Tislelizumab in Chinese Patients With Non-Small Cell Lung Cancer (NSCLC) and Nasopharyngeal Carcinoma (NPC)

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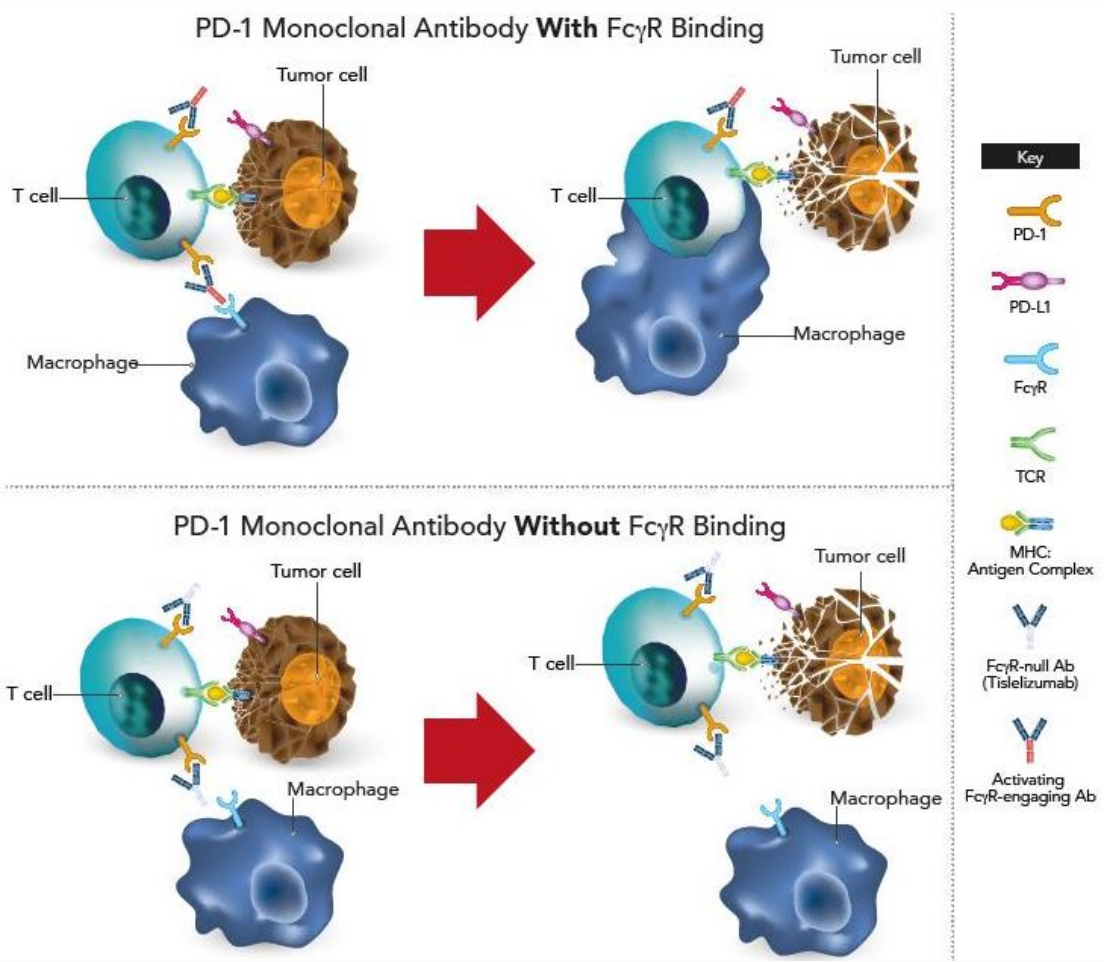
Tislelizumab: A Uniquely Engineered Anti-PD-1 Monoclonal Antibody

- 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]

