

MOLECULAR TARGETS AND CANCER THERAPEUTICS

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***nab*-Sirolimus improves mTOR pathway suppression and antitumor activity versus oral mTOR inhibitors in *PTEN* null bladder cancer (UMUC3) and *TSC2* null liver cancer (SNU398) xenografts**

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I have the following financial relationships to disclose:

Consultant for: None

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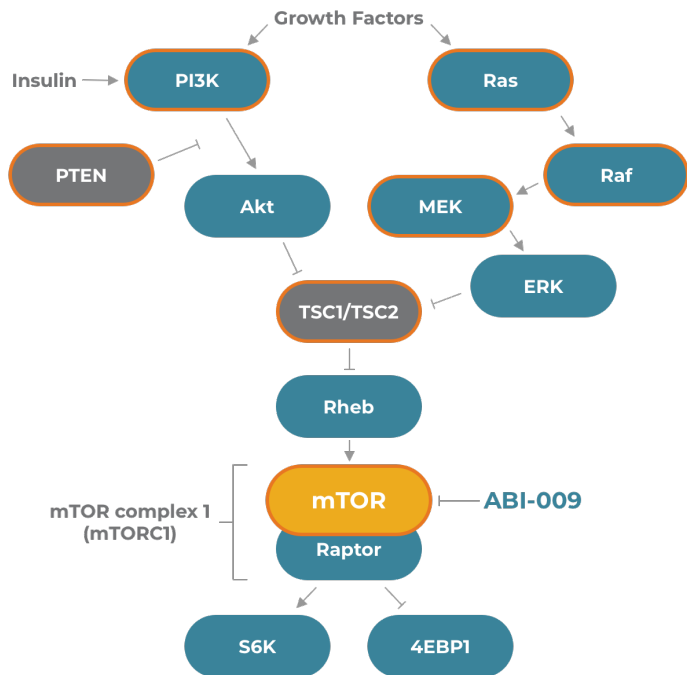
Stockholder in: Aadi Bioscience, Inc., Bristol-Myers Squibb Co

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I will discuss the following investigational use in my presentation: malignant Perivascular Epithelioid Cell Tumors (PEComa)

Introduction

PI3K/Akt/mTOR pathway



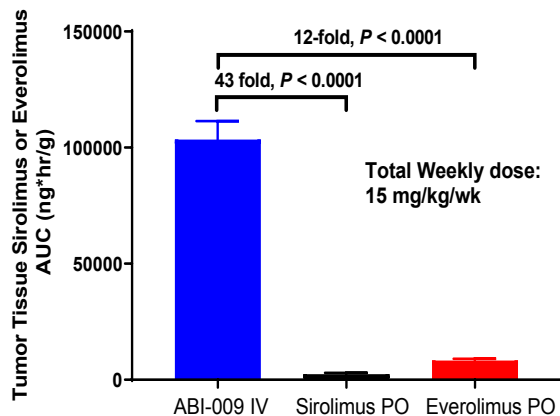
○ Frequently mutated in cancer and/or validated target

- *TSC1*, *TSC2*, and *PTEN* genes are tumor suppressors in the mTOR pathway and can be inactivated or deleted across many cancers, causing activation of mTOR pathway and phosphorylation of downstream targets S6K (activation) and 4EBP1 (inactivation).
- Oral mTOR inhibitors (mTORi) sirolimus and everolimus can effectively inhibit S6K but not 4EBP1 and may lead to therapeutic resistance (*Kang, Science 2013*).
- *nab*-Sirolimus (ABI-009) is a novel albumin-bound nanoparticle form of mTOR inhibitor sirolimus with a distinct PK profile (higher C_{max}, AUC, Half-life and tumor distribution) vs oral sirolimus or everolimus.

