

A Cercek, J Shia, M Capanu, P Raasch, D Reidy, Z Stadler, Y Janjigian, M Gollub, E O'Reilly, E Hollywood, D Ilson, N Kemeny, E Vakiani, D Solit, L Saltz  
 Memorial Sloan-Kettering Cancer Center, New York, NY 10065

## Abstract

**Purpose:** To evaluate the safety and efficacy of ganetespib, a heat shock protein 90 (Hsp90) inhibitor, as monotherapy in patients with refractory metastatic colorectal cancer.

**Patients and Methods:** A phase II study utilizing a two-stage design was performed in which patients received ganetespib 200 mg/m<sup>2</sup> intravenously (IV) one time per week for three weeks followed by a one week break. Patients underwent pre and 48 hour post treatment tumor biopsies. Immunohistochemistry (IHC) was performed for pErk, CyclinD1, pAkt, HIF-1a, VEGFr2, p70S6 and Hsp70. Archived and pre dose biopsy tissue was utilized for KRAS, BRAF and PIK3CA genotyping using a Sequenom platform.

**Results:** Seventeen patients were treated (median age 58, range 44-79). There were no responders. Two patients were removed from study due to events unrelated to treatment, thus fifteen patients were analyzed for efficacy. Two patients had stable disease lasting 31 and 23 weeks. This constituted insufficient activity to allow for accrual to the second stage of the two-stage phase II design. The most frequent grade 3 adverse events were diarrhea (12%), fatigue (24%), and elevated AST (12%) and Alk phos (29%). Three (20%) patients required dose reductions, 1 grade 3 AST, 1 grade 3 ALT and 1 grade 3 fatigue. Of the 15 evaluable patients 8 (53%) had KRAS mutated tumors. All were BRAF and PIK3CA wild type. KRAS status and IHC analyses did not correlate with progression free survival.

**Conclusion:** This was the first study of an Hsp90 inhibitor in colorectal cancer. Ganetespib treatment did not produce tumor responses when administered as a single agent in refractory metastatic colorectal cancer with this dosing regimen. Overall the drug was well tolerated and the toxicity profile was relatively mild.

## Background

Hsp90 belongs to a class of molecular chaperone proteins that help modulate cellular responses to environmental stress by supporting stabilization, folding and function of many "client" proteins. Cancer cells upregulate Hsp90 in response to stress,<sup>1-2</sup> allowing critical Hsp90-bound proteins to escape proteolytic degradation, and thus promote cellular proliferation.<sup>3,4</sup> Additionally, Hsp90 expression has been shown to enable the tumor cells to escape apoptosis.<sup>5</sup>

A number of Hsp90 client proteins are implicated in pathways responsible for colorectal cancer cell growth and survival.

Ganetespib is a novel small molecule Hsp90 inhibitor. Preclinical studies have demonstrated activity in colorectal cancer cell lines.<sup>6</sup> Data indicated that the mechanism of action was via suppression of key proteins in the signal transduction and microenvironment which led to cell death.<sup>7</sup>

After progression on standard chemotherapeutic regimens, there are no good treatment options for patients with mCRC.

We hypothesized that, based on preclinical data the Hsp90 inhibitor, ganetespib would have a clinically meaningful degree of antitumor activity in this patient population.

## Methods

An investigator initiated phase II study funded by *Synta* for patients with refractory metastatic colorectal cancer opened in April 2010 at MSKCC and accrued 17 subjects.

## Methods

### Study Population (key eligibility criteria)

- Pathologically confirmed CRC
- Measurable metastatic disease according to RECIST criteria
- Documentation of prior progression on at least one chemotherapeutic regimen
- ECOG performance status of 0 or 1
- Patients were required to agree to undergo pre-treatment and post-treatment tumor biopsies.

### Treatment and Evaluation

- Patients received 200mg/m<sup>2</sup> of ganetespib IV 3 weeks on 1 week off
- Imaging with CT or MRI every 8 weeks.

- Primary endpoint is overall response rate ORR (defined as partial and complete responses)

- The secondary endpoints were progression free survival (PFS) and overall survival (OS). Tumor biopsies were obtained from all patients pre and 48 hours post the initial dose of ganetespib.

