Tislelizumab in Chinese Patients With Esophageal Cancer (EC), Gastric Cancer (GC), Hepatocellular Carcinoma (HCC), and Microsatellite Instability-High/Mismatch Repair Deficient (MSI-H/dMMR) Tumors

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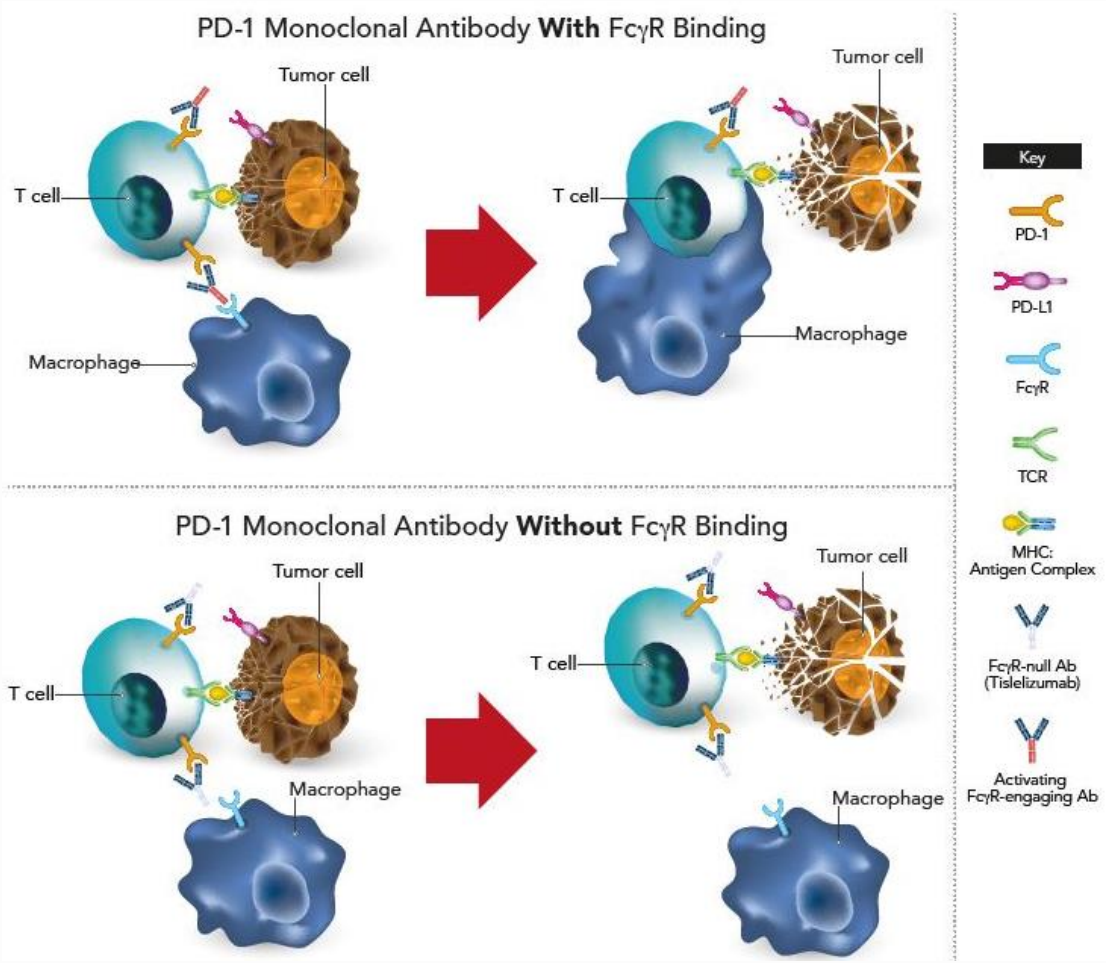
Tislelizumab: A Uniquely Engineered Anti-PD-1 Monoclonal Antibody

- Tislelizumab is an investigational humanized IgG4 monoclonal antibody with high affinity/specificity for PD-1[1]

- Tislelizumab was engineered to minimize binding to FcγR on macrophages, in order to abrogate antibody-dependent phagocytosis, a potential resistance to anti-PD-(L)1 therapy[1,2]

