IPI-504: a Novel HSP-90 Inhibitor

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Heat shock protein 90 (Hsp90) is an emerging cancer target

Function of Hsp90

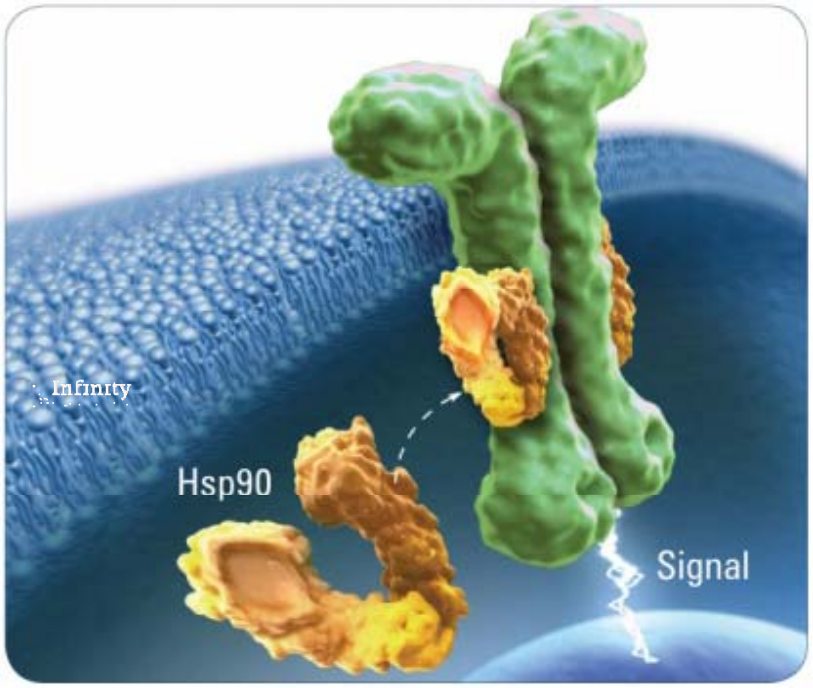
- "Chaperone" protein necessary for stability and function of certain 'client' proteins

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



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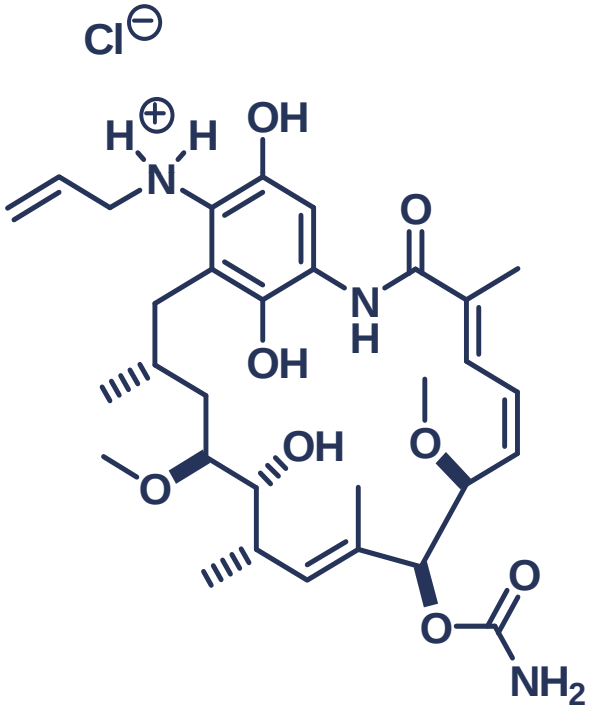
IPI-504 (Retaspimycin hydrochloride); A Selective Hsp90 Inhibitor

- Potent and selective inhibitor of HSP90
- Water soluble (administered in NS as 30 min infusion)
- Biologic and anti-neoplastic effects have been demonstrated in multiple human xenograft and murine orthotopic models
- The free base of IPI-504 inter-converts with 17-AAG and exists in a pH and enzyme-mediated dynamic redox equilibrium in humans



IPI-504 (Retaspimycin hydrochloride)

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

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Rationale for IPI-504 in NSCLC

