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

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Disclosures

Introduction

MSI-H/dMMR tumors share common histopathologic characteristics that may render them susceptible to immune CPI such as anti-PD-1/PD-L1 mAbs[1–3]

Pembrolizumab data indicates MSI-H/dMMR as a strong predictive biomarker for immunotherapy and supports a tissue-agnostic approach for the treatment of MSI-H/dMMR solid tumors

Tislelizumab is an anti-PD-1 mAb with high affinity and specificity for PD-1, designed to minimize binding to FcγR on macrophages and thereby potentially avoid antibody-dependent phagocytosis[4]

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 CRC[5]

We report the results of a Phase 2 study that evaluated the efficacy and safety of tislelizumab monotherapy in patients with previously treated, locally advanced unresectable or metastatic MSI-H/dMMR solid tumors

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4. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90; 5. Shen L, et al. J Immunother Cancer 2020;8:e000437
CPI, checkpoint inhibitors; CRC, colorectal cancer; dMMR, mismatch repair deficient; mAb, monoclonal antibody; MSI-H, microsatellite instability-high; PD-1, programmed death protein-1; PD-L1, programmed cell death ligand-1

Study design

A single-arm, nonrandomized, open-label, multicenter pivotal study (NCT03736889) was conducted at 26 sites in China

Key eligibility criteria:
- Histologically-confirmed locally advanced unresectable or metastatic solid tumors; MSI-H/dMMR confirmed by central laboratory
- Received/refused prior cancer therapy regimen(s) for advanced disease*
- ≥ 1 measurable lesion as per RECIST v1.1
- ECOG PS ≤ 1
- No prior checkpoint inhibitor treatment

N=80

Tislelizumab 200 mg IV Q3W

Treatment until unacceptable toxicity, disease progression, or withdrawal

Tislelizumab 200 mg IV Q3W

Optional continued tislelizumab treatment after investigator-assessed radiological progression per RECIST V1.1†

Continued safety and survival follow-up

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

Secondary endpoints:
- IRC-assessed: DOR, TTR, PFS, DCR per RECIST v1.1
- Investigator-assessed: ORR, PFS, DCR, DOR, TTR per RECIST v1.1
- OS
- Safety and tolerability

*≥ 2 prior regimens for CRC; ≥1 prior regimen for other cancer types; †Required patient re-consent, the absence of clinical signs and symptoms of disease progression, and ECOG PS ≤ 1
CRC, colorectal cancer; DCR, disease control rate; dMMR, mismatch repair deficient; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; IRC, independent committee review; 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

Baseline demographics and characteristics (primary efficacy analysis set)

Characteristic	All patients (N=74)
Median age (range), years	53 (19–75)
Male, n (%)	42 (56.8)
ECOG PS, n (%)	
0	33 (44.6)
1	41 (55.4)
Tumor type, n (%)	
CRC	46 (62.2)
Endometrial cancer	13 (17.6)
G/GEJ cancer	8 (10.8)
Small bowel adenocarcinoma	3 (4.1)
Other*	4 (5.4)
Disease status at baseline, n (%)	
Locally advanced	1 (1.4)
Metastatic	73 (98.6)
Prior therapies, n (%)†	
Median no. of prior regimens (range)	2 (0–7)

Data cut-off date: 07 December 2020

*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; ECOG PS, Eastern Cooperative Oncology Group performance score; G/GEJ, gastric or gastroesophageal junction

Primary endpoint: IRC-assessed ORR (primary efficacy analysis set)

	All patients (N=74)	CRC (N=46)	Non-CRC (N=28)
ORR (CR + PR)			
n (%)	34 (45.9)	18 (39.1)	16 (57.1)
95% CI	34.3, 57.9	25.1, 54.6	37.2, 75.5
P-value*	< 0.0001	–	–
Confirmed best overall response, n (%)			
CR	4 (5.4)	2 (4.3)	2 (7.1)
PR	30 (40.5)	16 (34.8)	14 (50.0)
SD	19 (25.7)	15 (32.6)	4 (14.3)
PD	14 (18.9)	9 (19.6)	5 (17.9)
NE†	7 (9.5)	4 (8.7)	3 (10.7)

ORR following tislelizumab treatment (45.9%) was s**ignificantly higher than the historical control rate** (10%)

ORR was **46.2% and 50.0%** in patients with endometrial cancer and G/GEJ cancer, respectively

Data cut-off date: 07 December 2020

*One-sided p-value calculated from a binomial exact test of tislelizumab vs historical rate of 0.1; †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); 95% CI calculated using Clopper-Pearson method