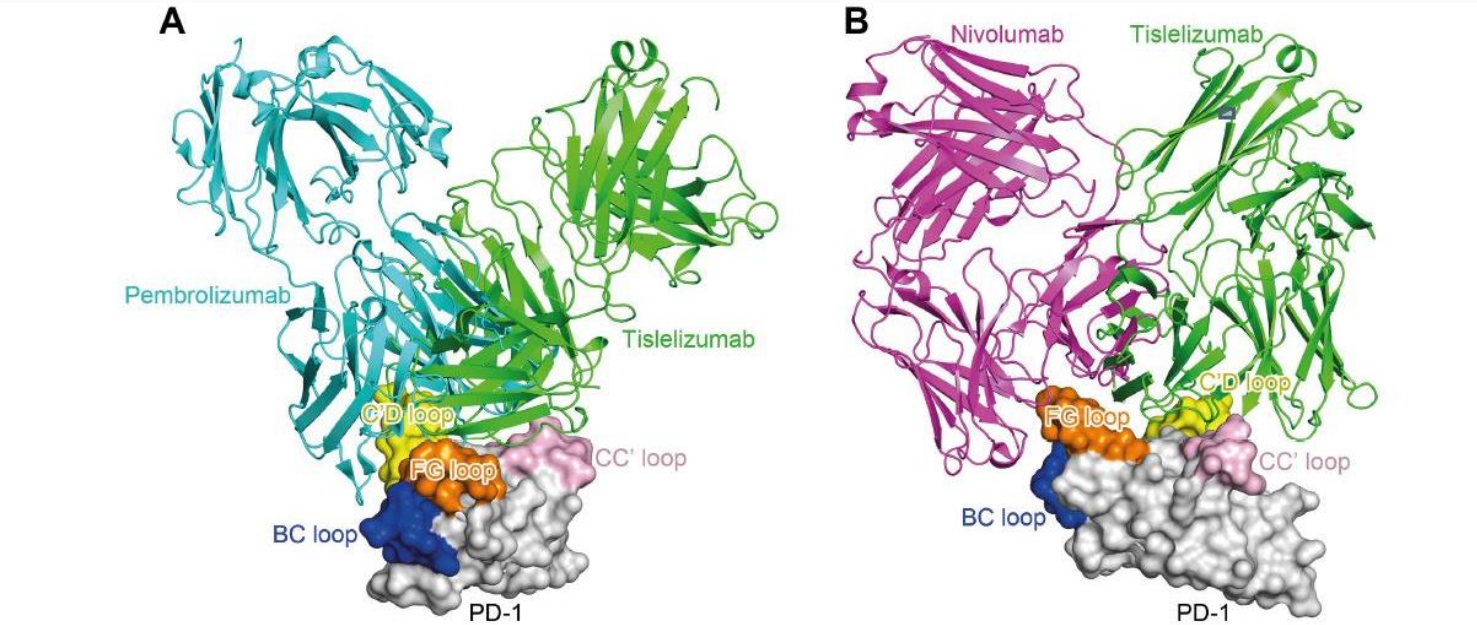


Abbreviations: Ab, antibody; MHC, major histocompatibility complex; PD-1, programmed death-1 receptor; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

1. Zhang T, et al. *Cancer Immunol Immunother.* 2018;67:1079-1090; 2. Dahan R, et al. *Cancer Cell*. 2015;28:543.

Tislelizumab Binding Orientation to PD-1 Is Different From Pembrolizumab (A) and Nivolumab (B)

- Tislelizumab has a unique binding surface on PD-1 that differs from that of pembrolizumab and nivolumab[1]
- Tislelizumab shows higher affinity to PD-1 than pembrolizumab and nivolumab with ~100- and 50-fold slower off-rates, respectively[1]



PD-1, tislelizumab, pembrolizumab, and nivolumab are colored in gray, green, cyan and magenta, respectively. The BC, CC', C'D and FG loops of PD-1 are colored in blue, pink, yellow and orange, respectively.

Abbreviation: PD-1, programmed death-1 receptor.

[1]Feng Y, et al. American Association of Cancer Research Annual Meeting; 2019. Abstract 4048.

