Tislelizumab in Chinese Patients With Melanoma, Urothelial Carcinoma (UC), and Renal Cell Carcinoma (RCC)

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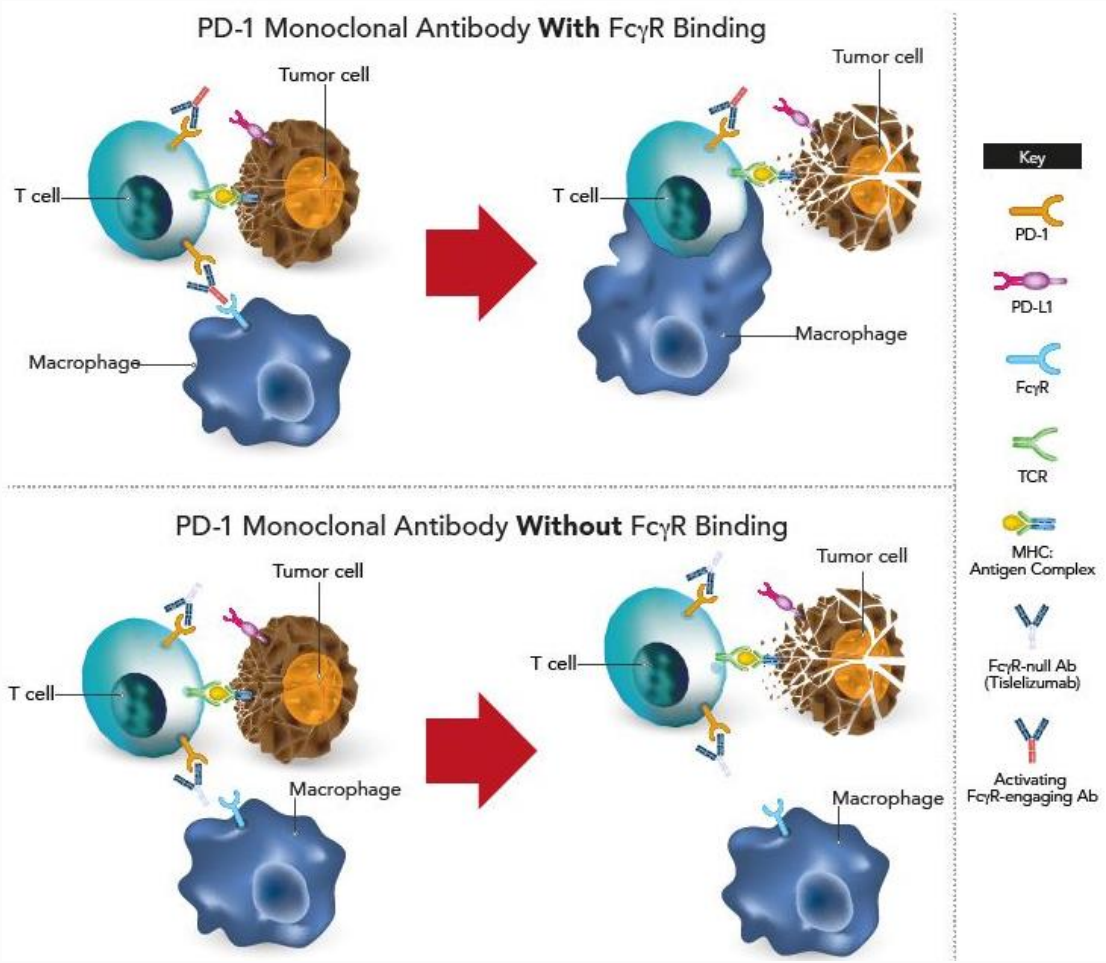
Tislelizumab: A Uniquely Engineered Anti-PD-1 Monoclonal Antibody

- 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]

