PRELIMINARY RESULTS WITH TISLELIZUMAB, AN INVESTIGATIONAL ANTI-PD-1 ANTIBODY, IN CHINESE PATIENTS WITH NASOPHARYNGEAL CANCER

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BACKGROUND

- Nasopharyngeal carcinoma (NPC) is a malignant neoplasm that arises in the epithelial lining of the nasopharynx[1]
- The epidemiology of NPC is characterized by a unique geographic distribution, with southern China having one of the highest incidence rates worldwide (**Supplemental Figure 1**)[2]
  - In addition to geography, sex and age are epidemiological characteristics of NPC that affect incidence and mortality[3,4]; Epstein-Barr virus has also been reported to be strongly linked with NPC in epidemic areas[5]
- Although NPC is a chemosensitive disease, outcomes are very poor in late stage disease (stage IV) where the 5-year survival rate is <10%[6]
- The programmed cell death-1 (PD-1)/programmed cell death ligand-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[7,8]
  - An infiltration of T cells in the primary tumor characterizes NPC; PD-1 is an immunosuppressive receptor expressed in T cells[9]
- Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1
  - Tislelizumab shows higher affinity to PD-1 than pembrolizumab and nivolumab with an ~100- and 50-fold slower off-rate, respectively[10]
- Tislelizumab has a different binding orientation to PD-1 compared with pembrolizumab and nivolumab; the binding surface on PD-1 for tislelizumab partially overlaps with that for pembrolizumab, but differs significantly from that for nivolumab[10]
- Tislelizumab was engineered to minimize binding to $Fc\gamma R$ on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy[11]
- Previous reports from this phase 1/2 study (CTR20160872) have shown that single-agent tislelizumab was generally well tolerated and demonstrated preliminary antitumor activity in Chinese patients with advanced solid tumors[12,13]
  - In the dose-verification part of this study, the recommended dose was established as 200 mg IV every 3 weeks (Q3W)[14]
- Here we present preliminary results from the NPC patients in this study

METHODS

- The overall design of the study is detailed in **Supplemental Figure 2**
- In the dose-verification (phase 1)/indication-expansion (phase 2) study, with a pharmacokinetic sub-study, patients were administered tislelizumab at 200 mg Q3W IV until they demonstrated no evidence of continued clinical benefit, developed unacceptable toxicity in the opinion of the investigator, or until a patient chose to withdraw informed consent
- Once the recommended phase 2 dose of tislelizumab was confirmed to be 200 mg Q3W IV, patients were enrolled into 11 groups of tumor types in the indication-expansion phase 2 study and were administered tislelizumab at this dose level
- Disease assessment by radiographic imaging (enhanced CT or MRI) was performed approximately every 9 weeks during the first 12 months and approximately every 12 weeks thereafter according to RECIST v1.1 criteria
- Adverse events (AEs) were graded and recorded throughout the study according to NCI-CTCAE v.4.03
- PD-L1 expressed on tumor cells was retrospectively assessed by the central lab with VENTANA PD-L1 (SP263) assay

Nasopharyngeal Carcinoma Study Population

- Adult patients (aged ≥18 years) with histologically or cytologically confirmed advanced/metastatic (unresectable) WHO type II-III (differentiated nonkeratinizing type and undifferentiated nonkeratinizing type) NPC, who had progressed on, or were unable to tolerate, standard antitumor treatment, and had no access to standard treatment or had refused standard therapy, were enrolled to receive tislelizumab 200 mg Q3W administered by IV infusion
- Patients were excluded if they had a history of severe hypersensitivity reactions to other monoclonal antibodies, received prior therapies targeting PD-1 or PD-L1, or had a prior active malignancy other than NPC within the previous 2 years

Study Assessments

- The objective response rate (ORR), based on investigator-assessed RECIST v1.1 criteria, was the primary efficacy endpoint in the indication-expansion phase
  - Key secondary efficacy endpoints included disease control rate (DCR) = complete response (CR) + partial response (PR) + stable disease (SD), clinical benefit rate (CBR) = CR + PR + SD with a duration of ≥24 weeks, progression-free survival (PFS), and overall survival (OS)
- Tislelizumab's safety/tolerability profile was assessed as a secondary endpoint in the indication-expansion phase

RESULTS

Patient Disposition

- As of 01 December 2018, 21 Chinese patients with NPC (n=1, phase 1; n=20, phase 2) were enrolled in the study (**Table 1**)
  - Across the 21 patients, median study follow-up time was 11.7 months (range: 4.9-15.7)
- At the time of data cut-off, nine patients remained on treatment; 12 discontinued tislelizumab
  - Eleven patients discontinued due to disease progression; one patient discontinued due to emergence of an AE (grade 4 cutaneous reaction considered possibly related to tislelizumab)
- The median duration of tislelizumab treatment was 7.5 months (range: 2.1-15.8)

