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Abstract No: 1

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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Background

- MSI-H/dMMR tumors share common histopathologic characteristics that may render them susceptible to immune checkpoint inhibitors, such as anti-PD-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[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

dMMR, mismatch repair-deficient tumors; Fcγ, Fc gamma receptor; MSI-H, microsatellite instability-high; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1

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Methods: Study design

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

Key eligibility criteria:

- Adults aged ≥ 18 years with locally advanced unresectable or metastatic histologically-confirmed MSI-H/dMMR solid tumors; confirmed by central laboratory
- Received/refused prior cancer therapy regimen(s) for advanced or metastatic disease*
- ≥ 1 measurable lesion per RECIST v1.1
- ECOG PS ≤ 1
- No prior checkpoint inhibitor treatment

N=80

Tislelizumab 200 mg IV Q3W → **Treatment until disease progression, unacceptable toxicity, or withdrawal for other reasons** → **Continued safety and survival follow-up**

Primary endpoint: IRC-assessed ORR per RECIST v1.1

Secondary endpoints: IRC-assessed DoR, TTR, DCR and PFS per RECIST v1.1, OS, investigator-assessed ORR, DoR, TTR, DCR and PFS per RECIST v1.1, and safety and tolerability

Exploratory endpoints: Retrospective analysis of PD-L1 expression

*≥ 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; PFS, progression-free survival; Q3W, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response

Results: Efficacy/biomarker analysis

- Tislelizumab monotherapy demonstrated an improvement in ORR as compared with historical data
- No association was observed between PD-L1 expression and tumor response

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

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

		Response by tumor type		
	All tumor types (N=75)	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 (44.4)	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; IC, immune cells; IRC, independent review committee; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TC, tumor cells

Results: Safety

Safety summary (safety analysis set)

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)

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

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 5.0)
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment emergent adverse event; TRAE, treatment-related adverse event

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

dMMR, mismatch repair-deficient tumors; MSI-H, microsatellite instability-high; ORR, objective response rate; PD-L1, programmed death ligand-1; TRAE, treatment-related adverse event