Clinical Profile of Tislelizumab in Chinese Patients With MSI-H or dMMR Solid Tumors: Preliminary Results From an Indication-Expansion Cohort

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Relationship Between MSI Status and Immunologic Response

- Tumors with DNA mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H) are sensitive to PD-1 blockade
  - Tumors with MSI-H and dMMR have a significant upregulation of immune checkpoint proteins (including PD-1 and PD-L1), which enables them to survive

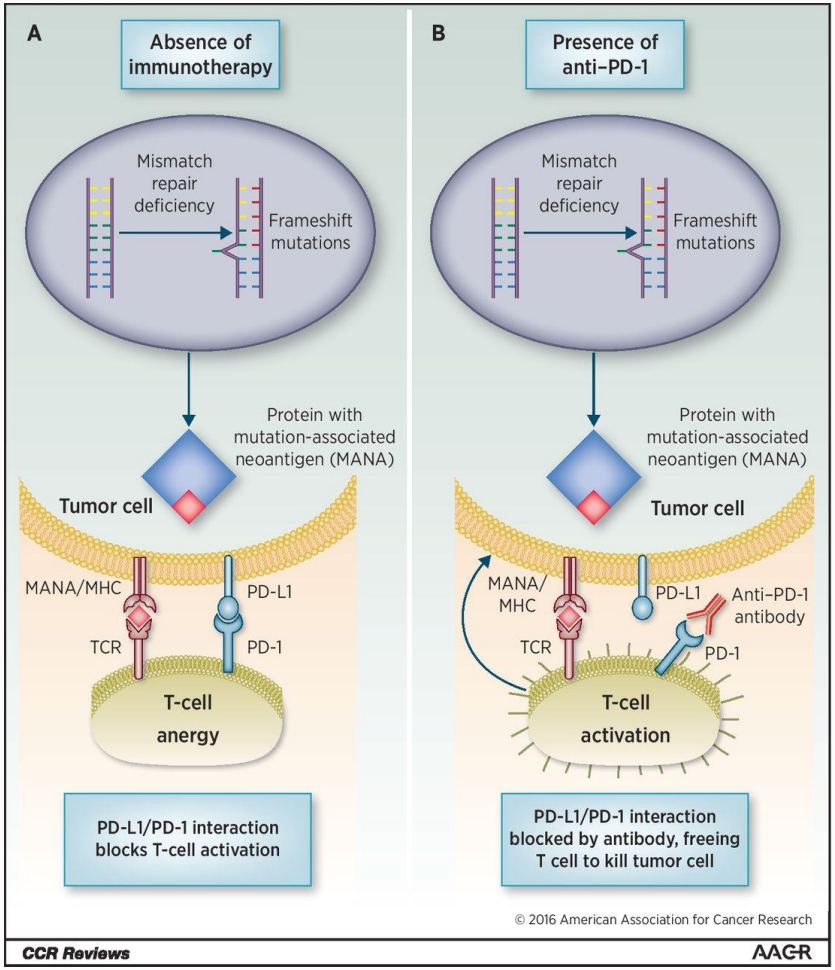


Figure: Dudley, et al. *Clin Cancer Res.* 2016;22:813–820.

Tislelizumab: A Uniquely Engineered Anti–PD-1 Monoclonal Antibody

- Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity/specificity for PD-1
- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages, thereby abrogating antibody-dependent T-cell clearance, a potential mechanism of resistance to anti-PD-1 therapy