BGB-A317-102: Ongoing, Phase 1/2 Study of Tislelizumab in Chinese Patients With Advanced Solid Tumors

Phase 1
Dose verification

Tislelizumab 200 mg Q3W*

Phase 1
PK substudy

Tislelizumab (A) 200 mg Q3W***

Tislelizumab (B) 200 mg Q3W***

RP2D

Phase 2
Indication expansion**

Arm 1 Melanoma n=20	Arm 2 PD-L1-positive NSCLC n=20	Arm 3 PD-L1-negative NSCLC n=20	Arm 4 Gastric cancer n=20
Arm 5 Esophageal squamous cell carcinoma 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, small cell neuroendocrine carcinoma, or other tumors with MSI-H/dMMR n=20		Arm 10 NPC n=20	Arm 11 Child-Pugh A HCC n=20

*In the dose-verification study, three to six subjects were enrolled to assess DLT and RP2D; if no DLT was found, this cohort would expand to 20 subjects.
**In the indication-expansion phase, ~20 subjects were enrolled into each arm. For tumors that are difficult to enroll, the sponsor may early terminate the enrollment of subjects.
***In the PK substudy, a total of 48 subjects (24 per arm) are planned to be enrolled to receive treatment of tislelizumab of two manufacturing process and scales.
Abbreviations: CRC, colorectal cancer; DLT, dose-limiting toxicity; dMMR, defective mismatch repair; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; MSI-H, microsatellite instability-high; NPC, nasopharyngeal cancer; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; PK, pharmacokinetics; Q3W, every 3 weeks; RP2D, recommended phase 2 dose; TNBC, triple-negative breast cancer.

Adverse Events Considered Related to Tislelizumab (All Patients; N=300)

- Across the entire study, the most common treatment-related AEs (TRAEs) were anemia (23%) and increased AST (22%); most TRAEs were grade ≤2 in severity
  - The most common grade ≥3 TRAEs were increased GGT (4%), anemia (3%), and increased AST (3%)
- After the first dose of study treatment, one patient with gastric cancer experienced grade 5 brain edema, which was considered possibly related to tislelizumab by the investigator
  - The patient had multiple brain metastases with surrounding edema at baseline, and had significant progression of brain metastases before death

Treatment-Related Adverse Events Occurring in ≥10% of Overall Patients

	Grade 1-2	Grade ≥3	All Grades
Patients who experienced ≥1 TRAE	**162 (54)**	**99 (33)**	**261 (87)**
Anemia	61 (20)	9 (3)	70 (23)
Transaminases increased			
Increased AST	59 (20)	8 (3)	67 (22)
Increased ALT	55 (18)	4 (1)	59 (20)
Proteinuria	42 (14)	1 (<1)	43 (14)
Increased blood bilirubin	40 (13)	0	40 (13)
Hypothyroidism	33 (11)	0	33 (11)
Decreased white blood cell count	31 (10)	2 (<1)	33 (11)
Increased conjugated bilirubin	30 (10)	2 (<1)	32 (11)
Pyrexia	31 (10)	0	31 (10)

Data presented as n (%). **Abbreviations**: AE, Adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT; gamma-glutamytransferase (GGT) TRAE, treatment-related adverse event.

Data cut-off: 01 Dec 2018

Demographics and Baseline Disease Characteristics

- Enrolled patients (n=83) with ESCC, GC, HCC, and MSI-H/dMMR solid tumors were pooled from phase 1 and phase 2 of this study

