

## Maintenance Therapy for Advanced NSCLC A New Treatment Paradigm

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### Rationale

- 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.
  - Three active and approved agents in the second line setting (docetaxel, pemetrexed, erlotinib) are ideal candidates for evaluation as a maintenance therapy.
- A recently published meta-analysis of 13 trials from 1989 – 2008 showed
  - a substantial improvement in PFS (HR 0.75;  $p < .00001$ ) and a modest prolongation in OS (HR 0.92;  $P = .03$ ).

Soon YY, et al. J Clin Oncol 27:2009 (Epub)

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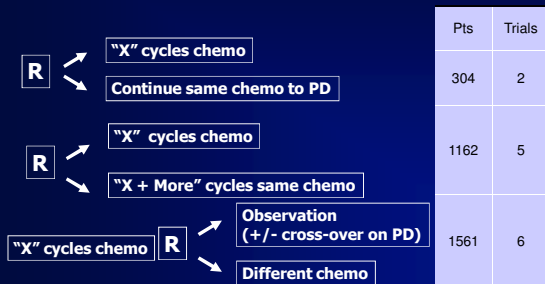
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### "Maintenance/Consolidation/Sequencing" Trials

Soon, et al JCO, 2009




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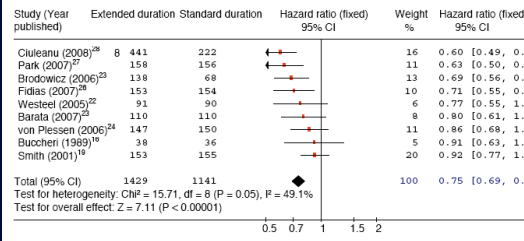
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### "Maintenance/Consolidation/Sequencing"

Soon, et al. JCO published on line, 2009

#### Progression-Free Survival

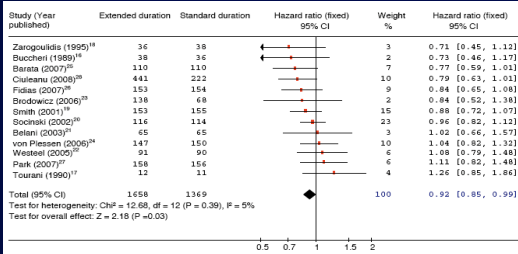


Hazard ratio = 0.75, 95% CI 0.69 – 0.81,  $p < 0.00001$

### "Maintenance/Consolidation/Sequencing"

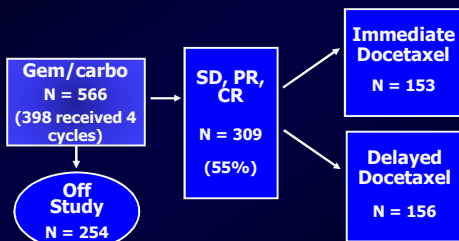
Soon, et al JCO, 2009

#### Survival



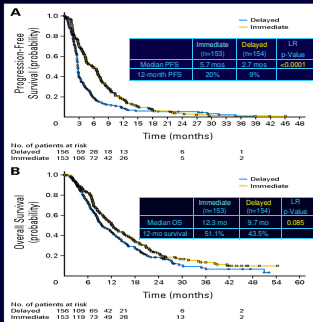
HR 0.92; 95% CI 0.86 to 0.99.  $p = 0.03$

### 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




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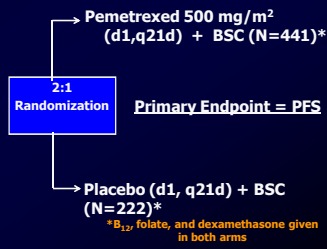
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### Maintenance Pemetrexed Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Advanced NSCLC

- 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




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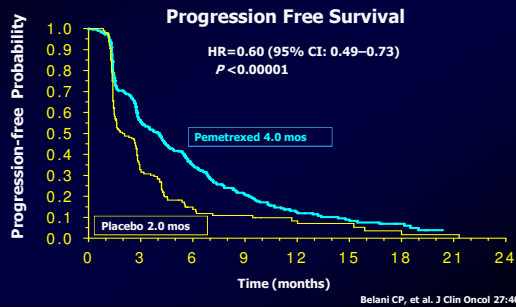
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### Maintenance Pemetrexed Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Advanced NSCLC




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## Is PFS in the Maintenance Setting Valid?