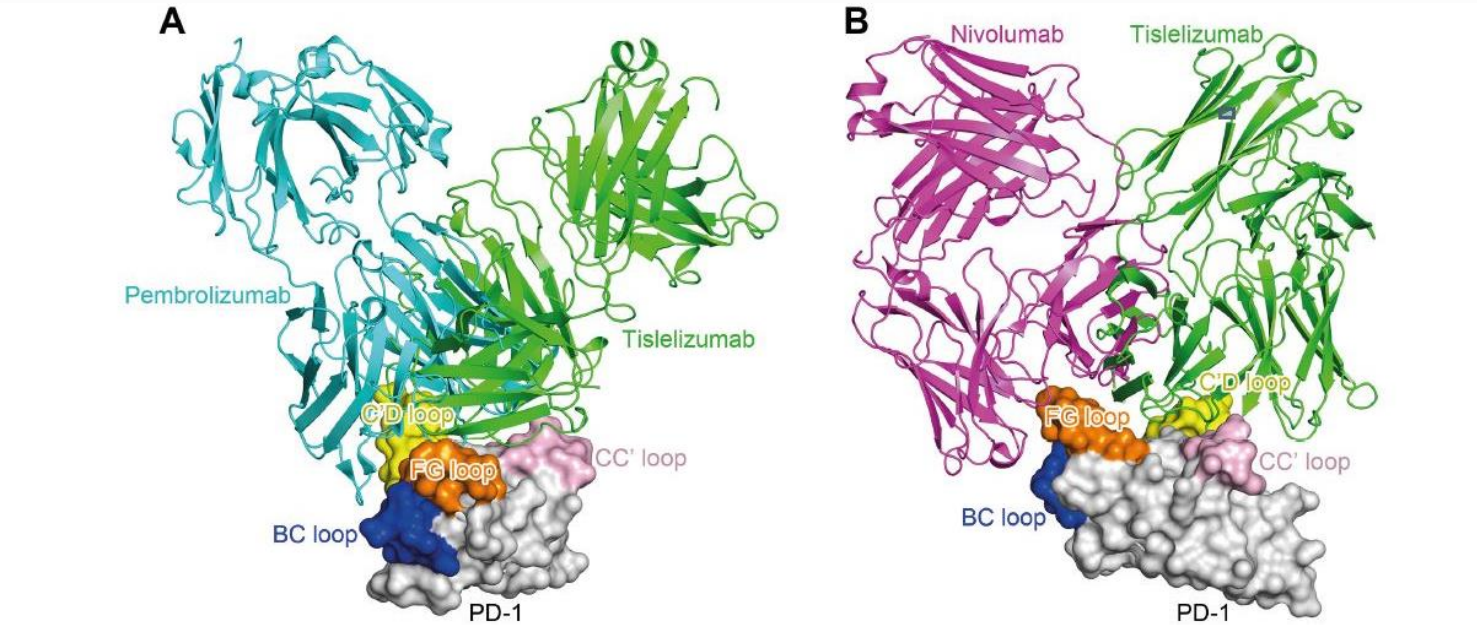


Abbreviations: Ab, antibody; MHC, major histocompatibility complex; PD-1, programmed death-1 receptor; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

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 (excluding uveal or ocular 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 (containing component of clear cell) 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=77) with melanoma, UC, and RCC were pooled from phase 1 and phase 2 of this study

	Melanoma (n=34)[a]	UC (n=22)	RCC (n=21)[b]
Median age, years (range)	54 (34-75)	62 (43-73)	53 (18-68)
Gender, n (%)			
Male	15 (44)	16 (73)	15 (71)
Female	19 (56)	6 (27)	6 (29)
ECOG PS, n (%)			
0	10 (29)	7 (32)	6 (29)
1	24 (71)	15 (68)	15 (71)
Tumor stage, n (%)			
Locally advanced	1 (3)	1 (5)	0
Metastatic disease	33 (97)	21 (95)	21 (100)
Patients with prior systemic anticancer therapy, n (%)	30 (88)	21 (96)	21 (100)
Number of lines of prior systemic anticancer therapy, n (%)[c]			
0	4 (12)	1 (5)	0
1	12 (35)	11 (50)	8 (38)
2	11 (32)	4 (18)	7 (33)
≥3	7 (21)	6 (27)	6 (29)
Prior treatment received, n (%)[d]			
Cytotoxic therapy	23 (77)	21 (100)	8 (38)
TKI	6 (20)	2 (10)	19 (90)
Monoclonal antibodies	1 (3)	0	0
Study follow-up duration, months (range)	8 (1-18)	4.2 (1-22)	16 (3-18)

