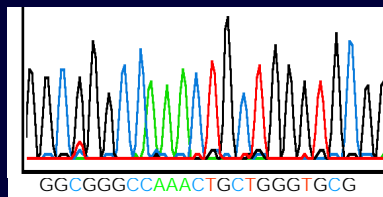

Interview with Dr. Suresh Ramalingam,
Director, Lung Cancer Program,
Winship Cancer Institute at Emory University:
First Line Advanced NSCLC & Maintenance Therapy



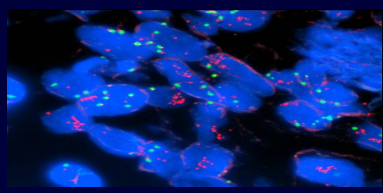
By
Howard (Jack) West, MD
Medical Oncologist
President & CEO
GRACE

May, 2009

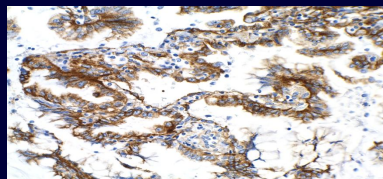
Common EGFR Molecular Marker Studies



- EGFR mutation status by gene sequencing



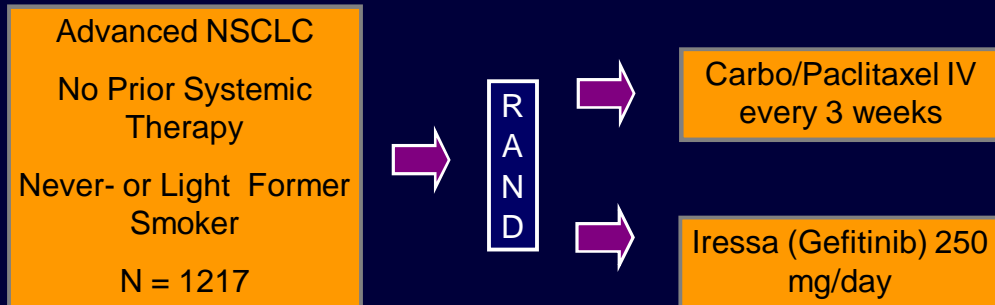
- EGFR gene copy number by fluorescence in situ hybridization (FISH)



- EGFR protein expression by immunohistochemistry (IHC)



IPASS: Gefitinib vs. Carbo/Paclitaxel as First Line Rx in Asian Never- or Light Ex-Smokers



Primary Endpoint: Progression-Free Survival (PFS)
Biomarker analysis

Mok, ESMO 2008, A # LBA2

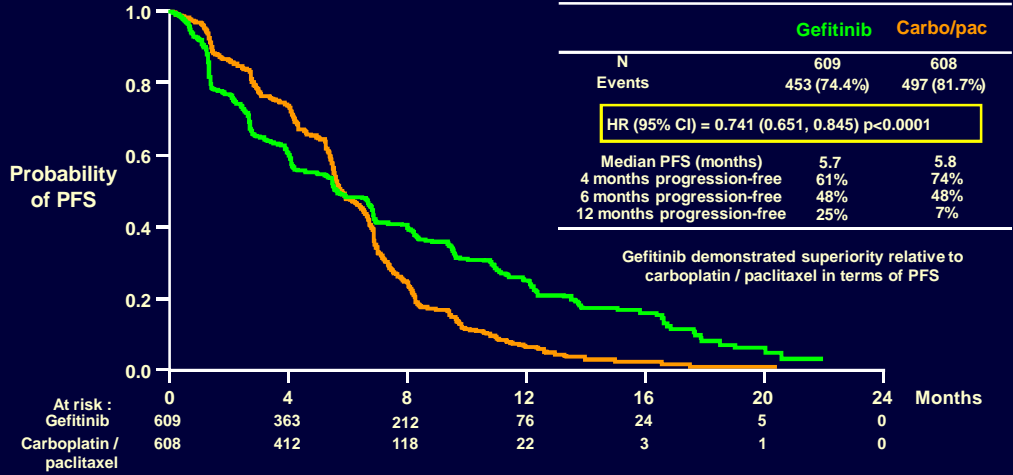


IPASS: Patient Characteristics

	Iressa (Gefitinib), % (N=609)	Carbo / paclitaxel, % (N=608)
Age <65 years	73	74
Median age (range), years	57 (24-84)	57 (25-84)
Female ^a	79	79
Never smoker ^a	94	94
Light ex-smoker ^a	6	6
Mean smoking duration, years	11.5 (N=38)	14.5 (N=39)
Mean time since cessation, years	24.6 (N=38)	23.4 (N=39)
Time since diagnosis: <6 months	96	94
Chinese ethnicity ^b	52	50
Japanese ethnicity ^b	19	20



