EGFR, ALK, PD1 and Novel Genomic Targets in Lung Cancer: A Best of ASCO Atlanta 2012 Update

EMORY
WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

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EGFR TKIs lung cancer in 2012

- EGFR TKIs have emerged as the standard of care for the front-line therapy of lung cancer patients with deletion mutations in exon 19 or L858R mutations[1].
- Combinations of gefitinib or erlotinib with chemotherapy have yet to show efficacy in the clinic (TRIBUTE, TALENT, INTACT I, INTACT II)

1 Mok et al, Rosell et al, both NEJM 2009

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IPASS: Study Design

Patients
- Chemonaive
- Age ≥8 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIB/ IV disease

Gefitinib (250 mg / day)

1:1 randomization

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m2) 3 weekly#

Endpoints

Primary
- Progression-free survival (non-inferiority)

Secondary
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

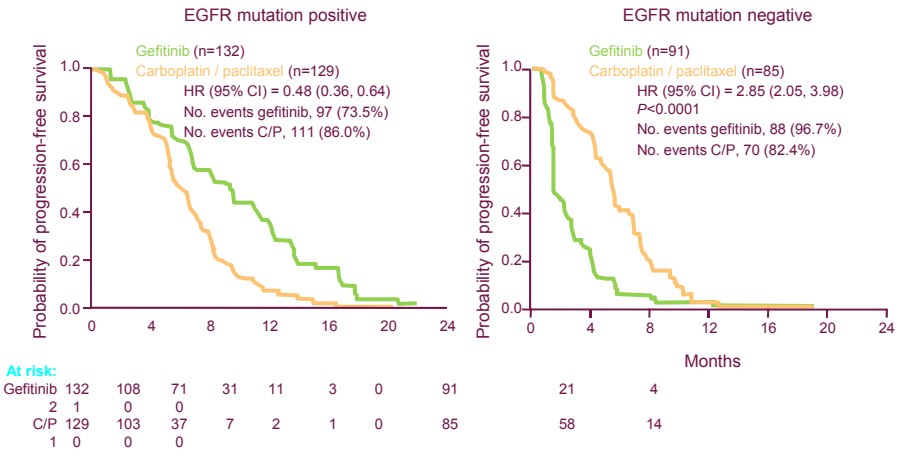
Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

* Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; # limited to a maximum of 6 cycles

Carboplatin / paclitaxel was offered to gefitinib patients upon progression

PS, performance status; EGFR, epidermal growth factor receptor

Progression-Free Survival in EGFR Mutation Positive and Negative Patients

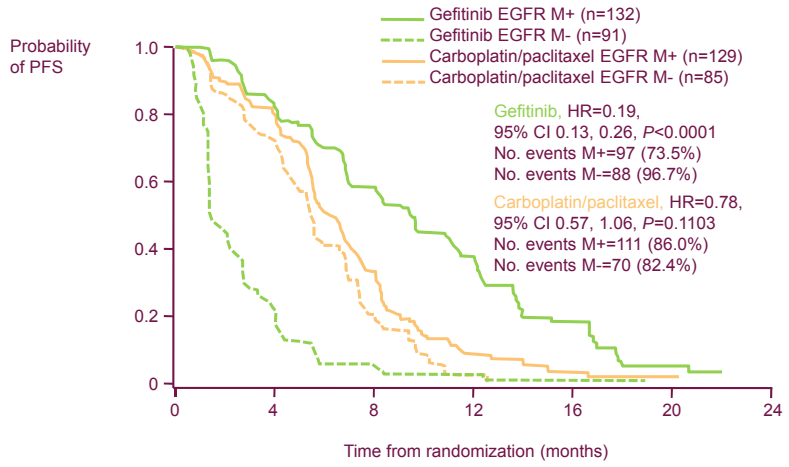


At risk:

Gefitinib	132	108	71	31	11	3	0	91	21	4
C/P	129	103	37	7	2	1	0	85	58	14

Treatment by subgroup interaction test, *P*<0.0001

Comparison of PFS by Mutation Status Within Treatment Arms



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LUX-Lung 3: a randomized, open-label, Phase III study of afatinib vs cisplatin/pemetrexed as 1st-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations

J.C.-H. Yang, M. Schuler, N. Yamamoto, K. O'Byrne, V. Hirsh, T. Mok, S.L. Geater, S. Orlov, C.-M. Tsai, M. Boyer, W.-C. Su, J. Bennouna, T. Kato, V. Gorbunova, K.H. Lee, R. Shah, D. Massey, R. Lorence, M. Shahidi, L. Sequist, on behalf of all LUX-Lung 3 investigators

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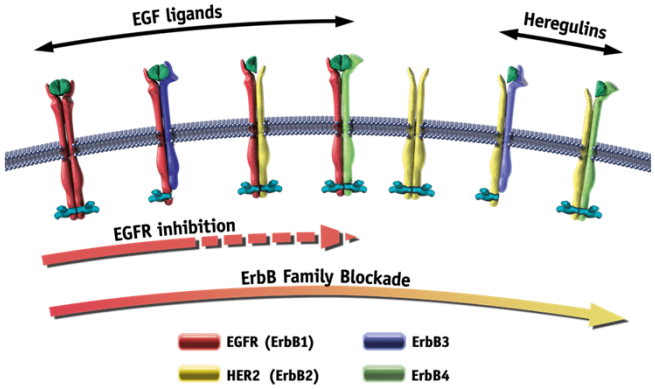
Afatinib: an Irreversible ErbB Family Blocker



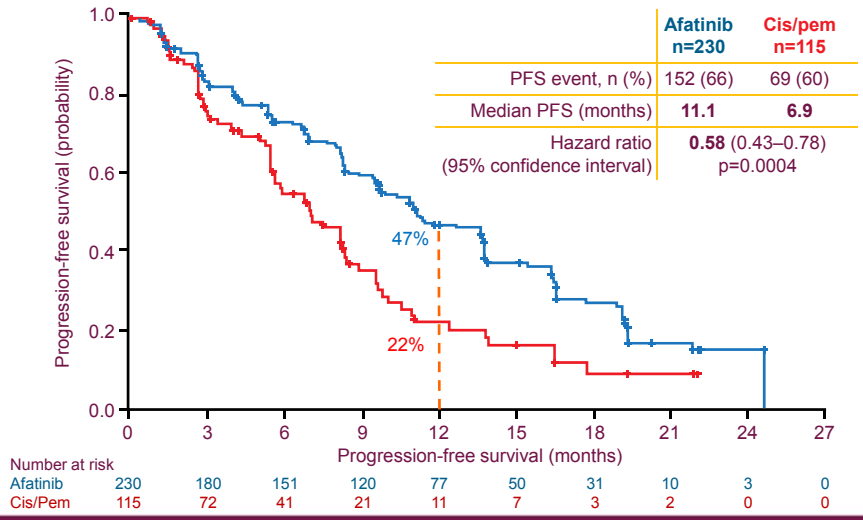
- Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential
  - Inhibition of ErbB Family receptor heterodimerization
  - *In vitro* activity against EGFR-resistant T790M mutation

Li D, et al. *Oncogene* 2008;27:4702–11.

Yang JC, et al. PRESENTED AT: ASCO Annual '12 Meeting

Primary endpoint: PFS

Independent review – all randomized patients

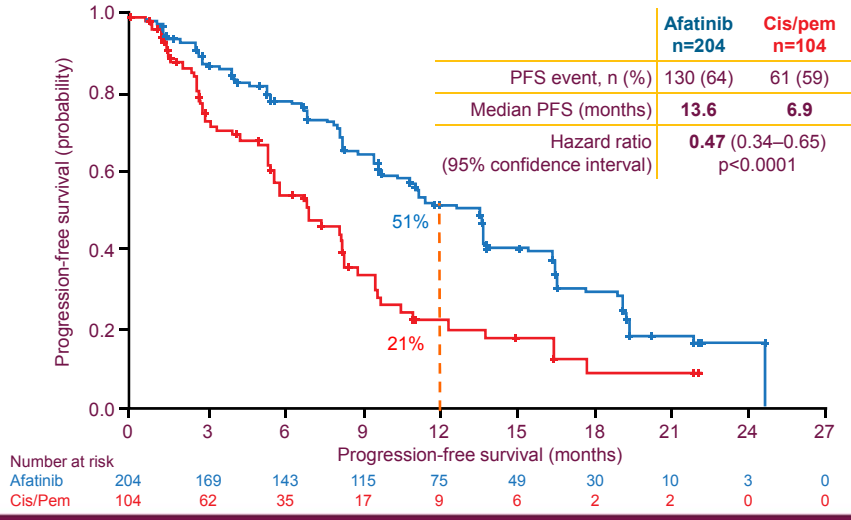


	Afatinib n=230	Cis/pem n=115
PFS event, n (%)	152 (66)	69 (60)
Median PFS (months)	**11.1**	**6.9**
Hazard ratio (95% confidence interval)	**0.58** (0.43–0.78) p=0.0004	

Yang JC, et al. PRESENTED AT: ASCO Annual '12 Meeting

PFS: Common mutations (Del19/L858R)

Independent review – patients with Del19/L858R (n=308)



	Afatinib n=204	Cis/pem n=104
PFS event, n (%)	130 (64)	61 (59)
Median PFS (months)	**13.6**	**6.9**
Hazard ratio (95% confidence interval)	**0.47** (0.34–0.65) p<0.0001	

Number at risk										
Afatinib	204	169	143	115	75	49	30	10	3	0
Cis/Pem	104	62	35	17	9	6	2	2	0	0

Yang JC, et al. PRESENTED AT: ASCO Annual '12 Meeting

First-line dacomitinib (PF-00299804), an irreversible pan-HER tyrosine kinase inhibitor for patients with *EGFR*-mutant lung cancer

Mark G Kris,[1] Tony Mok,[2] Sai-Hong Ignatius Ou,[3] Renato G. Martins,[4] Dong-Wan Kim,[5] Zelanna Goldberg,[6] Hui Zhang,[7] Ian Taylor,[8] Stephen Letrent,[9] and Pasi A. Jänne[10]

[1]Memorial Sloan-Kettering Cancer Center, New York, NY, US; [2]The Chinese University of Hong Kong, Shatin, Hong Kong; [3]School of Medicine, University of California at Irvine, Irvine, CA, US; [4]University of Washington, Seattle, WA, US; [5]Seoul National University Hospital, Seoul, Republic of Korea; [6]Pfizer Oncology, La Jolla, CA, US; [7]Pfizer (China) Research & Development Co. Ltd, Shanghai, China; [8]Pfizer Oncology, Groton, CT, US; [9]Pfizer Oncology, La Jolla, CA, US; [10]Dana-Farber Cancer Institute, Boston, MA, US.

