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Improved tumor penetration, anti-tumor activity, and survival of ABI-009 (*nab*-sirolimus) versus oral rapamycin and everolimus and investigation of mTOR pathway inhibition

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INTRODUCTION

- mTOR pathway is a key regulator of cell survival and proliferation and has been implicated in various indications, including oncology, hematology, and cardiovascular, metabolic, and central nervous system diseases.
- ABI-009, a novel mTOR inhibitor, is an intravenously (IV) administered nanoparticle form of albumin-bound sirolimus.
- ABI-009 is in a registrational clinical study for perivascular epithelioid cell carcinoma (PEComa), and also studied as combination or single agent in phase 1, 1/2, and 2 studies in neuroendocrine tumors, bladder cancer, glioblastoma, soft-tissue sarcomas, colorectal cancer, childhood cancers, as well as pulmonary arterial hypertension and refractory epilepsy.
- ABI-009 has a distinct PK profile vs oral mTOR inhibitors, and it is hypothesized that albumin binding to sirolimus may improve drug penetration and thus efficacy.
- This xenograft study was conducted to evaluate the antitumor activity, tissue penetration, and mTOR inhibition of ABI-009 vs equal doses of oral mTOR inhibitors at clinically relevant doses.

METHODS

- Athymic mice were injected with UMUC3 bladder cancer cells subcutaneously into both flanks.
- Upon development of tumors, ABI-009, oral rapamycin and everolimus were administered at equal weekly doses of 15 mg/kg for up to 5 wks of treatment (or when tumor size reached 2000 mm^3, whichever was earlier):
  - ABI-009 IV at 7.5 mg/kg, 2x /wk, on D1 and D4
  - Oral rapamycin and oral everolimus PO at 3 mg/kg/day, 5 days /wk
  - Saline IV at 10 ml/kg, 3x /wk

  Note: The 3 mg/kg/day dose (15 mg/kg weekly dose) for both oral rapamycin and everolimus in mice is equivalent to 45 mg/m^2/week human dose (11.6 mg/day assuming 1.8 m^2 BSA).
- Tumor and blood drug concentrations were also obtained (tumor: D1 1h and 24h, D4 1h, D7; blood: D4 1h, D7).

RESULTS

- Significant improvement in tumor growth inhibition and survival was observed with IV ABI-009 vs oral rapamycin and everolimus, dose for dose.
- No significant body weight loss following treatment.

Figure 1. Tumor Growth Inhibition and Survival

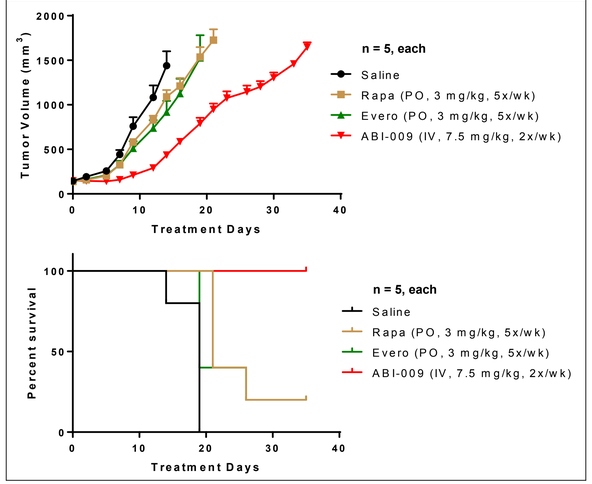

Table 1.

	TGI (%)	P vs Saline	P vs ABI-009	Median survival (days)	# Alive	P vs Saline	P vs ABI-009
Saline, IV 2x/wk	0	-	<0.0001	19	0/5	-	<0.01
ABI-009, IV 7.5 mg/kg, 2x/wk	69.6	<0.0001	-	Not Reached	5/5	<0.01	-
Rapamycin, PO 3 mg/kg, 5x/wk	24.3	<0.05	<0.0001	21	1/5	<0.01	<0.05
Everolimus, PO 3 mg/kg, 5x/wk	36.2	<0.01	0.0023	19	1/5	NS	<0.05

- After 1 hour, tumor drug level was over 50-fold higher with ABI-009 IV than oral rapamycin and oral everolimus, demonstrating rapid and efficient tumor distribution.
- After 1 week of treatment, tumor drug level remained high for ABI-009, and was 20-fold higher vs equal weekly dose of oral rapamycin and oral everolimus.
- Tumor AUC with ABI-009 IV over 1 week were significantly higher compared with equal weekly dose of oral rapamycin (43-fold) and oral everolimus (12-fold) ($P < 0.0001$, ANOVA).