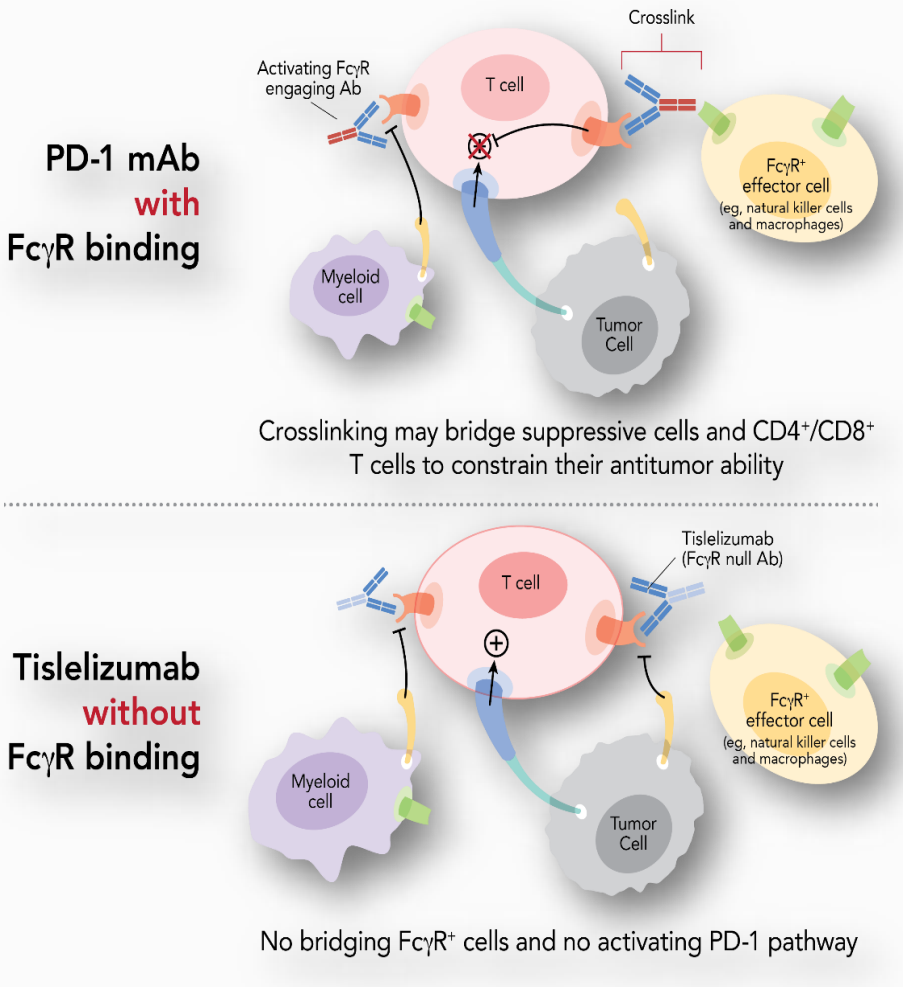


Figure modified from Dahan R, et al. *Cancer Cell*. 2015;28:285–295.
Abbreviations: Ab, antibody; PD-1, programmed cell death-1.

Design of BGB-A317-102 Study: Ongoing, Phase 1/2 Study of Tislelizumab in Chinese Patients

1: Dose verification*

200 mg Q3W → RP2D

Here, we report the preliminary results from the phase 2 cohorts (indication expansion) of this multicenter clinical study of tislelizumab in Chinese patients with MSI-H or dMMR solid tumors

2: Indication expansion**

- Arm 1: Melanoma (n=20)
- Arm 2: NSCLC（PD-L1 ≥10%; n=20）
- Arm 3: NSCLC（PD-L1 <10%; n=20）
- Arm 4: Gastric cancer (n=20)
- Arm 5: Esophageal cancer (n=20)
- Arm 6: Renal cell carcinoma (n=20)
- Arm 7: Urothelial carcinoma (n=20)
- Arm 8: MSI-H or dMMR CRC‡ (n=20)
- Arm 9: TNBC, HNSCC, SCNEC, or other tumors with MSI-H or dMMR‡ (n=20)
- Arm 10: Nasopharyngeal carcinoma (n=20)
- Arm 11: Child-Pugh A HCC (n=20)

Abbreviations: CRC, colorectal cancer; DLT, dose-limiting toxicity; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability high; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; RP2D, recommended phase 2 dose; SCNEC, small cell neuroendocrine carcinoma; TNBC, triple-negative breast carcinoma.

‡MSH-H and dMMR is defined based on local assessment

Patient Demographics and Baseline Disease Characteristics

- As of 11 May 2018, 22 patients have been enrolled
  - A total of 16 patients had a centrally confirmed MSI-H/dMMR tumor assessed by PCR or IHC
- The study population was primarily male (54%) with a median age of 54 years; 82% had received ≥1 prior line of systemic therapy and colorectal cancer was the most common primary tumor type

	MSI-H/dMMR* (n=16)	Other (n=6)	Overall (N=22)
Median age, years (range)	60.5 (38, 74)	47.5 (37, 71)	54.0 (37, 74)
Male, n (%)	6 (37.5)	6 (100)	12 (54.5)
Primary site of tumor, n (%)			
CRC	14 (87.5)	6 (100)	20 (90.9)
GC	1 (6.3)	0 (0)	1 (4.5)
Unknown/ missing	1 (6.3)	0 (0)	1 (4.5)
Prior lines of systemic therapy, median (range)	2 (0, 5)	2.5 (1, 7)	2 (0, 7)
Number of prior anticancer therapy regimens, n (%)			
0	4 (25.0)	0 (0)	4 (18.2)
1	3 (18.8)	1 (16.7)	4 (18.2)
2	6 (37.5)	2 (33.3)	8 (36.4)
≥3	3 (18.8)	3 (50.0)	6 (27.3)
Median study follow-up duration, months (range)	4.4 (1.7, 10.7)	3.9 (0.10, 9.8)	4.4 (0.10, 10.7)

*Confirmed by central laboratory.

