Long-Term Follow-up of 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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Conclusions

With a longer median follow-up time of 28.9 months, updated analysis showed that tislelizumab monotherapy continued to demonstrate clinically meaningful and durable benefits in Chinese patients with previously treated, advanced microsatellite instability-high or mismatch repair-deficient (MSI-H/dMMR) solid tumors.

Tislelizumab was well tolerated in the longer-term follow-up analysis, with no new safety signals identified. The updated data from the RATIONALE-209 study further support the clinical benefit of tislelizumab in this MSI-H/dMMR biomarker-defined population.

Background

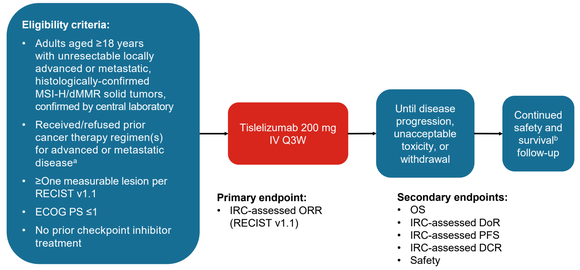
MSI-H/dMMR tumors are a unique group of tumors with a common defect in MMR activity[1] and share histopathologic characteristics that render them susceptible to immune checkpoint inhibitors, such as anti-programmed cell death protein 1 (PD-1) antibodies.[1,2] Tislelizumab is an anti-PD-1 monoclonal antibody engineered to minimize Fcγ receptor binding on macrophages.[3]

Primary results of the phase 2 RATIONALE-209 study showed that tislelizumab was generally well tolerated and demonstrated a clinically meaningful objective response rate (ORR) in patients with previously treated, locally advanced or metastatic MSI-H/dMMR solid tumors.[4] Here we report the updated analysis of the phase 2 RATIONALE-209 study in Chinese patients with advanced MSI-H/dMMR solid tumors (NCT03736889) with longer follow-up.

Methods

- RATIONALE-209 is a single-arm, open-label, multicenter, phase 2 study evaluating the efficacy and safety of tislelizumab in Chinese patients with MSI-H/dMMR solid tumors (**Figure 1**)

Figure 1. Study Design



[a]Two or more prior regimens for CRC; one or more prior regimens for other cancer types. Patients should have progressed on the most recent regimen; [b]The efficacy-evaluable analysis set included all patients who received any dose of tislelizumab and had measurable disease per IRC according to RECIST v1.1 at baseline. The safety analysis set included all patients who received any dose of tislelizumab. **Abbreviations:** CRC, colorectal cancer; DCR; disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenously; MSI-H/dMMR, microsatellite instability-high or mismatch repair-deficient; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Results

Baseline Characteristics

- Of 80 patients treated, 75 had measurable disease at baseline and were included in the efficacy-evaluable (EE) set; baseline characteristics are presented in **Table 1**
- At data cutoff (December 5, 2022), median study follow-up in the EE set was 28.9 months (range: 0.8-50.5)

Table 1. Baseline Characteristics and Disease History[a]

Characteristics	All Patients (N=80)
Median age, years (range)	53 (19-81)
Age <65 years, n (%)	67 (83.8)
Male sex, n (%)	43 (53.8)
Eastern Cooperative Oncology Group performance status, n (%)	
0	35 (43.8)
1	45 (56.3)
Tumor type, n (%)	
Colorectal cancer	49 (61.3)
Endometrial cancer	15 (18.8)
Gastric or gastroesophageal junction cancer	9 (11.3)
Small bowel adenocarcinoma	3 (3.8)
Ampullary carcinoma	1 (1.3)
Cervical cancer	1 (1.3)
Ovarian cancer	1 (1.3)
Pelvis clear cell carcinoma	1 (1.3)
Disease status at study entry, n (%)	
Locally advanced	1 (1.3)
Metastatic	79 (98.8)
Prior anticancer therapy, n (%)	79 (98.8)
Prior chemoradiation	6 (7.5)
Prior therapies for locally advanced/metastatic disease, n (%)	
None	1 (1.3)
1 line	43 (53.8)
2 lines	24 (30.0)
≥3 lines	12 (15.0)

[a]Data presented for the safety analysis set, which included all patients who received any dose of tislelizumab.

Efficacy Results

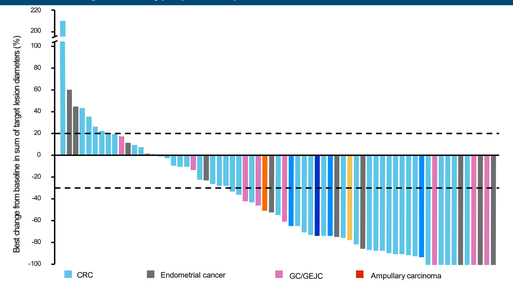
- Independent review committee (IRC)-assessed ORR in the EE set (n=75) was 49.3% (95% confidence interval [CI]: 37.6, 61.1), including 10 patients with complete response (13.3%); ORR was 45.9% (95% CI: 34.3, 57.9) in the EE set at the primary analysis (n=75)[4]
- No significant difference in ORR was observed between programmed death-ligand 1 (PD-L1)-positive and -negative subgroups (PD-L1 positivity was defined as positive staining of ≥1% of tumor cells or ≥5% of the tumor area covered by tumor-associated immune cells with positive staining)
- IRC-assessed tumor responses by tumor type are reported in **Table 2**
- The majority of patients in the EE set experienced tumor shrinkage during the study (**Figure 2**)
- Median progression-free survival (PFS) and overall survival (OS) were not reached; at 24 months, the PFS rate in the EE set was 56.7% (95% CI: 44.1, 67.4), and the OS rate in the safety analysis set was 68.6% (95% CI: 56.6, 77.9)