Improved Drug Delivery, mTOR Pathway Inhibition, and Efficacy in UMUC3 Model

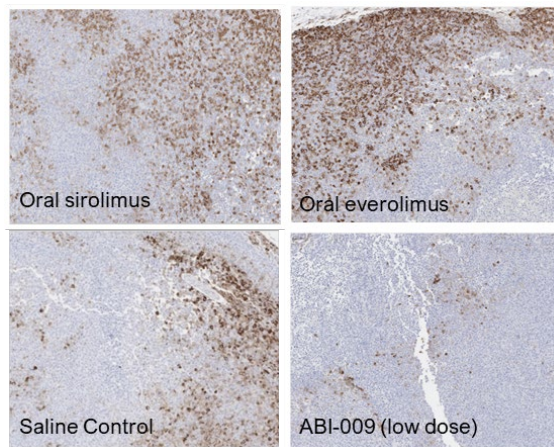
■ UMUC3: human bladder cancer, *PTEN*-null

Drug conc in tumor (n=3/group)



Tumor concentration of *nab*-sirolimus (ABI-009), oral sirolimus, and oral everolimus measured by LC-MS/MS over 7 days at equal weekly dose (15 mg/kg/wk) in mice bearing tumor xenografts

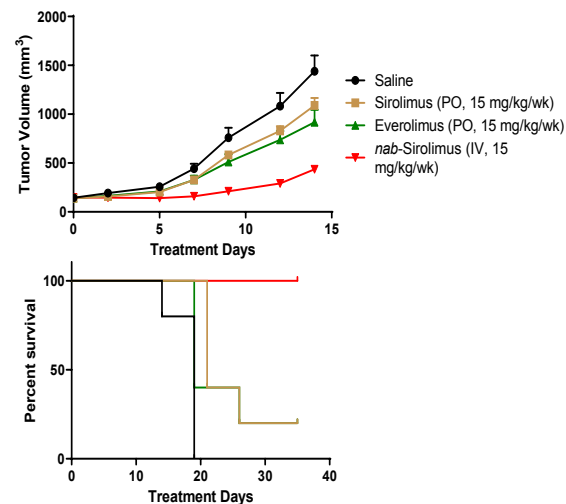
IHC for pS6 (n=3/group)



Tumor IHC pS6 suppression on D7 post dose at equal doses (15 mg/kg/wk). pS6 is a downstream target of mTOR.

Scored based on % positive area by pathologist
nab-sirolimus vs oral sirolimus: $P = 0.0001$; vs oral everolimus: $P = 0.0034$ (ANOVA)

Tumor size and Survival (n=5/group)

