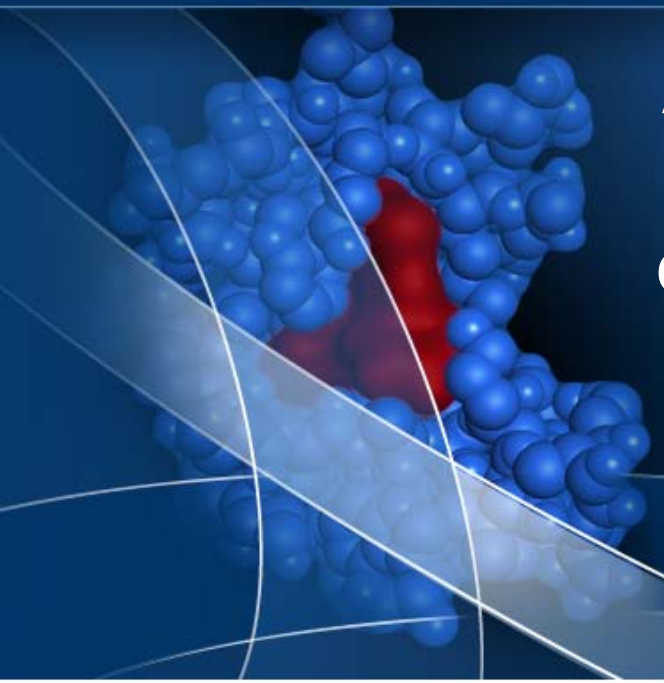


Activity of the proprietary Hsp90 inhibitor IPI-493 in models of colorectal cancer correlates with RAS pathway activation

AACR Annual Meeting, Orlando, FL, April 2nd-6th, 2011

Kip A. West, Nafeeza Hafeez, Emmanuel Normant, John MacDougall, Vito Palombella and Christian Fritz
Infinity Pharmaceuticals

Disclosure

- I am an employee of and stockholder in Infinity Pharmaceuticals, Inc.

Broadly Attacking Oncoproteins through Hsp90 Chaperone Inhibition

Function of Hsp90

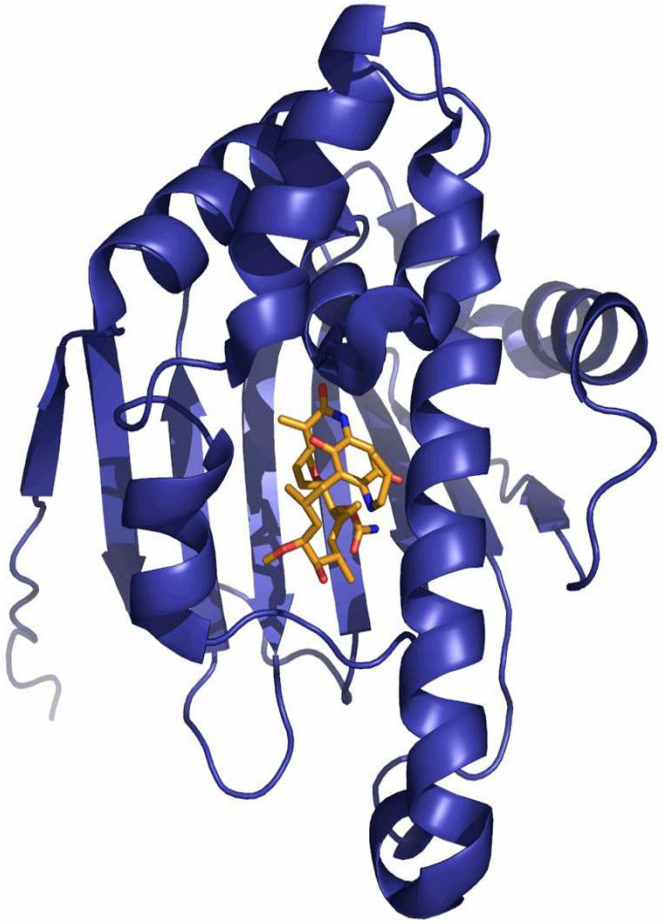
- Hsp90 is a “chaperone” protein necessary for stability and function of certain ‘client’ proteins

