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# A phase 2, open-label, single-arm, prospective, multicenter study of *nab*-sirolimus plus letrozole in advanced or recurrent endometrioid endometrial cancer

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## Objective

- 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 advanced/metastatic setting

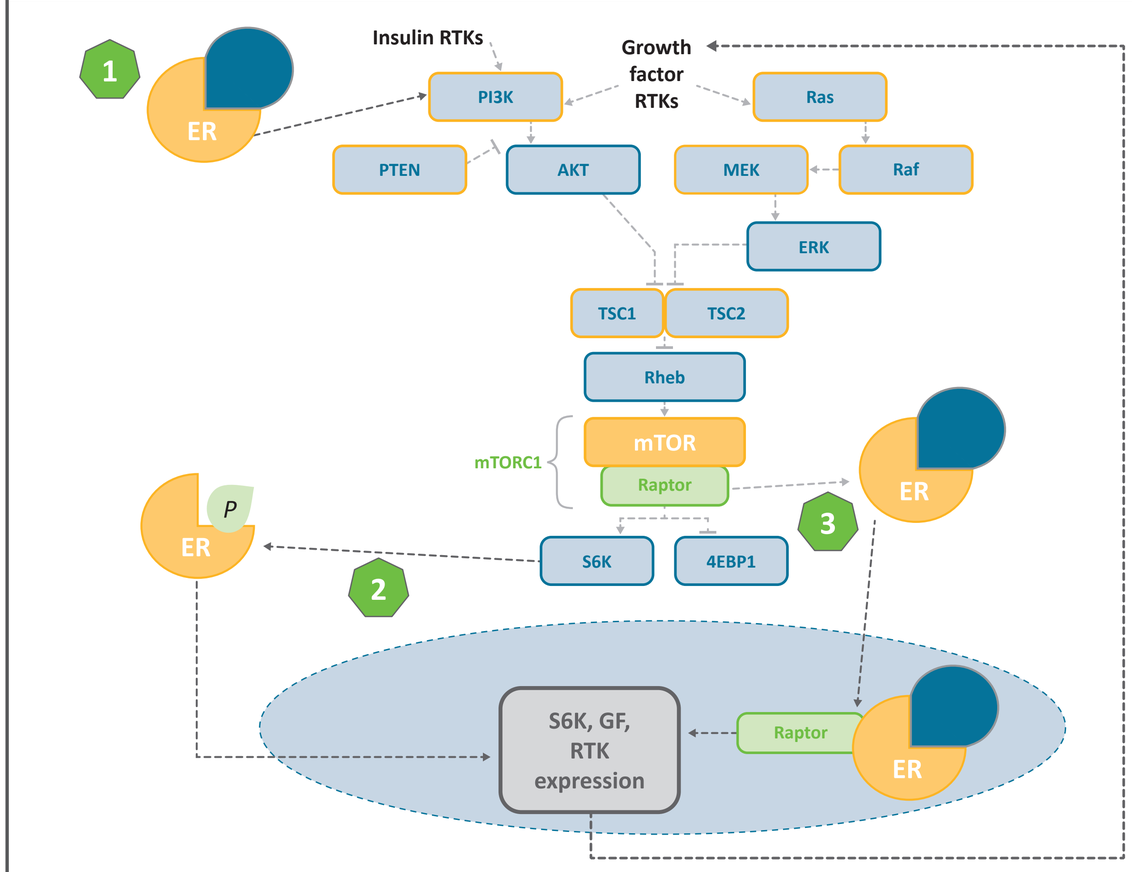
## KEY POINTS

- **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 other 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**

## BACKGROUND

- Dysregulation of mTOR signaling is implicated in the pathology of endometrial carcinoma (EC), particularly in endometrioid EC (EEC) in which >80% harbor PTEN or PI3K/AKT/mTOR pathway alterations[1]
  - 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[2]
- Moreover, crosstalk between the PI3K/AKT/mTOR pathway and estrogen signaling occurs at several points in the pathway[2,3] (**Figure 1**), including:
  1. Direct activation of the PI3K/AKT/mTOR pathway via activated estrogen receptors (ERs)
  2. Direct activation of ERs via the downstream signaling molecule S6K
  3. ER-induced expression of S6K in a feed-forward activation loop[3]

