Association between Anaplastic Lymphoma Kinase rearrangements (rALK) and the clinical activity of IPI-504 (retaspimycin hydrochloride), a novel Hsp90 inhibitor, in patients with non-small cell lung cancer (NSCLC)

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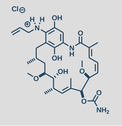
Background

- Hsp90 is a protein chaperone that maintains proper folding, function, and stability of key oncoproteins.
- IPI-504 is a novel, potent, water-soluble Hsp90 inhibitor.
- The biologic and anti-neoplastic effects of IPI-504 have been demonstrated in multiple pre-clinical models and in phase I studies in several cancers.[1,2]
- Models suggest mutant EGFR is a stronger Hsp90 client than wild-type EGFR; hence, we designed a phase 2 trial to examine IPI-504 salvage therapy after EGFR TKIs in NSCLC.
- Tumor tissue for molecular analysis was required for all patients; full molecular results are presented here.

IPI-504



1. Ge GD, et al. *J Med Chem*. 2006;49:4606-4615. 2. Demetri GD, et al. *J Clin Oncol 2007 ASCO Annual Meeting Proc. 2007;25:10024.*

Study Design

Mutant EGFR Cohort

Enroll 10 patients → If >1 CR, PR, or SD for at least 3 months → Expand to a total of 29 patients

Wild Type EGFR Cohort

Enroll 10 patients → If >1 CR, PR, or SD for at least 3 months → Expand to a total of 29 patients

Key Eligibility Criteria:

- Stage IIIB (effusion) or IV NSCLC
- Failed prior EGFR TKI therapy
- No limit on # of prior therapies
- RECIST-measurable disease
- Tissue available for EGFR mutation analysis (EGFR status not required for study entry)
- No untreated brain metastasis
- Adequate end-organ function

Treatment Schema

	Sun	Mon	Tue	Wed	Thu	Fri	Sat
Week 1		✖			✖		
Week 2		✖			✖		
Week 3	← No treatment →						

✖ = IPI-504 dose, IV

- The starting dose was 400 mg/m² for 75 patients.
- 17 months into study, dose was decreased to 225 mg/m² for 19 patients still on therapy, due to toxicity seen in a separate trial of IPI-504.
- One patient started after this change at an initial dose of 225 mg/m².

Molecular Analyses

- Tumor tissue from all patients was assessed for EGFR mutations via direct sequencing of exons 18-21, using standard methods.
- A subset of patients also underwent EGFR, KRAS, and BRAF genotyping analysis with the allele-specific ARMS assay.
- Post-hoc analyses of other molecular markers of interest were performed for all patients with sufficient tissue available, and consisted of:
  - SNaPshot assay adapted to detect key oncogenic mutations in EGFR, KRAS, PIK3CA, BRAF, PTEN, AKT, TP53, NRAS, Beta-catenin, NOTCH, and FLT3
  - Oncomap analysis covering 1155 mutations in 114 cancer genes
  - Fluorescence in-situ hybridization (FISH) break-apart assay for detection of ALK gene rearrangements

All data presented as n (%) unless otherwise specified

Demographics and Baseline Characteristics

		Total*	EGFR Status (n=68)		KRAS Status (n=38)		ALK Status (n=15)	
			Wild Type	Mutant	Wild Type	Mutant	Wild Type	Rearranged
Patients		76	40	28	26	12	12	3
Age (y)	Median	64.0	63.0	66.0	61.0	65.0	65.5	48.0
	Range	31-82	31-79	44-82	31-81	52-76	48-76	31-58
Sex	Female	48 (63)	22 (55)	20 (71)	17 (65)	7 (58)	9 (75)	1 (33)
	Male	28 (37)	18 (45)	8 (29)	9 (35)	5 (42)	3 (25)	2 (67)
Race	Asian	11 (14)	6 (15)	5 (18)	4 (15)	0	2 (17)	1 (33)
	Black	4 (5)	2 (5)	2 (7)	2 (8)	0	0	0
	White	61 (80)	32 (80)	21 (75)	20 (77)	12 (100)	10 (83)	2 (67)
Smoking Status	Never	34 (45)	13 (33)	17 (61)	13 (50)	0	3 (25)	3 (100)
	Former	42 (55)	27 (68)	11 (39)	13 (50)	12 (100)	9 (75)	0
Months since Dx	Median	27.5	24.6	37.2	25.7	20.6	28.5	29.7
	Range	8-120	8-120	11-108	10-120	11-71	11-71	10-120
Histology	AdenoCA	59 (78)	31 (78)	23 (82)	21 (81)	10 (83)	11 (92)	3 (100)
	BAC	4 (5)	2 (5)	2 (7)	0	1 (8)	0	0
	Squamous	6 (8)	4 (10)	1 (4)	3 (12)	0	1 (8)	0
	Other	7 (9)	3 (8)	2 (7)	2 (8)	1 (8)	0	0