[a]Included 16 (47%) patients with cutaneous melanoma, 13 (38%) with mucosal melanoma, 5 (15%) with melanoma of unknown primary site. [b]RCC containing the component of clear cell. [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; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; UC, urothelial carcinoma.

Data cut-off: 01 Dec 2018

Responses to Tislelizumab

	Melanoma (n=34)	UC (n=22)	RCC (N=21)
BOR per RECIST v1.1 (confirmed)			
Complete response (CR), n (%)	0	0	0
Partial response (PR), n (%)	5 (15)	3 (14)	2 (10)
Stable disease (SD), n (%)	8 (24)	6 (27)	9 (43)
Progressive disease (PD), n (%)	17 (50)	5 (23)	7 (33)
Missing/Not evaluable, n (%)	4 (12)	8 (36)	3 (14)
ORR (CR+PR), % (95% CI)	**15 (5-31)**	**14 (3-35)**	**10 (1-30)**
DCR (CR+PR+SD), % (95% CI)	**38 (22-56)**	**41 (21-64)**	**52 (30-74)**
CBR (CR+PR+durable SD)[a]	**35 (20-54)**	**27 (11-50)**	**52 (30-74)**

[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; ORR, objective response rate; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial carcinoma.

Data cut-off: 01 Dec 2018

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- Responses were observed in both PD-L1 positive[a] and negative UC tumors

	Melanoma (n=34)			UC (n=22)			RCC (N=21)		
	PD-L1$^+$ (n=4)	PD-L1$^-$ (n=26)	Unknown (n=4)	PD-L1$^+$ (n=5)	PD-L1$^-$ (n=16)	Unknown (n=1)	PD-L1$^+$ (n=2)	PD-L1$^-$ (n=18)	Unknown (n=1)
ORR, % (95% CI)	0	15 (4-35)	25 (1-81)	20 (1-72)	13 (2-38)	0	0	11 (1-35)	0
DCR, % (95% CI)	25 (1-81)	39 (20-59)	50 (7-93)	20 (1-72)	50 (25-75)	0	100 (16-100)	50 (26-74)	0

[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.

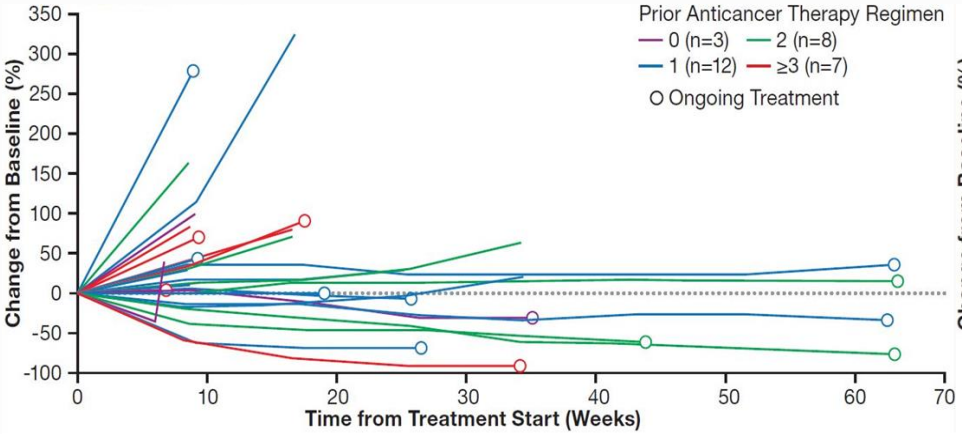
Abbreviations: BOR, best overall response; CI, confidence interval; ORR, objective response rate; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial carcinoma.

