ATLAS OF MOLECULAR ONCOLOGY

ALK Fusion Oncogenes in Lung Adenocarcinoma

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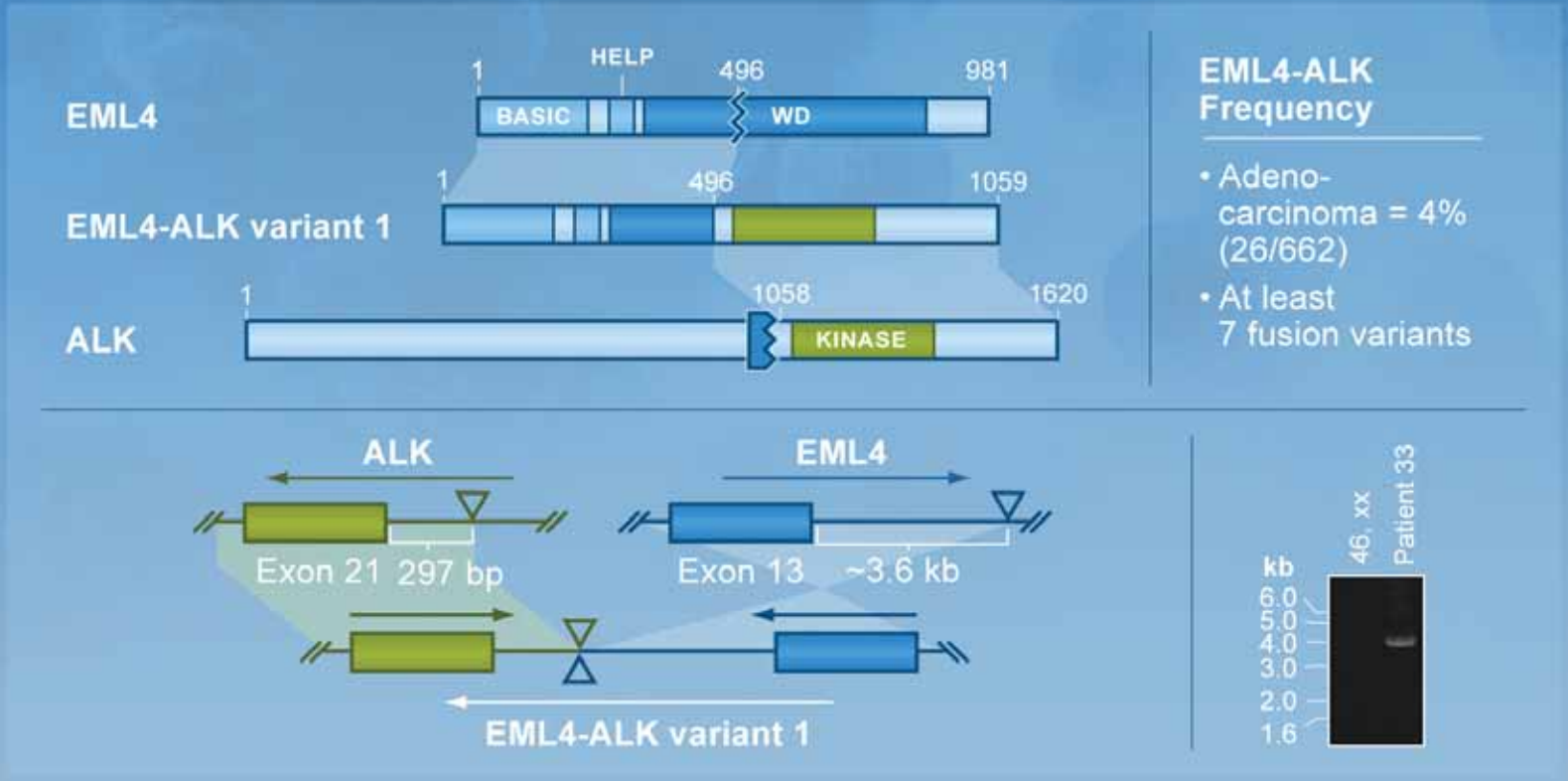
ALK Fusion Oncogenes in Lung Adenocarcinoma

- Translocations resulting in fusion genes
- A receptor tyrosine kinase (anaplastic lymphoma kinase [ALK]) fuses to the echinoderm microtubule-associated protein-like 4 (EML-4) [Soda Nature 2007]
- Multiple chimeras found – there are other fusion partners besides EML-4
- Oncogenic
- Activation enhances proliferation and survival, changes cell shape through KRAS-ERK, JAK3-STAT, PI3K