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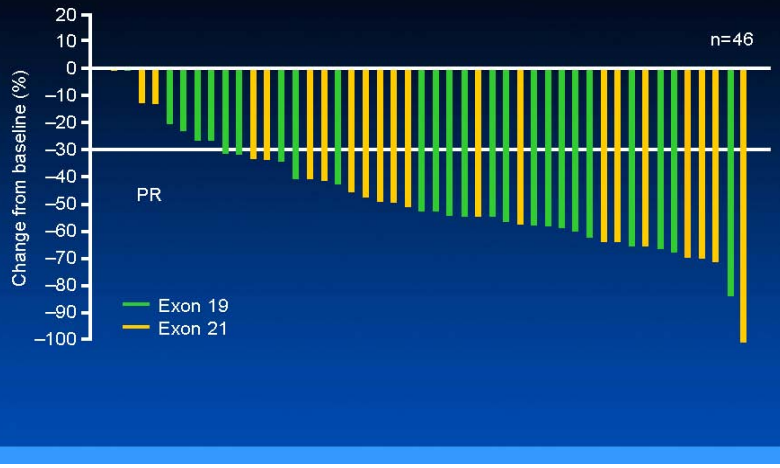
Waterfall Plot for Patients with *EGFR*-mutant Lung Cancers with Exon 19 and Exon 21 Mutations



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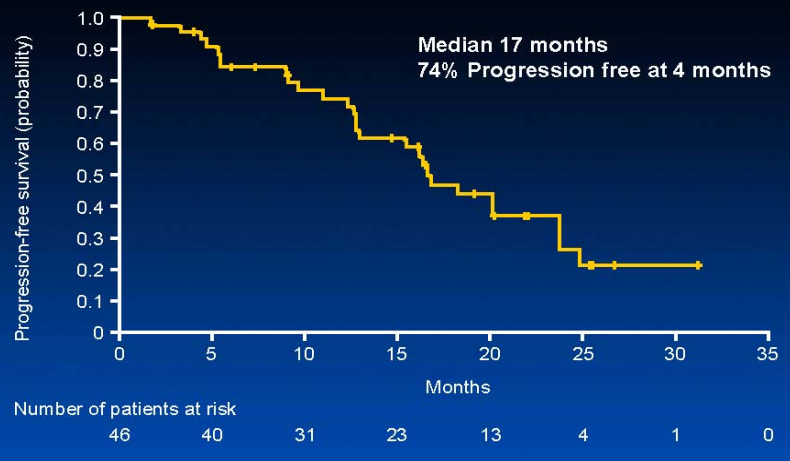
PPFS for Patients with *EGFR*-mutant Lung Cancers with Exon 19 and Exon 21 Mutations



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TAILOR

TArceva Italian Lung Optimization tRial

A phase III trial comparing erlotinib versus docetaxel as second-line treatment of NSCLC patients with wild-type EGFR

M.C. Garassino, O. Martelli, A. Bettini, I. Floriani, E. Copreni, C. Lauricella, M. Ganzinelli, M. Marabese, M. Broggini, S. Veronese, G. Gherardi, F. Longo, M.A. Fabbri, M. Tomirotti, O. Alabiso, M.G. Sarobba, R. Labianca, S. Marsoni, G. Farina, A. Scanni

Fatebenefratelli e Oftalmico Hospital, Milan, Italy

On behalf of the TAILOR investigators

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TAILOR Objectives

2007	2011
• TAILOR is designed as a prospective randomized biomarker-based study in wt-EGFR patients treated with erlotinib or docetaxel	• ASCO's provisional clinical opinions on EGFR status [2] • TAILOR planned interim analyses with IDMC
• The main objective was to test the interaction of EGFR expression and amplification (IHC/FISH) and KRAS mutations on treatment outcomes[1]	Based on IDMC suggestions TAILOR was amended. The sample size was re-calculated by 2 independent statisticians blinded to the interim analysis results

[1]*Farina G, Clin Lung Cancer. 2011*

TAILOR

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TAILOR Study Design

- Advanced/recurrent
- Previous platinum based doublet
- EGFR wild-type
- KRAS determined
- ECOG PS 0-2

R → 1:1

DOCETAXEL
75 mg/m2 iv day 1,21 OR
35 mg/m2 iv day 1,8,15,28

ERLOTINIB
150 mg po, daily

CROSS OVER NOT ALLOWED

STRATIFICATION
minimization approach
- centre
- recurrent/progressed
- type of prior chemotherapy regimen (pem vs gem vs vnb)
- ECOG-PS (0-1 vs 2)
- adequacy of tissue sample (optimal vs suboptimal)

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Molecular Study Work-Flow

52 CENTRES REGISTRATIO

CENTRALIZATION
OF SPECIMENS COLLECTED AT DIAGNOSIS
&
HISTOLOGICAL REVISION

max 7 days

EGFR /KRAS
CROSS-VALIDATED IN 2 INDEPENDENT LABS

MARIO NEGRI

EGFR Sanger's sequencing confirmed by RFLP
KRAS HRMA confirmed by Sanger's sequencing

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Baseline Patients Demographic

		DOCETAXEL (n=110)	ERLOTINIB (n=109)
Median Age, years (range)		67 (35-83)	66 (40-81)
		%	%
Gender	Male Female	66.4 33.6	70.6 29.4
ECOG PS	0 1 2	48.2 45.5 6.3	47.7 44.0 8.3
Histology	Squamous Adenocarcinoma Others	20.9 75.5 3.6	28.4 63.4 8.2
Smoking Habit	Smokers (also ex) Never-smokers	71.8 28.2	81.7 18.3
KRAS status	Mutated Wild-type	22.7 77.3	23.9 76.1

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Major Reported Toxicities

TOXICITY	G3-4 EVENTS	
	DOCETAXEL (n = 104)	ERLOTINIB (n = 107)
Non haematological toxicity	%	%
Nausea & Vomiting	3	1
Asthenia	8	6
Alopecia (all grades)	29	2
Dermatological toxicity	0	14
Diarrhoea	2	3
Neurological	8	1
Haematological toxicity	%	%
Neutropenia	27	1
Febrile neutropenia	4	0

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Safety Analysis

	DOCETAXEL (n=104) %	ERLOTINIB (n=107) %
Patients with SAE ≥ 1	14.4	13.1
Treatment-related SAEs	3.8	1.8
Treatment-related deaths	0	0.9
Treatment-related AEs leading to withdrawal	1.0	0.9
Treatment-related AEs leading to dose modification	22.1	29.0

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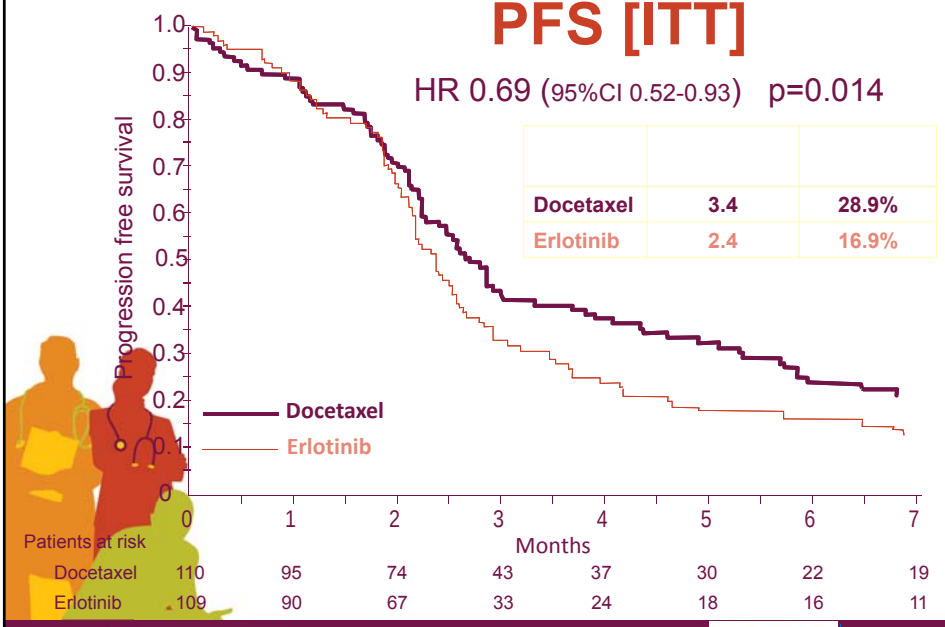
PFS [ITT]

HR 0.69 (95%CI 0.52-0.93) p=0.014



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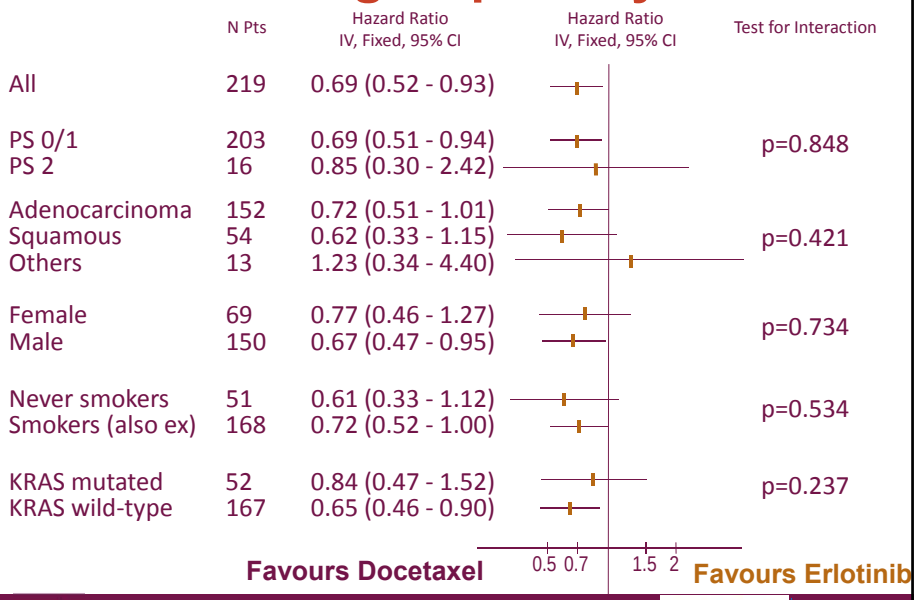
PFS Subgroup Analysis