	ESCC (n=26)	GC (n=24)	HCC (n=18)[a]	MSI-H/ dMMR (n=16)[b]
Median age, years (range)	63 (44-77)	57 (24-72)	61 (22-67)	61 (38-74)
Gender				
Male, n (%)	23 (88)	18 (75)	15 (83)	6 (38)
Female, n (%)	3 (12)	6 (25)	3 (17)	10 (63)
ECOG PS, n (%)				
0	3 (12)	3 (13)	7 (39)	4 (25)
1	23 (88)	21 (88)	11 (61)	12 (75)
Tumor stage, n (%)				
Local advanced	1 (3.8)	0	1 (5.6)	0
Metastatic disease	25 (96)	24 (100)	17 (94)	16 (100)
Patients with prior systemic anticancer therapy, n (%)	25 (96)	24 (100)	16 (89)	15 (94)
Number of lines of prior systemic anticancer therapy, n (%)[c]				
0	1 (4)	0	2 (11)	1 (6)
1	5 (19)	10 (42)	7 (39)	5 (31)
2	9 (35)	6 (25)	4 (22)	5 (31)
≥3	11 (42)	8 (33)	5 (28)	5 (31)
Prior treatment received, n (%)[d]				
Cytotoxic therapy	25 (100)	24 (100)	7 (44)	15 (100)
TKI	2 (8)	6 (25)	11 (69)	2 (13)
Monoclonal antibodies	6 (24)	5 (21)	0	6 (40)
Patients with prior local treatment for primary tumor site, n (%)	23 (88)	13 (54)	16 (89)	14 (88)
Alcohol use, n (%)				
Never	8 (31)	18 (75)	12 (67)	13 (81)
Irregular	3 (12)	1 (4)	3 (17)	0
Prior regular use	12 (46)	4 (17)	3 (17)	2 (13)
Current regular use	3 (12)	1 (4)	0	1 (6)
Median study follow-up duration, month (range)	5 (2-19)	6 (1-18)	8 (3-17)	11 (2-17)

[a]All patients had Child-Pugh A liver function. 16 HCC patients had HBV infection, one had HCV infection, and one patient was uninfected. [b]Among 16 MSI-H/dMMR patients, one patient with unknown primary tumor site, one patient had MSI-H/dMMR GC that was also analyzed in the GC cohort, and the remaining 14 patients had MSI-H/dMMR colorectal carcinoma. MSI-H or dMMR statuses of these patients were confirmed/detected in the central lab. [c]Including adjuvant, neoadjuvant, and palliative therapy(ies). [d]Percentages are based on the number of patients who received prior systemic anticancer therapy.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; TKI, tyrosine kinase inhibitor.

Data cut-off: 01 Dec 2018

Responses to Tislelizumab

	ESCC (n=26)	GC (n=24)	HCC (n=18)	MSI-H/dMMR (n=16)
BOR per RECIST v1.1 (confirmed)				
Complete response (CR), n (%)	0	0	0	0
Partial response (PR), n (%)	2 (8)	4 (17)	3 (17)	3 (19)
Stable disease (SD), n (%)	7 (27)	3 (13)	7 (39)	5 (31)
Progressive disease (PD), n (%)	13 (50)	9 (38)	8 (44)	6 (38)
Missing/Not evaluable, n (%)	4 (15)	8 (33)	0	2 (13)
ORR (CR+PR), % (95% CI)	**8 (1-25)**	**17 (5-37)**	**17 (4-41)**	**19 (4-46)**
DCR (CR+PR+SD), % (95% CI)	**35 (17-56)**	**29 (13-51)**	**56 (31-79)**	**50 (25-75)**
CBR (CR+PR+durable SD)[a]	**27 (12-48)**	**25 (10-47)**	**50 (26-74)**	**50 (25-75)**

[a]Durable SD represents stable disease ≥16 weeks.

Disease assessment by radiographic imaging was performed every 9 weeks during first 12 months and every 12 weeks thereafter.

Abbreviations: BOR, best overall response; CI, confidence interval; CBR, clinical benefit rate; DCR, disease control rate; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Data cut-off: 01 Dec 2018

Responses to Tislelizumab

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DCR (CR+PR+SD), % (95% CI)	**35 (17-56)**	**29 (13-51)**	**56 (31-79)**	**50 (25-75)**
CBR (CR+PR+durable SD)[a]	**27 (12-48)**	**25 (10-47)**	**50 (26-74)**	**50 (25-75)**

- Responses were observed regardless of PD-L1 status[a] in ESCC and GC

	ESCC (n=26)			GC (n=24)			HCC (n=18)			MSI-H/dMMR (n=16)		
	PD-L1$^+$ (n=13)	PD-L1$^-$ (n=13)	Unk (n=0)	PD-L1$^+$ (n=4)	PD-L1$^-$ (n=18)	Unk (n=2)	PD-L1$^+$ (n=0)	PD-L1$^-$ (n=16)	Unk (n=2)	PD-L1$^+$ (n=1)	PD-L1$^-$ (n=10)	Unk (n=5)
ORR, % (95% CI)	8 (0-36)	8 (0-36)	0	50 (7-93)	11 (1-35)	0	0	19 (4-46)	0	0	20 (3-56)	20 (1-72)
DCR, % (95% CI)	39 (14-68)	31 (9-61)	0	50 (7-93)	22 (6-48)	50 (1-99)	0	63 (35-85)	0	0	50 (19-81)	60 (15-95)

