# 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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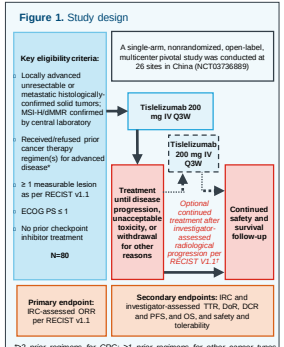
## Introduction

- 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]
- 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 a PD-1 monoclonal antibody with high affinity and specificity for PD-1, engineered 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 colorectal cancer (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

## Methods

**Figure 1.** Study design




*≥2 prior regimens for CRC; ≥1 prior regimens 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; IV, intravenously; MSI-H, microsatellite instability-high; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response*

- **Primary efficacy analysis set:** All patients who received any dose of tislelizumab and had measurable disease per IRC according to RECIST v1.1 at baseline
- **Safety analysis set:** All patients who received any dose of tislelizumab (safety and OS)
- Sample size calculation was based on the power of the comparison to the historical rate (assumed ORR of 24% in the study vs 10% in the historical control)

## Results

- From Sep 2018–Aug 2020, 80 patients were enrolled. 74 patients were included in the primary efficacy analysis set
- Median follow-up at the time of data cut-off (7 Dec 2020) was 11.78 months (range: 0.8–26.6 months) and 45 patients (56.3%) remained on-treatment in the safety analysis set (N=80)
- Median age was 53 years, almost all patients had locally advanced disease (98.6%), and the majority of patients had CRC (62.2%) in the primary efficacy analysis set (**Table 1**)

**Table 1.** Patient demographics and baseline 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) |

*Including one patient for each of the following: ampullary carcinoma, cervical cancer, ovarian cancer, and pelvis clear cell carcinoma G/GEJ, gastric or gastroesophageal junction.*
*†One patient with endometrial cancer had no prior anticancer therapy*

## Efficacy: Tumor response

- Tislelizumab monotherapy resulted in an ORR by IRC of 45.9% in the primary efficacy analysis set (N=74) (**Table 2**)
  - The one-sided p-value was <0.0001 in testing the null hypothesis of 10%, indicating that the ORR following tislelizumab treatment was significantly higher than the historical control rate of 10%
  - Concordance between IRC and investigator assessment for ORR was high (93.2%) and the investigator-assessed ORR was 47.3% (95% CI 35.6, 59.3)
- Observed ORR by IRC was 39.1% in patients with CRC and 57.1% in those with other tumor types (**Table 2**)
  - ORR was 46.2% (95% CI 19.2, 74.9) in patients with endometrial cancer and 50.0% (95% CI 15.7, 84.3) in patients with G/GEJ cancer
  - Partial responses (PR) were achieved in patients with CRC and all other tumor types, except one case of stable disease (SD) (the patient with ampullary carcinoma)
- Among all tumor types, 71.6% of patients achieved disease control and 52.7% achieved clinical benefit (**Table 2**)
- Among the 34 patients with responses for any tumor type (4 with CR and 30 with PR):
  - Median TTR was 10.5 weeks (range: 8.4–98.9 weeks)
  - CR was reached in 2 non-CRC tumors, G/GEJ cancer and endometrial cancer
  - Progressive disease was not reported in any patients, median DoR was not reached (12-month DoR rate: 100%), 33 responders still had an ongoing response, and one patient started new anti-cancer therapy
- A reduction in tumor burden from baseline was reported among 7 of 8 enrolled tumor types (**Figure 2**)
  - A total of 36 patients (48.6%) had a reduction of 30% or greater from baseline assessed by IRC

**Table 2.** Analysis of disease response per RECIST v1.1 by IRC (primary efficacy analysis set)

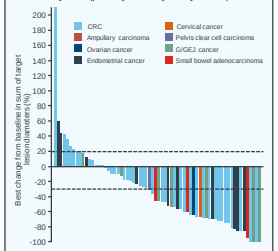
| | All patients (N=74) | CRC (N=46) | Non-CRC (N=28) |
|---|---|---|---|
| **ORR (CR + PR)** | | | |
| n (%) | 34 (45.9) | 18 (39.1) | 16 (57.1) |
| 95% CI | 34.3, 57.9 | 25.1, 54.6 | 37.2, 75.5 |
| P-value* | < 0.0001 | – | – |
| **Confirmed best overall response, n (%)** | | | |
| CR | 4 (5.4) | 2 (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) |
| Progressive disease | 14 (18.9) | 9 (19.6) | 5 (17.9) |
| Not evaluable† | 7 (9.5) | 4 (8.7) | 3 (10.7) |
| **Disease control rate (CR + PR + SD)** | | | |
| n (%) | 53 (71.6) | 33 (71.7) | 20 (71.4) |
| 95% CI | 60.0, 81.5 | 56.5, 84.0 | 51.3, 86.8 |
| **Clinical benefit rate (CR + PR + durable SD ≥ 24 weeks)** | | | |
| n (%) | 39 (52.7) | 23 (50.0) | 16 (57.1) |
| 95% CI | 40.8, 64.4 | 34.9, 65.1 | 37.2, 75.5 |

*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*

## 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 or dMMR solid tumors
- Tislelizumab treatment showed consistent efficacy across tumour types demonstrating the benefit of tissue-agnostic treatment
- Tislelizumab treatment demonstrated a durable response
- 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

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




*Data are presented for patients with post-baseline target lesion measurements*
*CRC, colorectal cancer; G/GEJ, gastric or gastroesophageal junction*

## Efficacy: Survival

- Median PFS and OS have not been reached
  - 12-month PFS and OS rates were 59.3% (95% CI 46.2, 70.2) and 75.3% (95% CI 62.6, 84.2) for all tumor types
  - 12-month PFS and OS rates were similar among those with CRC (57.7% [95% CI 40.6, 71.5] and 77.2% [95% CI 60.6, 87.5], respectively) and other cancer types (62.2% [95% CI 41.1, 77.6]) and 73.2% [95% CI 51.4, 86.4])

## Safety

- Among the safety analysis set (N=80), the median number of tislelizumab treatment cycles received was 10.5 (range: 1–34) with a median duration of exposure of 7.5 months (range: 0.7–26.6)
- All patients had ≥ 1 treatment-emergent AE (TEAE) and ≥ Grade 3 TEAEs were reported in 47.5% of patients
  - Laboratory abnormalities were the most common cause of ≥ Grade 3 TEAEs (in 17 patients [21.3%])
  - ≥ Grade 3 immune-mediated TEAEs were reported in 4 patients (5.0%), with no Grade 4 or 5 events reported
- Treatment-related AEs (TRAEs) were reported in 98.8% of patients, with ≥ Grade 3 TRAEs reported in 42.5% (**Table 3**)
  - TRAEs led to death in 3 patients (3.8%), including the following by preferred term: respiratory failure, large intestinal obstruction, and death (occurring in 1 patients [1.3%] each)
- Most TEAEs reported in the study population were consistent with expected manifestations of the disease under study, known effects of PD-1 antibodies and related to the mechanism of action. The common TEAEs or treatment related TEAEs are generally reversible and manageable

**Table 3.** Safety summary (safety analysis set)

| 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 reported in ≥ 15% of patients** | |
| 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) |

*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*

## References

1. Dudley JC, et al. Clin Cancer Res 2016;22:813–20
2. Llosa NJ, et al Cancer Discov 2015;5:43–51
3. Giannakis M, et al. Cell Rep 2016;15:857–65
4. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90
5. Shen L, et al. J Immunother Cancer 2020;8:e000437

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