Preoperative (Neoadjuvant) Therapy With Tislelizumab for Locally Advanced Colorectal Cancer With High Microsatellite Instability or Deficient Mismatch Repair: An Open-label, Single-arm, Multicenter Phase II Study

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Conclusions

Neoadjuvant tislelizumab (BGB-A317) was associated with high major pathological response (MPR) and pathological complete response (pCR) rates and an acceptable safety profile, and did not compromise surgery in patients with resectable microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) colorectal cancer (CRC).

Neoadjuvant therapy with tislelizumab could be a potential therapeutic option for further investigation in patients with locally advanced MSI-H or dMMR CRC.

Background

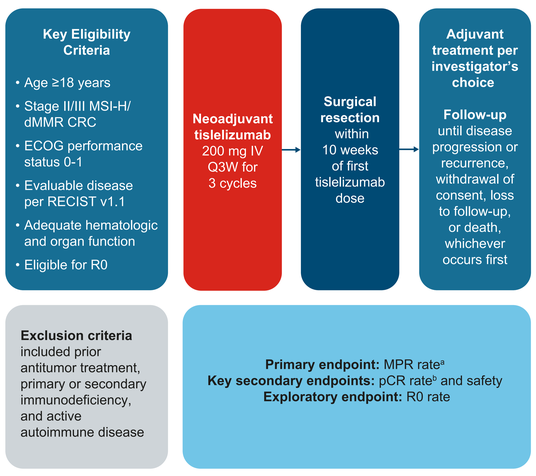
CRC is the fourth most common cancer globally; in 2022, the incidence of CRC was estimated at 2,736,276, with 1,513,085 deaths.[1] Approximately 15% of all CRCs are MSI-H/dMMR.[2] Tislelizumab, an anti-programmed cell death protein 1 (PD-1) antibody, demonstrated improved antitumor response and tolerable safety in patients with previously treated, locally advanced unresectable or metastatic MSI-H/dMMR solid tumors, including CRC, in the RATIONALE-209 study (NCT03736889).[3]

Recent studies of other anti–PD-1 antibodies indicate potential clinical benefit of neoadjuvant anti–PD-1 therapy in patients with resectable MSI-H/dMMR CRC.[4-7] Here, we report efficacy and safety outcomes of neoadjuvant tislelizumab treatment in this patient population from the open-label, single-arm, multicenter phase II RATIONALE-214 study (NCT05116085).

Methods

- Adult patients from China were enrolled in this open-label, single-arm, multicenter study. The study design is shown in **Figure 1**

Figure 1. Study Design



[a] Proportion of patients with ≤10% residual viable tumor in the surgically resected primary tumor. [b] Proportion of patients with absence of residual tumor in the surgically resected specimen. **Abbreviations:** CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; MPR, major pathological response; MSI-H, microsatellite instability-high; Q3W, once every 3 weeks; pCR, pathological complete response; R0, complete tumor resection; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Results

Patient Disposition and Baseline Characteristics

- At the time of data cutoff (September 26, 2023), 33 patients were enrolled across 8 sites in China
- Median study follow-up time was 6.5 months (range: 0.9-20.0)
- The median age of enrolled patients was 52.0 years (range: 23-84); 14 patients (42.4%) were male and all patients were Chinese (**Table 1**)
- Ten patients (30.3%) had rectal cancer and 23 (69.7%) had colon cancer
- Clinical tumor stage at study entry is reported in **Table 1**
- A total of 29 patients (87.9%) received surgery (Efficacy Analysis Set)
- Surgery was not performed in 4 patients, 3 of whom were managed nonoperatively (1 patient had progressive disease)

Table 1. Patient Baseline Characteristics (Safety Analysis Set)

		Total (N=33)
Median age (range), years		52.0 (23.0-84.0)
Male, n (%)		14 (42.4)
Race, n (%)	Chinese	33 (100.0)
Cancer type, n (%)	Colon (total)	23 (69.7)
	Right colon	15 (45.5)
	Left colon	5 (15.2)
	Transverse colon	2 (6.1)
	Right and left colon	1 (3.0)
	Rectal	10 (30.3)
ECOG performance status, n (%)	0	27 (81.8)
	1	6 (18.2)
Disease stage, n (%)	II	6 (18.2)
	III	27 (81.8)
TNM stage	T2	1 (3.0)
	T3	7 (21.2)
	T4	25 (75.8)
	N0	6 (18.2)
	N1	14 (42.4)
	N2	13 (39.4)

The Safety Analysis Set includes all enrolled patients who received ≥1 dose of study drug. **Abbreviations:** ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastasis.