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Conclusions

- TAILOR is the only prospective head-to-head trial comparing erlotinib vs docetaxel in wild-type EGFR patients
- Docetaxel significantly improves the PFS, Response Rate and Disease Control Rate over erlotinib
- Reported toxicity was as expected
- KRAS does not seem to be a prognostic factor in second line

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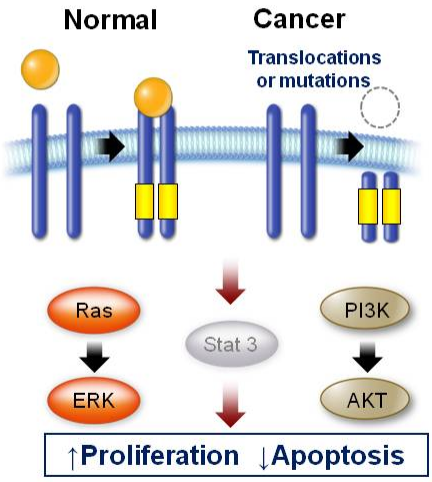
Anaplastic Lymphoma Kinase (ALK) activation in cancer



- Activating mutations or translocations
  - NSCLC, lymphoma, neuroblastoma
- Account for ~6% of NSCLC
  - More prevalent in non-smokers, younger patients and adenocarcinomas
- EML4 is the most common translocation partner in NSCLC

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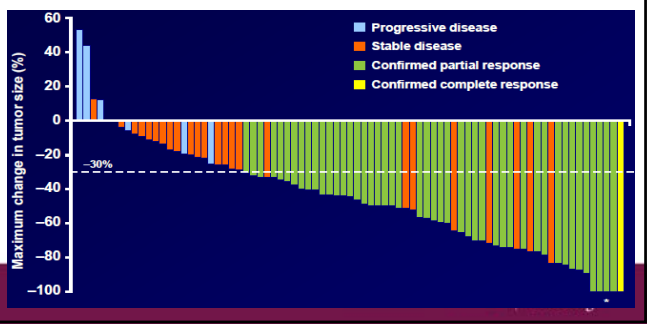
Crizotinib in Patients with Advanced NSCLC

- Objective response rate – 57% of patients (95% CI: 46%-68%)
- Disease control rate at 8 wks – 90%
- Duration of response – 1-15 mos
- Patients had 72% probability of being progression-free at 6 mos
- Median PFS: 9.2 mos
- Most common adverse events:
  - Grade 1 nausea
  - Diarrhea
  - Vomiting
  - Light-dark accommodation



Abstract #7508

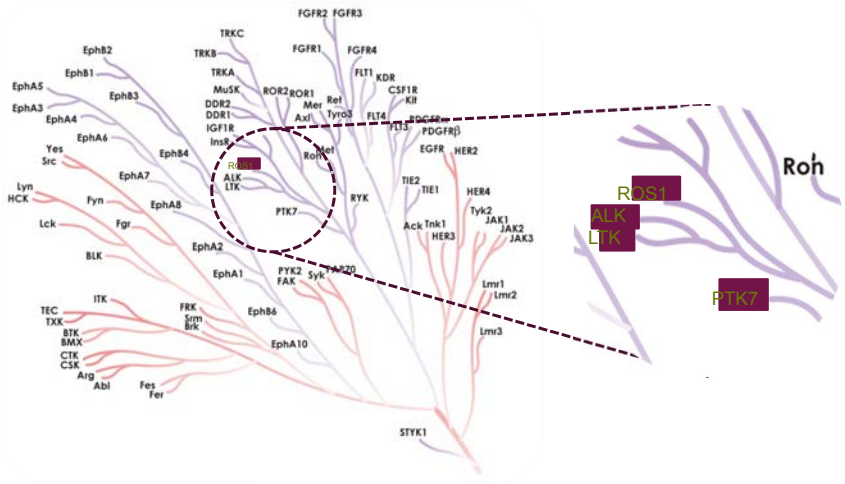
Clinical Activity of Crizotinib in Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring ROS1 Rearrangement

Alice T. Shaw[1], D. Ross Camidge[2], Jeffrey A. Engelman[1], Benjamin J. Solomon[3], Eunice L. Kwak[1], Jeffrey W. Clark[1], Ravi Salgia[4], Geoffrey I. Shapiro[5], Yung-Jue Bang[6], Weiwei Tan[7], Lesley Tye[7], Keith D. Wilner[7], Patricia Stephenson[8], Marileila Varella-Garcia[2], Kristen Bergethon[1], A. John Iafrate[1], and Sai-Hong I. Ou[9]

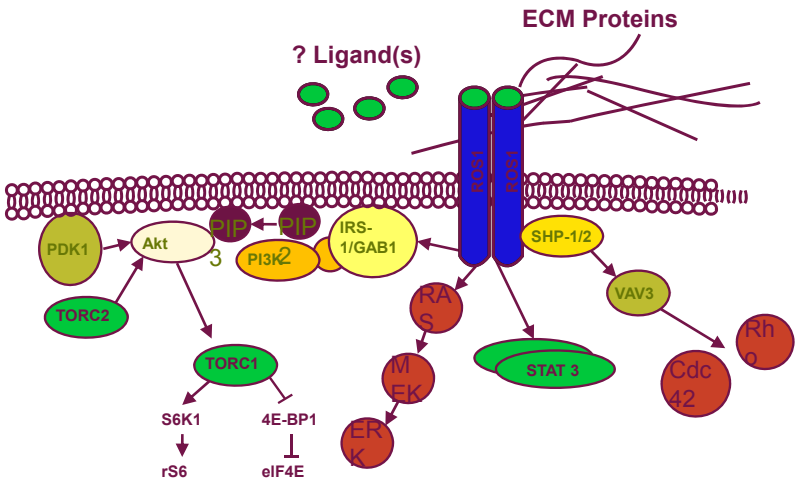
[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]University of Colorado Cancer Center, Aurora, CO, USA; [3]Peter MacCallum Cancer Centre, East Melbourne, Australia; [4]University of Chicago Cancer Center, Chicago, IL, USA; [5]Dana Farber Cancer Institute, Boston, MA, USA; [6]Seoul National University, Seoul, Korea; [7]Pfizer Inc, La Jolla, CA, USA; [8]Rho, Inc, Chapel Hill, NC; [9]Chao Family Comprehensive Cancer Center, Orange, CA, USA

Presented at the 2012 ASCO Annual Meeting. ASCO Annual '12 Meeting

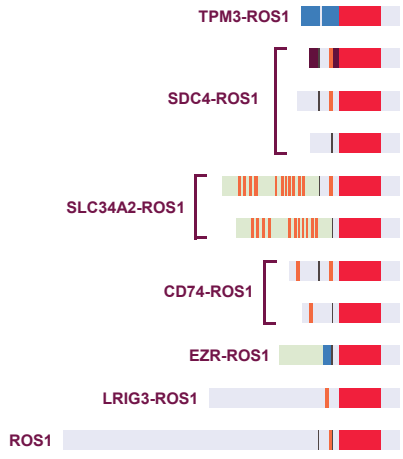
ROS1 Encodes a Receptor Tyrosine Kinase



Signaling Pathways Activated by ROS1

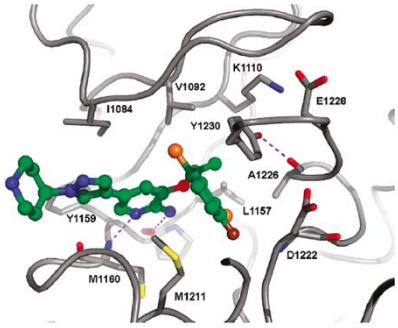


ROS1 Rearrangements in NSCLC



- Present in ~1% of NSCLC cases (also found in some GBMs and cholangiocarcinomas)
- Enriched in younger never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers

Crizotinib: A Small Molecule Tyrosine Kinase Inhibitor of c-MET, ALK and ROS1



Co-crystal structure of crizotinib (PF-02341066) bound to c-MET

Kinase	IC_{50} (nM) mean*	Selectivity ratio
c-MET	8	–
ALK	40-60	5-8X
ROS1	60	7X
RON	80	10X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1,000X
VEGFR2	>10,000	>1,000X
PDGFRβ	>10,000	>1,000X

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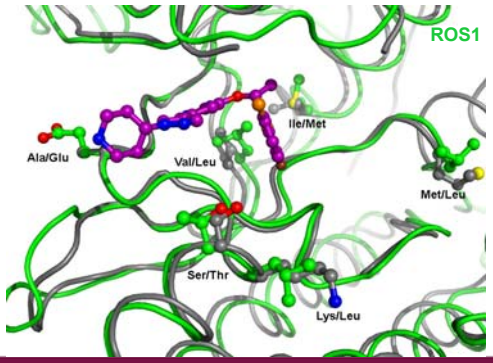
ROS1 and ALK TK Domains are Similar

77% Identity in ATP-Binding Site

	G-Loop		N-Terminus					GK						Extended Hinge Region							C-Terminus							
Kinase	L1	L9	N1	N2	N3	N4	N5	H1	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	C1	C2	C3	C4	C5	C6	C7	C8
ALK	L	V	A	K	E	I	V	I	L	E	L	M		G	G	D	L			R	N	L	G	D	F	G	
ROS1	L	V	A	K	E	M	L	I	L	E	L	M		G	G	D	L			R	N	L	G	D	F	G	