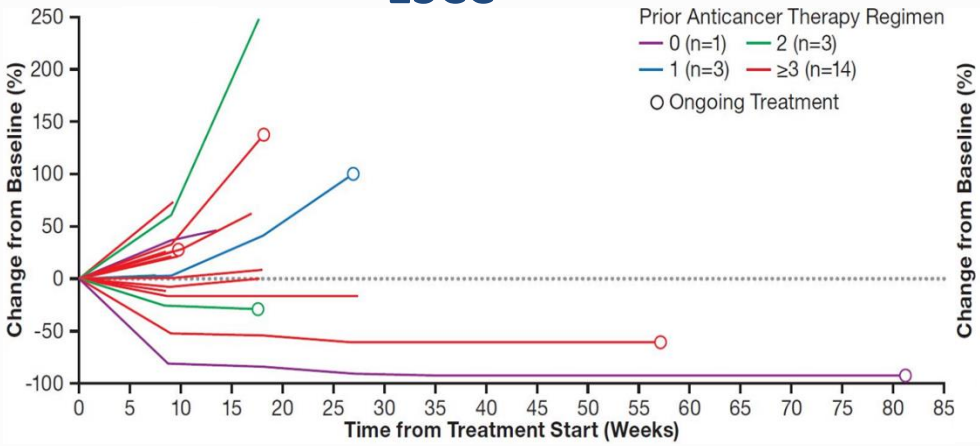
[a]PD-L1 positivity was defined by ≥10% of tumor cells with PD-L1 membrane staining at any intensity by using the VENTANA™ PD-L1 (SP263) assay.
Disease assessment by radiographic imaging was performed every 9 weeks during first 12 months and every 12 weeks thereafter.
Abbreviations: BOR, best overall response; CI, confidence interval; DCR, disease control rate; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; unk, unknown.

Data cut-off: 01 Dec 2018

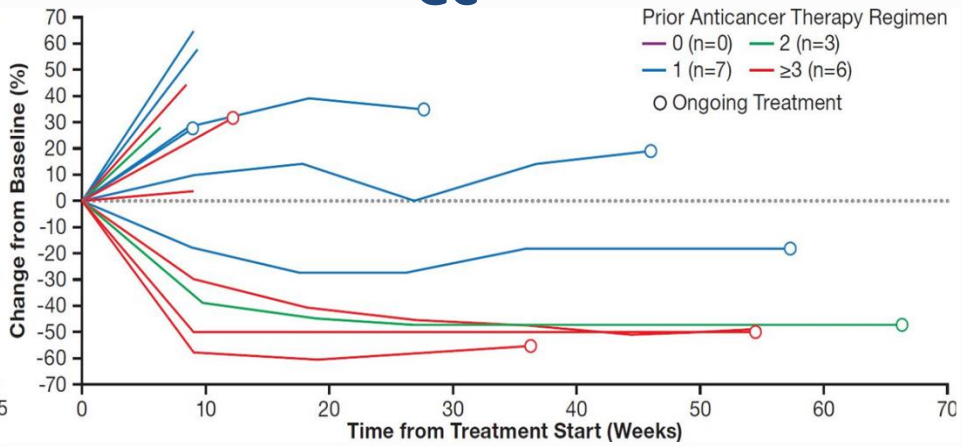
Change in Target Lesion Diameter

- In patients with ESCC, GC, HCC, and MSI-H/dMMR solid tumors, durable decreases in sum of target lesion diameters were observed even in patients who were heavily pretreated

