Tislelizumab Plus Chemotherapy as First-line Treatment for Chinese Patients With Lung Cancer

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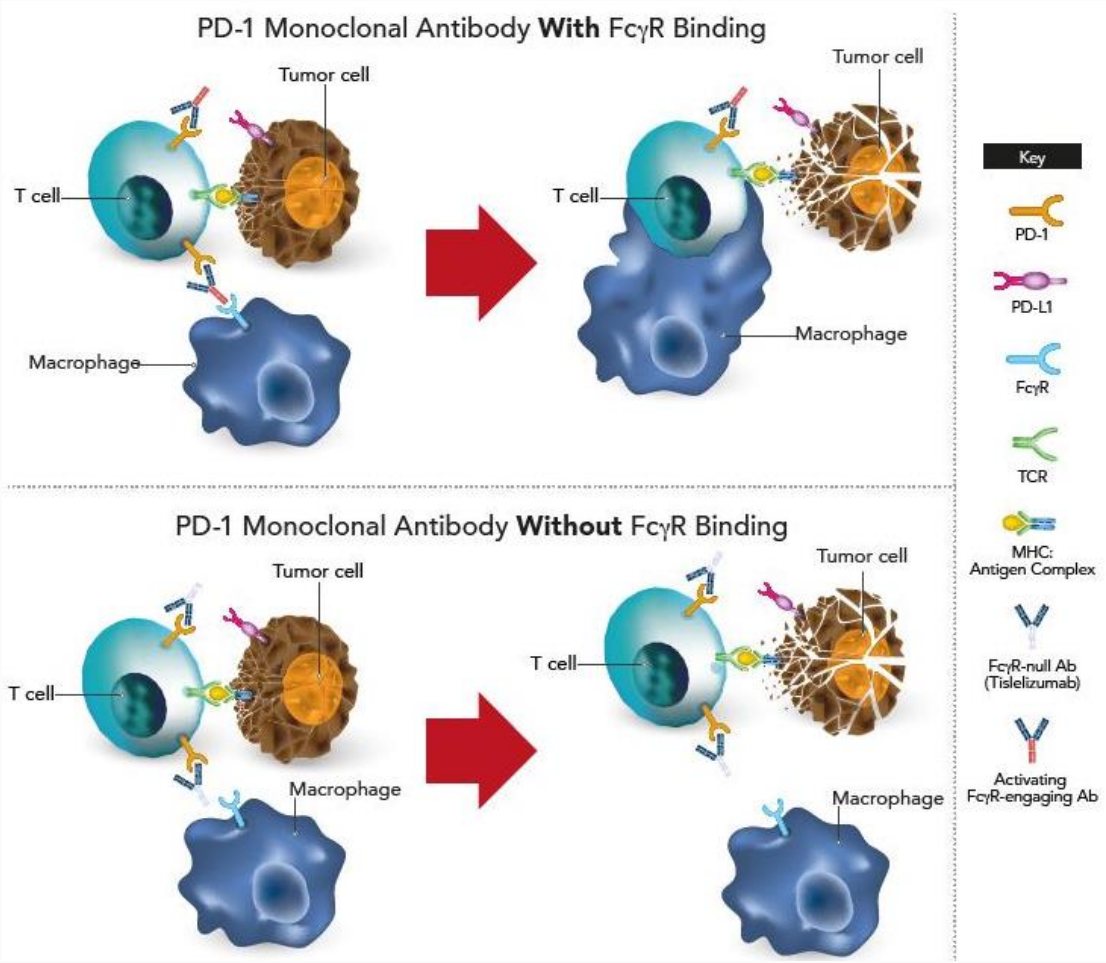
Introduction

- Lung cancer has been the leading cause of cancer death in both men and women in China[1]
- Recent studies of immune checkpoint inhibitors targeting PD-1 and PD-L1 have shown efficacy in patients with advanced non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) as a monotherapy and in combination with chemotherapy[2-7]
- In early phase studies, tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and demonstrated evidence of antitumor activity in patients with lung cancer, including Asian patients[7-10]

[1]Bray, et al. *CA Cancer J Clin.* 2018;68(66):394-424; [2]Herbst, et al. *Lancet*. 2016:387:1540-1550; [3]Rizvi, et al. *Lancet Oncol*. 2015;16:257-265; [4]Gadgeel, et al. *J Thorac Oncol*. 2018;13:1393-1399; [5]Jotte, et al. *J Clin Oncol*. 2018;36(suppl):Abstract LBA9000; [6]Gandhi, et al. *N Engl J Med*. 2018;378:2078-2092; [7]Wu, et al. *J Thorac Oncol*. 2018;13:S741-S742; [8]Deva, et al. *Ann Oncol*. 2018;29(suppl 10); [9]Desai, et al. AACR; 2019:Abstract 4048; [10]Bai, et al. *J Clin Oncol*. 2019;37(suppl 4):11.

