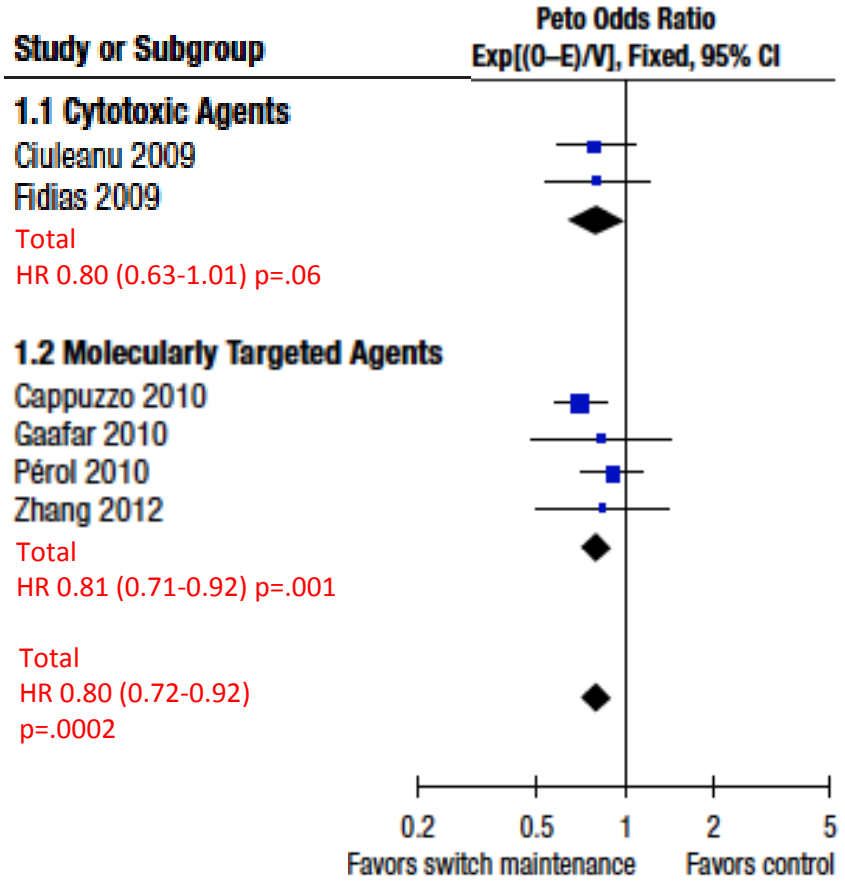
Cai H, et al. Clin Lung Cancer 14:333-41, 2013

Meta-Analysis of Maintenance Therapy: Overall Survival

Continuation Maintenance



Switch Maintenance



7 trials report no detrimental effect on QOL

Cai H, et al. Clin Lung Cancer 14:333-341, 2013

Pros & Contra of Maintenance Therapy

PRO

- Maintain Disease control
- Improves Progression-free Survival
- Improves Overall Survival
- Maintains Quality of Life
- Opportunity to treat more patients
- Patients support maintenance therapy

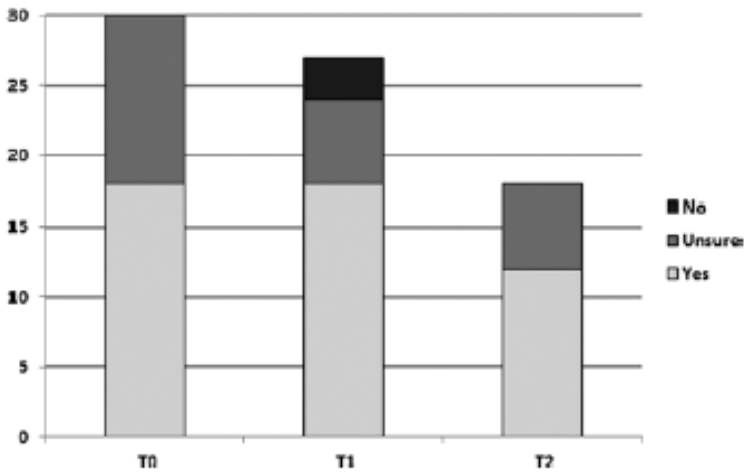
CONTRA

- Induction regimens of 4 vs 6 cycles may accomplish the same improvement in PFS
- The marked drop off in the % patients available for second line therapy in earlier reports appears not to be the case when patients are carefully followed
- Grade 3-4 AE rates of 30-40% are too high
- Cost of this intervention is just too expensive
- Need good biomarkers