EML4-ALK Fusion Gene in NSCLC (Non-Small-Cell Lung Cancer)



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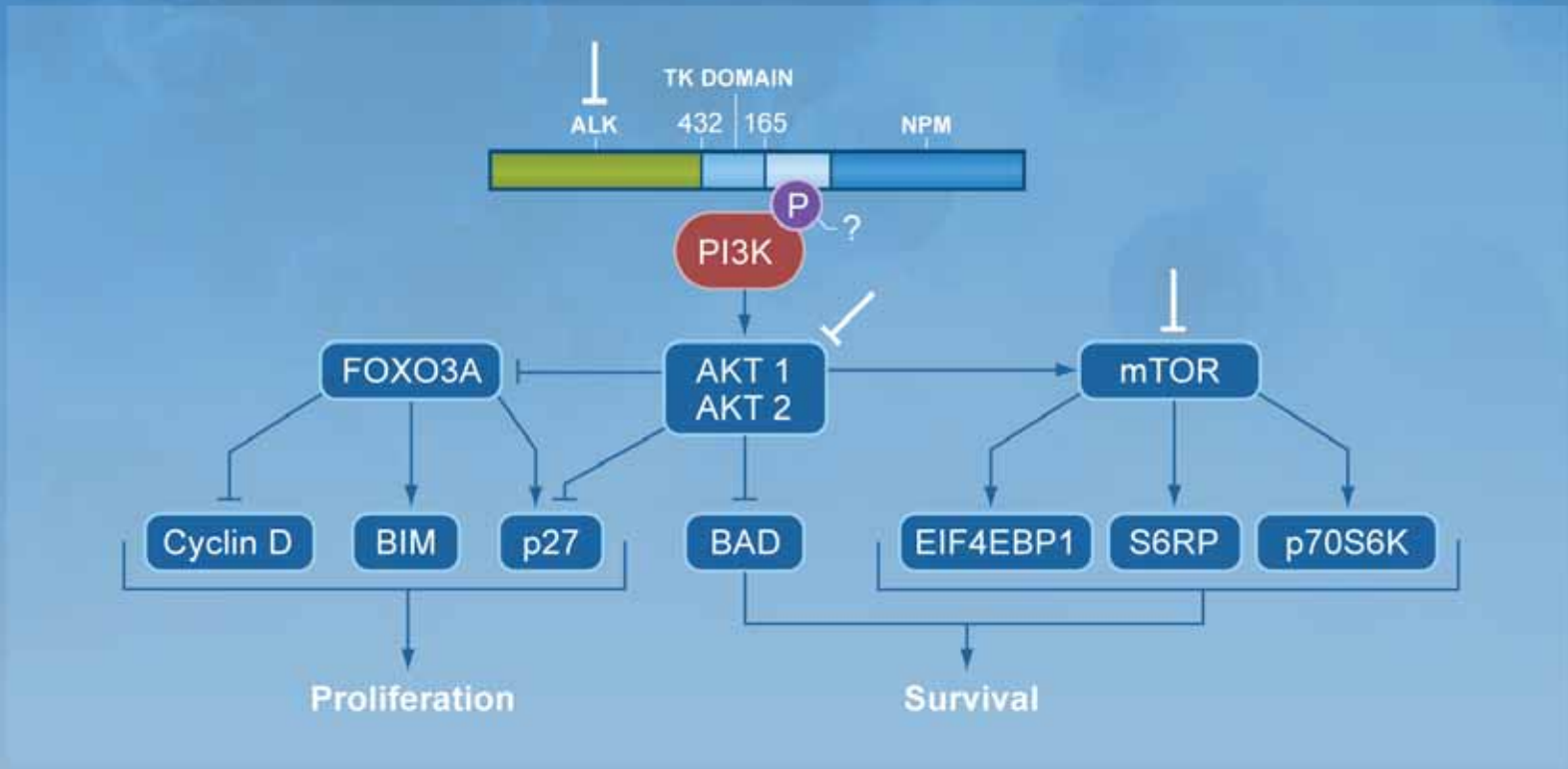
ALK Anti-Apoptotic Signaling Occurs via PI3K



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Clinical Activity Observed in a Phase 1 Dose-Escalation Trial of an Oral MET and ALK Inhibitor PF-02341066

Source: Kwak EL et al. *Proc ASCO* 2009;Abstract 3509.

