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KRAS G12C-Mutated NSCLC and Bladder Cancer Xenografts Treated With Sotorasib and Adagrasib in Combination With the mTOR Inhibitor *nab*-Sirolimus Show Improved Antitumor Activity

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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[2]; a combination of mTOR and *KRAS* inhibitors may mitigate resistance
- *nab*-Sirolimus is a novel albumin-bound nanoparticle form of the mTOR inhibitor sirolimus and is approved for the treatment of locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa)[3]
- Previous nonclinical studies have shown superior antitumor activity of *nab*-sirolimus vs everolimus as single agent in *PTEN*-null bladder cancer and *TSC2*-deficient hepatocellular carcinoma models[4]
- Adagrasib (MRTX849) is an investigational small molecule inhibitor of *KRAS G12C* with registration-enabling ongoing studies in NSCLC and colorectal cancer; sotorasib is an inhibitor of the *RAS GTPase* family and is US Food and Drug Administration-approved for the treatment of *KRAS G12C*-mutated 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 (NCI-H2030 and NCI-H2122, respectively) and *KRAS G12C*-mutated and *PTEN*-null UMUC3 bladder cancer (**Table 1**) were treated with the following:
  - **Saline**
  - **mTOR inhibitors:** *nab*-sirolimus or everolimus (in NCI-H2030) at a clinically relevant and equal weekly dose of 15 mg/kg/week (45% and ~115% of the respective clinical dose)
  - ***KRAS* inhibitors:** sotorasib or adagrasib (in NCI-H2030, NCI-H2122 and UMUC3) at 30 mg/kg/day (~16% and ~13% of the respective clinical daily dose), alone or in combination (**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

Table 1. Mutation Profile

Tumor Type	Histological Type	Mutation Profile
NCI-H2030	Adenocarcinoma (NSCLC)	*KRAS G12C*, *STK11 E317**, *TP53 G262V*
NCI-H2122	Squamous cell (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

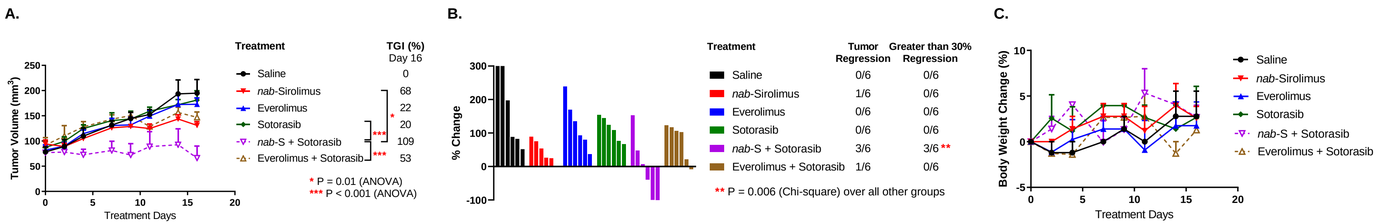
Table 2. Treatment Regimen

Material	Dose/Frequency[a]	Weekly Dose (mg/kg)	Route
Saline	10 mL/kg, twice weekly	0	IV
***nab*-Sirolimus**	7.5 mg/kg, twice weekly	15	IV
Everolimus	3 mg/kg, 5 days/week	15	PO
Sotorasib[b]	30 mg/kg, 5 days/week	150	PO
Adagrasib[b]	30 mg/kg, 5 days/week	150	PO

[a]Dosing was once per day for 6 weeks; dosing regimen for each drug was consistent across models. [b]Martin et al.[6]
IV, intravenous; PO, orally.