*Patients may be counted in more than one column dependent upon molecular analysis

Chemotherapy Treatment History

		Total*	EGFR Status (n=68)		KRAS Status (n=38)		ALK Status (n=15)	
			Wild Type	Mutant	Wild Type	Mutant	Wild Type	Rearranged
Prior treatment regimens	Median	4.0	4.0	3.0	3.0	3.5	4.0	3.0
	Range	1-11	1-7	1-11	1-6	2-7	2-7	3-5
Best prior response to EGFR TKIs	CR	1 (1)	0	1 (4)	1 (4)	0	0	0
	PR	18 (24)	2 (5)	14 (50)	3 (12)	1 (8)	1 (8)	0
Total months on EGFR TKIs	Median	1.8	1.5	10.5	1.7	1.2	1.9	0.0
	Range	0-61	0-25	0-61	0-61	0-16	0-16	0-1

Most Frequent Adverse Events

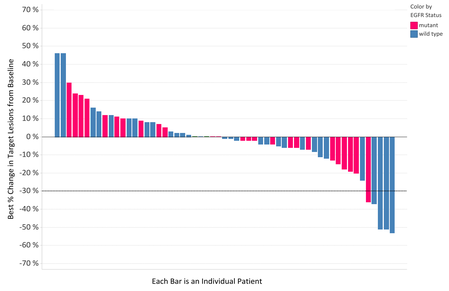
	Any Event	Grade 1 or 2 Event	≥Grade 3 Event
Fatigue	44 (57.9)	41 (53.9)	6 (7.9)
Nausea	43 (56.6)	41 (53.9)	6 (7.9)
Diarrhea	40 (52.6)	37 (48.7)	8 (10.5)
Vomiting	28 (36.8)	25 (32.9)	6 (7.9)
Cough	24 (31.6)	24 (31.6)	2 (2.6)
Urine color abnormal	22 (28.9)	22 (28.9)	0 (0.0)
Anorexia	19 (25.0)	18 (23.7)	4 (5.3)
Arthralgia	19 (25.0)	17 (22.4)	2 (2.6)
Myalgia	19 (25.0)	18 (23.7)	1 (1.3)
Headache	19 (25.0)	19 (25.0)	0 (0.0)
Abdominal pain	18 (23.7)	18 (23.7)	1 (1.3)
Constipation	18 (23.7)	18 (23.7)	2 (2.6)
Dyspnea	18 (23.7)	15 (19.7)	6 (7.9)
Back pain	16 (21.1)	16 (21.1)	0 (0.0)
Infusion site pain	15 (19.7)	15 (19.7)	0 (0.0)
Dehydration	14 (18.4)	11 (14.5)	3 (3.9)
Musculoskeletal chest pain	13 (17.1)	11 (14.5)	3 (3.9)
Pyrexia	12 (15.8)	12 (15.8)	0 (0.0)
Vision blurred	12 (15.8)	12 (15.8)	0 (0.0)
Insomnia	12 (15.8)	12 (15.8)	0 (0.0)
Dizziness	12 (15.8)	12 (15.8)	0 (0.0)
Liver Function Tests (Maximum post-baseline grade based on laboratory results)			
Alkaline phosphatase	47 (61.8)	43 (56.6)	4 (5.3)
AST	37 (48.7)	30 (39.5)	7 (9.2)
ALT	31 (40.8)	26 (34.2)	5 (6.6)
Total bilirubin	3 (3.9)	3 (3.9)	0 (0.0)

- Three deaths have been reported on study. All were assessed as possibly related to IPI-504.