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]

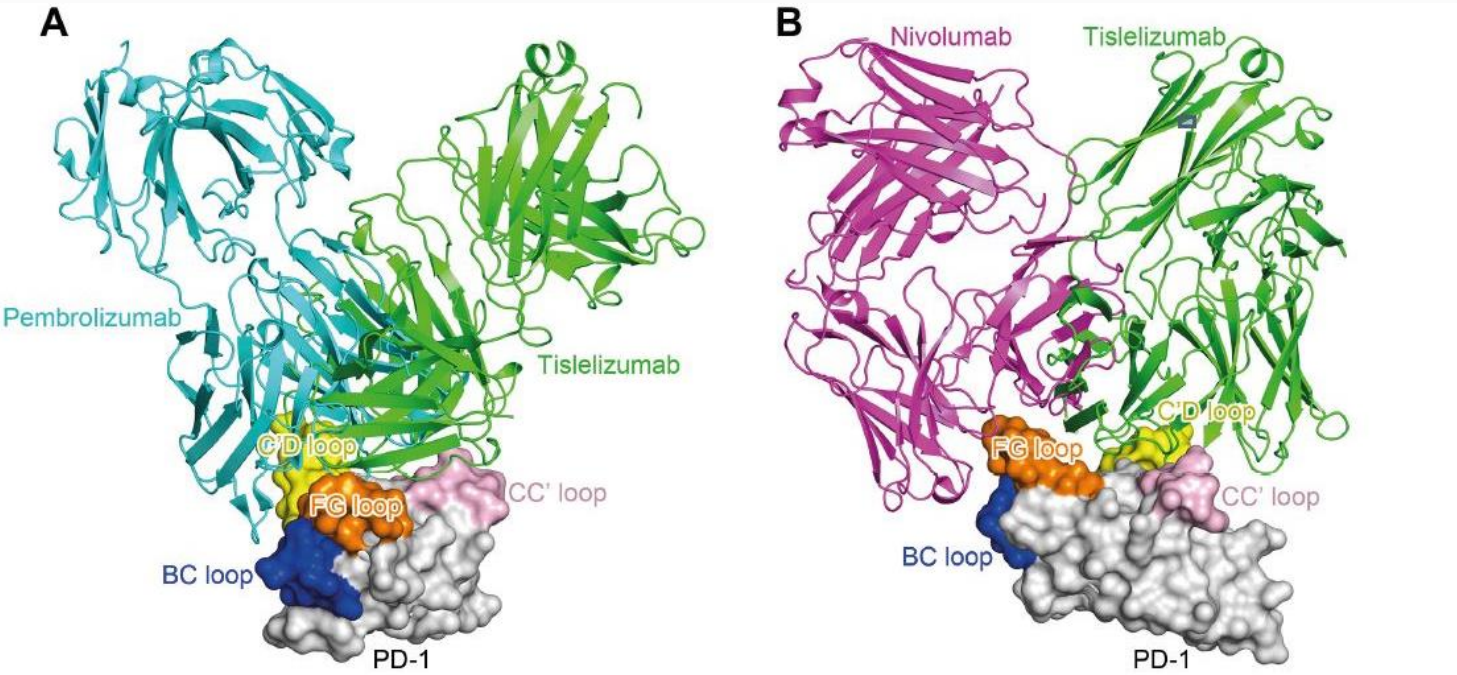


Abbreviations: Ab, antibody; MHC, major histocompatibility complex; PD-1, programmed death-1 receptor; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

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

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

- Tislelizumab shows higher affinity to PD-1 than pembrolizumab and nivolumab with ~100- and 50-fold slower off-rates, respectively[1]
- The binding surface on PD-1 for tislelizumab partially overlaps with that for pembrolizumab, but differs significantly from that for nivolumab[1]