Abbreviations: CRC, colorectal cancer; GC, gastric cancer; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability high.

Patient Disposition

- As of the data cut-off, a total of 10 of the 22 patients (45.5%) remain on treatment; the majority (n=9) have a confirmed MSI-H/dMMR tumor
  - Disease progression was the most common reason for treatment discontinuation
  - One patient discontinued due to an unrelated grade 3 lower gastrointestinal haemorrhage
  - Two patients discontinued due to death; both deaths were due to disease progression and considered unrelated to tislelizumab
- Across the study, median treatment duration of tislelizumab was 2.2 months (range: 0.69–11.1 months)
  - Treatment duration was higher in patients with tumors with confirmed MSI-H/dMMR than tumors with confirmed non-MSI-H/non-dMMR (3.6 vs 2.1 months)

	MSI-H/dMMR* (n=16)	Other (n=6)	Overall (N=22)
Active on tislelizumab, n (%)	**9 (56.3)**	**1 (16.7)**	**10 (45.5)**
Reason for tislelizumab discontinuation, n (%)	**7 (43.7)**	**5 (83.3)**	**12 (54.4)**
AE	1 (6.3)†	0 (0)	1 (4.5)
Death	1 (6.3)	1 (16.7)	2 (9.1)
Withdrawal of consent	1 (6.3)	0 (0)	1 (4.5)
Disease progression	4 (25.0)	4 (66.7)	8 (36.4)
Median treatment duration, months (range)	**3.6 (1.3, 11.1)**	**2.1 (0.69, 4.1)**	**2.2 (0.69, 11.1)**
Median follow-up duration, months (range)	**4.4 (1.7, 10.7)**	**3.9 (0.10, 9.8)**	**4.4 (0.10, 10.7)**

*Confirmed by central laboratory; †Grade 3 lower gastrointestinal hemorrhage unrelated to tislelizumab.
Abbreviations: AE, adverse event; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability high.

Data cut-off: 11 May 2018

Tislelizumab Response in Patients With Confirmed MSI-H/dMMR Tumors

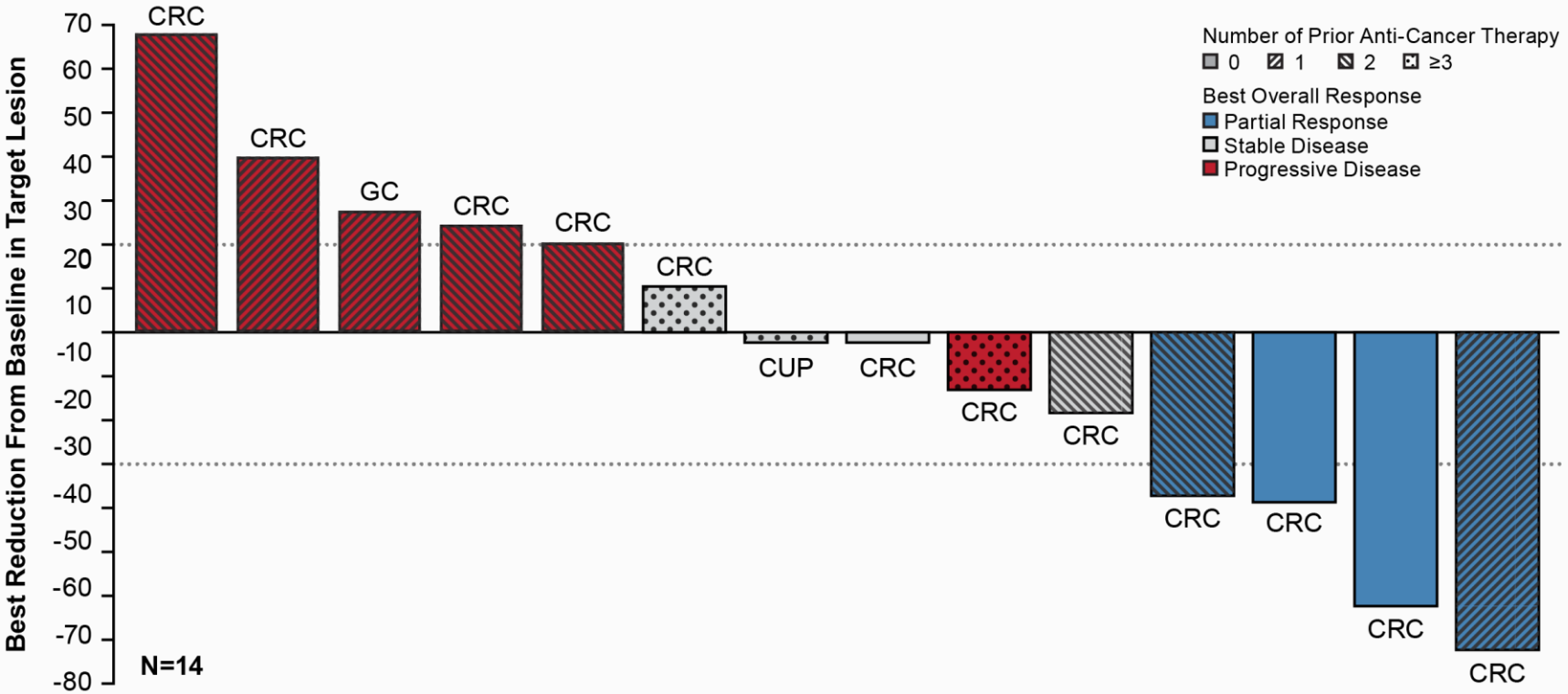
- Fourteen patients with centrally confirmed MSI-H/dMMR tumors were evaluable for antitumor activity per RECIST v1.1 criteria
  - Across these 14 patients, the objective response rate was 28.6%
- Progressive disease was the best response in the three patients centrally negative for MSI-H/dMMR who were evaluable according to RECIST v1.1

