

## **Maintenance Therapy for Advanced NSCLC: When, What, Why & What's Left After Post-Maintenance Relapse?**

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**This program is made possible with support from an education grant from Eli Lilly Oncology, who had no role in the development of its content.**

## Disclosures

- **Research Support**  
Lilly, Genentech, Pfizer, Celgene, Abraxis, Synta, Imclone
- **Speaker's Bureau**  
Lilly, Genentech
- **This activity is supported by a grant from Lilly**

## Drug Names Used in the Presentation

**Avastin = Bevacizumab**

**Erbix = Cetuximab**

**Alimta = Pemetrexed**

**Tarceva = Erlotinib**

**Taxotere = Docetaxel**

**Iressa = Gefitinib**

## Paradigms Established in Advanced NSCLC

- Platinum-based chemotherapy improves survival in the 1<sup>st</sup> line setting
- The benefit of platinum-based therapy is achieved early and prolonging therapy beyond 3-4 cycles does not yield clinically relevant benefits
- The addition of selected targeted agents to platinum-based therapy in the 1<sup>st</sup> line setting improves survival (bevacizumab, cetuximab)
- Selected single agents improve survival when administered after platinum-based therapy
- Chemotherapy has a palliative effect in symptomatic patients across multiple lines of therapy
- All chemotherapy agents have toxicity, costs and the inconvenience of adhering to a treatment/assessment schedule
- We do NOT cure this disease; chronicity with acceptable toxicity is our goal

## Paradigms Not Established in Advanced NSCLC

- The value continuation of bevacizumab or cetuximab beyond the end of chemotherapy truly provides
- The role of biomarkers in making routine treatment decisions in daily clinical practice (EGFR mutations excluded)
- The optimal surveillance strategy during a treatment break (between lines of therapy)
- The most appropriate treatment strategy in times of multiple “active” agents and three lines of FDA-approved therapies (i.e., the timing of 2<sup>nd</sup> and 3<sup>rd</sup> line therapies)
- The concept of exposure to multiple lines of therapy (from “one and done” to “3 strikes before you are retired”)

## NCCN Guidelines for Advanced NSCLC

### ➤ 1<sup>st</sup> line

Platinum-based doublet ± bevacizumab or cetuximab

Pemetrexed-based therapy for non-squames

- Erlotinib for EGFR mutants

### ➤ Maintenance

Continuation or Switch

### ➤ 2<sup>nd</sup> Line

Docetaxel, Pemetrexed (non-squames) or Erlotinib

### ➤ 3<sup>rd</sup> Line

Erlotinib

## Agents tested in the 2<sup>nd</sup> line treatment of advanced NSCLC (Phase III)

- FDA approved (US)
  - Docetaxel
  - Pemetrexed
  - **Erlotinib**
- Phase III tested
  - **Gefitinib**
  - Topotecan (oral)
  - Vinflunine
  - Vinorelbine
  - Ifosfamide

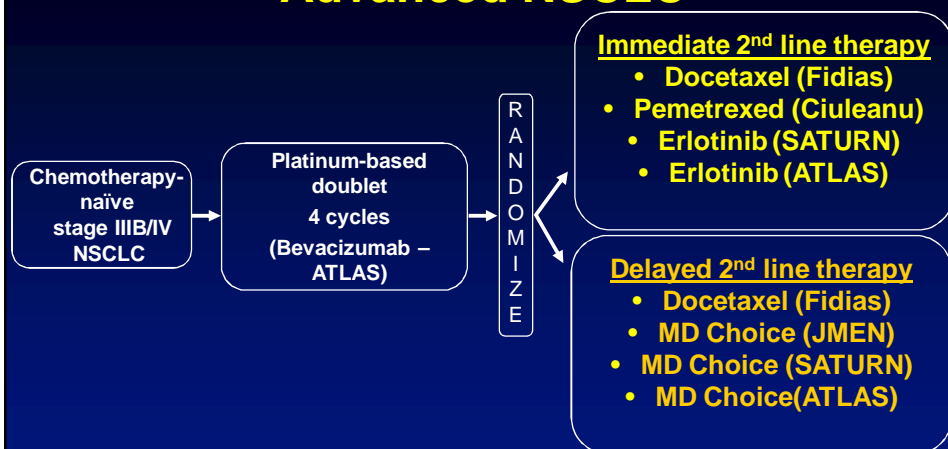
Cytotoxic agents  
Targeted agents (EGFR)

## Considerations Regarding Maintenance Versus 2<sup>nd</sup> Line (and beyond) Therapy

- Agents approved based on survival (BR.21 and TAX 317) and palliative advantage
- Historically, 2<sup>nd</sup> line has been given at the time of disease progression
- Maintenance\*
  - Continuation – Biologic agent given initially with CT should be continued until PD or unacceptable toxicity (bevacizumab, cetuximab)
  - Switch – Use of a new agent not initially part of the original CT (docetaxel, pemetrexed, erlotinib) in non-PD patients following 4 cycles of therapy