Data cut-off: 01 Dec 2018

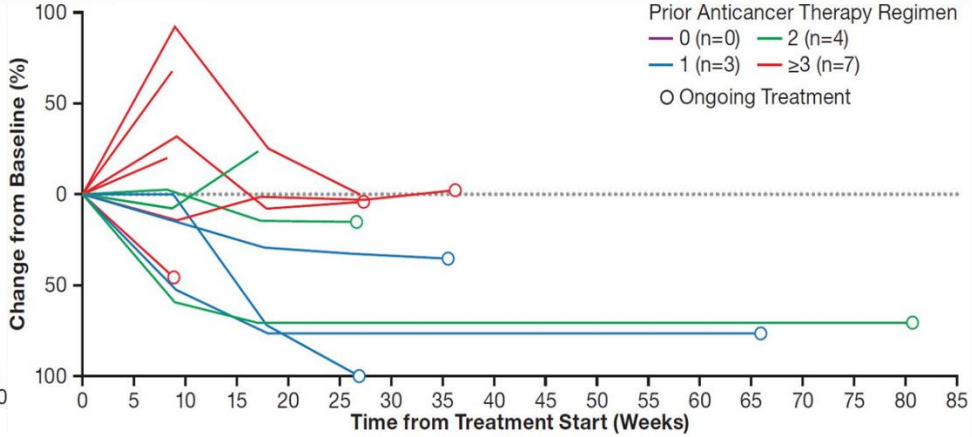
Change in Target Lesion Diameter

- In patients with melanoma, UC, and RCC, durable decreases in sum of target lesion diameters were observed even in heavily pretreated patients

