A Phase 2 Exploratory, Multicenter, Open-Label Trial to Determine the Safety and Preliminary Clinical Activity of GEN1046 in Combination With Anticancer Agents in Subjects With Advanced Endometrial Cancer

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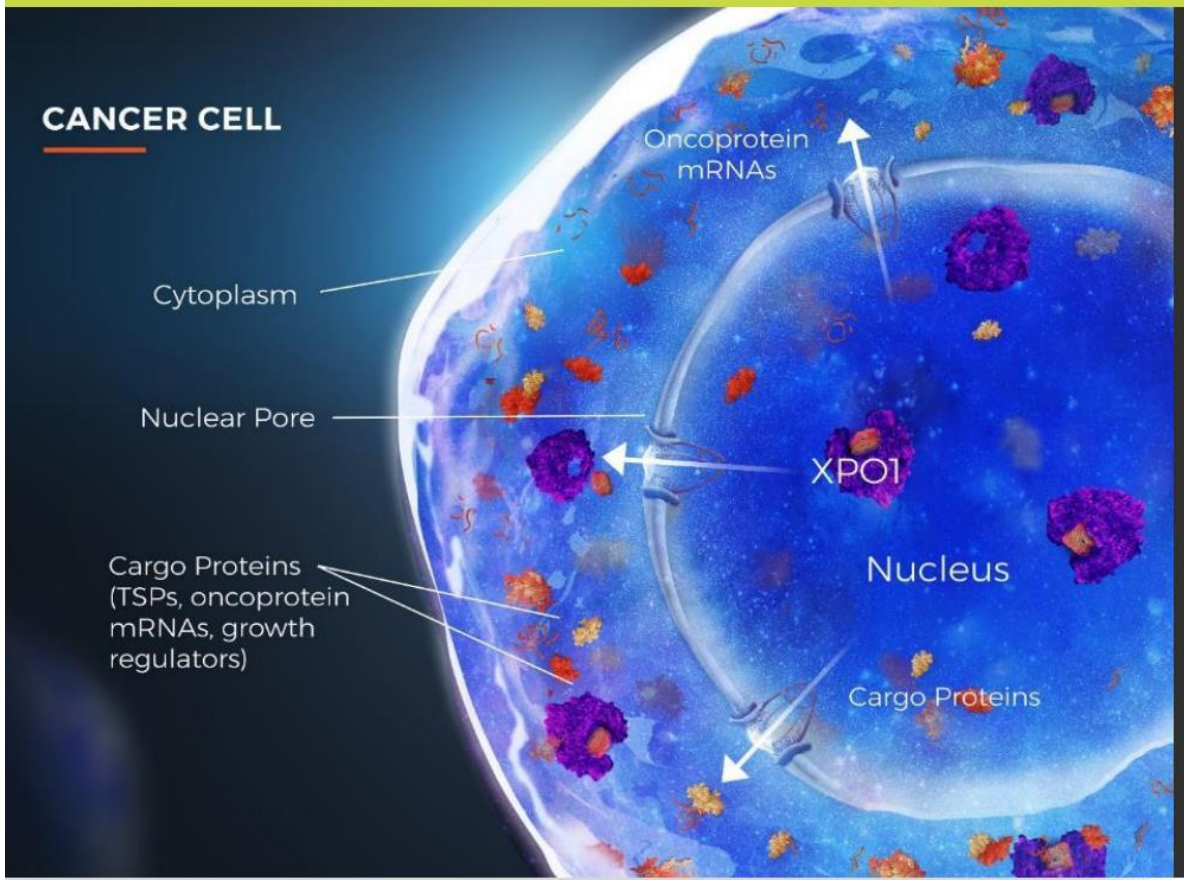
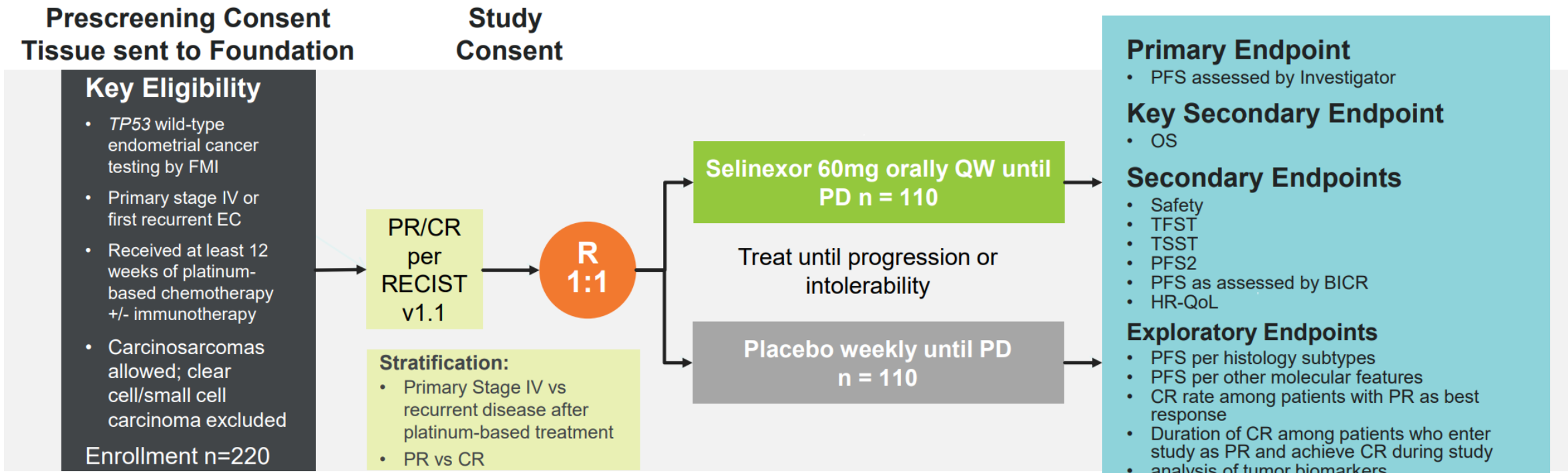
Selinexor Is an Oral, Selective Inhibitor of XPO1-mediated Nuclear Export (SINE) Compound, Allowing for the Nuclear Retention of Major Tumor Suppressor Proteins Such As *p53*



