Heat Shock Protein 90 (Hsp90) Inhibition as a Potential Novel Approach to the Treatment of Patients with ALK Mutated Non-small Cell Lung Cancer (NSCLC)

Rob Ross, MD

Infinity Pharmaceuticals

March 9th, 2011

Disclosure

- I am an employee of Infinity Pharmaceuticals

Heat Shock Protein 90 (Hsp90) is an Emerging Cancer Target

Function of Hsp90

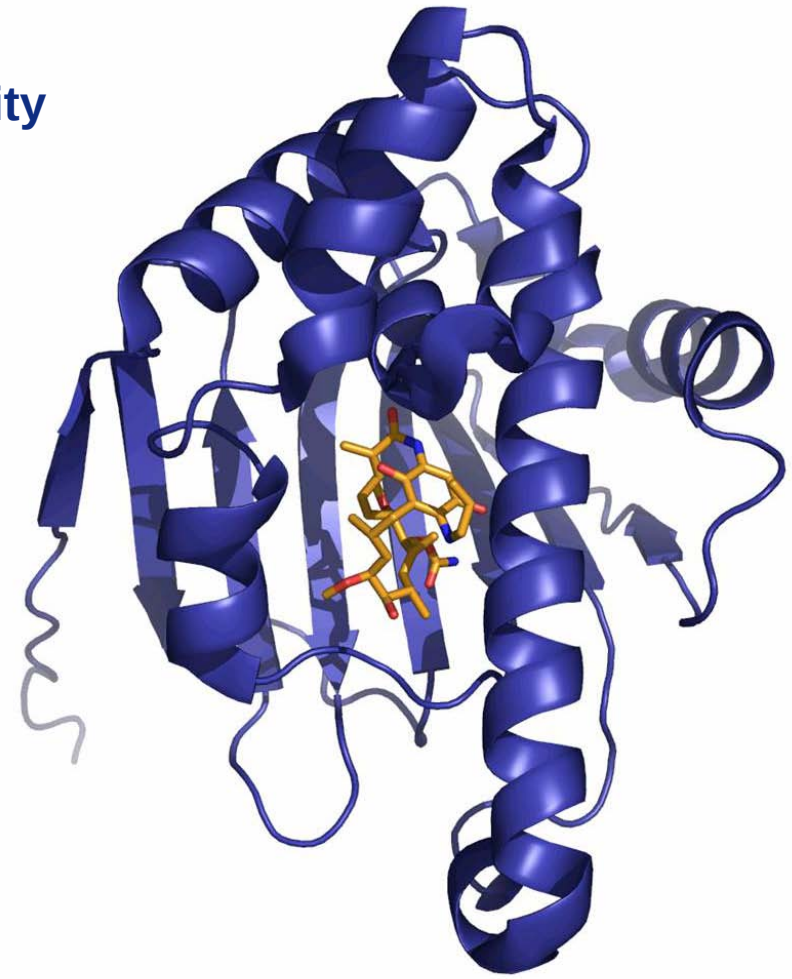
- "Chaperone" protein necessary for stability and function of certain "client" proteins

Function of Hsp90 in Cancer Cells

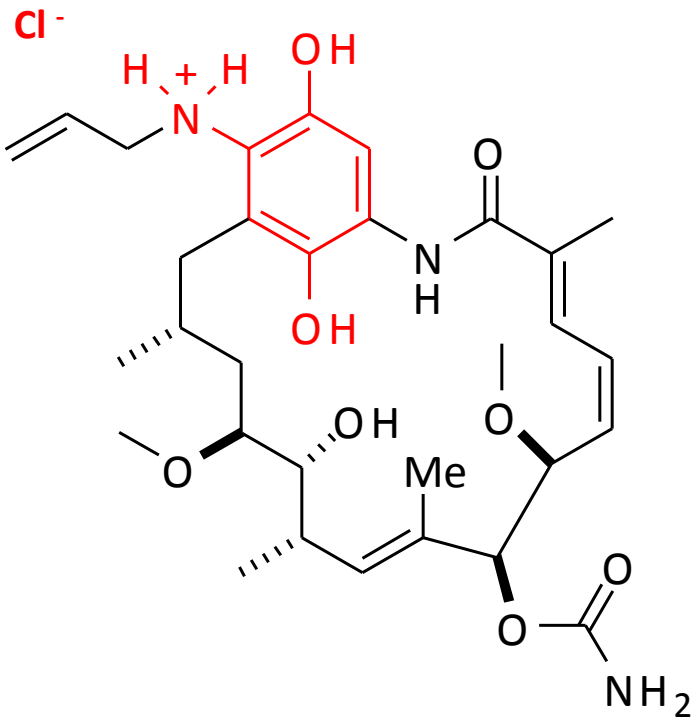
- Many oncoproteins are dependent on Hsp90 for function

Therapeutic Rationale

- Inhibiting Hsp90 induces degradation of oncoproteins, provides an alternative to directly inhibiting these proteins



IPI-504 (Retaspimycin Hydrochloride)



- Highly potent and selective Hsp90 inhibitor
- Novel analog of the natural product geldanamycin
- Water soluble IV formulation, administered to patients in normal saline
  - >250 mg / mL aqueous solubility
- Preclinical evidence of broad therapeutic potential
- Two ongoing clinical studies focused on patients with non-small cell lung cancer

VOLUME 28 · NUMBER 33 · NOVEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Activity of IPI-504, a Novel Heat-Shock Protein 90 Inhibitor, in Patients With Molecularly Defined Non–Small-Cell Lung Cancer

Lecia V. Sequist, Scott Gettinger, Neil N. Senzer, Renato G. Martins, Pasi A. Jänne, Rogerio Lilenbaum, Jhanelle E. Gray, A. John Iafrate, Ryohei Katayama, Nafeesa Hafeez, Jennifer Sweeney, John R. Walker, Christian Fritz, Robert W. Ross, David Grayzel, Jeffrey A. Engelman, Darrell R. Borger, Guillermo Paez, and Ronald Natale