CI, confidence interval; CR, complete response; CRC, colorectal cancer; G/GEJ, gastric or gastroesophageal junction; IRC, independent review committee; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

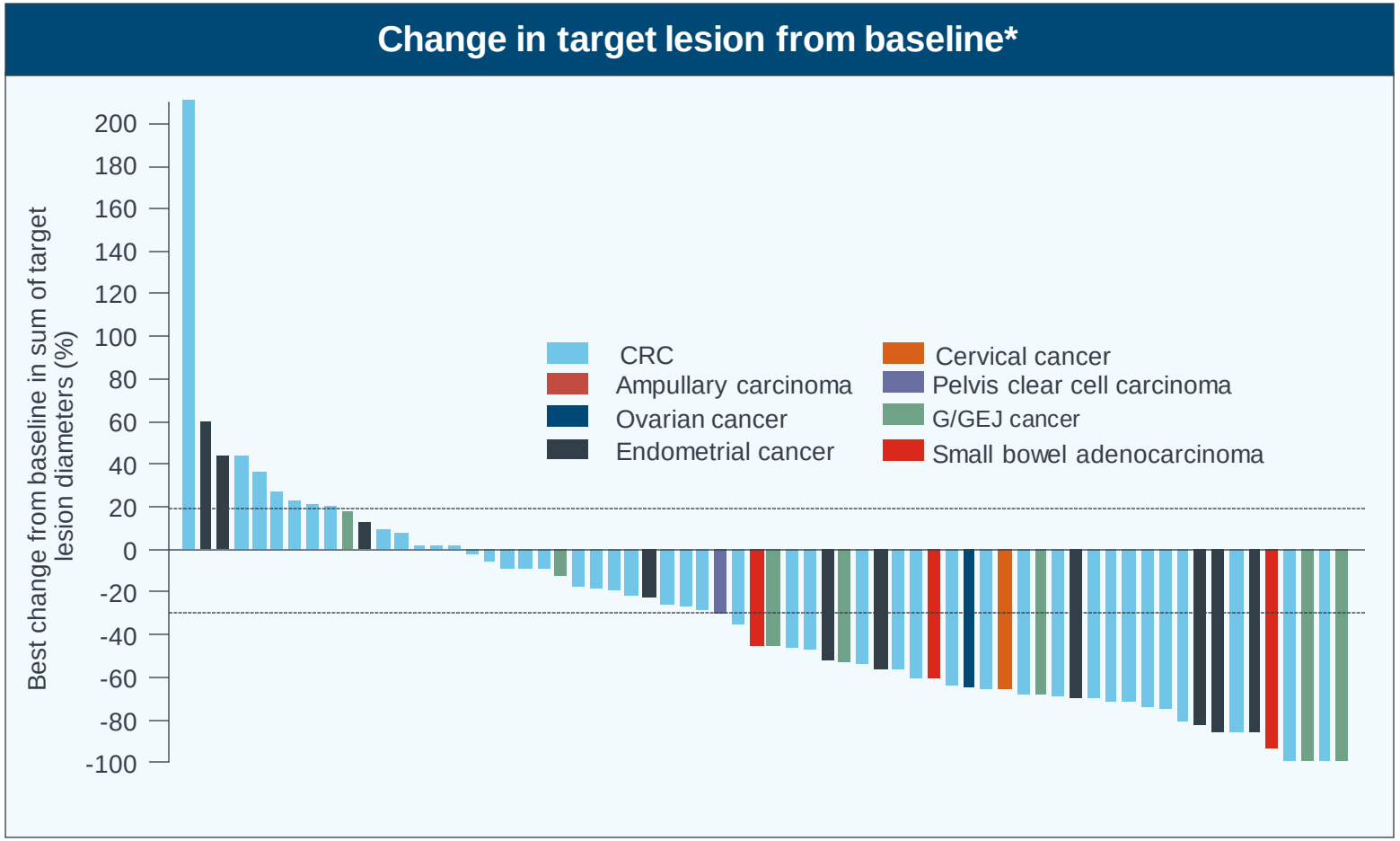
Secondary endpoints: DCR, TTR, and DOR (primary efficacy analysis set)

DCR for all tumor types was: **71.6%**

Median TTR was: 10.5 weeks (range: 8.4–98.9 weeks)