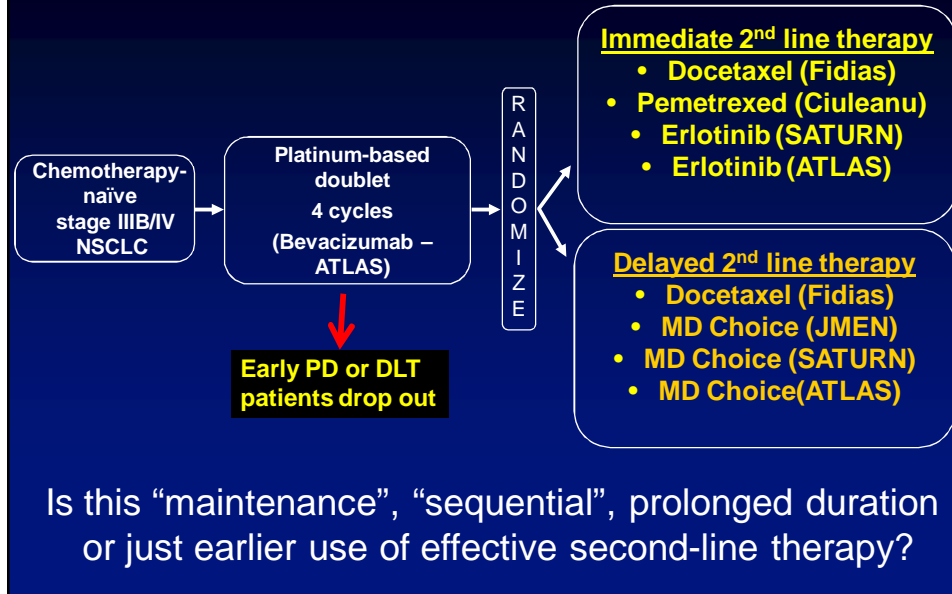
\*NCCN Guidelines modified by MA Socinski

## Timing of Second Line Therapy in Advanced NSCLC

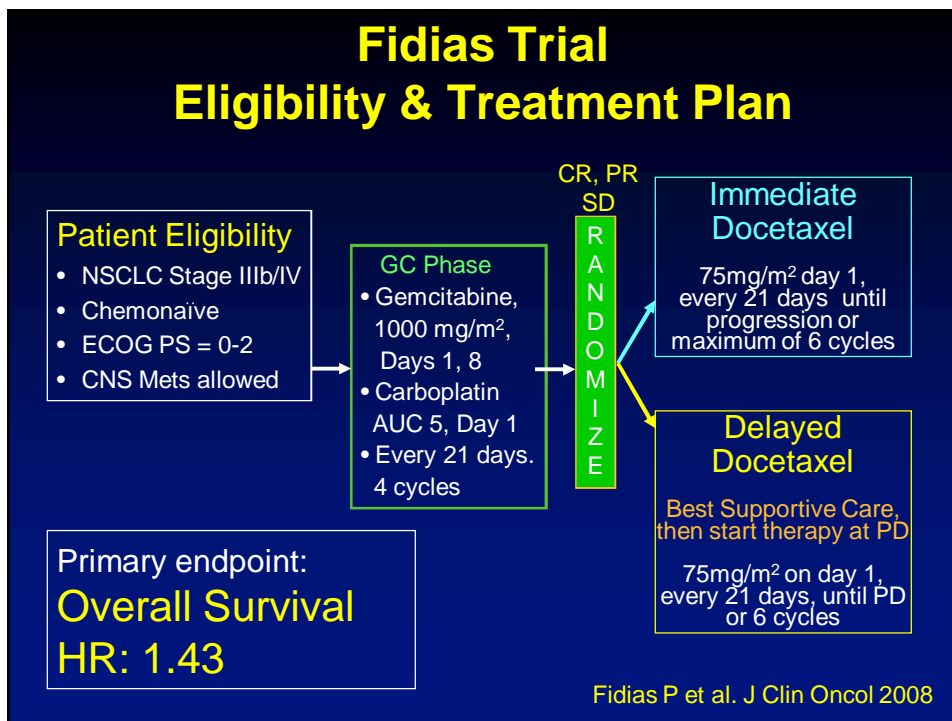


Is this “maintenance”, “sequential”, prolonged duration or just earlier use of effective second-line therapy?

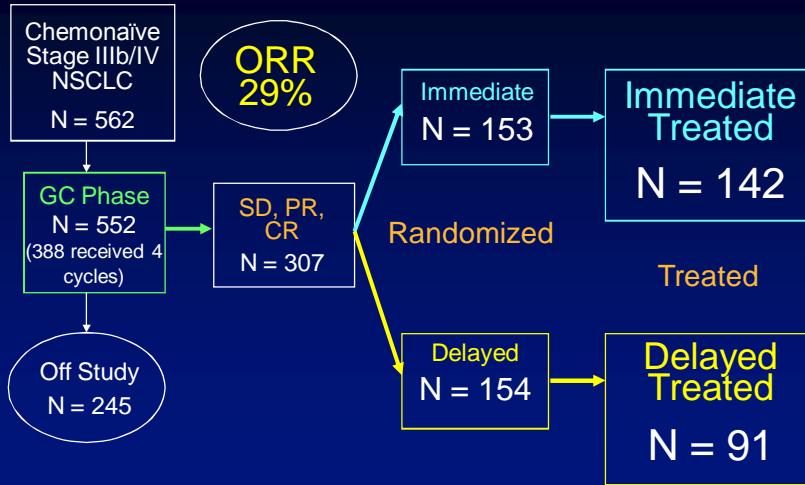
## Timing of Second Line Therapy in Advanced NSCLC



