Phase 2 Study of *nab*-Sirolimus in Patients with Well-differentiated and Advanced or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, or Pancreas

T-4

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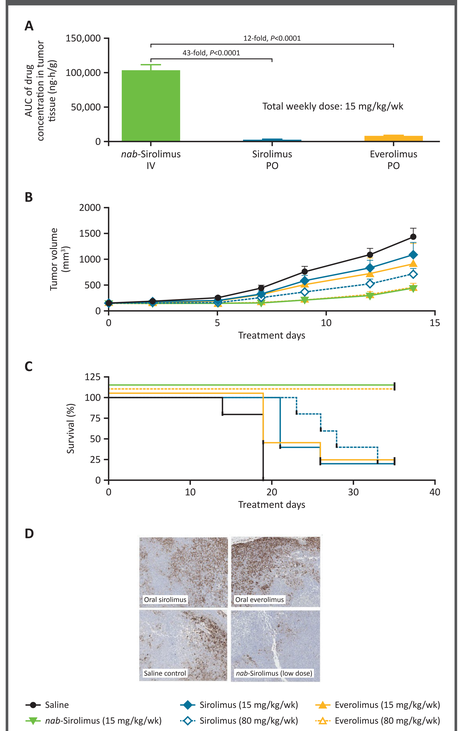
BACKGROUND

- Neuroendocrine tumors (NETs; ~2% of all malignancies) are a group of rare, heterogeneous cancers that originate in neuroendocrine cells; while they can affect almost any part of the body, they most commonly arise in the gastrointestinal (GI) tract, pancreas, and lung[1]
- Because of their heterogeneity and non-specific symptoms, NETs are often diagnosed late and many (up to 75%) present with metastases at diagnosis[2]
- In recent years, the PI3K/AKT/mTOR pathway has been implicated in the pathogenesis and progression of NETs.[2] The oral mTOR inhibitor (mTORi) everolimus is currently approved in the United States for the treatment of advanced NETs of the GI tract, lung, and pancreas;[3] this approval was based on results of the phase 3 studies RADIANT-3 (NETs of pancreatic origin)[4,5] and RADIANT-4 (NETs of lung or GI origin)[6]
  - In RADIANT-3, everolimus led to a significant decrease in risk of disease progression (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.27–0.45 [*P*<0.001]; median progression-free survival [PFS] 11.0 vs 4.6 months) compared with placebo.[4] However, response rates to everolimus and placebo were both minimal (5% and 2%, respectively). There was no significant difference in overall survival (OS) between groups; however, OS was confounded by crossover permitted after placebo failure[5]
  - In RADIANT-4, everolimus led to a significant decrease in risk of disease progression (HR 0.48, 95% CI 0.35–0.67 [*P*<0.00001]; median PFS 11.0 vs 3.9 months) compared with placebo.[6] Response rates were nearly absent at 2% and 1% for everolimus and placebo, respectively. There was no significant difference in OS between groups,[3,6] though crossover after placebo failure was not permitted
- The utility of oral mTORis may be restricted by low bioavailability and dose-limiting toxicities.[7,8] Given the poor response rates with everolimus, an improved mTORi may provide additional benefit for patients with NET
- To improve the utility of oral mTORis, *nab*-sirolimus, a nanoparticle albumin-bound mTORi designed to preferentially target tumors, was developed[9]
  - *nab*-Sirolimus is currently approved in the United States for the treatment of malignant perivascular epithelioid cell neoplasms based on data from the AMPECT trial (overall response rate 39%, median PFS 10.6 months, median OS 40.8 months)[9,10]
- In preclinical animal models, *nab*-sirolimus demonstrated higher intratumoral drug accumulation, improved target suppression, greater tumor inhibition, and prolonged survival, compared with equal weekly doses of sirolimus or everolimus (**Figure 1**).[11] These results warrant further exploration of *nab*-sirolimus for the treatment of NETs

Figure 1. (A) Intratumoral drug concentration, (B) tumor growth inhibition, (C) survival, and (D) mTOR activity in preclinical animal models



AUC, area under the concentration-time curve; **IV**, intravenous; **mTOR**, mammalian target of rapamycin; **PO**, oral administration; **wk**, week.

