FIRST REPORT OF EFFICACY AND SAFETY FROM A PHASE 2 TRIAL OF TISLELIZUMAB, AN ANTI-PD-1 ANTIBODY, FOR THE TREATMENT OF PD-L1+ LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA IN ASIAN PATIENTS

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BACKGROUND

- Urothelial carcinoma (UC) is the most common histologic type of bladder cancer, one of the most common urologic malignancies in China[1]
  - In China, bladder cancer accounted for approximately 80,500 new cancer cases and 32,900 deaths in 2015[2]
- Until recently, initial treatments for patients with metastatic UC were limited to platinum-based chemotherapy regimens[3]
  - Median overall survival (OS) of 14.1 to 15.5 months was reported for patients who were eligible for cisplatin-containing regimens[4,5] and 13.8 months for patients who were eligible for carboplatin-containing regimens[4]
- The programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) axis plays a central role in suppressing antitumor immunity; dysregulation of the PD-1/PD-L1 axis can be used by cancer cells to evade the immune system[6,7]
  - While tumor overexpression of PD-L1 has been shown to be associated with poor outcomes for patients with melanoma, ovarian cancer, and lung cancers,[8] the role of PD-L1 in bladder cancer as a predictive biomarker remains less clear[9]
- Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1
  - Tislelizumab shows higher affinity for PD-1 than pembrolizumab and nivolumab, with an approximate 100- and 50-fold slower off-rate, respectively[10]
- Data from two phase 1 studies (NCT02407990; CTR20160872) suggested that single-agent tislelizumab was generally well tolerated and demonstrated antitumor activity in patients with UC
  - Clinical responses were observed in both PD-L1 positive (PD-L1+) and PD-L1 negative (PD-L1–)/unknown UC tumors; objective response rates (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria were 24% for PD-L1+ and 21% for PD-L1–/unknown (data on file)
- This phase 2 clinical trial (CTR20170071), conducted in China and other Asian countries, assessed the safety, tolerability, and efficacy of tislelizumab at the recommended phase 2 dose (200 mg every 3 weeks [Q3W]) in patients with locally advanced or metastatic PD-L1+ UC previously treated with ≥1 platinum-containing therapy

METHODS

- This single-arm, multicenter, phase 2 study was composed of an initial screening phase (up to 28 days), a treatment phase (until disease progression, intolerable toxicity, or treatment withdrawal for other reasons), safety follow-up phase, and survival follow-up phase
  - All patients received 200 mg of tislelizumab intravenously (IV) Q3W
  - Radiological assessment of tumor-response status is performed every 9 weeks; response was assessed by an independent review committee (IRC), based on the RECIST v1.1 criteria, and by the investigators, based on RECIST v1.1 and immune-related RECIST (irRECIST)

Study Population

- The study population includes adult patients (aged ≥18 years) with histologically or cytologically documented locally advanced or metastatic UC previously treated with ≥1 platinum-containing therapy, with at least one measurable lesion, as defined per RECIST v1.1
  - Prior treatment with a PD-1/PD-L1 inhibitor was not allowed
- During screening, archival tissue or fresh biopsy from all patients was sent to a central laboratory for PD-L1 testing via the VENTANA SP263 immunohistochemistry assay
  - Patients were considered PD-L1+ if ≥25% of tumor cells or immune cells (IC) had PD-L1 expression, if ICs involve >1% of the tumor area
  - If the tumor area involves ≤1% of ICs, patients were considered PD-L1+ if ≥25% of tumor cells or 100% of ICs expressed PD-L1

Study Assessments and Statistical Analyses

- The ORR, assessed by the IRC per RECIST v1.1, was the primary endpoint
- Secondary efficacy endpoints included:
  - Duration of response (DoR), progression-free survival (PFS), and disease control rate (DCR), as assessed by IRC per RECIST v1.1
  - The ORR, DoR, PFS, and DCR, as assessed by investigators per RECIST v1.1 and irRECIST
- The safety/tolerability profile of tislelizumab was also a secondary objective
  - Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v18.1 (or higher) and were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03

RESULTS

Patient Disposition, Demographics, and Baseline Disease Characteristics

- As of 28 February 2019, 113 patients with PD-L1+ locally advanced/metastatic UC were enrolled in the study and all were treated with tislelizumab (Table 1)
  - Thirty patients remained on treatment and 83 discontinued tislelizumab (reasons for discontinuation included disease progression [n=49], AEs [n=14], withdrawal of consent [n=11], and symptomatic deterioration [n=9])
  - The median duration of tislelizumab treatment was 15.3 weeks (range: 2, 72)
- The median patient age was 63 years (range: 36, 81); most patients were male (74%) with an Eastern Cooperative Oncology Group score of 1 (53%)
- The primary tumor was most commonly found in the urinary bladder (n=51); commonly known metastatic sites included the lymph nodes (n=68), lung (n=43), and liver (n=27)