## Fidias Trial Eligibility & Treatment Plan

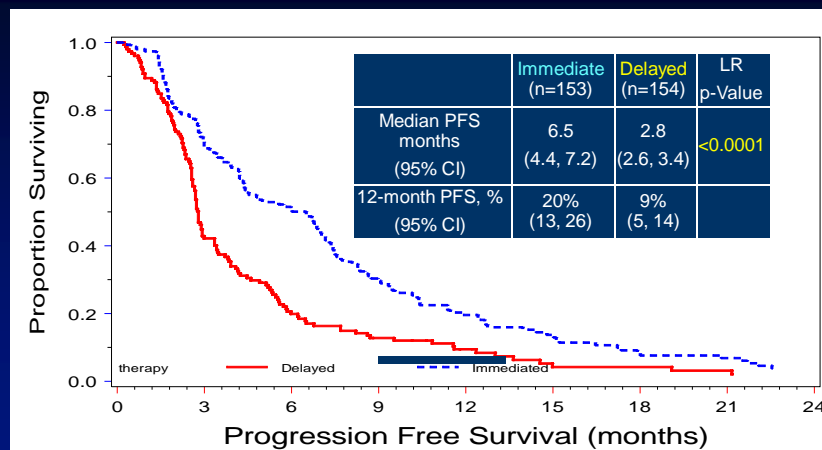


## Patient Disposition

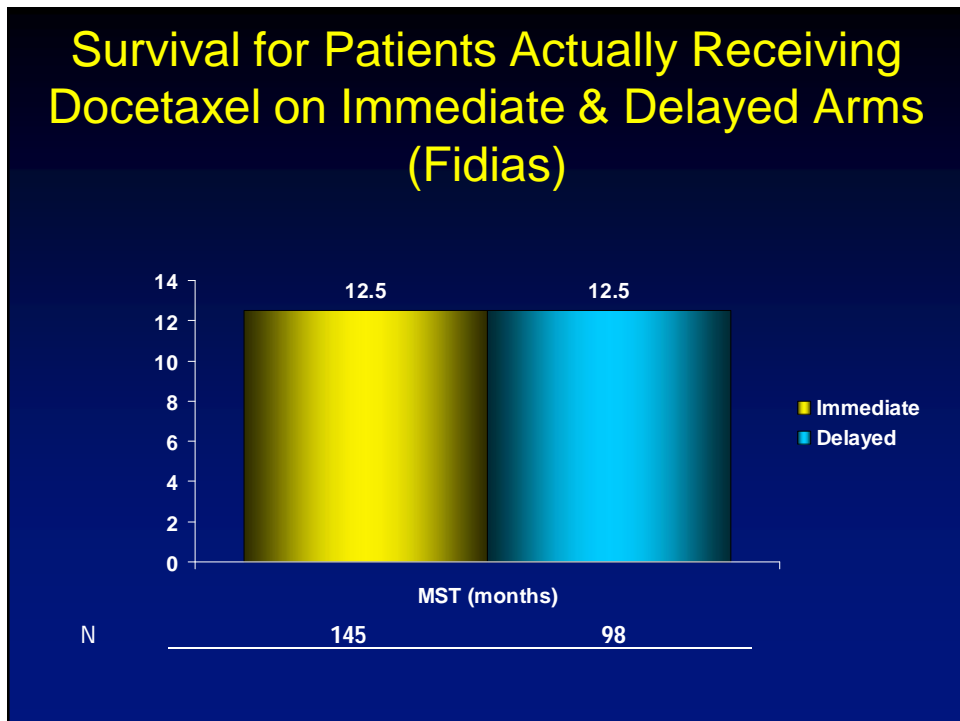
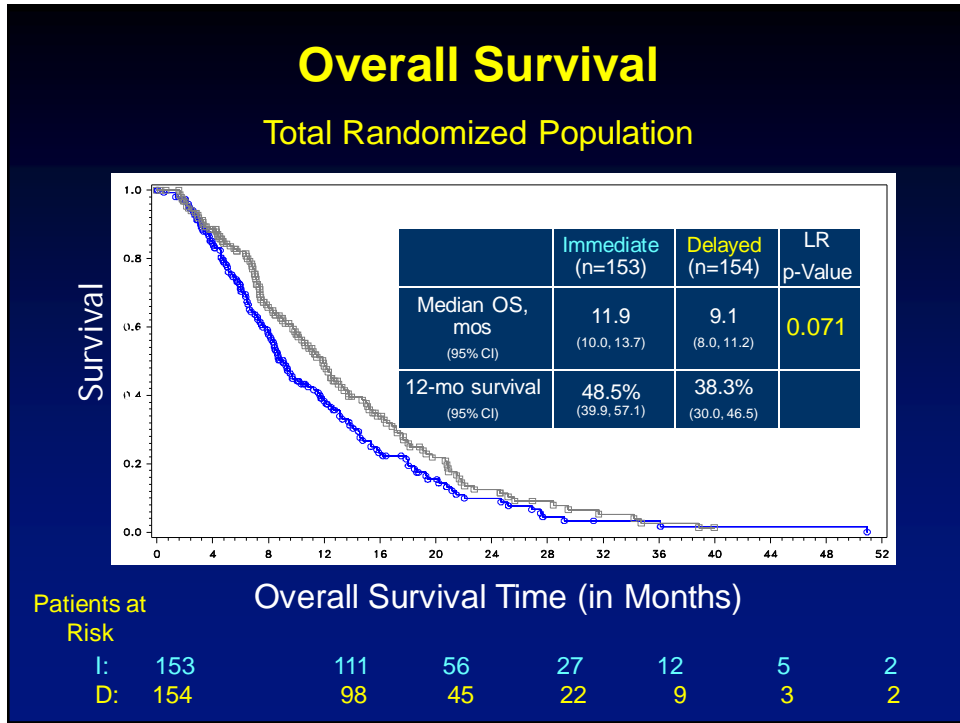


