Best of ASCO for Advanced NSCLC

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Disclosure and Conflict of Interest Management

- I am a consultant for Pfizer and Sanofi-Aventis.
- I have received research funding from Sanofi-Aventis, BMS, Onyx, Ligand , Oxigene, Pfizer, Genentech, and Novartis for investigator initiated research in drug development and head & neck, and lung cancers over the last 15 years.
- I have received more than ten-fold more peer reviewed government funding (NCI, DoD) than total pharmaceutical funding over the last 15 years.
- My opinions on approaches to the treatment of lung cancer are my own and, while evidence based, are potentially controversial.

Learning Objectives

- To understand the present role of maintenance therapy in advanced NSCLC
- Appropriate utilization of EGFR inhibitors
- Discussion of individualized treatment approaches

Outline

- Continuation Maintenance Therapy
- EGFR tyrosine kinase inhibition
  - First-line therapy
  - Maintenance therapy
  - Combination therapy
- VEGF Inhibition
- Individualized therapy

Maintenance Therapy for Advanced NSCLC

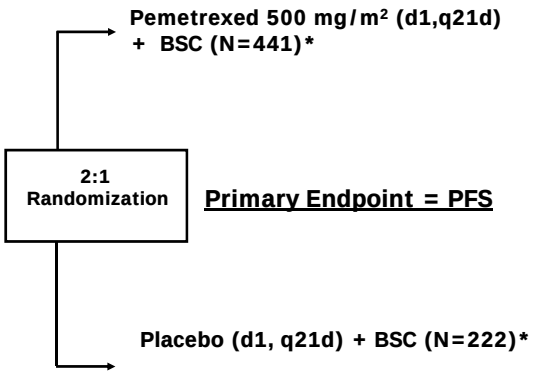
- Refers to the use of systemic therapy following 4 to 6 cycles of combination chemotherapy in the front-line setting
- FDA-approved agents
  - Pemetrexed
  - Erlotinib
  - Improvement in survival noted with both of these agents

JMEN: Maintenance Pemetrexed vs Placebo

- **Stage IIIB/IV NSCLC**
- **PS 0-1**
- **4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD**

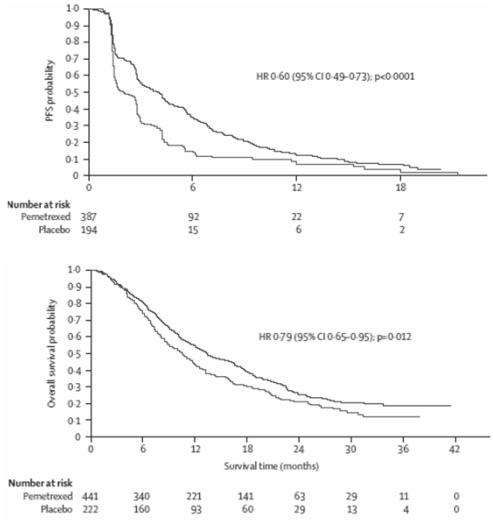
Randomization factors:
- **gender**
- **PS**
- **stage**
- **best tumor response to induction**
- **non-platinum induction drug**
- **brain mets**

Ciuleanu et al, Lancet, 2009.



*B_{12}, folate, and dexamethasone given in both arms

PFS and OS in the Overall Population



'Switch' or 'Continuation' Maintenance Therapy?

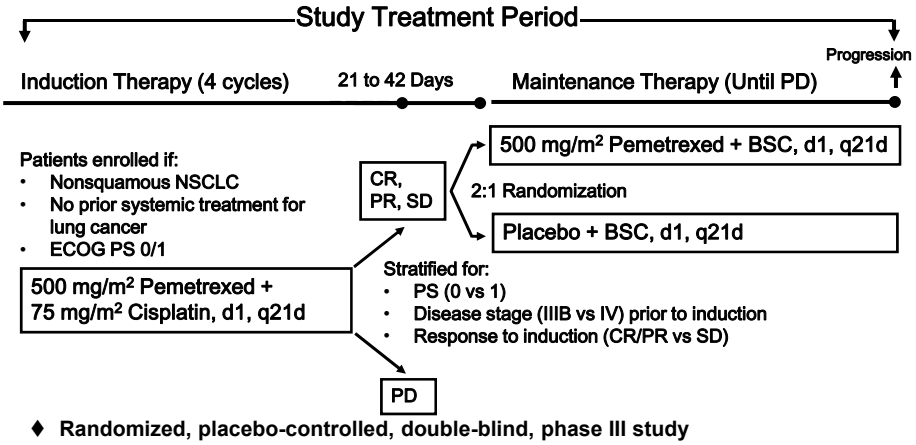
- Pemetrexed and erlotinib were both studied as switch maintenance therapy
- Bevacizumab and cetuximab are used as continuation maintenance following administration in combination with chemotherapy
  - Their role in this setting is unproven

PARAMOUNT: Phase III Study of Maintenance Pemetrexed (Pem) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC Immediately Following Induction Treatment with Pem Plus Cisplatin for Advanced Nonsquamous Non-small Cell Lung Cancer

Abstract # 7510

L. G. Paz-Ares[1], F. de Marinis[2], M. Dediu[3], M. Thomas[4], J.L. Pujol[5], P. Bidoli[6], O. Molinier[7], T.P. Sahoo[8], E. Laack[9], M. Reck[10], J. Corral[1], S. Melemed[11], W. John[11], N. Chouaki[12], A. H. Zimmermann[11], C. Visseren-Grul[13], C. Gridelli[14]

PARAMOUNT: Study Design

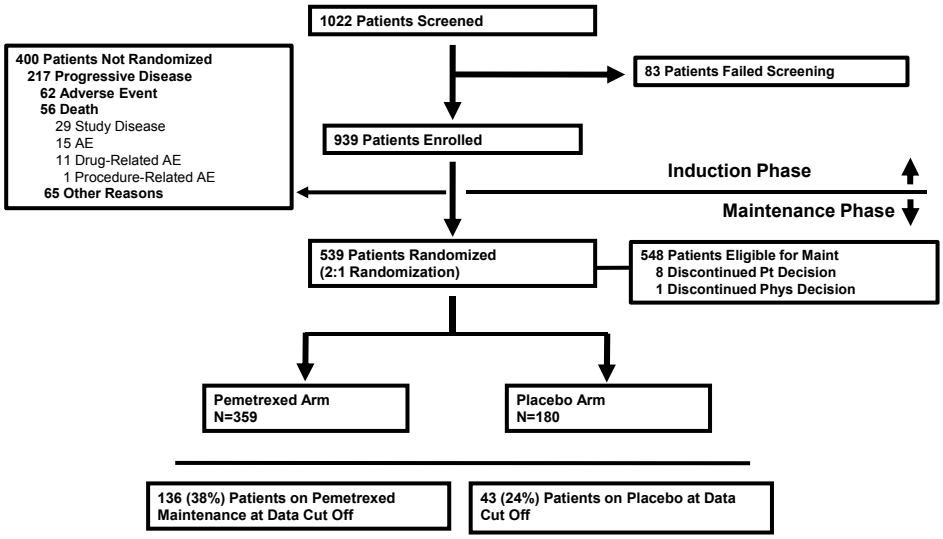


- Randomized, placebo-controlled, double-blind, phase III study
- Folic acid and vitamin B_{12} administered to both arms

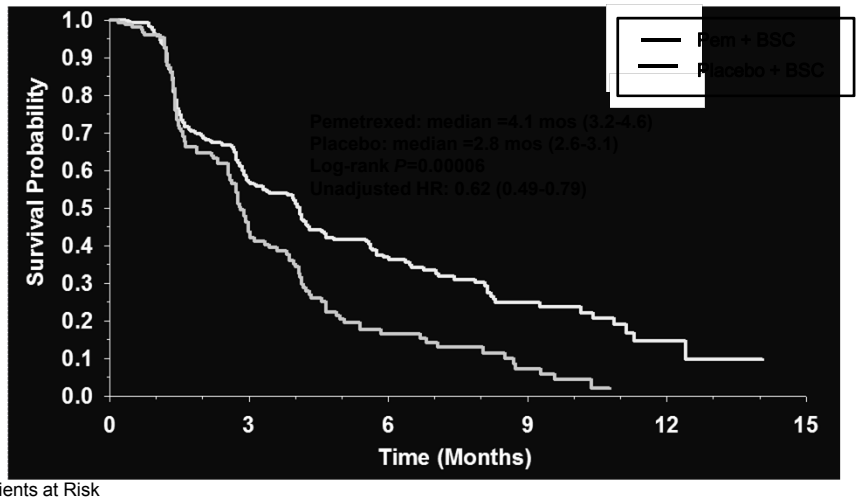
PARAMOUNT: Study Objectives

- Primary objective: progression-free survival (PFS)
- Secondary objectives:
  - Overall survival (OS)
  - Objective tumor response rate (RR) (RECIST 1.0)
  - Patient-reported outcomes (EQ-5D)
  - Resource utilization
  - Adverse events (AEs)
- All endpoints measured from date of randomization, after completion of induction chemotherapy