Demographics and Baseline Disease Characteristics

- The majority of patients were male (n=17; 81%), never smoked (n=14; 67%), and had received ≥1 lines of prior anticancer therapy (n=20; 95%)
- The majority of patients had metastatic disease (n=18; 86%) and a NPC histologic grade of undifferentiated (n=16; 76%)
- Most patients (n=16; 76%) had PD-L1 membrane staining in ≥10% of tumor cells

Table 1: Demographics and Disease Characteristics in Patients With NPC

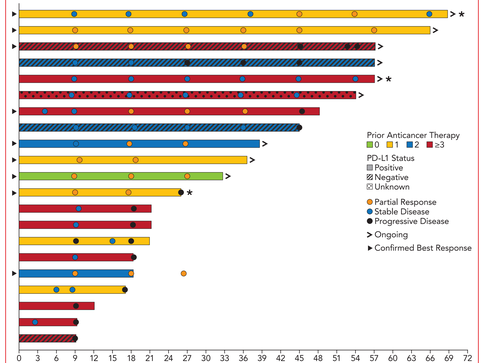
		NPC (N=21)
Median age, years (min, max)		48 (35, 61)
Sex	Male	17 (81)
	Female	4 (19)
Prior anticancer radiotherapy		21 (100)
Prior anticancer therapy regimens	0	1 (5)
	1	6 (29)
	2	4 (19)
	≥3	10 (48)
ECOG status	0	8 (38)
	1	13 (62)
Histologic grade	Poorly differentiated	2 (10)
	Undifferentiated	16 (76)
	Unknown	3 (14)
Tumor stage	Locally advanced	3 (14)
	Metastatic	18 (86)
PD-L1 status	PD-L1 positive (PD-L1+)*	16 (76)
	PD-L1 negative (PD-L1-)†	4 (19)
	Unknown	1 (5)

Data presented as n (%).
*PD-L1-positive status defined as ≥10% of tumor cells with PD-L1 membrane staining, as retrospectively assessed by central lab; †PD-L1-negative status defined as <10% of tumor cells with PD-L1 membrane staining, as retrospectively assessed by central lab.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NPC, nasopharyngeal carcinoma; PD-L1, programmed cell death ligand-1.

Preliminary Antitumor Activity

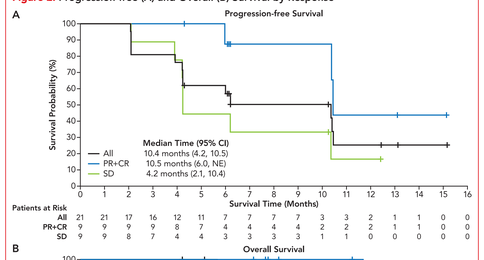
- A total of 21 patients were evaluable for antitumor activity, defined as any patient who had measurable disease at baseline and at least one postbaseline tumor assessment
- A total of nine patients (n=8, PD-L1+; n=1, PD-L1-) achieved a confirmed PR, nine patients (n=6, PD-L1+; n=2, PD-L1-; n=1, unknown) achieved confirmed SD
- Confirmed ORR was 43% (95% confidence interval [CI]: 21.8-66.0)
  - CBR and DCR were 62% (95% CI: 38.4-81.9) and 86% (95% CI: 63.7-97.0), respectively
- Median duration of response was 8.3 months (95% CI: 3.9, not reached); follow-up time for responders was 4.8 months (95% CI: 2.1-11.1)
- The antitumor activity of tislelizumab is presented in **Figures 1-3**
- Progression-free and overall survival are presented in **Figure 2**
  - Median follow-up time for PFS was 12.4 months (95% CI: 6.1, 15.2); median OS follow-up time was 11.4 months (95% CI: 8.2, 12.5)

Figure 1: Duration of Treatment and Response in Evaluable Patients With NPC



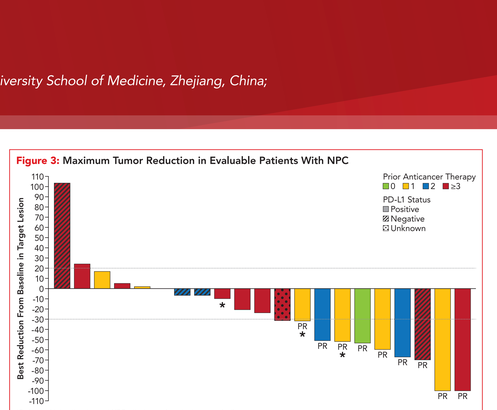
*Patients with locally advanced NPC; all other patients had metastatic disease.
PD-L1 positive defined as ≥10% of tumor cells with PD-L1 membrane staining; PD-L1 negative is defined as <10% of tumor cells with PD-L1 membrane staining.
Abbreviations: NPC, nasopharyngeal carcinoma; PD-L1, programmed cell death ligand-1.