## Progression-Free Survival

Total Randomized Population



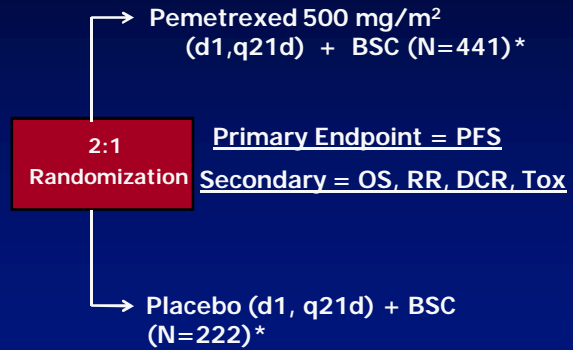
I: 153      72      27      11      5 Patients at Risk  
 D: 154      28      10      4      2



## JMEN – “Maintenance” Pemetrexed Study Design Belani CP et al. ASCO 2009, abstr #8000

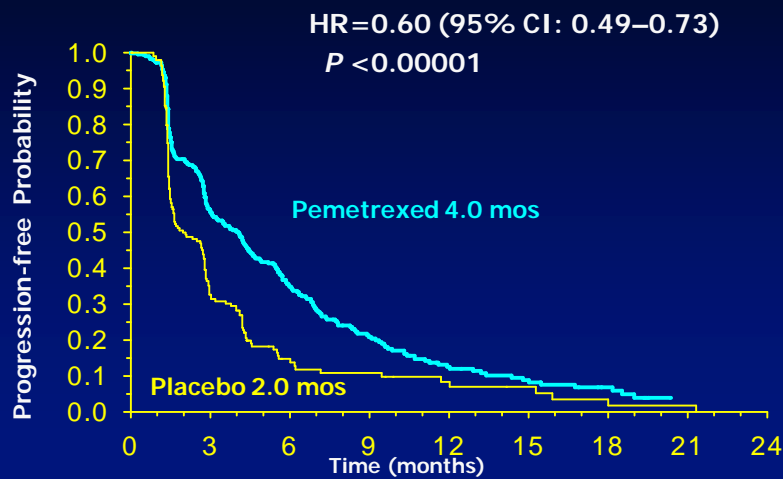
Double-blind, Placebo-controlled, Multicenter, Phase III Trial

- 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

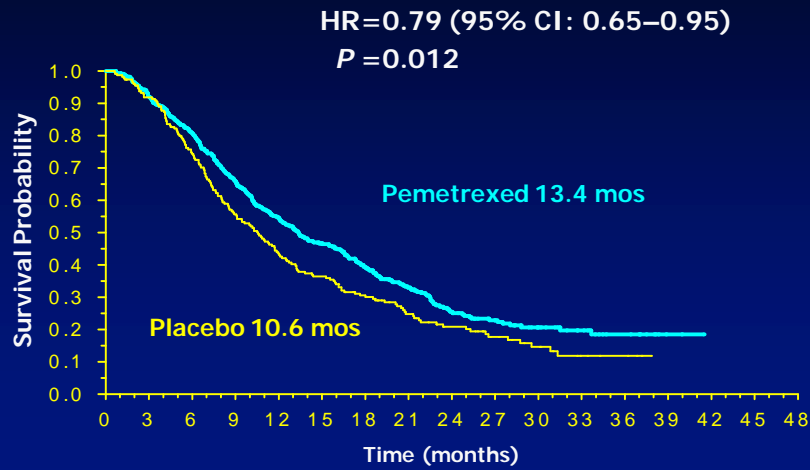


\*B<sub>12</sub>, folate, and dexamethasone given in both arms

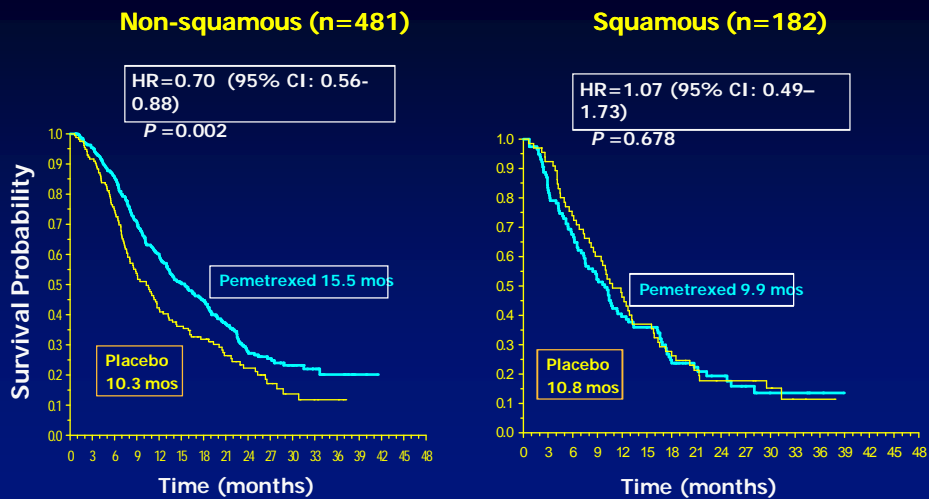
## Progression-Free Survival



## Overall Survival (Intent-to-treat Population)



## Overall Survival by Histology



## Systemic Post-study Therapy

	Pemetrexed (N=441) %	Placebo (N=222) %
Patients with post-study therapy	52	67
<b>Most common post-study therapies</b>		
Carboplatin	7	10
Cisplatin	5	6
Docetaxel	22	29
Erlotinib	22	21
Gefitinib	13	10
Gemcitabine	9	14
Paclitaxel	4	6
Pemetrexed	1	19
Vinorelbine	13	17