Hsp90 Function in Cancer Cells

- Many oncoproteins are dependent on Hsp90 for function

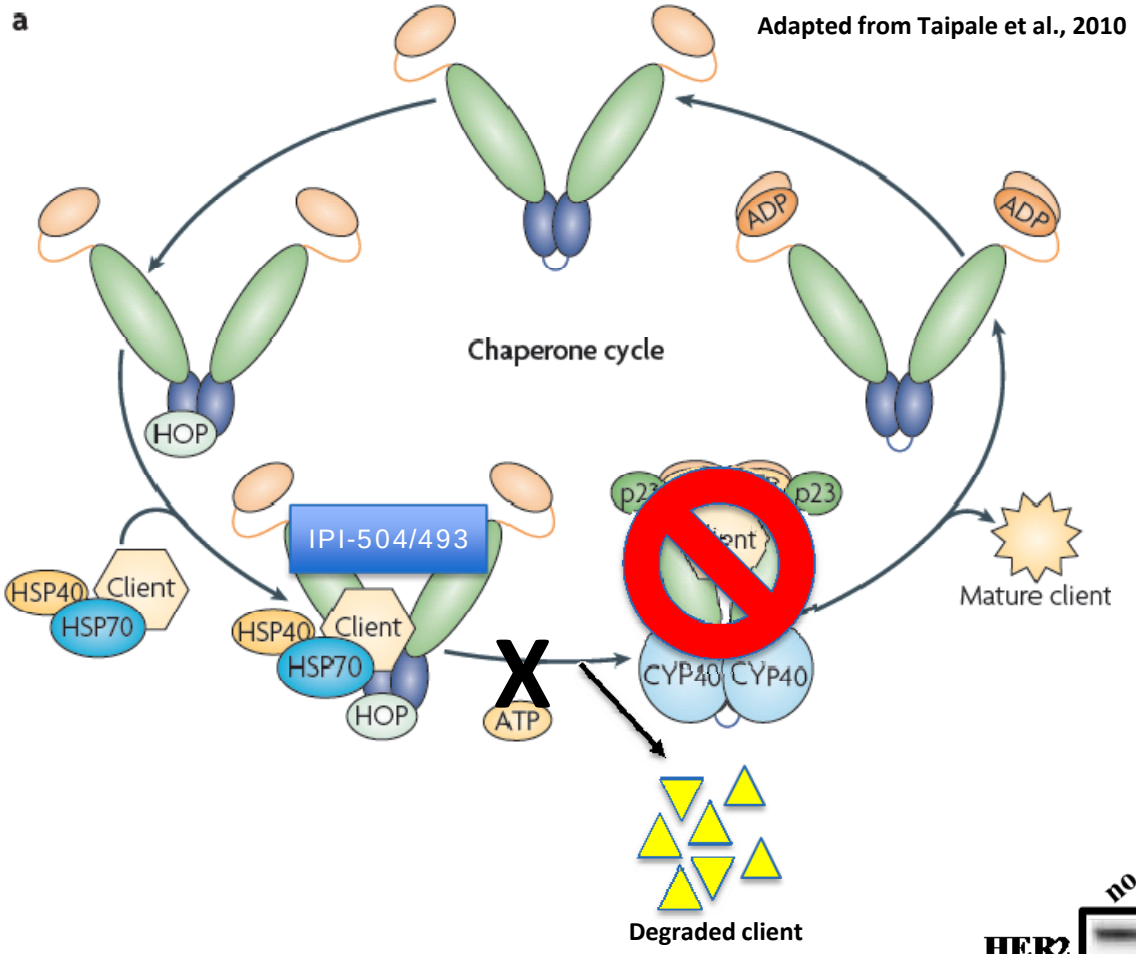
Therapeutic Rationale

- Inhibiting Hsp90 induces degradation of oncoproteins, providing an alternative to inhibiting these proteins directly
- The broad Hsp90 client list also provides a unique opportunity to simultaneously target feedback loops involved in drug resistance



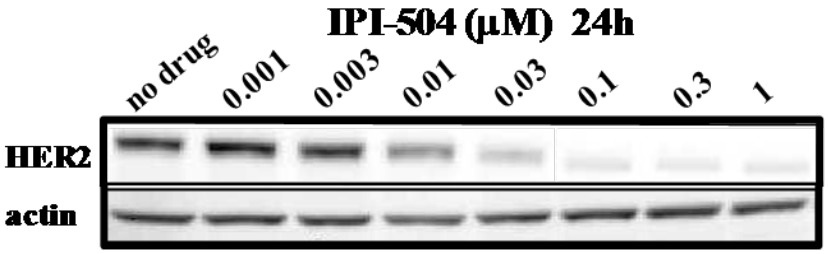
Ge et al., 2006

Inhibition of Hsp90 Activity by IPI-504 and IPI-493 causes "client" protein degradation



Hsp90 Chaperone cycle

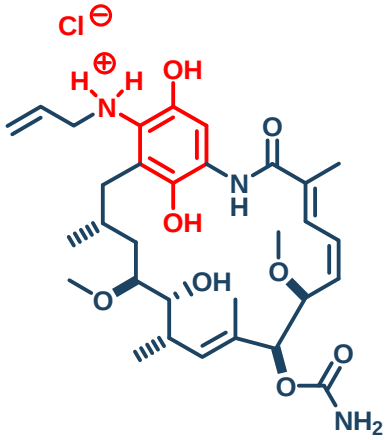
- **Under normal, uninhibited conditions Hsp90 regulates the stabilization and activity of its client proteins**
- **In the presence of inhibitors such as IPI-504/493, Hsp90 function is compromised resulting in the loss of client protein activity and protein degradation**



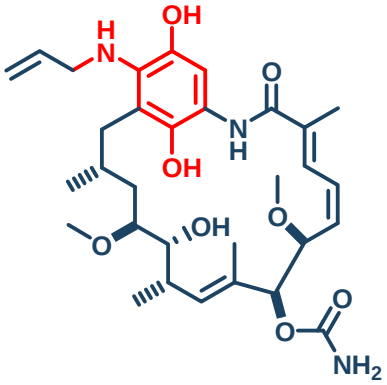
IPI-493 is a novel formulation of the primary active metabolite of IPI-504 and 17-AAG

IPI-504
Retaspimycin hydrochloride

17-allylamino-17-demethoxygeldanamycin hydroquinone hydrochloride salt



physiologic pH

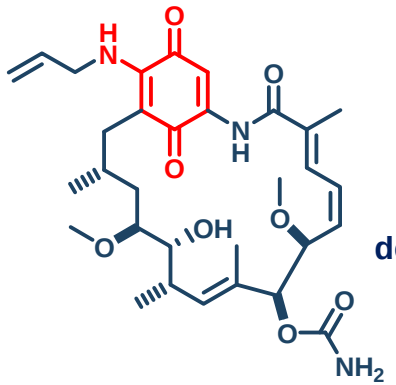


17-AAG HQ

17-allylamino-17-demethoxygeldanamycin hydroquinone

O_2

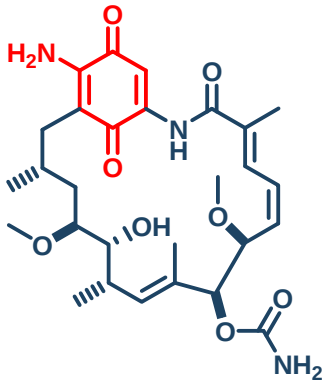
Oxidoreductase + NADH



17-AAG
tanespimycin

17-allylamino-17-demethoxygeldanamycin

Metabolism

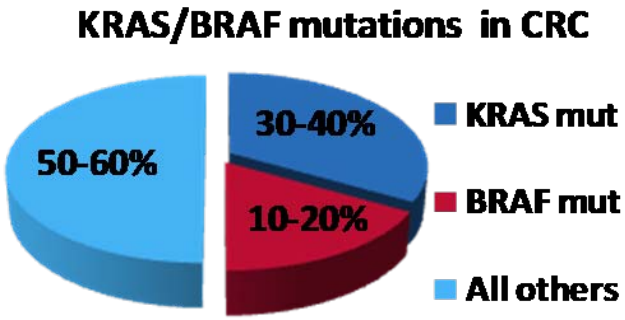


IPI-493

17-amino-17-demethoxygeldanamycin (17-AG)