PARAMOUNT: Patient Disposition



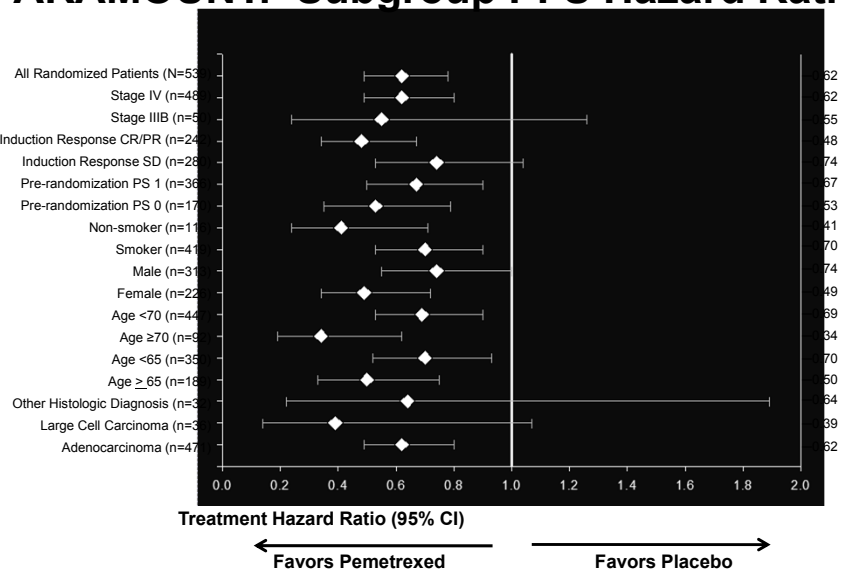
PARAMOUNT: Investigator Assessed PFS (from Maintenance)



Patients at Risk

Pem + BSC	N=359	132	57	21	4	0
Placebo + BSC	N=180	52	15	5	0	0

PARAMOUNT: Subgroup PFS Hazard Ratios



♦ **PFS results were internally consistent; benefit was seen across all subgroups**

PARAMOUNT Study: Implications

- First randomized study to evaluate the role of continuation maintenance therapy (monotherapy)
- Pemetrexed is an agent with good therapeutic index
- Demonstrated modest PFS benefit
- No detrimental effects of QOL with pemetrexed
- Survival data are awaited

Our Approach

- Maintenance therapy for patients that present with symptomatic or 'large disease burden'
- For patients with EGFR mutation, EGFR TKI therapy is recommended
- Switch maintenance therapy
  - Await survival data from PARAMOUNT
- For patients on bevacizumab-based regimen, continuation of bevacizumab

EGFR Inhibition in NSCLC

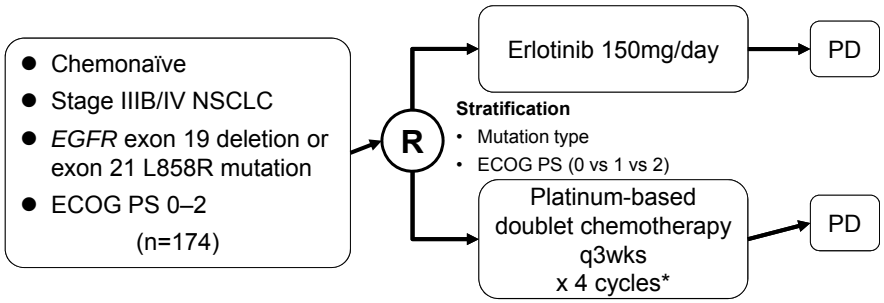
- Erlotinib is approved for maintenance and 2nd/3rd line therapy of advanced NSCLC
- Presence of EGFR mutation predicts for robust response rates and PFS
- Gefitinib has a superior PFS and RR compared to chemotherapy in patients with an EGFR mutation (exon 19 or 21)

Erlotinib vs chemotherapy (CT) in advanced non-small-cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) activating mutations: Interim results of the European Tarceva® vs Chemotherapy (EURTAC) phase III randomized trial

R Rosell, R Gervais, A Vergnenegre, B Massuti, E Felip, F Cardenal, R Garcia-Gomez, C Pallarès, JM Sanchez, R Porta, M Cobo, M Di Seri, P Garrido, A Insa, F de Marinis, R Corre, M Carreras, E Carcereny, M Taron, L Paz-Ares on behalf of the Spanish, French and Italian Lung Cancer Groups

Abstract # 7503

EURTAC study design



Primary endpoint

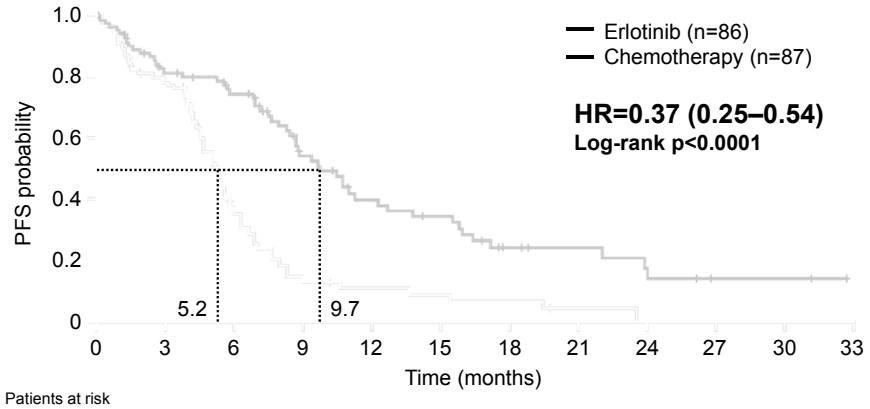
- Progression-free survival (PFS)
  - interim analysis planned at 88 events

Secondary endpoints

- Objective response rate
- Overall survival (OS)
- Location of progression
- Safety
- *EGFR* mutation analysis in serum
- Quality of life

ECOG = Eastern Cooperative Oncology Group; PS = performance status; PD = progressive disease
*Cisplatin 75mg/m^2 d1 / docetaxel 75mg/m^2 d1; cisplatin 75mg/m^2 d1 / gemcitabine 1250mg/m^2 d1,8; carboplatin AUC6 d1 / docetaxel 75mg/m^2 d1; carboplatin AUC5 d1 / gemcitabine 1000mg/m^2 d1,8

PFS in ITT population
(updated analysis 26 Jan 2011)



Patients at risk

Erlotinib	86	63	54	32	21	17	9	7	4	2	2	0
Chemo	87	49	20	8	5	4	3	1	0	0	0	0

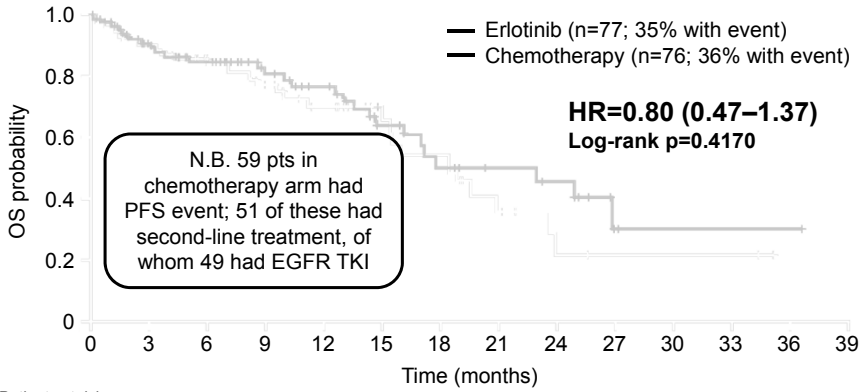
Data cut-off: 26 Jan 2011

Baseline characteristics

	Interim analysis (Aug 2, 2010)		Updated analysis (Jan 26, 2011)	
	Erlotinib (n=77)	Chemotherapy (n=76)	Erlotinib (n=86)	Chemotherapy (n=87)
Median age, yrs (range)	64 (24–82)	64 (29–82)	65 (24–82)	65 (29–82)
Gender, %				
Male	32	21	33	22
Female	68	79	67	78
ECOG PS, %				
0	30	34	31	34
1	57	54	55	52
2	13	12	14	14
Smoking status, %				
Current smoker	4	13	8	14
Former smoker	26	13	26	14
Never smoker	70	74	66	72
EGFR mutation type, %				
Exon 19 deletion	64	63	66	67
L858R mutation	36	37	34	33

