Synergistic Antitumor Activity of *nab*-Sirolimus in Combination With *KRAS* Inhibitors Sotorasib and Adagrasib in *KRAS G12C* Non-Small Cell Lung Cancer and Bladder Cancer Xenografts

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INTRODUCTION

- *KRAS* is frequently mutated in non-small cell lung cancer (NSCLC) and other tumor types, with *KRAS G12C* mutation representing ~12% of patients with NSCLC[1]
- The mTOR pathway is often activated in patients with *KRAS* mutation and contributes to adaptive resistance to *KRAS* inhibitors (KRASis)[2]; a combination of mTOR and KRASis may mitigate resistance
- *nab*-Sirolimus is a novel albumin-bound nanoparticle form of the mTOR inhibitor sirolimus approved in the United States for the treatment of locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumors.[3] *nab*-Sirolimus is being investigated for the treatment of patients with advanced solid tumors harboring *TSC1* or *TSC2* inactivating alterations (PRECISION I, ClinicalTrials.gov: NCT05103358)
- Previous nonclinical studies have shown superior antitumor activity of *nab*-sirolimus vs everolimus as single agents in *PTEN*-null bladder cancer and *TSC2*-deficient hepatocellular carcinoma models[4]
- Adagrasib and sotorasib are inhibitors of the *RAS* GTPase family and are approved for the treatment of *KRAS G12C*-mutated locally advanced or metastatic NSCLC
- This study investigated the antitumor activity of *nab*-sirolimus or everolimus in combination with sotorasib and adagrasib in *KRAS G12C*-mutated cancer xenografts

METHODS

- Athymic mice bearing subcutaneous xenografts of *KRAS G12C*- and *STK11*-mutated NSCLC adenocarcinoma (NCI-H2030 and NCI-H2122) and *KRAS G12C*-mutated and *PTEN*-null UMUC3 bladder cancer (**Table 1**) were treated with saline, the mTOR inhibitors *nab*-sirolimus or everolimus (in NCI-H2030), and the KRASis sotorasib or adagrasib (in NCI-H2030, NCI-H2122, and UMUC3; **Table 2**)
- Tumors were harvested for analysis of downstream markers for *KRAS* and mTOR inhibition
- The waterfall plots depicting tumor volume change (**Figures 1B**, **2B**, and **3B**) represent the final tumor volume change at the end of the study (Day 42 or day of animal sacrifice) relative to the starting tumor volume
- Tumor samples were harvested for analysis of tumor drug levels by liquid chromatography-mass spectrometry

Table 1. Mutation Profiles

Tumor Type	Histological Type	Mutation Profile
NCI-H2030	Adenocarcinoma (NSCLC)	*KRAS G12C*, *STK11 E317**, *TP53 G262V*
NCI-H2122	Adenocarcinoma (NSCLC)	*KRAS G12C*, *STK11* null, *TP53 C176F*
UMUC3	Transitional cell carcinoma (bladder cancer)	*KRAS G12C*, *PTEN* null, *TP53 F113C*, *ATM Q2800fs*, *CDKN2A* null, *UGT2B17* null

NSCLC, non-small cell lung cancer.

Table 2. Treatment Regimens

Material	Dose/Frequency[a]	Weekly Dose (mg/kg)	% of Equivalent Human Weekly Dosing	Route
Saline	10 mL/kg, twice weekly	0	NA	IV
nab-Sirolimus	7.5 mg/kg, twice weekly	15	45	IV
Everolimus	3 mg/kg, 5 days/week	15	115	PO
Sotorasib[b]	30 mg/kg, 5 days/week	150	11	PO
Adagrasib[b]	30 mg/kg, 5 days/week	150	9	PO

[a]Doses have been used in previous nonclinical studies. Dosing was once per day for 6 weeks; dosing regimen for each drug was consistent across models. [b]From Martin et al.[5] IV, intravenous; NA, not available; *nab*, nanoparticle albumin-bound; PO, orally.

