TISLELIZUMAB, AN ANTI-PD-1 ANTIBODY, IN PATIENTS WITH UROTHELIAL CARCINOMA (UC): RESULTS FROM AN ONGOING PHASE 1/2 STUDY

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BACKGROUND

- Until recently, treatment options for urothelial carcinoma (UC) have been limited
- In the last few years, monoclonal antibodies (mAbs) against immune checkpoint inhibitory receptors, like programmed cell death-1 (PD-1), have demonstrated promising antitumor activity across multiple malignancies,[1] including UC[2–7]
- PD-1 is relatively overexpressed on CD8+ effector tumor-infiltrating T lymphocytes (TILs); anti-PD-1 antibodies induce an increase in CD8+ T-cell percentages within the tumor microenvironment
- In vivo evidence has shown that anti-PD-1 antibodies demonstrate reduced tumor cytotoxicity when the Fc domain of the antibody engages with Fc-gamma receptors ($Fc\gamma Rs$)
  - $Fc\gamma R$ engagement results in preferential depletion of these CD8+ TILs[8]; this decrease may correlate with the dampening of the tumor cytotoxicity of anti-PD-1 therapy
- Tislelizumab (also known as BGB-A317) is an investigational humanized IgG4 mAb that has been shown to have high affinity and binding specificity against PD-1[9]
- Tislelizumab was engineered to minimize binding to $Fc\gamma R$ on macrophages, in order to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy[10]
- Previous reports from an ongoing phase 1A/1B study (NCT02407990) of tislelizumab in patients with advanced solid tumors suggested that tislelizumab has antitumor activity and is generally well tolerated[11]
  - Adverse events (AEs) were generally of low-to-moderate severity, manageable, and reversible[12]
- Here, we present updated results of patients with UC enrolled in this phase 1A/1B study

METHODS

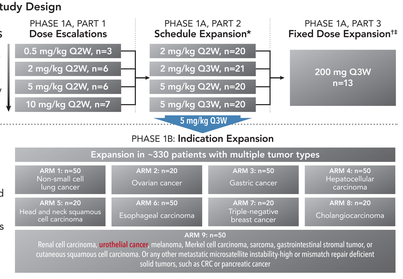
Overall Design and Study Objectives

- The study design is detailed in **Figure 1**
  - Patients with UC received tislelizumab at doses of 2, 5, or 10 mg/kg once every 2 or 3 weeks (Q2W or Q3W), and 200 mg Q3W
    - In phase 1A, 10 mg/kg Q2W was the maximum administered dosage of tislelizumab; the maximum tolerated dose (MTD) was not reached
    - All patients in phase 1B received tislelizumab as a 5 mg/kg intravenous (IV) infusion Q3W
  - Radiographic assessments were performed every 9 weeks per Response Evaluation Criteria In Solid Tumors guidelines version 1.1 (RECIST v1.1)

Key Eligibility Criteria of the UC Subset

- Adult patients (aged ≥18 years) with histologically or cytologically confirmed UC who have at least one measurable lesion, as defined per RECIST v1.1; who have received standard therapy, but no prior anti-PD-1 or programmed death ligand-1 (PD-L1) treatment; and who have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 were enrolled
- Patients who had a prior malignancy that was active within the previous 2 years, except for UC, and who had locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast, were excluded
- Pretreatment tumor samples were evaluated for PD-L1 membrane expression by immunohistochemistry performed on an automated platform (VENTANA PD-L1 [SP263] assay)
- PD-L1 expression status of any intensity was assessed on tumor cells (TC) and tumor-associated immune cells (IC)
  - PD-L1 high (PD-L1+) was defined as follows[13]:
    - If ICs involve >1% of the tumor area, either ≥25% of TCs or ≥25% of ICs express PD-L1
    - If ICs involve ≤1% of the tumor area, TCs ≥25% or ICs=100%

Figure 1: Study Design



*In select tumors for RP2D determination and preliminary differentiation, †In select tumors at fixed doses that do not exceed the exposure of MTD, ‡Conducted in parallel with phase 1B.

Abbreviations: CRC, colorectal cancer; MTD, maximum tolerated dose; Q2W/Q3W, every 2/3 weeks; RP2D, recommended phase 2 dose.

RESULTS

Patient Disposition

- As of 31 Aug 2018, 17 patients with UC had enrolled in this study, most (n=11) of whom received 5 mg/kg Q3W (**Table 1**)
- All patients with UC were Caucasian, 13 had ≥1 prior systemic anticancer therapy, and six patients had prior radiotherapy
  - A total of two patients remain on treatment

Table 1: Demographics and Disease Characteristics of Patients With UC

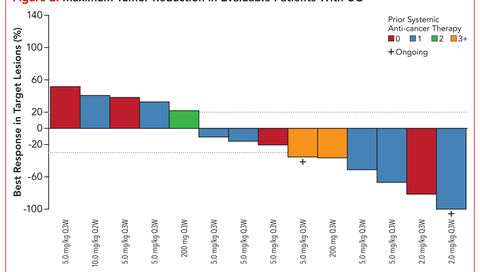
		UC Population (N=17)
Median age, years (min, max)		71 (39–79)
Sex, n	Male	14
	Female	3
Race, n	Caucasian	17
Median treatment duration, months (min, max)		4.1 (0.7, 30.4)
Prior systemic anticancer therapy regimens, n	0	4*
	1	7
	2	3
	≥3	3
Prior radiotherapy	No	11
	Yes	6

*Patients received prior treatment in the adjuvant and/or neoadjuvant setting.
Abbreviations: max, maximum; min, minimum; UC, urothelial carcinoma.