N.B. All patients were Caucasian and the majority (~90%) had stage IV disease and adenocarcinoma

Overall survival in ITT population (interim analysis 2 Aug 2010)



Patients at risk

Erlotinib	77	61	53	41	34	22	14	11	9	2	1	1	1	0
Chemo	76	59	43	35	25	18	14	7	3	2	2	2	0	0

Data cut-off: 2 Aug 2010

EURTAC Study: Implications

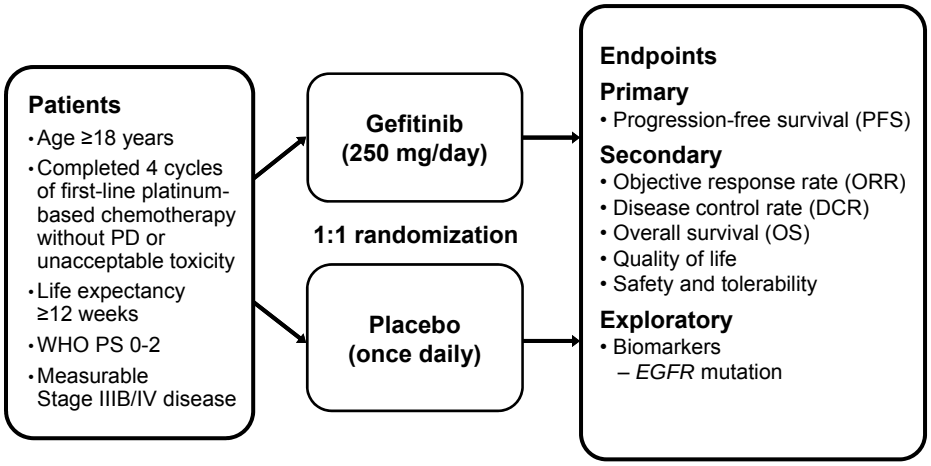
- Confirms the superiority of erlotinib over chemotherapy in patients with EGFR mutated tumors
- Lack of survival benefit is not surprising given the potential cross-over
- Screening for EGFR mutations is recommended in patients with adenocarcinoma
- For patients with wild-type or unknown EGFR status, combination chemotherapy is the standard approach

Efficacy and tolerability data from a randomized, placebo-controlled, parallel-group study of gefitinib as maintenance therapy in patients with locally advanced or metastatic NSCLC (INFORM) (C-TONG 0804)

L Zhang, SL Ma, XQ Song, BH Han, Y Cheng, C Huang, SJ Yang, XQ Liu, YP Liu, MZ Wang, XW Zhang on behalf of the INFORM investigators

Abstract # 7511

Study design

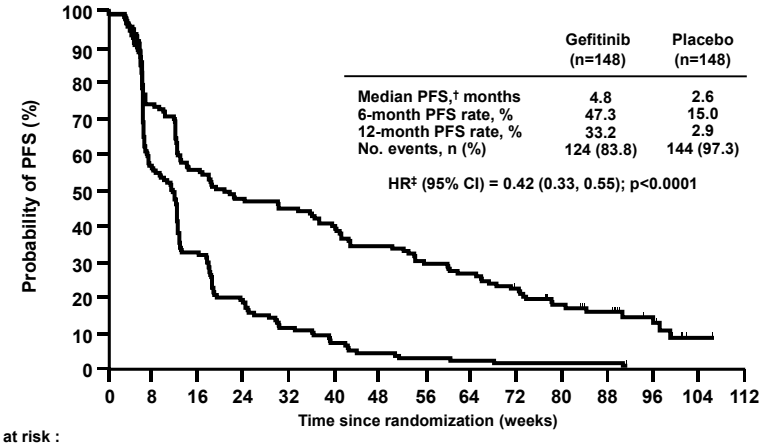


Demography (ITT population)

	Gefitinib (n=148)	Placebo (n=148)
Age <65 years, n (%)	129 (87.2)	130 (87.9)
Median age (range), years	54 (31-79)	54 (20-75)
Gender,† n (%) Female Male	 65 (43.9) 83 (56.1)	 56 (37.8) 92 (62.2)
Asian ethnicity, n (%)	148 (100.0)	148 (100.0)
WHO PS, n (%) 0, 1, 2	 69 (46.6), 76 (51.4), 3 (2.0)	 72 (48.6), 72 (48.6), 4 (2.7)
Smoking history,† n (%) Smoker (ex- or current smoker) Never smoker	 69 (46.6) 79 (53.4)	 67 (45.3) 81 (54.7)
Histology,† n (%) Adenocarcinoma Squamous	 105 (70.9) 27 (18.2)	 104 (70.3) 30 (20.3)
Disease stage, n (%) IIIB IV	 42 (28.4) 106 (71.6)	 32 (21.6) 115 (77.7)
First-line taxane-based chemotherapy, n (%)	60 (40.5)	66 (44.6)
Response (CR/PR, SD) to first-line therapy, n (%)	58 (39.2), 90 (60.8)	51 (34.5), 97 (65.5)

†Stratification factor

Progression-free survival (ITT population)



	Gefitinib (n=148)	Placebo (n=148)
Median PFS,† months	4.8	2.6
6-month PFS rate, %	47.3	15.0
12-month PFS rate, %	33.2	2.9
No. events, n (%)	124 (83.8)	144 (97.3)

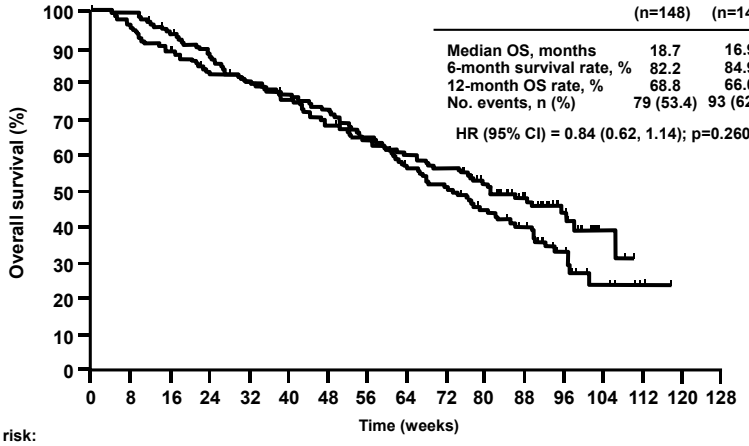
HR‡ (95% CI) = 0.42 (0.33, 0.55); p<0.0001

Patients at risk :

Placebo	148	82	46	26	16	10	6	4	3	2	2	2	0	0	0
Gefitinib	148	109	82	70	65	56	49	42	38	31	20	15	6	1	0

†Estimated using the Kaplan-Meier method
‡Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib

Overall survival (ITT population)



	Gefitinib (n=148)	Placebo (n=148)
Median OS, months	18.7	16.9
6-month survival rate, %	82.2	84.9
12-month OS rate, %	68.8	66.0
No. events, n (%)	79 (53.4)	93 (62.8)