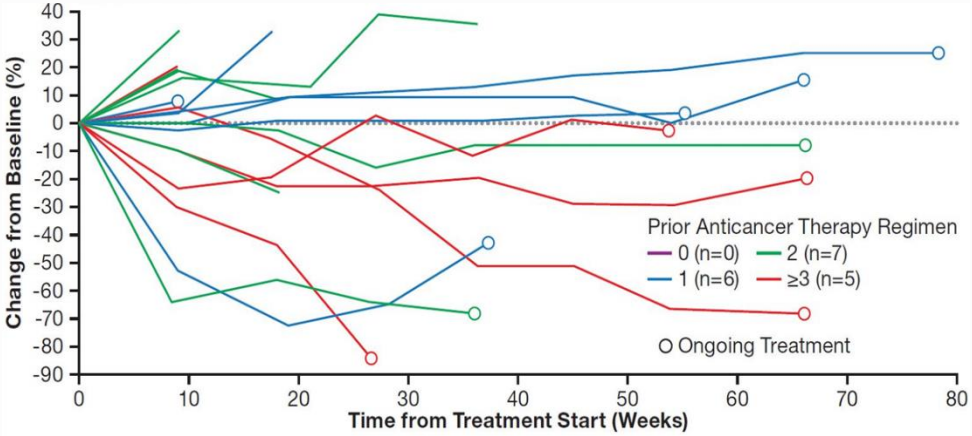
Melanoma



UC



RCC



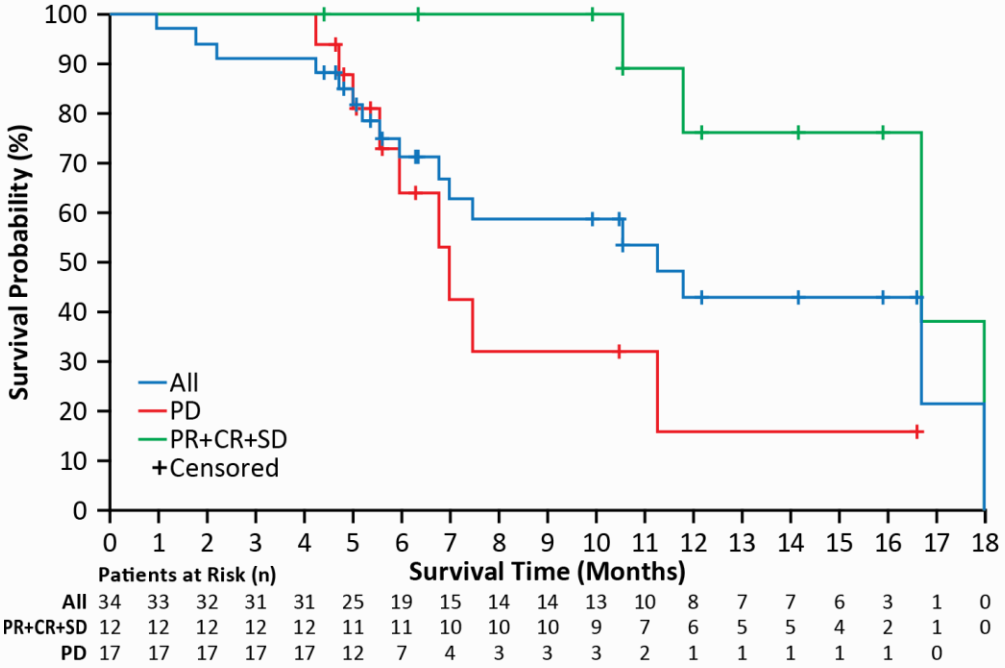
Data cut-off: 01 Dec 2018

Overall Survival

- Median overall survival was 11.3 months for patients with melanoma
- Melanoma patients with controlled disease had an increased probability of survival at 6 and 9 months compared to those with progressive disease

Melanoma

	All	PR+CR+SD	PD
Median OS	11.3 (6.8-18.0)	16.7 (10.6-18.0)	7.0 (5.6-11.3)
Probability of OS at 6 mos	0.7 (0.5-0.8)	1.0 (NE-NE)	0.6 (0.3-0.8)
Probability of OS at 9 mos	0.6 (0.4-0.7)	1.0 (NE-NE)	0.3 (0.1-0.6)



Data presented as months (95% CI). **Abbreviations:** CI, confidence interval; CR, complete response; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

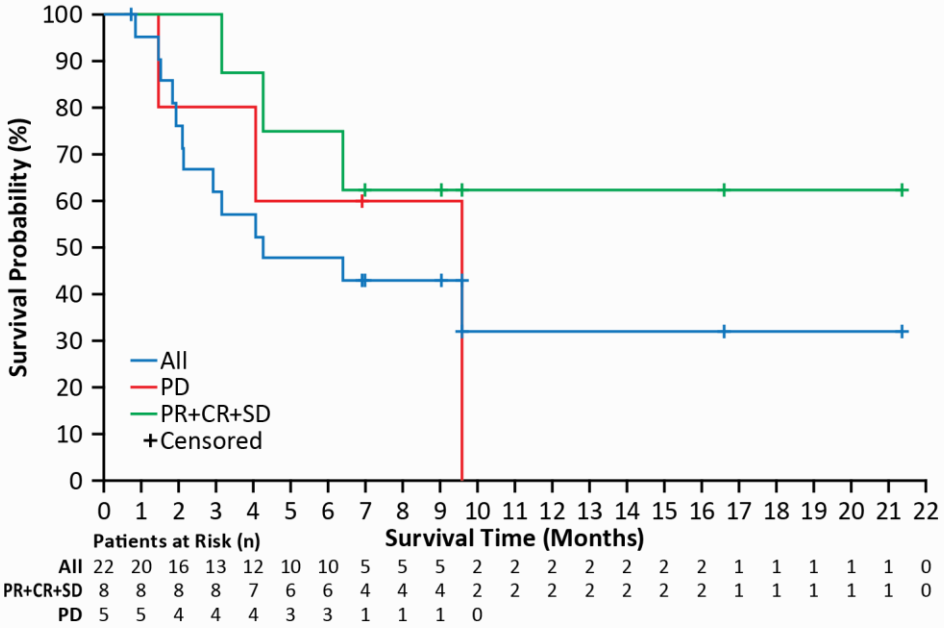
Data cut-off: 01 Dec 2018

Overall Survival

- Median overall survival was 4.3 months for patients with UC and was not reached for those with RCC

