STUDY REPORT SYNOPSIS

PREVAIL

A Prospective, Non-Interventional Study to Assess the Prevalence of PD-L1 Expression in the First-Line Setting of Locally Advanced/Unresectable or Metastatic Urothelial Carcinoma

Milestones:
Development of study design concept: 29Jun2018
Study kick-off meeting: 05Nov2018
First patient in: 17Jan2019
Last patient in: 01Feb2021
Initial protocol (v1.0): 17Oct2018
Protocol Amendment (v2.0): 17Jun2020
Database lock: 11Jul2023
Final results: 29Sep2023
Final report sign-off: 08Dec2023

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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale: Advanced urothelial carcinoma (UC) (locally advanced and unresectable or metastatic UC) is uniformly a fatal disease with 5-year survival rate of 5%. Cisplatin-based chemotherapy is the preferred first-line (1L) therapy for patients with advanced UC. However, many patients cannot tolerate cisplatin so 1L carboplatin-based chemotherapy is typically used in those patients. While patients who are cisplatin-ineligible can receive monotherapy with immune checkpoint inhibitors (anti-programmed death-ligand 1 [anti-PD-L1]/programmed cell death protein 1 [PD-1]), only 23% to 29% of patients respond in 1L setting.

Not all patients benefit from those therapies; therefore, there is an urgent need for biomarker-directed/targeted therapy strategy to enable patient selection and improve outcomes. The

most frequently studied diagnostic test for advanced UC is the PD-L1 protein expression by immunohistochemistry in tumor tissue.

Presently, the majority of data regarding PD-L1 prevalence in 1L advanced UC are derived from randomized clinical trials, with variable prevalence based on the used assay. Assessing the 'real-world' prevalence of PD-L1 in the 1L advanced UC setting will provide evidence to help both clinicians and researchers gain a more in-depth understanding of PD-L1 as a prognostic and/or predictive biomarker and could impact the role of PD-L1 testing in patient management and in clinical trials.

There has been increased interest in precision oncology and the search for meaningful biomarkers in UC. There are numerous additional predictive biomarkers under evaluation in UC, including but not limited to: tumor mutational burden (TMB), gene expression profiling, microsatellite instability, cell-free circulating tumor DNA (ctDNA), and DNA damage response (DDR) genomic alterations, among others. Observational studies focused on biomarker discovery and validation, aim to expand our understanding of UC biology and provide findings useful for clinical trial designs.

Objectives:

Primary objective: To assess the prevalence of pre-treatment tumor tissue PD-L1 high expression in the 1L setting in advanced UC patients using the Ventana SP263 assay.

Secondary objectives: The secondary objectives were as follows:

- To assess the association of pre-treatment tumor tissue PD-L1 expression with pre-treatment tumor tissue TMB (tTMB) based on the Tempus xT assay
- To describe the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), as well as treatment patterns, in the 1L setting of advanced UC
- To assess the association between pre-treatment tumor tissue PD-L1 expression with objective response (OR), PFS, and OS among treated patients (anti-PD-L1/PD-1 or chemotherapy or other)

Exploratory objectives:

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Study design: This was a prospective, non-interventional cohort study comprised of patients diagnosed with advanced UC using 1L therapy, who had pre-treatment tumor tissue available for testing. The study aimed to enroll 165 patients (for a total estimated 150 evaluable PD-L1 results and 50 baseline blood samples in newly diagnosed 1L advanced UC patients for ctDNA analysis) from approximately 60 sites across the United States. Sites were selected with preference for community-based oncology practices with large group practices with interest in research and preferably experience in conducting observational research (not a requirement). The study was conducted over a 54-month period (January 2019 – June 2023). Patients were identified to participate per the study inclusion and exclusion criteria and asked to provide informed consent to participate; the enrollment period lasted 26 months (January 2019 – February 2021). The per patient follow-up was up to 30 months from their study enrollment date until death, loss to follow-up, withdrawal of consent, or end of follow-up (whichever occurred first).

Data source: Site Investigators or trained site staff were responsible for enrolling patients, obtaining informed consent, submitting the patient's tumor tissue and blood to Q2 Solutions, and entering data. Electronic case report forms (eCRFs) were used to collect data required to address the study objectives. Study data were collected and entered directly into an eCRF using the electronic data capture (EDC) platform, by the site Investigator (or trained site staff). The site Investigator (or trained site staff) was responsible for ensuring that the required retrospective data (eg, comorbidities) from the medical chart was extracted accurately, and all the prospective data for each patient was collected and entered into the EDC approximately every 6 months (±4 weeks) through end of follow-up.

Study population: The study included patients with a diagnosis of locally advanced (unresectable) or metastatic UC (referred to as 'advanced UC') prior to or during 1L therapy (anti-PD L1/PD-1/chemotherapy/other).