Table 2. Tumor Response per Independent Review Committee Assessment[a]

	Response by Tumor Type			
	All Tumor Types (N=75)	CRC (n=46)	GC/GEJC (n=9)	Other[b] (n=20)
ORR, n (%)	37 (49.3)	20 (43.5)	5 (55.6)	12 (60.0)
95% CI	37.6-61.1	28.9-58.9	21.2-86.3	36.1-80.9
BCR, n (%)				
CR	10 (13.3)	4 (8.7)	1 (11.1)	5 (25.0)
PR	27 (36.0)	16 (34.8)	4 (44.4)	7 (35.0)
SD	17 (22.7)	13 (28.3)	2 (22.2)	2 (10.0)
PD	14 (18.7)	9 (19.6)	1 (11.1)	4 (20.0)
DCR[c], 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
Median DoR , months	NR	NR	NR	NR
95% CI	NE, NE	NE, NE	11.1, NE	NE, NE
DoR event-free rate at 36 months (%)	97.0	100.0	75.0	100.0
95% CI	80.4, 99.6	100.0, 100.0	12.8, 96.1	100.0, 100.0

[a]Data presented are for the efficacy-evaluable set, which included all patients who received any dose of tislelizumab and had measurable disease per independent review committee according to RECIST v1.1 at baseline. Patients without postbaseline target lesion tumor measurements are not included; [b]Other tumors include small bowel carcinoma, ampullary carcinoma, cervical cancer, ovarian cancer, and pelvis clear cell carcinoma; [c]DCR is CR + PR + SD. **Abbreviations:** BCR, best confirmed response; CI, confidence interval; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DoR, duration of response; GC/GEJC, gastric or gastroesophageal junction cancer; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Figure 2. Best Percent Change in Sum of Target Lesion Diameters From Baseline by Tumor Type per Independent Review Committee Assessment[a]



[a]Data presented are for the efficacy-evaluable set, which included all patients who received any dose of tislelizumab and had measurable disease per independent review committee according to RECIST v1.1 at baseline. Patients without postbaseline target lesion tumor measurements are not included. **Abbreviations:** CRC, colorectal cancer; GC/GEJC, gastric or gastroesophageal junction cancer; RECIST v 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Safety Analysis

- In the safety analysis set (n=80), median duration of exposure was 22.5 months (range: 0.7-50.5); median number of treatment cycles was 25.0 (range: 1-60); 43 patients (53.8%) received ≥12 months of treatment
- All patients had one or more treatment-emergent adverse event (TEAE); grade ≥3 TEAEs and treatment-related adverse events (TRAEs) were reported in 48 (60.0%) and 43 patients (53.8%), respectively (**Table 3**)
- Six patients (7.5%) discontinued treatment due to TRAEs; TRAEs leading to death occurred in three patients (3.8%) (**Table 3**)
- TRAEs that occurred in ≥15% of patients are reported in **Table 4**

Table 3. Safety Summary[a]

	All Patients (N=80)	
Patients, n (%)	**TEAE**	**TRAE**
Any adverse event	80 (100.0)	79 (98.8)
Grade ≥3 adverse event	48 (60.0)	43 (53.8)
Serious adverse event	31 (38.8)	24 (30.0)
Leading to death[b]	5 (6.3)	3 (3.8)
Leading to treatment discontinuation[c]	6 (7.5)	6 (7.5)
Leading to treatment modification[d]	38 (47.5)	32 (40.0)

[a]Data presented are for the safety analysis set, which included all patients who received any dose of tislelizumab; [b]Adverse events leading to death included multiple organ dysfunction syndrome (two patients), cause unknown (one patient), large intestinal obstruction (one patient), and respiratory failure (one patient). Three of the adverse events leading to death were treatment-related and included cause unknown (one patient), large intestinal obstruction (one patient), and respiratory failure (one patient); [c]Adverse events leading to treatment discontinuation included two events of pneumonitis (grade 2), one event each of death (grade 5), edema peripheral (grade 2), large intestinal obstruction (grade 5), localized edema (grade 2),and respiratory failure (grade 5); [d]Treatment modification included dose delay and infusion interruption. **Abbreviations:** TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 4. Treatment-Related Adverse Events Reported in ≥15% of Patients[a]

	All Patients (N=80)	
Patients, n (%)	**All Grades**	**Grade ≥3**
Anemia	36 (45.0)	9 (11.3)
Alanine aminotransferase increased	27 (33.8)	4 (5.0)
Aspartate aminotransferase increased	24 (30.0)	2 (2.5)
Blood bilirubin increased	22 (27.5)	1 (1.3)
White blood cell count decreased	20 (25.0)	1 (1.3)
Rash	19 (23.8)	2 (2.5)
Hypothyroidism	19 (23.8)	0
Blood creatinine phosphokinase increased	16 (20.0)	5 (6.3)
Neutrophil count decreased	14 (17.5)	1 (1.3)
Vomiting	13 (16.3)	1 (1.3)
Hypoalbuminemia	12 (15.0)	0
Hyponatremia	12 (15.0)	2 (2.5)
Abdominal pain	12 (15.0)	2 (2.5)

[a]Data presented are for the safety analysis set, which included all patients who received any dose of tislelizumab.

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Disclosures

Quanli Gao reports a principal investigator role for BeiGene, Ltd.