Response, n (%)	MSI-H/dMMR (N=14)
Best overall response per RECIST v1.1 (confirmed)	
Complete response (CR)	0 (0.0)
Partial response (PR)	4 (28.6)
Stable disease (SD)	4 (28.6)
Progressive disease (PD)	6 (42.9)
Objective response rate (CR+PR), % (95% CI)	**28.6 (8.39, 58.10)**

Disease assessment by radiographic imaging was performed every 9 weeks during first 12 months and every 12 weeks thereafter.
Abbreviations: CI, confidence interval; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability high.

Data cut-off: 11 May 2018

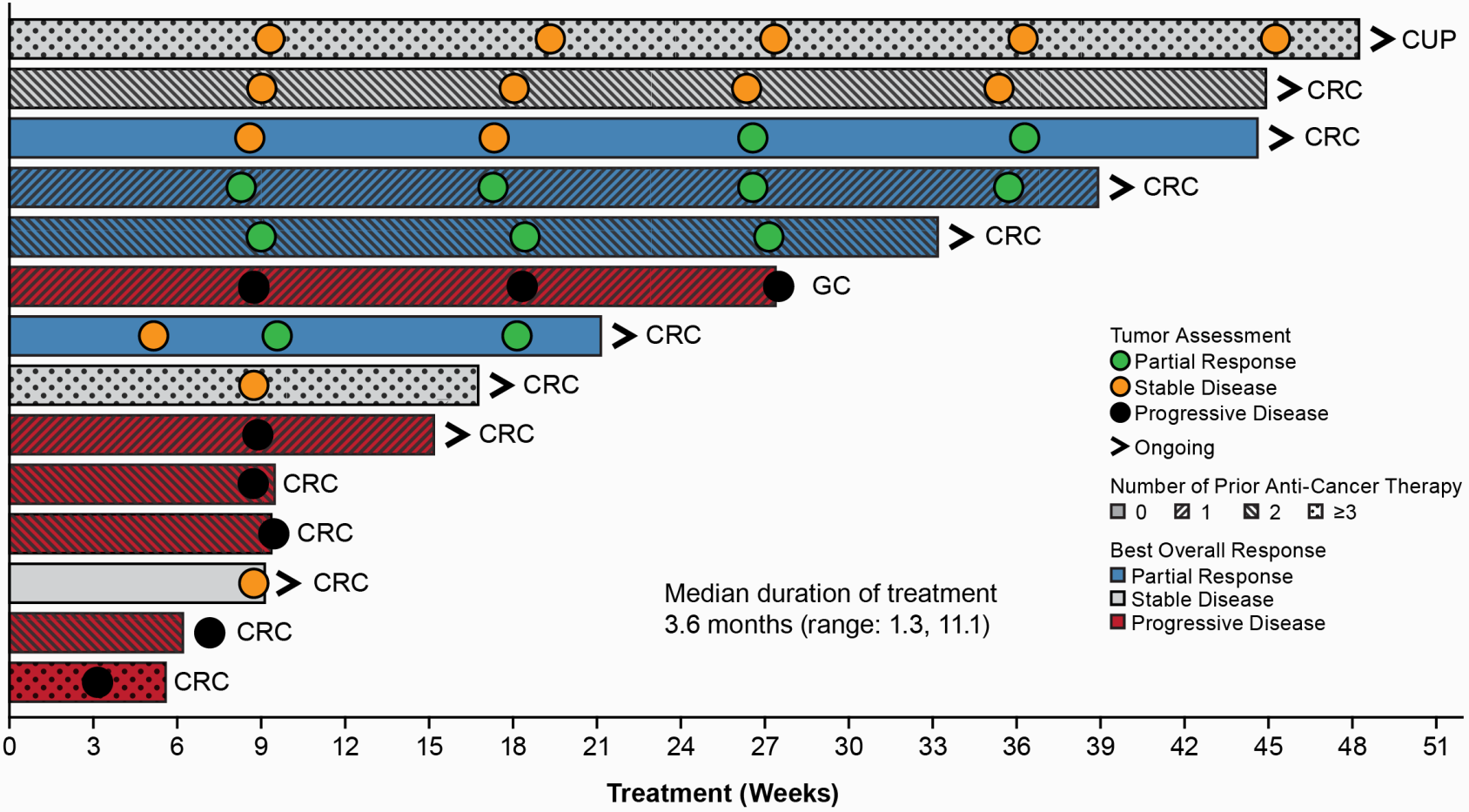
Best Overall Response to Tislelizumab in Evaluable Patients With Confirmed MSI-H/dMMR Solid Tumors