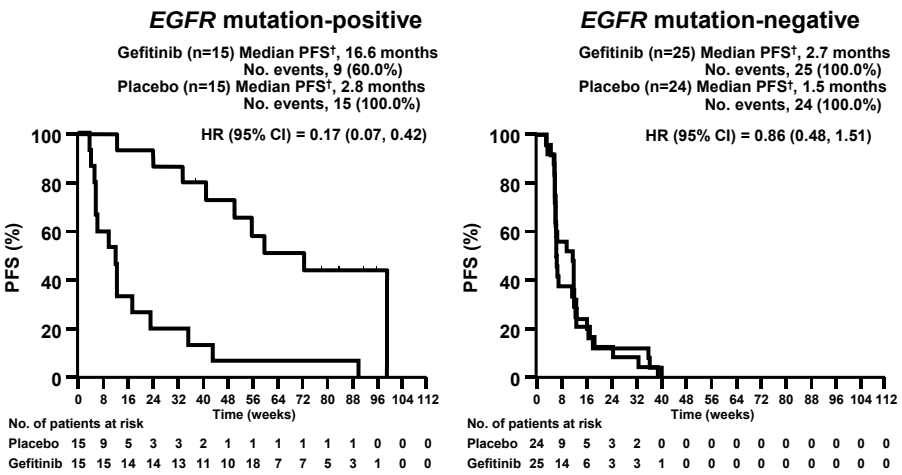
HR (95% CI) = 0.84 (0.62, 1.14); p=0.2608

Patients at risk:

Placebo	148	147	136	127	115	107	97	91	78	66	47	37	13	6	0	0	0
Gefitinib	148	141	129	119	114	108	102	90	84	75	56	39	18	4	0	0	0

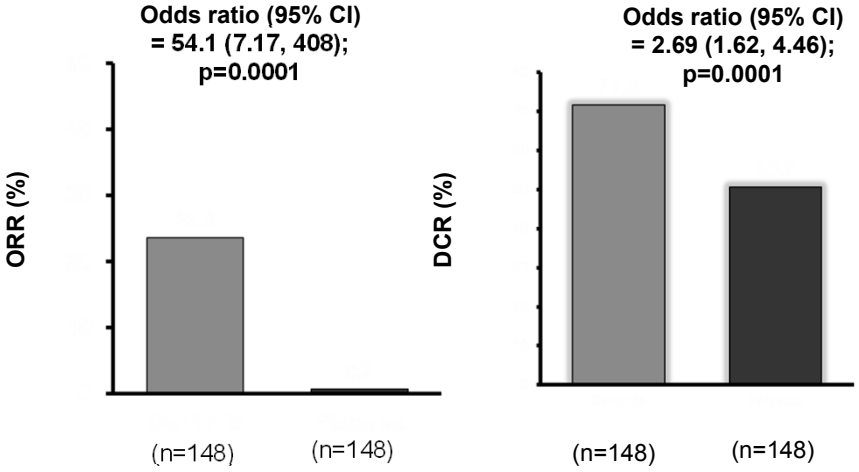
HR <1 implies a lower risk of death on gefitinib

PFS by *EGFR* mutation status



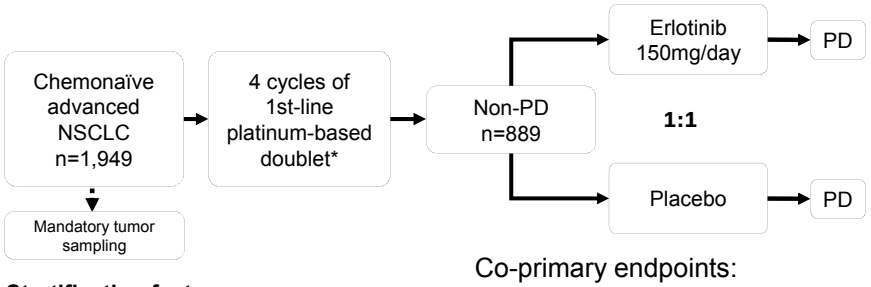
†Estimated using the Kaplan-Meier method
HR <1 implies a lower risk of progression on gefitinib

Objective response rate and disease control rate (RECIST; ITT population)



Odds ratio >1 implies a greater chance of response on gefitinib
Odds ratio and p-value from logistic regression with covariates
ITT, intent-to-treat; RECIST, Response Evaluation Criteria In Solid Tumors

SATURN



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:

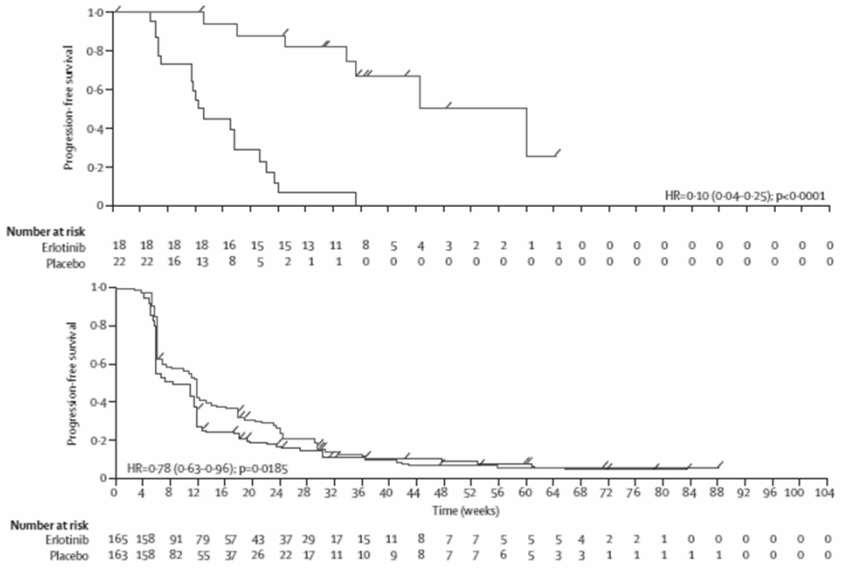
- PFS in all patients
- PFS in patients with EGFR IHC+ tumors

Secondary endpoints:

- Overall survival (OS) in all patients and those with EGFR IHC+ tumors, OS and PFS in EGFR IHC– tumors; biomarker analyses; safety; time to symptom progression; quality of life (QoL)

Cappuzzo et al, Lancet Oncol, 2010

SATURN: PFS by EGFR Mutation Status



EGFR TKI as Maintenance Therapy

- Gefitinib improved PFS, but there was no improvement in OS as maintenance therapy
- The effect in EGFR mutated tumors is similar to that seen with erlotinib
- Benefit in patients with wild-type EGFR was minimal
- Once again supports the notion that EGFR mutation is a predictive marker for EGFR TKIs

Improving the Efficacy of EGFR TKIs

Strategies to Improve Efficacy of EGFR TKIs

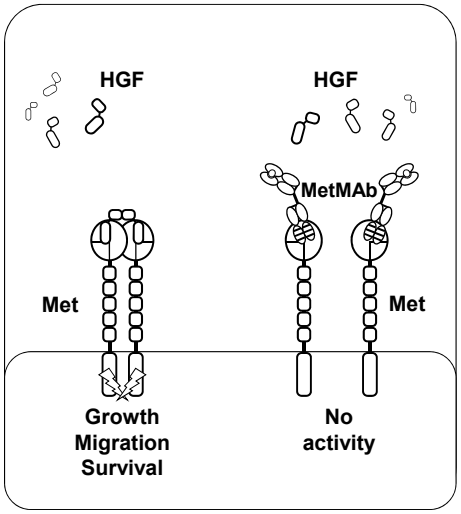
- Erlotinib in combination with VEGF inhibitors
  - No improvement in OS
- Erlotinib in combination with IGF-1R inhibitors
  - No efficacy advantage in unselected patients
- Erlotinib in combination with HDAC inhibitors
  - Benefit may be predicted by E-cadherin expression status

Final efficacy results from OAM4558g, a randomized Phase II study evaluating MetMAb or placebo in combination with erlotinib in advanced NSCLC

David R Spigel,[1,2] Thomas J Ervin,[1,3] Rodryg Ramlau,[4] Davey B Daniel,[1,5] Jerome H Goldschmidt Jr,[6] George R Blumenschein Jr,[7] Maciej J Krzakowski,[8] Gilles Robinet,[9] Christelle Clement-Duchene,[10] Fabrice Barlesi,[11] Ramaswamy Govindan,[12] Taral Patel,[13] Sergey V Orlov,[14] Michael S Wertheim,[15] Jiping Zha,[16] Ajay Pandita,[17] Wei Y,[17] Robert L Yauch,[17] Premal H Patel,[17] Amy C Peterson[17]

