Poster #348

ABI-009 (*nab*-Sirolimus) Improves Tumor Accumulation and Antitumor Activity over Oral mTOR Inhibitors

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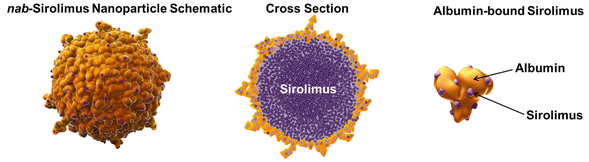
INTRODUCTION

- The mTOR pathway has been implicated in cell survival and proliferation and is an attractive target for cancer therapy.[1]
- The poor solubility, low oral bioavailability, adverse event profile and incomplete target inhibition of the known mTOR inhibitors can limit their activity in treatment of cancers and other diseases.
- ABI-009 (*nab*-sirolimus) is an injectable nanoparticle form of human albumin-bound sirolimus with a mean particle size of approximately 100 nm developed with a proprietary nanoparticle albumin-bound (*nab*®) technology.[2]



- ABI-009 is currently in phase 1 and 2 studies for multiple cancer types, including soft-tissue sarcomas, neuroendocrine tumors, colorectal cancer, glioblastoma, various childhood cancers, and a registrational phase 2 study for malignant PEComa.
- It is hypothesized that strong antitumor activity of ABI-009 may be associated with higher tumor drug accumulation.
- This study evaluated the antitumor effect and tumor drug concentrations by ABI-009 as compared with oral sirolimus and everolimus in an aggressive UMUC3 mouse xenograft model.[3]

METHODS

- UMUC3 human bladder cancer xenografts were established in athymic nude mice.
- Treatment: sirolimus/everolimus – 3 mg/kg, qdx5/weekly, PO, total dose 15 mg/kg/week; ABI-009 – 7.5 mg/kg, 2x/weekly, IV, total dose 15 mg/kg/week
- Antitumor treatment assessment was done with 5 mice/group.
- Pharmacokinetic assessment (3 mice/group) sacrificed to harvest tumors for drug concentration analysis at 4 predetermined time points (1 hr post Day 1; 24 hr post Day 1; 1 hr post Day 4; and 168 hr post Day 1).

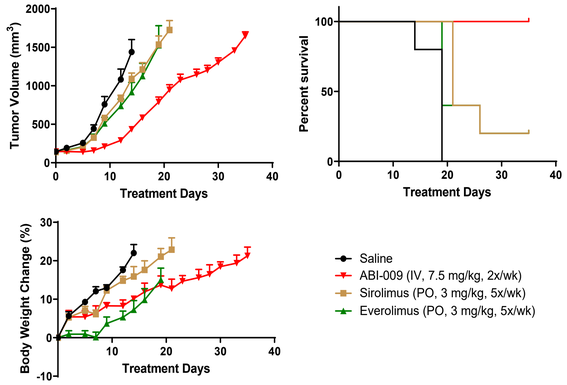
RESULTS

Antitumor Activity

Table 1. Antitumor treatment results

			Tumor Growth			Animal Survival			
Treatment (N = 5)	Dosing Schedule	Weekly Dose (mg/kg)	TGI (%)	P vs Saline	P vs ABI-009 7.5 mg/kg	Median Survival (Days)	Number of Animal Surviving	P vs Saline	P vs ABI-009 7.5 mg/kg
Saline	2x/wk, IV	0	0	-	<0.0001	19	0/5	-	<0.01
ABI-009	7.5 mg/kg, 2x/wk, IV	15	69.6	<0.0001	-	NR	5/5	<0.01	-
Sirolimus	3 mg/kg, 5x/wk, PO	15	24.3	<0.05	<0.0001	21	1/5	<0.01	<0.05
Everolimus	3 mg/kg, 5x/wk, PO	15	36.2	<0.01	0.0023	19	1/5	NS	<0.05

Figure 1. Tumor volume, animal survival, and body weight following ABI-009 IV, sirolimus PO, and everolimus PO treatments