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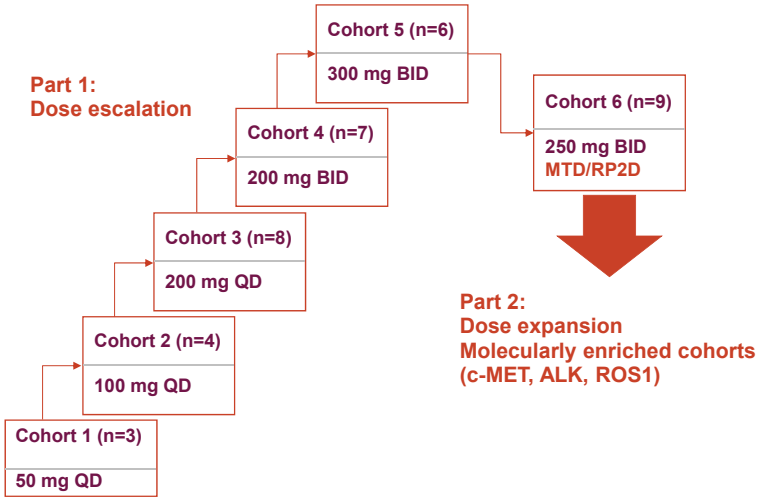
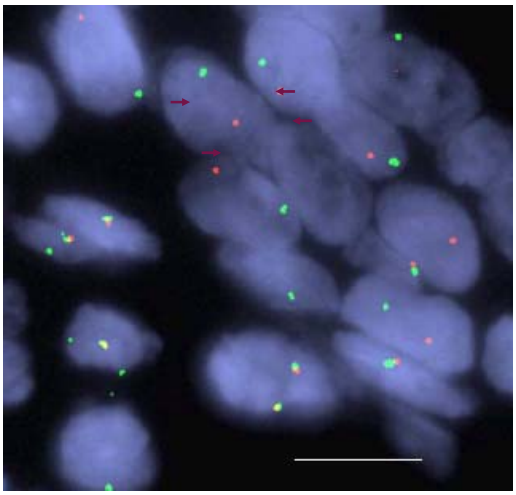
Phase 1 Study of Crizotinib (PROFILE 1001) ROS1-Positive NSCLC Expansion Cohort



Diagnostic "Break-Apart" FISH Assay for ROS1 Rearrangement



Clinical and Demographic Characteristics of Patients with Advanced ROS1+ NSCLC

		N=15
Age, yrs	Median (range)	54 (31, 72)
Sex, n	M/F	8/7
Smoking history, n (%)	Never	14 (93)
	Former	1 (7)
Race , n (%)	Caucasian	10 (67)
	Asian	4 (27)
	Other	1 (7)
Histology, n (%)	Adenocarcinoma	15 (100)
ECOG PS, n (%)	0	10 (67)
	1	5 (33)
Prior Treatment, n (%)	None	2 (13)
	≥1 regimen	12 (80)
	Not Reported	1 (7)

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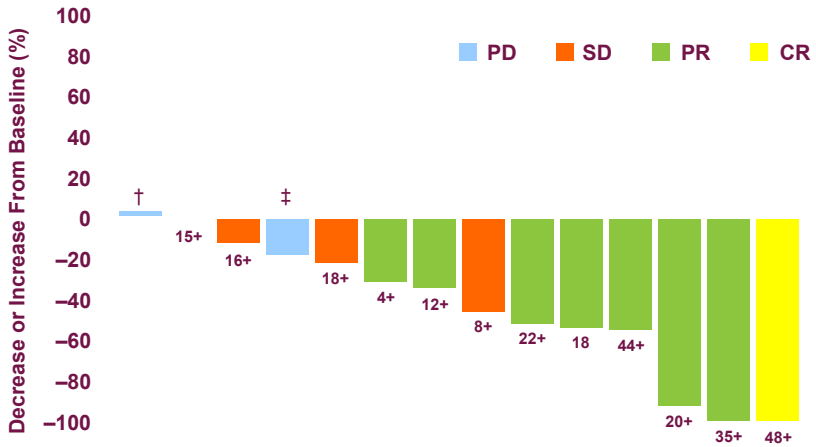
Summary of Tumor Responses in Patients with Advanced ROS1+ NSCLC (N=14*)



†Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression ‡Crizotinib held for >6 wks prior to first scans which showed PD.
ongoing patients, duration of response/SD is the time from first documentation of tumor response/first dose to last available on treatment scan. For discontinued patients, duration is to the time of PD or death. Duration is in weeks.

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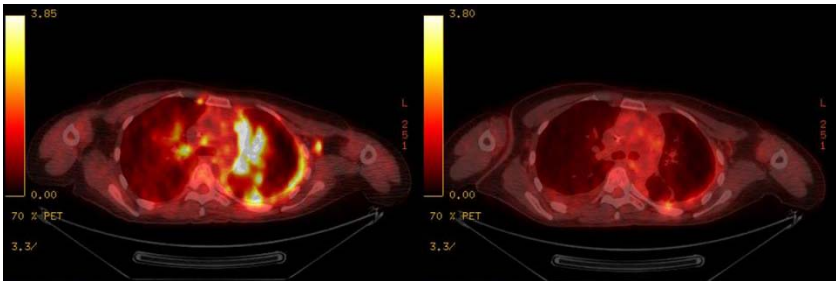
Rapid Responses to Crizotinib in Patients with ROS1-Positive NSCLC



Baseline | After 4 weeks of crizotinib

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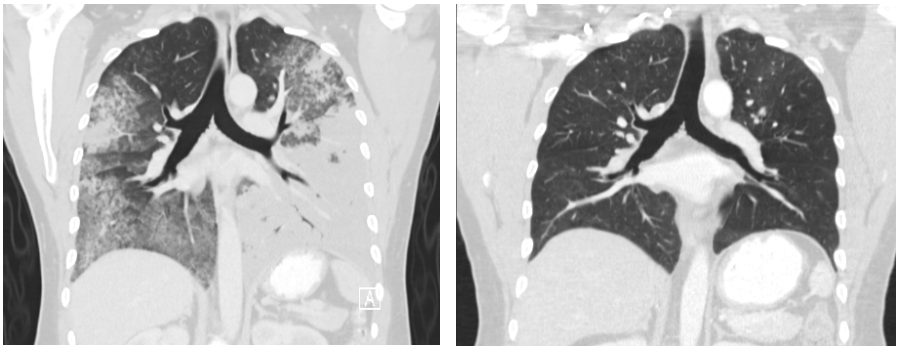
Significant Responses to Crizotinib in Patients with ROS1-Positive NSCLC



Baseline | After 3 months of crizotinib

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Antitumor Activity of Crizotinib in Evaluable ROS1-Positive Patients

	ROS1-Positive (N=14)	ALK-Positive (N=19)*
Best response†		
Complete response	1	0
Partial response	7	10
Stable disease	4	5
Progressive disease	2	3
Other	0	
ORR	57.1	52.6
Median duration of treatment (weeks)	25.7	–
Disease control rate at 8 weeks	79%	79%

†RECIST 1.0; *Kwak et al., ASCO 2009

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Treatment-related Adverse Events Reported in ≥ 10% of ROS1-Positive NSCLC Patients

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total* n (%)
Visual impairment	13 (87)	0	0	13 (87)
AST increased	3 (20)	0	1 (7)	4 (27)
Diarrhea	4 (27)	0	0	4 (27)
Hypophosphatemia	0	3 (20)	1 (7)	4 (27)
Peripheral edema	3 (20)	1 (7)	0	4 (27)
ALT increased	1 (7)	1 (7)	1 (7)	3 (20)
Dysgeusia	3 (20)	0	0	3 (20)
Nausea	3 (20)	0	0	3 (20)
Vomiting	3 (20)	0	0	3 (20)
Alk Phos increased	2 (13)	0	0	2 (13)
Neutropenia	1 (7)	0	1 (7)	2 (13)
Sinus bradycardia	2 (13)	0	0	2 (13)

Data in the database as of April 19, 2012

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Summary

- ROS1 rearrangement defines a distinct subset of NSCLC
- Crizotinib demonstrates marked antitumor activity in patients with advanced ROS1-positive NSCLC
- These results validate ROS1 as a therapeutic target in lung cancer

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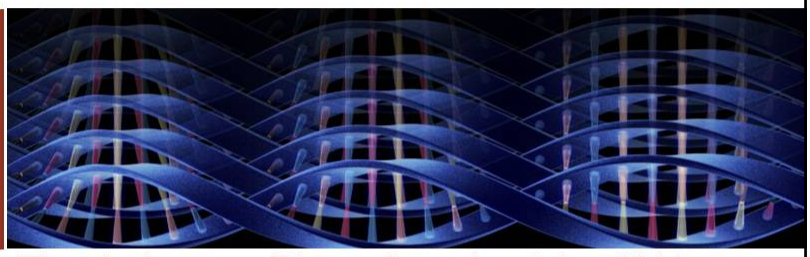

First-in-human Phase I study of the ALK inhibitor LDK378 in ALK+ solid tumors

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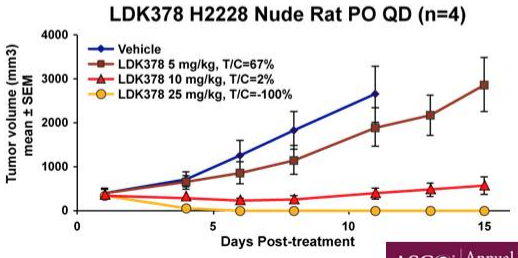
LDK378 is a potent and selective ALK inhibitor

- Potent activity in enzymatic and cell based assays

Assay	LDK378 IC_{50} (μM)	Crizotinib IC_{50} (μM)
Enzymatic		
ALK	0.00015	0.003
MET	3.2	0.008
Cell-based		
ALK	0.027	0.11
MET	1.3	0.028

- LDK378 treatment results in tumor regression in EML4-ALK expressing xenografts



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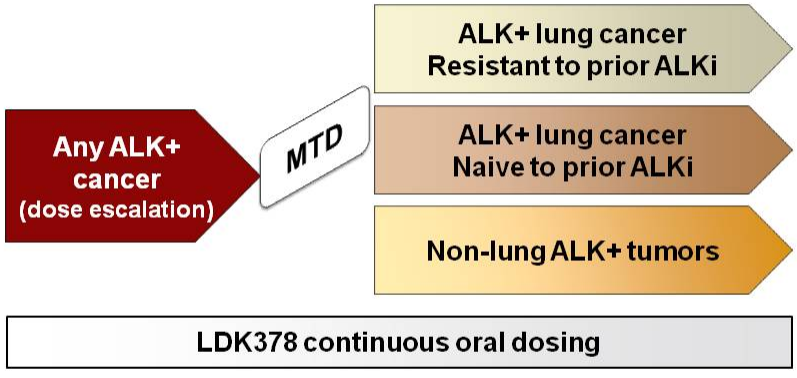
Phase I study of LDK378



Primary objective: Determine the MTD
Secondary objectives: Safety, pharmacokinetics, and antitumor activity

