LIO-1: A Phase 2 Study of Lucitanib + Nivolumab in Patients (pts) With Gynaecological Tumours

CO-3810-101; NCT04042116; ENTZ-003/GYN3/AGO/LIO

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SUMMARY

- Clinical studies have shown that the combination of tyrosine kinase inhibitors (TKIs) that inhibit angiogenesis and immune checkpoint inhibitors can result in improved efficacy compared with either monotherapy.

- The phase 2 part of the international, open-label LIO-1 study aims to assess the efficacy and safety of the combination of the TKI lucitanib and the programmed cell death receptor 1 (PD-1) inhibitor nivolumab in patients with advanced gynaecological solid tumours.

- A safety-based dose titration approach is being used for lucitanib dosing to manage tolerability and maintain dose intensity.

- Up to 161 patients will be enrolled across 6 countries.

INTRODUCTION

- Lucitanib is an oral, potent tyrosine kinase inhibitor (TKI) that selectively inhibits vascular endothelial growth factor receptors 1–3 (VEGFR1–3), platelet-derived growth factor receptors alpha and beta (PDGFR α/β) and fibroblast growth factor receptors 1–3 (FGFR1–3).

- Nivolumab is a human immunoglobulin G4 kappa antibody that binds to programmed death receptor 1 (PD-1) and blocks its interaction with programmed cell death factor 1 (PD-L1) and 2 (PD-L2), resulting in PD-1-mediated inhibition of the antitumour immune response.

- Proangiogenic growth factors secreted by tumours promote the generation of new blood vessels and mediate immunosuppression, which may dampen the effect of immune checkpoint inhibitors. Inhibiting angiogenesis with a TKI may therefore, release immunosuppression and enhance the efficacy of PD-1/L1 inhibitors.

TRIAL OVERVIEW

- LIO-1 (NCT04042116; ENTZ-003/GYN3/AGO/LIO) is a 2-part open-label study:
  - The phase 1b part of the study established the recommended starting dose of lucitanib as 10 mg orally once daily in combination with nivolumab (480 mg intravenously every 28 days) in patients with an advanced solid tumour.
  - The phase 2 part of the study is designed to evaluate the efficacy and safety of the combination of lucitanib and nivolumab in patients with an advanced gynaecological solid tumour.

- The primary objective is to evaluate the preliminary efficacy of the combination by investigator-assessed confirmed best overall response rate (Table 1).

Table 1. Endpoints

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<thead>
<tr>
<th>Endpoint</th>
<th>Primary endpoint</th>
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<td>[Investigator-assessed confirmed best overall response rate (ORR)]</td>
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- Secondary endpoints include:
  - Time to treatment failure (TTF): patients who meet the dose-titration criteria will dose escalate to lucitanib 8 mg and then 10 mg once daily.
  - Dose intensity and drug exposure.
  - Safety and tolerability.
  - Percentage of patients meeting the criteria at cycle 2 day 1 and cycle 3 day 1 but whose dose is not escalated may be permitted to dose escalate at a subsequent cycle provided no severe AEs related to dose escalation have occurred.
  - Dose reductions are not permitted.

- Patients with a treatment duration of ≥3 months are eligible for post-treatment on-treatment blood samples.

Table 2. Key Eligibility Criteria

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<thead>
<tr>
<th>Eligibility Criteria</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td></td>
<td>General criteria for doublet chemotherapy (≥2 prior chemotherapy regimens, including chemotherapy and/or hormone therapy or surgery for metastatic disease)</td>
<td>No</td>
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<td>No uncontrolled hypertension or serious or uncontrolled hyperlipidaemia</td>
<td>Yes</td>
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<td>No untreated or active infection</td>
<td>Yes</td>
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<td>No treatment-related grade 2 or higher toxicity (≥5 days)</td>
<td>Yes</td>
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<td>No grade ≥2 proteinuria (≥1+ or ≥1.0 g/24 h)</td>
<td>Yes</td>
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<td>No history of neoadjuvant chemotherapy</td>
<td>Yes</td>
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<td></td>
<td>No uncontrolled hypertension (BP &gt;150/90 mm Hg)</td>
<td>Yes</td>
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<td>No severe (≥grade 3) cardiac disease</td>
<td>Yes</td>
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<td></td>
<td>No active productive copathological malignancy</td>
<td>Yes</td>
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<td>No heavy smoker (≥20 pack years)</td>
<td>Yes</td>
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<td>No history of pre-existing, uncontrolled diabetes (independent of treatment)</td>
<td>Yes</td>
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<tr>
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<td>No history of uncontrolled diabetes (independent of treatment)</td>
<td>Yes</td>
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- Key exclusion criteria are:
  - No haematological, hepatic or renal dysfunction.
  - No active infections.
  - No recent exposure to investigational anticancer therapies.

- The trial is conducted in six centres: Belgium, Spain, Germany, France, Italy and the UK.

- The trial will be carried out in 20 sites across Europe.

REFERENCES

3. Dusek et al. Figure 1. Proposed Mechanism of Action of Lucitanib and Nivolumab.
4. Table 1. Endpoints.
5. Table 2. Key Eligibility Criteria.
6. Figure 3. Clinical Criteria for Lucitanib Dose Escalation.
7. Figure 4. Countries Participating in LIO-1.