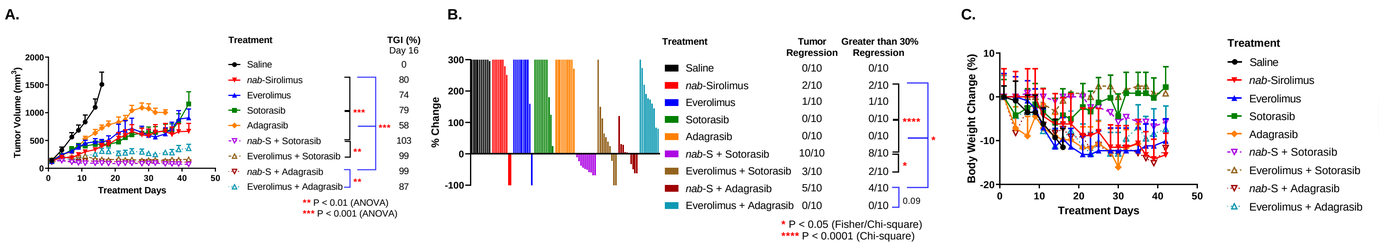
RESULTS

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



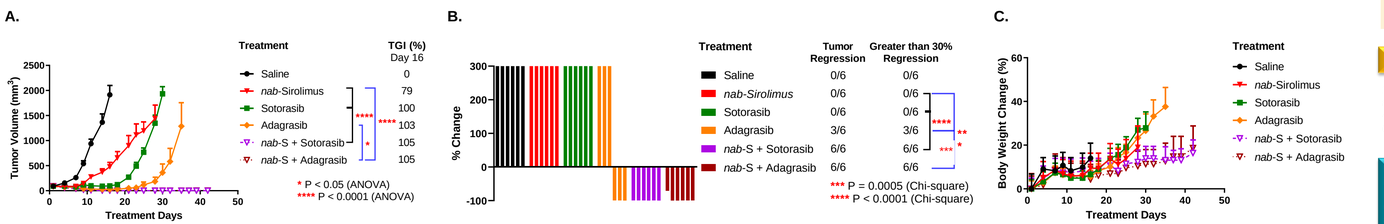
- When comparing tumor growth curves, statistical significance was observed with *nab*-sirolimus + sotorasib vs single-agents *nab*-sirolimus (*P*=0.01) or sotorasib (*P*=0.0002), and the combination of everolimus + sotorasib (*P*=0.0008; **Figure 1A**), which correlates with a significantly higher rate of tumor regression over 30% compared with all other groups (*P*=0.006; **Figure 1B**)

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



- When comparing tumor growth curves, statistical significance was observed with *nab*-sirolimus + sotorasib vs single-agents *nab*-sirolimus (*P*=0.0001) or sotorasib (*P*<0.0001), and the combination of everolimus + sotorasib (*P*=0.0036); *nab*-sirolimus + adagrasib vs single-agents *nab*-sirolimus (*P*=0.0002) or adagrasib (*P*<0.0001), and combination everolimus + adagrasib (*P*=0.0013; **Figure 2A**)
- A significantly higher rate of tumor regression greater than 30% was observed with *nab*-sirolimus + sotorasib or adagrasib vs single agents (*P*<0.0001 and *P*= 0.03, respectively); *nab*-sirolimus + sotorasib vs everolimus + sotorasib (*P*=0.02) with a trend for *nab*-sirolimus + adagrasib vs everolimus + adagrasib (*P*=0.09; **Figure 2B**)

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



- When comparing tumor growth curves, statistical significance was observed with *nab*-sirolimus + sotorasib vs single-agents *nab*-sirolimus (*P*<0.0001) or sotorasib (*P*<0.0001); *nab*-sirolimus + adagrasib vs single-agents *nab*-sirolimus (*P*<0.0001) or adagrasib (*P*=0.04; **Figure 3A**)
- A significantly higher rate of tumor regression greater than 30% was observed with *nab*-sirolimus + sotorasib or adagrasib vs single agents (*P*<0.0001 and *P*=0.0005, respectively; **Figure 3B**)

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

RESULTS

- Combining *nab*-sirolimus with either *KRAS* inhibitor, sotorasib or adagrasib, showed significantly greater tumor growth suppression compared with single-agent *nab*-sirolimus (**Figures 1A**, **2A**, and **3A**), sotorasib (**Figures 1A**, **2A**, and **3A**), or adagrasib (**Figures 2A** and **3A**), and the combination of everolimus with sotorasib (**Figures 1A** and **2A**) or adagrasib (**Figure 2A**)
- There was no significant difference in tumor growth suppression between combinations of *nab*-sirolimus with either sotorasib or adagrasib (*P* = not significant; **Figures 2A** and **3A**)
- In contrast, combining everolimus with sotorasib (**Figures 1B** and **2B**) failed to improve meaningful tumor regression rates over single agents
- UMUC3 bladder cancer was more sensitive to the combination of *nab*-sirolimus with sotorasib or adagrasib and resulted in 6/6 and 5/6 complete responses, respectively (**Figure 3B**)
- 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 (**Figures 1C**, **2C**, and **3C**)
- Meaningful tumor regressions >30% occurred more frequently with *nab*-sirolimus and *KRAS* inhibitor combinations vs monotherapy (**Figures 1B**, **2B**, and **3B**)

CONCLUSION

- *nab*-Sirolimus in combination with either sotorasib or adagrasib showed supra-additive antitumor activity with significantly greater suppression of tumor growth and meaningful tumor regressions compared to the single agents
- In contrast, everolimus in combination with *KRAS* inhibitors slowed tumor growth but did not increase meaningful tumor regression rate in the NSCLC NCI-H2030 model
- Results suggest that *nab*-sirolimus is the preferred mTOR inhibitor for combination treatment with adagrasib or sotorasib in the clinic
- Further studies examining pathway inhibition of the combination are ongoing

REFERENCES

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