Oncogene (2011) 1–6

www.nature.com/onc

SHORT COMMUNICATION

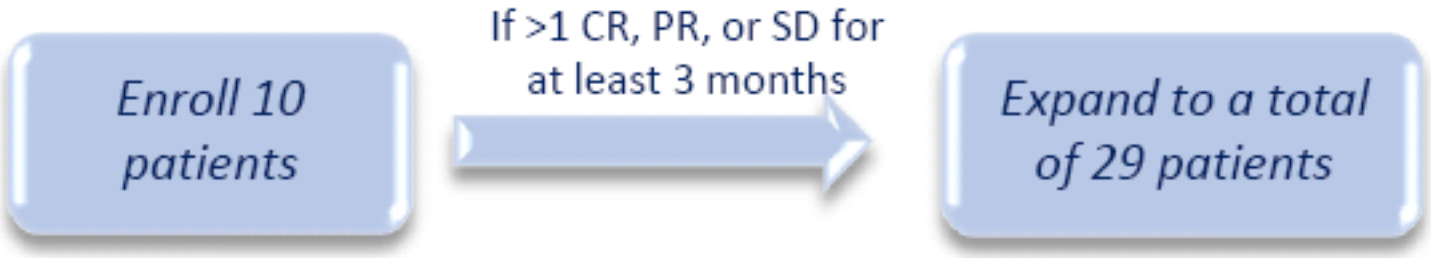
The Hsp90 inhibitor IPI-504 rapidly lowers EML4–ALK levels and induces tumor regression in ALK-driven NSCLC models

E Normant[1], G Paez[1], KA West, AR Lim, KL Slocum, C Tunkey, J McDougall, AA Wylie, K Robison, K Caliri, VJ Palombella and CC Fritz

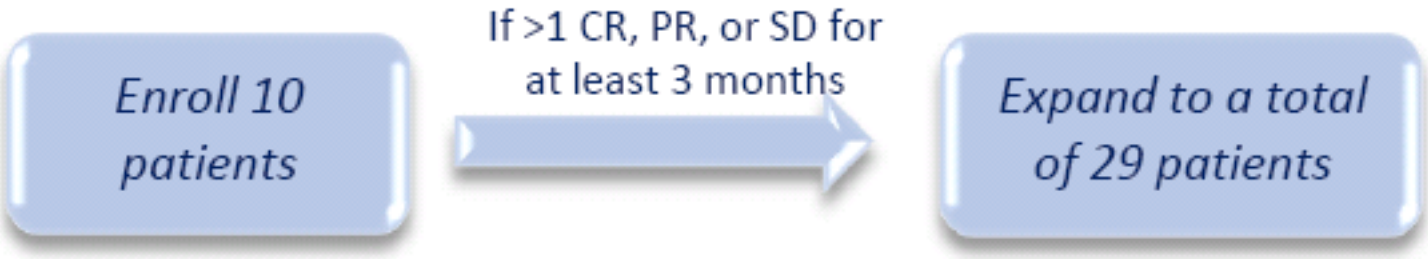
Infinity Pharmaceuticals, Cambridge, MA, USA