Table 1: Patient Demographics and Baseline Disease Characteristics

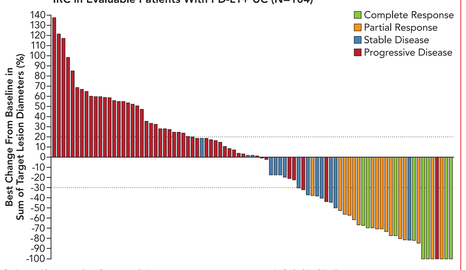
		(N=113)
Age (years), median (range)		63 (36, 81)
Gender, n (%)	Male	84 (74.3)
	Female	29 (25.7)
Country, n (%)	China	108 (95.6)
	Korea	5 (4.4)
ECOG performance at baseline, n (%)	0	53 (46.9)
	1	60 (53.1)
Site of primary tumor, n (%)	Urinary bladder	51 (45.1)
	Renal pelvis	31 (27.4)
	Ureters	24 (21.2)
	Urethra	3 (2.7)
	Other	4 (3.5)
Known metastasis, n (%)	Lymph node	68 (60.2)
	Lung	43 (38.1)
	Liver	27 (23.9)
	Bone	26 (23.0)
	Pelvic cavity	11 (9.7)
	Abdominal cavity	10 (8.8)
	Brain	2 (1.8)
	Other	36 (31.9)
Number of prior regimens, n (%)	1	69 (61.1)
	2	37 (32.7)
	≥3	7 (6.2)
PD-L1 expression, n (%)	TC <50% and IC <50%	77 (68.1)
	TC ≥50% or IC ≥50%	36 (31.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IC, immune cell; PD-L1, programmed cell death ligand-1; TC, tumor cell.

Antitumor Activity

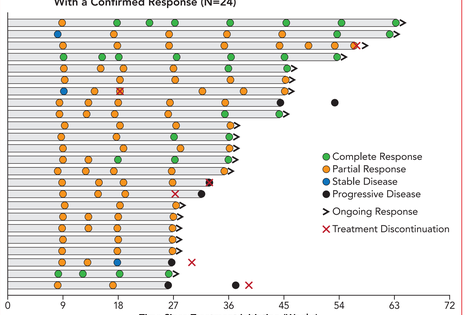
- A total of 104 patients were evaluable for tumor response, defined as any patient who had measurable disease at baseline per IRC assessment
- Of the 104 evaluable patients, a confirmed objective response was observed in 24 patients (ORR=23%, 95% CI: 15.4, 32.4), including eight complete responses (CRs) and 16 partial responses (PRs) per IRC assessment (Table 2)
  - Thirty-four (33%) of 104 patients had a reduction of 30% or more in the sum of target lesion diameter from baseline per IRC assessment (Figure 1)
  - At the data cut-off date, the median DoR per IRC assessment was not reached; 19/24 (79%) responders had ongoing responses at data cut-off (Figure 2)
- Most of the subgroups showed consistent results (Figure 3)
  - Differences between subgroups were not significant due to small sample size
- Median PFS and OS were 2.1 and 9.8 months, respectively (Table 3)

Figure 1: Best Percent Change in Sum of Target Lesion Diameters from Baseline per IRC in Evaluable Patients With PD-L1+ UC (N=104)



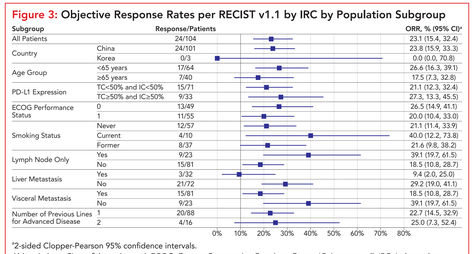
Patients without post-baseline target lesion tumor measurements were not included in this plot.
Abbreviations: IRC, independent review committee; PD-L1+, programmed cell death ligand-1 positive; UC, urothelial carcinoma.

Figure 2: Duration of Treatment and Response per RECIST v1.1 by IRC in Patients With a Confirmed Response (N=24)



Abbreviations: IRC, independent review committee; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 3: Objective Response Rates per RECIST v1.1 by IRC by Population Subgroup



*2-sided Clopper-Pearson 95% confidence intervals.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IC, immune cell; IRC, independent review committee; ORR, objective response rate; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell.

Table 2: Disease Response per RECIST v1.1 by IRC in Evaluable Patients With PD-L1+ UC

Response Category		N=104
Best overall response, n (%)	Complete response (CR)	8 (7.7)
	Partial response (PR)	16 (15.4)
	Stable disease (SD)	14 (13.5)
	Progressive disease (PD)	49 (47.1)
	Not evaluable for response (NE)	17 (16.3)
Objective response rate, % (95% CI)		23.1% (15.4, 32.4)
Disease control rate, % (95% CI)		36.5% (27.3, 46.6)
Clinical benefit rate, % (95% CI)		27.9% (19.5, 37.5)

Objective response rate was the proportion of patients who had confirmed complete response or partial response using RECIST v1.1; disease control rate was the proportion of patients who achieved confirmed complete response or partial response or stable disease using RECIST v1.1; clinical benefit rate was defined as patients with CR or PR or ≥24 weeks SD.
Abbreviations: CI, confidence interval; IRC, independent review committee; PD-L1+, programmed cell death ligand-1 positive; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial carcinoma.

