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Phase 2 study of tislelizumab monotherapy in previously-treated, locally advanced unresectable or metastatic microsatellite instability-high/mismatch repair-deficient solid tumors: Gynecological cancer subgroup

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Background

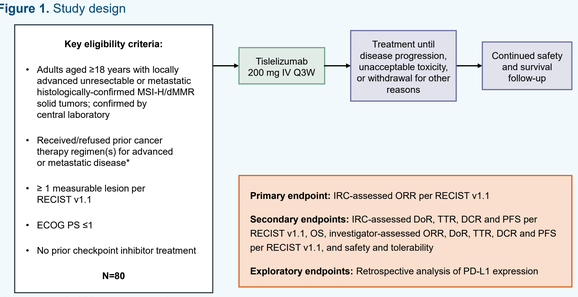
- Microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) tumors share common histopathologic characteristics that may render them susceptible to immune checkpoint inhibitors such as anti-programmed cell death protein 1(PD-1)/ programmed death ligand-1 (PD-L1) monoclonal antibodies[1–3]
- Clinical data indicate MSI-H/dMMR as a strong predictive biomarker for immunotherapy.[4] This is of particular interest in tumor types such as endometrial cancer, in which the incidence of MSI-H/dMMR has been reported to be nearly 30%[5]
- Tislelizumab is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for PD-1 that was engineered to minimize Fcγ receptor binding on macrophages, thereby abrogating antibody-dependent cellular phagocytosis[6,7]
- In early and late phase clinical studies, tislelizumab monotherapy was generally well tolerated and had antitumor activity in patients with solid tumors, including MSI-H/dMMR tumors[8–11]
- Primary results from the Phase 2 RATIONALE 209 study showed that tislelizumab was generally well tolerated and demonstrated a clinically meaningful improvement in the objective response rate (ORR) in patients with previously-treated, locally advanced, unresectable or MSI-H/dMMR solid tumors compared with the historical control rate (45.9% vs 10%, respectively)[12]
- Here, we report results from the updated analysis for patients with gynecological MSI-H/dMMR tumors

Methods

Study design

- RATIONALE 209 (NCT03736889) is an ongoing single-arm, non-randomized, 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 cell 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 $p \leq 0.025$ 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

Conclusions

- This subgroup analysis demonstrates that **tislelizumab was clinically active in patients with gynecological MSI-H/dMMR tumors** and was generally well tolerated with no new safety signals
- These data support **tislelizumab as a potential new treatment option** for patients with gynecological MSI-H/dMMR tumors
- **Further investigation with a larger population is warranted** to confirm the clinical benefit of tislelizumab in these patients

- 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)

Results

Patients

- Between Sep 2018–Jul 2021, 80 patients were enrolled, with 75 patients included in the EE analysis set. Of these, 17 had gynecological tumors (15 with endometrial cancer, 1 with cervical cancer, and 1 with ovarian cancer)
- Baseline demographic data for the gynecological subgroup are shown in **Table 1**

Table 1. Baseline demographic and clinical characteristics of patients with gynecological tumors (safety analysis set)

Characteristic	All gynecological (N=17)
Age (years), median (range)	55.0 (41–68)
<65 years, n (%)	15 (88.2)
Never smoker, n (%)	17 (100)
BMI (kg/m^2), median (range)	24.6 (21–32)
ECOG PS at baseline, n (%)	
0	7 (41.2)
1	10 (58.8)
Tumor type, n (%)	
Endometrial cancer	15 (88.2)
Cervical cancer	1 (5.9)
Ovarian cancer	1 (5.9)
Metastatic disease at study entry, n (%)	17 (100)
Time from initial diagnosis to study entry (months), median (range)	12.2 (4–86)
Number of prior anticancer therapeutic regimens, n (%)	
0	1 (5.9)
1	8 (47.1)
2	4 (23.5)
3	2 (11.8)
4	1 (5.9)
5	1 (5.9)

Data cut off: July 8, 2021. BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; EE, efficacy evaluable

- All 17 (100%) patients had undergone a prior anticancer procedure or surgery with curative intent (median 9.92 months prior to study entry), and 16 (94.1%) patients had received prior anticancer therapy, including 6/17 (35.3%) with prior chemoradiation. The median time from the end of the last therapy to study entry was 2.18 months, and 16 patients had discontinued treatment due to disease progression

Clinical outcomes

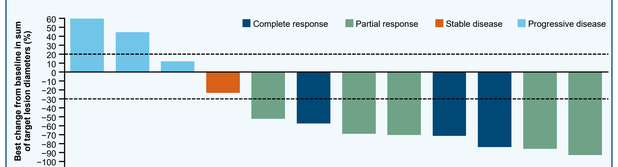
- ORR in patients with gynecological tumors was 53.3% (95% CI: 26.6, 78.7), including three complete responses in patients with endometrial cancer (**Table 2**). Median DoR was not reached, but responses were ongoing after 8.3–15.4 months for patients with endometrial cancer, 15.5 months for the patient with cervical cancer, and 23.5 months for the patient with ovarian cancer
- Median OS, PFS and DoR were not reached. Median TTR was 9.1 weeks and DCR was 60.0% (95% CI: 32.3, 83.7)
- Most patients experienced a reduction in tumor lesion diameter during the study (**Figure 2**)