### Correlative Laboratory Analyses of Tumor Tissue Samples

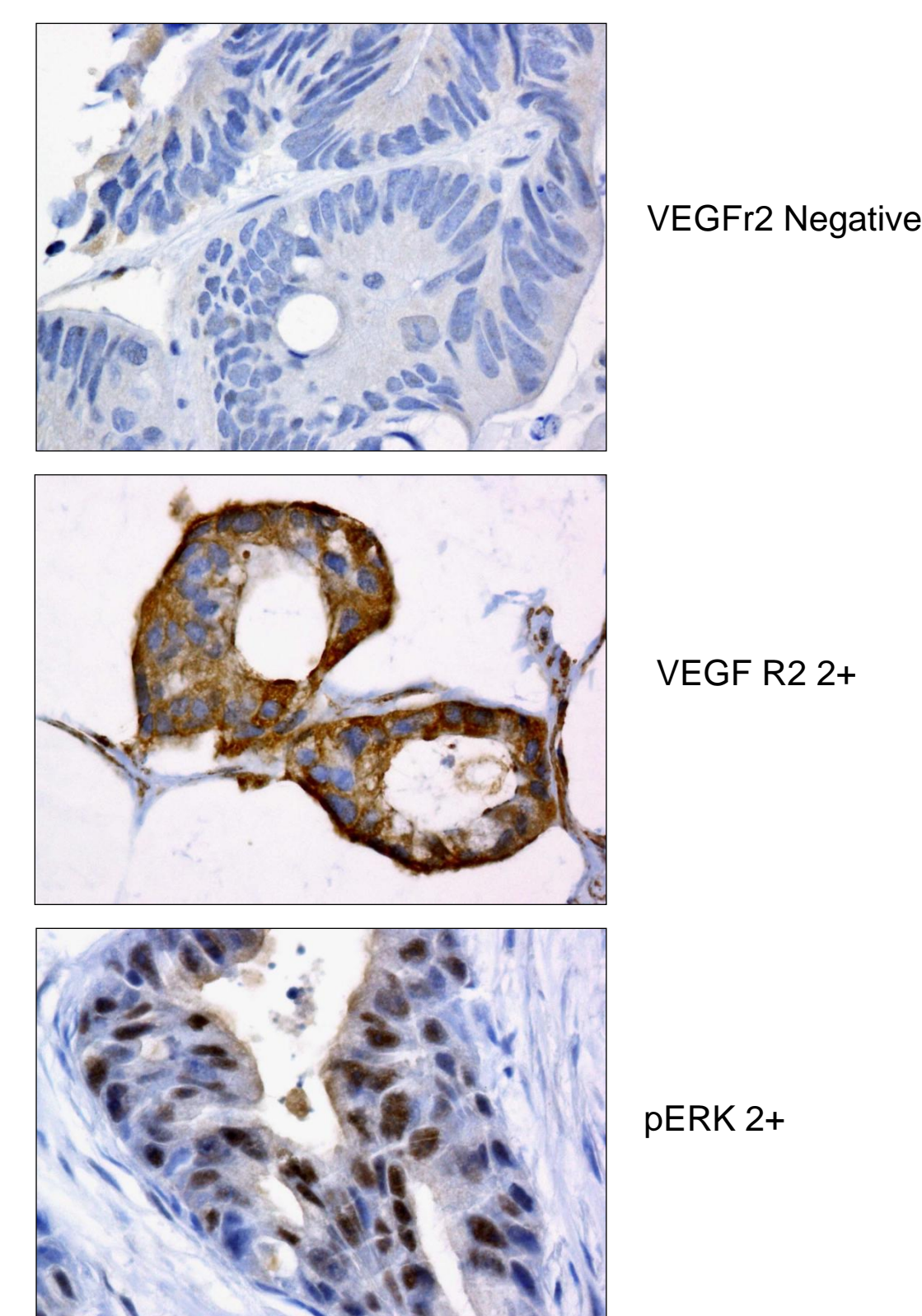
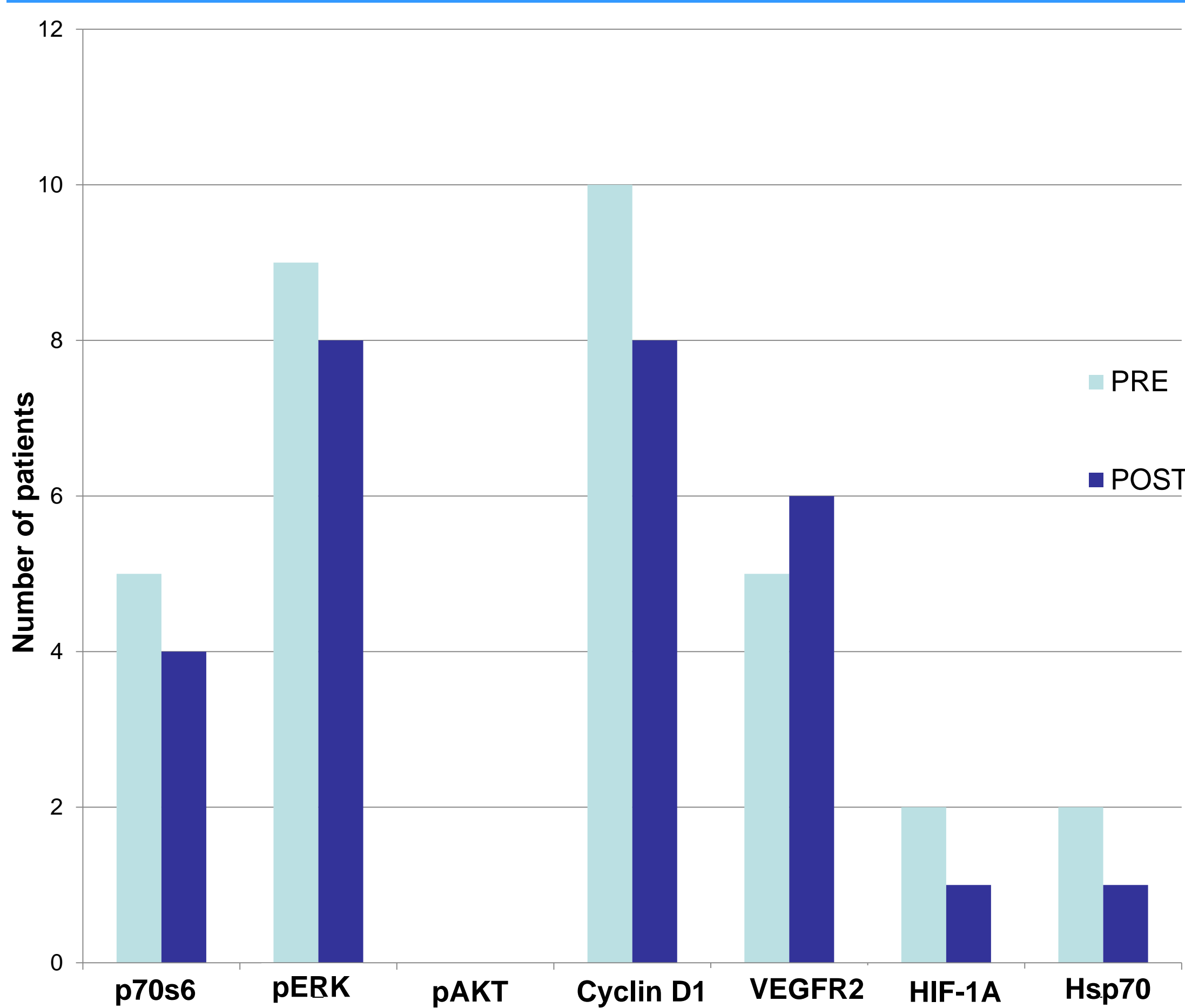
Two biopsies samples from each patient were tested by IHC. IHC was performed for pErk, CyclinD1, pAkt, HIF-1a, VEGFr2, p70S6 and Hsp70. The staining was scored based on intensity (0-3+) and the percentage of tumor cells stained. The tumor samples patients were genotyped for mutations in the MAPK pathway, including KRAS, BRAF, PIK3CA mutations by Sequenom