Efficacy

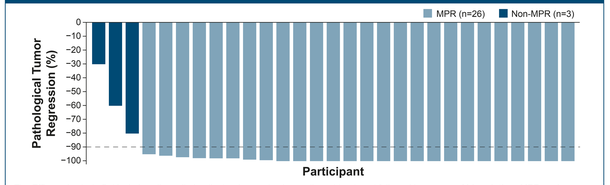
- The MPR rate was 89.7% and the overall pCR rate was 62.1% (**Table 2**)
- For most patients, the residual viable tumor was ≤10% of the resected primary tumor. There was 1 patient who had >50% residual viable tumor in the resected primary tumor (**Table 2** and **Figure 2**)
- Most patients had no residual viable lymph node tumor (28 patients; 96.6%) and were at pathological lymph node stage N0
- Eighteen patients (62.1%) had pathological tumor stage T0, and 3 patients (10.3%) had pathological tumor stage tumor in situ (Tis)
- As a result, 21 patients (72.4%) had pathological disease stage 0

Table 2. Efficacy Endpoints (Efficacy Analysis Set)

		Total (n=29)
MPR, n (%) [95% CI]		26 (89.7) [72.6, 97.8]
pCR, n (%) [95% CI]		18 (62.1) [42.3, 79.3]
R0 rate, n (%)		29 (100.0)
Percentage of residual viable tumor in the resected primary tumor, n (%)	0	18 (62.1)
	>0 to ≤10	8 (27.6)
	>10 to ≤25	1 (3.4)
	>25 to ≤50	1 (3.4)
	>50	1 (3.4)

The Efficacy Analysis Set includes all enrolled patients who received neoadjuvant treatment followed by surgery. **Abbreviations:** CI, confidence interval; MPR, major pathological response; pCR, pathological complete response; R0, complete tumor resection.

Figure 2. Pathological Tumor Regression in the Resected Tumor (Efficacy Analysis Set)



The Efficacy Analysis Set includes all enrolled patients who received neoadjuvant treatment followed by surgery. **Abbreviation:** MPR, major pathological response.

Safety

- Any-grade and grade ≥3 treatment-related adverse events (TRAEs) were reported in 20 patients (60.6%) and 1 patient (3.0%; grade 3 inflammation), respectively (**Table 3**)
- Two patients (6.1%) experienced serious TRAEs; no TRAEs led to death or surgery cancellation. One patient (3.0%) experienced a TRAE (grade 2 hypothyroidism) leading to surgery delay
- No grade ≥3 or serious surgery-relevant TRAEs were reported
- Immune-mediated adverse events were reported in 10 patients (30.3%; all grade 1-2)

Table 3. Overview of TRAEs (Safety Analysis Set)

n (%)	Total (N=33)
Any-grade TRAE	20 (60.6)
TRAE grade ≥3	1 (3.0)
Serious TRAE	2 (6.1)
TRAE leading to death	0
TRAE leading to discontinuation of tislelizumab	1 (3.0)
TRAE leading to dose delay of tislelizumab	0
TRAE leading to surgery cancellation	0
TRAE leading to surgery delay	1 (3.0)
Surgery-relevant TRAE	5 (17.2)
Surgery-relevant TRAE grade ≥3	0
Serious surgery-relevant TRAE	0
Surgery-relevant TRAE leading to death	0
Immune-mediated AE	10 (30.3)
Immune-mediated AE grade ≥3	0

The Safety Analysis Set includes all enrolled patients who received ≥1 dose of study drug. AEs were graded for severity using Common Terminology Criteria for Adverse Events version 5.0. TRAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship. A surgery-relevant AE is defined as an AE collected in the case report form from the date of surgery until up to 30 days after surgery. **Abbreviations:** AE, adverse event; TRAE, treatment-related adverse event.

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Disclosures

Kefeng Ding reports no conflicts of interest.

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