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AT13387, an HSP90 inhibitor, is effective in both vemurafenib-sensitive and -resistant melanoma models

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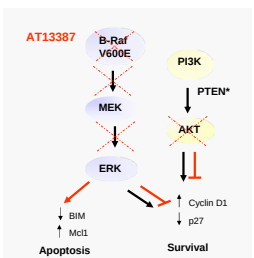
INTRODUCTION

Mutations in BRAF are found in approximately 50% of melanomas. Vemurafenib, the selective mutant BRAF inhibitor, is an effective treatment in this disease but is limited by the onset of resistance. A number of mechanisms of resistance to RAF inhibitors have been described, including alternative mechanisms for activating the MEK-ERK and AKT pathways.

AT13387 is a fragment-derived, potent HSP90 inhibitor, which is currently being evaluated in clinical trials. Based upon the results of this initial phase 1 study, a phase 2 study has been initiated in patients with refractory gastrointestinal stromal tumors (GIST).

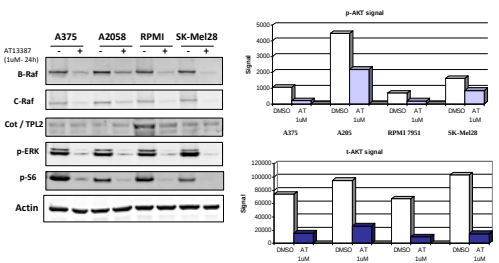
HSP90 inhibitors affect clients in both ERK and AKT pathways and so it has been suggested that HSP90 inhibition is a potential mechanism for overcoming resistance to RAF inhibitors in melanoma.

AT13387 was shown to be effective in both vemurafenib sensitive and resistant models of melanoma.



RESULTS: *In vitro* data

HSP90 client regulation in response to AT13387



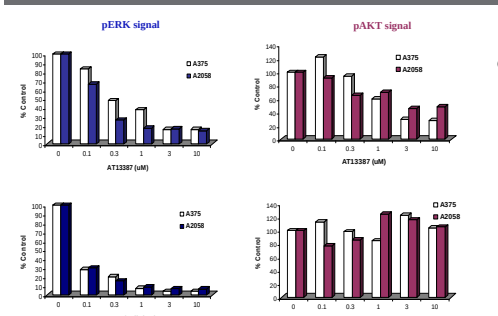
- AT13387 treatment of melanoma cell lines resulted in depletion of HSP90 client proteins including BRAF, CRAF, Cot and AKT.
- Elevated levels of P-AKT were observed in the vemurafenib resistant model A2058 (MSD, Meso Scale Discovery).

Growth inhibition in response to vemurafenib and AT13387 as single agents

Cell lines	B-Raf status	Additional genetic alterations	VM GI50 (nM)	AT13387 GI50 (nM)
A375	V600E	Ras WT	92	23
SK-Mel-28	V600E	Ras WT/ PTEN het	340	70
SK-Mel-5	V600E	Ras WT	390	470
RPMI 7951	V600E	MAP3K8/ COT gene copy gain	>10000	47
A2058	V600E	Ras WT /PTEN null	1700	34
SK- Mel-2	WT	N-Ras Q61R	>10000	55

- AT13387 inhibited cell proliferation in a range of melanoma cell lines, including cell lines with different mechanisms of resistance to vemurafenib.

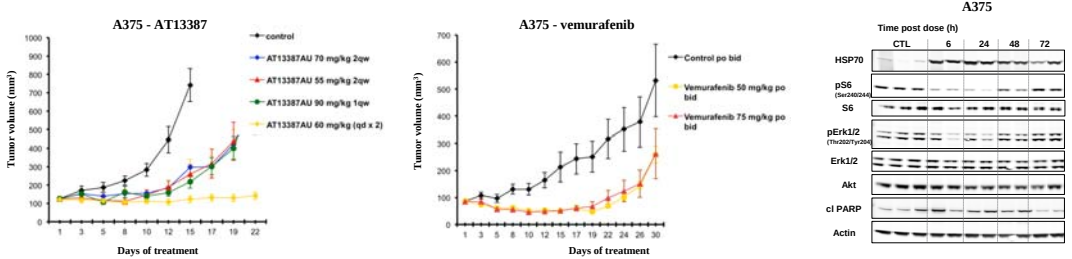
Biomarker evaluation of AT13387 and vemurafenib as single agents



- In response to AT13387 the levels of phospho-ERK and phospho-AKT were depleted in both vemurafenib-sensitive (A375) and vemurafenib-resistant (A2058) lines indicating that the MEK-ERK and AKT signalling pathways were both inhibited.
- Vemurafenib inhibits the BRAF(V600E)-MEK-ERK pathway in both cell lines.

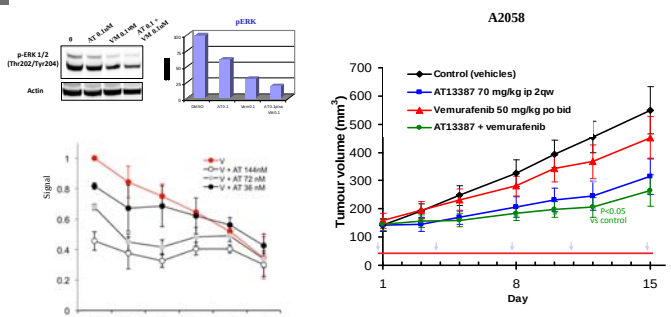
RESULTS: *In vivo data*

Single agent anti-tumor activity against A375 xenografts



- Treatment with AT13387 or vemurafenib as monotherapy significantly inhibited growth of A375 melanoma xenografts. No significant changes in body weight were observed after the treatments.
- Pharmacodynamic downregulation of the MEK-ERK and AKT pathways was observed in response to AT13387 treatment (single dose AT13387 90mg/kg).

Combination of vemurafenib with AT13387 in A2058 vemurafenib – resistant cell line



- A moderate additive effect was observed when both compounds were combined in vitro in A205 cell line, which carries a BRAF V600E activation mutation in a PTEN null background
- The combination index (CI) at the GI50 for both compounds was 1.1 (additive effect).
- Tumor growth of a vemurafenib resistant xenograft model (A2058) was inhibited by AT13387 treatment compound alone or in combination with vemurafenib.
- The combination of AT13387 and vemurafenib is well tolerated and not antagonistic.

CONCLUSIONS

- These results demonstrate the activity of AT13387 in both vemurafenib-sensitive and -resistant models and show that HSP90 inhibition results in downregulation of signalling pathways that may be activated as a result of resistance to RAF inhibitors.
- These data support further clinical evaluation of AT13387 in melanoma.

References

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