- Higher rate of follow-up treatment on the placebo arm
- Balanced selection of therapies between arms and low rate of crossover

## SATURN – Phase III trial of Maintenance Erlotinib in Non-Progressors following 1<sup>st</sup> Line Platinum-based Chemotherapy

Mandatory tumour sampling

**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

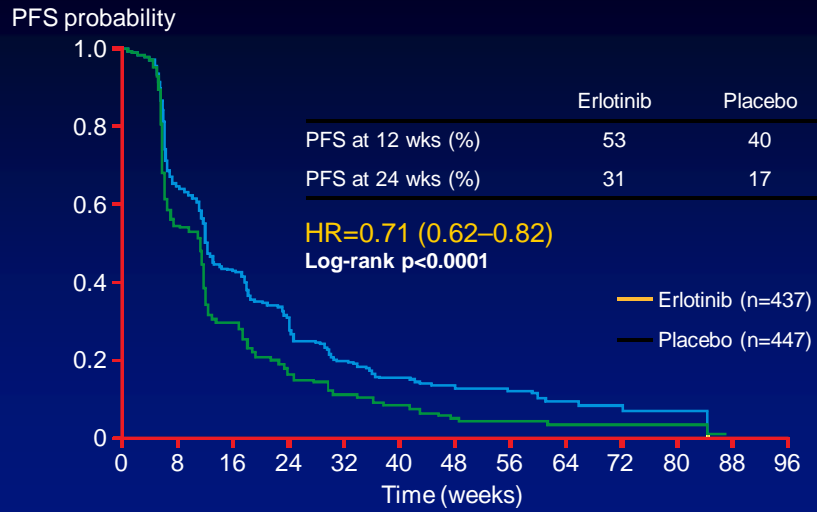
**Secondary endpoints:**

- 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

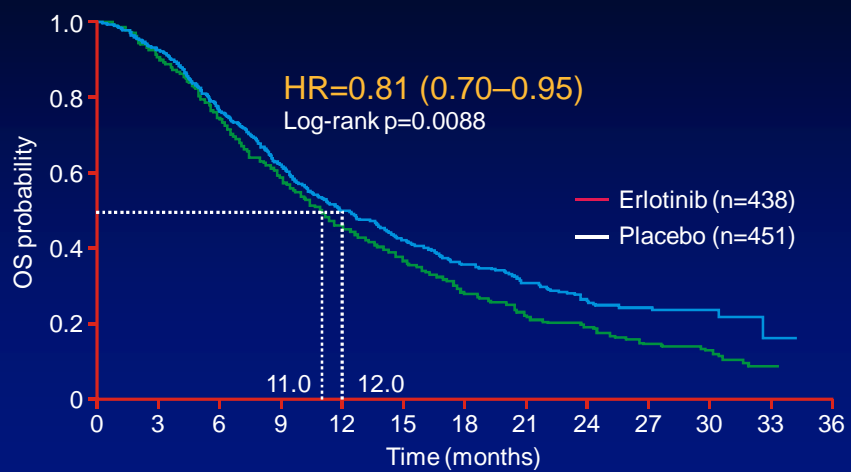
**Cappuzzo F et al. ASCO 2009, abstr #8001**

## SATURN PFS\*: all patients



\*PFS is measured from time of randomisation into the maintenance phase; assessments were every 6 weeks; ITT = intent-to-treat population

## SATURN OS\*: all patients



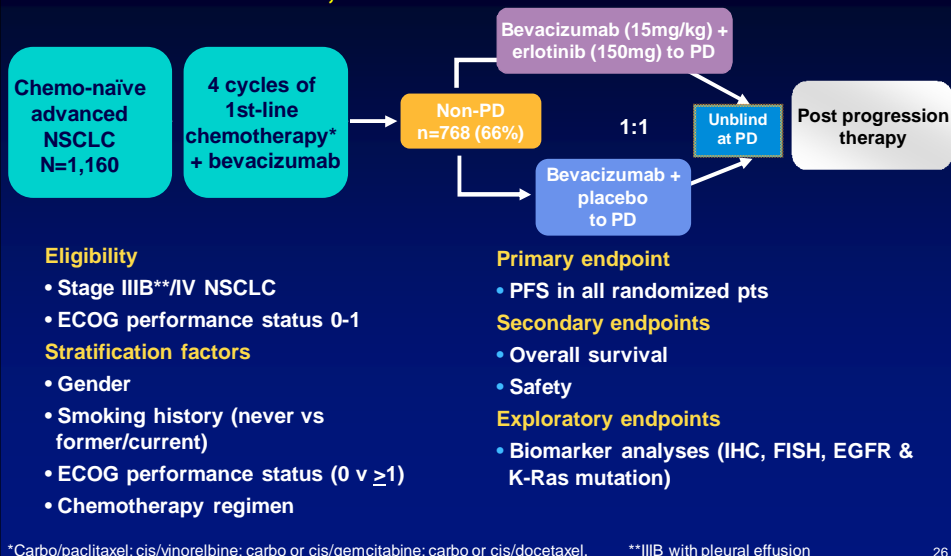
\*OS is measured from time of randomisation into the maintenance phase; ITT = intent-to-treat population

