# A Phase 2, Open-Label, Single-Arm, Prospective, Multi-Center Study of *nab*-Sirolimus Plus Letrozole in Advanced or Recurrent Endometrioid Endometrial Cancer

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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/metastatic setting**

## KEY POINTS

- **Dysregulation of the mTOR pathway has been demonstrated in most endometrial carcinomas and crosstalk between the mTOR pathway and the estrogen receptor 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 which 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, multi-center 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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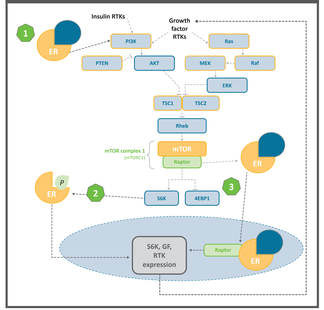
## INTRODUCTION

- 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 endometrial carcinoma (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 receptor signaling occurs at several points in the pathway[3–4] (**Figure 1**), including:
  - direct activation of the PI3K/AKT/mTOR pathway via activated estrogen receptors
  - direct activation of estrogen receptors via the downstream signaling molecule S6K
  - estrogen receptor induced expression of S6K in a feed-forward activation loop[4]
- Potentiation of estrogen receptor 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 GOG-3007, the median PFS for patients with advanced, persistent, or recurrent EC treated with everolimus plus letrozole was 28 months in chemotherapy-naïve patients versus 4 months for patients who had received prior chemotherapy[5]
  - All patients who benefited from the combined therapy had tumors with endometrioid histology[5]
- *nab*-Sirolimus is a nanoparticle albumin-bound, IV administered mTOR inhibitor approved in the USA for adults with advanced malignant perivascular epithelioid cell tumor[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

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




## 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**)

**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

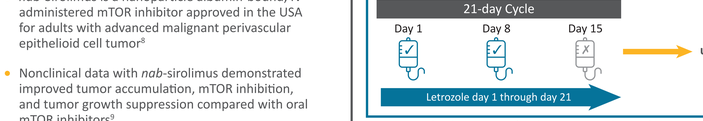
### Treatment phase

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

### Follow-up

- CT/MRI every 6 weeks for the 1st year, 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




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

NCT05997017

**AEs**, adverse events; **chemo**, chemotherapy; **CT**, computerized tomography; **ECOG PS**, Eastern Cooperative Oncology Group performance score; **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 1 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
- Non-chemotherapy-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 treament. [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 version 5.0

**AE**, adverse event; **CR**, complete response; **ctDNA**, circulating tumor DNA; **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 version 1.1.

### Trial enrollment information

- **Trial registration: NCT05997017**
- **Study start date: October 2023**
- **Current status: Open for enrollment in the United States**
- **Current study location: University of Oklahoma Stephenson Cancer Center**

### References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