- If PFS improved, implies the study drug(s) is active
- If PFS improved, but not survival
  - Implies cross-over
  - or
  - Treatment can be delayed till progression

	Randomized Pts MST	Pts Who Actually Received docetaxel-MST
Delayed Docetaxel	9.7 mo	12.5 mo
Immediate Docetaxel	12.3 mo	

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

**But the patient has to make it to second-line**

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## DIFFERENT (non-cross resistant chemo) vs. Just MORE of the same?

To the patient, it probably doesn't matter – As long as survival is improved\*  
\*without debilitating side effects

PFS*	N	HR	Interaction p
Maintenance w/ same chemo until PD vs. fixed number	74	0.91 (0.63-1.33)	0.61
Fixed number of maintenance cycles w/ same chemo vs. larger fixed number	1139	0.82 (0.73-0.91)	
Maintenance w/ same chemo until PD vs. fixed number	74	0.91 (0.63-1.33)	0.12
Maintenance w/ different chemo	1357	0.67 (0.60-0.75)	
Fixed number of maintenance cycles w/ same chemo vs. larger fixed number	1139	0.82 (0.73-0.91)	0.01
Maintenance w/ different chemo	1357	0.67 (0.60-0.75)	

Soon, et al JCO 2009

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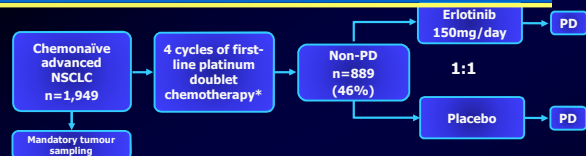
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## SATURN Study Design



### 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

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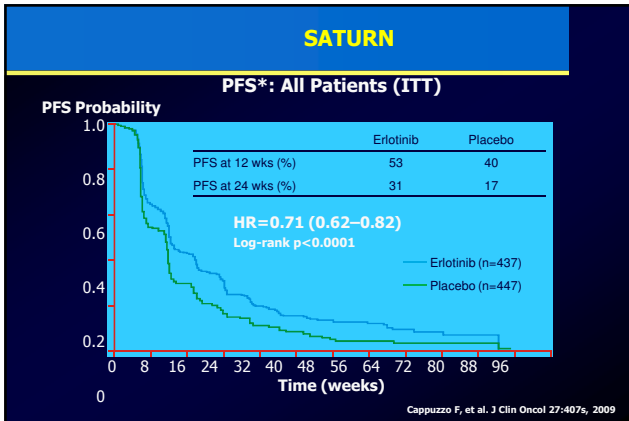
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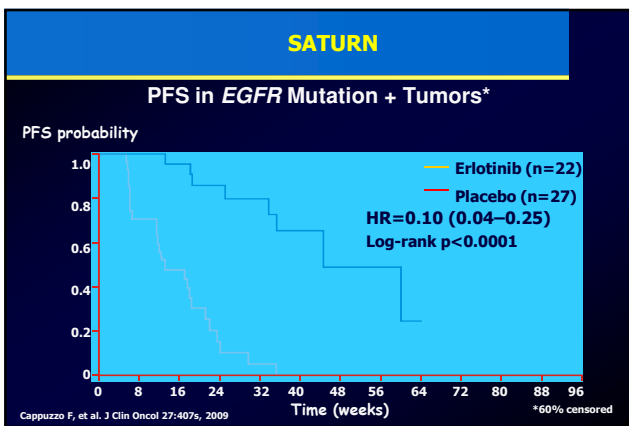
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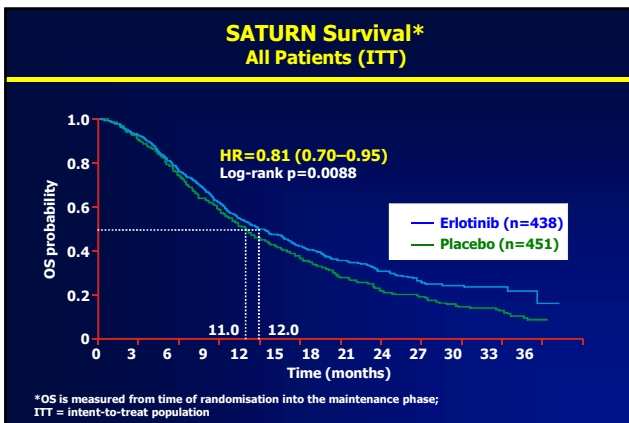
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## Quality of Life Data