## SATURN Post-study treatment

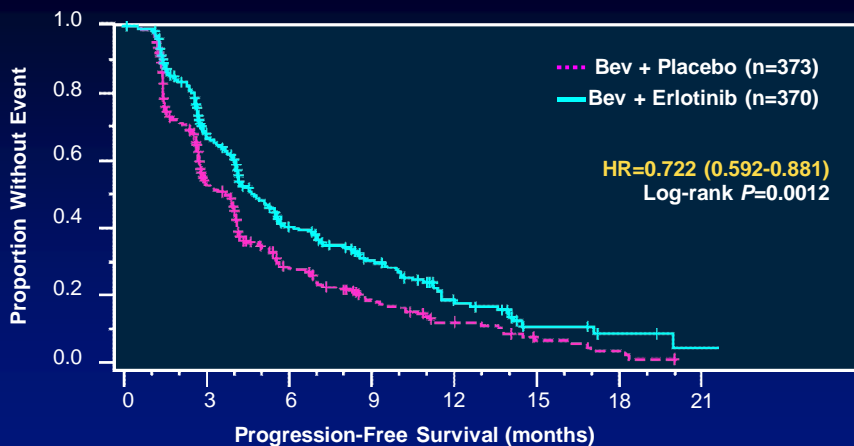
	Erlotinib (n=438)	Placebo (n=451)
	% with at least one treatment	
<b>All classes</b>	<b>71</b>	<b>72</b>
taxanes (including docetaxel)	30	31
antimetabolites (including pemetrexed)	24	23
antineoplastic agents	16	18
tyrosine-kinase inhibitors	11	21
platinum compounds	9	12

## ATLAS – Phase III trial of Maintenance Erlotinib in Non-Progressors following 1<sup>st</sup> Line Platinum-based Chemotherapy Combined with Avastin (Bevacizumab)

Miller V et al. ASCO 2009, abstr # 8002



## ATLAS: Progression-Free Survival



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

27

## Exposure to multiple lines of therapy on the JMEN, SATURN & ATLAS Trials

	JMEN		SATURN		ATLAS	
	Pem	Placebo	Erlotinib	Placebo	Erlotinib	Placebo
% rec'ing 1 <sup>st</sup> line	100	100	100	100	100	100
% rec'ing 2 <sup>nd</sup> line	100	67	100	64	100	55
% rec'ing 3 <sup>rd</sup> line	52	NR	55	NR	50	NR

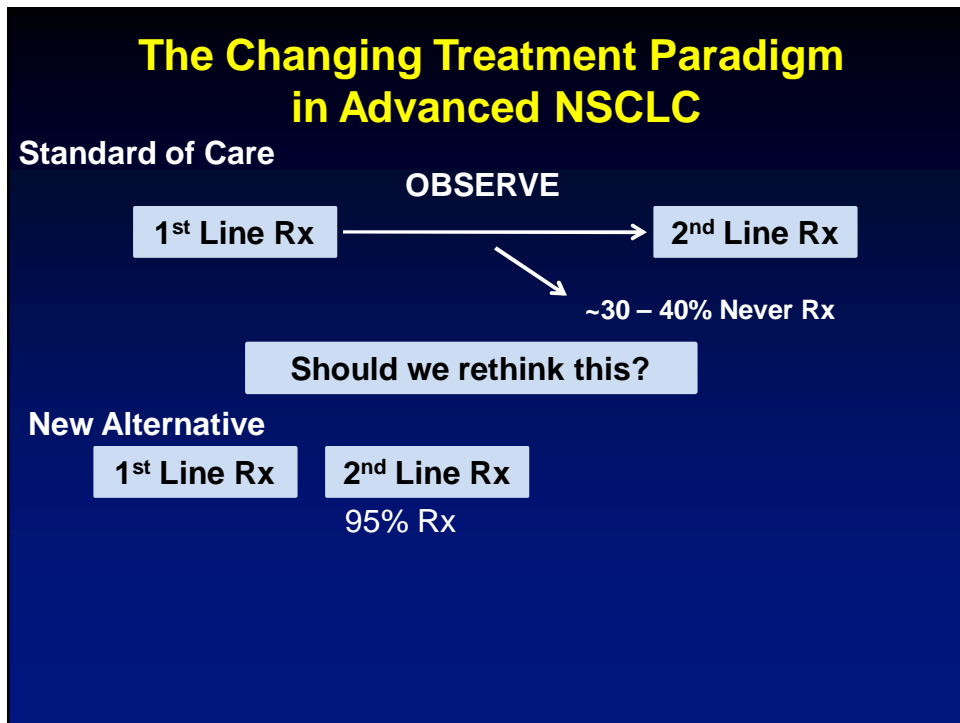
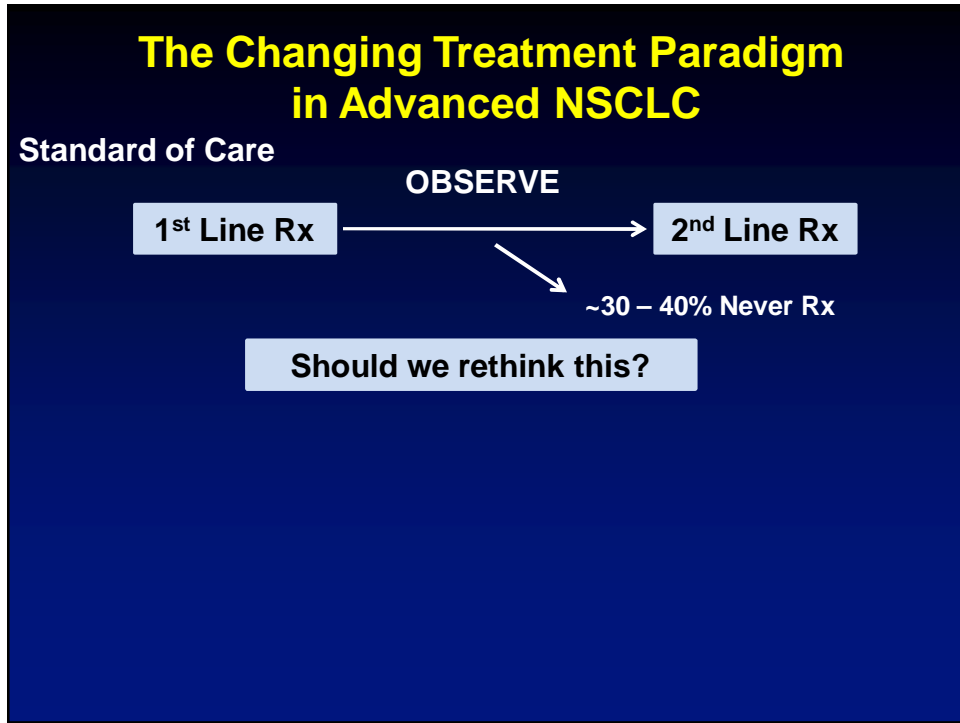
## 1<sup>st</sup> to 2<sup>nd</sup> Line Transition

