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Activity of nab-Sirolimus Alone or in Combination with Cabozantinib, Octreotide, or Talazoparib in Nonclinical Neuroendocrine Tumor Models

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BACKGROUND

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is strongly implicated in the pathogenesis and progression of neuroendocrine tumors (NETs). *nab*-Sirolimus, an injectable form of albumin-bound sirolimus, demonstrates greater tumor drug accumulation, mTOR target inhibition, and antitumor activity in human tumor models compared to conventional mTOR inhibitors including everolimus. This study utilized NET cell lines for *in vitro* and *in vivo* evaluation of the anti-proliferative and antitumor activity of *nab*-sirolimus as a single agent or in combination with targeted agents with known activity in NETs.

METHODS

In vitro cell viability assays evaluated the anti-proliferative effect of *nab*-sirolimus (20 or 80 nM) alone or in combination with clinically relevant concentrations (0.037 to 80 µM) of talazoparib, octreotide, or cabozantinib in 3 different NET cell lines: BON-1 (human pancreatic), NCI-H209 (human small cell lung carcinoma), and STC-1 (murine gastrointestinal). BON-1 was subsequently selected for *in vivo* evaluation. Athymic nude mice (N=8 per group) bearing subcutaneous (SC) BON-1 xenografts were treated with either saline, or clinically equivalent relevant doses of nab-sirolimus, cabozantinib, octreotide, or talazoparib alone or in combination for 6 weeks to assess antitumor activity (**Table**).

RESULTS

In vitro, *nab*-sirolimus showed anti-proliferative effects as a single agent across all 3 NET cell lines and additive effects were observed in combination with talazoparib and cabozantinib. In BON-1 xenografts, *nab*-sirolimus demonstrated greater antitumor activity compared to other single agent treatments, and significant additive effects were observed when *nab*-sirolimus was combined with cabozantinib, octreotide, or talazoparib (**Table**).

Table. Antitumor Activity of *nab*-Sirolimus Alone or in Combination in BON-1 Xenografts

Treatment	TGI[a] (P-value)[b]
***nab*-Sirolimus** 5mg/kg, IV weekly	77%
Cabozantinib-5 5 mg/kg, PO daily	44% (0.0019)
Cabozantinib-15 15 mg/kg, PO daily	66% (0.2646)
Octreotide 0.1 mg/kg, SC daily	12% (0.0012)
Talazoparib 0.33 mg/kg, PO daily	35% (0.0371)
***nab*-Sirolimus+Cabozantinib-5**	86% (0.0002)
***nab*-Sirolimus+Cabozantinib-15**	89% (0.0290)
***nab*-Sirolimus+Octreotide**	81% (0.0006)
***nab*-Sirolimus+Talazoparib**	90% (0.0075)

IV=intravenous; **PO**=oral; **TGI**=tumor growth inhibition.

[a]TGI is percent versus saline on Day 33.

[b]*P*-value (ANOVA) for single agents=comparison with nab-sirolimus;
P-value for combinations=comparison with non-nab-sirolimus component.

CONCLUSIONS

Single agent *nab*-sirolimus showed significant *in vitro* and *in vivo* activity in NET lines. Combinations of *nab*-sirolimus with other targeted agents demonstrated additive anti-proliferative and antitumor activity; however, the magnitude of response for select combinations compared with single agent activity warrants further investigation.

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