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nab-Sirolimus Plus Letrozole in Advanced or Recurrent Endometrioid Endometrial Cancer: A Phase 2, Open-Label, Single-Arm, Prospective, Multicenter Study

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Objective

- This trial is designed to evaluate the safety and efficacy of *nab*-sirolimus in combination with letrozole for the treatment of patients with advanced or recurrent endometrioid endometrial carcinoma who have received 0–1 prior lines of chemotherapy in the recurrent/advanced setting

KEY POINTS

- Dysregulation of the mTOR pathway has been demonstrated in most endometrial carcinomas and crosstalk between the mTOR pathway and the ER signaling pathway has been implicated in resistance to endocrine therapy
- Consistent with this, the combination of mTOR inhibitors and endocrine therapy has shown clinical activity in patients with advanced or recurrent endometrial carcinoma
- *nab*-Sirolimus is an mTOR inhibitor that demonstrated improved tumor accumulation, better mTOR suppression, and enhanced antitumor activity compared with oral mTOR inhibitors in animal models
- This phase 2, open-label, single-arm, multicenter study (NCT05997017) is evaluating *nab*-sirolimus in combination with letrozole for the treatment of patients with advanced or recurrent EEC, and is currently open for enrollment

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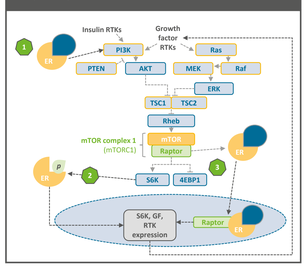
INTRODUCTION

- Despite recent data demonstrating improved outcomes with immunotherapy plus chemotherapy, regardless of mismatch repair status,[1] alternative treatment options for patients with advanced or recurrent endometrial carcinoma (EC) remain necessary
- Dysregulation of mTOR signaling is implicated in the pathology of EC, particularly in endometrioid EC (EEC) in which >80% harbor PTEN or PI3K/AKT/mTOR pathway alterations[2]
  - PTEN normally acts to reverse the activity of PI3K, and therefore inhibits activation of the pathway. Low PTEN expression can lead to overactivation of the PI3K/AKT/mTOR pathway[3]
- Moreover, crosstalk between the PI3K/AKT/mTOR pathway and estrogen signaling occurs at several points in the pathway[3,4] (**Figure 1**), including:
  - Direct activation of the PI3K/AKT/mTOR pathway via activated ERs
  - Direct activation of ERs via the downstream signaling molecule S6K
  - ER induced expression of S6K in a feed-forward activation loop[4]
- Potentiation of ER signaling can lead to the development of resistance to endocrine therapy;[4] thus, combining therapies is an attractive strategy to overcome potential resistance
- GOG-3007[5] and other phase 2 studies[6,7] have demonstrated that the combination of oral mTOR inhibitors and endocrine therapy provides clinical benefit in patients with recurrent EC. This benefit was particularly pronounced in chemotherapy-naïve patients[5]
  - In the GOG-3007 study of everolimus plus letrozole, the median PFS was 28 months in chemotherapy-naïve patients versus 4 months for patients with prior chemotherapy[5]
  - All patients who benefited from the combined therapy had tumors with endometrioid histology[5]

Figure 1. Crosstalk between ERs and the PI3K/AKT/mTOR pathway.
(1) Activated ERs directly bind PI3K leading to its phosphorylation and subsequent activation of the pathway. **(2)** S6K phosphorylates and activates ERs, leading to expression of receptor ligands, S6K, receptor tyrosine kinases and signaling adaptors, which result in upstream activation of the pathway. **(3)** Estrogen bound ERs recruit Raptor to the nucleus and promote expression of growth factors, which in turn activate the pathway.



- *nab*-Sirolimus is a nanoparticle albumin-bound, IV administered mTOR inhibitor approved in the United States for adults with advanced malignant perivascular epithelioid cell tumor (PEComa)[8]
- Nonclinical data with *nab*-sirolimus demonstrated improved tumor accumulation, mTOR inhibition, and tumor growth suppression compared with oral mTOR inhibitors[9]
- We hypothesize that *nab*-sirolimus in combination with letrozole may produce synergistic antitumor activity in patients with EEC

STUDY DESIGN

- This is a phase 2, open-label, single-arm, multicenter study, evaluating *nab*-sirolimus in adult patients (≥18 years) with advanced or recurrent EEC (**Figure 2**)