## Results: Patient characteristics and toxicities

Characteristics	Grade 1/2	Grade 3
<b>Sex</b>		
Male	11	
Female	6	
<b>Age, years</b>		
Median	58	
Range	44-79	
<b>ECOG PS</b>		
0	3	
1	14	
<b>No Prior Chemo</b>		
3	4	
>3	13	
<b>KRAS Mutations</b>		
G12D	3	
G12V	3	
G12S	1	
G12C	1	
<b>Toxicities</b>		
Diarrhea	14 (82%)	2 (12%)
Fatigue	9 (53%)	4 (24%)
Nausea	9(53%)	0
Vomiting	11 (65%)	1 (6%)
ALT (1)	12 (70%)	1 (6%)
AST (1)	9 (53%)	2 (12%)
Alk phos (1)	8 (47%)	5 (29%)
Anorexia	7 (41%)	0

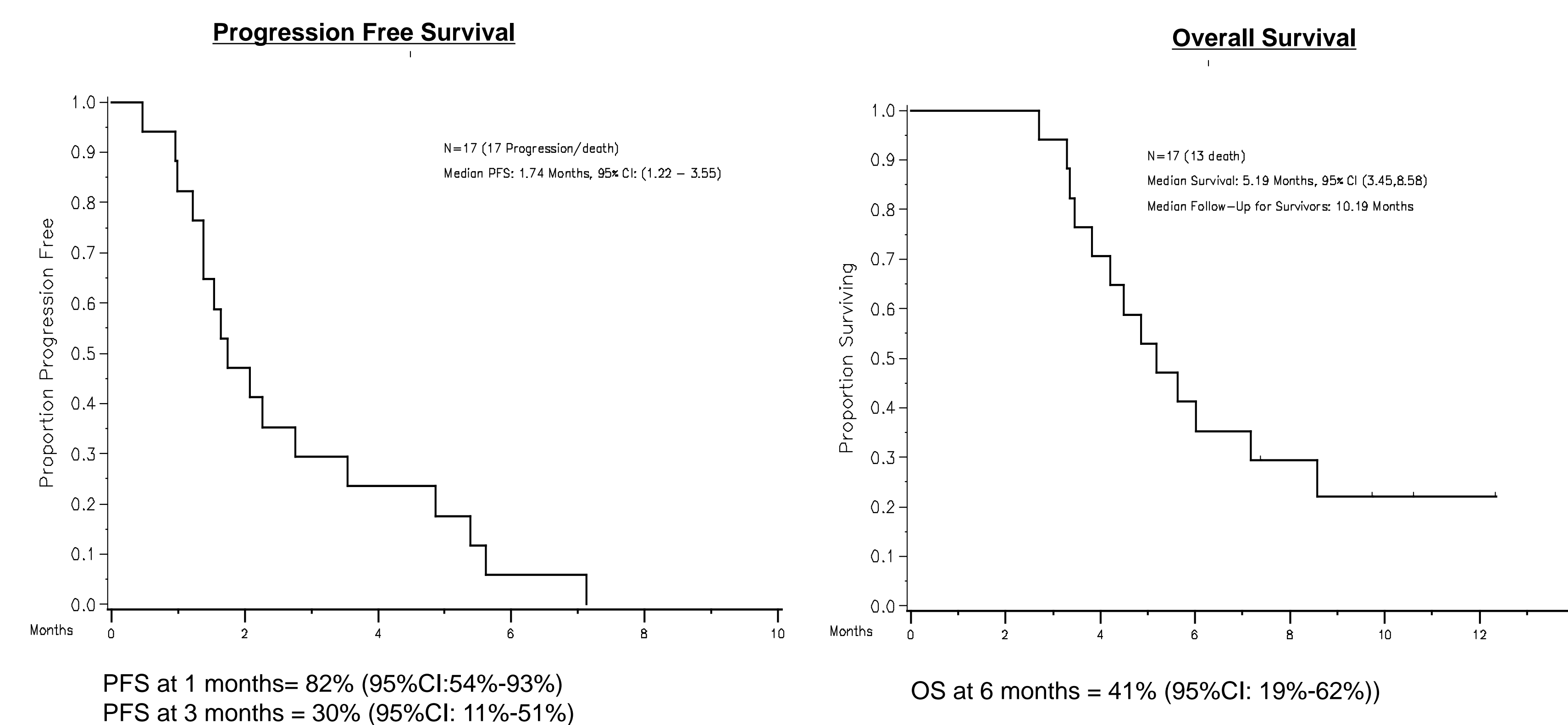
17 patients were evaluated for toxicity. The most common toxicities are listed above, one patient (6%) developed a grade 2 allergic reaction.

## Results: Correlative Analyses



Of the 15 evaluable patients, 13 had adequate tissue sampling for IHC analyses. 2-3+, >5% staining was considered positive.

## Results: Progression Free and Overall Survival



- No objective response was demonstrated with ganetespib in this heavily pretreated patient population

- Of the fifteen evaluable patients, two patients achieved stable disease for >16 weeks (23 and 31)

- Overall the drug was well tolerated with minimal toxicity

- Pre and 24-48 hour post treatment biopsies were obtained from all patients. Of those 13 had sufficient tissue for IHC analysis

- There were no significant changes observed in expression level of p70S6, pErk, pAkt, CyclinD1, HIF-1a, VEGFr2, and Hsp70

- Of the 15 evaluable patients 8 (53%) had KRAS mutated tumors. All were BRAF and PIK3CA wild type.

- The KRAS status did not correlate with progression free survival.

## Conclusions

- This was the first study of an Hsp90 inhibitor in colorectal cancer

- Although no objective responses were seen two patients achieved durable stable disease in this heavily pretreated patient population.

- Overall the drug was well tolerated with minimal toxicity

- IHC and molecular signal transduction pathway analyses did not correlate with clinical activity

- Single agent ganetespib had a relatively low toxicity profile and demonstrated durable stable disease, this warrants further investigation in combination with other cytotoxic or targeted agents.

### References

1. Protti MP, et al., Cancer Lett 85:211-6, 1994
2. Mileo AM, et al., Anticancer Res 10:903-6, 1990
3. Ehrenfried JA, et al., Surg Oncol 4:197-203, 1995
4. Pratt WB Proc Soc Exp Biol Med 217:420-34, 1998
5. Takayama S, et al., Oncogene 22:9041-7, 2003
6. Sang J, et al., AACR Annual Meeting, 2011 April 2-6, Orlando, FL.
7. Ying W, et al Mol Cancer Ther. 2011 Dec 5.