Abbreviations: CRC, colorectal cancer; CUP, carcinomas of unknown primary; GC, gastric cancer; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability high.

Data cut-off: 11 May 2018

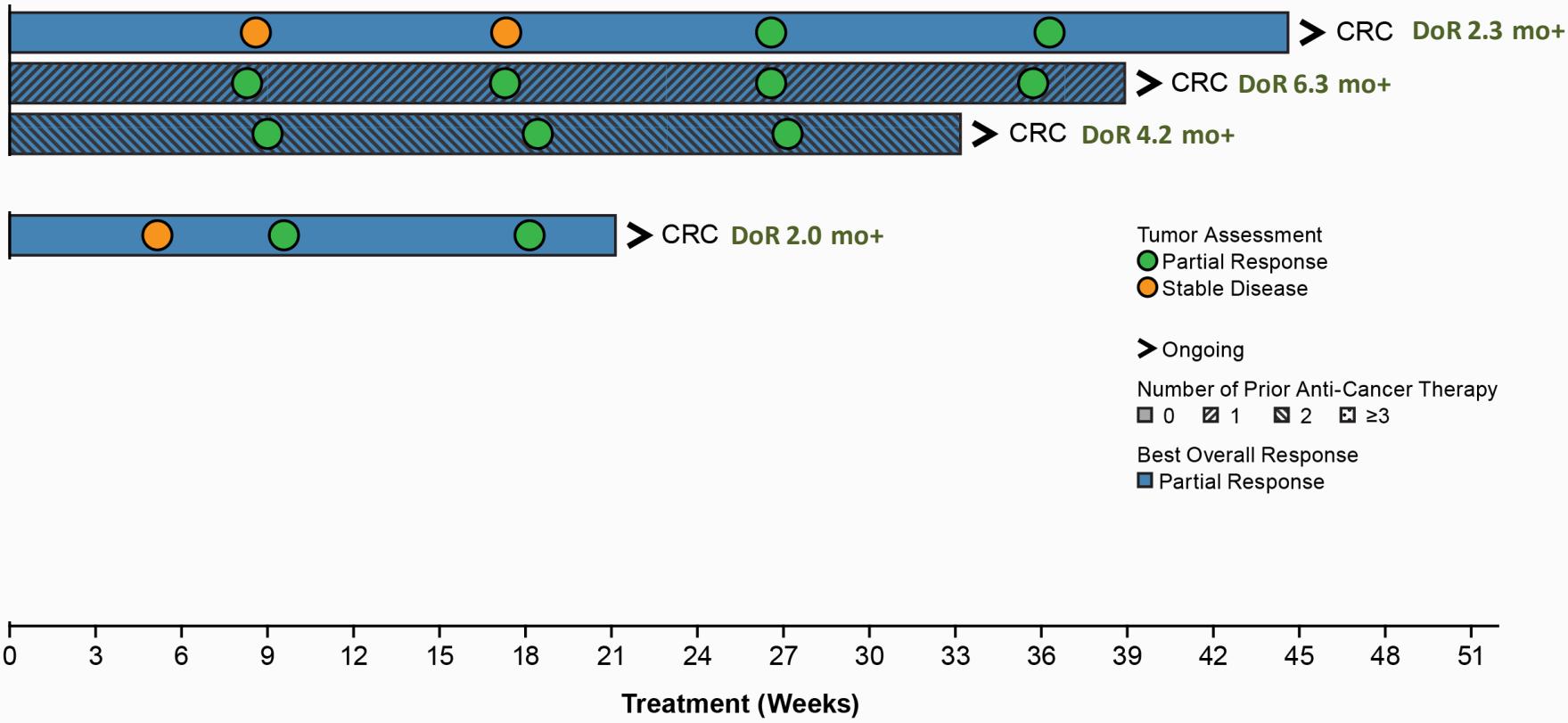
Duration of Tislelizumab Treatment and Response in Evaluable Patients With Confirmed MSI-H/dMMR Solid Tumors