Median DOR was not reached

48.6% of patients had a **reduction in tumor burden of ≥ 30% from baseline**



Data cut-off date: 07 December 2020

*Data are presented for patients with post-baseline target lesion measurements

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; G/GEJ, gastric or gastroesophageal junction; TTR, time to response

Secondary endpoints: PFS and OS (primary efficacy analysis set)

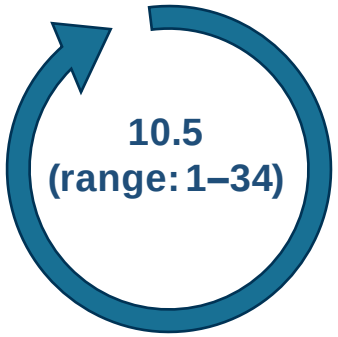
Median PFS and OS were not reached

12-month survival rates, % (95% CI)	PFS	OS
All tumor types	59.3 (46.2, 70.2)	75.3 (62.6, 84.2)
CRC	57.7 (40.6, 71.5)	77.2 (60.6, 87.5)
Other cancer types	62.2 (41.1, 77.6)	73.2 (51.4, 86.4)

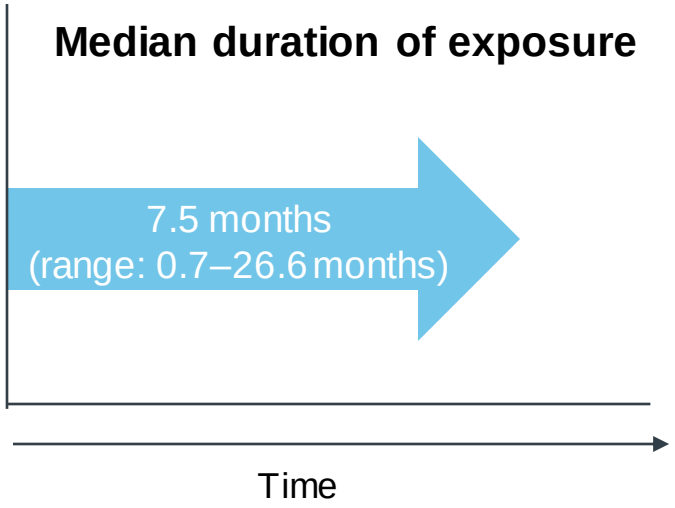
Data cut-off date: 07 December 2020
CI, confidence interval; CRC, colorectal cancer; OS, overall survival; PFS, progression-free survival

Secondary endpoints: Safety and tolerability (safety analysis set, 1/2)

Median number of tislelizumab treatment cycles received



Median duration of exposure



Patients, n (%)	All patients (N=80)
Any TEAE / TRAE	80 (100.0) / 79 (98.8)
≥ Grade 3 TEAE / TRAE	38 (47.5) / 34 (42.5)
Serious TEAE / TRAE	27 (33.8) / 21 (26.3)
≥ Grade 3 serious TRAE	14 (17.5)
TEAE / TRAE leading to death	5 (6.3) / 3 (3.8)
TEAE / TRAE leading to treatment discontinuation	4 (5.0) / 4 (5.0)
TEAE / TRAE leading to dose modification	29 (36.3) / 25 (31.3)

TRAEs leading to death were reported in three patients including one case each of: respiratory failure, large intestinal obstruction, and death

Data cut-off date: 07 December 2020
All AEs are treatment-emergent and graded based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 4.03)
AE, adverse event; TEAE, treatment-emergent AE; TRAE, treatment-related AE

Secondary endpoints: Safety and tolerability (safety analysis set, 2/2)

TRAEs reported in ≥ 15% of patients

Patients, n (%)	All patients (N=80)
ALT increased	23 (28.8)
≥ Grade 3	3 (3.8)
Blood bilirubin increased	20 (25.0)
≥ Grade 3	1 (1.3)
AST increased	19 (23.8)
≥ Grade 3	3 (3.8)
White blood cell count decreased	18 (22.5)
≥ Grade 3	1 (1.3)
Neutrophil count decreased	12 (15.0)
≥ Grade 3	0
Anemia	35 (43.8)
≥ Grade 3	8 (10.0)
Hypothyroidism	15 (18.8)
≥ Grade 3	0
Rash	15 (18.8)
≥ Grade 3	1 (1.3)

≥ Grade 3 immune-mediated TEAEs were reported in four patients, with no Grade 4 or 5 events reported

Data cut-off date: 07 December 2020

All AEs are treatment-emergent and graded based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 4.03)

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent AE; TRAE, treatment-related AE