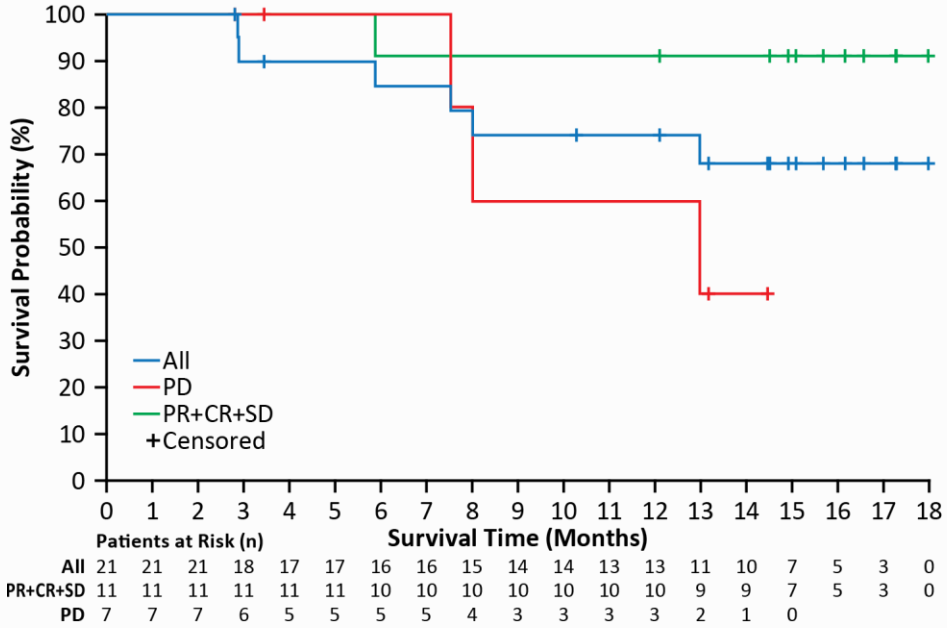
UC

	All	PR+CR+SD	PD
Median OS	4.3 (2.1-NE)	NR	9.6 (1.5-9.6)
Probability of OS at 6 mos	0.5 (0.3-0.7)	0.8 (0.3-0.9)	0.6 (0.1-0.9)
Probability of OS at 9 mos	0.4 (0.2-0.6)	0.6 (0.2-0.9)	0.6 (0.1-0.9)



RCC

	All	PR+CR+SD	PD
Median OS	NR	NR	13.0 (7.5-NE)
Probability of OS at 6 mos	0.8 (0.6-0.9)	0.9 (0.5-1.0)	1.0 (NE-NE)
Probability of OS at 9 mos	0.7 (0.5-0.9)	0.9 (0.5-1.0)	0.6 (0.1-0.9)



- In RCC, patients with controlled disease had an increased probability of survival at 9 months compared to patients with progressive disease

Data presented as months (95% CI). **Abbreviations:** CR, complete response; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial disease; RCC, renal cell carcinoma; SD, stable disease; UC, urothelial carcinoma.

Data cut-off: 01 Dec 2018

Conclusions

- Tislelizumab was generally well tolerated and demonstrated preliminary antitumor activity in patients with melanoma, UC, and RCC
  - The objective response rate was driven by partial responses and was 15% for patients with melanoma, 14% for UC, and 10% for RCC
  - Median overall survival was 11.3 months for patients with melanoma; median overall survival was 4.3 months for patients with UC and was not reached for those with RCC
- The preliminary safety profile and antitumor activity support continued development of tislelizumab in patients with melanoma, UC, and RCC
  - A phase 3 study of tislelizumab as treatment for UC (NCT03967977) currently ongoing and recruiting patients

Data cut-off: 01 Dec 2018

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