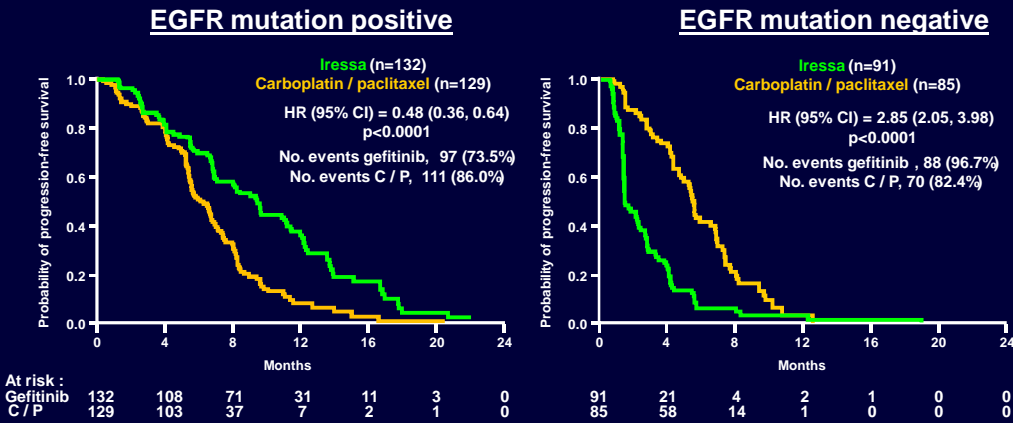
IPASS: Progression-Free Survival



Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib



IPASS: Progression-Free Survival by EGFR Mutation Status



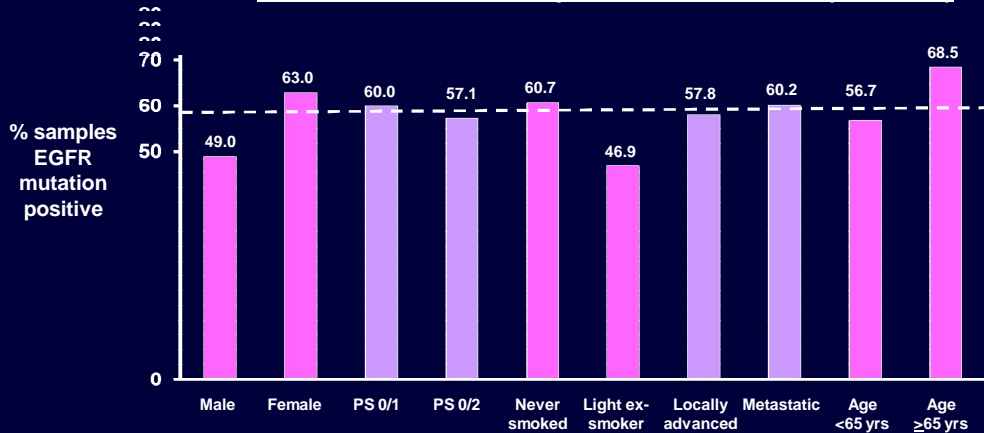
Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates



IPASS: EGFR Mutation Positive Status and Clinical Characteristics

Overall EGFR mutation positive rate = 59.7% (261 / 437)