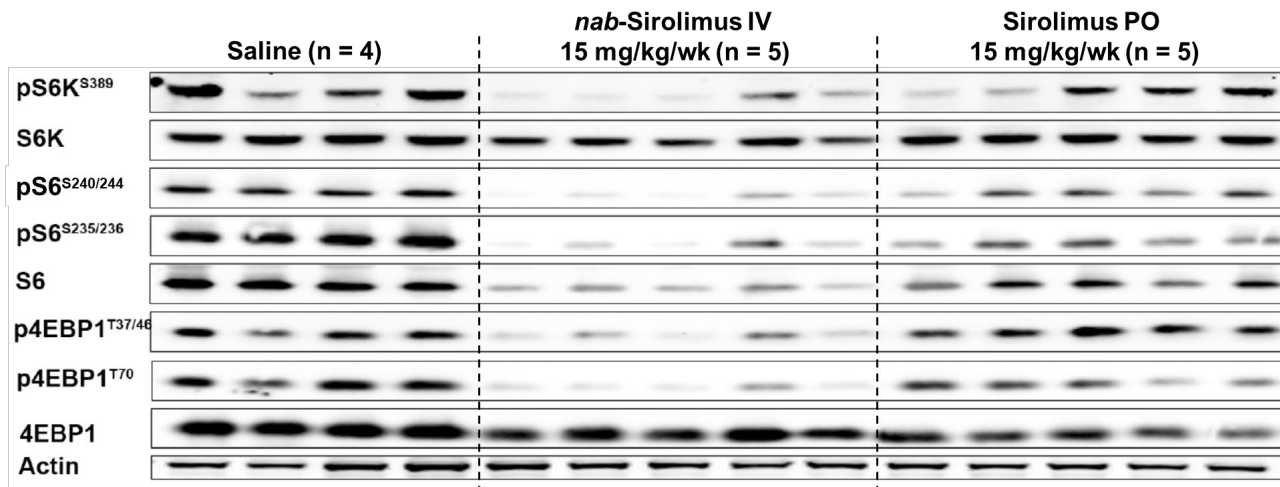


- Oral sirolimus and Everolimus 3 mg/kg, 5x/wk; IV *nab*-sirolimus 7.5 mg/kg, 2x/wk (all drugs 15 mg/kg/wk)
- Tumor volume: *nab*-sirolimus vs oral sirolimus: TGI 69.6% vs 24.3%, $P < 0.0001$; vs oral everolimus: TGI 69.6% vs 36.2%, $P = 0.0023$ (ANOVA)
- Survival: *nab*-sirolimus vs oral sirolimus: $P < 0.05$; vs oral everolimus $P < 0.05$ (Log-rank test)

Improved mTOR Pathway Inhibition in SNU398 Xenograft Model (pS6, pS6K and p4EBP1)

■ SNU398: human hepatocellular carcinoma, *TSC2*-null

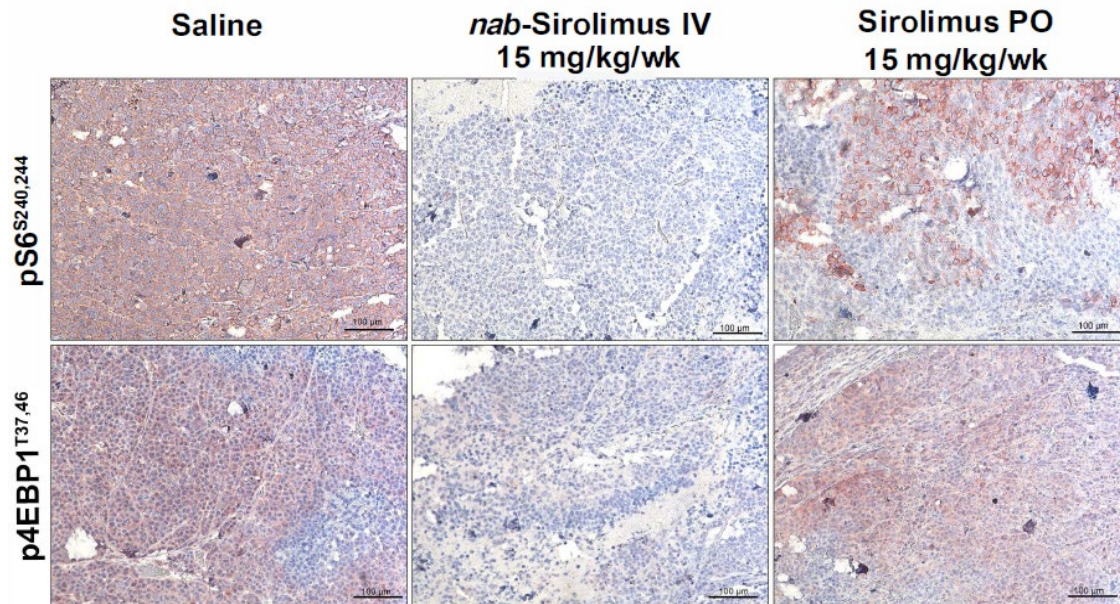
Western Blot for pS6K, pS6 and p4EBP1 (n=4-5/group)



- Antibodies against pS6K and pS6 showed consistent degree of inhibition.
- Two antibodies against different phosphorylation sites on both pS6 and p4EBP1 showed consistent degree of inhibition.