RESULTS

NCI-H2030 NSCLC (Adenocarcinoma)

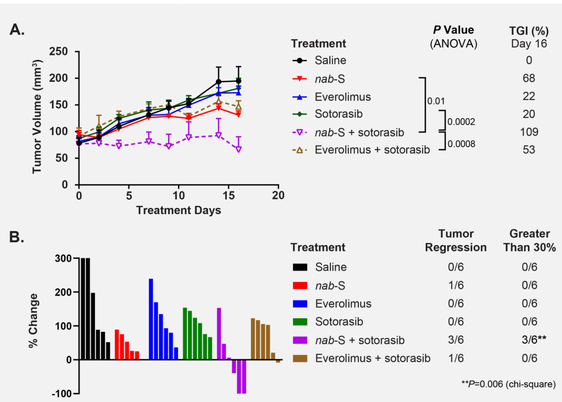
Tumor Growth (Figure 1A)

- Statistical significance was observed with *nab*-sirolimus + sotorasib vs single-agent *nab*-sirolimus (*P*=0.01) or sotorasib (*P*=0.0002), and the combination of everolimus + sotorasib (*P*=0.0008)
- Combining *nab*-sirolimus with either KRASi (sotorasib or adagrasib) showed significantly greater tumor growth suppression compared with single-agent *nab*-sirolimus, sotorasib, or adagrasib

Tumor Regression (Figure 1B)

- *nab*-Sirolimus + sotorasib achieved a significantly higher rate of tumor regression over 30% compared with all other groups (*P*=0.006)
- The combination of everolimus with sotorasib failed to improve meaningful tumor regression rates over single agents

Figure 1. NSCLC (Adenocarcinoma) NCI-H2030: (A) Tumor Volume and (B) Tumor Volume Change



ANOVA, analysis of variance; nab, nanoparticle albumin-bound; nab-S, nab-sirolimus; NSCLC, non-small cell lung cancer; TGI, tumor growth inhibition.

NCI-H2122 NSCLC (Adenocarcinoma)

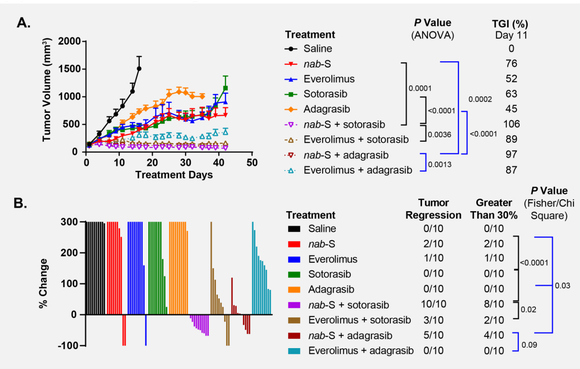
Tumor Growth (Figure 2A)

- Statistical significance was observed with *nab*-sirolimus + sotorasib vs single-agent *nab*-sirolimus (*P*=0.0001) or sotorasib (*P*<0.0001), and the combination of everolimus + sotorasib (*P*=0.0036). Statistical significance was also observed between *nab*-sirolimus + adagrasib vs single-agent *nab*-sirolimus (*P*=0.0002), single-agent adagrasib (*P*<0.0001), and everolimus + adagrasib (*P*=0.0013)
- *nab*-Sirolimus in combination with either KRASi (sotorasib or adagrasib) showed significantly greater tumor growth suppression compared with single-agent *nab*-sirolimus, sotorasib, or adagrasib, and the combination of everolimus with sotorasib or adagrasib
- No significant difference in tumor growth suppression was observed between combinations of *nab*-sirolimus with either sotorasib or adagrasib

Tumor Regression (Figure 2B)

- A statistically significantly higher rate of tumor regression ≥30% was observed with *nab*-sirolimus + sotorasib or adagrasib vs single-agent sotorasib or adagrasib (*P*<0.0001 and *P*=0.03, respectively) and for *nab*-sirolimus + sotorasib vs everolimus + sotorasib (*P*=0.02)
  - A similar trend was observed for *nab*-sirolimus + adagrasib vs everolimus + adagrasib, but it was not statistically significant (*P*=0.09)
  - The combination of everolimus + sotorasib failed to improve meaningful tumor regression rates over single-agent treatment with either agent

Figure 2. NSCLC (Adenocarcinoma) NCI-H2122: (A) Tumor Volume and (B) Tumor Volume Change



ANOVA, analysis of variance; *nab*, nanoparticle albumin-bound; *nab*-S, *nab*-sirolimus; NSCLC, non-small cell lung cancer; TGI, tumor growth inhibition.