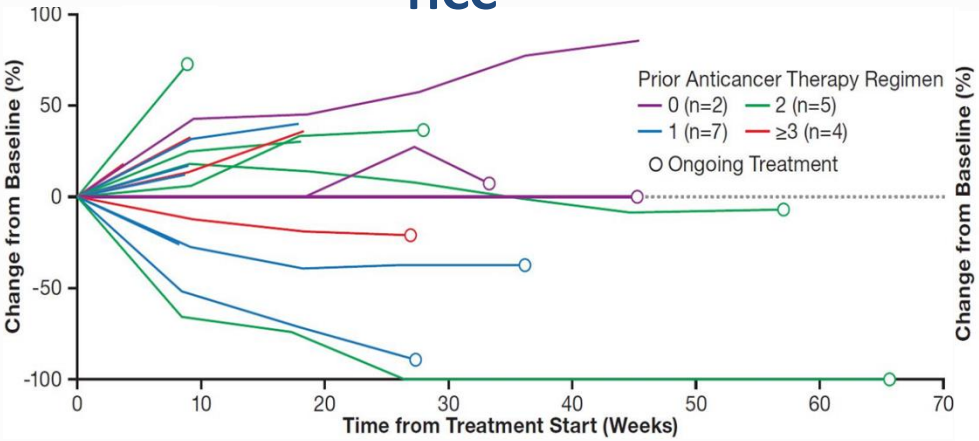
ESCC



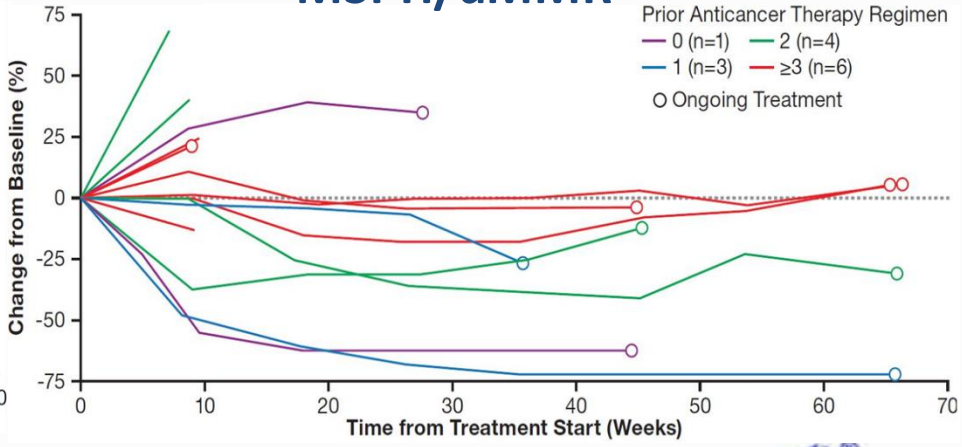
GC



HCC



MSI-H/dMMR



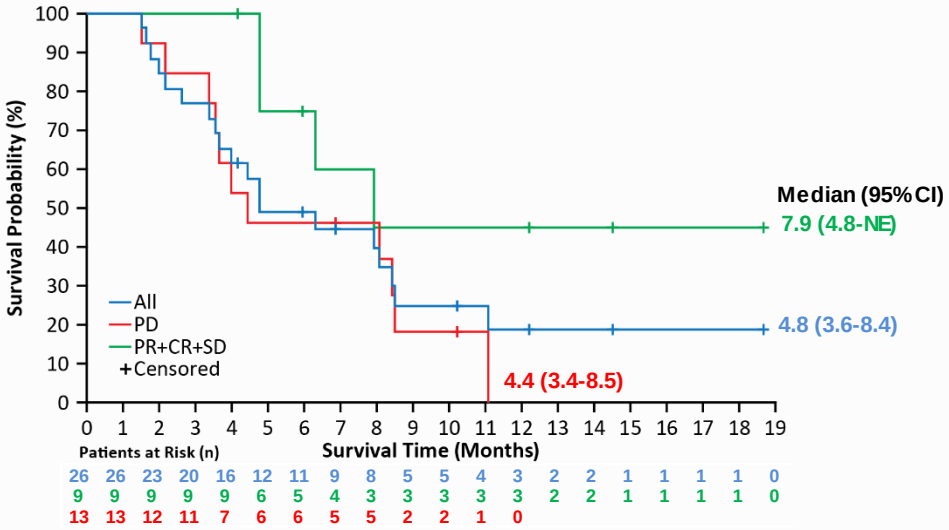
Data cut-off: 01 Dec 2018

Overall Survival

- Median overall survival was 4.8 and 4.7 months for patients with ESCC and GC, respectively