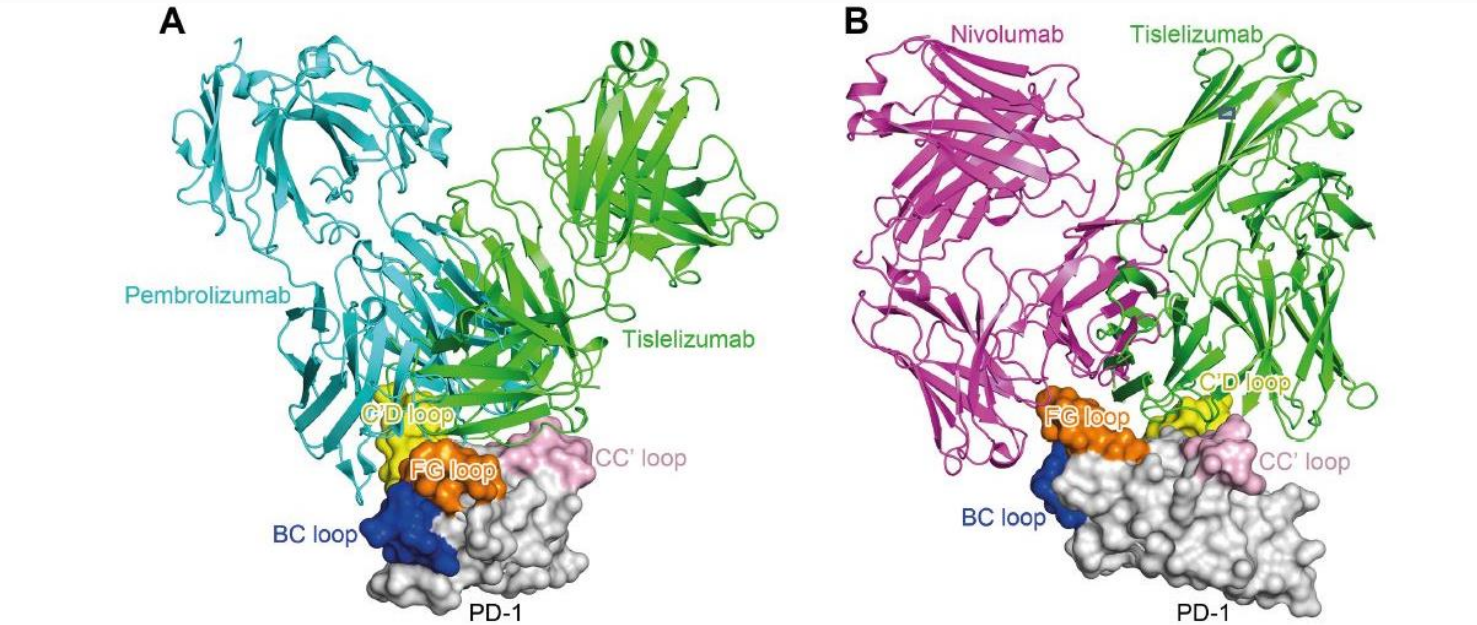


Abbreviations: Ab, antibody; MHC, major histocompatibility complex; PD-1, programmed death-1 receptor; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

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 [a] n=20	Arm 3 PD-L1-negative NSCLC [a] 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 (WHO type II-III) 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) were planned to be enrolled to receive treatment of tislelizumab of two manufacturing process and scales.
[a]Patients who had EGFR mutations or known ALK gene rearrangement were excluded.
Abbreviations: CRC, colorectal cancer; DLT, dose-limiting toxicity; dMMR, defective mismatch repair; EGFR, epidermal growth factor; 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.

Demographics and Baseline Disease Characteristics

- As of 01 Dec 2018, 300 patients across all indications had received tislelizumab 200 mg IV Q3W, and 77 (26%) remained on treatment