RP2D Molecular Cohort: NSCLC with ALK Fusion (n = 19)

	Characteristics	Number (Percentage)
	Median age (range), years	50 (28-73)
	Gender (male:female)	9:10
ECOG PS	0	4 (21%)
	1	12 (63%)
	2	3 (16%)
Smoking History	Current smoker	0
	Former smoker	5 (26%)
	Never smoker	14 (74%)
Histology	Adenocarcinoma	17 (90%)
	Squamous cell carcinoma	1 (5%)
	Unknown	1 (5%)
Prior Treatment	1 Regimen	7 (37%)
	2 Regimens	4 (21%)
	3 Regimens	4 (21%)
	> 3 Regimens	4 (21%)

Data in the database as of March 9, 2009

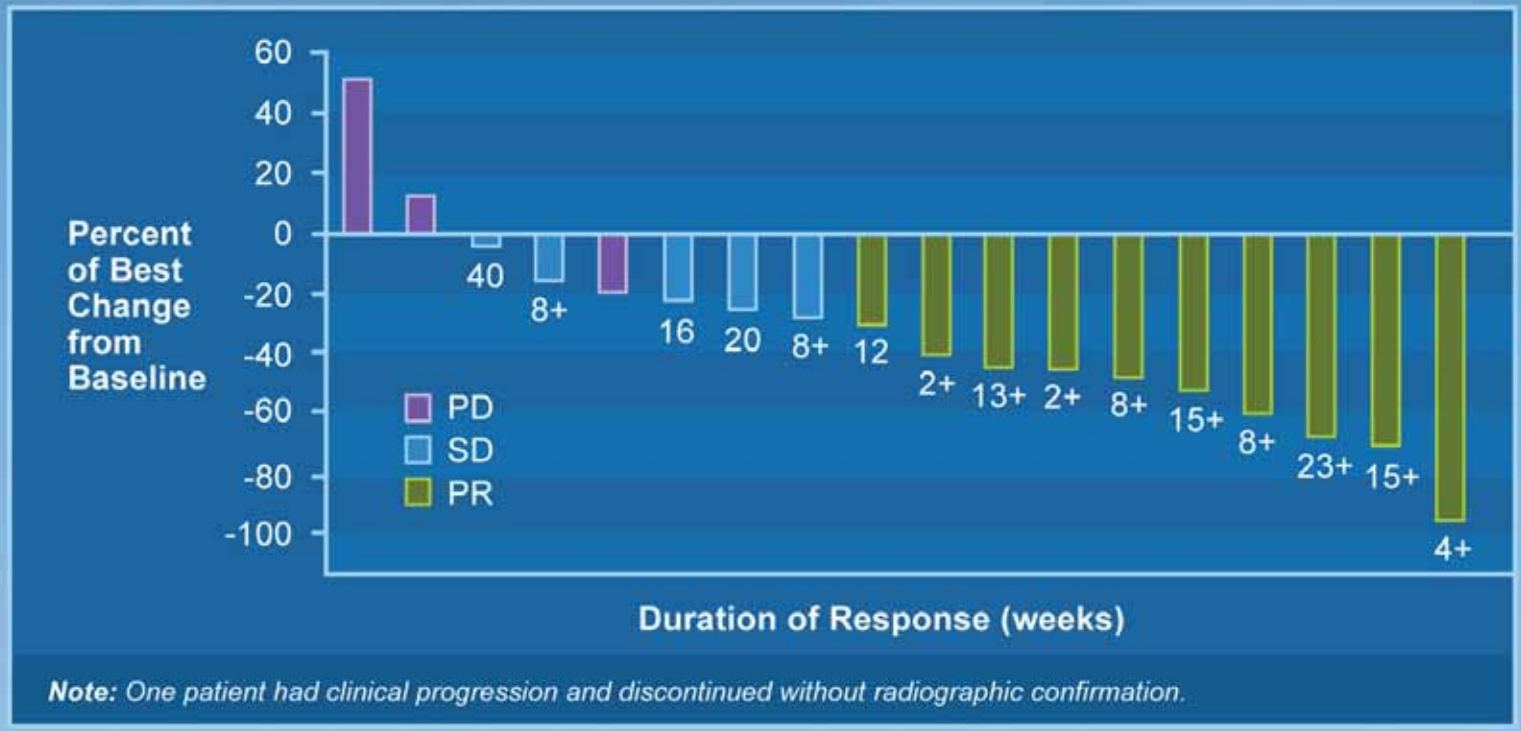
Source: With permission from Kwak EL et al. *ASCO 2009.* Abstract 3509.