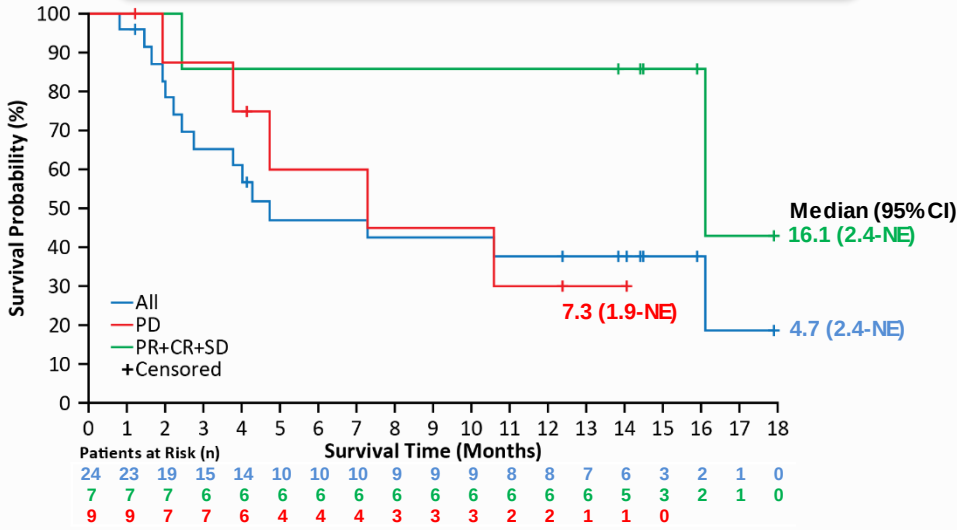
ESCC

	All	PR+CR+SD	PD
Probability of OS at 6 mos	0.5 (0.3-0.7)	0.8 (0.3-0.9)	0.5 (0.2-0.7)



GC

	All	PR+CR+SD	PD
Probability of OS at 6 mos	0.5 (0.3-0.7)	0.9 (0.3-1.0)	0.6 (0.2-0.9)
Probability of OS at 9 mos	0.4 (0.2-0.6)	0.9 (0.3-1.0)	0.5 (0.1-0.8)



Data presented as months (95% CI). **Abbreviations:** CI, confidence interval; CR, complete response; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