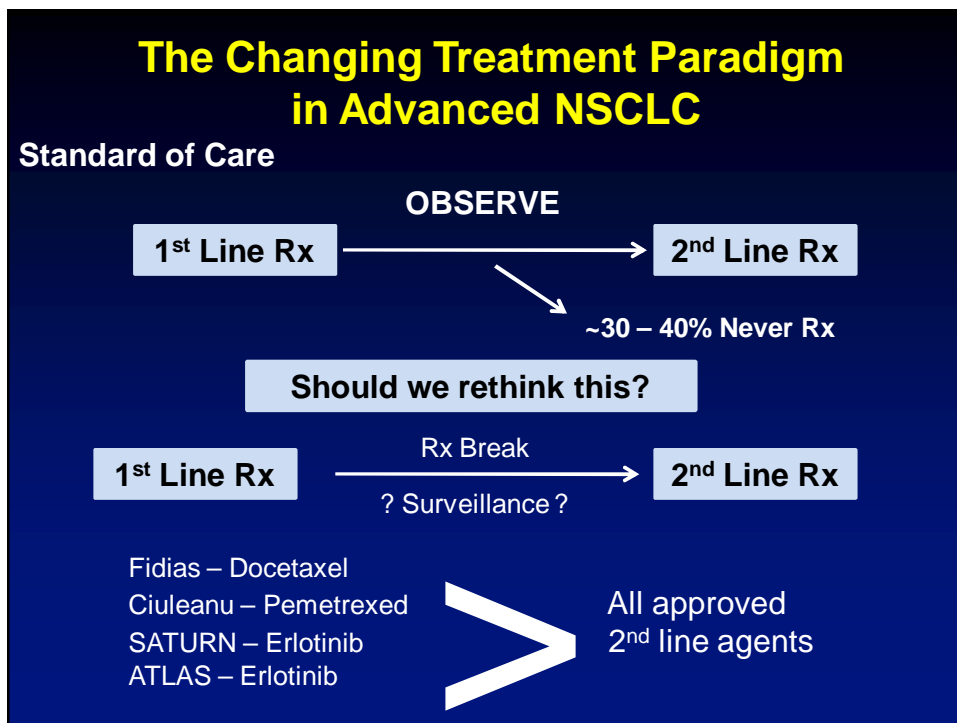
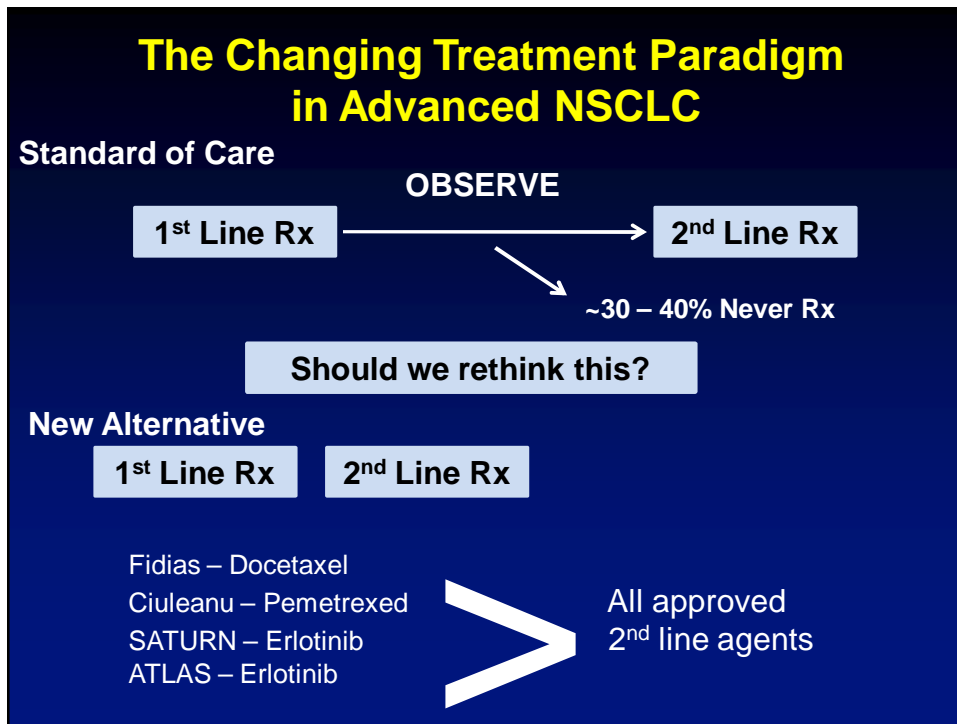
- On JMEN, SATURN and ATLAS, patients were followed q3 weeks and evaluated radiographically q6 weeks
- Despite this, 33-45% did not receive 2<sup>nd</sup> line therapy
- Reasons must be explored (one concern with regard to this issue is waiting for clear evidence of PD)
- What are the characteristics of these patients?
- Can we identify which patients will progress rapidly off therapy? Will early treatment make a difference?
- Can we identify which patients can safely have a treatment break & delay the benefit of 2<sup>nd</sup> line therapy?

