

Relacorilant (LIFYORLI™) and Albumin-Bound Paclitaxel (Nab-Paclitaxel) for Platinum-Resistant Ovarian Cancer

Description:

- The purpose of this document is to review the novel mechanism of action, appropriate patient selection, management of potential adverse effects, and other clinical considerations related to relacorilant administration in conjunction with nab-paclitaxel.

Background¹⁻⁵:

- Relacorilant is a first-in-class, selective glucocorticoid receptor (GR) antagonist that blocks cortisol-mediated GR signaling. Ovarian cancers express GR, through which cortisol suppresses anti-cancer immunity and provides survival signals that reduce the sensitivity of cancer cells to chemotherapy. Preclinical studies suggest that inhibition of GR signaling promotes anti-cancer immunity and restores the sensitivity of cancer cells to cytotoxic chemotherapy.
- Relacorilant is indicated in combination with nab-paclitaxel for the treatment of adults with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens, at least one of which included bevacizumab.
- Most common adverse reactions (> 20%), including laboratory abnormalities, that occurred in patients treated with relacorilant in combination with nab-paclitaxel were decreased hemoglobin, decreased neutrophils, fatigue, nausea, diarrhea, decreased platelets, rash, and decreased appetite.
 - No new safety signals were observed with the addition of relacorilant to nab-paclitaxel versus nab-paclitaxel alone

PQI Process:

- Patient Identification**
 - Platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
 - Undergone one to three prior systemic treatment regimens, at least one of which included bevacizumab
 - No biomarker testing is required for patient selection; patients may be considered for treatment regardless of folate receptor-alpha expression or PD-L1 status
 - Relacorilant is contraindicated in patients receiving systemic glucocorticoids for lifesaving purposes (e.g., immunosuppression after organ transplantation)
- Dosing/Administration**
 - Relacorilant:** 150 mg orally once on the day before, the day of, and the day after each nab-paclitaxel infusion until disease progression or unacceptable toxicity
 - Relacorilant is available as 100 mg and 25 mg capsules
 - To make up prescribed dose patients should take **one** 100 mg capsule PLUS **two** 25 mg capsules
 - Should be taken with food

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- **Nab-paclitaxel:** 80 mg/m² IV on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity
 - The recommended dosage and dosage modifications for nab-paclitaxel when administered in combination with relacorilant differ from those for other nab-paclitaxel indications
 - If a nab-paclitaxel infusion is rescheduled, patient should hold relacorilant as well
- **Recommended Monitoring and Adverse Reaction Management^{1,2}**
 - **Myelosuppression including anemia, thrombocytopenia, and neutropenia with risk of infection:**
 - Monitor complete blood counts prior to each weekly treatment with relacorilant in combination with nab-paclitaxel and as clinically indicated
 - Based on the severity of neutropenia, delay, reduce dose or permanently discontinue treatment (see Dose Modification tables below)
 - Prophylactic or supportive use of short-acting G-CSF in accordance with clinical practice may be used in lieu of or in combination with dose reduction for patients with neutropenia; In the phase 3 ROSELLA trial, 38% of patients were initiated on G-CSF during the first or second cycle of therapy.
 - **Gastrointestinal upset:**
 - Consider supportive care measures, including as-needed anti-emetic and anti-diarrheal medications, taking into account potential interactions with systemic glucocorticoids.
 - **Fatigue:**
 - Encourage regular physical activity/exercise as tolerated and self-monitoring of fatigue levels.⁶
 - Promote energy conservation strategies, including prioritizing activities, pacing, delegating tasks, scheduling activities during peak energy periods, and limiting daytime naps that interfere with nighttime sleep.⁶
 - **Adrenal Insufficiency:** No cases of adrenal insufficiency (AI) were seen in the phase 3 ROSELLA trial⁷, however, as relacorilant is a reversible GR antagonist, AI can occur.
 - Monitor patients for signs/symptoms of AI including but not limited to dizziness, hypotension, worsening fatigue or weakness
 - Withhold relacorilant and administer glucocorticoid therapy if AI is suspected
 - Relacorilant has a long half-life (27.5 hours) and glucocorticoid receptor antagonism may occur for up to 6 days after the last dose
 - **Exacerbation of conditions treated with glucocorticoids:** As relacorilant is a GR antagonist, it may make systemic glucocorticoids less effective. Use of relacorilant in patients who are taking systemic glucocorticoids for other conditions (e.g., autoimmune disorders) may exacerbate these conditions. Similarly, coadministration of systemic glucocorticoids may make relacorilant less effective.
 - Monitor patients for reduced effectiveness of relacorilant and glucocorticoids in patients receiving both.
 - Patients who require chronic or frequent use of glucocorticoids were excluded from clinical trials of relacorilant in combination with nab-paclitaxel
 - Relacorilant is contraindicated in patients receiving systemic glucocorticoids for lifesaving purposes (e.g., immunosuppression after organ transplantation)
 - **Embryo-fetal toxicity:** Relacorilant can cause fetal harm.
 - Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during treatment and for 1 week after the last dose of relacorilant.