Inclusion criteria: For inclusion in the study, patients had to fulfill all the following criteria:

1. Provision of written informed consent
2. Age ≥ 18 years old at the time of enrollment
3. Advanced UC diagnosis confirmed by their healthcare provider (HCP); histologically confirmed diagnosis of UC and HCP-confirmed advanced UC
4. Either currently receiving 1L systemic treatment for their advanced UC at the time of study start, or was starting 1L systemic treatment (ie, 'newly diagnosed' advanced UC); 1L therapy was defined as the first systemic therapy given for advanced UC)

Note:

a) A patient remained eligible for this study if they received neoadjuvant or adjuvant platinum-based chemotherapy, if their recurrence was more than 12 months after their last chemotherapy dose
b) Radio-sensitizing chemotherapy as part of chemoradiation (eg, for locoregional control) was not counted as neoadjuvant or adjuvant chemotherapy; thus, the 12 months interval mentioned above did not apply, and the patient was eligible

5. The patient must have had available tumor tissue (fresh or archival – up to 3 years old) that was collected as part of standard of care any time prior to the start date for 1L treatment of advanced UC. Already prepared slides must have been cut within 6 months prior to PD-L1 testing. In order for a patient to enroll, this study required tissue samples sufficient to generate a minimum of 7 slides (PD-L1 testing), and a preferred quantity of tissue sufficient to generate 18 slides available for all planned biomarker tests (PD-L1 and tissue genomic testing).

Exclusion criteria: Patients were excluded if they met any of the following criteria:

1. The patient was enrolled in a clinical trial(s) that prohibited participation in a non-interventional study
2. The patient had a resectable localized UC and had refused surgery
3. The patient had a history of non-urothelial active malignancy and completed systemic therapy within the last 2 years from study enrollment except:
   a) Any resected *in situ* carcinoma or non-melanoma skin cancer
   b) Localized (early stage) cancer treated with curative intent (without evidence of recurrence and intent for further therapy), and in which no systemic therapy was indicated

Statistical methods: All analyses were descriptive, and no formal hypothesis testing was planned. Descriptive analyses were performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables were reported as mean (and standard deviation [SD]) or median and range where appropriate. Categorical variables were summarized as number and proportion of the total study population, and by subgroups where appropriate. Time-to-event analyses were conducted using Kaplan-Meier and Cox Proportional Hazards methods.

All computations and generation of tables, listings and data for figures were performed using SAS® version 9.3 or higher.

Results:

Primary

The prevalence of pre-treatment PD-L1 high expression in the per-protocol set was 53.2% (95% confidence interval [CI]: 44.6-61.7) using the Ventana SP263 assay.

Secondary

There was no evidence that tTMB levels significantly differed (p = 0.337) among patients with PD-L1 high (CCI [redacted]) compared to patients with PD-L1 low (CCI [redacted]). The results were similar when tTMB was dichotomized.

The ORR for all 57 patients included in the analysis was 50.9% (95% CI: 37.3-64.4). The ORR was similar among patients with pre-treatment PD-L1 high (n = 17/33 [51.5%, 95% CI: 33.5-69.2%]) and PD-L1 low (n = 12/24 [50.0%, 95% CI: 29.1-70.9%]) status.

Chemotherapy was the most common class of 1L therapy (n = 56, 40.3%) followed by anti-PD-L1/PD-1 therapy (n = 47, 33.8%). 1L treatment duration was longest among patients using anti-PD-L1/PD-1 with a mean (SD) of 12.04 (10.746) months. The mean (SD) treatment duration for chemotherapy was 3.22 (3.031) months. Only 22 (15.9%) patients used antibiotics prior to their 1L treatment.

The median PFS was 15.1 months since first dose of 1L therapy among the 62 patients included in the analysis. Compared to patients who received anti-PD-L1/PD-1 1L therapy, there was no evidence that the risk of progression was significantly different (p = 0.634) in patients who received chemotherapy (hazard ratio [HR]: 1.39, 95% CI: 0.60-3.29) or patients who received 'other' 1L therapy (HR: 0.92, 95% CI: 0.31, 2.48).

Median OS was 25.4 months since first dose of 1L therapy. Compared to patients who received anti-PD-L1/PD-1 1L therapy, there was no evidence that the risk of death was significantly different (p = 0.692) in patients who received chemotherapy (HR: 1.18, 95% CI: 0.68-2.09) or patients who received 'other' 1L therapy (HR: 0.92, 95% CI: 0.48, 1.75).

Best OR was similar between patients with pre-treatment PD-L1 high and low.

There was no evidence that the risk of progression (HR: 0.72, 95% CI: 0.34-1.52; p = 0.385) or death (HR: 0.71, 95% CI: 0.44-1.15; p = 0.164) was significantly different in patients with PD-L1 high compared to PD-L1 low.

Exploratory

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Conclusion: In this study, PD-L1 high expression was only slightly more common among patients with locally advanced/metastatic UC than PD-L1 low using the Ventana SP263 assay. The findings from this study are consistent with the existing literature and suggest the utility of PD-L1 as a prognostic factor is limited among patients with locally advanced or metastatic UC who are initiating 1L therapy. In combination with literature published since this study's inception, these findings suggest additional evaluation in a larger sample of patients may be warranted to understand the potential prognostic capabilities of tTMB, bTMB, DDR alterations, and FGFR (1-4) alterations.

Publications:

Grivas P, Agarwal PK, Al-Ahmadie H, Friedlander T, Geynisman D, Hussain I, et al. Prevalence of PD-L1-High Expression in Advanced Urothelial Carcinoma (aUC): Results from the PREVAIL Prospective Cohort Study. Poster presented at ESMO Annual Congress; 9-13 September 2022; Paris, France