Study	Questionnaire
Docetaxel	Average symptom burden index from the LCSS was similar between the arms
*Pemetrexed	Time to worsening of symptoms showed no difference or favored pemetrexed using the LCSS
Erlotinib (Saturn)	FACT-L did not show a deterioration in QOL in either arm
Erlotinib (ATLAS)	Not Performed

\*Zelinski CC, et al J Clin Oncol 26:#8060, 2008

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## Maintenance (Consolidation) Quality of Life Data

Study	% of Patients Receiving Immediate TX	% of Patients Receiving Delayed TX
Docetaxel	95	63
Pemetrexed	98	67 (19% Pemetrexed)
Erlotinib (Saturn)	99	64 (16% TKI)
Erlotinib (ATLAS)	99	56 (40% TKI)

	No of patients who received drug	Median Survival
Delayed Docetaxel	98	12.5 mos
Immediate Docetaxel	145	12.5 mos

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## Controversy

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

Maintenance Therapy: What matters?

1. Improved survival
2. Prolonged PFS IF associated with:
  - Symptom control
  - Increased time to symptom deterioration
3. Minimal toxicities
4. Cost

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## Maintenance Therapy

### Recommendations

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

Maintenance Therapy is The NEW TREATMENT PARADIGM

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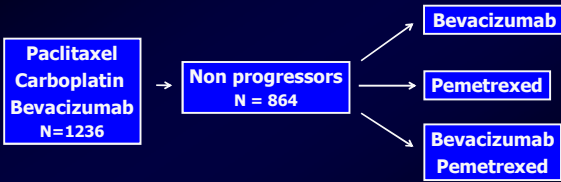
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## Future Directions

### ECOG 5508



Primary endpoint: Overall Survival

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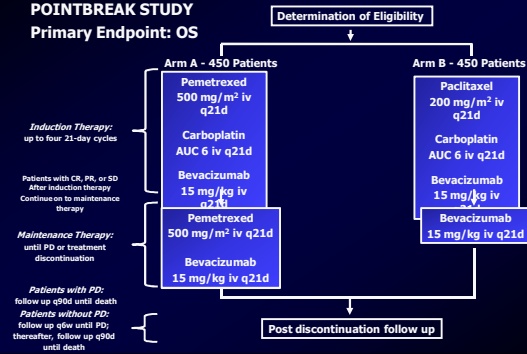
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## Future Directions

### POINTBREAK STUDY Primary Endpoint: OS



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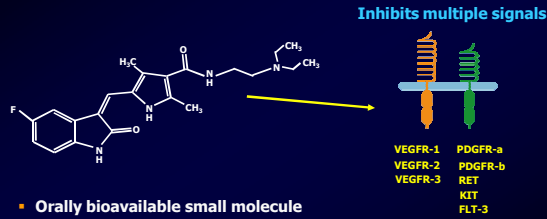
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### Sunitinib: an Oral Multitargeted Tyrosine Kinase Inhibitor with Antitumor and Antiangiogenic Activity



- Orally bioavailable small molecule
- Selective multitargeted inhibition
- Targets neovascular endothelium and pericytes as well as tumor cells
- Approved in the US for advanced RCC and imatinib-refractory GIST

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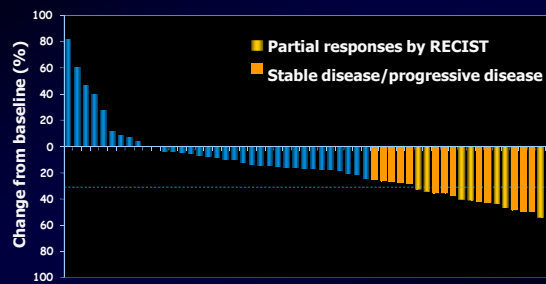
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### Response to Sunitinib in pts with relapsed NSCLC




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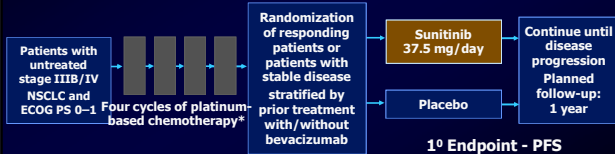
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### CALGB 30607: Sunitinib as Maintenance Therapy in Non-progressing Advanced NSCLC Patients Following Chemotherapy

Phase III, randomized, placebo-controlled trial

Planned randomization: 240 patients



\*Platinum-based regimen may include carboplatin/cisplatin plus paclitaxel, docetaxel, vinorelbine or gemcitabine with or without bevacizumab (bevacizumab discontinued after four cycles)

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## Fast Moving Paradigm



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