EML-4 ALK Fusion Oncogene in Lung Adenocarcinoma: Clinical and Pathologic Characteristics

- Patients may be younger and are more commonly male
- More common in adenocarcinoma and never or modest smokers
- Unlike EGFR mutation may NOT be prognostic
- Like EGFR mutation largely exclusive from KRAS mutation
- Rare to occur with EGFR mutation
- Occurs in 25% of EGFR/KRAS WT never smokers

Source: Shaw AT et al. *J Clin Oncol* 2009;27(26):4247-53.

Tumor Responses to PF-02341066 for NSCLC Evaluable Patients with ALK Fusions



Source: With permission from Kwak EL et al. *ASCO 2009.* Abstract 3509.

Molecular Cohort: NSCLC ALK Fusion

- **Overall response rate = 53% (10/19 pts)**
- **Disease control rate at 8 weeks = 79% (15/19 pts)**
- **4 patients had progression at first evaluation**

Sources: Kwak EL et al. *ASCO 2009.* Abstract 3509; Shaw AT et al. *J Clin Oncol* 2009;27:4247

48 yo Female Non-Smoker with NSCLC ALK Fusion

Source: With permission from Kwak EL et al. *ASCO 2009.* Abstract 3509.

ALK-Related Efficacy Evaluable Patients w/ NSCLC

Patient ID	Previous Treatments	Best Response	PF-1066 Best Response	Duration of Response	Status
10021042	1	SD	PR	12 wk	Discont. (5 mo)
10081001	2 (erlotinib)	PD*, PR*	PR	15 wk +	Ongoing (8 mo +)
10021038	2 (erlotinib)	SD, SD*	PR	23 wk +	Ongoing (7 mo +)
10021039	1	PD	PR	15 wk +	Ongoing (7 mo +)
10071016	3	PD, PD, PD	PR	8 wk +	Ongoing (4 mo +)
10021043	2	PD, SD	PR	13 wk +	Ongoing (4 mo +)
10071019	7 (gefitinib)	PD, SD, PD*, SD, SD, SD, PD	PR	8 wk +	Ongoing (2 mo +)
10071020	5 (gefitinib)	SD, SD, PD*, PR, PR	uPR	4 wk +	Ongoing (3 mo +)
10021023	3	SD, PD, PD	uPR	2 wk +	Ongoing (2 mo +)
10081002	3 (erlotinib)	SD*, PD, SD*	uPR	2 wk +	Ongoing (2 mo +)
10021045	1	SD	SD	N/A	Ongoing (2 mo +)
10021056	1	SD	SD	N/A	Ongoing (2 mo +)
10021026	3 (erlotinib)	SD*, SD, PD	SD	N/A	Discont. (PD) (10 mo)
10021040	1 (erlotinib)	PD*	SD	N/A	Discont. (PD) (4 mo)
10021014	2 (erlotinib)	SD, PD*	SD	N/A	Discont. (PD) (5 mo)
10021051	1	PD	PD	N/A	Discont. (<1 mo)
10021058	1	PD	PD	N/A	Discont. (1 mo)
10071021	3 (erlotinib)	SD, SD, PD*	PD	N/A	Discont. (<1 mo)
10051003	4 (erlotinib)	PD*, PR, PR, SD	PD	N/A	Discont. (1 mo)
* Best Response to EGFR			19 evaluable: 10 (7 confirmed, 3 unconfirmed), 5 SD, 4 PD		

Source: With permission from Kwak EL et al. *ASCO 2009.* Abstract 3509.

ALK Fusions: A Therapeutic Target in NSCLC

- ALK tyrosine kinase druggable
- Phase II and III trials of PF-02341066 in patients with ALK fusions are imminent
- Testing now available commercially and at certain institutions

Conclusions

- Non-small cell lung cancer is no longer one disease treated empirically with one or two chemotherapy regimens.
- NSCLC, and in particular adenocarcinoma, must be sub-typed both pathologically and genotypically.
- EGFR mutations served as a “watershed event” for this fundamental paradigm change, but other “druggable” kinase mutations will continue to be identified.