Updated analysis from a Phase 2 study of tislelizumab monotherapy in patients with previously treated, locally advanced unresectable or metastatic microsatellite instability-high or mismatch repair-deficient solid tumors

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Abstract No: 1

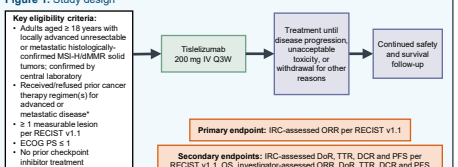
Background

- Microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) tumors share common histopathologic characteristics that may render them susceptible to immune checkpoint inhibitors, such as anti-programmed cell death protein 1 (PD-1)/programmed death ligand-1 (PD-L1) monoclonal antibodies[1–3]
- Clinical data indicate MSI-H/dMMR as a strong predictive biomarker for immunotherapy and support a tissue-agnostic approach for the treatment of MSI-H/dMMR solid tumors[4]
- Tislelizumab is an anti-PD-1 monoclonal antibody with high affinity and binding specificity for PD-1 that has been engineered to minimize Fcγ receptor binding on macrophages, thereby abrogating antibody-dependent cellular phagocytosis[5]
- In early phase clinical studies, tislelizumab monotherapy was generally well tolerated and had antitumor activity in patients with solid tumors, including MSI-H/dMMR solid tumors such as colorectal cancer (CRC)[6]
- We report the updated results of a Phase 2 study evaluating the efficacy and safety of tislelizumab monotherapy in patients with previously treated, locally advanced unresectable or metastatic MSI-H/dMMR solid tumors

Methods

- RATIONALE 209 (NCT03736889) is an ongoing single-arm, open-label, multicenter study conducted at 26 sites in China (**Figure 1**)

Figure 1. Study design



*≥ 2 prior regimens for CRC; ≥ 1 prior regimens for other cancer types
CRC, colorectal cancer; DCR, disease control rate; dMMR, mismatch-repair-deficient; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICR, independent review committee; IV, intravenously; MSI-H, microsatellite instability-high; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; Q3W, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response

- **Efficacy evaluable (EE) analysis set:** All patients who received any dose of tislelizumab and had measurable disease per independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) at baseline
- **Safety analysis set:** All patients who received any dose of tislelizumab (overall survival [OS] and safety)
- A binomial exact test with a one-sided p ≤ 0.025 was performed in the analysis of the primary endpoint to test the historical objective response rate (ORR) of 10%. Two-sided Clopper-Pearson 95% confidence intervals (CI) were also calculated. Disease control rate (DCR) was assessed in a similar way to ORR
- Duration of response (DoR) was analyzed among responders using the Kaplan-Meier method, with 95% CI constructed. Progression-free survival (PFS), in the EE analysis set, and OS, in the safety analysis set, were analyzed with similar methodology as DoR. Time to response (TTR) was assessed among responders using descriptive statistics
- Safety variables including the extent of exposure to study treatments and the incidence of adverse events (AEs) were assessed among responders using descriptive statistics
- PD-L1 expression was assessed retrospectively using the Ventana SP263 immunohistochemistry assay. Samples were deemed PD-L1 positive at a cut-off of ≥ 1% on tumor cells (TC) or ≥ 5% on immune cells (IC)

Conclusions

- **Tislelizumab monotherapy demonstrated a clinically meaningful improvement in ORR**, as compared with historical data, in patients with previously treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumors
- With a longer follow-up, this updated analysis confirmed the clinical benefit of tislelizumab across tumor types. **The treatment effect of tislelizumab was not associated with PD-L1 expression**
- Tislelizumab was **generally well tolerated** with few patients discontinuing treatment due to TRAEs, and no new safety signals were identified
- The results of this updated Phase 2 study support tislelizumab as a potential new treatment option in this MSI-H/dMMR biomarker-defined population

Results

- Between Sep 2018–Jul 2021, 80 patients were enrolled and received at least one dose of tislelizumab. Of these, 75 patients were included in the EE analysis set
- Median follow-up at the time of data cut-off (July 8, 2021) was 15.2 months (range: 0.8–33.6 months) and 38 patients (50.7%) remained on treatment in the EE analysis set
- The median age was 53.0 years (range: 19–81 years), most patients had metastatic disease (98.8%), and the majority of patients had CRC (61.3%) (**Table 1**)