Figure 2: Progression-free (A) and Overall (B) Survival by Response*



*Due to small sample size, patients with progressive disease (n=3) are not shown.
Abbreviations: CR, complete response; NE, not evaluable; PR, partial response; SD, stable disease.

Figure 3: Maximum Tumor Reduction in Evaluable Patients With NPC



*Patients with locally advanced NPC; all other patients had metastatic disease.
PD-L1 positive defined as ≥10% of tumor cells with PD-L1 membrane staining; PD-L1 negative is defined as <10% of tumor cells with PD-L1 membrane staining.
Abbreviations: NPC, nasopharyngeal carcinoma; PD-L1, programmed cell death ligand-1; PR, partial response.

Safety and Tolerability

- Treatment-emergent adverse events (TEAEs) were reported in 20 out of a total 21 patients with NPC (**Table 2**)
- One treatment-related AE (TRAE; grade 4 cutaneous reaction) led to treatment discontinuation; while tislelizumab was delayed due to TEAEs in four patients, no TEAE led to dose (infusion) interruption or dose reduction
- Fourteen patients experienced TRAEs as assessed by investigator
  - Hypothyroidism (n=5; 24%) and anemia (n=3; 14%) were the only TRAEs occurring in more than two patients (**Table 3**)
- Of the eight patients who experienced ≥1 immune-related AEs (irAEs), two patients experienced three grade ≥3 irAEs (drug eruption, rash, and increased γ-glutamyltransferase; n=1 each)
- No patients experienced fatal TRAEs

Table 2: Summary of Adverse Events Occurring in Patients With NPC

	NPC (N=21)
Patients with ≥1 AE	20 (95)
Patients with ≥1 AE grade ≥3	6 (29)
Patients with ≥1 serious AE	3 (14)
Patients with ≥1 TRAE	14 (67)
Patients with ≥1 TRAE grade ≥3	3 (14)
Patients with ≥1 serious TRAE	2 (10)
Patients with ≥1 immune-related AE (irAE)*	8 (38)
TEAE leading to death	0
TEAE leading to treatment discontinuation	1 (5)
TEAE leading to dose interruption	0
TEAE leading to dose delay	4 (19)

Data presented as n (%). *All reported irAEs were considered related to tislelizumab.
Abbreviations: AE, adverse event; NPC, nasopharyngeal carcinoma; TEAE, treatment-emergent adverse event; TRAE, treatment-related AE.

Table 3: Adverse Events Considered Related to Tislelizumab (Overall and Grade ≥3) Occurring in ≥2 Patients

	NPC (N=21)	
	All grades	Grade ≥3*
Hypothyroidism	5 (24)	0
Anemia	3 (14)	0
Increased AST	2 (10)	0
Hemoptysis	2 (10)	0

Data presented as n (%).
*Three patients experienced four grade ≥3 TRAEs (drug eruption, increased γ-glutamyltransferase, gingivitis, and rash; n=1 each).
Abbreviations: AST, aspartate aminotransferase; NPC, nasopharyngeal carcinoma.

CONCLUSIONS

- Treatment with tislelizumab was generally well tolerated and demonstrated preliminary antitumor activity in patients with NPC
  - Median follow-up was 11.7 months and nine (43%) patients remain on treatment
- Eighteen patients achieved confirmed PR (n=9) or SD (n=9); ORR and DCR were 43% and 86%, respectively
  - Clinical benefit was observed regardless of PD-L1 expression
  - Median duration of response was estimated as 8.3 months
- Median PFS was 10.4 months (95% CI: 4.2, 10.5); however, data were not yet mature enough to estimate OS
- Adverse events reported in patients with NPC were consistent with the overall safety profile of tislelizumab observed in previous studies with other tumor types and TRAEs were generally of severity grade ≤2
- The safety/tolerability profile and antitumor activity observed in this phase 1/2 study support continued development of tislelizumab in patients with NPC
  - A randomized double-blind phase 3 study (NCT03924986) comparing the safety, tolerability and efficacy of tislelizumab in combination with gemcitabine plus cisplatin versus placebo combined with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic NPC has been initiated

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