Abbreviations: CRC, colorectal cancer; CUP, carcinomas of unknown primary; GC, gastric cancer; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability high.

Data cut-off: 11 May 2018

Duration of Tislelizumab Treatment and Response in Responders With Confirmed MSI-H/dMMR colorectal cancer



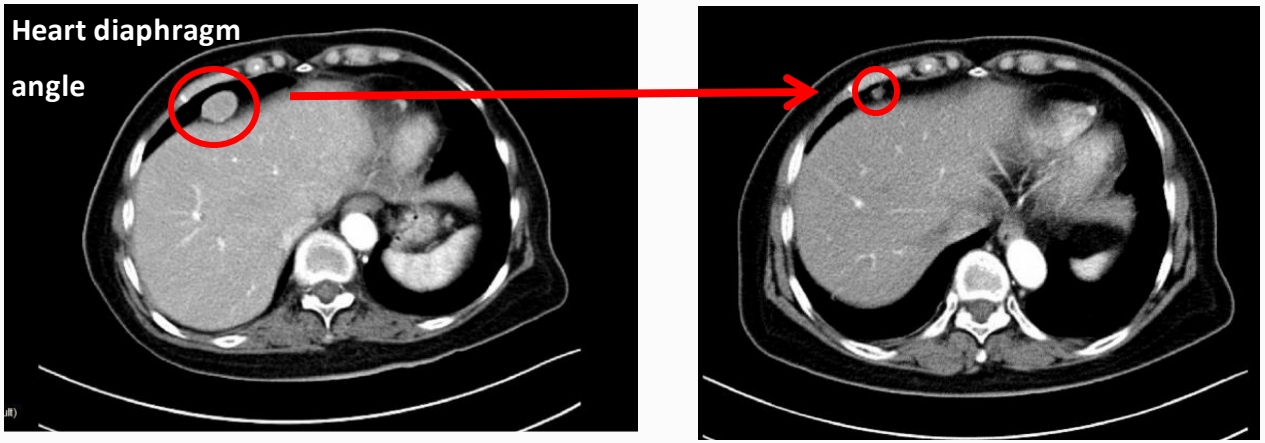
Abbreviations: DoR, duration of response; CRC, colorectal cancer; dMMR, mismatch repair-deficient; MSI-H, microsatellite instability high.

Data cut-off: 11 May 2018

Case Example 1: Radiographic Images of a Patient With MSI-H/dMMR CRC

- **Gender:** Female
- **Age:** 68 years
- **Metastases:** Lymph nodes, heart diaphragm angle
- **Prior Systemic treatments**: mFOLFOX (1st Line)
- **Best overall response**: PR