Table 3: Progression-Free and Overall Survival per RECIST v1.1 by IRC

Progression-Free Survival per IRC		n=104
Events, n (%)		81 (77.9)
Progressive disease		65 (62.5)
Death		16 (15.4)
Censor, n (%)		23 (22.1)
PFS (months), median (95% CI)		2.1 (2.00, 2.46)
Follow-up time (months), median (95% CI)		8.3 (8.11, 10.41)
Event-free rate at, % (95% CI)	6 months	30.2 (21.59, 39.27)
	12 months	16.8 (9.48, 26.00)
Overall Survival		**n=113**
Death, n (%)		58 (51.3)
Censor, n (%)		55 (48.7)
OS (months), median (95% CI)		9.8 (7.46, 13.50)
Follow-up time (months), median (95% CI)		10.2 (9.46, 11.73)
Event-free rate at, % (95% CI)	6 months	66.5 (56.89, 74.49)
	12 months	46.5 (35.83, 56.43)

Follow-up time was estimated by the reverse Kaplan-Meier method.
Abbreviations: CI, confidence interval; IRC, independent review committee; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 4: Treatment-Related AEs, ≥10% of Patients (N=113)

Event	All Grades, n (%)	Grades 3-4, n (%)
Patients with at least one treatment-related AE	**105 (92.9)**	**39 (34.5)**
Anemia	30 (26.5)	8 (7.1)
Decreased appetite	21 (18.6)	4 (3.5)
Pyrexia	19 (16.8)	0 (0.0)
Aspartate aminotransferase increased	17 (15.0)	2 (1.8)
Pruritus	17 (15.0)	0 (0.0)
Alanine aminotransferase increased	16 (14.2)	3 (2.7)
Hyponatremia	16 (14.2)	4 (3.5)
Blood creatinine increased	15 (13.3)	2 (1.8)
Constipation	15 (13.3)	0 (0.0)
Rash	15 (13.3)	0 (0.0)
Urinary tract infection	14 (12.4)	5 (4.4)
Hypoalbuminemia	13 (11.5)	0 (0.0)

Data presented as n (%).
Abbreviations: AE, adverse event.

CONCLUSIONS

- Tislelizumab was generally well tolerated and demonstrated clinical activity in patients with UC
  - At the data cut-off date, median study follow-up was 7.6 months (range: 0.4-17.4); 30 patients remain on treatment
- Anemia (27%), decreased appetite (19%), and pyrexia (17%) were the only treatment-related TEAEs occurring in >15% of patients
  - Anemia (7%) was the only grade 3-4 treatment-related AE occurring in ≥5% patients
- In evaluable patients, 24 patients achieved confirmed CR (n=8) or PR (n=16) per IRC; ORR per IRC was 23% (15.4, 32.4)
  - The subgroup analyses indicate that response rates were not considerably influenced by baseline factors
  - The response rates reported here were similar to pooled data from two phase 1 studies in which ORR in PD-L1+ and PD-L1–/unknown UC tumors were 24% and 21%, respectively
- Tislelizumab has received a priority review by China's National Medical Product Administration (NMPA) based on preliminary results from the current trial

Safety and Tolerability

- Per the investigator, treatment-related AEs (TRAEs) were reported in 93% (n=105/113) of patients with PD-L1+ UC
  - A total of 12 (11%) patients experienced a TRAE that led to treatment discontinuation
    - Drug eruption (n=2) was the only TRAE that led to treatment discontinuation in >1 patient
- Anemia (27%), decreased appetite (19%), and pyrexia (17%) were the only TRAEs occurring in >15% of patients; the majority of reported TRAEs were grade ≤2 in severity (Table 4)
  - Anemia (7%) was the only grade 3-4 TRAE occurring in ≥5% patients
- A total of 64% of patients experienced an immune-related TEAE
  - Common immune-related TEAEs included immune-mediated skin adverse reaction (n=38; 34%), immune-mediated hepatitis (n=27; 24%), thyroid disorders (n=15; 13%), and immune-mediated nephritis and renal dysfunction (n=13; 12%)
  - No immune-related TEAEs ≥ grade 3 occurred in over 5% of patients
- Four patients experienced a fatal TRAE (hepatic failure, n=2; respiratory arrest, n=1; renal impairment, n=1)
  - The events of hepatic failure and respiratory arrest were reported as possibly related by the investigator; the event of renal impairment was reported as possibly unrelated by the investigator

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CONFLICTS OF INTEREST

DY: nothing to disclose. **JL:** nothing to disclose. **AZ:** nothing to disclose. **QZ:** nothing to disclose. **HL:** nothing to disclose. **CF:** nothing to disclose. **HH:** nothing to disclose. **SZ:** nothing to disclose. **JJ:** nothing to disclose. **LM:** nothing to disclose. **BF:** nothing to disclose. **JG:** nothing to disclose. **JX:** nothing to disclose. **SHP:** nothing to disclose. **DZ:** nothing to disclose. **XQ:** Employee- BeiGene USA, Inc.; **YB:** Employee- BeiGene USA, Inc.; **LZ:** Employee- BeiGene USA, Inc.; **WS:** Employee- BeiGene USA, Inc.

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