Tislelizumab Combined With Chemotherapy as First-Line Treatment in Chinese Patients With Advanced Lung Cancer

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Immune Checkpoint Inhibitors in NSCLC

- Non-small cell lung cancer (NSCLC) accounts for 80–85% and small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers[1]
- First-line therapy for NSCLC and SCLC include platinum-doublet chemotherapy (eg, vinorelbine, gemcitabine, docetaxel, or paclitaxel plus platinum)[2]
- Chemotherapy has been shown to induce PD-L1 expression on tumor cells[3]
- Recent studies of immune checkpoint inhibitors have shown efficacy in patients with advanced NSCLC[4–6] as well as in patients with SCLC[7,8] as monotherapy and in combination with chemotherapy[9–11]

[1]PDQ Adult Treatment Editorial Board. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65909/. Accessed April 2018; [2]Shih Y, et al. *Asia Pac J Clin Oncol*. 2017;13(1):87–103; [3]McDaniel AS, et al. *Euro Urol Focus*. 2016;1(3):265–8; [4]Gettinger SN, et al. *J Clin Oncol*. 2015;33(18):2004–2012; [5]Herbst RS, et al. *Lancet*. 2016;387(10027):1540–1550; [6]Rizvi NA, et al. *Lancet Oncol*. 2015;16(3):257–265; [7]Gadgeel et al. *J Thorac Oncol*. 2018. pii: S1556-0864(18)30600-2; [8]Antonia SJ, et al. *Lancet Oncol*. 2016;17(7):883-895; [9]Gandhi L, et al. *N Engl J Med*. 2018;378(22):2078-2092; [10]Paz-Ares LG, et al. *J Clin Oncol*. 2018;36(suppl): Abstract 105; [11]Jotte RM, et al. *J Clin Oncol*. 2018;36(suppl); Abstract LBA9000.

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 phagocytosis, a potential mechanism of T-cell clearance and resistance to anti–PD-1 therapy