- **Hepatic impairment:** Avoid relacorilant in combination with nab-paclitaxel in patients with moderate or severe hepatic impairment (total bilirubin >1.5 to 10x ULN and any AST) because of the potential for increased relacorilant and paclitaxel exposures.

- **Dose Modifications**

Table 1. Dose Adjustments for Adverse Reactions (ARs) for Nab-Paclitaxel

Dose reduction	Nab-paclitaxel dose
First	60 mg/m ² on Days 1, 8, and 15 of each 28-day cycle
Second	60 mg/m ² on Days 1 and 15 of each 28-day cycle
Third	Permanently discontinue nab-paclitaxel if unable to tolerate after two dose reductions.

Table 2. Dose Adjustments for ARs for Relacorilant

Dose reduction	Relacorilant dose
First	125 mg once a day the day before, the day of, and the day after the nab-paclitaxel infusion
Second	Permanently discontinue relacorilant in patients unable to tolerate after one dose reduction.

Table 3. Dose Adjustments for Neutropenia

Cycle day	Severity*	Nab-paclitaxel	Relacorilant
1	ANC 1,000 to <1,500/mm ³	Withhold until ≥1,500/mm ³ ; resume at same dose	Withhold; resume at the same dose once nab-paclitaxel resumes
1	ANC <1,000/mm ³	Withhold until ≥1,500/mm ³ ; resume at reduced dose	
8, 15	ANC <1,000/mm ³	Omit dose; resume at reduced dose or continue at the same dose with short-acting G-CSF	Withhold; resume at the same dose once nab-paclitaxel resumes
Any	Febrile neutropenia (Grade 3 or 4)	Withhold until fever resolves and ANC ≥1,500/mm ³ ; resume at reduced dose	Withhold; resume at the same dose once nab-paclitaxel resumes

*Unless otherwise specified, Grade per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0; Prophylactic or supportive use of short-acting G-CSF in accordance with clinical practice may be used in lieu of or in combination with dose reduction for patients with neutropenia; If the delay in nab-paclitaxel dosing exceeds 7 days, omit the nab-paclitaxel dose.

- **Drug-Drug Interactions:** Relacorilant is a strong CYP3A inhibitor and both relacorilant and paclitaxel are CYP3A substrates. Paclitaxel is a substrate of CYP2C8.
 - Strong CYP3A Inducers: avoid coadministration
 - CYP2C8 Inducers and Moderate CYP3A Inducers: monitor for reduced effectiveness for relacorilant with nab-paclitaxel
 - CYP2C8 Inhibitors: monitor for increased adverse reactions and modify the dosage for adverse reactions as recommended
 - CYP3A Substrates: avoid coadministration unless otherwise recommended
 - Certain CYP2C8 Substrates: avoid concomitant use unless otherwise recommended in the Prescribing Information for CYP2C8 substrates where minimal concentration changes may lead to reduced effectiveness
 - Always conduct a thorough review of all medications a patient is taking before they start relacorilant to identify and address any potential drug-to-drug interactions

Patient-Centered Activities:

- Provide patients with a Patient Education Sheet reviewing [relacorilant and albumin-bound paclitaxel](#).
- Educate patients to take relacorilant as three softgel capsules once a day, with food, the day before, the day of, and the day after each nab-paclitaxel infusion.
- Counsel patients that they will need to use **two** different strength capsules to make up their once daily dose of relacorilant – one 100 mg capsule plus two 25 mg capsules
- Patients should take relacorilant capsules whole and should not crush, chew, dissolve, or split the capsules.
- Counsel patients that if a dose of relacorilant is missed by less than 12 hours, they should take the missed dose. If a dose of relacorilant is missed by 12 hours or more, skip the missed dose and take the next dose at the regularly scheduled time. Patients should not take 2 doses at the same time to make up for a missed dose.
- If a nab-paclitaxel infusion is rescheduled, patients should not take relacorilant. Instead, relacorilant should be taken the day before, the day of, and the day after the new infusion date.
- Advise patients **not** to take relacorilant if they are receiving or taking steroid medicine for lifesaving purposes.
- Counsel patients to report signs/symptoms of new infections including:

○ Fever of 100.4 F or higher	○ Painful urination or signs of UTI
○ Chills	○ Notably increased fatigue
○ New or worsening cough or sore throat	○ Red, swollen, warm, or painful areas on the skin
- Review chemotherapy-induced nausea/vomiting and diarrhea protocols and as-needed supportive care medications
- Educate patients of child-bearing potential to use effective contraception during treatment and for 1 week after last dose
- Advise patients to contact their care team if they experience new, worsening, or prolonged bleeding, including nosebleeds or blood in the urine or stool.
- Advise patients to reach out to the care team if they have symptoms of adrenal insufficiency including dizziness, worsening nausea and vomiting, low blood pressure, worsening weakness or tiredness, worsening loss of appetite or weight loss.
- Financial assistance: [LIFYORLI Savings Card](#)

References:

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