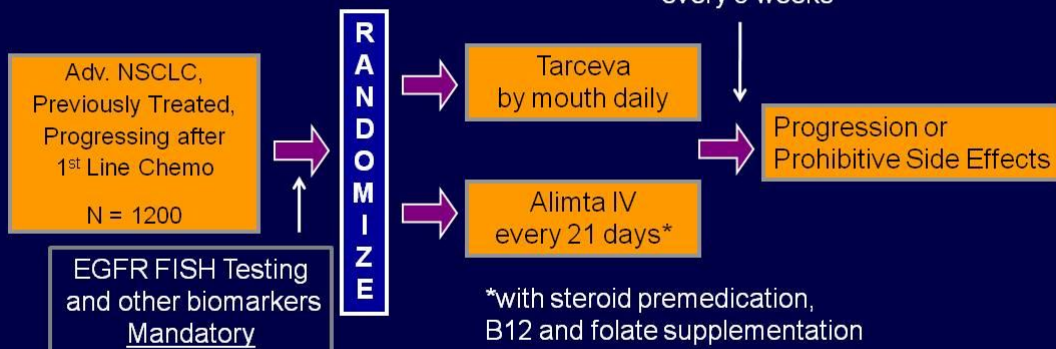
Even Asian never-smoker doesn't equal EGFR mutation



MARVEL Trial (N0723): Marker Validation for Erlotinib in Lung Cancer

Lead Investigator: Alex Adjei (Roswell Park)

Check CT every 6 weeks

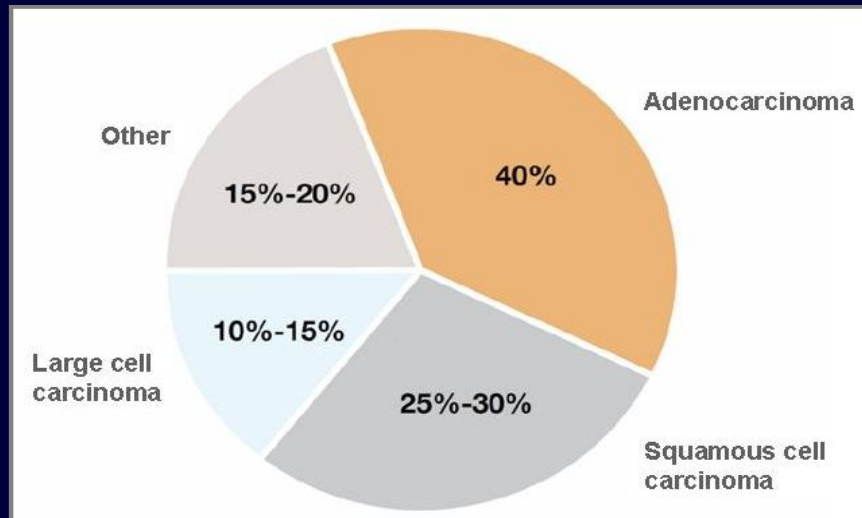


*with steroid premedication, B12 and folate supplementation

HYPOTHESIS:

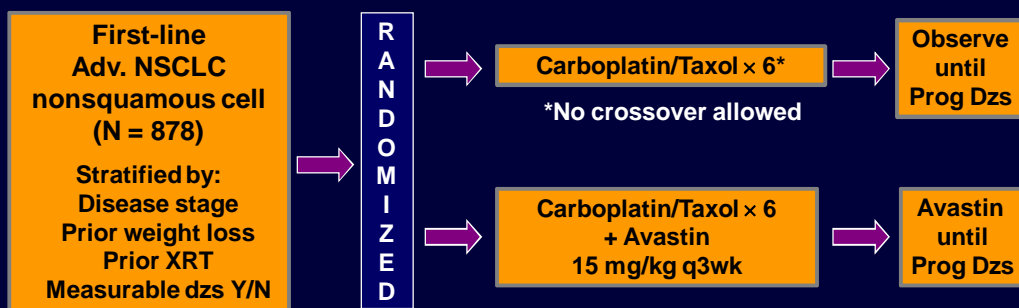
alimta will be superior for EGFR FISH negative patients
tarceva will be superior for EGFR FISH positive patients

Histology Breakdown of NSCLC in US



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CANCER EDUCATION

ECOG 4599: Carboplatin/Paclitaxel (Taxol) +/- Avastin (Bevacizumab)