IPI-504 Phase 2 Trial in NSCLC

Mutant EGFR Cohort



Wild Type EGFR Cohort

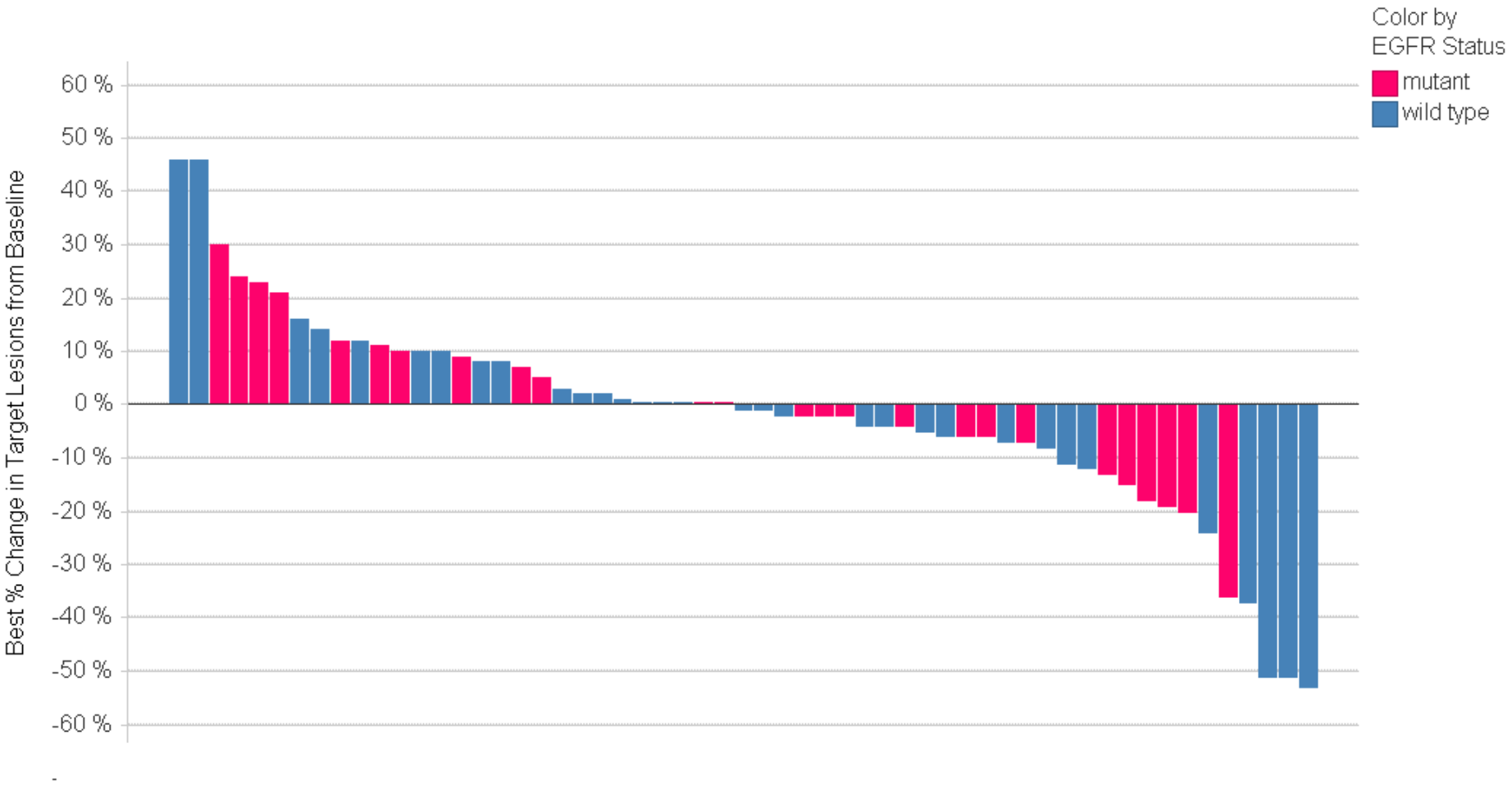


Demographics and Baseline Characteristics

		Total
Number of Patients		**76**
Age (years)	Median	64.0
	Range	31-82
Sex (n [%])	Female	48 (63)
	Male	28 (37)
Race (n [%])	Asian	11 (14)
	Black or African American	4 (5)
	White	61 (80)
Smoking Status (n [%])	Current Smoker	0
	Never Smoked	34 (45)
	Previous Smoker	42 (55)
Months since Diagnosis	Median	27.5
	Range	8-120
Histology (n [%])	Adenocarcinoma	59 (78)
	Bronchioloalveolar	4 (5)
	Large cell	2 (3)
	Squamous	6 (8)
	Unspecified NSCLC	5 (7)
Number of prior treatment regimens for NSCLC	Median	4.0
	Range	1-11
Best prior response to TKI treatment	CR	1 (1)
	PR	18 (24)
Total months on TKI prior to study	Median	1.8
	Range	0-61