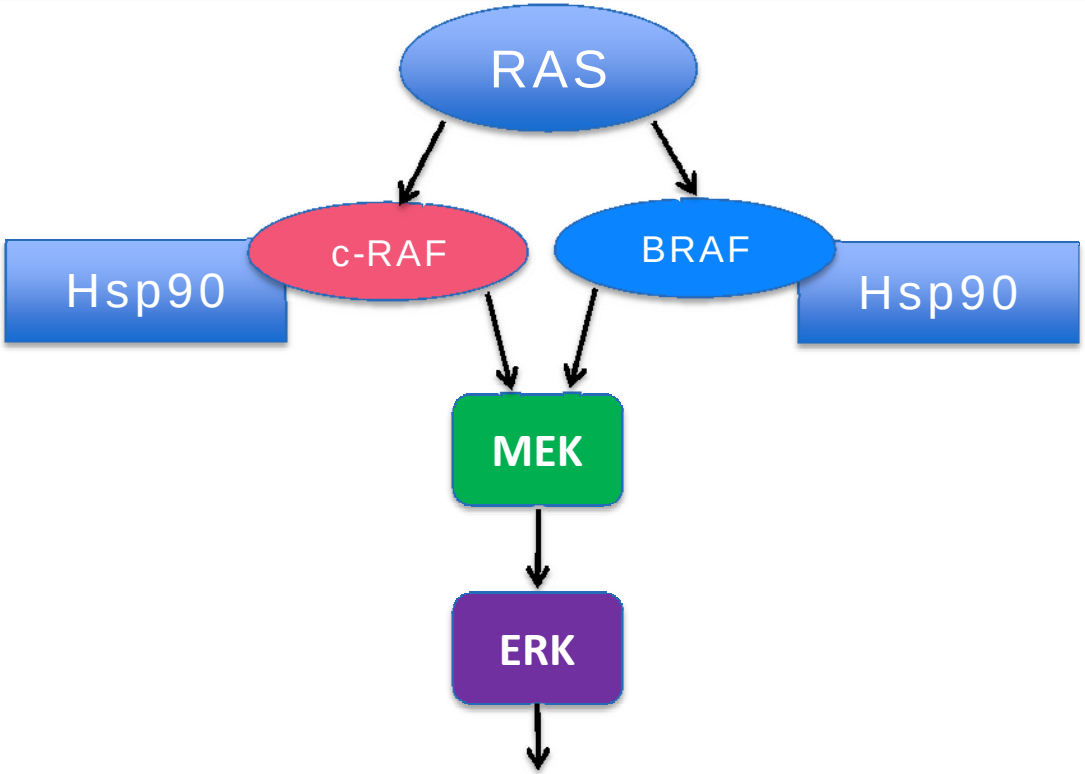
KRAS and BRAF Mutated Colorectal Cancer

- CRC is the third most common form of cancer and cause of cancer related deaths worldwide
  - >300,000 new cases and 100,000 deaths worldwide
  - 5yr survival rate <10% for pts with metastatic CRC
- KRAS and BRAF mutations are commonly found in CRC



- Standard of Care for advanced CRC is multi-agent combination therapy including EGFR antibodies (i.e. cetuximab) however, EGFR antibody treatment is contraindicated in patients with KRAS and BRAF mutations
- Thus, there is a clear need for novel therapeutics for patients with CRC that contains either KRAS or BRAF mutations

Hsp90 and the RAS/RAF/MEK Pathway



Hsp90 Inhibition by IPI-504/493 Demonstrates Potent Activity in Mutant kRAS/bRAF CRC Cell Lines

GI50 (Growth inhibition, nM)

	Colo 205	Colo 201	Colo 741	HT 29	HT 55	HCT 116	SW 480	SW 620	SW 48	Colo 320	NCI H716	SNU C1	C2BBe 1
IPI-504													
IPI-493													