Figure 2. Tumor and Blood Drug Concentrations

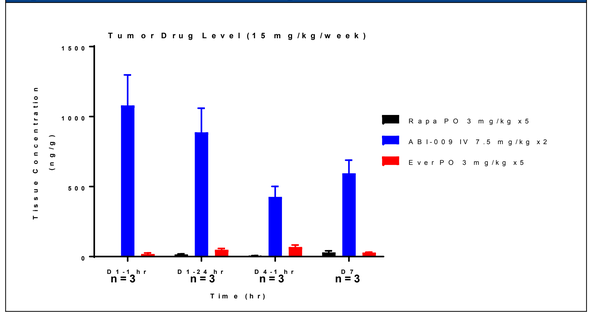

Table 2. [ ]

		Tumor Conc (ng/g) n = 3, each timepoint					Blood Conc (ng/ml)	
		D1, 1h	D1, 24h	D4, 1h	D7	AUC	D4, 1h	D7
ABI-009 IV (7.5 mg/kg x2/wk)	Conc	1080.0	888.0	427.0	595.3	103410.0	2173.3	3.9
	SD	217.7	171.7	74.5	93.6	7969.0	266.9	0.5
Rapamycin PO (3 mg/kg x5/wk)	Conc	0.0	15.2	6.3	29.4	2395.0	79.3	0.8
	SD	0.0	4.2	1.2	11.6	565.5	26.7	0.4
	ABI-009 ratio	-	58.3	68.1	20.3	43.2	27.4	4.6
	P vs ABI-009	0.0010	0.0009	0.0006	0.0005	<0.0001	0.0002	0.0014
Everolimus PO (3 mg/kg, 5x/wk)	Conc	18.5	48.6	68.7	28.7	8278.0	271.3	1.9
	SD	7.6	9.8	14.0	2.9	811.0	104.4	0.5
	ABI-009 ratio	58.3	18.3	6.2	20.7	12.5	8.0	2.0
	P vs ABI-009	0.0011	0.0011	0.0012	0.0005	<0.0001	0.0003	0.0094

- Based on its efficient tissue distribution, linear PK, and subsequent tolerable safety profile with evidence of efficacy in humans [1], ABI-009 is in clinical development for various oncology indications as well as cardiovascular and central nervous system disorders, in which mTOR inhibition is indicated.

Figure 3. ABI-009 in Clinical Development

Therapeutic Area	Phase 1b	Phase 2
Oncology		
Advanced Perivascular Epithelioid Cell Carcinoma (PEComa)	Single Agent, Ph 2, FDA OOPD Grant	Registrational Trial ★
Newly Diagnosed GBM, Recurrent High-grade Glioma	+ Various, Ph 2	
Nonmuscle-invasive Bladder Cancer (NMIBC)	+ Gemcitabine, Ph 1b/2, NIH STTR Grant	
Advanced Soft Tissue Sarcoma	+ Nivolumab, Ph 1b/2	
Advanced Neuroendocrine Tumors	Single agent, Ph 2 pilot	
Pediatric Solid Tumors (Childrens Oncology Group)	+ TMZ + IRI, Ph 1b	
Metastatic Colorectal Cancer, 1L	+ FOLFOX+Bev, Ph 1b/2	
Advanced Nonadipocytic Soft Tissue Sarcoma	+ Pazo, Ph 1b/2	
Cardiovascular System		
Pulmonary Arterial Hypertension (PAH)	+ Std PAH Rx, Ph 1b	
Central Nervous System		
Pediatric Leigh Syndrome (mitochondrial disease)	Single Agent, Ph 2a	
Pediatric Surgically Refractory Epilepsy	+ Std AEDs, Ph 1b	

CONCLUSIONS

- This study demonstrated significantly greater antitumor activity and prolonged survival at clinically relevant doses with ABI-009 vs equal weekly dosing of oral mTOR inhibitors, rapamycin and everolimus.
- The increased efficacy of ABI-009 over the oral mTOR inhibitors is associated with increased drug exposure and tumor penetration at equal doses.
- The lack of significant weight loss indicated acceptable toxicity at clinically relevant doses studied in each group.
- These findings suggest increased efficacy of ABI-009 vs oral mTOR inhibitors study and should be confirmed in the clinical setting

REFERENCES

1. Gonzalez-Angulo et al., Weekly nab-Rapamycin in patients with advanced nonhematologic malignancies: final results of a phase I trial. Clin Cancer Res 2013; 19: 5474-84.

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