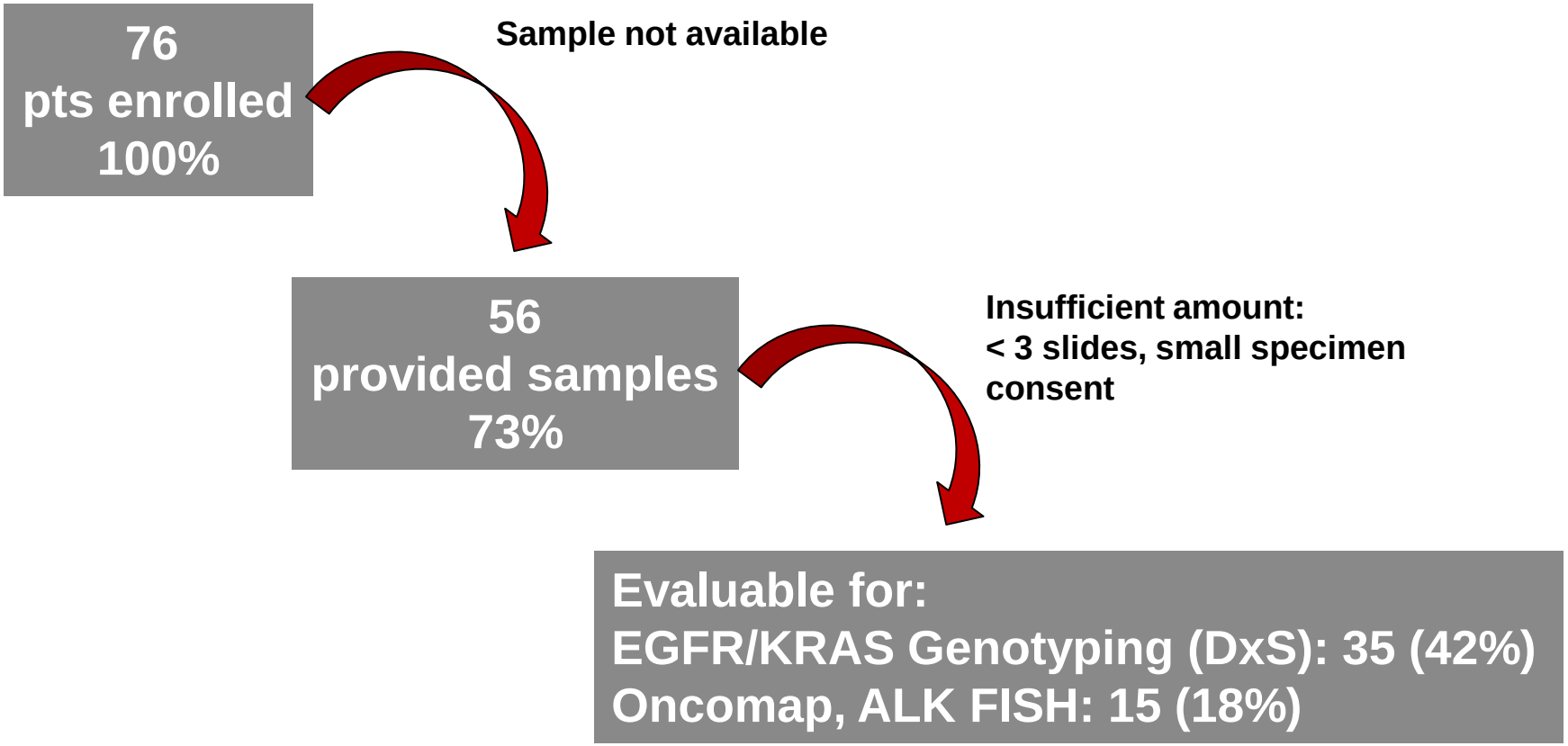
Sequist, ASCO 2010

Best Percent Change in Size of Target Lesions by EGFR Status

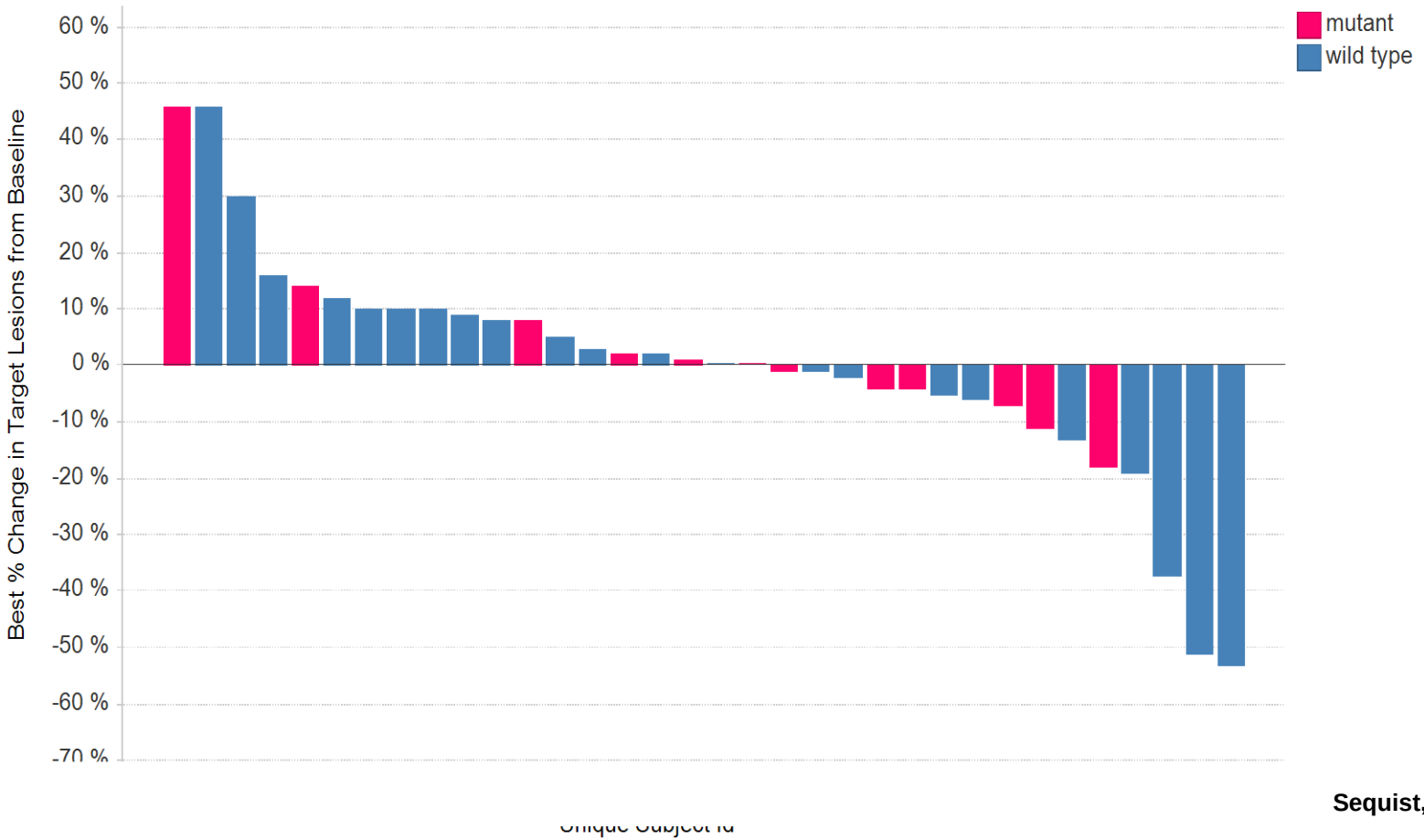


Sequist, ASCO 2010

Samples for Biomarker Analysis



Best Percent Change in Size of Target Lesions by KRAS Status



Sequist, ASCO 2010

Oncomap Analysis

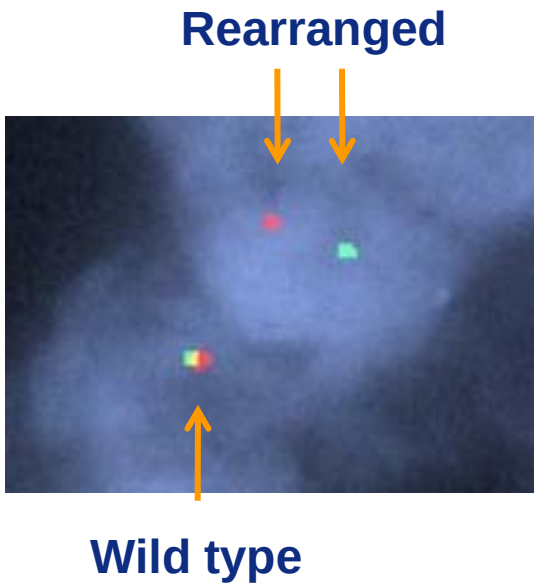
- **Oncomap:**
  - **A primer extension/mass spec-based analysis of mutations in oncogenes**
  - **Coverage: 1155 mutations in 114 genes**

- **Results:**
  - **No additional mutations found in any of the patient samples analyzed (including 3 PRs)**

