### INTRODUCTION

- Platinum-based chemotherapy, followed by switch maintenance with avelumab for patients without progression, is the standard first-line therapy for patients with metastatic urothelial carcinoma (MUC).<sup>1-3</sup>
- Avelumab is an immune checkpoint inhibitor used as maintenance treatment for patients with MUC whose cancer has not progressed with platinum-based chemotherapy and for patients with disease progression despite platinum-based chemotherapy.<sup>4-6</sup>
- Trilaciclib is an intravenous cyclin-dependent kinase 4/6 inhibitor indicated to decrease chemotherapy-induced myelosuppression (neutropenia, anemia, and thrombocytopenia) in adult patients when administered prior to platinumbased or topotecan-containing chemotherapy regimens for extensive-stage small cell lung cancer.<sup>7</sup>
- 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.<sup>8-10</sup>
- Additionally, in an exploratory, randomized, phase III 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.<sup>11</sup>

### TRILACICLIB MECHANISM OF ACTION

- **Trilaciclib (IV myeloprotection therapy)**
  - 
  - Previous treatment with any therapeutic antibody or drug that alters the tumor microenvironment or promotes immunotherapy
  - Malignancies other than UC within 3 years
  - CNS metastases and/or leptomeningeal disease
  - Immunosuppression within 3 months of cycle 1
  - Adequate organ function as demonstrated by medical history and physical examination
  - Prior treatment with chemotherapy
  - Carboplatin dose ≥ 450 mg/m² or cisplatin dose ≥ 100 mg/m² within the 60 days before the Cycle 1 day 1
  - Prior radiation therapy of ≥ 40 Gy outside the chemotherapy period
  - Systemic therapy for any malignancy within 3 years (except basal cell carcinoma of the skin and cervical dysplasia with virologic eradication)

### PATIENT ELIGIBILITY CRITERIA

- **Key eligibility criteria**
  - Patients with progressive disease after platinum-based chemotherapy (trilaciclib per RECIST v1.1 with ongoing CR, PR, or SD may receive qualitative switch maintenance therapy with trilaciclib)
  - Complete response (CR), metabolic response, undetectable immune checkpoint-related PFS, partial response (RECIST v1.1), Response Evaluation Criteria in Solid Tumors version 1.0, stable disease

- **Key exclusion criteria**
  - Prior treatment with any therapeutic antibody or drug targeting T-cell co-stimulators or immune checkpoint pathways in any setting
  - Malignancies other than UC within 3 years
  - CNS metastases and/or leptomeningeal disease
  - Immunosuppression within 3 months of cycle 1
  - Adequate organ function as demonstrated by medical history and physical examination
  - Prior treatment with chemotherapy
  - Carboplatin dose ≥ 450 mg/m² or cisplatin dose ≥ 100 mg/m² within the 60 days before the Cycle 1 day 1
  - Prior radiation therapy of ≥ 40 Gy outside the chemotherapy period
  - Systemic therapy for any malignancy within 3 years (except basal cell carcinoma of the skin and cervical dysplasia with virologic eradication)

### ENDPOINTS

**Primary endpoints**
- OS
- PFS
- Occurrence and severity of adverse events

**Secondary endpoints**
- Antitumor efficacy by CDK4/6-dependence and PD-L1 status
- Pharmacodynamic effects in tumor and peripheral blood
- Pharmacokinetics

### STATISTICS

- OS, PFS, and immunogenicity (neutralizing/anti-avelumab antibodies)
- DFS (OS, PFS, progression-free survival)
- Immunogenicity (neutralizing/anti-avelumab antibodies)
- OS
- ORR
- DCR
- DOR
- OS
- PFS
- Occurrence and severity of adverse events
- Exploratory endpoints

### PRESERVE 3 STUDY

- **Trial design**
  - 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

- **Study design**
  - Randomized to receive trilaciclib (IV myeloprotection therapy) or placebo with chemotherapy (cisplatin/carboplatin), followed by avelumab (maintenance therapy) as first-line treatment
  - Patients randomized to receive trilaciclib prior to chemotherapy

- **Preservation of hematopoietic progenitor cells**
  - Chemotherapy period
  - Myeloprotection effects on the neutrophil, RBC, and platelet lineages
  - Antitumor efficacy by CDK4/6-dependence and PD-L1 status
  - Pharmacodynamic effects in tumor and peripheral blood
  - Pharmacokinetics

- **Primary endpoint**
  - PFS

- **Secondary endpoints**
  - Antitumor efficacy by CDK4/6-dependence and PD-L1 status
  - Pharmacodynamic effects in tumor and peripheral blood
  - Pharmacokinetics

- **Exploratory endpoints**
  - Pharmacodynamic effects in tumor and peripheral blood
  - Pharmacokinetics
  - Pharmacodynamics

- **Additional information**
  - Additional information may be found at https://clinicaltrials.gov/ct2/show/NCT04887831
  - The PRESERVE 3 study is sponsored by G1 Therapeutics, Inc.

- **Medical writing assistance**
  - Farhana Burnett, Scientific Writing and Publishing, Envision Therapeutics

- **Medical writing**
  - Medical writing assistance was provided by Farhana Burnett, Scientific Writing and Publishing, Envision Therapeutics

- **Clinical trial**
  - The PRESERVE 3 study is sponsored by G1 Therapeutics, Inc.

- **Patient eligibility**
  - Patients with progressive disease after platinum-based chemotherapy (trilaciclib per RECIST v1.1 with ongoing CR, PR, or SD may receive qualitative switch maintenance therapy with trilaciclib)
  - Complete response (CR), metabolic response, undetectable immune checkpoint-related PFS, partial response (RECIST v1.1), Response Evaluation Criteria in Solid Tumors version 1.0, stable disease

- **Key eligibility criteria**
  - Patients with progressive disease after platinum-based chemotherapy (trilaciclib per RECIST v1.1 with ongoing CR, PR, or SD may receive qualitative switch maintenance therapy with trilaciclib)
  - Complete response (CR), metabolic response, undetectable immune checkpoint-related PFS, partial response (RECIST v1.1), Response Evaluation Criteria in Solid Tumors version 1.0, stable disease

- **Key exclusion criteria**
  - Prior treatment with any therapeutic antibody or drug targeting T-cell co-stimulators or immune checkpoint pathways in any setting
  - Malignancies other than UC within 3 years
  - CNS metastases and/or leptomeningeal disease
  - Immunosuppression within 3 months of cycle 1
  - Adequate organ function as demonstrated by medical history and physical examination
  - Prior treatment with chemotherapy
  - Carboplatin dose ≥ 450 mg/m² or cisplatin dose ≥ 100 mg/m² within the 60 days before the Cycle 1 day 1
  - Prior radiation therapy of ≥ 40 Gy outside the chemotherapy period
  - Systemic therapy for any malignancy within 3 years (except basal cell carcinoma of the skin and cervical dysplasia with virologic eradication)

- **Primary endpoint**
  - OS
  - PFS
  - Occurrence and severity of adverse events

- **Secondary endpoints**
  - Antitumor efficacy by CDK4/6-dependence and PD-L1 status
  - Pharmacodynamic effects in tumor and peripheral blood
  - Pharmacokinetics

- **Exploratory endpoints**
  - Pharmacodynamic effects in tumor and peripheral blood
  - Pharmacokinetics
  - Pharmacodynamics

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