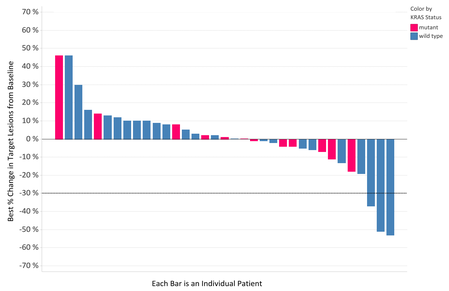
Activity Summary

	Total	EGFR Status (n=68)		KRAS Status (n=38)		ALK Status (n=15)	
		Wild Type	Mutant	Wild Type	Mutant	Wild Type	Rearranged
Patients	76	40 (53)	28 (37)	26 (34)	12 (16)	12 (16)	3 (4)
Objective Responses	5 (7)	4 (10)	1 (4)	3 (12)	0 (0)	1 (8)	2 (67)
RECIST SD or better for ≥ 3 mo	18 (24)	10 (25)	6 (21)	4 (15)	5 (42)	3 (25)	3 (100)
Med. PFS in months (95% CI)	2.9 (2.4-4.2)	2.9 (1.2-5.3)	2.8 (2.4-3.9)	2.9 (1.2-10.2)	3.9 (1.1-4.2)	2.4 (1.1-5.3)	Unable to determine

Response by EGFR Mutation Status

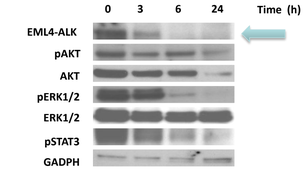


Response by KRAS Mutation Status



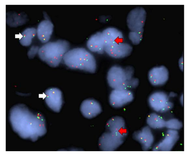
rALK Results

The EML4-ALK Fusion Protein is a Sensitive Client of Hsp90



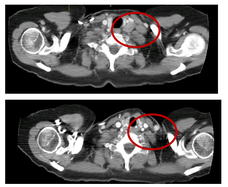
IPI-504 treatment induces degradation of EML4-ALK and inhibits downstream signaling pathways in vitro. H3122 NSCLC cells (EML4-ALK fusion positive) were incubated with 1 μM IPI-504 for different times and the level of the fusion protein and as well as several downstream signaling proteins were determined by western blotting.

Example of FISH Break-Apart Assay Result for a Patient Positive for ALK Rearrangement

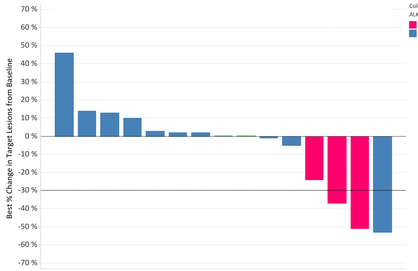


White arrows: wild type allele as one yellow signal
Red arrows: ALK rearrangement (separated: one red & green probe signal for the rearranged allele)

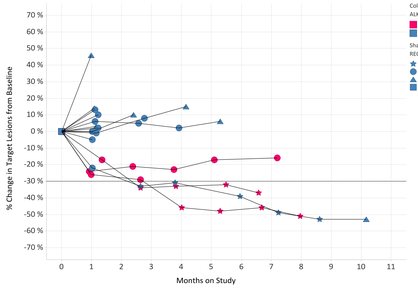
Partial Response in a patient with rALK



Response by ALK FISH Status



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



Conclusions

- **This is the first trial of an Hsp90 inhibitor in molecularly-defined cohorts of patients with advanced NSCLC. IPI-504 is generally well-tolerated and active in NSCLC, with response rates of:**
  - **7% in the overall study population**
  - **10% in EGFR wild type patients**
  - **4% in EGFR mutants with acquired resistance to TKIs**
  - **12% in KRAS wild type patients**
  - **67% in ALK rearranged patients (2 of 3 patients with PR and the third with 24% disease reduction durable 7.2 months)**
- **These are the first clinical data to suggest that ALK rearranged NSCLC patients may preferentially respond to Hsp90 inhibition.**
- **Validation is ongoing in a trial of IPI-504 at Massachusetts General Hospital in patients with NSCLC and an ALK rearrangement.**