NCT01283516

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Adverse events associated with LDK378

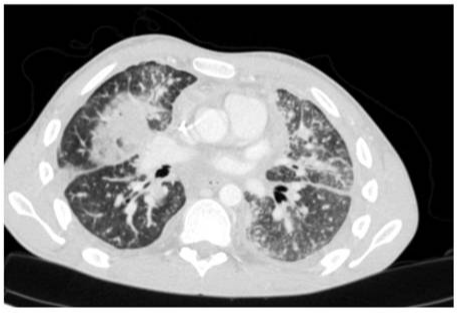
- Common adverse events included
  - Nausea (59%), vomiting (54%), and diarrhea (48%), fatigue (21%), and dyspnea (16%)
- SAEs related to LDK378 have occurred in 5 patients
  - Transaminase elevation (400 mg), vomiting (500 mg), dehydration (600 mg), and interstitial lung disease (750 mg)
- All SAEs were reversible upon cessation of LDK378
  - Two patients resumed treatment with LDK378 at a lower dose level
  - Two patients had simultaneous progressive disease
- Two patients discontinued treatment due to adverse events

LDK378 has antitumor activity in ALK+ NSCLC

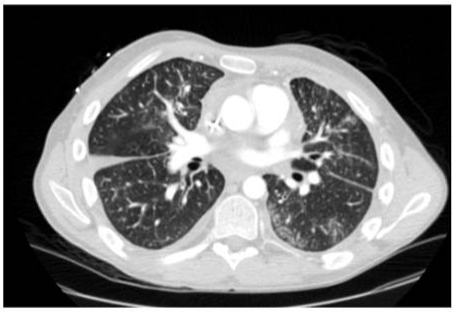
	Initial dose (mg)	Evaluable Patients (n)	Responses (PR)
NSCLC	< 400	8	2 (25)
	≥ 400	33	22 (67)
Other diseases	50 – 600	6	0

- Of the 24 responding patients, 11 responses were confirmed, and 7 are awaiting confirmatory scans
- Response rate was 81% (21/26) in patients with NSCLC treated at ≥ 400 mg who progressed following crizotinib

Responses to LDK378 were observed at 400 mg



Baseline



After 6 weeks on LDK378

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Summary

- The MTD of LDK378 is 750 mg administered daily
- The 36 hour half-life of LDK378 supports daily dosing
- The most common adverse events are nausea, vomiting and diarrhea
- LDK378 exhibits potent antitumor activity in patients with ALK+ NSCLC, including those who have progressed following crizotinib
- LDK378 is active in patients with brain metastases
- Accrual to the dose expansion cohorts is ongoing

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Clinical Activity and Safety of Anti-PD-1 (BMS-936558, MDX-1106) in Patients with Advanced Non-Small-Cell Lung Cancer

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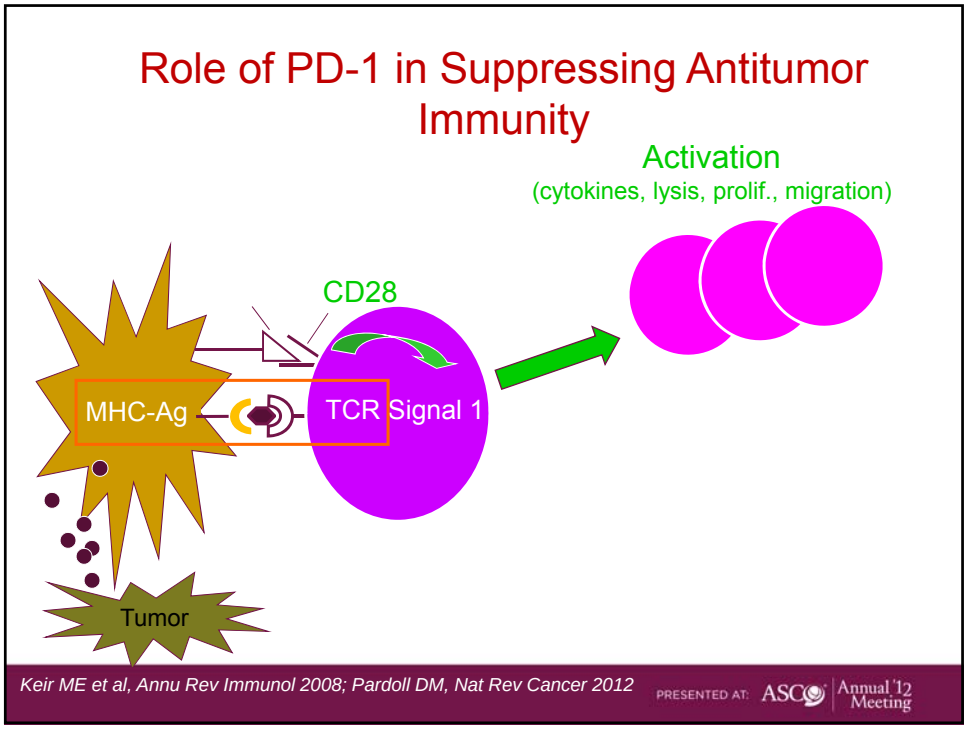
Background

Immunotherapy in NSCLC:

- Immunotherapy historically not successful in NSCLC
- Resurgence of interest over past decade
- Vaccines
- Check-point inhibitors:
  - Preliminary evidence of activity with CTLA-4 and chemotherapy [1,2]

[1]Lynch TJ, et al. J Clin Oncol. 2012. [2]Genova C, et al. Expert Opin Biol Ther 2012.


Role of PD-1 in Suppressing Antitumor Immunity
Activation
(cytokines, lysis, prolif., migration)
CD28
MHC-Ag
TCR Signal 1
Tumor
Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012
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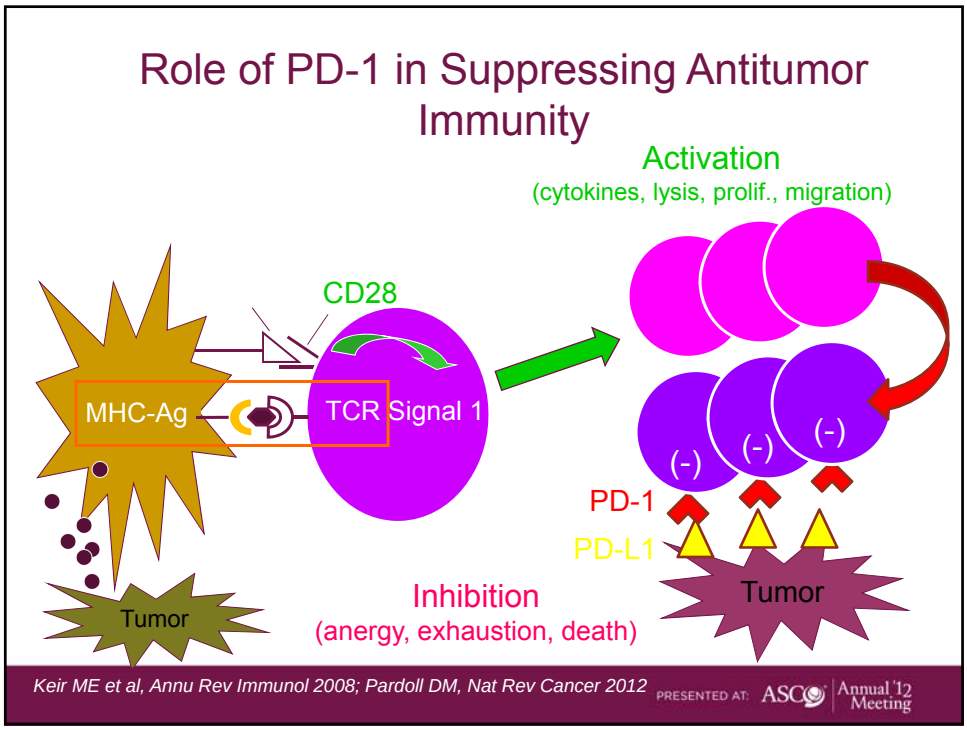
Role of PD-1 in Suppressing Antitumor Immunity
Activation
(cytokines, lysis, prolif., migration)
CD28
MHC-Ag
TCR Signal 1
(-)
(-)
(-)
PD-1
PD-L1
Tumor
Inhibition
(anergy, exhaustion, death)
Tumor
Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012
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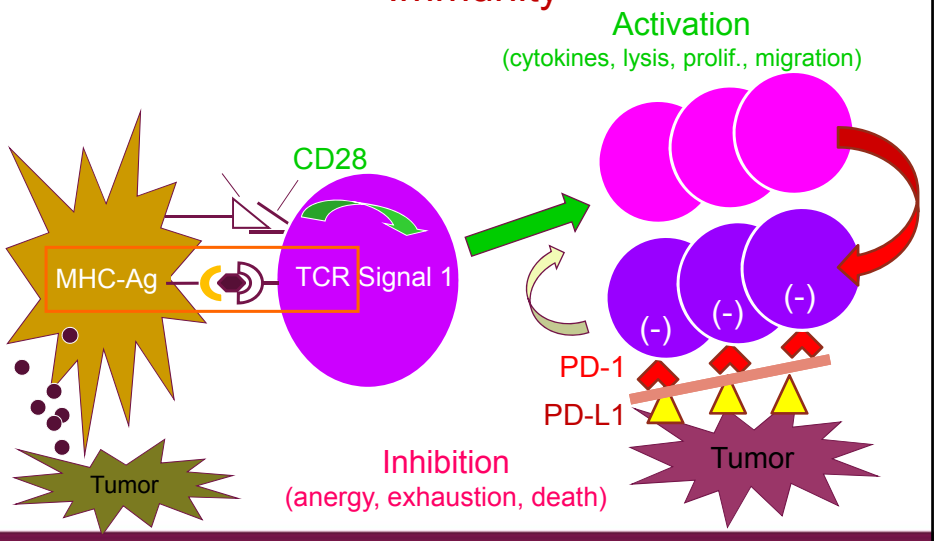
Role of PD-1 in Suppressing Antitumor Immunity



Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

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Role of PD-1 Pathway in NSCLC

- PD-1 expression on tumor infiltrating lymphocytes (TILs) in NSCLC has shown:
  - Decreased cytokine production and decreased effector function[1,2]
- PD-L1 expression noted in NSCLC[2,3]
- Increase of PD-L1 expression on tumor cells correlated with a decrease in the number of TILs in the same region[4]
- Preliminary correlation of PD-L1 expression by tumor cells with response to PD-1 blockade[5]