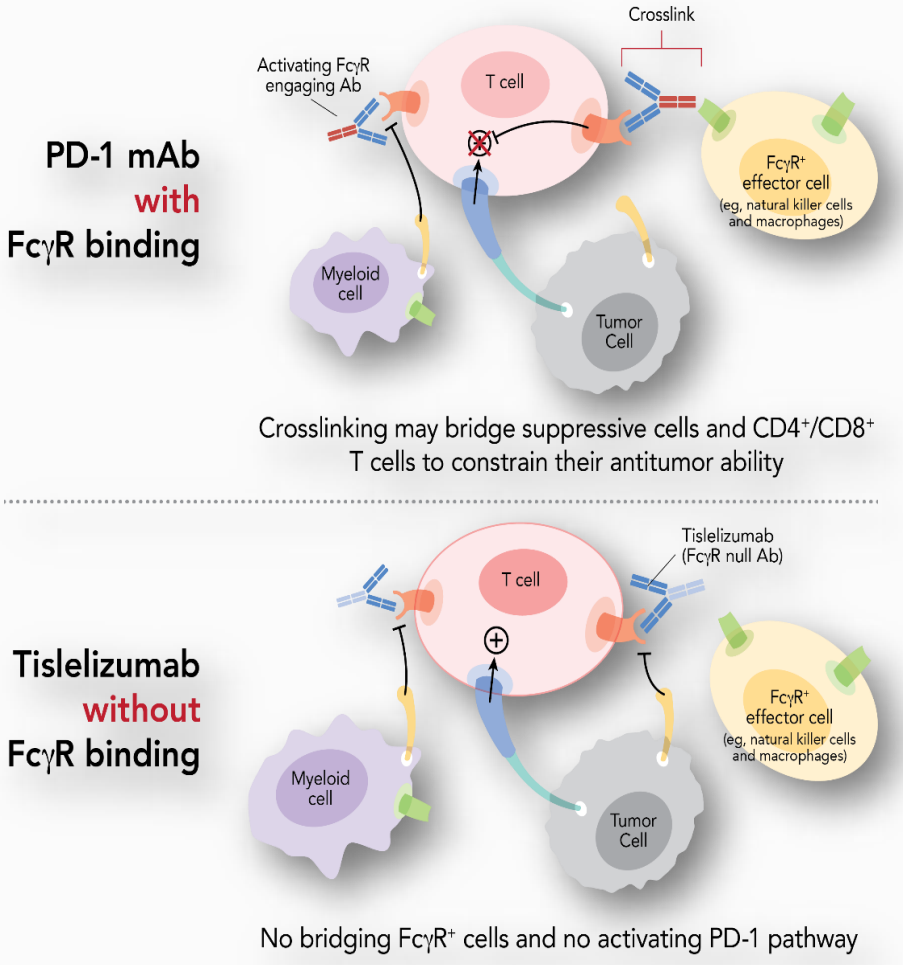
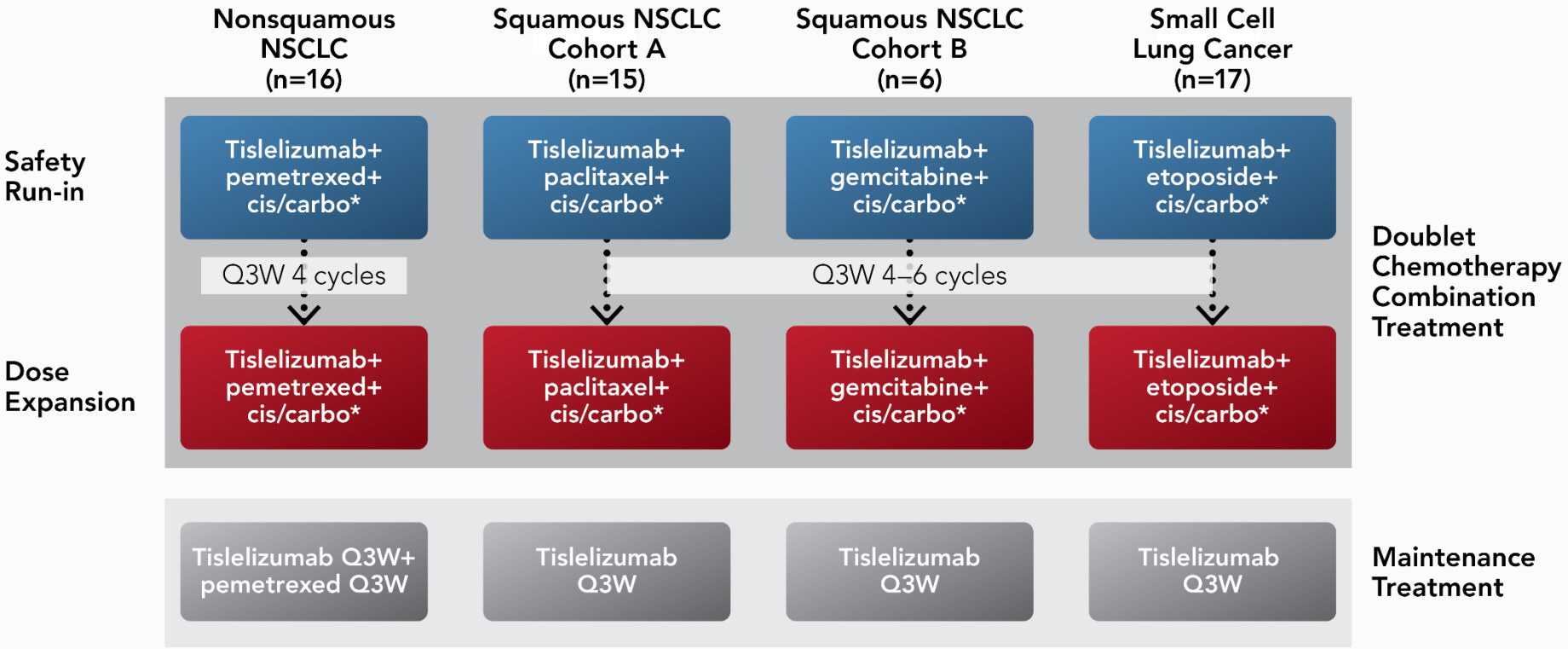