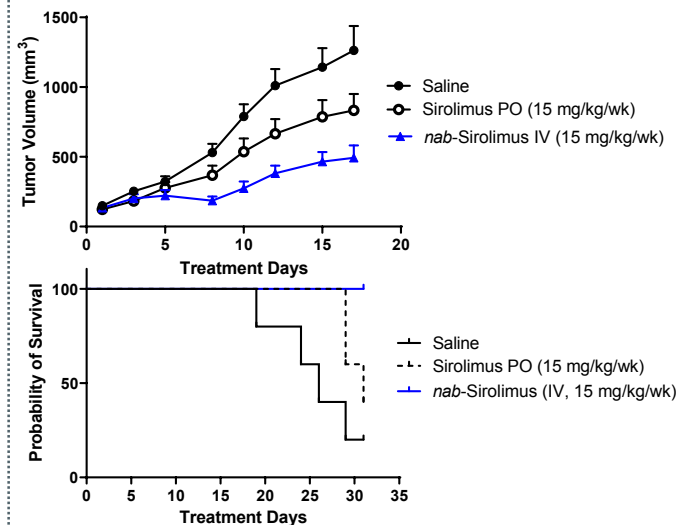
- Athymic mice bearing subcutaneous *TSC2*-null SNU398 hepatocellular carcinoma xenografts were treated with either saline or equal weekly doses (15 mg/kg) of *nab*-sirolimus (IV, 7.5 mg/kg, 2x/wk), and sirolimus (PO, 3 mg/kg/day, 5 days/wk).
- Tumors were harvested following the last dose (72 hr for *nab*-sirolimus, 24 hr for oral sirolimus) and analyzed for pS6K, pS6, and p4EBP1 via western blot (WB).
- IV *nab*-sirolimus (ABI-009) consistently inhibited mTOR targets pS6K, pS6, and p4EBP1, whereas oral sirolimus only partially decreased pS6K and pS6 and did not appear to reduce p4EBP1 levels.

Improved mTOR Pathway Inhibition (pS6, p4EBP1) and Efficacy in SNU398 Xenograft Model



- Tumors were harvested following the last dose (72 hr for *nab*-sirolimus, 24 hr for oral sirolimus) and stained for pS6 and p4EBP1 by IHC.
- Consistent with WB results, IHC appeared to show that IV *nab*-sirolimus inhibited mTOR targets pS6 and p4EBP1, whereas oral sirolimus only partially decreased pS6K and pS6 and did not appear to reduce p4EBP1 levels.

Tumor size and Survival (n=5/group)



- Tumor volume: *nab*-sirolimus vs oral sirolimus: TGI 67.8% vs 36.2%, $P < 0.05$ (ANOVA)
- Survival: *nab*-sirolimus vs oral sirolimus: $P < 0.05$ (Log-rank test)

Conclusions

- The relatively low tumor concentrations achieved with oral mTORi may limit their effectiveness as anticancer therapies.
- Albumin-bound *nab*-sirolimus at equal dose showed significantly higher tumor accumulation than sirolimus or everolimus.
- Correspondingly, there was increased inhibition of mTOR target pS6 in a *PTEN*-null bladder cancer and pS6K, pS6, and p4EBP1 in a *TSC2*-null hepatocellular carcinoma xenograft confirmed by both Western Blot and Immunohistochemistry.
- This was accompanied by significantly greater antitumor activity and prolonged animal survival in both tumor models, suggesting that *nab*-sirolimus may have a more optimal pharmacologic profile than the oral mTORi.
- In a registrational phase 2 trial (AMPECT) with malignant PEComa, *nab*-sirolimus had a response rate of 64% (9/14) in patients with *TSC1* or *TSC2* mutations.
- In an expanded access program (NCT03817515), of 8 patients with *TSC1* or *TSC2* mutations (2 had prior mTORi) treated with *nab*-sirolimus, 5 had partial responses (all mTORi naïve).
- Further clinical studies with *nab*-sirolimus in cancers harboring mTOR pathway gene alterations are planned.