Figure 2. Study design

Key eligibility criteria

N = up to 29 patients

- Adult patients with metastatic or locally advanced EEC where surgical resection is not an option
- mTOR inhibitor-naïve
- ECOG PS 0 or 1
- ≥1 measurable target lesion at baseline by RECIST v1.1
- Other prior therapy allowed:
  - **Adjuvant setting** – chemotherapy, hormonal therapy, checkpoint inhibitors, and/or other therapy, as long as the adjuvant therapy was completed ≥6 months prior to enrollment
  - **Recurrent/advanced/metastatic setting** – treatment with 0–1 prior chemotherapy regimens; chemotherapy must have been completed ≥3 months prior to enrollment
  - Nonchemotherapy-based treatment as long as therapy ended ≥4 weeks prior to enrollment

Treatment phase

- *nab*-Sirolimus 100 mg/m^2 administered as an intravenous infusion over 30 minutes on days 1 and 8 of each 21-day cycle
  - Starting dose of 100 mg/m^2 may be reduced to 75 mg/m^2, if 3/6 or 4/10 patients have a dose reduction within the first 4 months
  - Maximum of 3 sequential dose reductions to 75 mg/m^2, 56 mg/m^2, and 45 mg/m^2 are permitted for management of AEs
- Letrozole 2.5 mg administered orally, daily

Follow-up

- CT/MRI every 6 weeks for the first year and every 12 weeks thereafter, until disease progression
- Safety is continuously monitored; AEs are collected throughout treatment
- Quarterly follow-up until study closure, death, or consent withdrawal

***nab*-Sirolimus dosing schedule**

21-day cycle: Day 1, Day 8, Day 15

Letrozole day 1 through day 21

Repeat until disease progression, unacceptable toxicity, withdrawal of consent, or at investigator discretion

Decisions related to treatment (e.g., discontinuation, change of treatment, dose reduction) will be at the discretion of the investigator

NCT05997017

AEs, adverse events; **CT**, computerized tomography; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EEC**, endometrioid endometrial carcinoma; **MRI**, magnetic resonance imaging; **RECIST**, Response Evaluation Criteria in Solid Tumors.

- Patients with advanced or recurrent EEC who are chemotherapy-naïve or who have received one line of chemotherapy in the recurrent, advanced, or metastatic setting are eligible
  - Patients who received prior therapy in the recurrent, advanced, or metastatic setting must have attained at least a partial response
- Prior adjuvant therapy is permitted as long as it was completed at least 6 months prior to enrollment
- Nonchemotherapy-based treatment is permitted at any point as long as therapy ended at least 4 weeks prior to enrollment
- Using a Simon's optimal 2-stage design, the study will enroll 10 patients in stage 1. If one patient achieves a response, stage 2 will enroll 19 patients

Study Endpoints

- The primary objective of the study is to determine the proportion of patients with a best overall response rate of a confirmed complete or partial response to *nab*-sirolimus in combination with letrozole in patients with advanced or recurrent EEC (**Figure 3**)

Figure 3. Study endpoints

1 PRIMARY
- Investigator-assessed best overall response rate per RECIST v1.1[a]

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

EXPLORATORY
- Baseline molecular biomarkers and genomics; association between molecular/genomic profile and clinical outcome using NGS and IHC

[a]Defined as the proportion of patients who achieved a confirmed PR or CR from the time of study treatment initiation until end of study treatment. [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 due to any cause; OS defined as the number of months from treatment initiation to death. [c]AEs defined per the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.
AE, adverse event; **CR**, complete response; **DCR**, disease control rate; **DOR**, duration of response; **IHC**, immunohistochemistry; **NGS**, next-generation sequencing; **OS**, overall survival; **PFS**, progression-free survival; **PR**, partial response; **RECIST**, Response Evaluation Criteria for Solid Tumors.

Trial enrollment information

- Trial registration: NCT05997017
- Study start date: December 2023
- Current status: Open for enrollment in the United States
- Current study locations: Mount Sinai Comprehensive Cancer Center, Miami Beach, Florida; Women's Cancer Center of Nevada, Las Vegas, Nevada; Oklahoma University Stephenson Cancer Center, Oklahoma City, Oklahoma; Women & Infants Hospital, Providence, Rhode Island; Texas Oncology – Tyler, Tyler, Texas; Swedish Cancer Institute, Seattle, Washington

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For disclosures of co-authors please see abstract.

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