Baseline **Week 45**

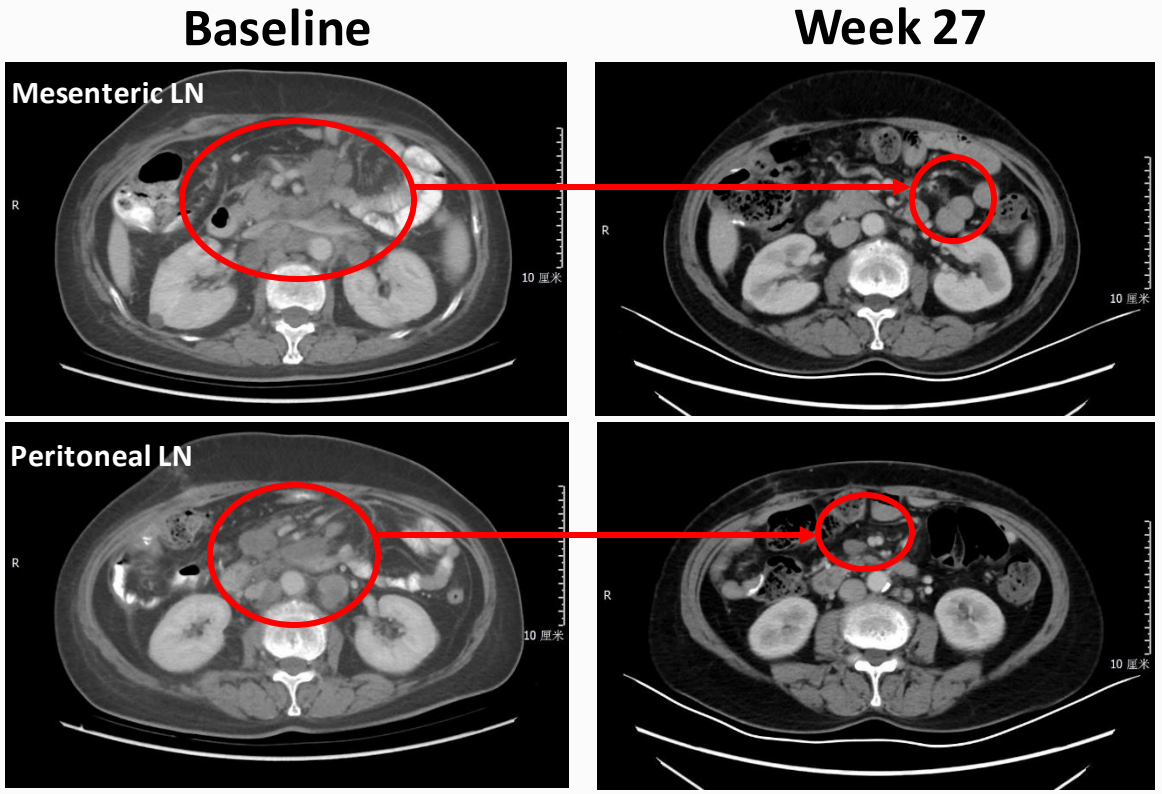


	Baseline	Week 45
Target lesion SLD (mm)	25	7
Non Target Lesion		Non-CR/Non-PD
New Lesion		None

Abbreviations: CR, Complete response; mFOLFOX, L-OHP + 5-Fu + LV; PD, progressive disease; PR, partial response; SLD, sum of the lesion diameters.

Case Example 2: Radiographic Images of a Patient With MSI-H/dMMR CRC

- **Gender:** Female
- **Age:** 67 years
- **Metastases:** Lymph nodes, Lung, Peritoneum, Ascites
- **Prior systemic treatments**: None
- **Best overall response**: PR



Abbreviations: CR, Complete response; PD, progressive disease; PR, partial response; SLD, sum of the lesion diameters.

	Baseline	Week 27
Target lesion SLD (mm)	40	15
Non Target Lesion		Non-CR/Non-PD
New Lesion		None

Adverse Events Considered Related to Tislelizumab

- As of 11 May 2018, 18 of the 22 patients experienced ≥1 treatment-related AE (TRAE)
- The most common TRAEs were related to changes in clinical laboratory value (eg, increased bilirubin; increased transaminase)
  - No TRAE was ≥3 grade in severity

Treatment-Related AEs Occurring in ≥2 Patients

	Overall	
	All Grades (N=22)	Grade ≥3 (N=22)
Subjects who experienced ≥1 TRAE	**18 (81.2)**	**0 (0)**
Increased bilirubin	8 (36.4)	0 (0)
Increased conjugated bilirubin	*5 (22.7)*	*0 (0)*
Increased blood bilirubin	*4 (18.2)*	*0 (0)*
Increased unconjugated blood bilirubin	*2 (9.1)*	*0 (0)*
Transaminases increased	6 (27.3)	0 (0)
Increased AST	*5 (22.7)*	*0 (0)*
Increased ALT	*4 (18.2)*	*0 (0)*
Anemia	5 (22.7)	0 (0)
Increased blood creatine phosphokinase	5 (22.7)	0 (0)
Decreased WBC and/or neutrophil count	4 (18.2)	0 (0)
Decreased WBC count	*3 (13.6)*	*0 (0)*
Decreased neutrophil count	*2 (9.1)*	*0 (0)*
Cough	3 (13.6)	0 (0)
Diarrhea	3 (13.6)	0 (0)
Proteinuria	3 (13.6)	0 (0)
Pyrexia	3 (13.6)	0 (0)
Fatigue	2 (9.1)	0 (0)

Data presented as n (%). **Abbreviations**: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event; WBC, white blood cell.

