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 and G12D being most prevalent.

• The RAS pathway is often activated in patients with KRAS mutation and contributes to adaptive resistance in KRAS inhibitors (KRASi).

• A combination of mTOR and KRASi 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 transitional cell carcinoma of the bladder (Uro社会稳定安定) and hepatocellular carcinoma (Liver Cancer).

• Previous nonclinical studies have shown superior antitumor activity of nab-sirolimus vs everolimus as single agents in PTEN-null bladder cancer and T24-deficient hepatocellular carcinoma models.

METHODS

• Athymic mice bearing subcutaneous xenografts of KRAS G12C and STK11-mutated NSCLC and adenocarcinoma xenograft models (NCI-H2030 and NCI-H2122), and KRAS G12C-mutated and Pten-null UMUC3 bladder cancer (Table 1) were treated with nab-sirolimus (mTOR inhibitor), sirolimus (mTOR inhibitor for single-agent treatment), and/or nab-sirolimus combination treatment with either KRASi (sotorasib or adagrasib).

• Tumors were harvested for analysis of downstream markers for KRAS and mTOR inhibition.

• The waterfall plots depicting tumor volume change (Figure 1A, 1B, and 2A) were presented as an average of all timepoints.

RESULTS

NAB-H2030 NSCLC (Adenocarcinoma)

Tumor Growth (Figure 1A)

• Statistical significance was observed with nab-sirolimus + sotorasib vs single-agent nab-sirolimus (P=0.0003) and the combination of everolimus + sotorasib (P=0.0004) and everolimus + adagrasib (P=0.0003).

• 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 single-agent treatments (P=0.013).

• 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

NAB-H2122 Adenocarcinoma (Colon Cancer)

Tumor Growth (Figure 1A)

• Statistical significance was observed with nab-sirolimus + sotorasib vs single-agent nab-sirolimus (P=0.012) or sotorasib (P=0.006) and for nab-sirolimus + adagrasib vs single-agent nab-sirolimus (P=0.003) 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.

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

UMUC3 Bladder Cancer (Transitional Cell)

Tumor Growth (Figure 2A)

• Statistical significance was observed with nab-sirolimus + sotorasib vs single-agent nab-sirolimus (P=0.006), or sirolimus, or adagrasib (P=0.0055, respectively).

• Combination of everolimus with nab-sirolimus vs sirolimus or nab-sirolimus + adagrasib and resulted in n=6 and 5-complete responses, respectively.

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

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, 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.

• 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 I/2 clinical trial.

REFERENCES


Pharmacokinetics

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

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Presented at the American Cancer Society Research Annual Meeting, April 14-19, 2023, Orlando, FL