Abs # 7505

MetMAb is an anti-Met one-armed antibody that inhibits HGF-mediated activation



- Rationale for targeting Met:
  - Met is amplified, mutated, or overexpressed, corresponding to pathway activation in many tumors
  - Met expression is associated with a worse prognosis in many cancers including NSCLC
  - Met activation is implicated in resistance to erlotinib/gefitinib in patients with activating EGFR mutations
- MetMAb:
  - One-armed (monovalent) format designed to inhibit HGF-mediated stimulation of pathway
  - Preclinical activity across multiple tumor models

HGF: hepatocyte growth factor

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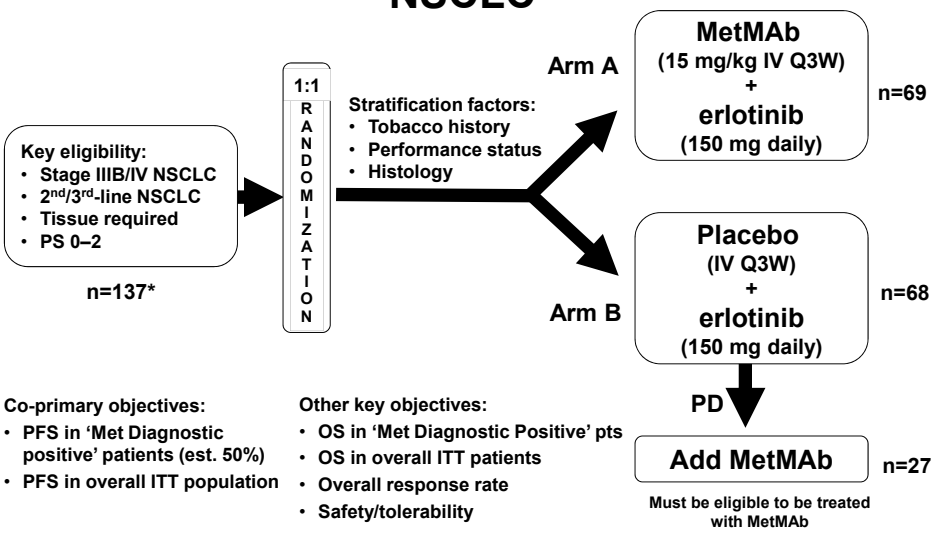
Phase II: Erlotinib +/- MetMAb in 2nd/3rd-line NSCLC



Co-primary objectives:
- PFS in 'Met Diagnostic positive' patients (est. 50%)
- PFS in overall ITT population

Other key objectives:
- OS in 'Met Diagnostic Positive' pts
- OS in overall ITT patients
- Overall response rate
- Safety/tolerability

*128 NSCLC patients enrolled from 3/2009 to 3/2010 plus 9 SCC patients enrolled through 8/2010
Data presented includes >5 additional months of follow-up

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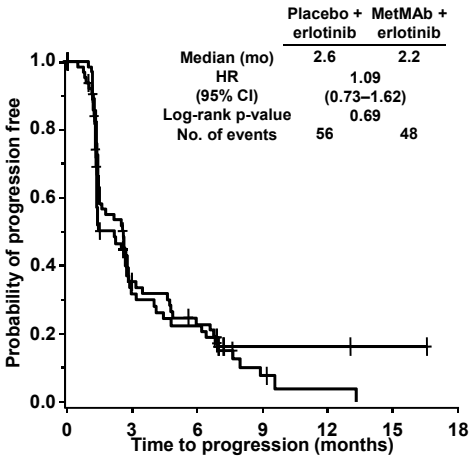
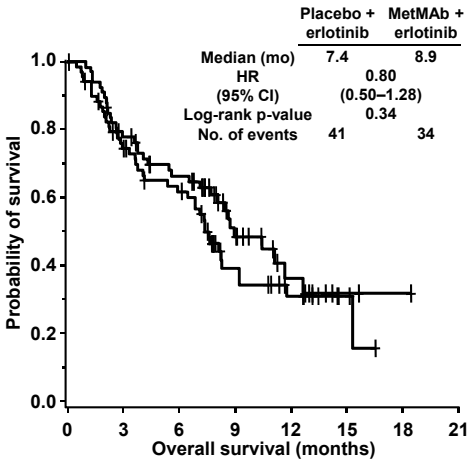
MetMAb plus erlotinib in ITT population

PFS: HR=1.09



OS: HR=0.8



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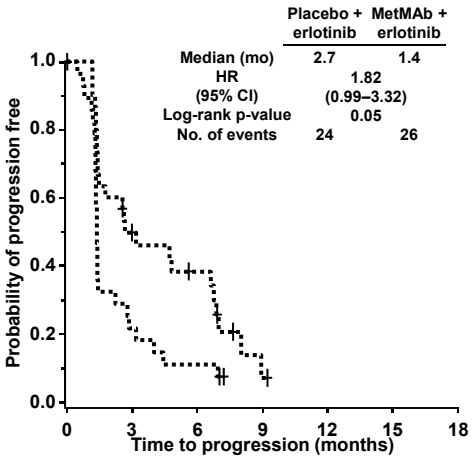
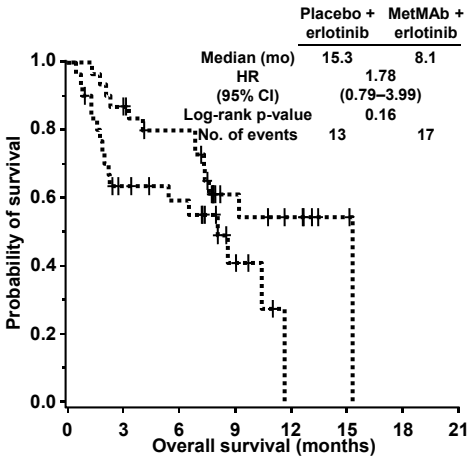
MetMAb plus erlotinib in Met Dx- patients

PFS: HR=1.82



OS: HR=1.78



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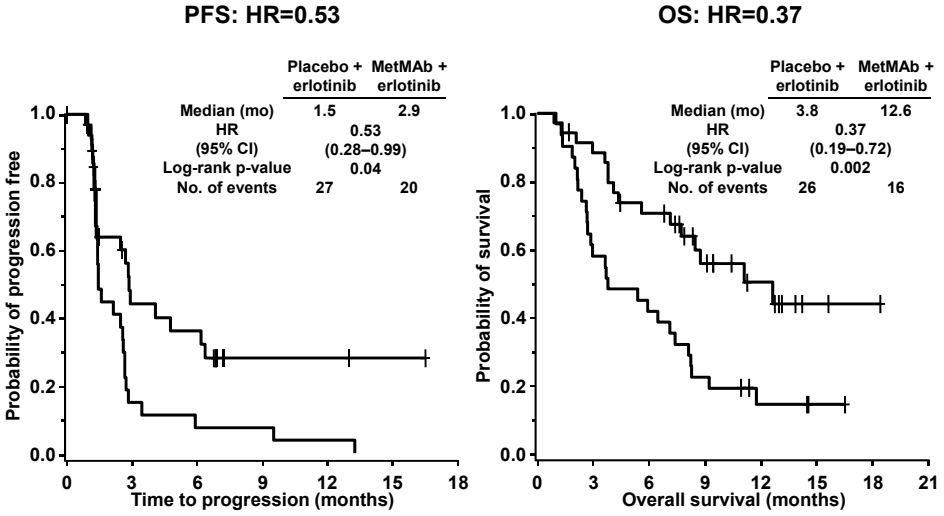
MetMAb plus erlotinib in Met Dx+ patients



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Met inhibition in NSCLC

- The study demonstrates modest improvement in efficacy for MetMab a molecularly selected group of patients
- ARQ197, a Met TKI, has also demonstrated promising results in combination with erlotinib
- Phase III studies are planned/ongoing
- C-Met is a rational therapeutic target to improve efficacy of EGFR TKIs

VEGF Inhibition in NSCLC

- Bevacizumab improves survival in combination with carboplatin and paclitaxel in advanced non-squamous NSCLC
- VEGF tyrosine kinase inhibitors have demonstrated single agent activity in NSCLC
- Combination strategies with VEGFR TKIs have been disappointing to date