	Dose Verification (n=20)	PK Substudy (n=57)	Phase 2 (n=223)	Total (N=300)
Median age, years (range)	49.5 (22-73)	58.0 (18-82)	57.0 (24-75)	56.5 (18-82)
<65, n (%)	15 (75)	41 (72)	167 (75)	223 (74)
≥65, n (%)	5 (25)	16 (28)	56 (25)	77 (26)
Gender, n (%)				
Male	16 (80)	41 (72)	150 (67)	207 (69)
Female	4 (20)	16 (28)	73 (33)	93 (31)
ECOG PS, n (%)				
0	6 (30)	14 (25)	60 (27)	80 (27)
1	14 (70)	43 (75)	163 (73)	220 (73)
Tumor stage, n (%)				
Locally advanced	0	7 (12)	9 (4)	16 (5)
Metastatic disease	20 (100)	50 (88)	214 (96)	284 (95)
Patients with prior systemic therapy, n (%)	18 (90)	53 (93)	217 (97)	288 (96)
Number of regimens of prior systemic anticancer treatment, n (%)[a]				
1	3 (17)	12 (23)	69 (32)	84 (29)
2	4 (22)	10 (19)	60 (28)	74 (26)
3	6 (33)	15 (28)	42 (19)	63 (22)
≥4	5 (28)	16 (30)	46 (21)	67 (23)
Prior treatment received, n (%)[a]				
Cytotoxic therapy	17 (94)	49 (93)	192 (89)	258 (90)
TKI	7 (39)	11 (21)	48 (22)	66 (23)
Monoclonal antibodies	3 (17)	10 (19)	32 (15)	45 (16)

[a]Percentages are based on the number of patients who received prior systemic anticancer therapy.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PK, pharmacokinetic; TKI, tyrosine kinase inhibitor.

Data cut-off: 01 Dec 2018

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

Immune-Related Adverse Events (All Patients; N=300)

- The most common immune-related AEs (irAEs) were increased AST/ALT (24%) and hyperbilirubinemia (15%); most irAEs were grade ≤2 in severity
  - The most common grade ≥3 irAEs were increased GGT (4%) and increased AST/ALT (3%)

Immune-Related Adverse Events Occurring in >2% Patients

	Grade 1-2	Grade ≥3	All Grades
Patients who experienced ≥1 irAE	**138 (46)**	**33 (11)**	**171 (57)**
Increased AST/ALT	63 (21)	8 (3)	71 (24)
Hyperbilirubinemia	43 (14)	2 (<1)	45 (15)
Hypothyroidism	38 (13)	0	38 (13)
Increased GGT	13 (4)	12 (4)	25 (8)
Rash	23 (8)	2 (<1)	25 (8)
Pruritus	15 (5)	0	15 (5)
Hyperthyroidism	14 (5)	0	14 (5)
Increased CK/CK-MB	12 (4)	1 (<1)	13 (4)
Diarrhea	12 (4)	1 (<1)	13 (4)
Pneumonitis	6 (2)	6 (2)	12 (4)
Hypercreatinemia	7 (2)	0	7 (2)

Data presented as n (%). **Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK/CK-MB, creatine kinase/creatine kinase-muscle/brain; GGT, gamma-glutamyl transferase; irAE, immune-related adverse event.

Data cut-off: 01 Dec 2018

Demographics and Baseline Disease Characteristics of Patients With NSCLC and NPC From Phase 1 and Phase 2

	NSCLC (n=56)		NPC (n=21)	
Median age, years (range)	58 (26-72)		48 (35-61)	
Gender				
Male, n (%)	40 (71)		17 (81)	
Female, n (%)	16 (29)		4 (19)	
ECOG PS, n (%)				
0	14 (25)		8 (38)	
1	42 (75)		13 (62)	
Tumor stage, n (%)				
Locally advanced	3 (5)		3 (14)	
Metastatic disease	53 (95)		18 (86)	
Smoking status, n (%)				
Never	23 (41)		14 (67)	
Current	2 (4)		1 (5)	
Former	31 (55)		6 (29)	
Patients with prior systemic anticancer therapy, n (%)	55 (98)		21 (100)	
Number of lines of prior systemic anticancer therapy, n (%)[a]				
0	1 (2)		0 (0)	
1	19 (34)		9 (43)	
2	20 (36)		3 (14)	
≥3	16 (29)		9 (43)	
Histological type, n (%)	Nonsquamous cell carcinoma[b]	Squamous cell carcinoma	Undifferentiated non-keratinized	Differentiated non-keratinized
	31 (55)	25 (45)	17 (81)	4 (19)
Median study follow-up duration, months (range)	9 (0-19)		12 (5-16)	

[a]Including adjuvant, neoadjuvant, and palliative therapy(ies). [b]Among non-squamous NSCLC patients, three had lymphoepithelioma-like carcinoma and the remainder had adenocarcinoma. One patient had an *EGFR* mutation, 4 patients had unknown *EGFR* status, and the remaining patients had no EGFR mutation; one patient had a known *ALK* rearrangement.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer.