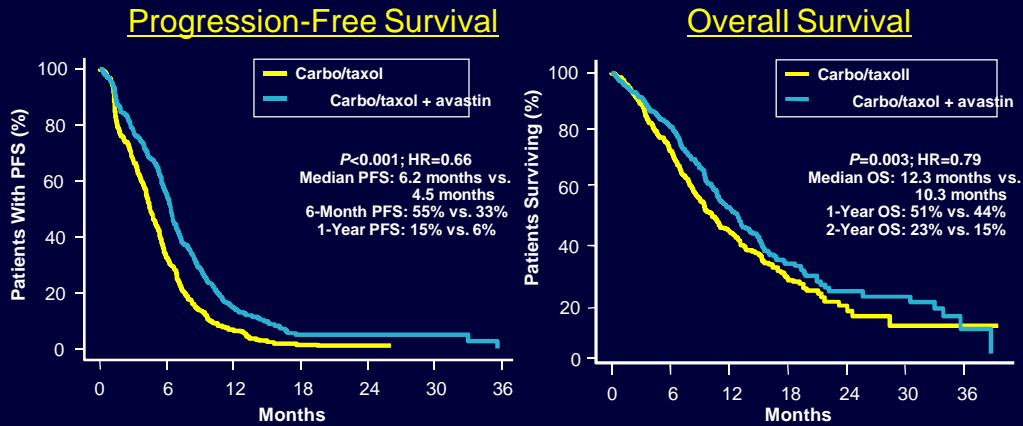
- This trial excluded patients with squamous tumors, history of hemoptysis, brain metastases, on therapeutic anticoagulation, or with a history of active cardiovascular disease or uncontrolled hypertension

Sandler et al. *N Engl J Med.* 2006;355:2542.

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CANCER EDUCATION

Carbo/Taxol +/- Avastin (Bevacizumab): Key Clinical Outcomes

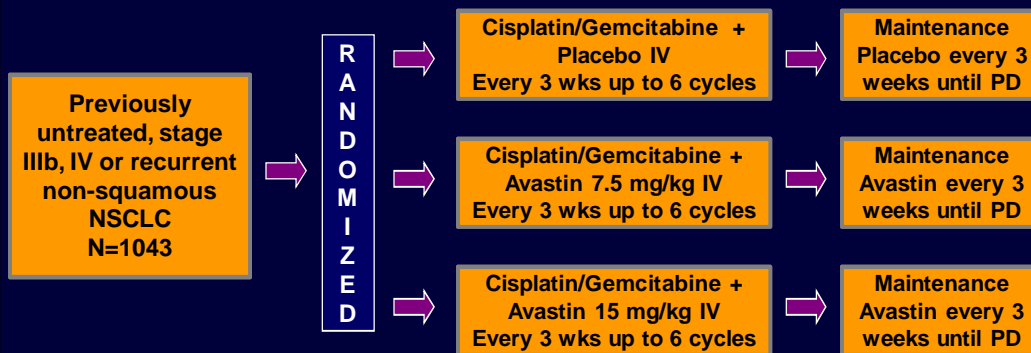
- Response rate: 15% for carbo/taxol vs. 35% for same chemo + avastin



Sandler et al. *N Engl J Med.* 2006;355:2542; Sandler et al. *ASCO.* 2005 (abstr 4).



AVAiL Study design

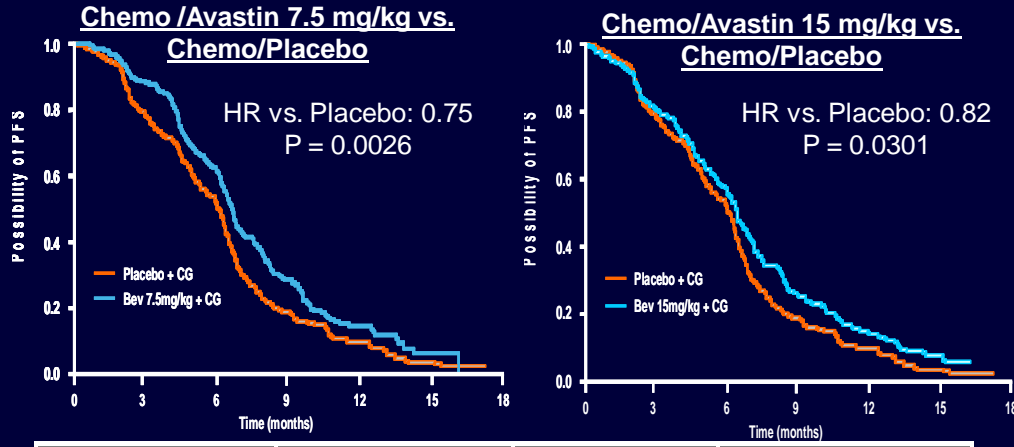


- All Arms received Cisplatin 80 mg/m² day 1 & Gemcitabine 1250 mg/m² day 1,8 q 3 wk
- Tumor assessment every 3 cycles (9 weeks)
- Excluding patients with squamous NSCLC, brain mets, grade 2 or worse hemoptysis.