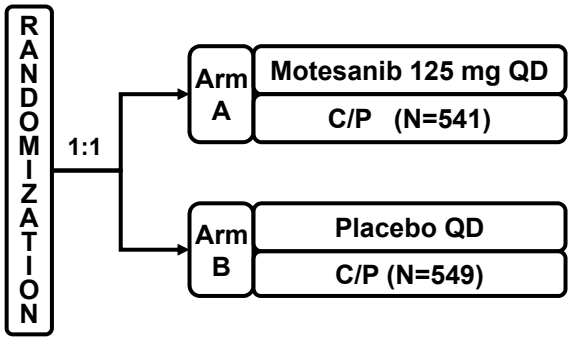
An international, randomized, placebo-controlled, double-blind phase III study (MONET1) of motesanib plus carboplatin/paclitaxel (C/P) in patients with advanced nonsquamous non–small-cell lung cancer (NSCLC)

Giorgio Scagliotti,[1] Ihor Vynnychenko,[2] Yukito Ichinose,[3] Keunchil Park,[4] Kaoru Kubota,[5] Fiona Blackhall,[6] Robert Pirker,[7] Rinat Galiulin,[8] Tudor-Eliade Ciuleanu,[9] Oleksandr Sydorenko,[10] Mircea Dediu,[11] Zsolt Papai-Szekely,[12] Natividad Martinez Banaclocha,[13] Sheryl McCoy,[14] Bin Yao,[15] Yong-jiang Hei,[15] David R. Spigel[16]

Abstract # 7512

MONET1 DESIGN

International, double-blind, placebo-controlled, randomized study (208 centers; 32 countries)



Treatment until
- Disease progression
- Unacceptable toxicity
- Consent withdrawn

Tumor assessments
- CT or MRI scans of the chest, abdomen, and pelvis every 6 weeks
- Per RECIST v1.0 by investigator

Chemotherapy

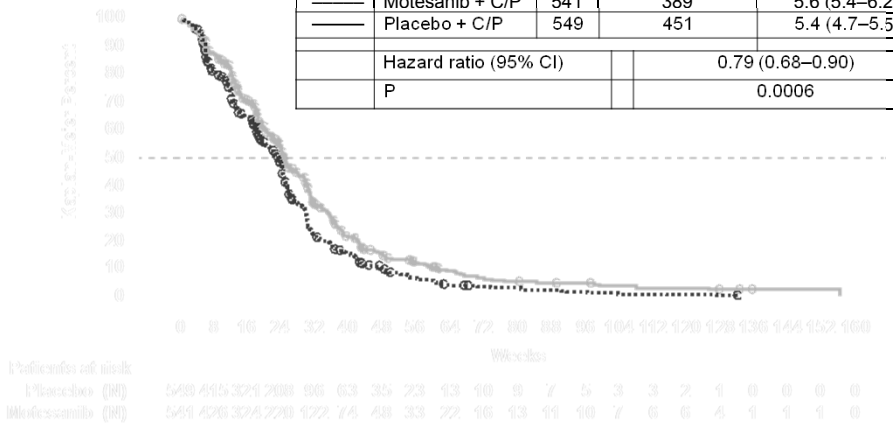
Up to 6 three-week cycles of carboplatin (AUC 6 mg/mL•min) and paclitaxel (200 mg/m^2)

Stratification

Randomization was stratified by sex, disease stage, prior adjuvant chemotherapy, & weight loss <5%

PFS — All Nonsquamous Patients*

		N	Patients With Events, n	Median PFS, mo (95% CI)
———	Motesanib + C/P	541	389	5.6 (5.4–6.2)
———	Placebo + C/P	549	451	5.4 (4.7–5.5)
	Hazard ratio (95% CI)			0.79 (0.68–0.90)
	P			0.0006

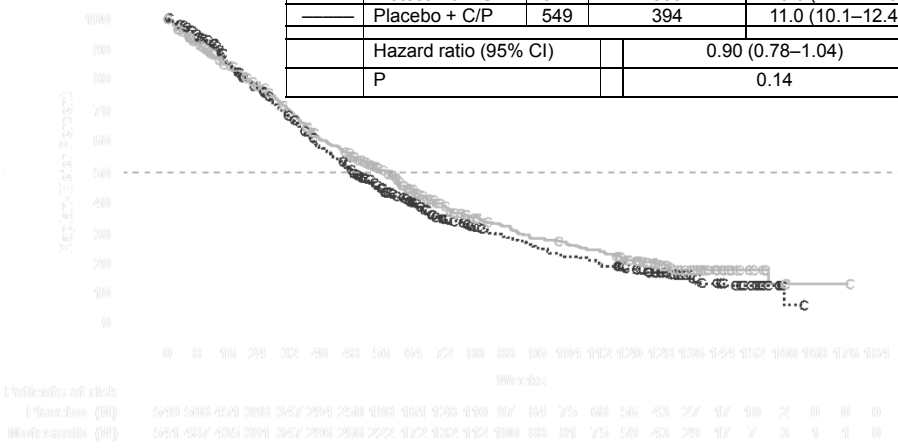


C = censored

*All randomized patients with nonsquamous histology

OS — All Nonsquamous Patients*

		N	Patients With Events, n	Median OS, months (95% CI)
———	Motesanib + C/P	541	359	13.0 (11.2–14.0)
———	Placebo + C/P	549	394	11.0 (10.1–12.4)
	Hazard ratio (95% CI)		0.90 (0.78–1.04)	
	P		0.14	



C = censored
*All randomized patients with nonsquamous histology

Summary of Adverse Events and Serious Adverse Events

	Arm A Motesanib + C/P (N = 533)	Arm B Placebo + C/P (N = 539)
Patients with grade ≥3 adverse events, n (%)	388 (73)	319 (59)
Grade 3	201 (38)	192 (36)
Grade 4	113 (21)	77 (14)
Grade 5	74 (14)	50 (9)
Serious adverse events	**261 (49)**	**184 (34)**
Patients with serious grade ≥3 adverse events, n (%)*	239 (45)	161 (30)
Neutropenia	**28 (5)**	**12 (2)**
Diarrhea	25 (5)	4 (<1)
Febrile neutropenia	23 (4)	15 (3)
Pneumonia	20 (4)	7 (1)
Dehydration	19 (4)	4 (<1)
Non–small-cell lung cancer	16 (3)	12 (2)
Thrombocytopenia	14 (3)	6 (1)
Pulmonary embolism	12 (2)	17 (3)
Anemia	12 (2)	11 (2)
Dyspnea	11 (2)	20 (4)
Vomiting	11 (2)	7 (1)
General physical health deterioration	11 (2)	4 (<1)
Cholecystitis	11 (2)	0 (0)

*Patient incidence ≥2%

VEGFR TKIs in NSCLC: Yet Another Negative Trial

- Lack of survival benefit with VEGFR TKIs
  - Vandetanib
  - Sunitinib
  - Sorafenib
  - Motesanib
- These agents are associated with additional AEs besides the class effects

Anti-Angiogenic Therapy in NSCLC

- Every agent tested to date in NSCLC has failed to demonstrate survival benefit with the exception of bevacizumab
- No predictive marker in the horizon
- Further development will hinge on the ability to select subset of patients that will derive robust benefits

Lung Cancer Genomics and Proteomics: Towards Personalized Therapy of Lung Cancer

Identification of driver mutations in tumor specimens from 1000 patients with lung adenocarcinoma: The Lung Cancer Mutation Consortium (LCMC)

Abstract # 7506

Mark G Kris

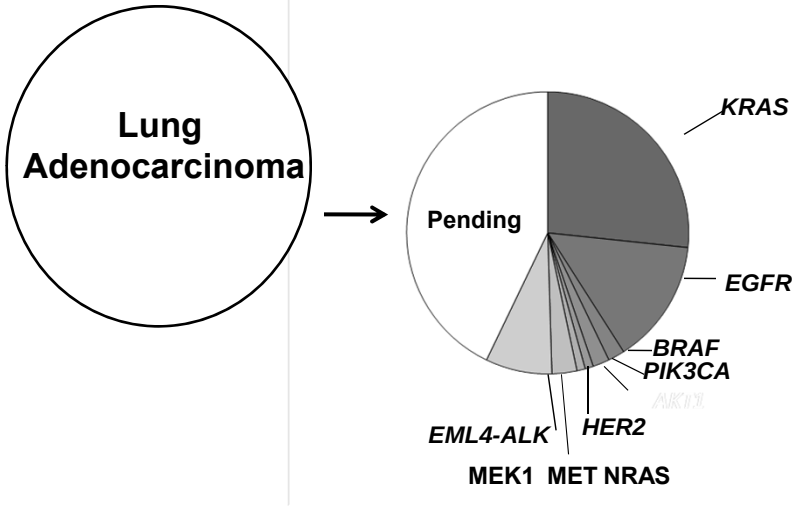
On behalf of the Lung Cancer Mutation Consortium Investigators