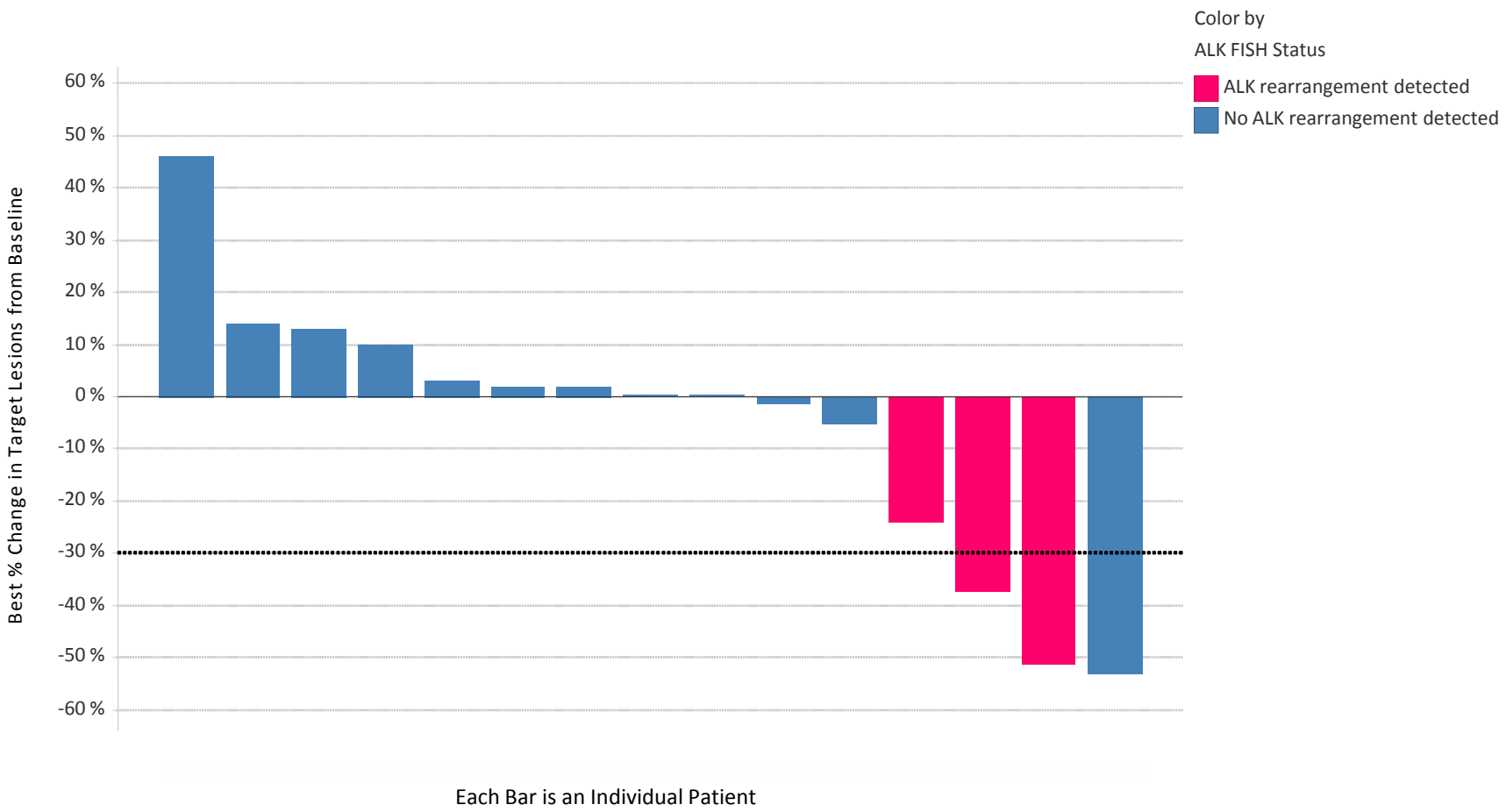
Assay for ALK Translocations: Fluorescent In Situ Hybridization (FISH)