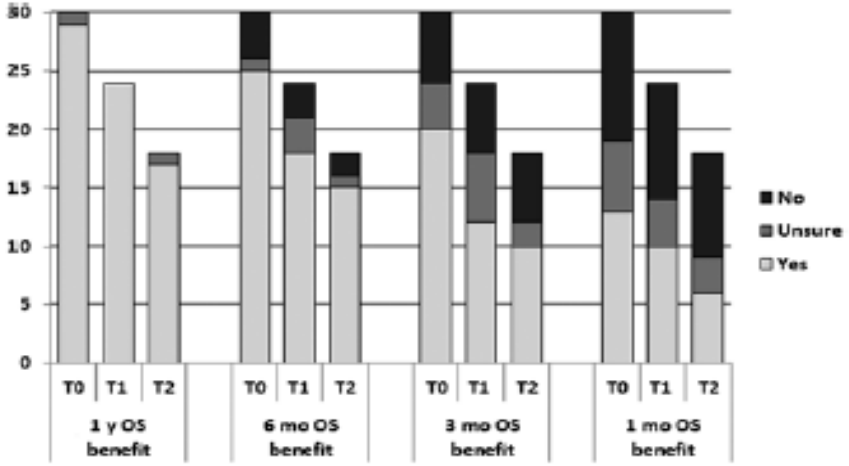
Efficacy:
Quality of Life

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

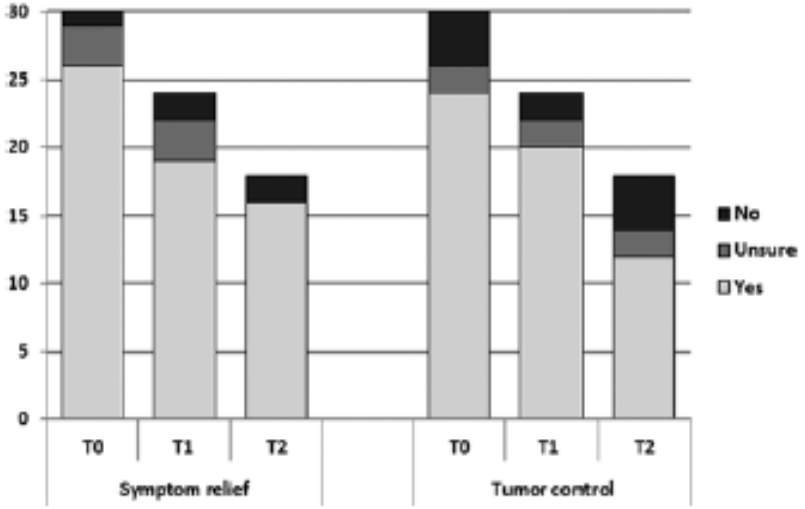
Patient Perception of Maintenance



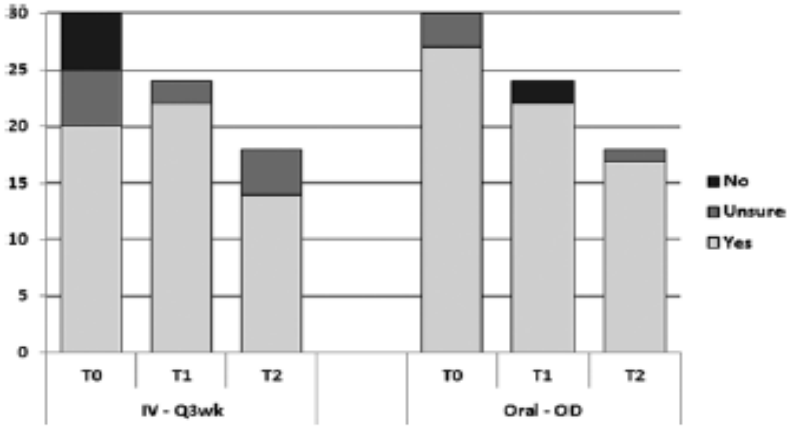
Do you think Maintenance therapy is worthwhile?



Do you think Maintenance therapy is worthwhile depending on the magnitude of the survival benefit?



Do you think Maintenance therapy is worthwhile if there was no survival benefit but symptom control benefit?



Do you think Maintenance therapy is worthwhile depending on mode of administration?

75% of patients would take MT for mild to moderate toxicity

Peeters L, et al. J Thorac Oncol 7:1291-5, 2012

Conclusion

- Maintenance therapy offers the possibility of continued active treatment to delay disease progression and symptom deterioration

- Continuation maintenance represents true maintenance.
  - Available data with pemetrexed are relevant and robust (and not inferior to those of switch maintenance), and claim for a change in the treatment paradigm
  - Further studies are ongoing

- Meta-analyses and patients' preference support the use of maintenance in advanced NSCLC

Maintenance in Advanced NSCLC

Treating Before Disease Progression Until Progression or Intolerance