American Recovery and Relief Act

Grand Opportunity Grant

NCI 1 RC2 CA148394-01 (Paul Bunn, PI)

Molecular Profiling Can Explain The Heterogeneity of Lung Adenocarcinoma and Define Targets for Therapy

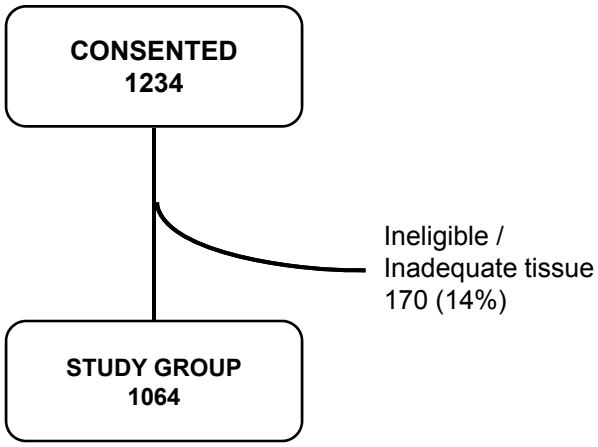


Lung Cancer Mutation Consortium
Organization

- University of Colorado – Headquarters
- Paul Bunn, Principal Investigator
- 14 Sites: SPORE, P01, NCI Intramural Programs
- Plan: Genotype 1000 patients with advanced lung adenocarcinoma, 2009-2011
- Assay 10 “driver” mutations in CLIA-certified laboratories: *EGFR, KRAS, BRAF, HER2, AKT1, NRAS, PIK3CA, MEK1, EML4-ALK, MET amp*

Lung Cancer Mutation Consortium

LCMC enrollment as of 13 May 11

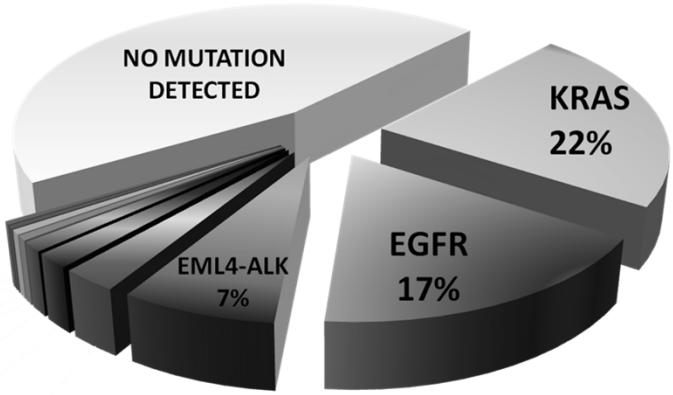


Lung Cancer Mutation Consortium
Objectives

- To test 1000 tumor specimens from patients with lung adenocarcinoma for *KRAS, EGFR, BRAF, HER2, PIK3CA, AKT1, NRAS, MEK1,* and *EML4-ALK,* and *MET* amplification
- To use the information in real time to either select erlotinib with *EGFR* mutations or recommend a “LCMC-linked” clinical trial of an agent targeting the specific mutation identified

Lung Cancer Mutation Consortium

Incidence of Single Driver Mutations



Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)

Lung Cancer Mutation Consortium

97% of mutations mutually exclusive

# Single Mutations	ALK	AKT	BRAF	EGFR	HER2	KRAS	MEK1	MET	NRAS	PIK3CA
ALK (38)	X		1	2		1		1		
AKT1 (0)		X								
BRAF (9)			X							1
EGFR (89)				X				1		3
HER2 (3)					X					
KRAS (114)						X		1		1
MEK1 (2)							X	1		1
MET AMP (3)								X		
NRAS (2)									X	
PIK3CA (6)										X

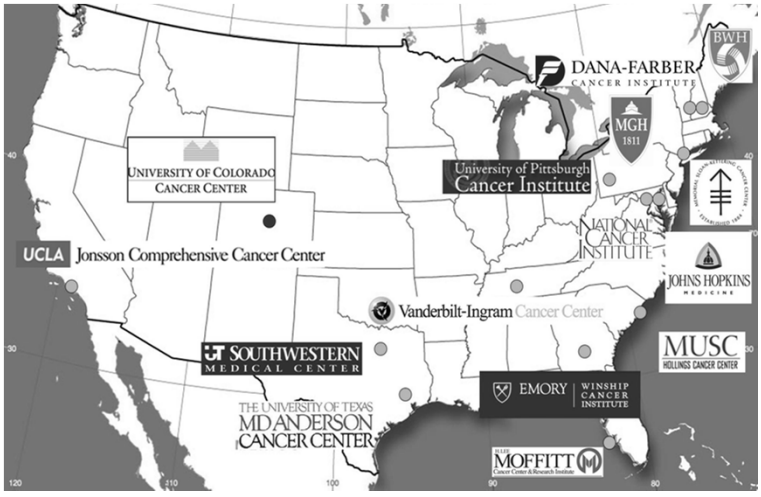
Number of patients with variants in indicated combination of genes , 3% (14/516)

Lung Cancer Mutation Consortium

LCMC protocols linked to specific molecular lesions detected (I)

Target	Agent(s)	LCMC Lead
EGFR	Erlotinib + OSI 906 Erlotinib + MM 121	C Rudin L Sequist
KRAS	Tivantinib + Erlotinib GSK1120212	J Schiller P Jänne
MET Amplification		
EML4-ALK	Crizotinib	R Camidge
NRAS	GSK1120212	P Jänne

Lung Cancer Mutation Consortium



American College Of Surgeons Oncology Group
Thoracic Committee

Prospective Phase II Z4031
Serum Proteomic Detection of NSCLC in Patients with Suspicious Lung Nodules

David Harpole, Jr., M.D.
Professor Of Surgery
Associate Professor of Pathology
Duke University Medical Center
Durham, NC

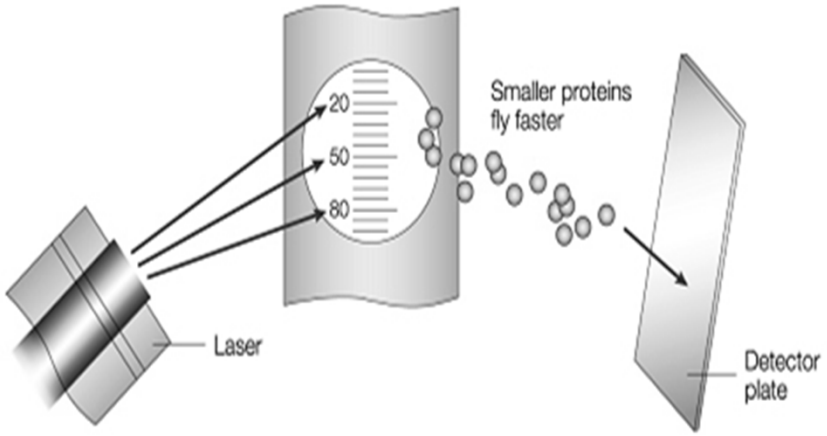
CP127150
4-61

Background: Proteomics in NSCLC

Analysis of 100s to 1000s of proteins at once

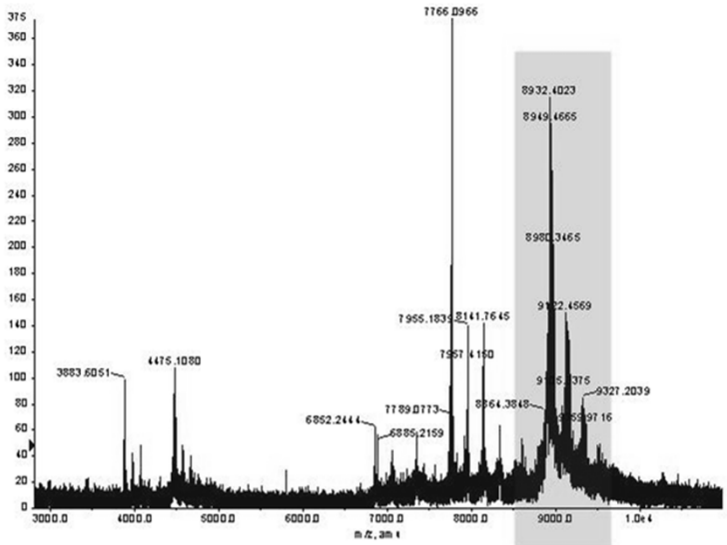
- Potential for improved prognosis
- ID novel prognostic markers
- Define novel protein pathways
- ID potential novel molecular targets
- Potential for improved early diagnostics
- ID serum / sputum correlates of cancer