Wild type ALK locus: probes overlap

Rearranged ALK locus: probes apart

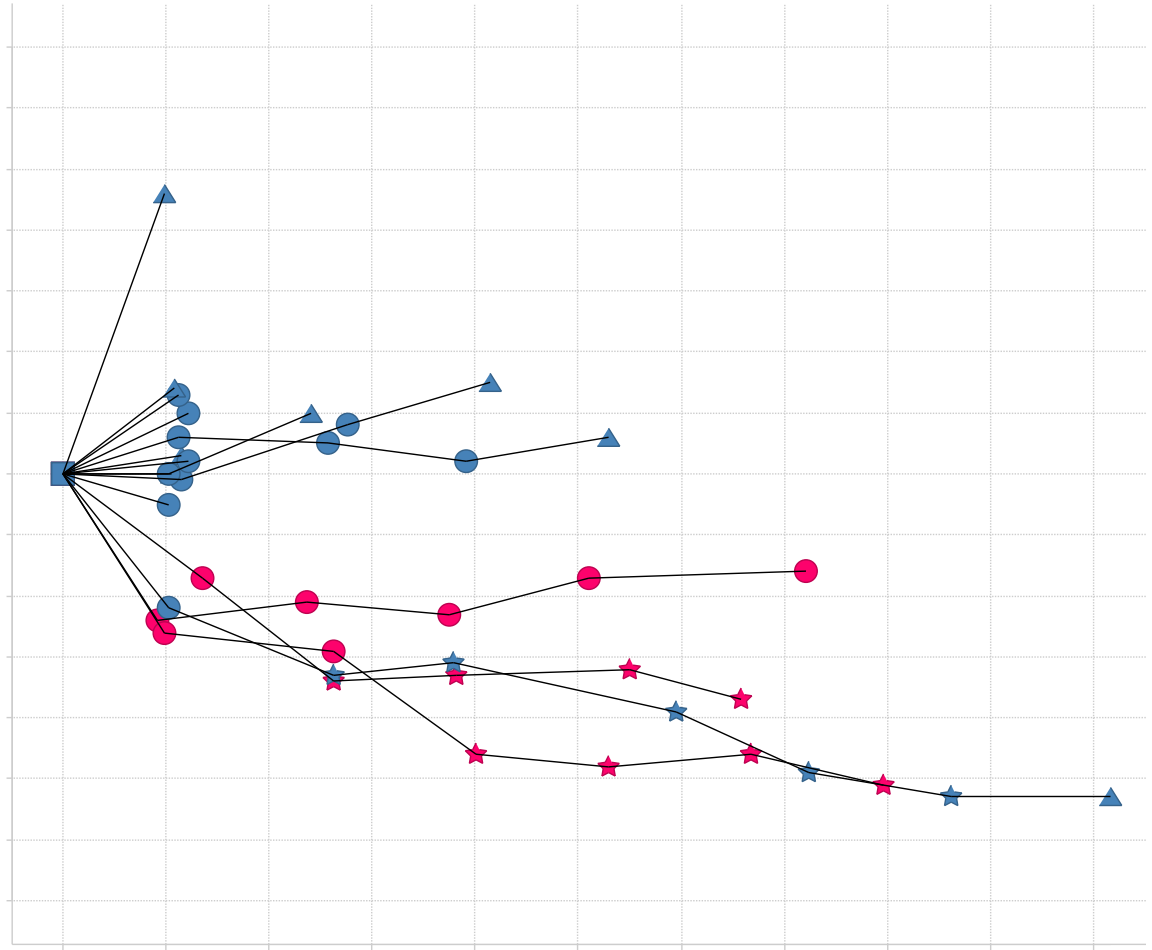


Best Percent Change in Size of Target Lesions by ALK FISH Status



Sequist, ASCO 2010

Change in Size of Target Lesions Over Time for Patients Tested for ALK Rearrangement



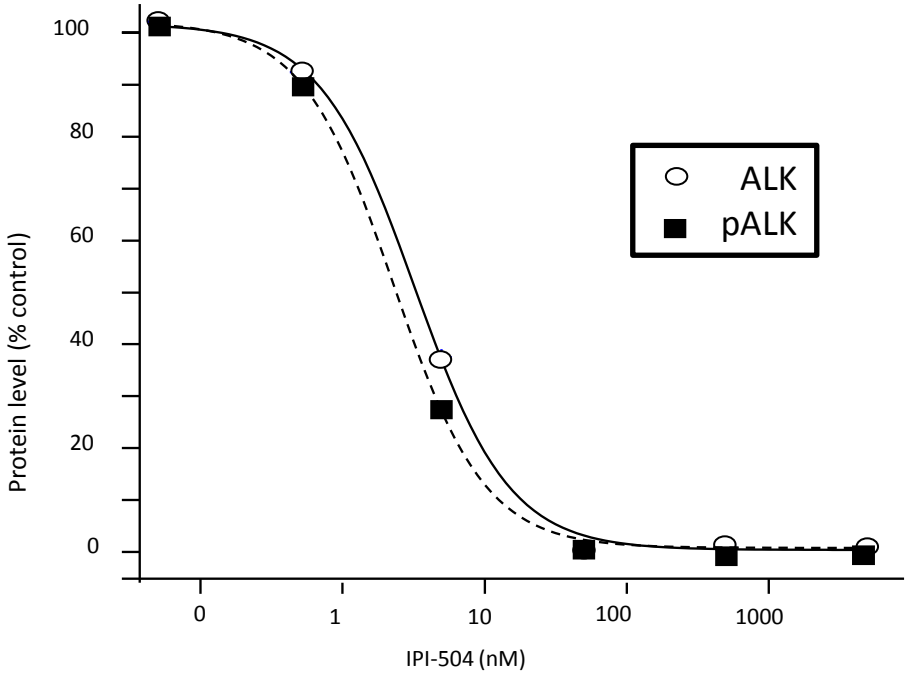
Sequist, ASCO 2010

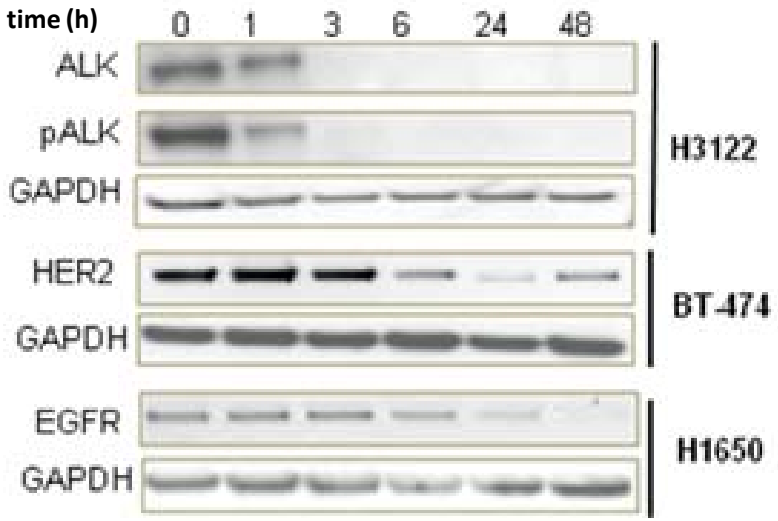
Overall Efficacy

	Total	EGFR Status (n=68)		KRAS Status (n=38)		ALK Status (n=15)	
		Wild Type	Mutant	Wild Type	Mutant	Wild Type	Rearranged
Number of Patients (n [%])	76	40 (53)	28 (37)	26 (34)	12 (16)	12 (16)	3 (4)
Objective Response Rate (All PRs) (n [%])	5 (7)	4 (10)	1 (4)	3 (12)*	0 (0)	1 (8)	2 (67)
RECIST Stable Disease or better for at least 3 months (n [%])	18 (24)	10 (25)	6 (21)	4 (15)	5 (42)	3 (25)	3 (100)
Median PFS in Months (95% CI)	2.86 (2.43-4.18)	2.86 (1.18-5.33)	2.76 (2.40-3.91)	2.86 (1.22-10.20)	3.91 (1.12-4.18)	2.43 (1.13-5.33)	Unable to determine

