INTRODUCTION
- Ovarian granulosa cell tumors (OvGCT) represent 5–7% of all ovarian cancers and account for 70% of all ovarian sex cord-stromal tumors.
- Surgery is the initial treatment with postoperative therapy considered for high-risk patients.
- In relapsed patients, chemotherapy regimens have shown only modest activity.
- Notch signaling, the FZD2 CL444 mutation, and dysregulation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway are integral to the molecular pathogenesis of OvGCT (Figure 1).
- The investigational agent nirogacestat (PT-080104) is a potent, selective, noncompetitive inhibitor of γ-secretase, an enzyme that plays a pivotal role in Notch signaling.
- Treatment with nirogacestat might be expected to impede granulosa cell proliferation in OvGCT by inhibiting Notch signaling, spurring the Notch intracellular domain (NICD), compensating for impaired induction of apoptosis by the FZD2 CL444 mutation, and restoring negative regulation of PI3K and pAKT.
- The primary objective of the current trial is to determine the anti-tumor activity of nirogacestat in relapsed patients with relapsed/refractory OvGCT.

Figure 1. Schematic representation of the cell signaling pathways in OvGCT development.

Approximately 43 patients are expected to enroll
- Currently recruiting at 30 sites in the US

OUTCOME EVALUATIONS
- Study objectives and outcome evaluations are summarized in Table 2.
- Efficacy:
  - The primary endpoint is ORR by RECIST v1.1.
  - Secondary endpoints include overall survival and 2-year survival, change from baseline in the Functional Assessment of Cancer Therapy-Gyn Oncology (FACT-G) symptom index, and duration of response.
- Safety:
  - Incidence of treatment-emergent adverse events, changes in clinical laboratory parameters, vital signs, physical examination findings, and electrocardiograms.
- Pharmacokinetic:
  - Serum concentrations to evaluate systemic exposure of nirogacestat.
- Exploratory:
  - Changes in relevant biomarkers and tumor genomics alterations.

Ovarian granulosa cell tumors (OvGCT) represent 5–7% of all ovarian cancers and account for 70% of all ovarian sex cord-stromal tumors. Surgery is the initial treatment with postoperative therapy considered for high-risk patients. In relapsed patients, chemotherapy regimens have shown only modest activity. Notch signaling, the FZD2 CL444 mutation, and dysregulation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway are integral to the molecular pathogenesis of OvGCT. The investigational agent nirogacestat (PT-080104) is a potent, selective, noncompetitive inhibitor of γ-secretase, an enzyme that plays a pivotal role in Notch signaling. Treatment with nirogacestat might be expected to impede granulosa cell proliferation in OvGCT by inhibiting Notch signaling, spurring the Notch intracellular domain (NICD), compensating for impaired induction of apoptosis by the FZD2 CL444 mutation, and restoring negative regulation of PI3K and pAKT. The primary objective of the current trial is to determine the anti-tumor activity of nirogacestat in relapsed patients with relapsed/refractory OvGCT.

Figure 1. Schematic representation of the cell signaling pathways in OvGCT development.

Table 1. Key inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Females ≥ 18 years of age</td>
<td>• Known reproductive potential in women (i.e., negative serum pregnancy test)</td>
</tr>
<tr>
<td>• Histologically confirmed adult-type OvGCT</td>
<td>• Serous, clear, low-grade, or mucinous ovarian epithelial tumors</td>
</tr>
<tr>
<td>• History of major cardiac or cerebrovascular event ≤ 6 months of signing informed consent</td>
<td>• Active infection (with the exception of localized skin infections)</td>
</tr>
<tr>
<td>• Adequate bone marrow, renal, or hepatic function</td>
<td>• Previous treatment with other investigational products</td>
</tr>
<tr>
<td>• Adequate bone marrow, renal, and hepatic function</td>
<td>• Using concomitant hormones (optional at investigator discretion)</td>
</tr>
<tr>
<td>• Currently recruiting at 30 sites in the US</td>
<td>• Cerebrovascular accident within 2 years</td>
</tr>
</tbody>
</table>

OvGCT, ovarian granulosa cell tumor; ORR, objective response rate; NGS, next generation sequencing; NICD, Notch intracellular domain.

Table 2. Study objectives and outcome evaluations.

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>Summary</th>
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<tbody>
<tr>
<td>To determine the anti-tumor activity of nirogacestat in participants with relapsed/refractory OvGCT</td>
<td>ORR, defined as the proportion of participants with CR or PR by RECIST v1.1 criteria.</td>
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</tbody>
</table>

Secondary Objectives
- Estimation of proportion of participants with PFS by RECIST v1.1 criteria
- Evaluation of efficacy, safety, and tolerability of nirogacestat in baseline tumor tissue
- Duration of response, defined as time from response (CR + PR) by RECIST v1.1 criteria to disease progression and/or death
- Description of the PK profile of nirogacestat

Safety Objectives
- Change from baseline in quality of life (FACT-G) symptoms as measured by FOSI
- Changes in clinical laboratory parameters, vital signs, physical examination findings, and electrocardiograms
- Baseline NICD expression in tumor tissue
- NGS status in baseline tumor tissue

Outcome Evaluations
- Study objectives and outcome evaluations are summarized in Table 2.
- Efficacy:
  - The primary endpoint is ORR by RECIST v1.1.
  - Secondary endpoints include overall survival and 2-year survival, change from baseline in the Functional Assessment of Cancer Therapy-Gyn Oncology (FACT-G) symptom index, and duration of response.
- Safety:
  - Incidence of treatment-emergent adverse events, changes in clinical laboratory parameters, vital signs, physical examination findings, and electrocardiograms.
- Pharmacokinetic:
  - Serum concentrations to evaluate systemic exposure of nirogacestat.
- Exploratory:
  - Changes in relevant biomarkers and tumor genomics alterations.

Figure 2. Study design with continuous monitoring for futility analysis.

Currently recruiting at 10 sites in the US

REFERENCES


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Presenting Author Disclosure
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PATTERNS • PURPOSE • PROGRESS

TRIAL IN PROGRESS: A PHASE 2 TRIAL OF NIROGACESTAT, A γ-SECRETASE INHIBITOR, IN PATIENTS WITH RECURRENT OVARIAN GRANULOSA CELL TUMORS (NCT05348356)

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