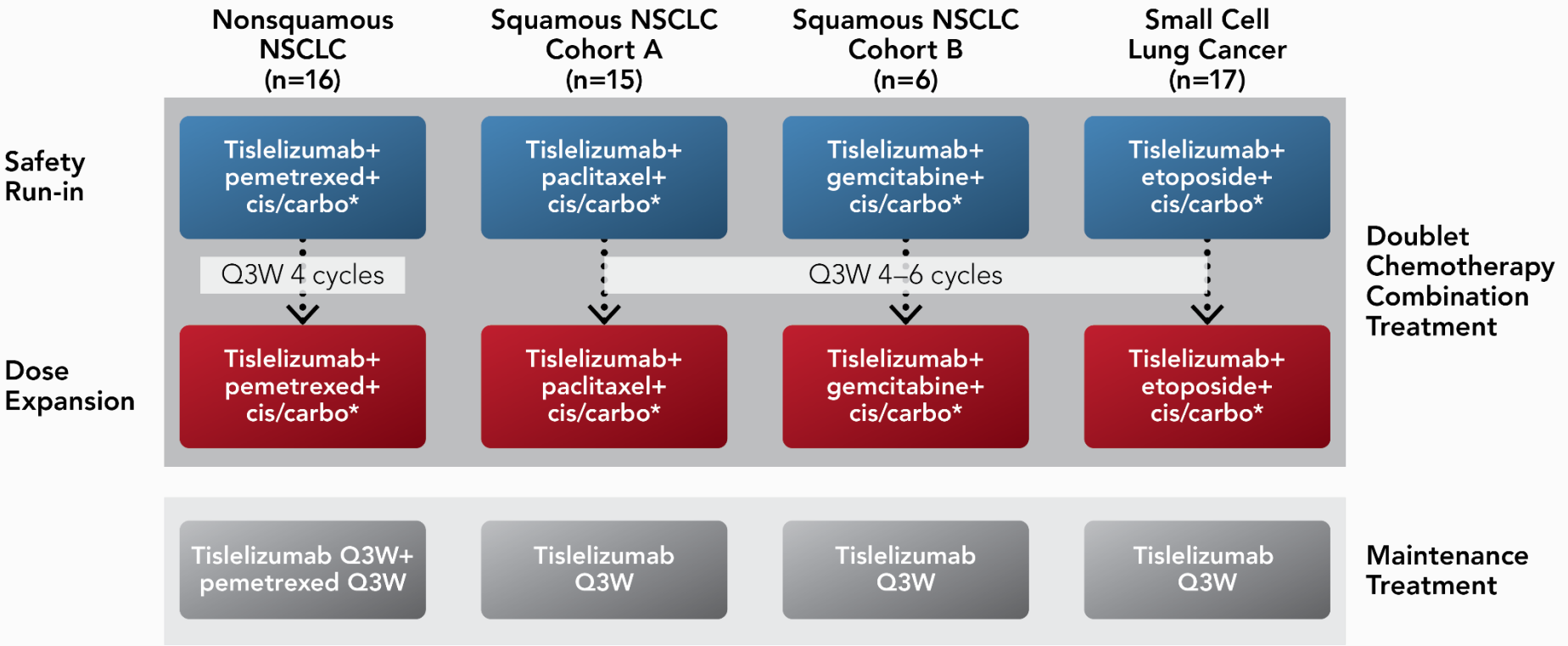


PD-1, tislelizumab, pembrolizumab, and nivolumab are colored in gray, green, cyan and magenta, respectively. The BC, CC', C'D and FG loops of PD-1 are colored in blue, pink, yellow and orange, respectively.

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

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

An Ongoing, Proof-of-Concept, Phase 2 Study (NCT03432598) in China for First-line Treatment of Advanced Lung Cancer



*Either cisplatin or carboplatin could be selected as initial treatment per investigators discretion.
Enrollment in squamous NSCLC cohort B was limited to six patients.
Abbreviations: carbo, carboplatin; cis, cisplatin; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks.