**Figure 1. Crosstalk between ERs and the PI3K/AKT/mTOR pathway**




**GF**, growth factor; **mTORC1**, mTOR complex 1; **RTK**, receptor tyrosine kinase.

- Potentiation of ER signaling can lead to the development of resistance to endocrine therapy[3]; thus, combining therapies is an attractive strategy to overcome potential resistance
- GOG-3007[4] and other phase 2 studies[5,6] have demonstrated that the combination of oral mTOR inhibitors and endocrine therapy provides clinical benefit in patients with recurrent EC[4]
  - In GOG-3007, everolimus plus letrozole resulted in a median PFS of 28 months for chemotherapy-naïve patients versus 4 months for patients with prior chemotherapy[4]
  - The magnitude of benefit was greatest in subgroups of patients who were chemotherapy-naïve or those with endometrioid histology[4–6]
- *nab*-Sirolimus is a nanoparticle albumin-bound, IV administered mTOR inhibitor approved in the United States for adults with advanced malignant perivascular epithelioid cell tumors (PEComa)[7]
- Nonclinical data with *nab*-sirolimus demonstrated improved tumor accumulation, mTOR inhibition, and tumor growth suppression compared with other mTOR inhibitors[8]
- 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, multi-center study evaluating *nab*-sirolimus in adult patients (≥18 years) with advanced or recurrent EEC (**Figure 2**)
- Using a Simon's optimal 2-stage design, the study will enroll 10 patients in stage 1. If ≥1 patient achieves a response, stage 2 will enroll 19 patients

**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**

21-day Cycle

***nab*-Sirolimus on days 1 and 8 of each 21-day cycle**

- Intravenous infusion over 30 minutes
- Starting dose: 100 mg/m$^2$
- Maximum of 3 sequential dose reductions to 75 mg/m$^2$, 56 mg/m$^2$, and 45 mg/m$^2$ are permitted

+

**Letrozole daily throughout each 21-day cycle**

- 2.5 mg administered orally, daily

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

**Follow-up**

- CT/MRI every 6 weeks for one 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 withdrawal of consent

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

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

### Study Endpoints

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

**Figure 3. Study endpoints**

1 **PRIMARY**
- Investigator-assessed best overall response rate per RECIST v1.1

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

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

[a]DCR defined as the proportion of patients with confirmed PR/CR or SD for ≥12 weeks. [b]Adverse events defined per the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0. **DCR**, disease control rate; **DOR**, duration of response; **IHC**, immunohistochemistry; **NGS**, next generation sequencing; **OS**, overall survival; **PFS**, progression-free survival; **RECIST v1.1**, Response Evaluation Criteria for Solid Tumors version 1.1.

### Trial enrollment information

- **Trial registration: NCT05997017**
- **Study start date: Dec 2023**
- **Visit ClinicalTrials.gov for latest information**
- **Current status open for enrollment at these study locations:**
  - **Oklahoma University Stephenson Cancer Center; Oklahoma City, Oklahoma**
  - **Atrium Health Levine Cancer Institute; Charlotte, North Carolina**
  - **Memorial Sloan Kettering Cancer Center; New York, New York**
  - **Mount Sinai Comprehensive Cancer Center; Miami Beach, Florida**
  - **Swedish Cancer Institute; Seattle, Washington**
  - **Texas Oncology —Tyler; Tyler, Texas**
  - **University of Arkansas for Medical Sciences Winthrop P. Rockefeller Cancer Institute; Little Rock, Arkansas**
  - **Women and Infants Hospital; Providence, Rhode Island**
  - **Women's Cancer Center of Nevada; Las Vegas, Nevada**

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