Sequist, ASCO 2010

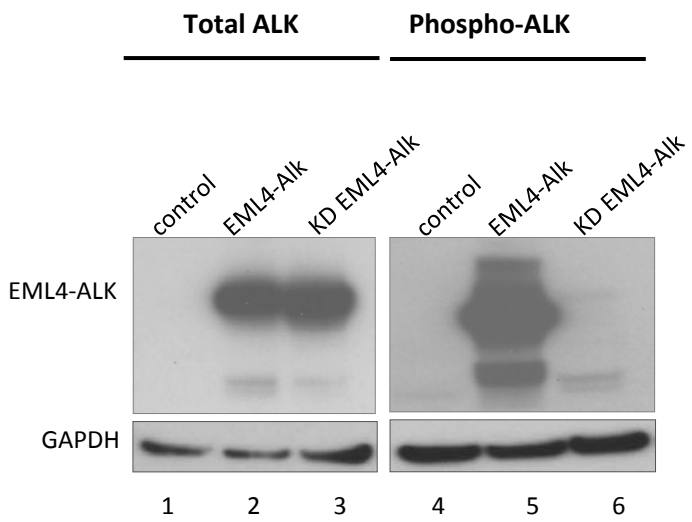
Nonclinical Findings: EML4-ALK is a More Sensitive Client Protein than mut EGFR or HER2