Preliminary Antitumor Activity

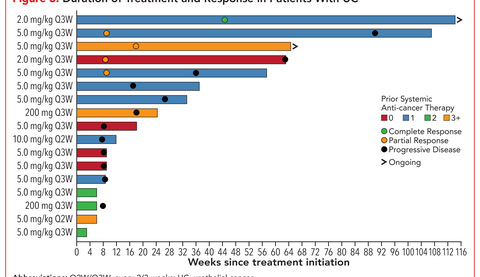
- All 17 patients were response evaluable (defined as having a measurable baseline tumor assessment and at least one evaluable post-baseline tumor response assessment, or had progressed or died prior to the initial tumor assessment)
- Confirmed objective response and disease control rates were 29.4% (95% CI: 10.31, 55.96) and 47.1% (95% CI: 22.98, 72.19), respectively
  - One patient achieved a confirmed complete response (CR), four achieved a confirmed partial response (PR), and three achieved stable disease (SD)
  - Tumor responses did not appear to be dose dependent
- Median duration of response was 18.7 months (range: 6.2–18.7)
  - Median treatment duration was 4.1 months (range: 0.7–26.3) and median time to response was 2.1 months (range: 2.0–10.3)
- The antitumor activity of tislelizumab is presented in **Figures 2–4**

Figure 2: Maximum Tumor Reduction in Evaluable Patients With UC



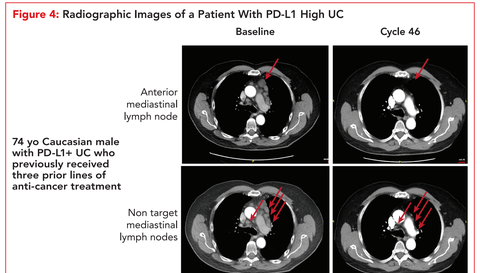
Abbreviations: Q2W/Q3W, every 2/3 weeks; UC, urothelial cancer.

Figure 3: Duration of Treatment and Response in Patients With UC



Abbreviations: Q2W/Q3W, every 2/3 weeks; UC, urothelial cancer.

Figure 4: Radiographic Images of a Patient With PD-L1 High UC



Abbreviations: PD-L1, programmed cell death ligand-1; UC, urothelial cancer.

Response by PD-L1 Status

- As of 31 Aug 2018, a total of 16 patients were evaluable for both PD-L1 status and clinical response
- Clinical responses were observed in patients with both PD-L1+ and PD-L1– patients (**Table 2** and **Figure 4**)

Table 2: Confirmed Best Overall Response for Each Evaluable Patient by PD-L1 Status

Best Overall Response–Confirmed	PD-L1+ (n=8)	PD-L1– (n=8)	Missing (n=1)	Overall (N=17)
CR, n (%)	1 (12.5)	0	0	1 (5.9)
PR, n (%)	1 (12.5)	2 (25.0)	1 (100)*	4 (23.5)
SD, n (%)	1 (12.5)	2 (25.0)	0	3 (17.6)
PD, n (%)	3 (37.5)	3 (37.5)	0	6 (35.3)
NE/Missing, n (%)	2 (25)	1 (12.5)	0	3 (17.6)
ORR, % (95% CI)	25 (3.2,65.1)	25 (3.2,65.1)	100	29.4 (10.31, 55.96)
DCR, % (95% CI)	37.5 (8.5,75.5)	50 (15.7,84.3)	100	47.1 (22.98, 72.19)

*PD-L1 status was not evaluable due to insufficient tumor tissue.
Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; ORR, objective response rate; SD, stable disease.

Safety and Tolerability

- Treatment with tislelizumab was generally well tolerated in patients with UC
- Treatment-related AEs (TRAEs) occurred in 15 of the 17 patients with UC (**Table 3**)
  - Two patients experienced a total of three AEs considered related to treatment that were grade ≥3 in severity (fatigue, hyperglycemia, and latent autoimmune diabetes in adults); none were fatal
- One patient discontinued treatment due to recurrent infusion-related reactions considered related to tislelizumab
  - Reactions included lower back pain, facial flushing, and rigor, all of which were grade 1 or 2 in severity

Table 3: Treatment-Related AEs Occurring in ≥2 Patients with UC

UC Population (N=17)	All Grades, n	Grades ≥3, n
Fatigue	5	1
Infusion-related reaction	3	0
Rash	3	0
Nausea	2	0
Pain in extremity	2	0
Peripheral oedema	2	0
Proteinuria	2	0

Abbreviations: AE, adverse event; UC, urothelial carcinoma.

CONCLUSIONS

- Treatment with tislelizumab was generally well tolerated in pretreated patients with UC
- As of 31 August 2018, two patients remained on treatment; the median treatment duration was 4.1 months (range: 0.7–26.3)
- Adverse events reported in patients with UC were consistent with the overall safety profile observed in the study and were considered manageable and generally of low or moderate severity
- Across the 17 evaluable patients, five patients achieved confirmed responses (CR, n=1; PR, n=4) and three patients achieved a confirmed best overall response of SD
  - Objective responses were observed in patients with PD-L1+ and PD-L1– disease
- The safety/tolerability profile and antitumor activity from this ongoing study support continued development of tislelizumab in patients with UC
  - Tislelizumab is currently being investigated in China as monotherapy for patients with PD-L1+ UC (CTR20170071)

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