Mass Spectrometry produces ions, separating them according to their mass to charge ratio

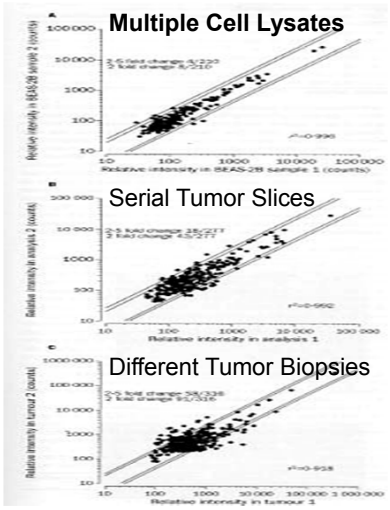


MALDI Time of Flight Proteomics

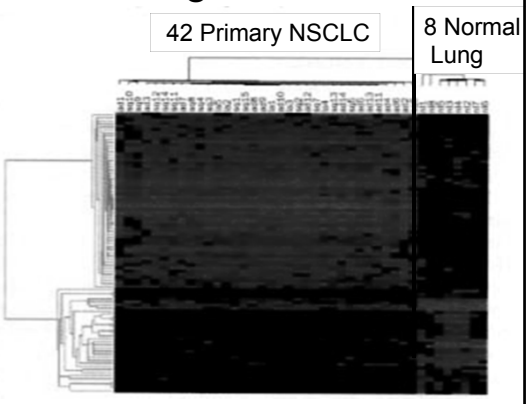
Signal Intensity



MALDI Proteomics: Lung Tumors



Good Reproducibility



Diagnostic Ability by Unsupervised Heirarchical Clusters

Yanagiasawa Lancet 2003

Z4031 Objectives

- Primary

  Determine whether a serum proteomic profile can predict the presence of NSCLC in patients with suspicious nodules

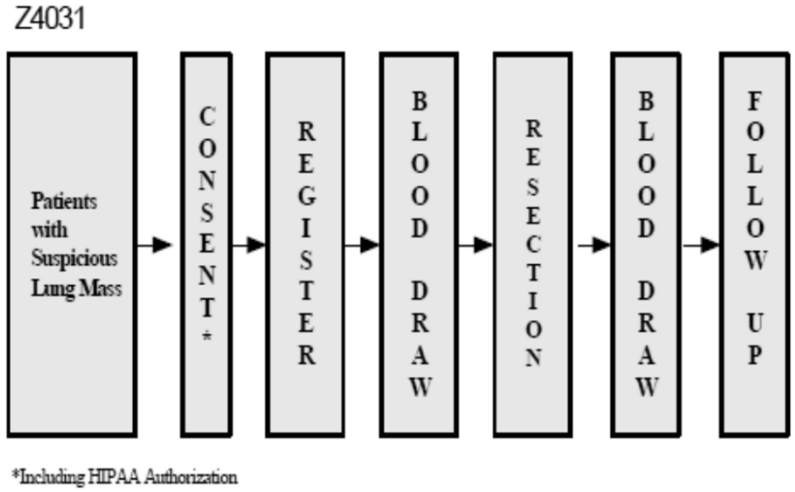
- Secondary

  Correlate the serum proteomic profile with
  - Pathological nodal status
  - Histopathologic features of NSCLC
  - Survival

  Correlative pre- and post-surgery changes in the serum proteomic profile with survival

CP1271504-66

Schema



CP1271504-67

Inclusion / Exclusion

- Inclusion
  - ≥ 18 years of age
  - Clinically suspicious stage I (cT1-2 N0 M0) lung lesion
  - Helical CT of chest and CT of upper abdomen within 60 days pre-surgery
  - PET within 60 days recommended
- Exclusion
  - Previous lung resection within 30 days
  - Prior chemotherapy or radiotherapy for lesion
  - Received any blood product transfusion within 60 days pre-surgery

CP1271504-68

Trial Logistics

- Initial Blood draw day of surgery prior to Anesthesia (Acute phase proteins)
- Resection for NSCLC: Lobectomy with MLNS
- Fresh tissue (tumor and non-cancerous lung)
  - Snap frozen on dry ice after OCT embedding
  - Overnight shipment to Washington University
- 60-90 Days Post-resection Blood
  - (After wound healing)
  - FFPE Tumor and non-cancerous lung
  - Overnight shipment

CP1271504-69

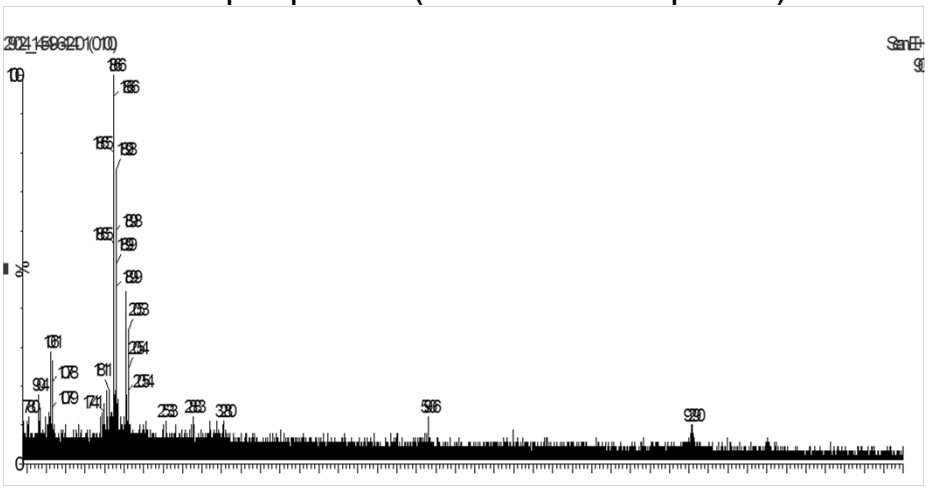
Patient Population

- Accrual
  - April 2004 to April 2006
  - 1074 patients enrolled
- 913 eligible patients
- Specimens collected (eligible pts)
  - 913 pts with pre-surgery serum
  - 507 pts with post-surgery serum
  - 245 pts with frozen normal tissue specimens
  - 456 pts with frozen tumor tissue specimens
  - 503 pts with FFPE normal tissue specimens
  - 609 pts with FFPE tumor tissue specimens

CP1271504-70

Results

Lack of high signal proteins in the spectra; only a few per patient (20-25 usable spectra)



Results

- M/Z Bins with significant p-values
  - Were often in the noise region of the spectra
    - Did not contain identifiable proteins
- MS proteomic profiles failed to accurately discriminate between the groups ($p<0.05$)
  - Benign vs. NSCLC
  - Squamous vs. Benign
  - Adenocarcinoma vs. Benign,
  - Squamous vs Adenocarcinoma

CP1271504-72

Conclusions

- Z4031 is the largest prospective multi-institutional lung cancer trial that collected biological materials:
  - Blood before and after resection (plasma, WBCs)
  - Frozen tumor and frozen non-cancerous lung
  - FFPE tumor and non-cancerous lung
- Usable serum MALDI Proteomic profiles were successfully created from more than 90% of samples
- The predictive accuracy of the proteomic model lacked sufficient power for clinical utility
  - Limit of detection for the newest MS platforms is not sufficient for discovering discriminate protein profiles

CP1271504-73

Conclusions

- The outcomes for advanced NSCLC continues to improve
  - Stage migration
  - Improved systemic therapy
  - Maintenance therapy
  - Targeted agents
  - Improved supportive care
- Individualized therapy based on tumor characteristics is a reality
  - EGFR mutation
  - ALK translocation
- Patients are open to re-biopsy for molecular studies
  - Are we?