Responses to Tislelizumab in NSCLC and NPC

	NSCLC (n=56)	NPC (n=21)
BOR per RECIST v1.1 (confirmed)		
Complete response (CR), n (%)	0	0
Partial response (PR), n (%)	10 (18)	9 (43)
Stable disease (SD), n (%)	21 (38)	9 (43)
Progressive disease (PD), n (%)	21 (38)	3 (14)
Missing/Not evaluable, n (%)	4 (7)	0
ORR (CR+PR), % (95% CI)	**18 (9-30)**	**43 (22-66)**
DCR (CR+PR+SD), % (95% CI)	**55 (42-69)**	**86 (64-97)**
CBR (CR+PR+durable SD)[a]	**52 (38-65)**	**81 (58-95)**

[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; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Data cut-off: 01 Dec 2018

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- Responses were observed in both PD-L1 positive[a] and negative NSCLC and NPC

	NSCLC (n=56)			NPC (n=21)		
	PD-L1^{+} (n=24)	PD-L1^{-} (n=31)	Unknown (n=1)	PD-L1^{+} (n=16)	PD-L1^{-} (n=4)	Unknown (n=1)
ORR, % (95% CI)	**17 (5-37)**	**19 (8-38)**	**0**	**50 (25-75)**	**25 (1-81)**	**0**
DCR, % (95% CI)	**50 (29-71)**	**58 (39-76)**	**100 (3-100)**	**88 (62-98)**	**75 (19-99)**	**100 (3-100)**

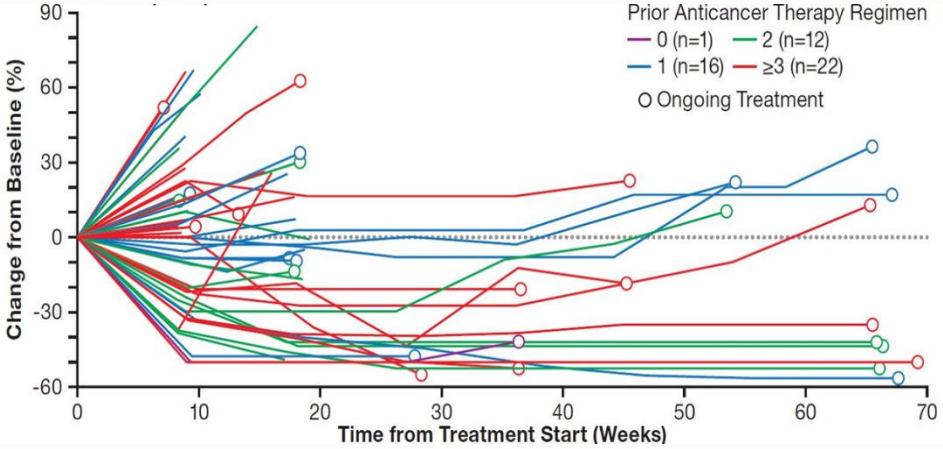
[a]PD-L1 positivity was defined by ≥10% of tumor cells with PD-L1 membrane staining at any intensity by using the VENTANA™ PD-L1 (SP263) assay.
Disease assessment by radiographic imaging was performed every 9 weeks during first 12 months and every 12 weeks thereafter.
Abbreviations: BOR, best overall response; CI, confidence interval; CBR, clinical benefit rate; DCR, disease control rate; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Data cut-off: 01 Dec 2018