Manegold, Proc of ASCO 2007,A#7514; ESMO, 2008



AVAiL Trial: Efficacy



	Chemo/Placebo	Chemo/ Avastin 7.5 mg/kg	Chemo/ Avastin 15 mg/kg
Median Overall Surv	13.1 mo.	13.6 mo.	13.4 mo.

Manegold, Proc of ASCO 2007, A#7514; ESMO, 2008



Efficacy Endpoints on ECOG 4599: Elderly vs. Non-Elderly Patients

	Elderly (> 70)		Non-Elderly (< 70)	
	Chemo	Chemo/Avastin	Chemo	Chemo/Avastin
Response Rate	17%	29%	14%	36%
Median PFS	4.9 mo	5.9 mo P=0.063	4.4 mo	6.2 mo P<0.001
1-Yr Survival	50%	46%	42%	53%
Median survival	12.1 mo	11.3 mo P = 0.4	9.6 m	12.8 mo P = 0.0027

Ramalingam, J Clin Oncol., 2008



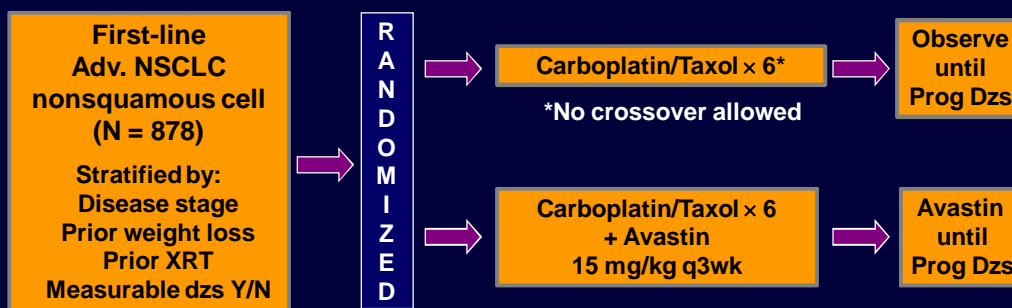
Toxicity on Chemo/Avastin in Elderly vs. Non-Elderly Patients

<u>Grade 3/4</u>	<u>> 70 yrs</u>	<u>< 70 yrs</u>	<u>P value</u>
Neutropenia (Gr 4)	34%	22%	0.02
GI Bleed	3.5%	0.9%	0.005
Proteinuria	7.9%	1.3%	0.001
Muscle weakness	7.8%	2.2%	0.02
Motor neuropathy	3.5%	0.6%	0.05
Dizziness	7.9%	1.6%	0.003
Worst Grade	87%	70%	< 0.001
Treatment-Related Deaths	6.3%	2.6%	0.08

Ramalingam, J Clin Oncol 2008



ECOG 4599: Carboplatin/Paclitaxel (Taxol) +/- Avastin (Bevacizumab)



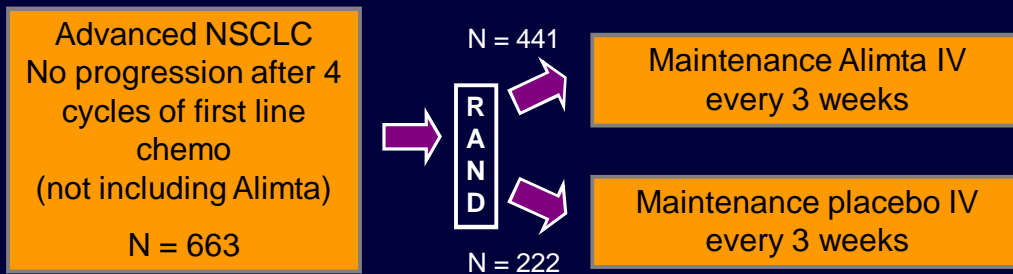
- This trial excluded patients with squamous tumors, history of hemoptysis, brain metastases, on therapeutic anticoagulation, or with a history of active cardiovascular disease or uncontrolled hypertension

Sandler et al. *N Engl J Med.* 2006;355:2542.



