PRESERVE 3: A PHASE II, RANDOMIZED, OPEN-LABEL STUDY OF TRILACICLIB WITH FIRST-LINE, PLATINUM-BASED CHEMOTHERAPY AND AVELUMAB MAINTENANCE IN UNTREATED PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA

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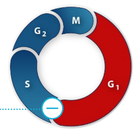
INTRODUCTION

- Platinum-based chemotherapy, followed by switch maintenance with avelumab for patients without progression, is the standard first-line (1L) treatment for patients with metastatic urothelial carcinoma (mUC)[1,2]
- Avelumab, an immune checkpoint inhibitor, is used as maintenance treatment for patients with mUC whose cancer has not progressed with 1L platinum-based chemotherapy and for patients with disease progression despite platinum-based chemotherapy[1,2]
- Trilaciclib is an intravenous cyclin-dependent kinase 4/6 inhibitor indicated to decrease the incidence of chemotherapy-induced myelosuppression (ie, neutropenia, anemia, and/or thrombocytopenia) in adult patients when administered prior to a platinum/etoposide- or topotecan-containing chemotherapy regimen for extensive-stage small cell lung cancer[3]
- Data from three randomized, placebo-controlled, phase II clinical trials showed that administering trilaciclib prior to chemotherapy reduced the incidence of chemotherapy-induced myelosuppression and the need for best supportive care interventions and chemotherapy dose reductions/delays[4–6]
- Additionally, in an exploratory, randomized, phase II trial in patients with metastatic triple-negative breast cancer, administering trilaciclib prior to gemcitabine/carboplatin improved overall survival compared with chemotherapy alone, regardless of programmed death-ligand 1 expression[7,8]

Trilaciclib Mechanism of Action

Trilaciclib (IV myeloprotection therapy)

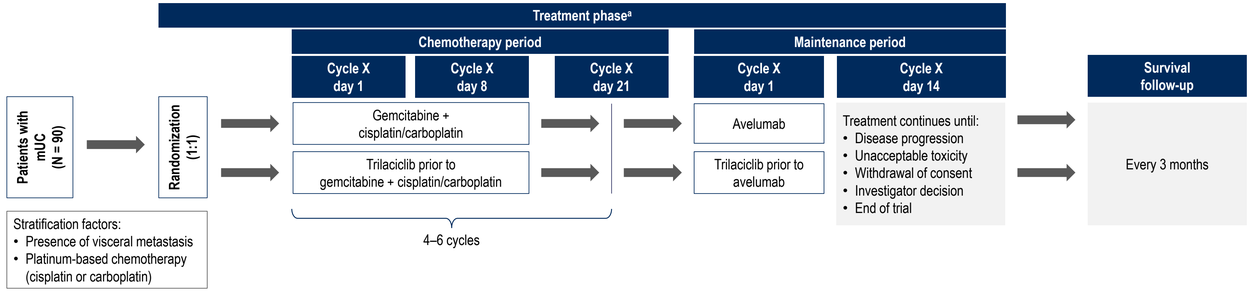
- IV inhibitor of CDK4/6, administered prior to chemotherapy[3]
- Transiently arrests HSPCs and immune cells in the G_1 phase of the cell cycle during chemotherapy exposure, helping to protect them from chemotherapy-induced damage[3–6,9,10]



Myeloprotection impact[3–6]		Antitumor efficacy impact[7,8,11]
Reduces rate of hematologic adverse events (less neutropenia, anemia, and thrombocytopenia)	Protects multiple myeloid cell lineages	**Increases** patients' ability to receive longer duration of chemotherapy-based regimens
Decreases rescue interventions (fewer transfusions, less G-CSF, and fewer chemotherapy-induced myelosuppression–related hospitalizations)	Protects lymphoid cell lineages	**Protects** the immune system from damage by chemotherapy
Improves patients' quality of life (improved well-being and less fatigue)	Improves immune response	**Enhances** T-cell responses and favorably alters the tumor microenvironment

CDK4/6, cyclin-dependent kinase 4/6; G-CSF, granulocyte colony-stimulating factor; HSPC, hematopoietic stem and progenitor cell; IV, intravenous.

STUDY DESIGN



[a] Patients without progressive disease after platinum-based chemotherapy ± trilaciclib per RECIST v1.1 (ie, with ongoing CR, PR, or SD) may receive avelumab switch maintenance therapy ± trilaciclib.
CR, complete response; mUC; metastatic urothelial carcinoma; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease.