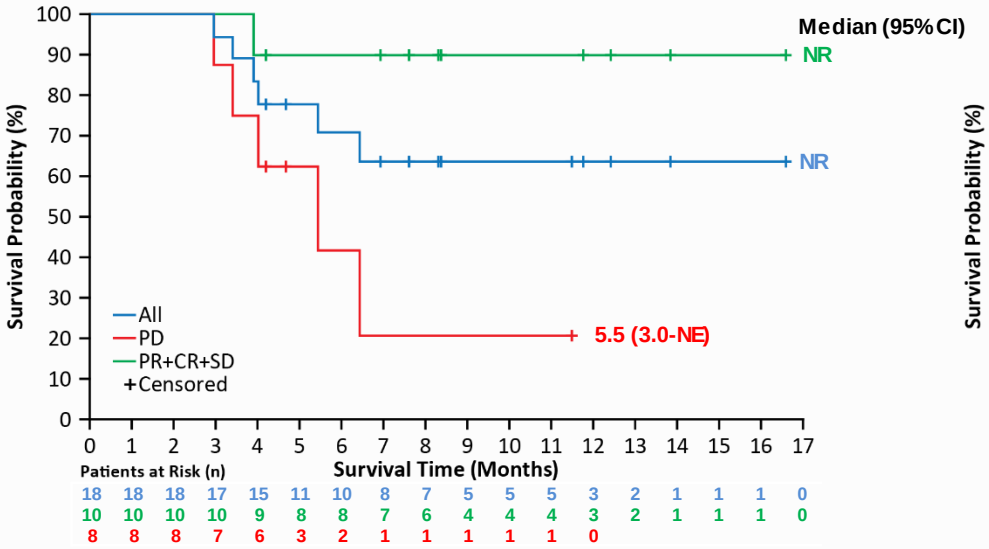
Data cut-off: 01 Dec 2018

Overall Survival

- Median overall survival was not reached for HCC and MSI-H/dMMR solid tumors

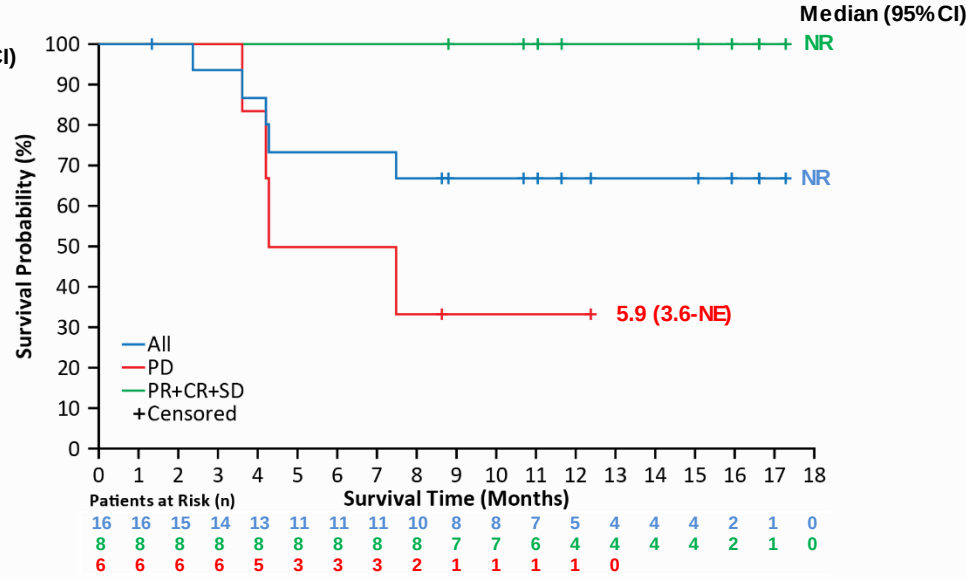
HCC

	All	PR+CR+SD	PD
Probability of OS at 6 mos	0.7 (0.4-0.9)	0.9 (0.5-1.0)	0.4 (0.1-0.7)
Probability of OS at 9 mos	0.6 (0.4-0.8)	0.9 (0.5-1.0)	0.2 (0.0-0.6)



MSI-H/dMMR

	All	PR+CR+SD	PD
Probability of OS at 6 mos	0.7 (0.4-0.9)	1.0 (NE-NE)	0.5 (0.1-0.8)
Probability of OS at 9 mos	0.7 (0.4-0.8)	1.0 (NE-NE)	0.3 (0.0-0.7)



- In all four indications, patients with controlled disease had an increased probability of survival at 6 months compared to patients with progressive disease

Data presented as months (95% CI). **Abbreviations:** CI, confidence interval; CR, complete response; HCC, hepatocellular carcinoma; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

Data cut-off: 01 Dec 2018

Conclusions

- Tislelizumab was generally well tolerated and demonstrated preliminary antitumor activity in patients with ESCC, GC, HCC, or MSI-H/dMMR solid tumors
  - The objective response rate was driven by partial responses and was 8% (ESCC), 17% (GC), 17% (HCC), and 19% (MSI-H/dMMR)
  - Median overall survival was 4.8 months for patients with ESCC and 4.7 months for those with GC; despite a long median follow-up, median overall survival was not reached for patients with HCC and MSI-H/dMMR solid tumors
- The preliminary safety profile and antitumor activity support continued development of tislelizumab in patients with ESCC, GC, HCC, and MSI-H/dMMR solid tumors
  - Ongoing phase 2 studies in patients with MSI-H/dMMR solid tumors (NCT03736889) and HCC (NCT03419897)
  - Ongoing phase 3 studies of tislelizumab have been initiated in patients with ESCC (NCT03783442, NCT03430843, and NCT03957590), GC (NCT03777657), and HCC (NCT03412773)

Data cut-off: 01 Dec 2018

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