- NSCLC with activating mutations in EGFR
  - Mutated EGFR is a sensitive client protein of Hsp90
  - Both T790M and Met amplification are susceptible to Hsp90 inhibition (Park et al, Abstract 2450 AACR Annual Meeting 2008)
- NSCLC containing wild type EGFR
  - Many NSCLC cell lines are sensitive to IPI-504 in vitro
  - Multiple proteins important in the progression of NSCLC are client proteins of Hsp90
    - HER2
    - p-AKT
    - EML4-ALK
    - c-RAF

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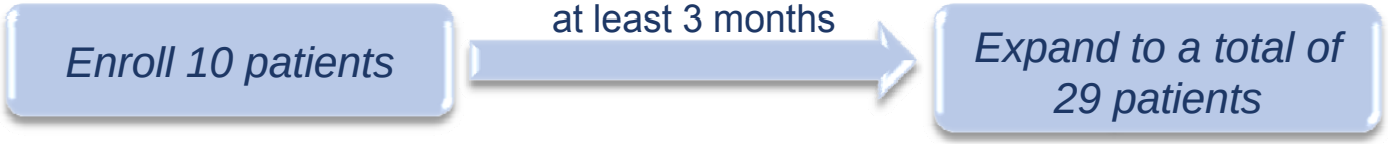
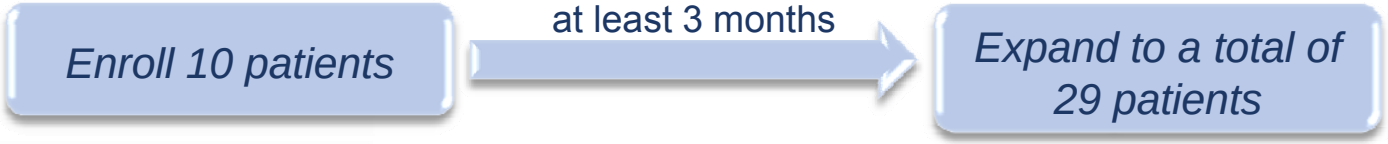
Methods: Study Design

- Key Eligibility:
  - Advanced NSCLC, no limit on number of prior therapies
  - Failed prior EGFR TKI therapy
  - Tissue available for EGFR mutation analysis
  - Adequate end-organ function

Mutant EGFR Cohort



Wild-Type EGFR Cohort



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Demographics and Baseline Characteristics

		EGFR Mutant	EGFR Wild-Type	EGFR Status Pending/Unk	Total
N		19	28	10	57
Sex	Male	73.7%	60.7%	60%	64.9%
	Female	26.3%	39.3%	40%	35.1%
Median age (years)		66	60	60	64
Smoking history (%)*	Non-smoker	68.4%	50%	60%	57.9%
	Previous smoker	31.6%	50%	40%	42.1%
	Current	0%	0%	0%	0%
Median months since dx		23.6	24.5	25.7	24.5
Histology (%)	Adeno	84.2%	82.1%	70%	80.7%
	BAC	10.5%	7.1%	0%	7%
	Squamous	0%	10.7%	10%	7%
	Other	5.3%	0%	20%	5.3%
Stage (%)	IIIB	10.6%	0%	0%	3.6%
	IV	89.5%	100%	100%	96.5%

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EGFR TKI Treatment History

		EGFR Mutant	EGFR Wild-Type	EGFR Pending/ Unknown	Total
N		19	28	10	57
Prior treatment	TKI	100%	100%	100%	100%
Best response to TKI	CR	5.3%	0%	0%	1.8%
	PR	57.9%	7.1%	20%	26.3%
Median months on TKI-containing regimen		20.9	3.3	1.9	9.5
# of prior TKIs	1	73.7%	89.3%	90%	84.2%
	2	15.8%	10.7%	10%	12.3%
	>2	10.6%	0%	0%	3.6%

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Chemotherapy Treatment History

