A Phase 3, Randomized, Open-Label, Multicenter, Global Study of First-Line Durvalumab + SoC Chemotherapy and Durvalumab + Tremelimumab and SoC Chemotherapy vs SoC Chemotherapy Alone in Unresectable Locally Advanced or Metastatic Urothelial Cancer

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Introduction	
<ul style="list-style-type: none">Bladder cancer is the ninth most common cancer diagnosis worldwide.More than 330,000 new cases each year.<ul style="list-style-type: none">More than 130,000 deaths per year.^{1,2}At initial diagnosis, over 5% of patients present with metastatic bladder cancer.³<ul style="list-style-type: none">Approximately 70% of cases are non-muscle-invasive bladder cancer (NMIBC) and 30% are muscle-invasive bladder cancer (MIBC).²<ul style="list-style-type: none">Nearly 40% of patients with NMIBC progress to MIBC within 5 years.^{4,5}Despite the high rate of disease control (over 80%) in the first-line (1L) setting, disease progression invariably occurs.⁶Combining immunotherapy with chemotherapy (CTX) could be a key option for improving clinical outcomes.	<ul style="list-style-type: none">The mechanisms of action of programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) are nonredundant; therefore, targeting both checkpoint pathways may have additive or synergistic efficacy compared with monotherapy.Durvalumab (D) is a selective, high-affinity, engineered human IgG1 monoclonal antibody (mAb) that blocks programmed cell death ligand-1 (PD-L1) binding to PD-1 and CD80.Tremelimumab (T) is a human IgG2 mAb directed against CTLA-4.Studies in other tumor types of platinum-based CTX combined with immunotherapy have demonstrated improved efficacy with acceptable safety and support exploration of this approach for 1L locally advanced or metastatic urothelial carcinoma (UC).⁷⁻⁹

Figure 1: Study design

D, durvalumab; OS, overall survival; PD, progressive disease; Q3W, every 3 weeks; Q4W, every 4 weeks; SoC, standard of care; T, tremelimumab.

Methods

Study Design

- This is a randomized, open-label, controlled, multicenter, global Phase 3 study to determine the efficacy and safety of combining D ± T with 6 cycles of SoC CTX (cisplatin + gemcitabine or carboplatin + gemcitabine doublet) followed by D monotherapy versus SoC alone as 1L CTX in patients with histologically or cytologically documented, unresectable, locally advanced, or metastatic transitional cell carcinoma of the urothelium (NCT02516241) (Figure 1).
- The study opened for enrollment in September 2018.

Outcome Measures

- The primary outcome measures of this study are to assess the efficacy of D + SoC CTX versus SoC CTX in terms of progression-free survival and OS in patients with unresectable, locally advanced, or metastatic UC.
- In addition to the primary outcome measures, several additional outcome measures will be explored.

Study Population

- Patients are eligible to be included in the study only if all of the inclusion criteria are met and no exclusion criteria apply (Tables 1 and 2).

Additional Outcome Measures

- OS at 24 months.
- Alive and progression-free survival at 12 months.
- Objective response rate.
- Duration of response.
- Disease control rate.
- Time from randomization to second progression.
- Assessment of disease-related symptoms, physical functioning, and other health-related quality of life measures.
- Summary of adverse events.
- Pharmacokinetics of D and T.
- Immunogenicity of D and T.

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Table 1: Inclusion criteria

Inclusion criteria
Histologically or cytologically documented transitional cell carcinoma of the urothelium not previously treated with 1L CTX
World Health Organization/Eastern Cooperative Oncology Group performance status of 0 or 1 at enrollment
At least 1 lesion, not previously irradiated, that qualifies as a Response Evaluation Criteria In Solid Tumors v.1.1 target lesion at baseline
Adequate organ and marrow function
Life expectancy ≥12 weeks in the opinion of the investigator

Table 2: Exclusion criteria

Exclusion criteria
Prior exposure to immune-mediated therapy (with exclusion of bacillus Calmette-Guérin), including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies
No severe concomitant condition that requires immunosuppression medication
Untreated central nervous system metastases and/or carcinomatous meningitis
Patients who may be eligible for, or are being considered for, radical resection during the course of the study
Any medical contraindications to platinum-based doublet CTX and/or known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients

Conclusions

- Exploring novel strategies, such as combining CTX with immunotherapy, offers hope for improving clinical outcomes.
- The preliminary efficacy, safety, and tolerability data of D ± T generated to date, together with positive signals with other immune-checkpoint inhibitors in combination with CTX in other tumor types,⁷⁻⁹ support the development of these treatments in combination with SoC CTX for metastatic or locally advanced unresectable UC in the 1L setting.
- Given the synergistic potential of D + T, the combination of both of these drugs with SoC CTX has the potential to further improve response rates and response durability in refractory UC.

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