Patient Demographics and Baseline Disease Characteristics

- As of 25 February 2019, 54 patients had received tislelizumab with a median duration of treatment of 38.4 weeks (range: 3-79)
  - A total of 14 (25.9%) remained on treatment
  - Most patients were male (n=40; 74.1%) and former/current smokers (n=39; 72.2%)

		NSQ Tislelizumab + pemetrexed + plat (n=16)	SQ-A Tislelizumab + paclitaxel + plat (n=15)	SQ-B Tislelizumab + gemcitabine + plat (n=6)	SCLC Tislelizumab + etoposide + plat (n=17)	Total (N=54)
Median age, years		63.5	59.0	63.0	60.0	61.0
Sex, n (%)	Male	9 (56.3)	12 (80.0)	6 (100.0)	13 (76.5)	40 (74.1)
Tobacco use, n (%)	Never	10 (62.5)	2 (13.3)	0	3 (17.6)	15 (27.8)
	Current	0	3 (20.0)	2 (33.3)	3 (17.6)	8 (14.8)
	Former	6 (37.5)	10 (66.7)	4 (66.7)	11 (64.7)	31 (57.4)
ECOG PS score, n (%)	0	2 (12.5)	4 (26.7)	1 (16.7)	2 (11.8)	9 (16.7)
	1	14 (87.5)	11 (73.3)	5 (83.3)	15 (88.2)	45 (83.3)
PD-L1 on TC, n (%)	<10%	9 (56.3)	5 (33.3)	1 (16.7)	15 (88.2)	30 (55.6)
	≥ 10% and <25%	1 (6.3)	2 (13.3)	0	1 (5.9)	4 (7.4)
	≥ 25% and <50%	3 (18.8)	1 (6.7)	0	0	4 (7.4)
	≥ 50%	1 (6.3)	5 (33.3)	3 (50.0)	0	9 (16.7)
	Not evaluable	2 (12.5)	2 (13.3)	2 (33.3)	1 (5.9)	7 (13.0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; NSQ, non-squamous NSCLC; PD-L1, programmed cell death ligand-1; PD-L1 TC, PD-L1 % expression on tumor cells; plat, platinum therapy; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 25 Feb 2019

Overview of Treatment-Emergent Adverse Events

	NSQ Tislelizumab + pemetrexed + plat (n=16)	SQ-A Tislelizumab + paclitaxel + plat (n=15)	SQ-B Tislelizumab + gemcitabine + plat (n=6)	SCLC Tislelizumab + etoposide + plat (n=17)	Total (N=54)
Any adverse event (AE)	16 (100.0)	15 (100.0)	6 (100.0)	17 (100.0)	54 (100.0)
≥Grade 3 AE	12 (75.0)	14 (93.3)	4 (66.7)	13 (76.5)	43 (79.6)
Serious AE	4 (25.0)	4 (26.7)	1 (16.7)	5 (29.4)	14 (25.9)
Fatal AE*	0	1 (6.7)	0	0	1 (1.9)
Immune-related AE	2 (12.5)	4 (26.7)	2 (33.3)	6 (35.3)	14 (25.9)
AEs reported as related to tislelizumab or chemotherapy	16 (100.0)	15 (100.0)	6 (100.0)	17 (100.0)	54 (100.0)
Treatment-related ≥ grade 3 AE	11 (68.8)	13 (86.7)	2 (33.3)	13 (76.5)	39 (72.2)
Treatment-related serious AE	3 (18.8)	4 (26.7)	1 (16.7)	5 (29.4)	13 (24.1)
AEs reported as related to tislelizumab	13 (81.3)	12 (80.0)	5 (83.3)	16 (94.1)	46 (85.2)
Tislelizumab-related ≥ grade 3 AE	2 (12.5)	4 (26.7)	0	1 (5.9)	7 (13.0)
Tislelizumab-related serious AE	2 (12.5)	4 (26.7)	0	0	6 (11.1)
AEs leading to treatment discontinuation	0	6 (40.0)	1 (16.7)	0	7 (13)

Data presented as n (%). *After one tislelizumab dose the sq NSCLC pt (A) experienced dyspnea, myocarditis, and rhabdomyolysis with a fatal outcome.
Abbreviations: AE, adverse event; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; plat, platinum therapy; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Grade ≥3 Treatment-Emergent Adverse Events Related to Any Study Drug Occurring in >5% of the Total Study Population