		EGFR Mutant	EGFR Wild-Type	EGFR Status Pending/ Unknown	Total
N		19	28	10	57
Prior treatment	Chemotherapy	78.9%	96.4%	100%	91.2%
Best response to chemotherapy treatment	CR	5.3%	3.6%	0%	3.5%
	PR	31.6%	35.7%	60%	38.6%
Median months on chemotherapy regimen		2.6	13.9	7.4	6.8
# of prior chemotherapy regimens	0	21%	3.6%	0%	8.8%
	1	31.6%	21.4%	0%	21.1%
	2	31.6%	25%	30%	28.1%
	>2	15.8%	50%	70%	42.2%
Median # of chemotherapy regimens		1	2.5	4	2

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Epidermal Growth Factor Receptor Mutations

Mutation Type	N (%)
Exon 19 deletion only	11 (58%)
L858R in exon 21 only	4 (21%)
T790M plus exon 19 deletion	2 (11%)
Other[1]	2 (11%)

[1]*One patient with an insertion in exon 20; one patient with G719S in exon 18 and L861Q in exon 21*

- Samples for mutation analysis were primarily from archival tissue from initial diagnosis of NSCLC and analyzed using Sanger sequencing

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Adverse Events Experienced by >15% of Patients, by Grade, Regardless of Relationship to IPI-504 (n=57)

Event	Grade 1-2	Grade 3	Grade 4	Total
Any	30 (52.6%)	16 (28.1%)	8 (14%)	54 (94.7%)
Nausea	30 (52.6%)	2 (3.5%)	0	32 (56.1%)
Fatigue	28 (49.1%)	2 (3.5%)	0	30 (52.6%)
Diarrhea	21 (36.8%)	7 (12.3%)	0	28 (49.1%)
Vomiting	20 (35.1%)	3 (5.3%)	0	23 (40.4%)
Cough	16 (28.1%)	1 (1.8%)	0	17 (29.8%)
Myalgia	14 (24.6%)	1 (1.8%)	0	15 (26.3%)
Abdominal pain	15 (26.3%)	0	0	15 (26.3%)
Headache	14 (24.6%)	0	0	14 (24.6%)
Urine color abnormal	14 (24.6%)	0	0	14 (24.6%)
Constipation	13 (22.8%)	1 (1.8%)	0	14 (24.6%)
Anorexia	12 (21.1%)	1 (1.8%)	0	13 (22.8%)
Arthralgia	12 (21.1%)	1 (1.8%)	0	13 (22.8%)
Dyspnea	10 (17.5%)	1 (1.8%)	1 (1.8%)	12 (21.1%)
Back pain	12 (21.1%)	0	0	12 (21.1%)
Infusion site pain	11 (19.3%)	0	0	11 (19.3%)

- Two deaths have been reported on study, both secondary to sepsis and assessed by the investigator as unrelated to IPI-504

Lab abnormalities: increase to Grade 3-4 in ≥ 2 patients regardless of relationship (n=57)

Laboratory test	Grade 3	Grade 4
PTT	6 (10.5%)[1]	0
Hyperglycemia	6 (10.5%)[2]	0
Aspartate aminotransferase	2 (3.5%)	2 (3.5%)
Alanine aminotransferase	2 (3.5%)	1 (1.8%)
Alkaline phosphatase	2 (3.5%)	0
INR	2 (3.6%)[3]	0
Lipase	2 (3.6%)	0
Hypophosphatemia	2 (3.6%)	0
Hypokalemia	2 (3.6%)	0

[1]All 6 resolved with the next laboratory draw and were felt to be artifactual or due to a heparinized port
[2]Non-fasting hyperglycemias. 3 are from patients with known diabetes
[3]Both in patients on warfarin

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Responses (RECIST, Investigator Assessed)

	EGFR Mutant	EGFR Wild-Type	EGFR Status Pend/Unk	Overall
N	19	28	10	57
ORR[1]	0	4 (14.2%)	0	4 (7%)
Confirmed ORR[2]	0	2 (7.1%)	0	2 (3.5%)
Stable disease lasting ≥ 3 months	6 (31.6%)[3]	6 (21.4%)[4]	1 (10%)[5]	13 (22.8%)[6]
Clinical benefit	6 (31.6%)	10 (35.7%)	1 (10%)	17 (29.8%)

[1]All responses were partial responses
[2]Confirmed on an imaging assessment at least 4 weeks after initial response.
[3]Too early to tell for 3 patients
[4]Too early to tell for 3 patients
[5]Too early to tell for 1 patient
[6]Too early to tell for 7 patients