STUDY DESIGN

- NET-202 (NCT05997056) is a phase 2, multicenter, open-label, single-arm study to evaluate the efficacy and safety of intravenous *nab*-sirolimus in patients with well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas (**Figure 2**)

Figure 2. NET-202 study design

Key eligibility criteria

- Functional[a] or non-functional, well-differentiated, locally advanced or metastatic NET of the GI tract, lung, or pancreas
- ≥18 years of age
- mTORi naive
- ≥1 measurable target lesion by RECIST v1.1
- Received ≤2 prior lines of therapy, excluding SSA therapy
- ECOG PS 0 or 1
- Adequate liver/renal function and hematologic parameters

Treatment

Simon's 2-stage study design

- **Stage 1:** 12 patients
- **Stage 1:** 9 additional patients will be enrolled if 1 or more responses are achieved in stage 1 of the study

***nab*-Sirolimus dosing schedule**

21-day Cycle: Day 1, Day 8, Day 15 → Repeat until disease progression, unacceptable toxicity, withdrawal of consent, or at investgator discretion

- *nab*-Sirolimus 100 mg/m² administered as an intravenous infusion over 30 minutes on days 1 and 8 of each 21-day cycle (+SSA therapy for functional tumors)

Follow-up[b]

CT/MRI every 6 weeks for 12 weeks and every 12 weeks thereafter

Patient enrolment at ~3 sites in the United States
NCT05997056

[a]Patients with functional NETs may enroll if they have been on a stable dose of an SSA for ≥12 weeks and experienced disease progression while on a stable SSA dose.

[b]Follow-up is for survival and initiation of new therapy, including surgery or anticancer therapy. Follow-up is initiated after the end-of-treatment visit.

CT, computed tomography; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **GI**, gastrointestinal; **MRI**, magnetic resonance imaging; **mTORi**, mammalian target of rapamycin inhibitor; **NET**, neuroendocrine tumor; **NGS**, next-generation sequencing; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SSA**, somatostatin analog.

- Enrolled patients will receive *nab*-sirolimus 100 mg/m² by intravenous infusion on days 1 and 8 of every 21-day cycle, until disease progression or unacceptable toxicity
  - For the management of adverse events (AEs), sequential dose reductions to 75, 56, and 45 mg/m² will be permitted
- Study endpoints are shown in **Figure 3**

Figure 3. Study endpoints

1 PRIMARY
- Investigator-assessed ORR per RECIST v1.1 criteria[a]

2 SECONDARY
- DOR, DCR, time to response, PFS, OS,[b] and safety[c]

EXPLORATORY
- Correlation of baseline molecular markers and chromogranin A levels with clinical outcomes[d]

[a]Defined as the proportion of patients with best overall response of a confirmed PR or CR.

[b]DOR defined as the time from first PR/CR to disease progression or death; DCR defined as the proportion of patients with confirmed PR/CR or stable disease for ≥12 weeks; time to response defined as the time from the first dose of study medication to confirmed PR/CR; PFS defined as the number of months from treatment initiation to disease progression or death; OS defined as the number of months from treatment initiation to death.

[c]AEs graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

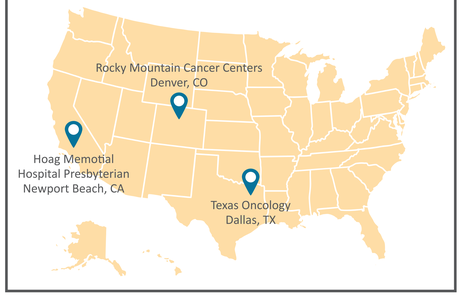
[d]NGS mutational analysis of baseline tumor tissue (archival or fresh biopsy, if available) and blood (peripheral blood mononuclear cells) to understand the concomitant alterations and allele frequency at baseline, and evaluate the association between mutational profile and clinical outcomes. Expression of pS6 and other relevant markers conducted via immunohistochemistry.

AE, adverse event; **CR**, complete response; **DCR**, disease control rate; **DOR**, duration of response; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors.

SUMMARY

- The PI3K/AKT/mTOR pathway has been implicated in the pathogenesis and progression of NETs,[2] though the use of oral mTORis as a treatment for NETs is limited by low bioavailability and the heterogeneity of the disease[2,7]
- *nab*-Sirolimus is a nanoparticle albumin-bound mTORi designed to preferentially target tumors and overcome the limitations of oral sirolimus. *nab*-Sirolimus is currently approved in the United States for the treatment of malignant perivascular epithelioid cell neoplasms[9]
- The efficacy and safety of *nab*-sirolimus in patients with advanced or metastatic NETs will be evaluated in this phase 2, multicenter, open-label, single-arm, US-based study
- The study will enroll up to 21 efficacy evaluable patients at approximately three US centers (**Figure 4**). Enrollment for the study is planned to begin in the third quarter of 2023, with completion expected within 12–18 months

Figure 4. Current NET-202 study sites



FOR MORE INFORMATION

- ClinicalTrials.gov: https://classic.clinicaltrials.gov/ct2/show/NCT05997056
- Correspondence to: MedInfo@AadiBio.co

Acknowledgments & Disclosures

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