	NSQ Tislelizumab + pemetrexed + plat (n=16)	SQ-A Tislelizumab + paclitaxel + plat (n=15)	SQ-B Tislelizumab + gemcitabine + plat (n=6)	SCLC Tislelizumab + etoposide + plat (n=17)	Total (N=54)
Decreased neutrophil count	6 (37.5)	11 (73.3)	1 (16.7)	8 (47.1)	26 (48.1)
Anemia	2 (12.5)	2 (13.3)	1 (16.7)	5 (29.4)	10 (18.5)
Decreased white blood cell count	4 (25.0)	2 (13.3)	0	1 (5.9)	7 (13.0)
Decreased platelet count	2 (12.5)	0	1 (16.7)	4 (23.5)	7 (13.0)
Thrombocytopenia	0	1 (6.7)	0	5 (29.4)	6 (11.1)
Neutropenia	1 (6.3)	0	0	3 (17.6)	4 (7.4)
Increased ALT	1 (6.3)	2 (13.3)	0	0	3 (5.6)

Data presented as n (%).

Abbreviations: ALT, alanine aminotransferase; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; plat, platinum therapy; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 25 Feb 2019

Treatment-Emergent Adverse Events Related to Tislelizumab and Occurring in >5 Patients

- A total of 46 patients (85.2%) had adverse events (AEs) that were reported to be related to tislelizumab
  - The majority were mild to moderate in severity

	NSQ Tislelizumab + pemetrexed + plat (n=16)		SQ-A Tislelizumab + paclitaxel + plat (n=15)		SQ-B Tislelizumab + gemcitabine + plat (n=6)		SCLC Tislelizumab + etoposide + plat (n=17)		Total (N=54)	
CTCAE grade AE	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**
Asthenia	3 (18.8)	0	4 (26.7)	0	1 (16.7)	0	2 (11.8)	0	10 (18.5)	0
Decreased appetite	2 (12.5)	0	1 (6.7)	0	0	0	3 (17.6)	0	6 (11.1)	0
Increased ALT	1 (6.3)	0	1 (6.7)	0	1 (16.7)	0	3 (17.6)	0	6 (11.1)	0
Increased AST	1 (6.3)	0	1 (6.7)	0	1 (16.7)	0	3 (17.6)	0	6 (11.1)	0
Hypothyroidism	1 (6.3)	0	1 (6.7)	0	2 (33.3)	0	3 (17.6)	0	7 (13.0)	0
Increased blood thyroid stimulating hormone	1 (6.3)	0	1 (6.7)	0	0	0	3 (17.6)	0	5 (9.3)	0

Data presented as n (%).

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; plat, platinum therapy; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Immune-Related Adverse Events Occurring in Patients Across Cohorts

- A total of 14 patients (25.9%) experienced ≥1 immune-related AE

	NSQ Tislelizumab + pemetrexed + plat (n=16)		SQ-A Tislelizumab + paclitaxel + plat (n=15)		SQ-B Tislelizumab + gemcitabine + plat (n=6)		SCLC Tislelizumab + etoposide + plat (n=17)		Total (N=54)	
CTCAE grade AE	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**	**Any**	**≥3**
Thyroid disorders	1 (6.3)	0	1 (6.7)	0	2 (33.3)	0	5 (29.4)	0	9 (16.7)	0
Immune-mediated pneumonitis	1 (6.3)	0	2 (13.3)	0	0	0	1 (5.9)	0	4 (7.4)	0
Type 1 diabetes mellitus	0	0	0	0	0	0	1 (5.9)	0	1 (1.9)	0
Immune-mediated hepatitis	0	0	2 (13.3)	2 (13.3)	0	0	0	0	2 (3.7)	2 (3.7)
Immune-mediated myositis/rhabdomyolysis/ cardiomyopathy	0	0	1 (6.7)	1 (6.7)	0	0	0	0	1 (1.9)	1 (1.9)

Data presented as n (%).

Abbreviations: AE, adverse event; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; plat, platinum therapy; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 25 Feb 2019

Serious Adverse Events Occurring in ≥2 Patients

- Fourteen patients (25.9%) experienced at least one serious treatment-emergent AE
- One patient had a fatal AE
  - After one dose of tislelizumab, a squamous NSCLC patient (A) experienced dyspnea, myocarditis, and rhabdomyolysis with a fatal outcome

	NSQ Tislelizumab + pemetrexed + plat (n=16)	SQ-A Tislelizumab + paclitaxel + plat (n=15)	SQ-B Tislelizumab + gemcitabine + plat (n=6)	SCLC Tislelizumab + etoposide + plat (n=17)	Total (N=54)
Anemia	0	0	0	2 (11.8)	2 (3.7)
Thrombocytopenia	0	0	0	2 (11.8)	2 (3.7)
Pneumonitis	0	2 (13.3)	0	0	2 (3.7)
Decreased platelet count	1 (6.3)	0	1 (16.7)	0	2 (3.7)

Data presented as n (%).

