Poster #3896

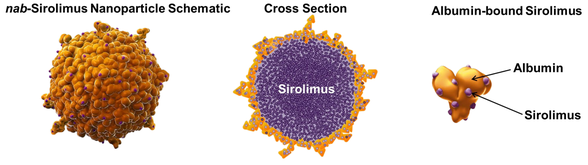
Distinct Pharmacokinetics, Tissue Distribution and CNS Penetration of ABI-009 (*nab*-Sirolimus)

Shihe Hou, Anita N. Schmid, and Neil Desai

Aadi Bioscience, Inc., Pacific Palisades, CA

INTRODUCTION

- The mammalian target of rapamycin (mTOR) regulates cell growth, survival, and proliferation, and is often overexpressed in various cancers, making it a promising target in tumor 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 developed with a proprietary nanoparticle albumin-bound (nab®) technology.



- ABI-009 was well tolerated and showed evidence of responses and stable disease in various solid tumors in a phase 1 study.[2]
- ABI-009 demonstrates a distinct nonclinical and clinical PK profile compared with oral mTOR inhibitors.[2, 3, 4]
- Compared to published clinical PK of other mTOR inhibitors, ABI-009 has significantly higher Cmax and AUC when normalized to dose. [2, 3, 4]

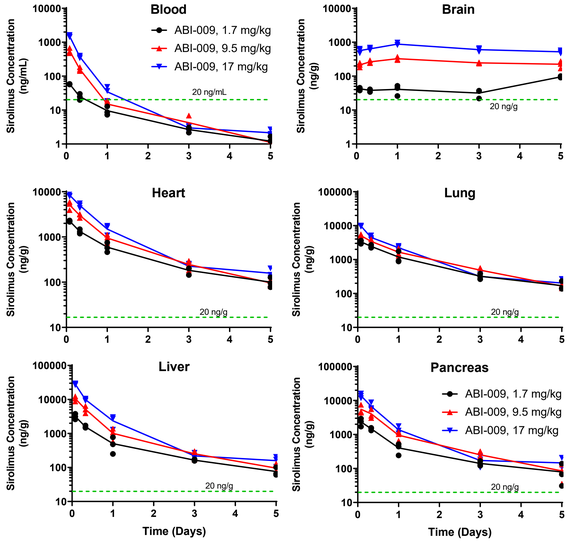
Therapeutic Area	Phase 1b	Phase 2
Oncology		
Advanced Perivascular Epithelioid Cell Carcinoma (PEComa)	Single Agent, Ph 2, FDA OOPD Grant	
Newly Diagnosed GBM, Recurrent High-grade Glioma	+ Various combinations w SOC, Ph 2	
Advanced Soft Tissue Sarcoma	+ Nivolumab, Ph 1b/2	
Advanced Neuroendocrine Tumors	Single agent, Ph 2 pilot	
Pediatric Solid Tumors (Childrens Oncology Group)	+ TMZ + IRI, Ph 1b	
Metastatic Colorectal Cancer, 1st Line	+ FOLFOX+Bev, Ph 1b/2	
Advanced Nonadipocytic Soft Tissue Sarcoma	+ Pazopanib, Ph 1b/2	
Cardio-Vascular 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	

METHODS

- Female Sprague-Dawley rats received a single dose of ABI-009 IV at 3 different dose levels: 1.7, 9.5, and 17 mg/kg.
- Whole blood, brain, lungs, liver, heart and pancreas were collected at the following time points: 2, 8, 24, 72, and 120 hr to analyze sirolimus levels by LC/MS/MS.

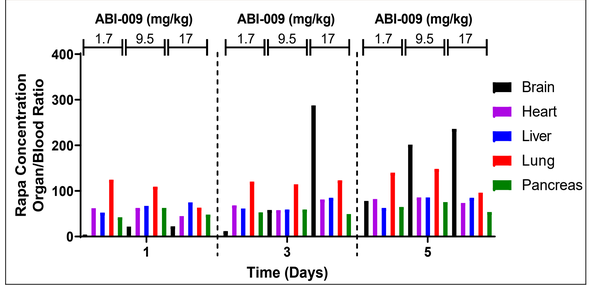
RESULTS

Figure 1. Blood and tissue sirolimus concentration-time profiles



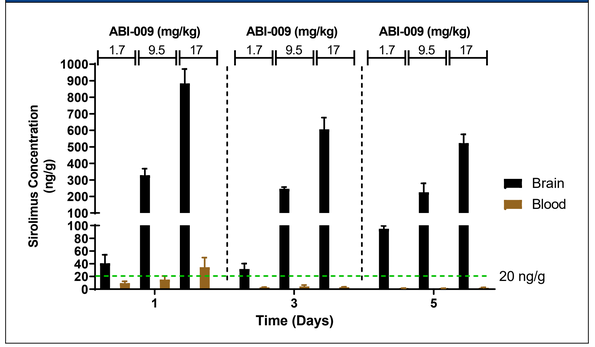
- A single IV administration was able to maintain therapeutic drug levels in tissues for at least 5 days, well in excess of 5-15 ng/ml(g) range often considered the therapeutic range for mTOR inhibitors, even at the lowest dose tested.
- In contrast to the several tissues tested which showed a drop in sirolimus over time, brain levels were maintained steady over the 5-day period tested suggesting a retention/accumulation of ABI-009 in brain tissue.

Figure 2. Tissue vs blood sirolimus concentration ratios at days 1, 3, and 5 after administration



- Five days after ABI-009 IV administration, sirolimus level in the brain was similar to other organs, suggesting substantial and prolonged sirolimus distribution to the brain with ABI-009.
- Tissue/blood ratios of most organs increased with time, with the brain/blood ratios increasing more significantly over time.
- Sirolimus levels in all tissues tested remained high and well in the therapeutic range, even though blood sirolimus levels were significantly lower by Day 5.
- The results support a weekly administration schedule in the clinic.

Figure 3. . Brain and blood sirolimus concentrations at days 1, 3, and 5 after administration



- Higher initial dose of ABI-009 resulted in increased sirolimus levels in the brain at all time points tested up to Day 5.

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. Garrido-Laguna I, et al.,(2010). Integrated preclinical and clinical development of mTOR inhibitors in pancreatic cancer. Br J Cancer 103(5): 649-655.
4. Danesi R, Boni JP, Ravaud A (2013). Oral and intravenously administered mTOR inhibitors for metastatic renal cell carcinoma: pharmacokinetic considerations and clinical implications. Cancer Treat Rev 39(7): 784-792.

CONCLUSIONS

- ABI-009 administered IV demonstrated a PK profile characterized by higher Cmax and AUC, and rapid tissue distribution, which is distinct from oral mTOR inhibitors.
- ABI-009 IV results in efficient delivery to different tissues including lung, brain, liver, and pancreas, as well as higher accumulation in tumors [AACR 2019, Poster #348], supporting the potential use of ABI-009 for the treatment of multiple cancers.
- Efficient delivery of sirolimus into the lung and across the blood-brain barrier (BBB) further supports clinical studies in non-oncology indications in lung and brain, such as PAH and epilepsy.

Correspondence: Shawn Hou, shou@aadibio.com

Presented at AACR Annual Meeting 2019, Atlanta, GA, Mar 29- Apr 3, 2019,