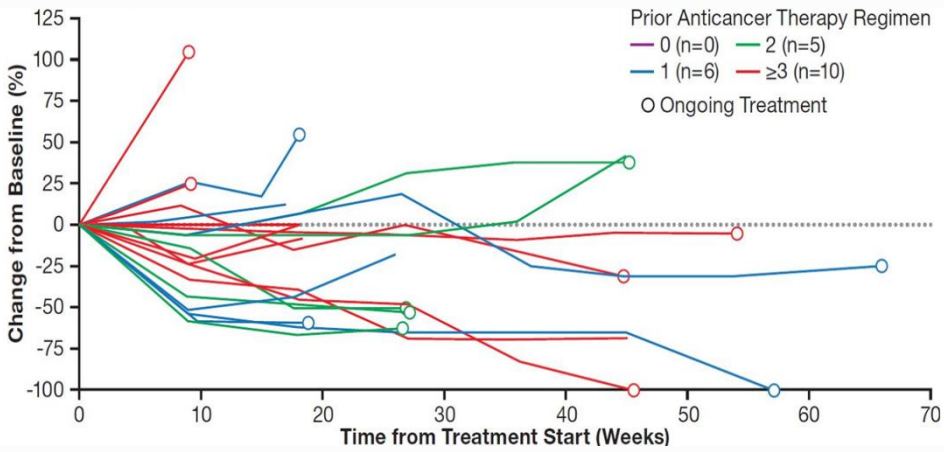
Change in Target Lesion Diameter in NSCLC and NPC

- In patients with NSCLC and NPC, durable decreases in the sum of target lesion diameters were observed, even in patients who were heavily pretreated