JMEN: Maintenance Alimta (Pemetrexed) vs. Placebo after First-Line Chemotherapy

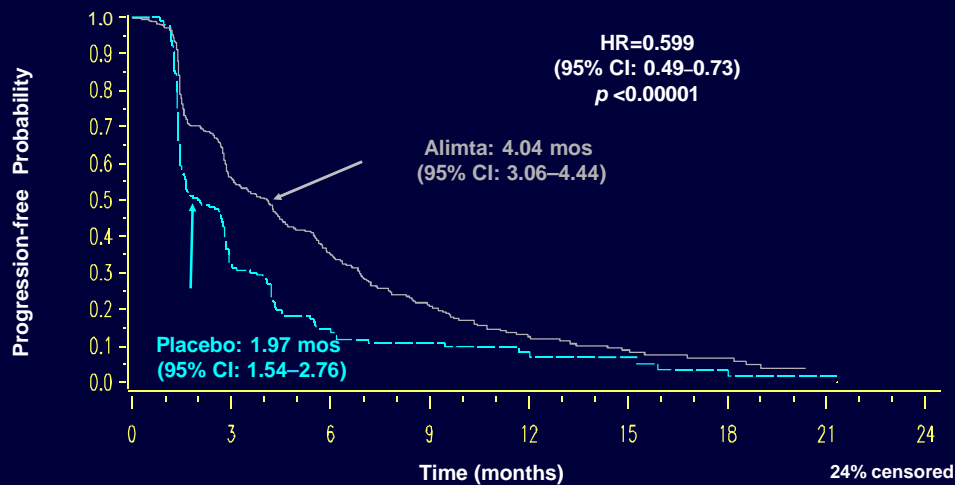
- Does going on maintenance Alimta (pemetrexed) after four cycles of first-line chemo improve progression-free survival (PFS)?



Ciuleanu, Proc ASCO 2008, A #8011.



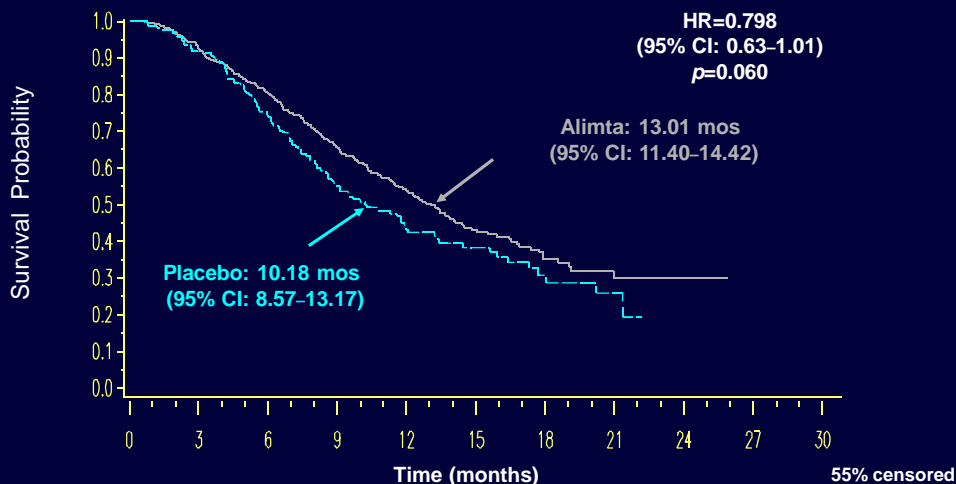
Maintenance Alimta vs. Placebo: Progression-Free Survival



Ciuleanu, Proc ASCO 2008, A #8011.