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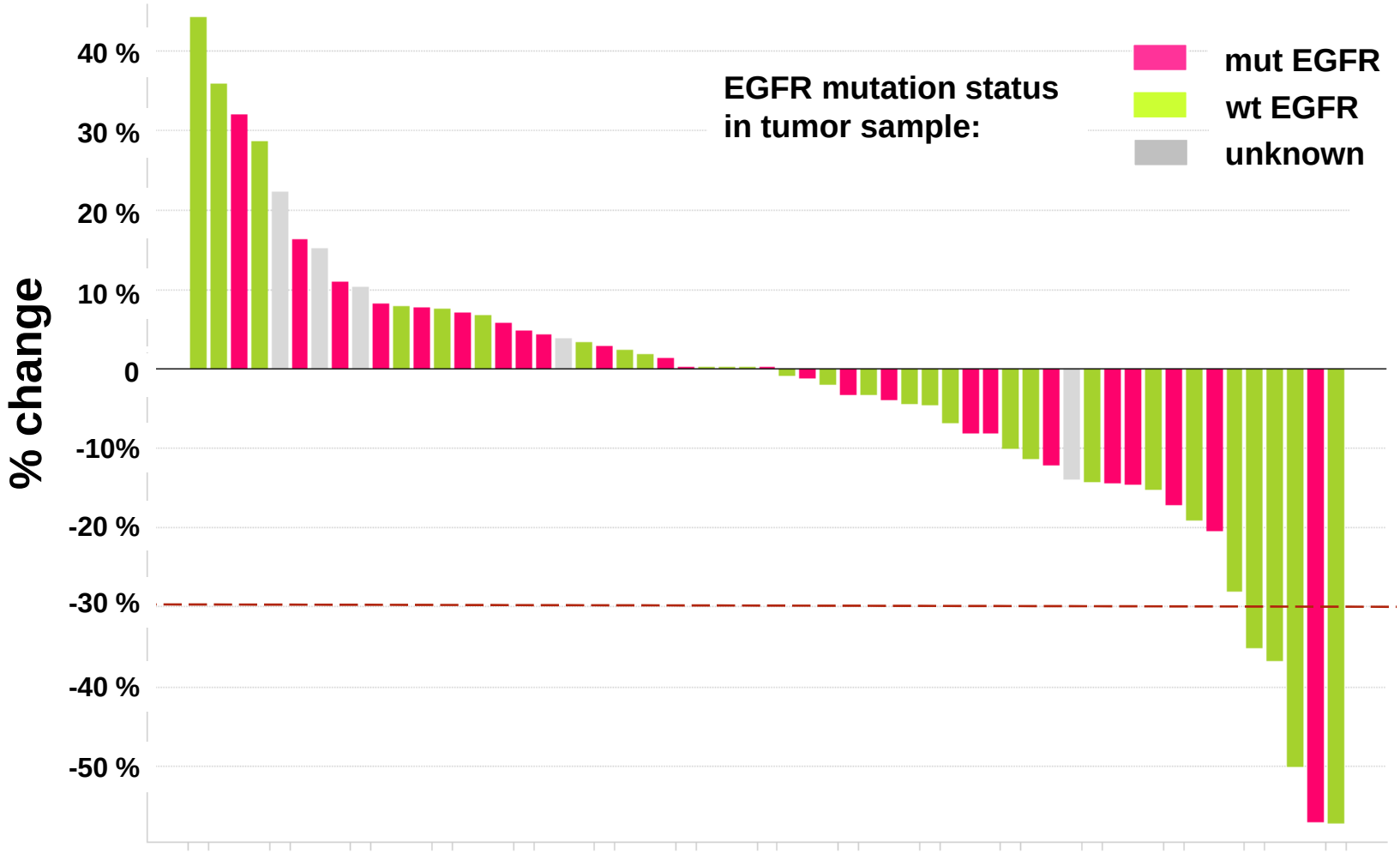
Best response by EGFR status