Abbreviations: NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; plat, platinum-therapy; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 25 Feb 2019

Best Tumor Response Following Tislelizumab in Combination With Chemotherapy

- Confirmed objective response rate was observed in 66.7% of patients (n=36)
- Median time to response among all four cohorts was 6.0 weeks (range: 5-19)

Responses	NSQ Tislelizumab + pemetrexed + plat (n=16)	SQ-A Tislelizumab + paclitaxel + plat (n=15)	SQ-B Tislelizumab + gemcitabine + plat (n=6)	SCLC Tislelizumab + etoposide + plat (n=17)
BOR, n (%)				
CR	0	0	0	0
PR	7 (43.8)	12 (80.0)	4 (66.7)	13 (76.5)
SD	8 (50.0)	2 (13.3)	1 (16.7)	2 (11.8)
PD	1 (6.3)	0	0	1 (5.9)
Missing	0	1 (6.7)	1 (16.7)	1 (5.9)
Confirmed objective response rate, % (95% CI)	43.8 (19.8, 70.1)	80.0 (51.9, 95.7)	66.7 (22.3, 95.7)	76.5 (50.1, 93.2)
Disease control rate, % (95% CI)	93.8 (69.8, 99.8)	93.3 (68.1, 99.8)	83.3 (35.9, 99.6)	88.2 (63.6, 98.5)
Time to initial response (week), median (range)	12.0 (5, 19)	5.9 (6, 12)	5.7 (6, 7)	6.0 (6, 13)

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; PD, progressive disease; PD-L1, programmed cell death ligand-1; plat, platinum therapy; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 25 Feb 2019

Progression-Free Survival Following Tislelizumab Plus Chemotherapy Treatment

- With longer follow-up (30 June 2019 data cut-off) progression-free survival (NSQ, 9.0 months; SQ-A, 7.0 months; SCLC, 6.9 months) is not yet mature for the SQ-B cohort

	NSQ Tislelizumab + pemetrexed + plat (n=16)	SQ-A Tislelizumab + paclitaxel + plat (n=15)	SQ-B Tislelizumab + gemcitabine + plat (n=6)	SCLC Tislelizumab + etoposide + plat (n=17)
Progression-free survival (months), median (95% CI)	9.0 (4.27, NR)	7.0 (5.52, NR)	NR (4.27, NR)	6.9 (4.90, 10.09)
Event-free rate at				
6 months, % (95% CI)	57 (27, 78)	71 (40, 88)	75 (13, 96)	63 (36, 82)
12 months, % (95% CI)	41 (15, 65)	39 (15, 64)	50 (6, 84)	25 (8, 48)
18 months, % (95% CI)	32 (10, 57)	30 (8, 55)	50 (6, 84)	NR (NR, NR)

Abbreviations: CI, confidence interval; NR, not reached; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; plat, platinum; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 30 June 2019

Overall Survival of Patients Treated With Tislelizumab in Combination With Chemotherapy

- Despite long follow-up (NSQ, 17.4 months; SQ-A, 18.3 months; SQ-B, 18.1 months; SCLC, 15.3 months), overall survival is not yet mature for all cohorts except SCLC