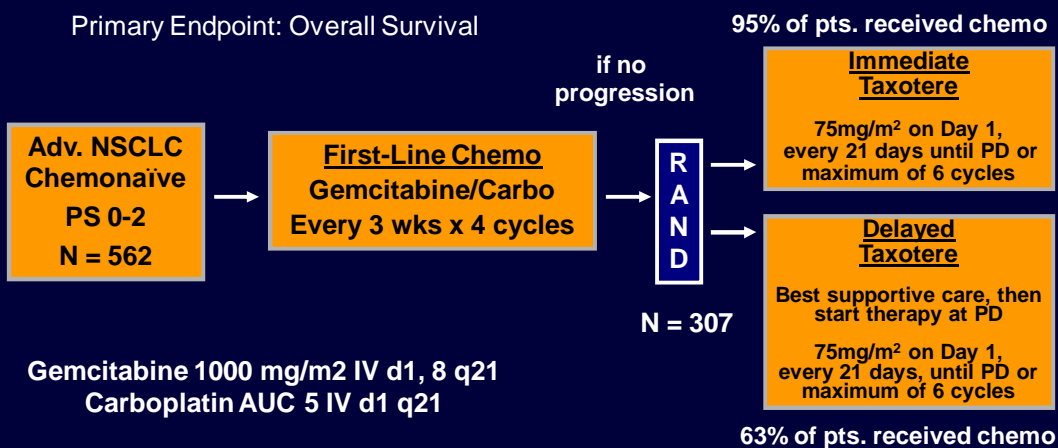
Maintenance Alimta vs. Placebo: Preliminary Overall Survival



Ciuleanu, Proc ASCO 2008, A #8011.



Immediate vs. Delayed Second-Line Taxotere (Docetaxel)



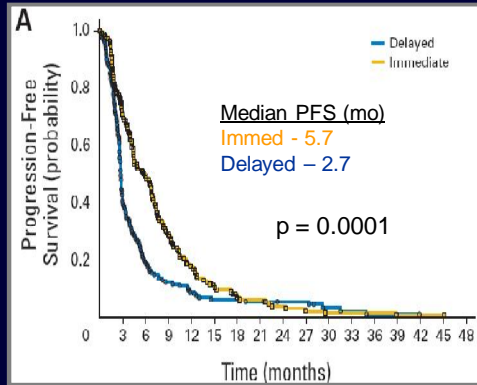
BUT 3 month wait to assess for PD!!

Fidias, J Clin Oncol 2009

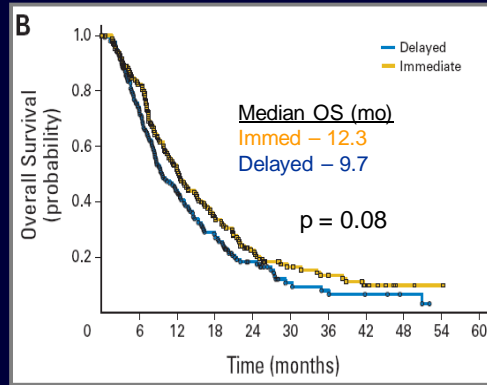


Immediate vs. Delayed Second-Line Taxotere: Efficacy

Progression-Free Survival



Overall Survival

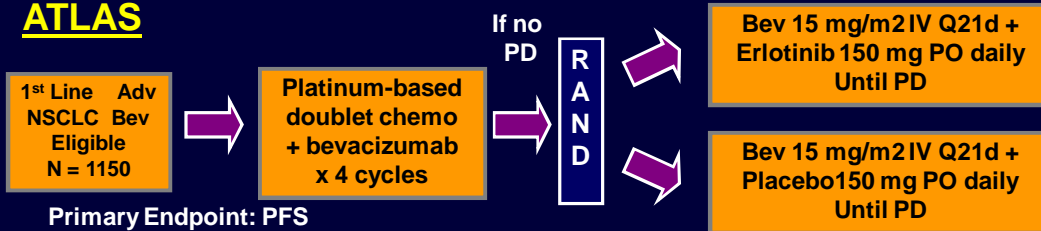


Fidias, J Clin Oncol 2009

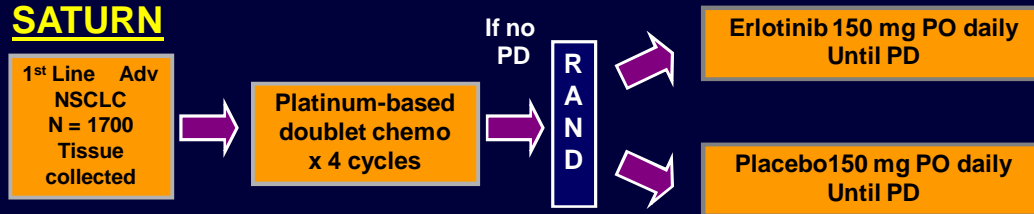


Genentech Maintenance Therapy Trials in Advanced NSCLC

ATLAS



SATURN



Primary Endpoint: PFS (All, and EGFR IHC +)



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