NSCLC



NPC

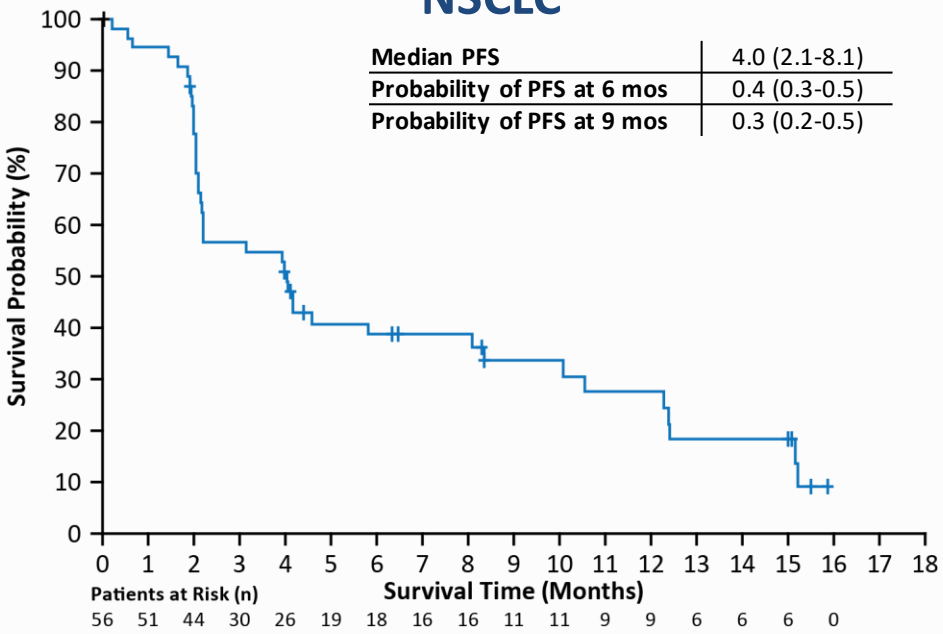


Data cut-off: 01 Dec 2018

Progression-Free Survival in NSCLC and NPC

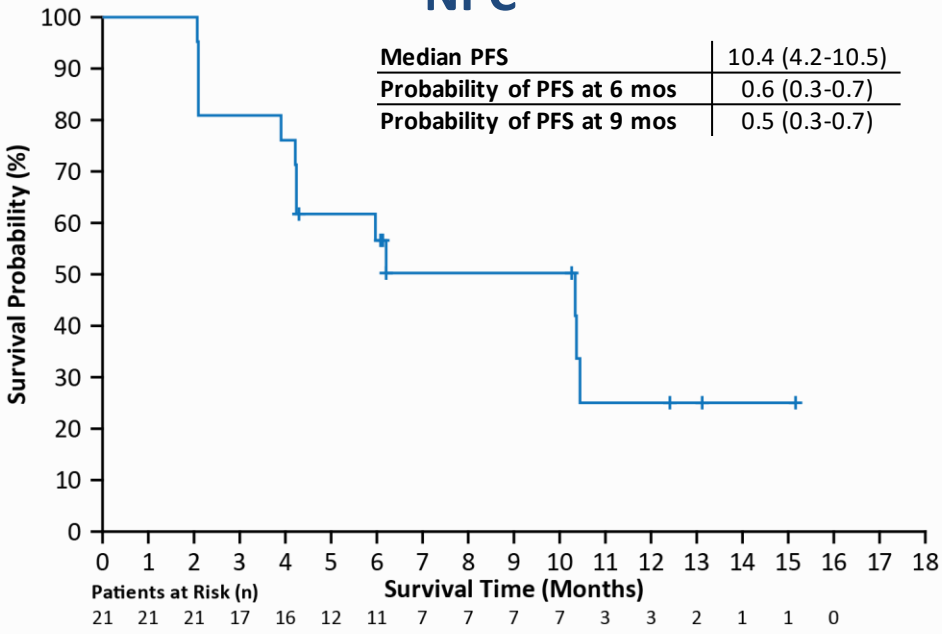
- Median progression-free survival was 4.0 months in patients with NSCLC and 10.4 months in patients with NPC

NSCLC



Median PFS	4.0 (2.1-8.1)
Probability of PFS at 6 mos	0.4 (0.3-0.5)
Probability of PFS at 9 mos	0.3 (0.2-0.5)

NPC



Median PFS	10.4 (4.2-10.5)
Probability of PFS at 6 mos	0.6 (0.3-0.7)
Probability of PFS at 9 mos	0.5 (0.3-0.7)

Data presented as months (95% CI). **Abbreviations:** NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

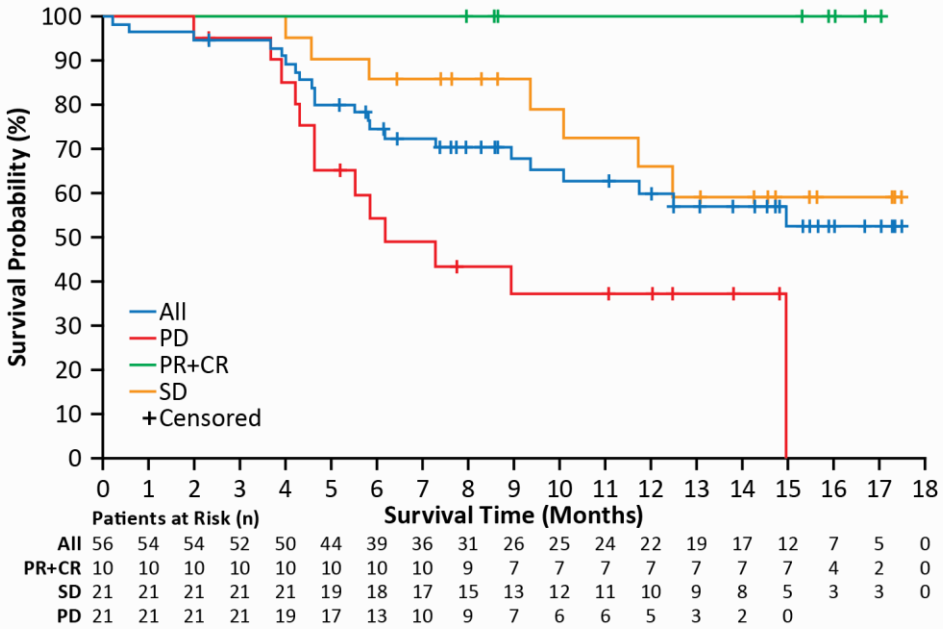
Data cut-off: 01 Dec 2018

Overall Survival in NSCLC and NPC

- Median overall survival was not reached for NSCLC and NPC
- In both indications, patients with responses had an increased probability of survival at 6 and 12 months compared to patients with progressive disease or stable disease