- XPO1 exports the major tumor suppressor proteins (TSPs) including *TP53* (*p53*) away from the nucleus, where TSPs carry out their function
- Cancer cells overexpress XPO1
- Cancer cells inactivate cytoplasmic *p53* through protein degradation
- Selinexor inhibits XPO1 nuclear export, leads to retention/ reactivation of TSPs in the nucleus and stabilization of p53
- Retention of wild-type *TP53* (*p53*wt) and other TSPs in the cell nucleus leads to selective killing of cancer cells, while largely sparing normal cells

XPORT-EC-042 is a Phase 3, Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial of Selinexor in Maintenance Therapy After Systemic Therapy for Patients With *TP53* Wild-Type, Advanced or Recurrent EC



*118 PFS events needed to provide 90% power to detect a HR of 0.55 with a two-sided alpha of 0.05

Key Inclusion Criteria

- Histologically confirmed EC including: **endometrioid, serous, undifferentiated, and carcinosarcoma**
- *TP53*wt assessed by NGS, evaluated by Foundation Medicine
- Completed a single line, at least 12 weeks of platinum-based therapy and achieved confirmed PR or CR by imaging review, according to RECIST v1.1 for primary stage IV disease or at first relapse
- Able to initiate study drug 3 to 8 weeks after completion of final dose of chemotherapy
- ECOG 0-1
- Patients must have adequate bone marrow function and organ function within 2 weeks before starting study drug as defined by the following laboratory criteria:

1

Hepatic function:
Total bilirubin up to <3.0 x ULN;
ALT and AST ≤2.5 x ULN in patients without liver mets *(AST and ALT ≤5 x ULN for patients with known liver involvement of their tumor)*

2

Hematopoietic function:
anC ≥1.5 x 10^9/L;
Platelet count ≥100 x 10^9/L;
Hemoglobin ≥9.0 g/dL

3

Renal function:
CrCl of ≥20 mL/min

Dual Antiemetic Prophylaxis Is Critical During the First 2 Cycles of Study Drug Treatment and Is an Inclusion Criteria in XPORT-EC

Treatment Options Recommendations

5-HT3 receptor antagonist (ondansetron 8 mg or equivalent) starting Q8 hours before each dosing and continue 2-3 times daily for a few days after dosing for the first 2 cycles of the study or longer if needed

+

Neurokinin (NK)-1 receptor antagonist or mixed serotonergic antagonist (eg, aprepitant) starting from the initiation of study drug, and continuing for the first 2 cycles of the study treatment and longer if needed

OR

Combination 5-HT3 receptor antagonist plus NK-1 receptor antagonist (eg, Akynzeo)

If above treatments are not available or not beneficial to the patient, contact sponsor for guidelines related to other dual antiemetics

Key Exclusion Criteria

- Have any uterine sarcomas, clear cell, or small cell carcinoma with neuroendocrine differentiation
- Received a blood or platelet transfusion during the 2 weeks prior to C1D1
- Concurrent systemic steroid therapy higher than physiologic dose (>10 mg/day of prednisone or equivalent)
  - Insufficient time since or not recovered from procedures or active cancer therapy
  - Major surgery ≤28 days prior to day 1 dosing
  - Have ongoing clinically significant anti-cancer therapy related toxicities CTCAE gr >1
  - Palliative XRT w/in 14 days of C1D1
- Active, ongoing, or uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week of screening

Key Exclusion Criteria (cont.)

- Stable disease or PD on the post-chemotherapy scan or clinical evidence or progression prior to randomization
- Active brain metastases or patients who have received any systemic anticancer therapy including investigational agents ≤3 weeks (or ≤5 half-lives) prior to C1D1
- Major surgery w/in 14 days prior to C1D1 or planned major surgery during the on-treatment study period.
- Other malignant disease with disease-free ≤3 years with exception of carcinoma in situ of cervix, basal cell carcinoma of the skin, or ductal carcinoma in situ of the breast
- Patients who are unable to tolerate 2 forms of antiemetics for at least 2 cycles