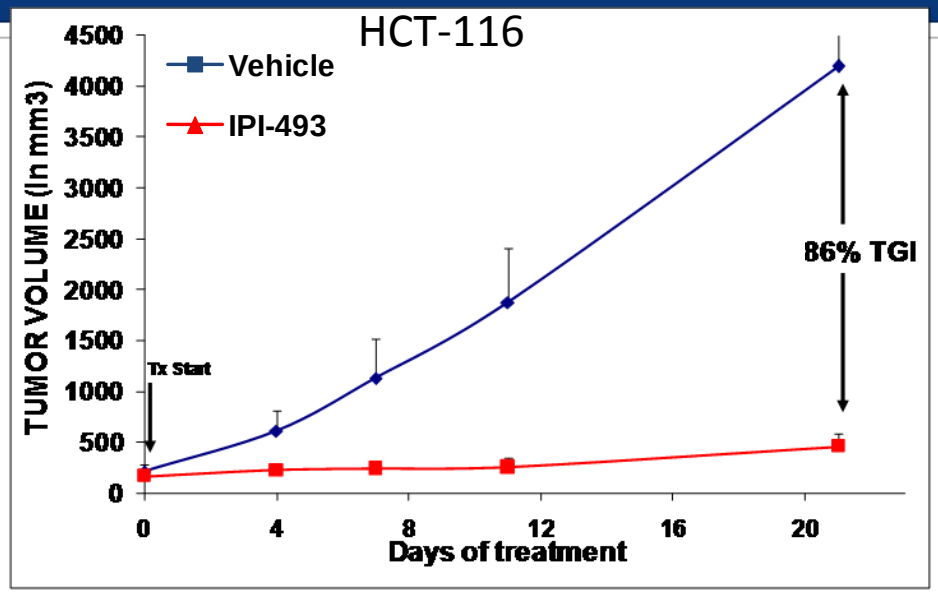
Mutation status

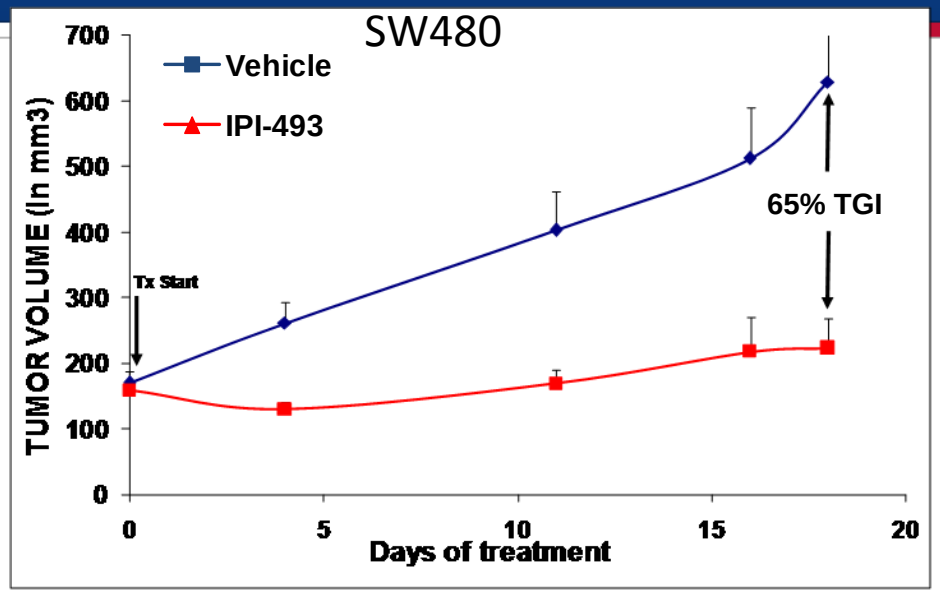
KRAS	wt	wt	wt	wt	wt	Mut G13D	Mut G12V	Mut G12V	wt	wt	wt	wt	wt
bRAF	Mut V600E	Mut V600E	Mut V600E	Mut V600E	Mut N581Y	wt	wt	wt	wt	wt	wt	wt	wt
EGFR	wt	wt	wt	wt	wt	wt	wt	wt	G719S	wt	wt	wt	wt

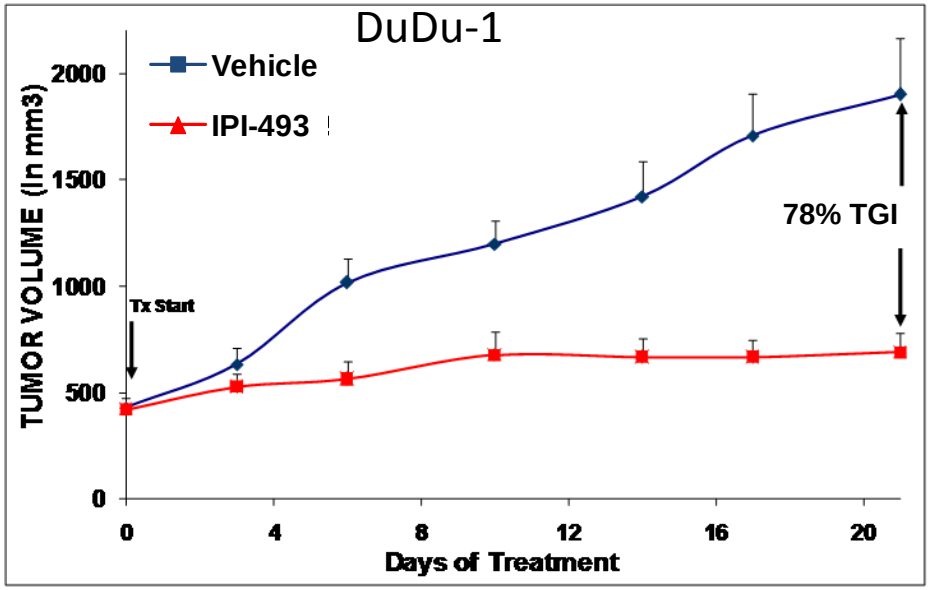
=Sensitive

=Insensitive

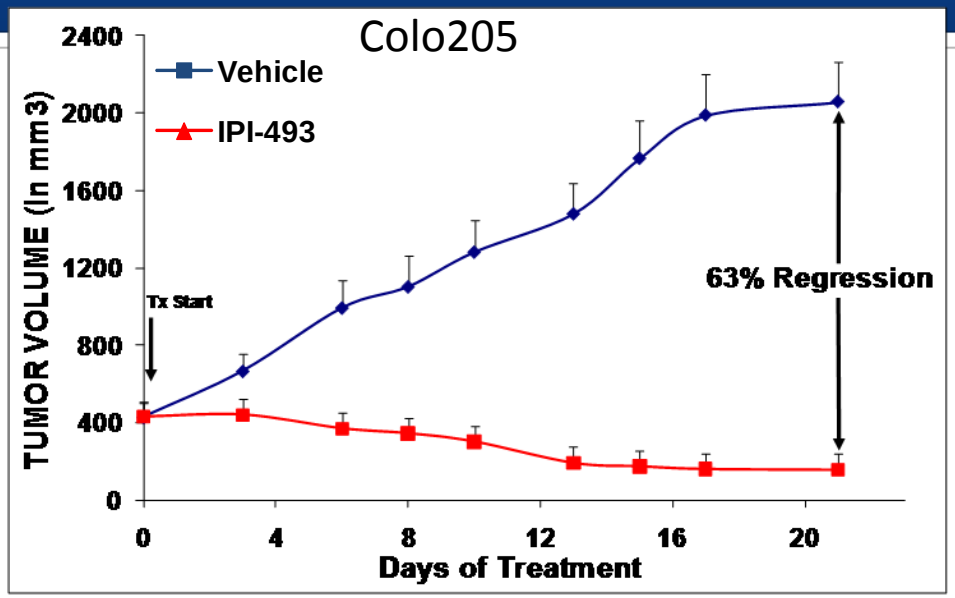
Inhibiting Hsp90 with IPI-493 Exhibits Anti-tumor Activity in Mutant kRAS CRC Models