[1]Ahmadzadeh M, et al. Blood 2009;114:1537-44. [2]Zhang Y, et al. Cell Mol Immunol 2010;7:389-95. [3]Mu C-Y et al. Med Oncol 2010. [4]Konishi J, et al. Clin Cancer Res 2004;10:5094-100. [5]Brahmer J, et al. J Clin Oncol 2010;28:3167-75

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BMS-936558 (MDX-1106/ONO-4538)

- Fully human IgG4 anti-human PD-1 blocking Ab[1]
- No known Fc function (ADCC, CDC)
- High affinity for PD-1 (K_D ~ 3 nM), blocks binding of both PD-L1 (B7-H1) and PD-L2 (B7-DC)
- Manageable safety profile and preliminary evidence of clinical activity in patients with treatment-refractory solid tumors in a first-in-human, single-dose, dose-escalation study[1]

[1]Brahmer J, et al. J Clin Oncol 2010;28:3167-75

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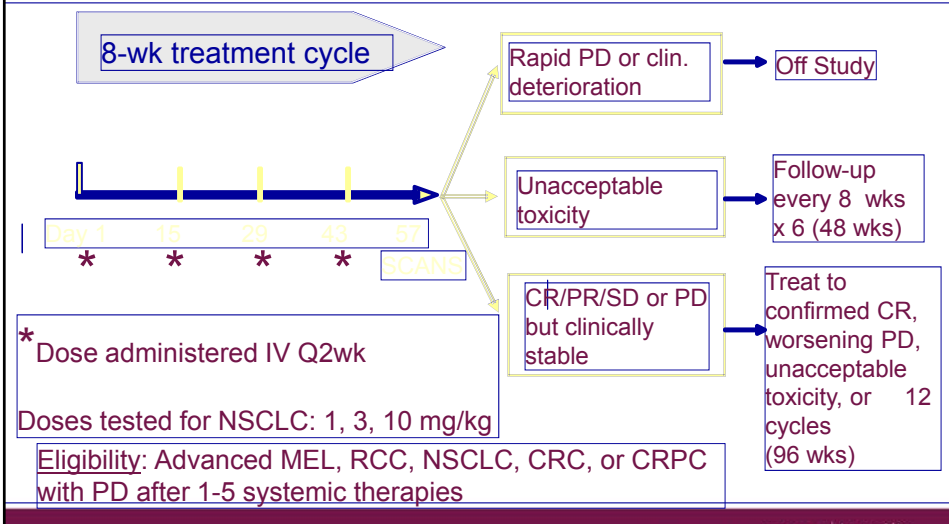
Study Design: Phase I Multi-dose Regimen



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Study Objectives and Conduct

- Primary
  - Assessment of safety and tolerability of BMS-936558
- Secondary/Exploratory
  - Assessment of antitumor activity
  - Pharmacodynamic evaluation
- Accrual completed (Dec. 2011); patient assessment ongoing
- Current analysis for patients treated through Feb. 2012
  - 296 patients (122 with NSCLC) were evaluable for safety
  - 236 patients (76 with NSCLC) were evaluable for clinical activity

Baseline Characteristics

Baseline Characteristic	n=122
Median age (range), yr	65 (38-85)
Male, no. (%)	74 (61)
Tumor histology, no. (%)*	
Squamous	47 (39)
Non-squamous	73 (60)
ECOG PS, no. (%)†	
0-1	117 (96)
2	2 (2)
Number of prior therapies, no. (%)‡	
1-2	49 (40)
≥3	67 (55)
Nature of prior therapy, no. (%)	
Platinum-based chemotherapy	115 (94)
Tyrosine-kinase inhibitor	41 (34)
Radiotherapy	40 (33)

BMS-936558-Related Adverse Events

Drug-Related Adverse Event	All Grades		Grades 3-4	
	Tot Pop*	NSCLC	Tot Pop	NSCLC†
	No. (%) of Patients, All Doses			
Any adverse event	207 (70)	78 (64)	41 (14)	10 (8)
Fatigue	72 (24)	22 (18)	5 (2)	2 (2)
Rash	36 (12)	5 (4)	—	—
Diarrhea	33 (11)	7 (6)	3 (1)	1 (1)
Pruritus	28 (9)	6 (5)	1 (0.3)	—
Nausea	24 (8)	9 (7)	1 (0.3)	—
Appetite ↓	24 (8)	12 (10)	—	—
Hemoglobin ↓	19 (6)	10 (8)	1 (0.3)	—
Pyrexia	16 (5)	7 (6)	—	—

*AEs occurring in ≥5% of the total population.
† The most common grade 3-4 AEs were fatigue, pneumonitis, and elevated AST (2 pts each). An additional 16 grade 3-4 drug-related AEs were observed and one or more occurred in a single patient.

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Summary of Key Safety Results

- A maximum tolerated dose was not identified at doses up to 10 mg/kg
- There was no apparent relationship between drug dose and AE frequency in all treated patients or NSCLC patients
- In the total patient population across all tumor types:
  - Grade 3-4 drug-related AEs occurred in 14% of patients
  - Grade 1-2 pneumonitis was noted in 6 (2%) patients
  - Three drug-related deaths occurred in patients with pneumonitis (2 with NSCLC and 1 with CRC)
- In NSCLC patients:
  - Grade 3-4 drug-related AEs occurred in 8% of patients
  - Grade 1-2 pneumonitis was noted in 4 (3%) patients

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Clinical Activity of BMS-936558 in NSCLC Patients

Pop	Dose (mg/kg)	Pts n	ORR n (%)	Duration of Response (mo)	SD ≥24 wk n (%)	PFSR at 24 wk (%)
ALL NSCLC	1-10	76	14 (18)	1.9+ to 30.8+	5 (7)	26
NSCLC	1	18	1 (6)	9.2+	1 (6)	16
	3	19	6 (32)	1.9+ to 30.8+	2 (11)	41
	10	39	7 (18)	3.7 to 14.8+	2 (5)	24

- ORR was assessed using modified RECIST v1.0
- 3 NSCLC patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the ORR calculation

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Clinical Activity by Histology, Efficacy Population

Parameter	BMS-936558 Dose, mg/kg		
	1	3	10
ORR, No. patients* (%)			
Squamous	0 n=5	3 (50) n=6	3 (43) n=7
Non-squamous	0 n=12	3 (23) n=13	4 (13) n=31
SD ≥24 wk, No. patients (%)			
Squamous	0	0	0
Non-squamous	1 (8)	2 (15)	2 (6)
PFSR at 24 wk, (%)			
Squamous	0	50	43
Non-squamous	14	37	21

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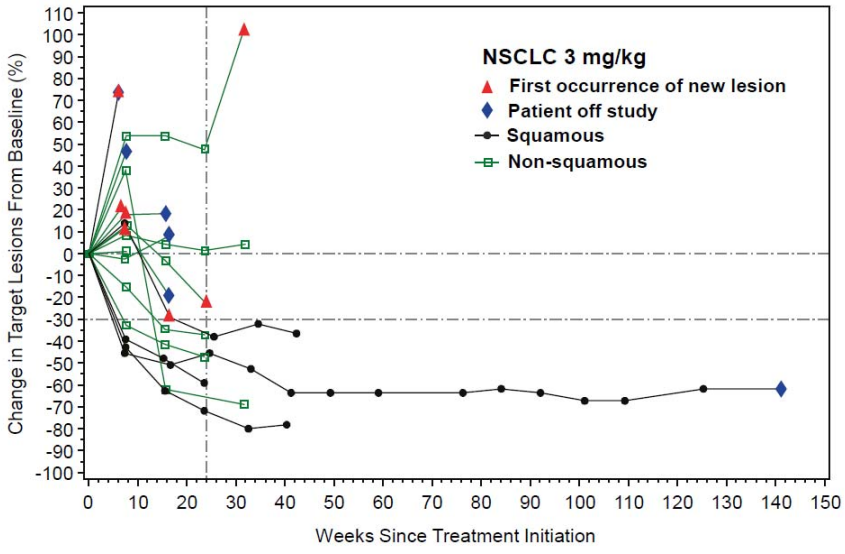
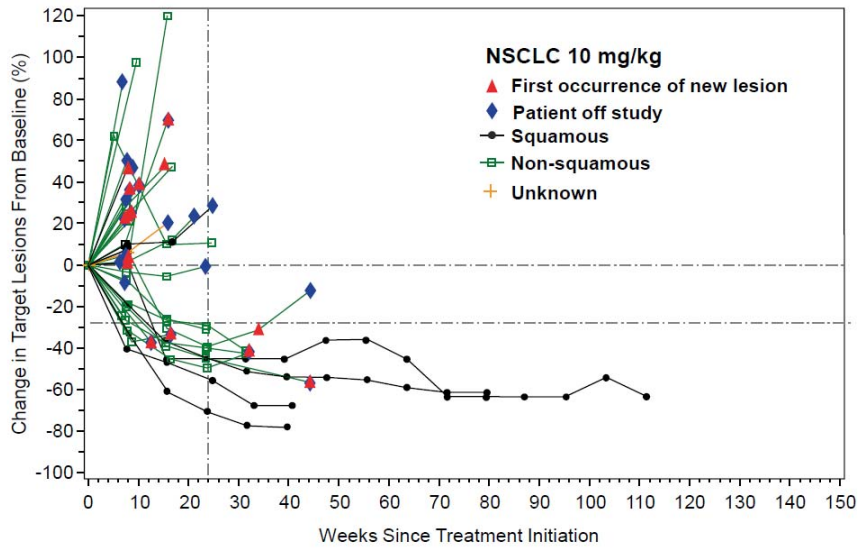
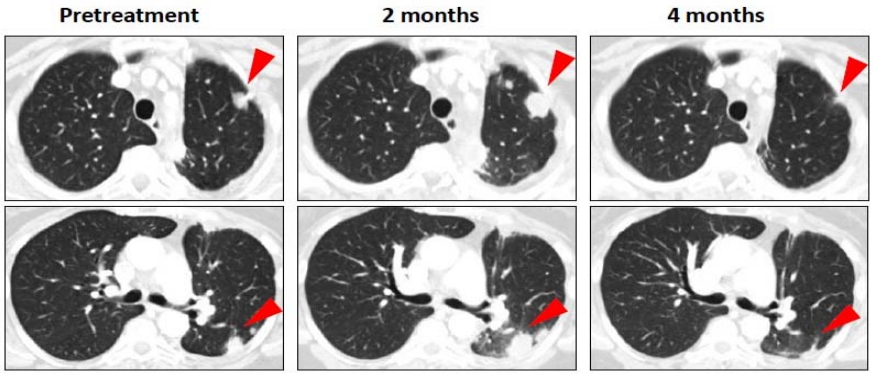
Changes in Target Lesions Over Time in NSCLC Patients