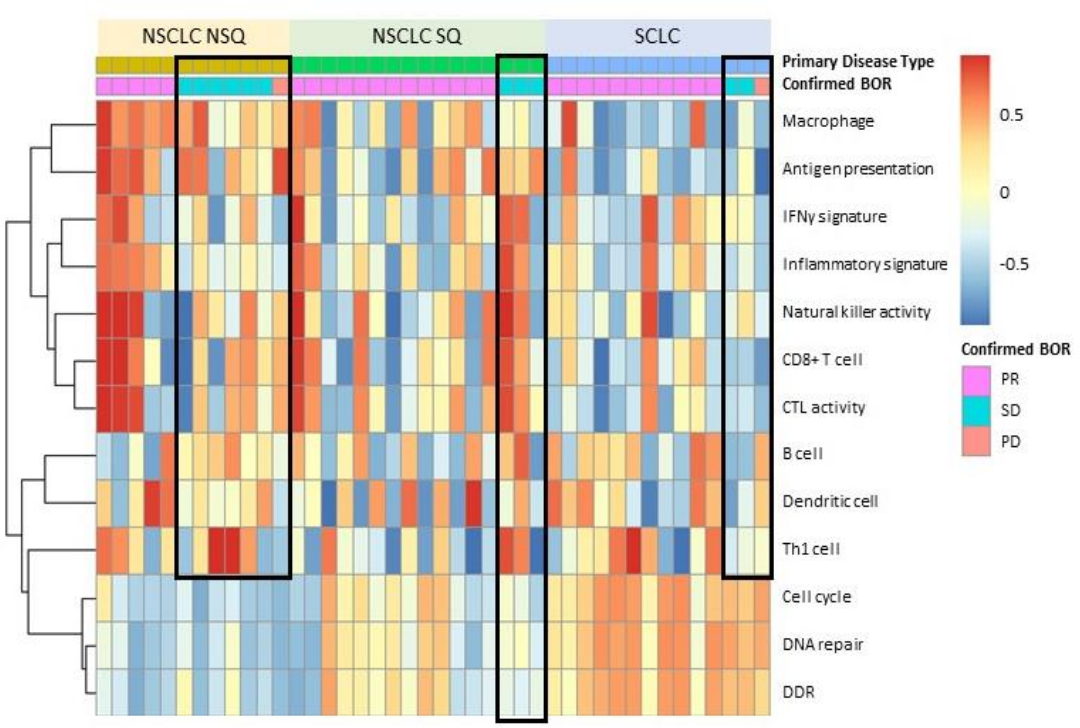
	NSQ Tislelizumab + pemetrexed + plat (n=16)	SQ-A Tislelizumab + paclitaxel + plat (n=15)	SQ-B Tislelizumab + gemcitabine + plat (n=6)	SCLC Tislelizumab + etoposide + plat (n=17)
Follow-up time (months), median (95% CI)	17.4 (16.07, 18.10)	18.3 (16.23, 19.48)	18.1 (0.33, 19.45)	15.3 (12.52, 16.92)
Overall survival (months), median (95% CI)	NR (13.31, NR)	NR (15.44, NR)	NR (8.25, NR)	15.6 (11.79, NR)
Survival rate at				
6 months, % (95% CI)	100 (NR, NR)	93 (61, 99)	100 (NR, NR)	100 (NR, NR)
12 months, % (95% CI)	88 (59, 97)	93 (61, 99)	80 (20, 97)	76 (47, 90)
18 months, % (95% CI)	74 (45, 89)	72 (41, 88)	80 (20, 97)	NR (NR, NR)

Abbreviations: CI, confidence interval; NR, not reported; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; plat, platinum; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 30 June 2019

Analysis of Gene Expression Signatures in Patient Tumor Tissue Samples

- There were different immune and cell cycle related gene signatures in the NSQ, SQ, and SCLC cohorts; NSQ nonresponders tended to have low immune related gene signatures
  - NSQ had relatively low cell cycle gene signatures and nonresponders tended to have lower immune signatures compared with responders
  - SCLC had relatively high cell cycle gene signatures, but low immune signatures; three nonresponders had low immune signatures



Black boxes denote gene signatures of interest for nonresponding patients.

Data cut-off: 25 Feb 2019

Summary

- Treatment with tislelizumab in combination with chemotherapy was generally well tolerated and preliminary data suggest antitumor activity in patients with advanced lung cancer
  - As of 25 February 2019, 14 (25.9%) patients remain on treatment
  - Most AEs were reported to be mild or moderate in severity
- Adverse events were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy
- Across all cohorts, ORRs ranged from 43.8% (NSQ) to 80% (SQ-A)
  - The majority of responses were observed within the first two tumor assessments
- Despite a long follow-up time (>1 year), survival data from this study is not mature
- Preliminary data from gene expression analyses suggest a consistent pattern of low immune signatures among nonresponding patients, except the NSCLC SQ cohort

Future Directions

- The results presented support continued development of tislelizumab in patients with advanced lung cancer
  - A phase 3 study is ongoing to evaluate tislelizumab as a single agent as second-line/third-line treatment (NCT03358875)
  - Three phase 3 studies are ongoing to evaluate tislelizumab in combination with chemotherapy as first-line treatment (NCT03594747, NCT03432598, NCT03663205)

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