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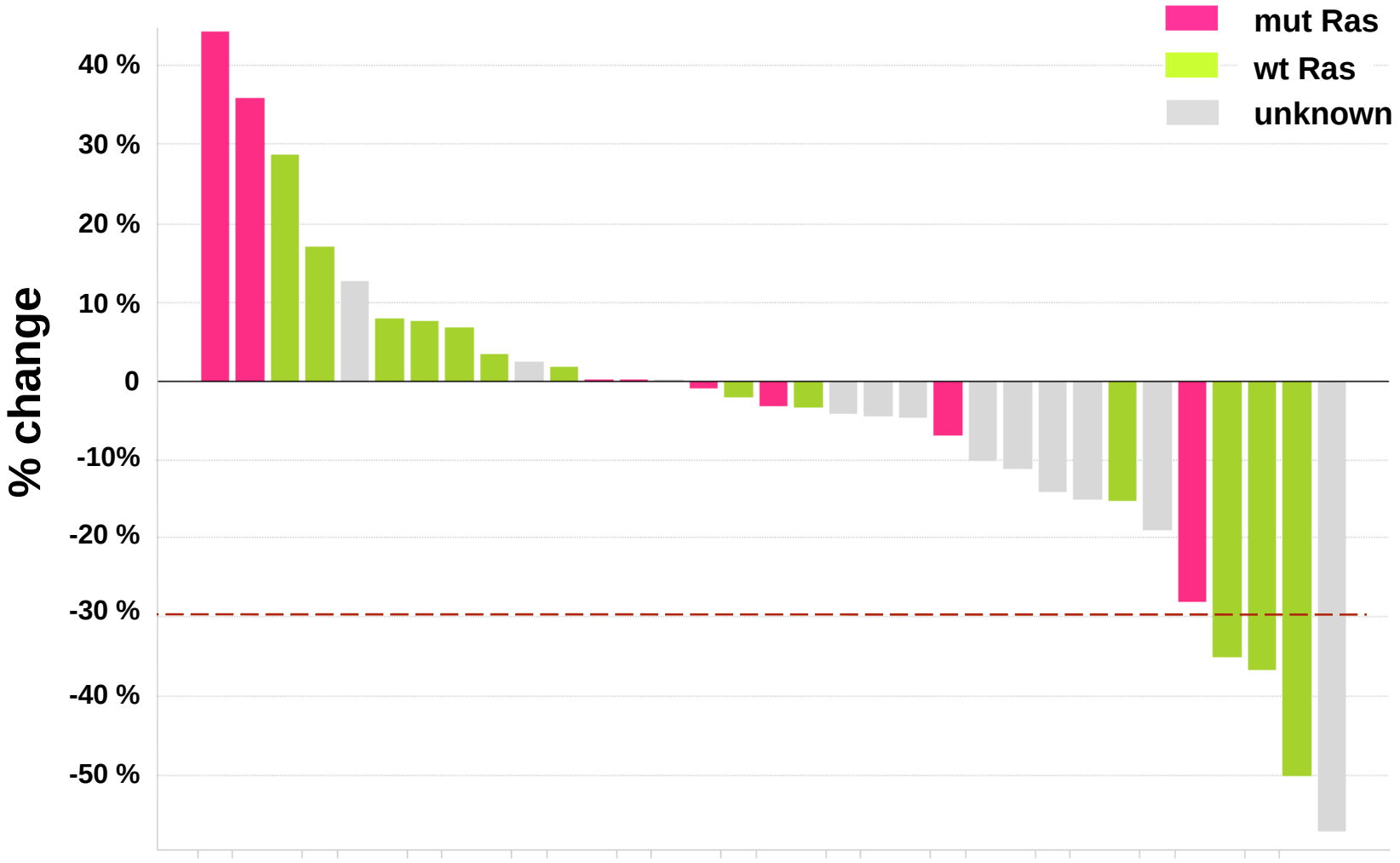
Best response by KRAS mutation status among wild type EGFR pts



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Preliminary Conclusions

- In this heavily pretreated NSCLC population (average time since dx >2 y), there is evidence of biologic activity of IPI-504, with an ORR of 14.2% in patients with wild type EGFR tumors and 7.1% in the total population
- IPI-504 has been generally well-tolerated in this study
- The trial is ongoing, work is continuing to identify genetic predictors of benefit in this patient population which is expected to be updated at ASCO 2010

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