PRESERVE 3 STUDY

- PRESERVE 3 (NCT04887831) is an exploratory, randomized, open-label, multicenter, phase II trial designed to assess whether trilaciclib can (1) improve antitumor efficacy when administered with platinum-based chemotherapy followed by avelumab maintenance therapy, and (2) reduce myelosuppression resulting from platinum-based chemotherapy, in patients receiving 1L treatment for advanced/metastatic urothelial carcinoma

PATIENT ELIGIBILITY CRITERIA

Key inclusion criteria[a]	Key exclusion criteria[a]
Adult patients (aged ≥ 18 years)	Prior treatment with any therapeutic antibody or drug targeting T-cell co-stimulation or immune checkpoint pathways in any setting
Histologically confirmed locally advanced UC or mUC	Malignancies other than UC within 3 years prior to randomization
No prior systemic therapy in the inoperable, locally advanced or metastatic setting	CNS metastases and/or leptomeningeal disease requiring immediate treatment with radiation therapy or steroids
Measurable disease per RECIST v1.1 and eligible to receive platinum-based chemotherapy and avelumab maintenance therapy	Known hypersensitivity to avelumab, gemcitabine, cisplatin, or carboplatin
Archival or fresh tumor specimen	Active autoimmune disease that may deteriorate when receiving an immunostimulatory agent
ECOG PS ≤ 2	
Adequate organ function as demonstrated by laboratory values	

[a] Protocol Amendment Version 2.0.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; UC, urothelial carcinoma.

ENDPOINTS

Primary endpoint

PFS

Secondary endpoints

Antitumor efficacy (ORR, DCR, DOR, OS, PFS)

Myeloprotection effects on the neutrophil, RBC, and platelet lineages (DSN in cycle 1 and occurrence of SN, FN, grade 3/4 decreased hemoglobin/platelet counts)

Supportive care interventions (G-CSF, ESA, RBC transfusions on/after week 5, platelet transfusions)

Hospitalizations due to chemotherapy-induced myelosuppression

All-cause dose reductions or delays

Occurrence and severity of adverse events

Exploratory endpoints

Pharmacodynamic effects in tumor and peripheral blood

Antitumor efficacy by CDK4/6-dependence and PD-L1 status

Pharmacokinetics

Immunogenicity (neutralizing/anti-avelumab antibodies)

CDK4/6, cyclin-dependent kinase 4/6; DCR, disease control rate; DOR, duration of objective response; DSN, duration of severe (grade 4) neutropenia; ESA, erythropoiesis-stimulating agent; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RBC, red blood cell; SN, severe (grade 4) neutropenia.

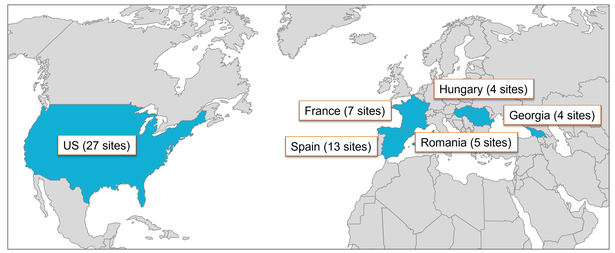
Statistics

- 63 progression-free survival (PFS) events will be required to achieve 77% power to detect a hazard ratio of 0.6 in PFS with 2-sided significance of 0.2, corresponding to median PFS of 11.7 months for the trilaciclib arm
- Assuming a 10-month enrollment period, final PFS analysis approximately 22 months after the first randomization, and 5% loss to follow-up, 90 patients are required for 1:1 randomization
- PFS will be analyzed in the intention-to-treat population

Planned Analysis	Analyses	Timing
First	• ORR • Myelosuppression • Safety	• Completion of chemotherapy period
Intermediate	• PFS • Probability of survival at month 16	• Following 63 PFS events • Day 1 of month 17
Final	• OS	• When 60% of required events (ie, 54 deaths) have been observed

ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

STUDY STATUS



- **Total study sites:** 60
- **First patient randomized:** September 21, 2021
- **Number of patients randomized:** 14 as of January 28, 2022

Additional information may be found at **https://clinicaltrials.gov/ct2/show/NCT04887831**

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