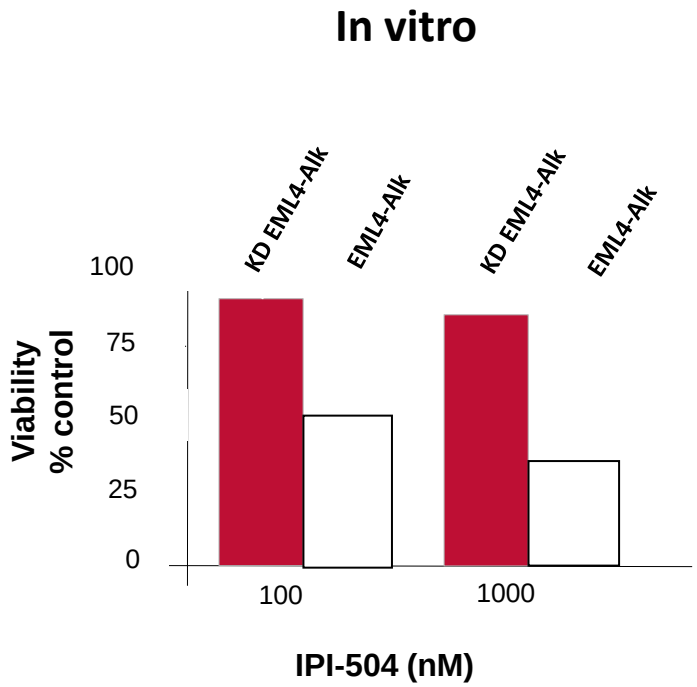




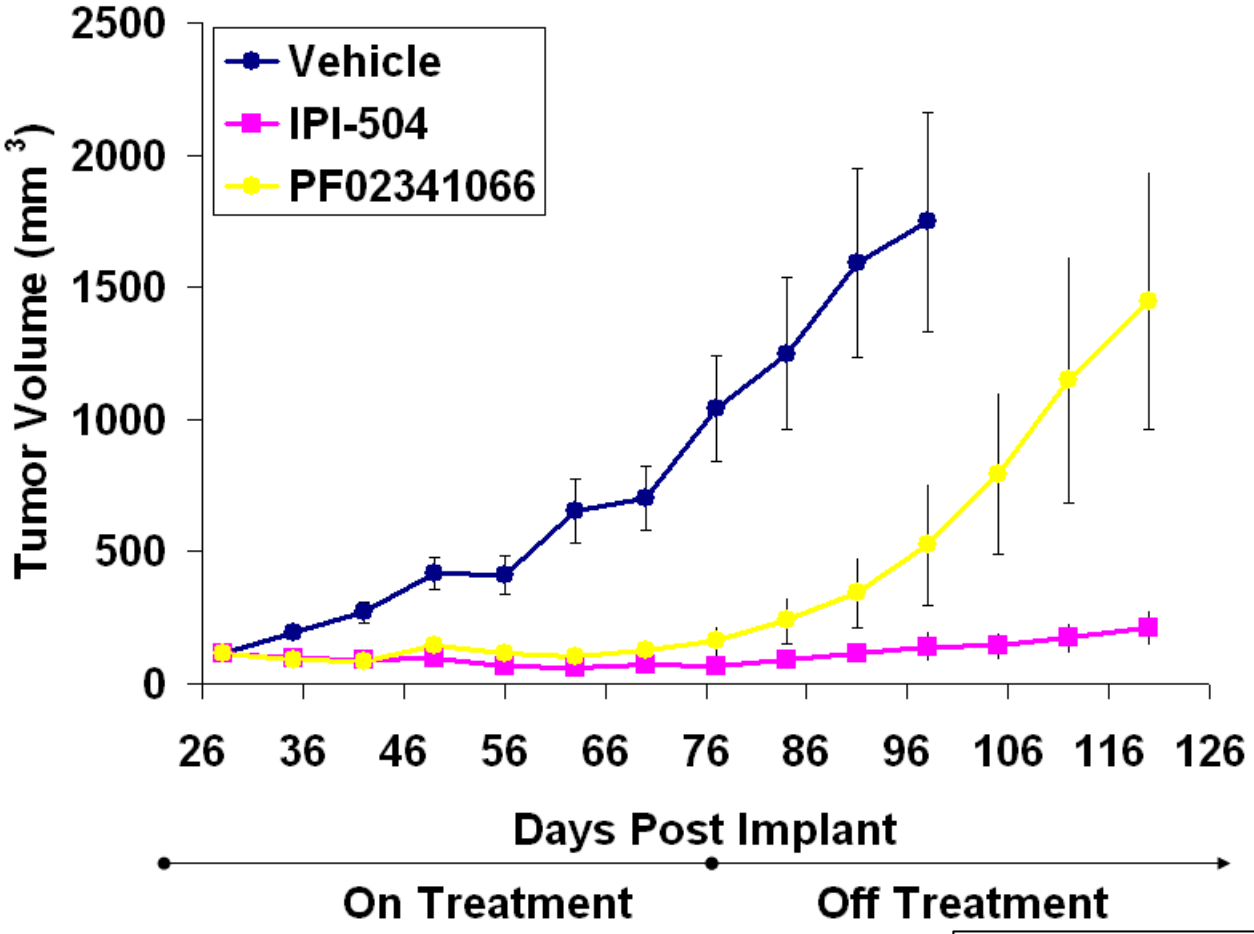
1 µM IPI-504

EML4-ALK Expression Sensitizes HEK293 Cells to IPI-504



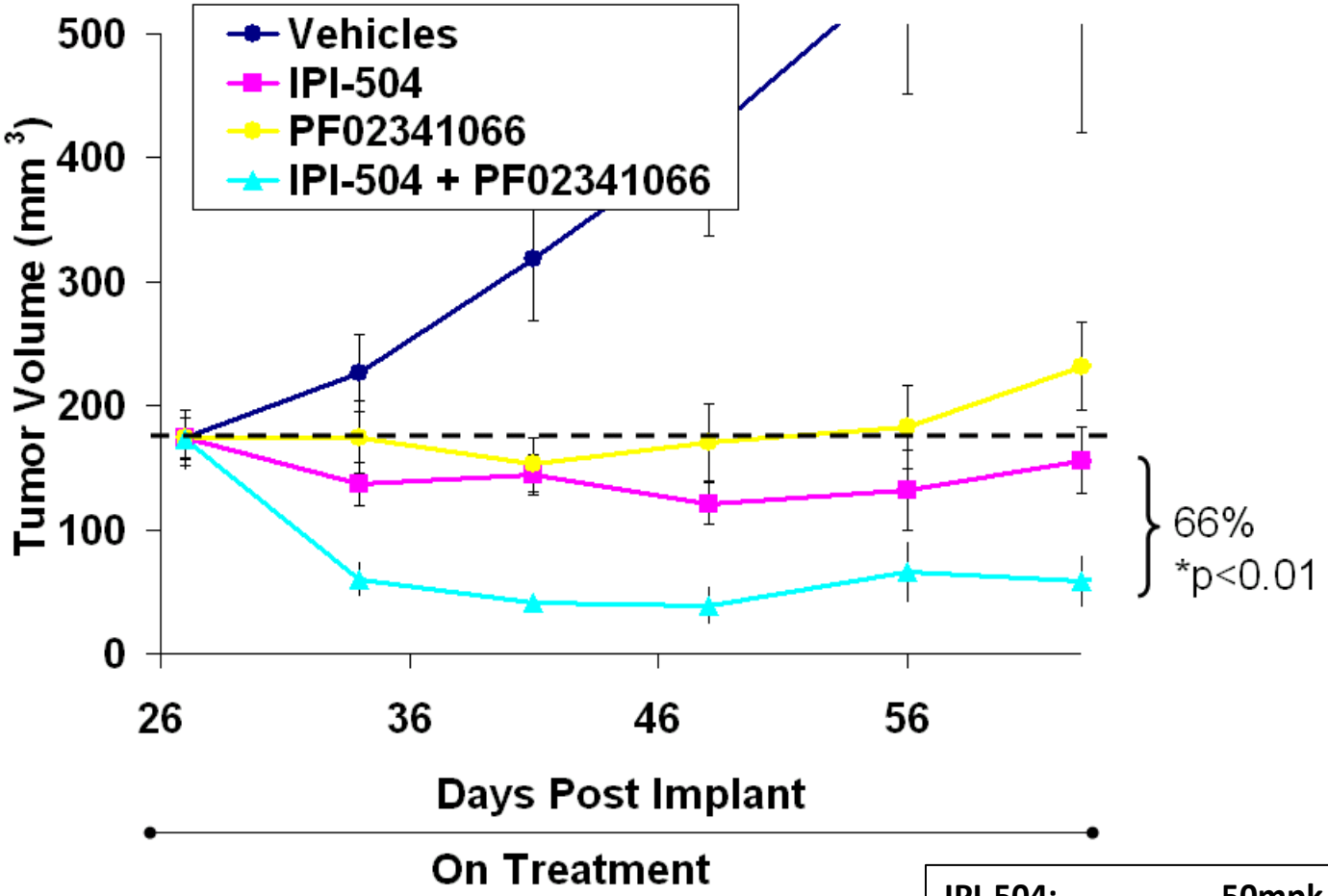


IPI-504 Treatment Results in Tumor Regressions in the H3122 Xenograft Model



IPI-504:	75mg/kg, IP, BIW
PF-02341066:	37.5mg/kg, PO, QDX5

IPI-504 Combination With PF-1066 in the H3122 Xenograft Model



IPI-504:	50mpk, IP, BIW
PF-02341066:	37.5mpk, PO, QDX5

H3122 NSCLC Cells Selected for Resistance to ALK Kinase Inhibitor Retain Sensitivity to IPI-504

	Wt H3122 (GI_{50}, nM)	Res. H3122 (GI_{50}, nM)	Fold change
IPI-504	22	76	3.4
PF-02341066	166	2000	12.0
TAE-684	50	3141	63.0

Conclusions

- EML4-ALK is the most sensitive Hsp90 client protein we have studied to date
- Expression of EML4-ALK can sensitize cells to IPI-504 treatment
- Combinations of IPI-504 and ALK kinase inhibitors lead to pronounced tumor regressions in xenograft models of human NSCLC
- Cells selected for resistance to ALK kinase inhibitors retain sensitivity to IPI-504
- In patients, rearrangements in the ALK locus are associated with responses to IPI-504 as a single agent
- Validation of this finding is ongoing in a prospective trial of IPI-504 in patients with NSCLC and an ALK rearrangement

Acknowledgements

- The patients, families and caregivers who participate in our clinical trials
- The clinical investigators who have worked with IPI-504
- The team at Infinity Pharmaceuticals and our collaborators