Changes in Target Lesions Over Time in NSCLC Patients



Response of Metastatic NSCLC (BMS-936558, 10mg/kg)



- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx '04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed

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Conclusions

- BMS-936558 can be administered safely in an outpatient setting to heavily pretreated NSCLC patients
- Durable clinical benefit was seen in both squamous and non-squamous NSCLC
- These findings support the importance of the PD-1 pathway in NSCLC therapy across different histologies
- Preliminary data correlating PD-L1 expression in pretreatment tumor biopsies with clinical outcomes will be further explored
- Clinical registration trials of BMS-936558 in patients with NSCLC are planned

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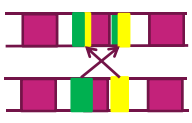
Comprehensive Characterization of Squamous Cell NSCLC

Ramaswamy Govindan, Peter Hammerman, Neil Hayes, Matthew Wilkerson, Steve Baylin and Matthew Meyerson

On Behalf of the Lung Cancer Working Group of The Cancer Genome Atlas (TCGA) Project

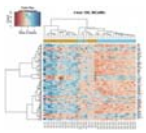
Genomic alterations in cancer

Structural variants	Copy number alterations	Point mutations & indels	Gene expression
• Translocations • Fusions • Inversion	• Amplifications • Deletions • LOH	• Missense • Nonsense • Splice site • Frameshift	• Outlier expression • Isoform usage • Pathways & signatures



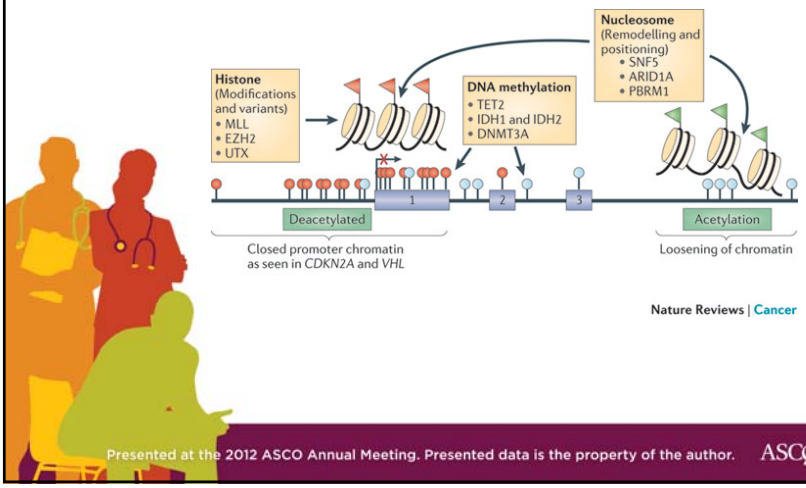
Wild type AGTGA

Mutant AGAGA

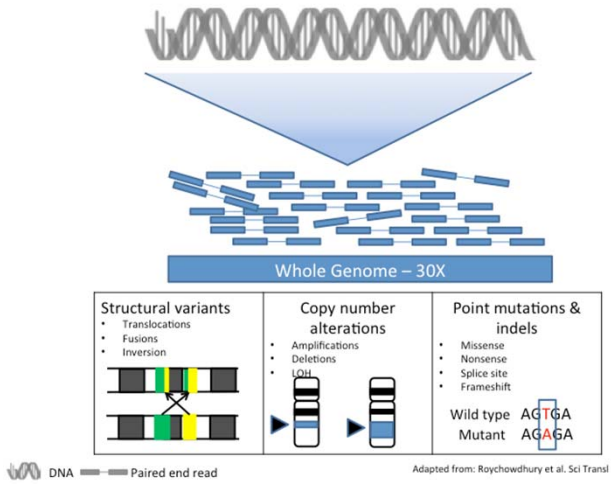


Adapted from: Roychowdhury et al. Sci Transl Med; 20122

Epigenetic Changes



Whole Genome Sequencing



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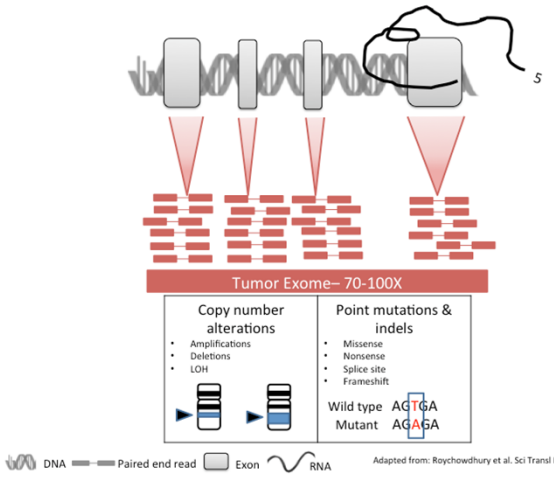
Exome Sequencing



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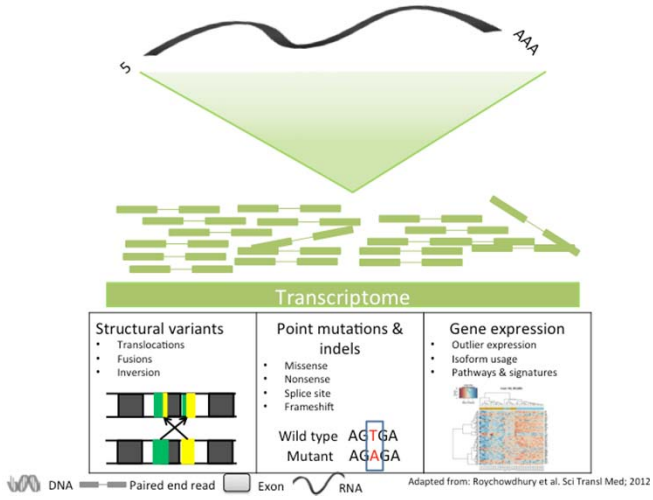
Transcriptome Sequencing (RNA Seq)



Adapted from: Roychowdhury et al. Sci Transl Med; 2012

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TCGA Lung Cancer Project Status

- **Adenocarcinoma**
  - **Goal 500**
  - **Accrued so far 320**
  - **Analysis ongoing**
- **Squamous Cell Cancer**
  - **Goal 500**
  - **Accrued so far 300**
  - **Analysis completed 178**

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Squamous Cell Lung Cancer Introduction

- Squamous cell lung cancers account for roughly 30% of lung cancer deaths, or roughly 45,000 deaths per year in the US
- No molecularly targeted therapy has yet been approved for use in squamous cell lung cancer
- Very little is known about the molecular genetics of squamous cell lung cancer

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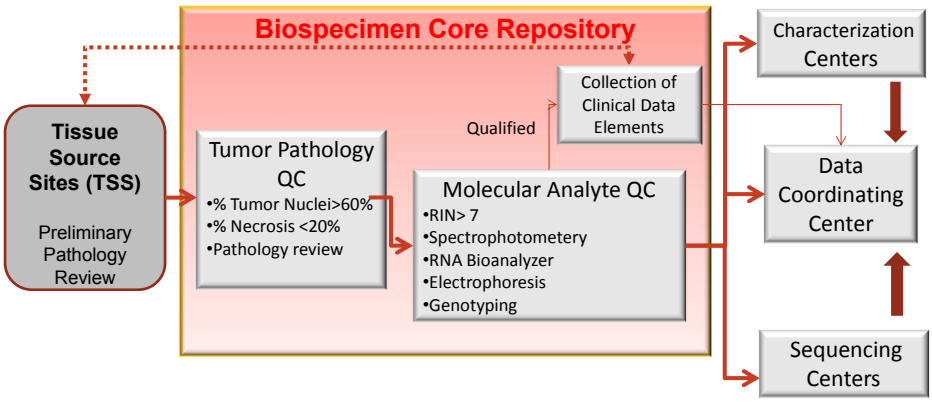
Specimen Processing



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Methods

- For all 178 samples
  - SNP arrays (copy number variation)
  - Exome sequencing (somatic mutations in the exons)
  - Transcriptome sequencing–"RNA-seq" (gene expression, gene fusions)
  - Microarrays (gene expression)
  - DNA methylation (methylation status)
- Additional data
  - miRNA sequencing for 159/178 samples
  - Whole genome sequencing of 19 samples

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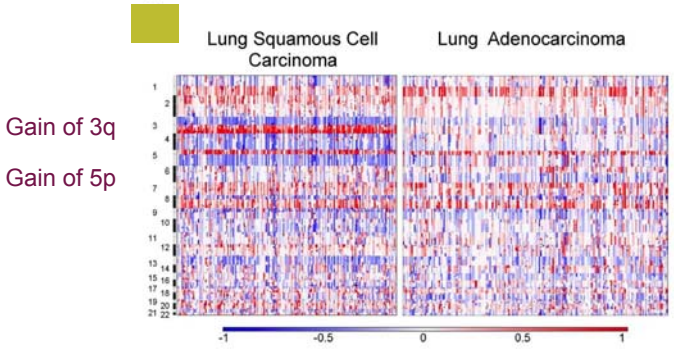
Copy number analysis

Chromosomal arm level alterations

178 tumor/normal DNA pairs, analyzed on Affymetrix SNP 6.0 arrays and Agilent CGH arrays