Table 1. Patient demographics and baseline characteristics (safety analysis set)

Characteristic	All patients (N=80)
Median age (range), years	53 (19–81)
Male, n (%)	43 (53.8)
ECOG PS, n (%)	
0	35 (43.8)
1	45 (56.3)
Tumor type, n (%)	
CRC	49 (61.3)
Endometrial cancer	15 (18.8)
G/GEJ cancer	9 (11.3)
Small bowel adenocarcinoma	3 (3.8)
Other*	4 (5.0)
Disease status at baseline, n (%)	
Locally advanced	1 (1.3)
Metastatic	79 (98.8)
Number of prior lines of therapy, n (%)†	
≤ 1 line	44 (55.0)
2 lines	24 (30.0)
≥ 3 lines	12 (15.0)

Including one patient for each of the following: ampullary carcinoma, cervical cancer, ovarian cancer, and pelvis clear cell carcinoma; †One patient with endometrial cancer had no prior anticancer therapy. CRC, colorectal cancer; Eastern Cooperative Oncology Group performance status; G/GEJ, gastric or gastroesophageal junction

Efficacy: Tumor response

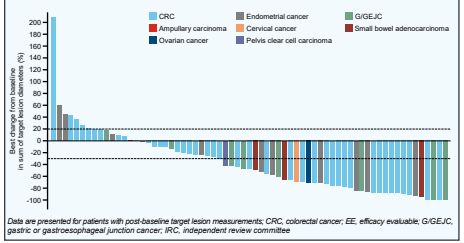
- In this updated EE analysis set, tislelizumab monotherapy resulted in an ORR_{IRC} of 46.7% (95% CI: 35.1, 58.6) in all tumor types (1-sided p < 0.0001), which was significantly higher than the historical control rate of 10% (**Table 2**)
- Among responders (n=35), only one patient (with G/GEJC) subsequently had progressive disease, of the remaining responders, two patients started a new anticancer therapy and 32 had an ongoing response at the time of the data cut. Therefore, median DoR was not reached for the EE analysis set or tumor-specific subgroups
- Most patients (n=52) experienced a reduction in tumor lesion diameter during the study (**Figure 2**) in the EE analysis set

Table 2. Tumor response by IRC assessment per RECIST v1.1 (EE analysis set)

	All tumor types (N=75)	Response by tumor type: CRC (n=46)	G/GEJC (n=9)	Other (n=20)
ORR (CR + PR)				
n (%)	35 (46.7)	18 (39.1)	5 (55.6)	12 (60.0)
95% CI	35.1, 58.6	25.1, 54.6	21.2, 86.3	36.1, 80.9
P-value	< 0.0001	–	–	–
Confirmed best overall response, n (%)				
CR	5 (6.7)	1 (2.2)	1 (11.1)	3 (15.0)
PR	30 (40.0)	17 (37.0)	4 (44.0)	9 (45.0)
SD	19 (25.3)	15 (32.6)	2 (22.2)	2 (10.0)
Progressive disease	14 (18.7)	9 (19.6)	1 (11.1)	4 (20.0)
Not evaluable*	7 (9.3)	4 (8.7)	1 (11.1)	2 (10.0)
Disease control rate (CR + PR + SD)				
n (%)	54 (72.0)	33 (71.7)	7 (77.8)	14 (70.0)
95% CI	60.4, 81.8	56.5, 84.0	40.0, 97.2	45.7, 88.1
Clinical benefit rate (CR + PR + durable SD ≥ 24 weeks)				
n (%)	42 (56.0)	25 (54.3)	5 (55.6)	12 (60.0)
95% CI	44.1, 67.5	39.0, 69.1	21.2, 86.3	36.1, 80.9
Time to response				
Median (range), weeks	11.9 (8.4–98.9)	14.6 (8.7–98.9)	9.1 (8.7–15.0)	9.1 (8.4–63.0)