## Efficacy Outcomes in Trials of Sequential Versus Delayed 2<sup>nd</sup> line Therapy

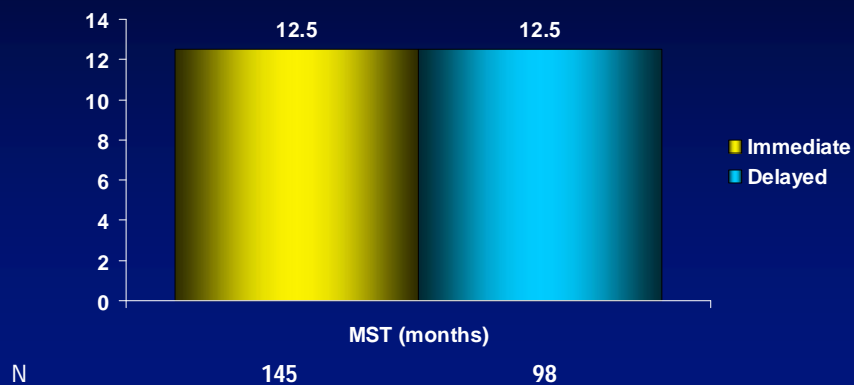
	Fidias	JMEN	SATURN	ATLAS
# pts (entered/rand after 4 cycles)	562/307 (55%)	?/663 (?)	1949/889 (46%)	1160/768 (66%)
RR (%) Rx vs control	11 vs 11*	3 vs 1	12 vs 5	NR
DCR (%) Rx vs control	67 vs 56*	49 vs 29	61 vs 51	NR
PFS HR (p value)	NR (<0.0001)	0.60 (<0.00001)	0.71 (<0.0001)	0.72 (0.0012)
Δ in Med PFS	3.7 months	2 months	1 week	1 month
OS HR (p value)	NR (0.085)	0.79 (0.012)	0.81 (0.008)	NR
Δ in MST	2.6 months	2.8 months	1 month	NR

\* Compares patients treated on the immediate vs delayed docetaxel arms





## Survival for Patients Actually Receiving Docetaxel on Immediate & Delayed Arms (Fidias)



## My Conclusions

- Patients randomized to the “maintenance” or early treatment arms of these trials were exposed more often to effective chemotherapy
- Patients randomized to the placebo arms less often rec'd 2<sup>nd</sup> and presumably 3<sup>rd</sup> line therapy
- A benefit in PFS and OS using agents approved for 2<sup>nd</sup> line therapy in “Rx-sensitive” patients is not surprising (we already know this from BR.21 and TAX317)
- If 2<sup>nd</sup> line therapy is delayed but delivered, survival outcomes may not be compromised (need more data from JMEN, SATURN and ATLAS)

## My Conclusions

- It seems intuitive that exposure of more patients to multiple lines of effective therapy will improve survival
- Heightened surveillance allowing 2<sup>nd</sup>/3<sup>rd</sup> line therapy to be administered early seems reasonable but carries a risk
- Sequencing to approved 2<sup>nd</sup> line agents immediately following 1<sup>st</sup> line therapy will increase exposure to multiple lines of therapy
- This strategy does improve PFS and OS in advanced NSCLC

## Maintenance Therapy in Advanced NSCLC

- When? After 4 cycles of chemo in non-progressors
- Who? Patients you are worried about
- What? Docetaxel, Pemetrexed (non-squames), Erlotinib
- Why? Phase III data showing PFS and OS benefit
- What's Left? Whatever you did not already use

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