Data cut-off: 11 May 2018

Immune-Related Adverse Events Regardless of Attribution

- A total of 13 patients experienced immune-related AEs (irAEs)*
  - The most common irAEs (defined as occurring in ≥10% of patients) were increased AST (n=5), increased conjugated bilirubin (n=5), increased blood creatine phosphokinase (n=5), increased ALT (n=4), increased blood bilirubin (n=4), and diarrhea (n=3)
  - All irAEs were Grade ≤2 in severity

Immune-related AEs Occurring in ≥2 Patients

	Overall	
	All grades (N=22)	Grade ≥3 (N=22)
Subjects with ≥1 immune-related AE	**13 (59.1)**	**0 (0)**
Increased bilirubin	8 (36.4)	0 (0)
Increased conjugated bilirubin	*5 (22.7)*	*0 (0)*
Increased blood bilirubin	*4 (18.2)*	*0 (0)*
Increased unconjugated blood bilirubin	*2 (9.1)*	*0 (0)*
Transaminases increased	6 (27.3)	0 (0)
Increased AST	*5 (22.7)*	*0 (0)*
Increased ALT	*4 (18.2)*	*0 (0)*
Increased blood creatine phosphokinase	5 (22.7)	0 (0)
Diarrhea	3 (13.6)	0 (0)

Data presented as n (%).
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*Treatment-related adverse events reported in this study were categorized as immune related according to a predefined list of terms from the study sponsor

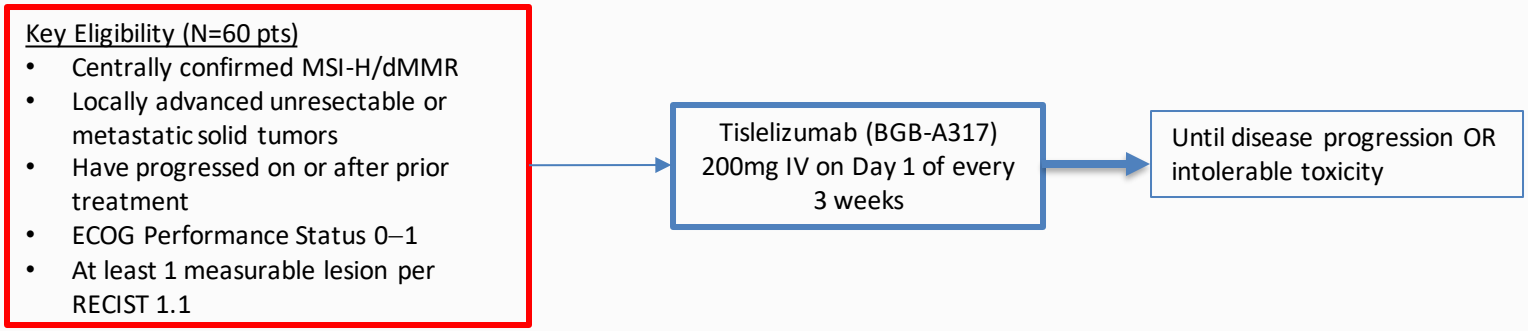
Data cut-off: 11 May 2018

Summary

- Preliminary data suggest tislelizumab may have antitumor activity in patients with MSI-H/dMMR tumors
  - As of the cut-off date, the objective response rate was ~29%; median duration of response was still maturing
- Tislelizumab was generally well tolerated in this subgroup of patients and demonstrated a safety profile consistent with what has been previously reported
  - Overall, 45.5% of patients (n=10/22) remained on treatment at the 11 May 2018 data cut-off
    - Disease progression was the most common reason for treatment discontinuation
- These data support the continued development of tislelizumab as a treatment for patients with MSI-H/dMMR tumors
  - A phase 2 study of single-agent tislelizumab in Chinese patients with previously treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumors is ongoing (CTR20180867)

Ongoing BGB-A317-209 Study (CTR20180867)

A **Single-Arm, Multi-Center, Open-Label, Phase 2 Study** to Evaluate Efficacy and Safety of Tislelizumab (BGB-A317), an anti-PD-1 Monoclonal Antibody, as Monotherapy in Patients with Previously-Treated Locally Advanced Unresectable or Metastatic MSI-H or dMMR Solid Tumors



Primary endpoint:

- Objective response rate (ORR) assessed by Independent Review Committee per RECIST v1.1

Secondary endpoints:

- Duration of Response (DoR), Time to Response (TTR), Progression-free Survival (PFS), Disease control rate (DCR) assessed by Independent Review Committee per RECIST v1.1
- Overall survival
- Objective response rate (ORR), Duration of response (DoR), Time to response (TTR), Progression-free survival (PFS), Disease control rate (DCR) evaluated by the Investigator per RECIST v1.1
- Safety and tolerability assessment

*CTR Number: CTR20180867

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