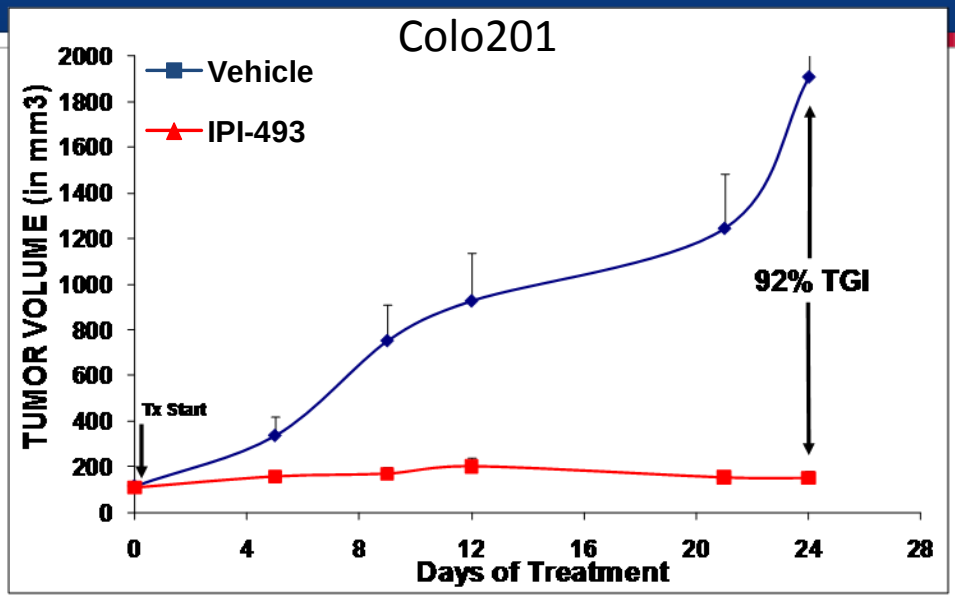


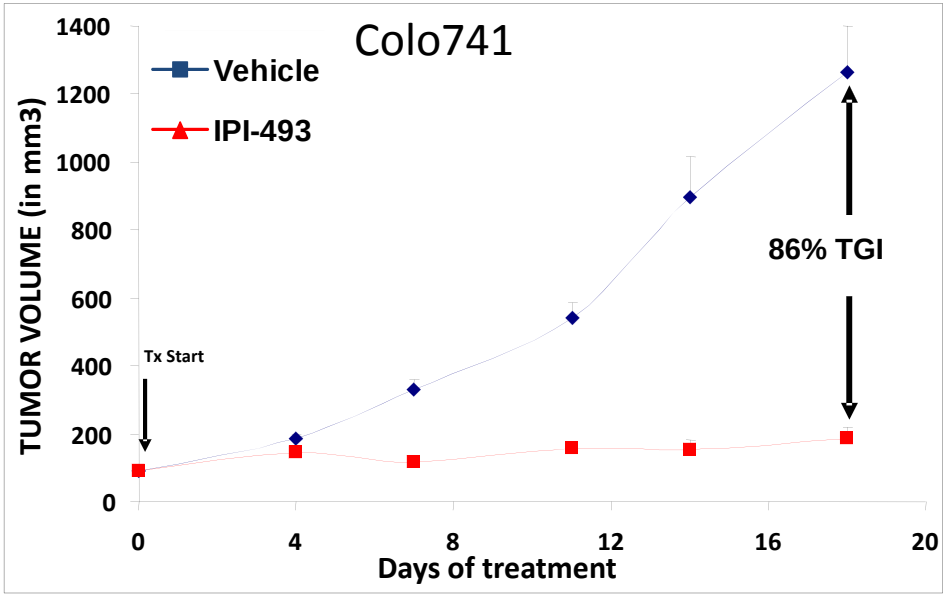


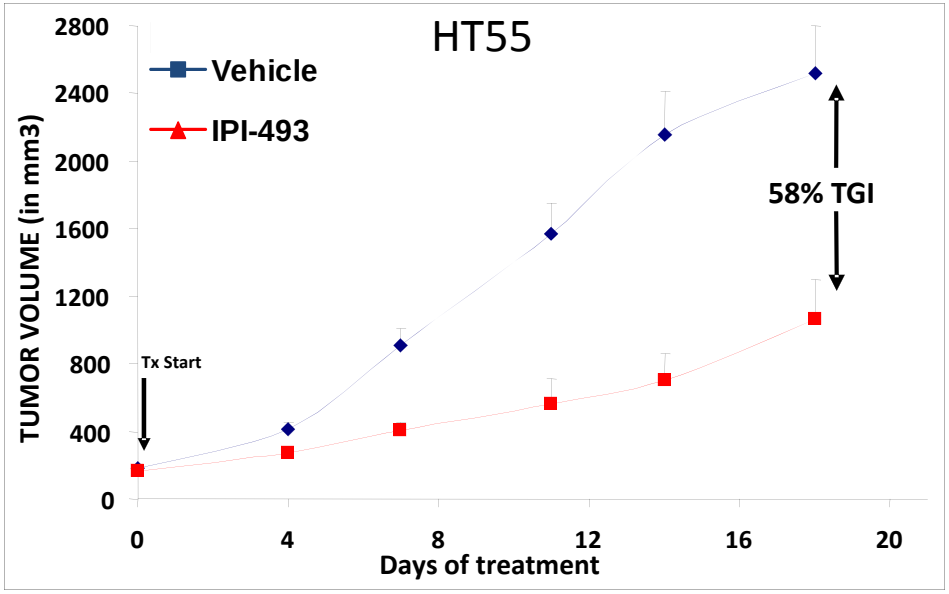


Hsp90 Inhibition by IPI-493 Also Displays Anti-tumor Activity in Mutant bRAF CRC Models