Includes patients with non-evaluable tumor assessments and patients without tumor assessments (due to death, withdrawal of consent, lost to follow-up or any other reasons). CI, confidence interval; CR, complete response; CRC, colorectal cancer; EE, efficacy evaluable; G/GEJC, gastric or gastroesophageal junction cancer; IRC, independent review committee; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Figure 2. Best change in target lesion size from baseline by IRC (EE analysis set)



Data are presented for patients with post-baseline target lesion measurements; CRC, colorectal cancer; EE, efficacy evaluable; G/GEJC, gastric or gastroesophageal junction cancer; IRC, independent review committee

Efficacy: Survival

- At the time of this updated analysis, median PFS was not reached (95% CI 7.5 months, not estimable [NE]). The PFS rate at 12 months was 59.8% (95% CI 47.3, 70.3)
- Median OS was not reached (95% CI 28.7, NE). The OS rate at 12 months was 76.9% (95% CI 65.5, 85.0)

Biomarker analysis

- A total of 39 patients had evaluable PD-L1 data
- Defined cut-offs for PD-L1 tumor cell or immune cell expression were used to investigate whether there was an association between PD-L1 expression and tumor response
- Based on current results, no association was observed (**Table 3**) and further exploration is required in a larger population

Table 3. PD-L1 expression and association with ORR (EE analysis set)

	Patients with evaluable PD-L1 expression (n=39)			
	PD-L1 TC ≥ 1%	PD-L1 TC < 1%	PD-L1 IC ≥ 5%	PD-L1 IC < 5%
n (%)	5 (12.8)	34 (87.2)	16 (41.0)	23 (59.0)
ORR, n (%)	3 (60.0)	16 (47.1)	8 (50.0)	11 (47.8)
95% CI	14.7, 94.7	29.8, 64.9	24.7, 75.4	26.8, 69.4

CI, confidence interval; EE, efficacy evaluable; IC, immune cells; ORR, objective response rate; PD-L1, programmed death ligand-1; TC, tumor cells

Safety

- The median number of tislelizumab treatment cycles received was 17.0 (range: 1–43 cycles) with a median duration of exposure of 12.0 months (range: 0.7–33.6 months)
- All patients had ≥1 treatment-emergent adverse events (TEAEs) and 48.8% (n=39) of patients had at least one ≥ Grade 3 TEAE (**Table 4**)
- Treatment-related AEs (TRAEs) were reported in 98.8% (n=79) of patients, with ≥ Grade 3 TRAEs occurring in 43.8% (n=35) (**Table 4**). Five patients (6.3%) discontinued treatment owing to a TRAE
- Anemia was the most common ≥ Grade 3 TRAE, occurring in 8 patients (10.0%) (**Table 5**). Immune-mediated TEAEs ≥ Grade 3 were reported in 7 patients (8.8%)
- TRAEs leading to death were reported in 3 patients (3.8%), including one instance of large intestinal obstruction, death and respiratory failure, which were also related to disease under study

Table 4. Safety summary (safety analysis set)

Patients, n (%)	All patients (N=80)	
	TEAE	TRAE
Any	80 (100.0)	79 (98.8)
≥ Grade 3	39 (48.8)	35 (43.8)
Serious	27 (33.8)	21 (26.3)
Leading to death	5 (6.3)	3 (3.8)
Leading to treatment discontinuation	5 (6.3)	5 (6.3)
Leading to dose modification*	30 (37.5)	27 (33.8)

Table 5. TRAEs in ≥15% of patients (any grade), by all grades and ≥ Grade 3 (safety analysis set)

Event, n (%)	All patients (N=80)	
	Any grade	≥ Grade 3
Anemia	35 (43.8)	8 (10.0)
ALT increased	25 (31.3)	3 (3.8)
AST increased	21 (26.3)	3 (3.8)
Blood bilirubin increased	20 (25.0)	1 (1.3)
White blood cell decreased	20 (25.0)	1 (1.3)
Rash	18 (22.5)	2 (2.5)
Hypothyroidism	17 (21.3)	0
Neutrophil count decreased	14 (17.5)	0

Treatment modification included dose delay and infusion interruption; all AEs are treatment-emergent and graded based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 4.03). ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment emergent adverse event; TRAE, treatment-related adverse event

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