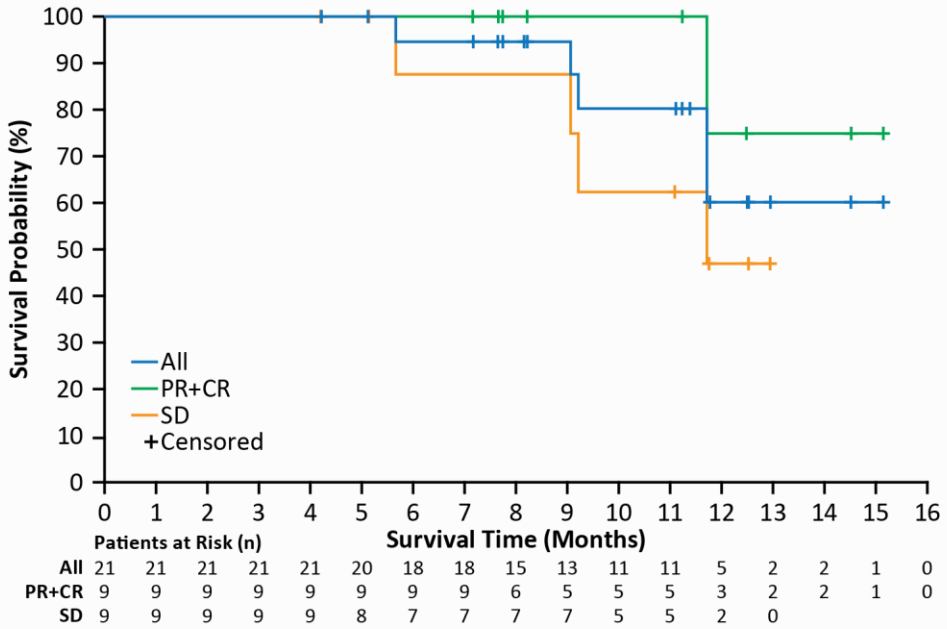
NSCLC

	All	PR+CR	SD	PD
Median OS	NR	NR	NR	6.2 (4.6-15.0)
Probability of OS at 6 mos	0.7 (0.6-0.8)	1.0 (NE-NE)	0.9 (0.6-1.0)	0.5 (0.3-0.7)
Probability of OS at 12 mos	0.6 (0.4-0.7)	1.0 (NE-NE)	0.7 (0.4-0.8)	0.4 (0.2-0.6)



NPC*

	All	PR+CR	SD
Median OS	NR	NR	11.7 (5.7-NE)
Probability of OS at 6 mos	0.9 (0.7-1.0)	1.0 (NE-NE)	0.9 (0.4-1.0)
Probability of OS at 12 mos	0.6 (0.6-0.8)	0.8 (0.1-1.0)	0.5 (0.1-0.8)



*Due to small sample size, patients with progressive disease (n=3) are not shown.

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

- Adverse events reported in the overall patient population of this study were consistent with the safety profile of tislelizumab observed in previous studies and were generally of low severity
- Tislelizumab demonstrated preliminary antitumor activity in patients with advanced NSCLC and NPC
  - The objective response rate was 18% in patients with NSCLC and 43% in those with NPC
  - Responses were observed regardless of PD-L1 status
  - Despite a long median follow-up, median overall survival was not reached for patients with NSCLC and NPC; median progression-free survival was 4.0 months in patients with NSCLC and 10.4 months in patients with NPC
- The preliminary safety profile and antitumor activity support continued development of tislelizumab in patients with advanced NSCLC and NPC
  - Ongoing phase 3 studies of tislelizumab as treatment for NSCLC (NCT0335887, NCT03594747, and NCT03663205) and NPC (NCT03924986)

Data cut-off: 01 Dec 2018

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