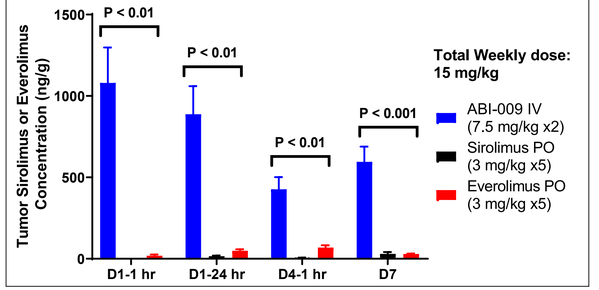
- ABI-009 showed significant antitumor effect and longer survival compared with equal weekly dose of oral sirolimus and everolimus.
- All treatment groups were well tolerated with no significant weight loss, but a delay in weight gain for everolimus and ABI-009.

Comparison of Tumor Drug Levels

Table 2. Pharmacokinetic treatment groups

Treatment	Sirolimus/Everolimus 3 mg/kg, qdx5 (Oral); N = 3/time point								ABI-009: 7.5 mg/kg Days 1 and 4 (IV); N = 3/time point							
Study Procedure \ Days	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
Drug Treatment	x	x	x	x	x				x			x				
Animal sacrifice, blood/tumor PK																
1 hr after drug treatment (N=3)	x			x					x			x				
Prior to drug treatment (N=3)		x								x						
168 hrs after Day 1 treatment (N=3)								x								x

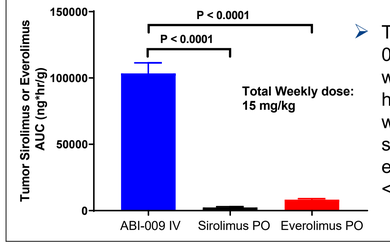
Figure 2. Tumor drug concentrations



- ABI-009 IV resulted in 6.2-68.1 fold higher tumor drug levels compared with oral mTOR inhibitors at all time points tested.

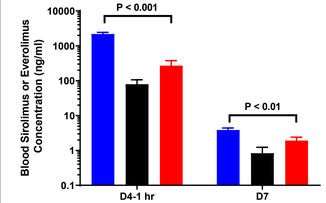
Comparison of Tumor and Blood Drug Levels

Figure 3. Tumor drug accumulation



- Tumor AUC with ABI-009 IV over 1 week were significantly higher vs equal weekly dose of oral sirolimus (43 fold) and everolimus (12 fold) ($p < 0.0001$).

Figure 4. Blood drug concentrations



- ABI-009 IV resulted in blood drug levels 8.0-27.4 fold higher 1 hr post Day 4 dosing and 2.0-4.6 folder higher after 1 week compared with oral mTOR inhibitors.

REFERENCES

1. Corradetti MN, Guan KL (2006). Upstream of the mammalian target of rapamycin: do all roads pass through mTOR? Oncogene 25(48): 6347-6360.
2. Gonzalez-Angulo, A.M., et al., Weekly nab-Rapamycin in Patients with Advanced Nonhematologic Malignancies: Final Results of a Phase I Trial. Clin Cancer Res, 2013. 19(19): p. 5474-5484.
3. Makhlin I, et al., (2011). The mTOR pathway affects proliferation and chemosensitivity of urothelial carcinoma cells and is upregulated in a subset of human bladder cancers. BJU Int 108(2 Pt 2): E84-90.

CONCLUSIONS

- Compared with clinically relevant doses of oral mTOR inhibitors, ABI-009 given IV at equal weekly dose demonstrated significantly greater tumor accumulation, stronger antitumor activity, and prolonged animal survival.
- ABI-009's distinct PK profile can be attributed to its nanoparticle structure and complexation with albumin.
- Multiple oncology clinical studies are currently ongoing with ABI-009, including a Phase 2 registrational trial in advanced malignant PEComa (PEC-001, NCT02494570).

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