UMUC3 Bladder Cancer (Transitional Cell)

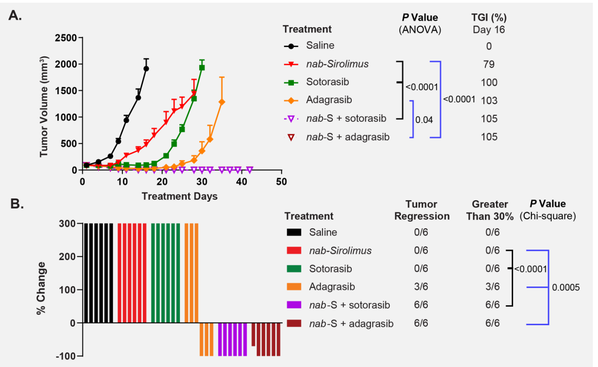
Tumor Growth (Figure 3A)

- Statistical significance was observed with *nab*-sirolimus + sotorasib vs single-agent *nab*-sirolimus (*P*<0.0001) or sotorasib (*P*<0.0001) and for *nab*-sirolimus + adagrasib vs single-agent *nab*-sirolimus (*P*<0.0001) or adagrasib (*P*=0.04)
- Combining *nab*-sirolimus with either KRASi, sotorasib or adagrasib, showed significantly greater tumor growth suppression compared with single-agent *nab*-sirolimus, sotorasib, or adagrasib
- There was no significant difference in tumor growth suppression between combinations of *nab*-sirolimus with either sotorasib or adagrasib

Tumor Regression (Figure 3B)

- A statistically significantly higher rate of tumor regression ≥30% was observed with *nab*-sirolimus + sotorasib or adagrasib vs single-agent sotorasib or adagrasib (*P*<0.0001 and *P*=0.0005, respectively)
- UMUC3 bladder cancer was more sensitive to the combinations of *nab*-sirolimus + sotorasib or *nab*-sirolimus + adagrasib and resulted in 6/6 and 5/6 complete responses, respectively

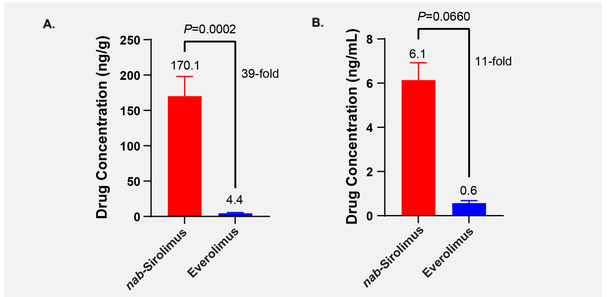
Figure 3. Bladder Cancer (Transitional Cell) UMUC3: (A) Tumor Volume and (B) Tumor Volume Change



ANOVA, analysis of variance; *nab*, nanoparticle albumin-bound; *nab*-S, *nab*-Sirolimus; TGI, tumor growth inhibition.

Pharmacokinetics

Figure 4. NSCLC (Adenocarcinoma) NCI-H2122: Comparison of *nab*-Sirolimus and Everolimus Trough (A) Tumor and (B) Blood Concentrations



Tumor samples were harvested at trough points (Days 15 and 42, 72 hours after last dose of *nab*-S and 24 hours after last dose of everolimus at the end of study). Blood samples were harvested at trough points (Days 4, 8, 11, 15, and 42, 72 hours after last dose of *nab*-S; and 24 hours after last dose of everolimus at the end of study). The end of study is defined as animal sacrifice or 6 weeks, whichever is earlier. Data presented are an average of all timepoints. *nab*, nanoparticle albumin-bound.

- Greater concentration levels were observed in tumor (*P*=0.0002) and blood (*P*=0.0660) for *nab*-sirolimus versus single-agent everolimus (**Figure 4**)

CONCLUSIONS

- *nab*-Sirolimus, when combined with either sotorasib or adagrasib, showed synergistic antitumor activity with significantly greater suppression of tumor growth and meaningful tumor regressions compared to the single agents
- As seen in previously reported study results,[6] this study confirms that consistent tumor growth inhibition and significantly higher tumor drug levels were observed with *nab*-sirolimus than with everolimus
- All treatments were tolerable with no overt signs of toxicity and produced a similar body weight change pattern when compared to the saline controls in each study[6]
- Results suggest that *nab*-sirolimus should be the preferred mTOR inhibitor for combination treatment with adagrasib or sotorasib in the clinic
- The efficacy, safety, and pharmacokinetics of adagrasib in combination with *nab*-sirolimus in patients with advanced NSCLC and other solid tumors with *KRAS G12C* mutation will be further explored in a planned dose-finding phase 1/2 clinical trial

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