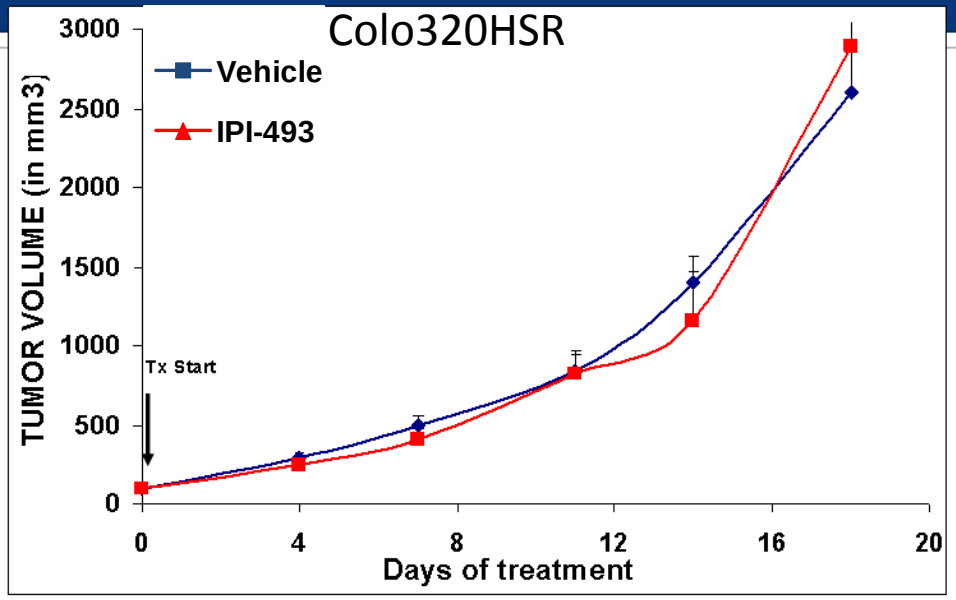


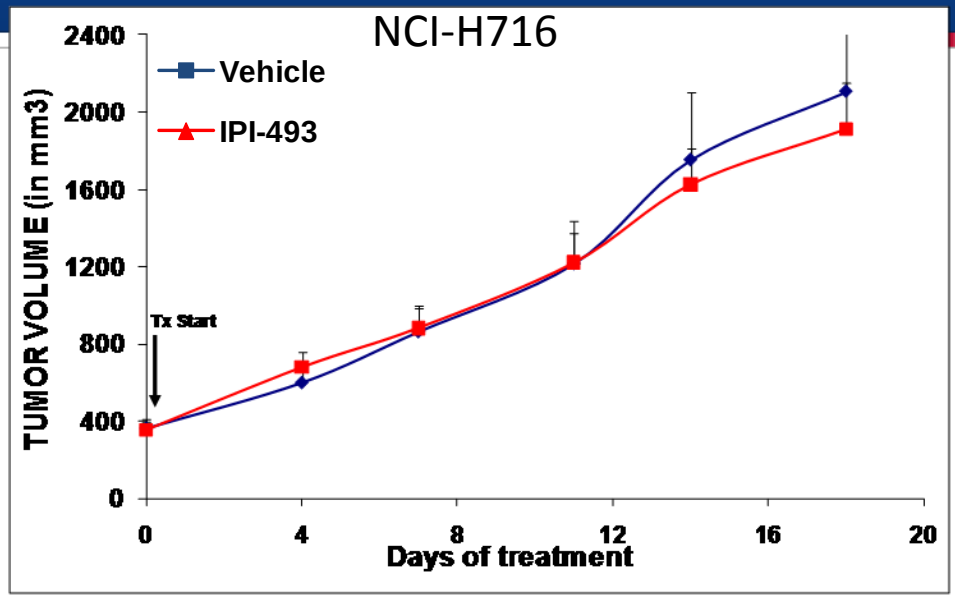


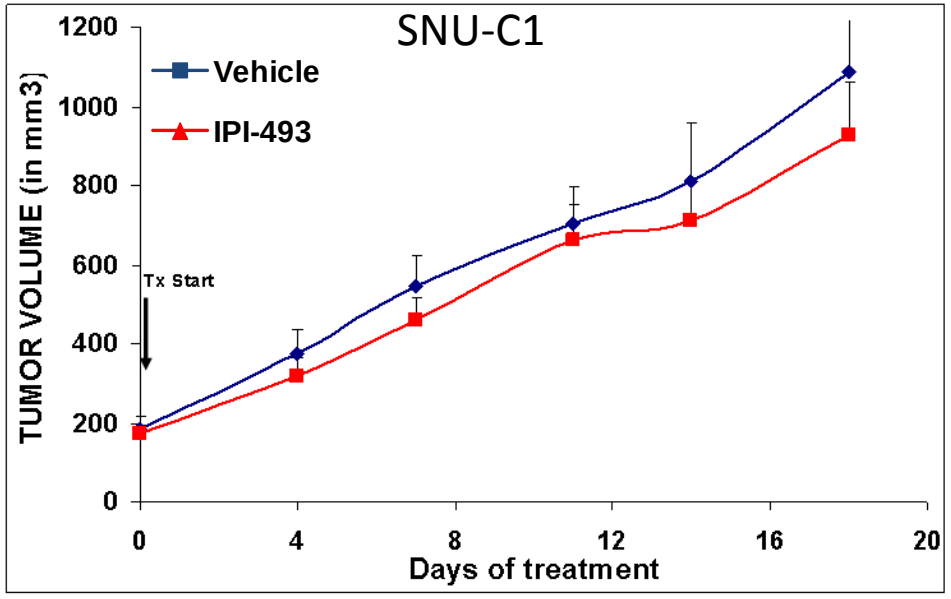


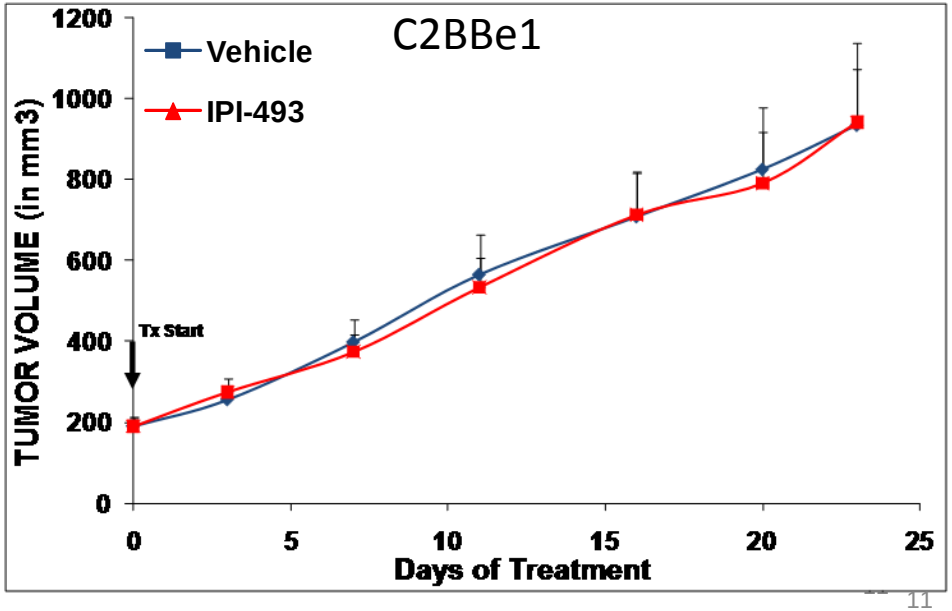


IPI-493 Demonstrates a Lack of Activity in CRC Models wt for Both kRAS and bRAF

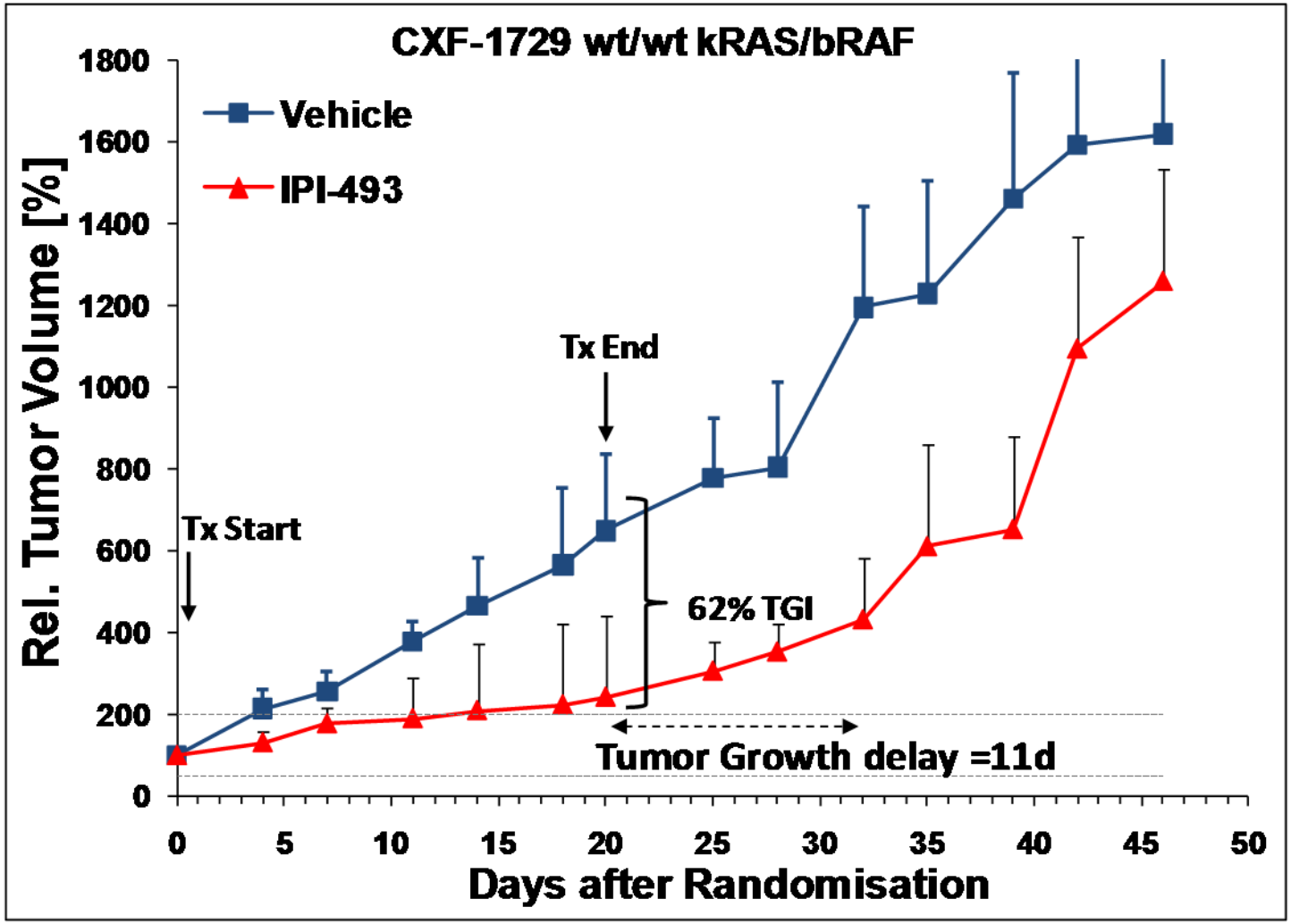






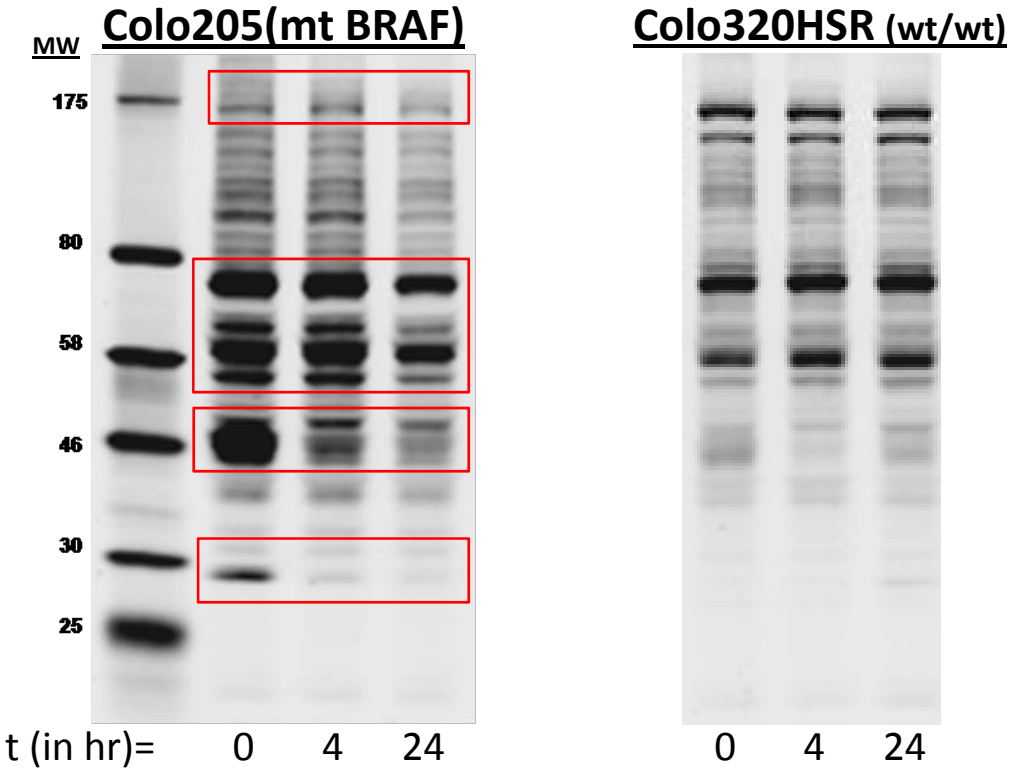


Activation of the MAPK Pathway Predicts Sensitivity to Hsp90 Inhibition by IPI-493 In Vivo

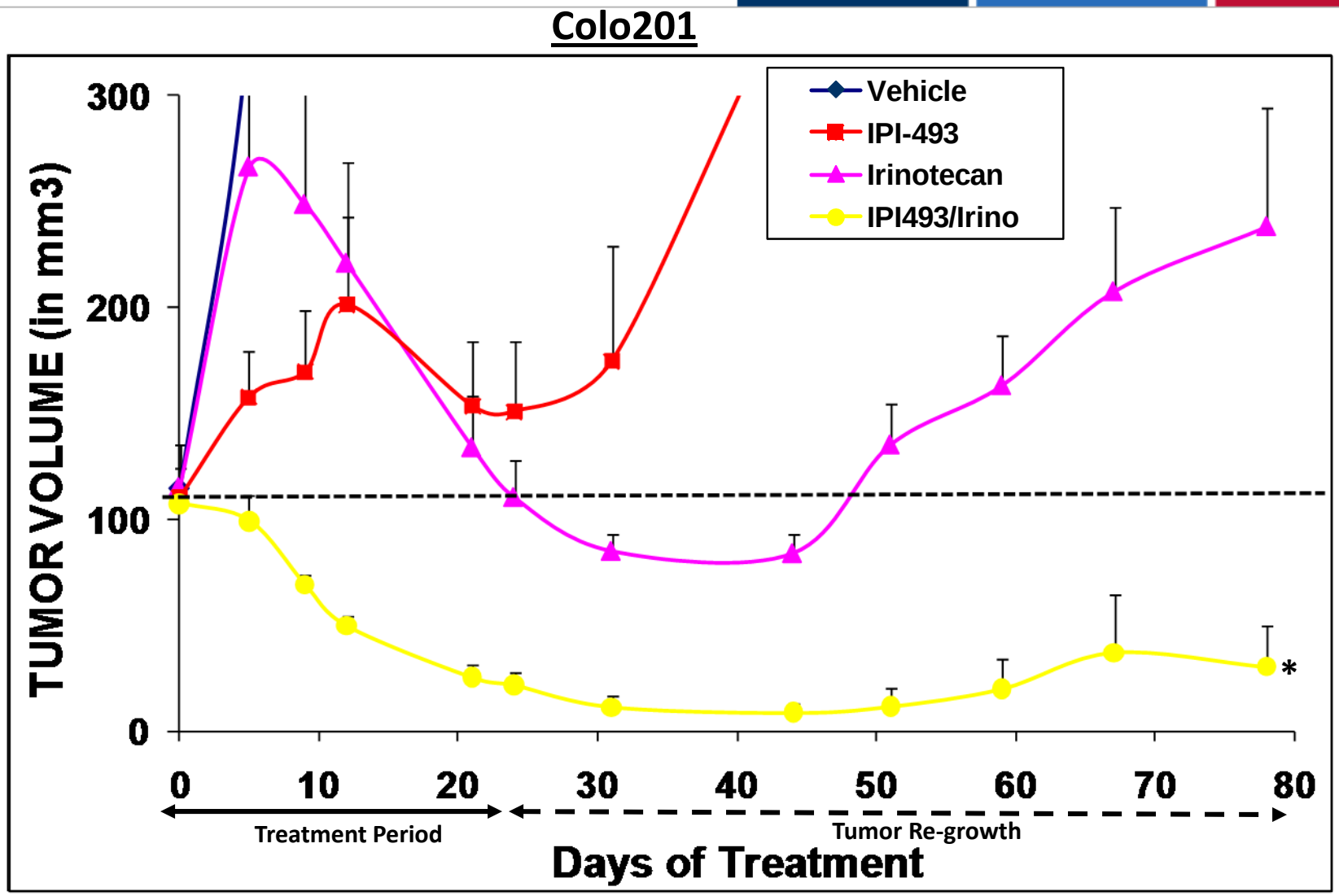


Phosphoproteomic Analysis Shows Differential Effects of Hsp90 Inhibition on Signaling In Vivo

Akt Substrate Motif Ab- RXX(s/t)



IPI-493 in Combination with Irinotecan Demonstrates Regression in Mutant bRAF CRC Model



*=4/10 animals without palpable tumors

Summary and Conclusions

- Hsp90 inhibition by IPI-493 results in anti-tumor activity in mutant kRAS/bRAF models, but not in wt models, of colorectal cancer
- Molecular pathway analysis in those tumors demonstrates that activation of the MAPK pathway is a predictor of IPI-493 sensitivity
- IPI-493 in combination with Irinotecan leads to regressions in mutant kRAS/bRAF models of CRC
- These data support the use of Hsp90 inhibition in RAS/RAF mutated CRC and, more generally, support the hypothesis that patient selection approaches (such as phosphorylated MEK expression) could be used to identify patients for clinical trials of IPI-504/493, particularly in combination with chemotherapy

The Infinity Team