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

	All gynecological (N=15)	Cervical cancer (n=1)	Endometrial cancer (n=13)	Ovarian cancer (n=1)
ORR (CR + PR)				
n (%)	8 (53.3)	1 (100)	6 (46.2)	1 (100)
95% CI	26.6, 78.7	2.5, 100	19.2, 74.9	2.5, 100
P-value	<0.0001	–	–	–
Confirmed best overall response, n (%)				
CR	3 (20.0)	0	3 (23.1)	0
PR	5 (33.3)	1 (100)	3 (23.1)	1 (100)
SD	1 (6.7)	0	1 (7.7)	0
Progressive disease	4 (26.7)	0	4 (30.8)	0
Not assessable*	2 (13.3)	0	2 (15.4)	0
Disease control rate (CR + PR + SD)				
n (%)	9 (60.0)	1 (100)	7 (53.8)	1 (100)
95% CI	32.3, 83.7	2.5, 100	25.1, 80.8	2.5, 100
Clinical benefit rate (CR + PR + durable SD ≥24 weeks)				
n (%)	8 (53.3)	1 (100)	6 (46.2)	1 (100)
95% CI	26.6, 78.7	2.5, 100	19.2, 74.9	2.5, 100
Time to response				
Median (range), weeks	9.1 (8.4–39.1)	9.1 (9.1–9.1)	9.1 (8.4–39.1)	8.7 (8.7–8.7)

**Not assessable captured patients for whom no post-baseline tumor assessments were performed*
Data cut off: July 8, 2021. CI, confidence interval; CR, complete response; EE, efficacy evaluable; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

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



**One patient was assessed as progressive disease based on new lesion and therefore the target lesion was not evaluated for this patient*
Data cut off: July 8, 2021. Patients without post-baseline target lesion tumor measurements were not included. IRC, independent review committee

Safety

- All patients had ≥ 1 treatment-emergent adverse events (TEAEs) and ≥ Grade 3 TEAEs were reported in 10/17 (58.8%) of patients (**Table 3**)
- Immune-mediated TEAEs were reported in 7/17 (41.2%) of patients
- The most common Grade ≥ 3 TEAE was urinary tract infection (3/17 [17.6%], **Table 4**)

Table 3. Safety summary (safety analysis set)

	All gynecological (N=17)	
Adverse event	**TEAE**	**TRAE**
Any / ≥ Grade 3	17 (100) / 10 (58.8)	17 (100) / 9 (52.9)
Serious	6 (35.3)	4 (23.5)
Leading to death	1 (5.9)*	0 (0.0)
Leading to treatment discontinuation	1 (5.9)	1 (5.9)
Leading to treatment modification	4 (23.5)	3 (17.6)

**Due to multiple organ dysfunction syndrome. Treatment modification included dose delay and infusion interruption*
Data cut off: July 8, 2021. TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 4. TEAEs in ≥ 15% of patients (any grade), by all grades and ≥ Grade 3 (safety analysis set)

n (%)	All gynecological (N=17)	
	All grade	**≥ Grade 3**
AST increased	9 (52.9)	1 (5.9)
ALT increased	8 (47.1)	1 (5.9)
White blood cell count decreased	7 (41.2)	0 (0.0)
Anemia	7 (41.2)	1 (5.9)
Neutrophil count decreased	5 (29.4)	0 (0.0)
Weight increased	5 (29.4)	0 (0.0)
Pyrexia	5 (29.4)	0 (0.0)
Hypoalbuminemia	5 (29.4)	0 (0.0)
Hypothyroidism	5 (29.4)	0 (0.0)
Vomiting	4 (23.5)	0 (0.0)
Rash	4 (23.5)	0 (0.0)
Blood alkaline phosphatase increased	3 (17.6)	0 (0.0)
Gamma-glutamyltransferase increased	3 (17.6)	1 (5.9)
Platelet count decreased	3 (17.6)	0 (0.0)
Malaise	3 (17.6)	0 (0.0)
Edema peripheral	3 (17.6)	0 (0.0)
Hyperuricemia	3 (17.6)	0 (0.0)
Abdominal pain	3 (17.6)	0 (0.0)
Constipation	3 (17.6)	0 (0.0)
Nausea	3 (17.6)	0 (0.0)
Urinary tract infection	3 (17.6)	3 (17.6)
Cough	3 (17.6)	0 (0.0)

Data cut off: July 8, 2021. ALT, alanine aminotransferase; AST, aspartate aminotransferase

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Disclosures

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