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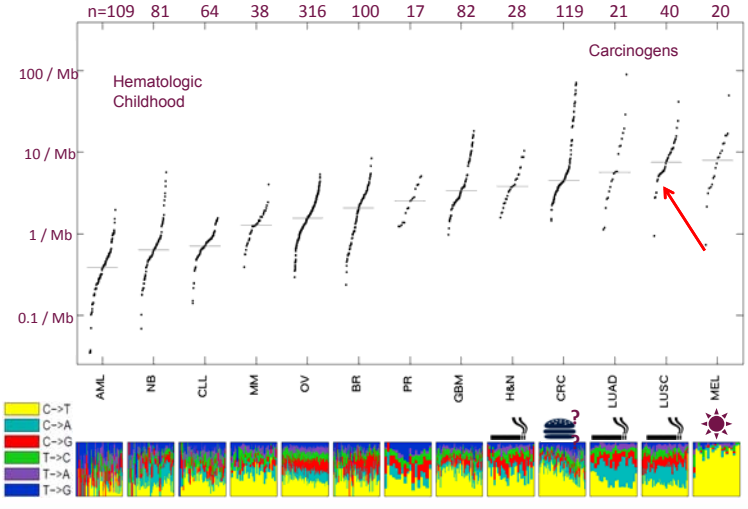
Squamous cell lung cancer has a very high rate of somatic mutations



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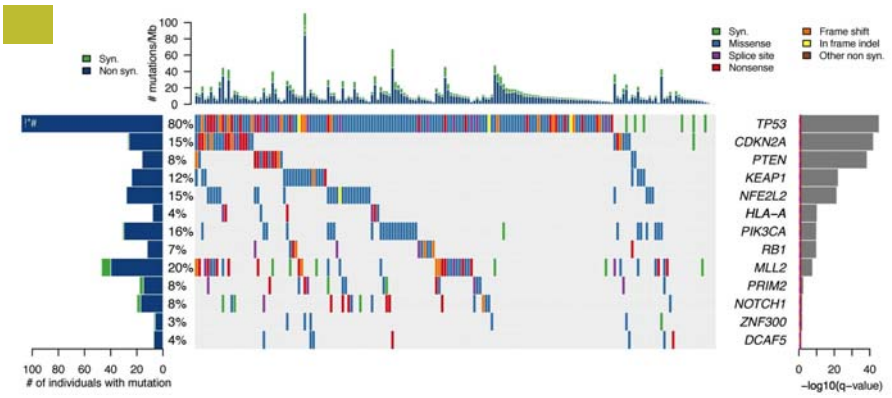
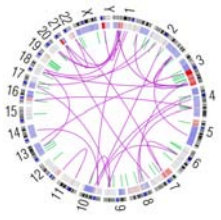
Significantly Mutated Genes in Squamous Cell Lung Cancer



PTEN translocation leading to loss of phosphatase domain

LUSC-60-2713



SNP Array

PAPSS2-PTEN

Exon 1-Exon6

There are multiple means of *PTEN* inactivation/PI3K activation in squamous cell lung carcinoma

Mutation, deletion, translocation, and potentially methylation

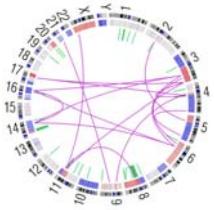
NOTCH1 rearrangement causing loss of intracellular domain

SNP Array

NOTCH1-SEC18

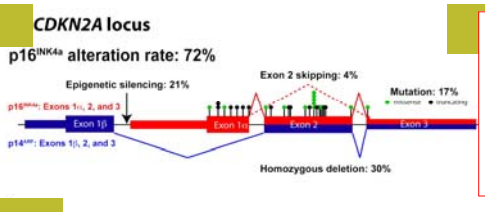
Exon 28-5'UTR

LUSC-66-2757



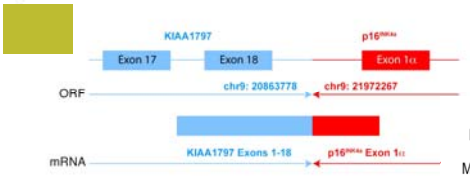
There is recurrent loss of function of *NOTCH* genes in squamous cell lung carcinoma, similar to but less common than head & neck carcinoma

CDKN2A: Loss of Function Through Multiple Mechanisms

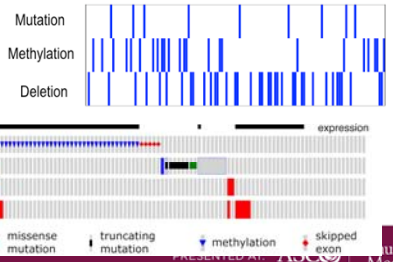


Three most common mechanisms

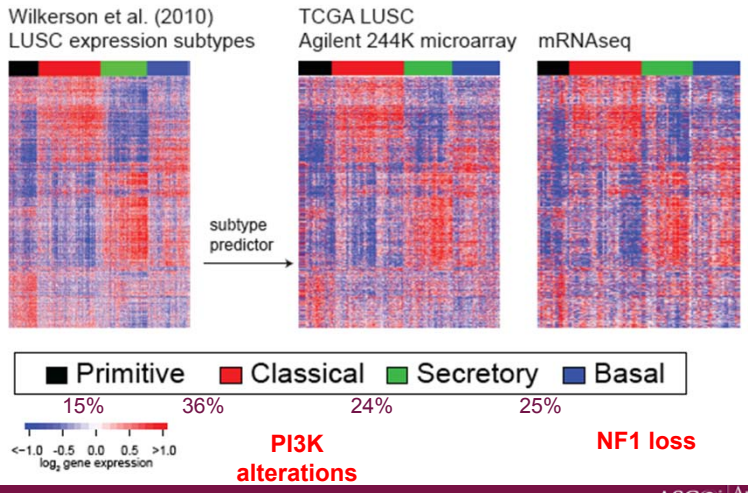
Homozygous deletion	30%
Methylation	21%
Mutation	17%



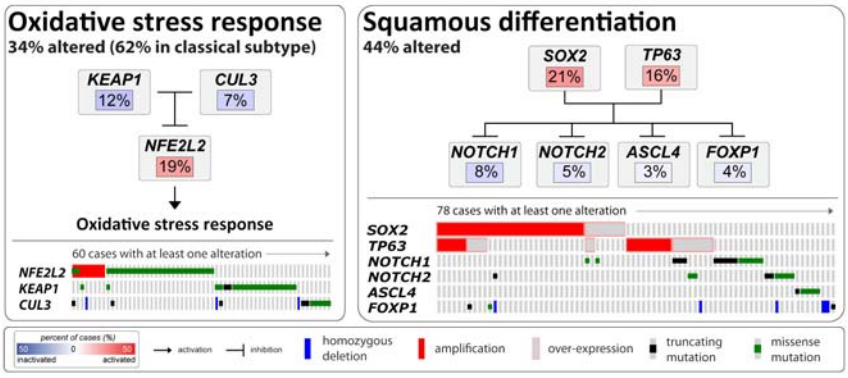
Tumor samples



mRNA Expression Analysis



Pathway Alterations in Squamous Cell Lung Cancer



Therapeutic targets in squamous cell lung carcinoma

Gene	Event Type	Frequency
CDKN2A	Deletion/Mutation/ Methylation	72%
PI3KCA	Mutation	16%
PTEN	Mutation/Deletion	15%
FGFR1	Amplification	15%
EGFR	Amplification	9%
PDGFRA	Amplification/Mutation	9%
CCND1	Amplification	8%
DDR2	Mutation	4%
BRAF	Mutation	4%
ERBB2	Amplification	4%
FGFR2	Mutation	3%

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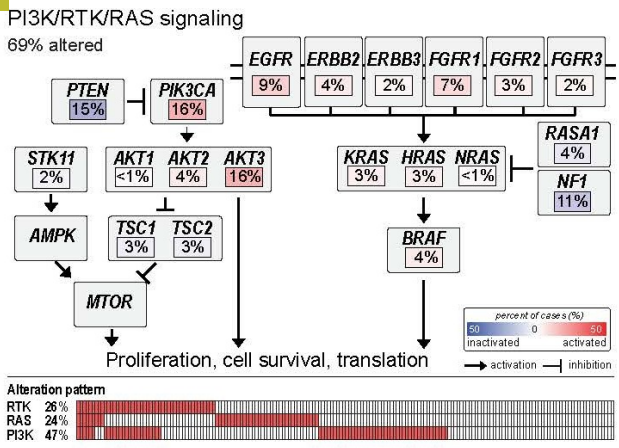
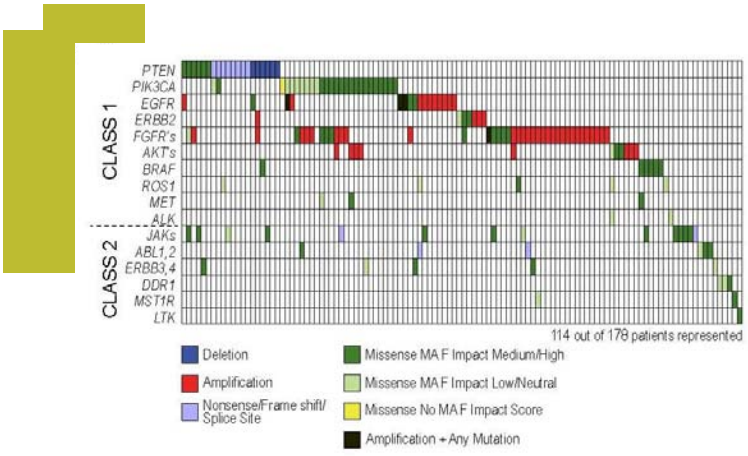
Therapeutic targets in squamous cell lung carcinoma



Therapeutic targets in squamous cell lung carcinomas, defined by TCGA



Summary

- Complex genomes with frequent and unique rearrangements
- A clear and reproducible sub-classification
- Distinct transforming mechanism defined by common *NFE2L2* activation in the classical subtype
- High somatic mutation rates includes near universal *TP53* mutation and frequent loss of *CDKN2A* function
- Multiple mechanisms for *CDKN2A* inactivation
- Therapeutic identified in 127 patients (75%) including FGFRs, PI3 kinase pathway, EGFR/ERBB2 and Cyclin/CDK complexes

EGFR, ALK PD-1 and Other Novel Genomic Targets: Conclusions post ASCO

- LUX-1 study suggests afatinib is a potent front-line irreversible EGFR TKI for EGFR mutant lung cancer and Dacomitinib also looks promising in this population.
- Docetaxel appears more effective than erlotinib in second line therapy of EGFR wild type NSCLC.
- Crizotinib is just as active in ROS1 translocations as it is in ALK translocated lung cancer and LDK378,a highly potent new ALK inhibitor, is moving quickly into ALK translocated NSCLC.
- Targeting PD1 is a viable and exciting approach, especially in squamous cell lung cancer.
- Exciting new targets in squamous cell cancer are being described via the TCGA.

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