Summary and conclusions

- Tislelizumab monotherapy demonstrated a **statistically significant and clinically meaningful improvement in ORR** in patients with previously treated, locally advanced unresectable or metastatic MSI-H/dMMR solid tumors
- Tislelizumab treatment demonstrated **consistent efficacy across tumor types** and a **durable response**
  - This supports the rationale that MSI-H/dMMR solid tumors are a unique set of cancers that have the same pharmacological effects regardless of tumor site

- Tislelizumab was generally well tolerated, with few patients discontinuing treatment due to TRAEs, and no new safety signals were identified

- The results of this Phase 2 study support tislelizumab as a potential new treatment option in this MSI-H/dMMR biomarker-defined population
- Longer follow-up time will further verify the clinical benefit of tislelizumab in MSI-H/dMMR solid tumors

dMMR, mismatch repair deficient; MSI-H, microsatellite instability-high; ORR, objective response rate; TRAE; treatment-related adverse events

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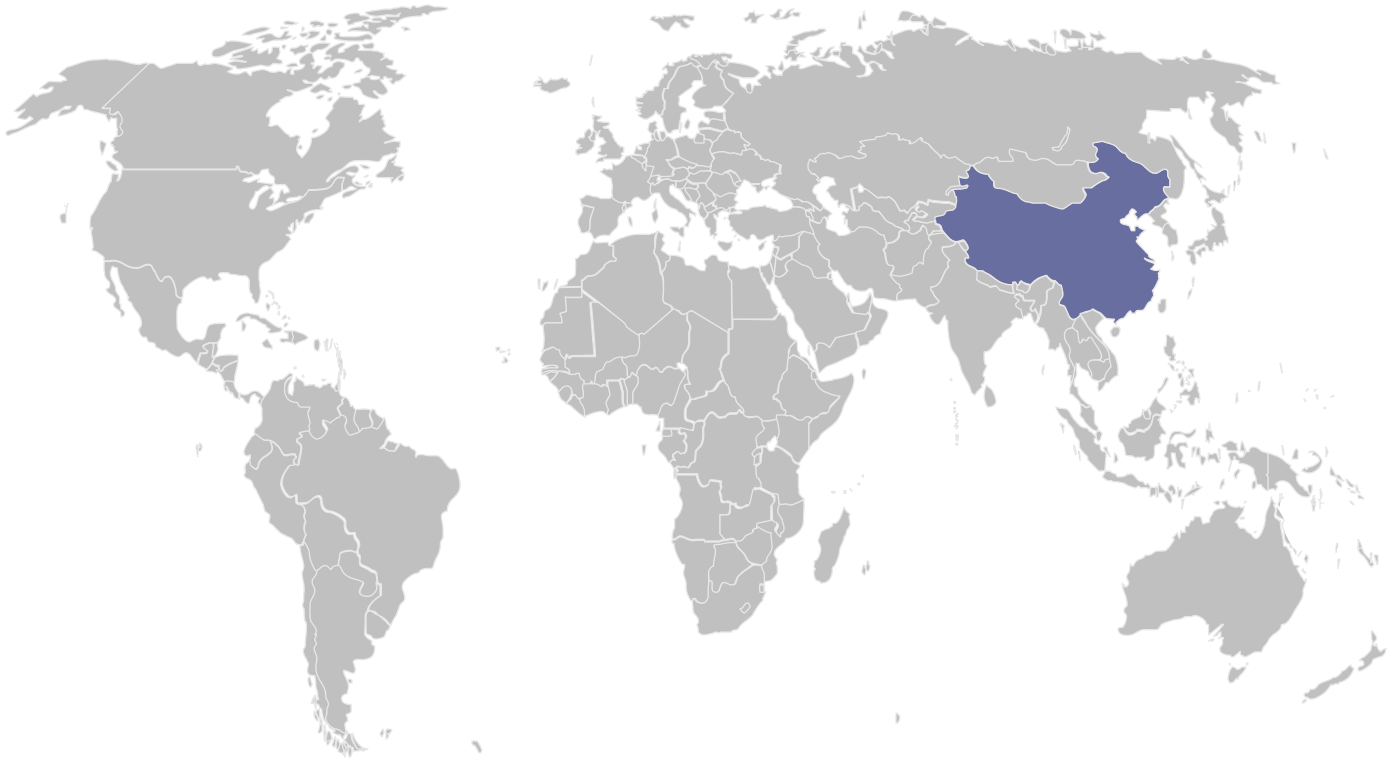

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