Figure modified from Dahan R, et al. *Cancer Cell*. 2015;28:285–295.
Abbreviations: Ab, antibody; PD-1, programmed cell death-1.

Study Design

At least 3 evaluable patients who completed 21 days of the safety run-in stage were enrolled in the dose expansion stage, if no new unexpected safety signal occurred as assessed by the Safety Monitoring Committee



*Either cisplatin or carboplatin could be selected as initial treatment per investigators discretion

Enrollment in squamous NSCLC cohort B was limited to 6 patients

Abbreviations: cis: cisplatin; carbo: carboplatin; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; Q3W: every 3 weeks

Data cut-off: 5 June 2018

Baseline Demographics and Patient Disposition

- As of 5 June 2018, 54 patients with lung cancer were enrolled in the study
  - A total of 35 remained on treatment, 19 discontinued treatment (AE [n=3], disease progression [n=9], and other [n=7]); all 54 patients were evaluated for response
  - Majority of patients were male (n=40; 74.1%) and former/current smokers (n=39; 72.2%)

		NSQ Tislelizumab + pemetrexed + P (n=16)	SQ-A Tislelizumab + paclitaxel + P (n=15)	SQ-B Tislelizumab + gemcitabine + P (n=6)	SCLC Tislelizumab + etoposide + P (n=17)	Total (N=54)
Median age, years		63.5	59.0	63.0	60.0	61.0
Sex, n (%)	Female	7 (43.8)	3 (20.0)	0	4 (23.5)	14 (25.9)
	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 status, 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 in 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)
Platinum treatment, n	Carboplatin	13 (81.3)	14 (93.3)	3 (50.0)	15 (88.2)	45 (83.3)
	Cisplatin	3 (18.8)	1 (6.7)	3 (50.0)	2 (11.8)	9 (16.7)

Abbreviations: NSCLC, non-small cell lung cancer; NSQ, non-squamous NSCLC; P, platinum therapy; PD-L1, programmed cell death ligand-1; PD-L1 TC, PD-L1 % expression on tumor cells.; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 5 June 2018

Overview of Treatment-Emergent Adverse Events

	NSQ Tislelizumab + pemetrexed + P (n=16)	SQ-A Tislelizumab + paclitaxel + P (n=15)	SQ-B Tislelizumab + gemcitabine + P (n=6)	SCLC Tislelizumab + etoposide + P (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	10 (62.5)	13 (86.7)	4 (66.7)	13 (76.5)	40 (74.1)
Serious AE	3 (18.8)	3 (20.0)	1 (16.7)	5 (29.4)	12 (22.2)
Fatal AE*	0	1 (6.7)	0	0	1 (1.9)
Immune-related AE	3 (18.8)	4 (26.7)	2 (33.3)	4 (23.5)	13 (24.1)
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	9 (56.3)	12 (80.0)	2 (33.3)	13 (76.5)	36 (66.7)
Treatment-related serious AE	2 (12.5)	3 (20.0)	1 (16.7)	5 (29.4)	11 (20.4)
AEs reported as related to tislelizumab	9 (56.3)	10 (66.7)	5 (83.3)	13 (76.5)	37 (68.5)
Tislelizumab-related ≥ grade 3 AE	1 (6.3)	2 (13.3)	0	2 (11.8)	5 (9.3)
Tislelizumab-related serious AE	1 (6.3)	2 (13.3)	0	0	3 (5.6)
AE leading to tislelizumab discontinuation	0	3 (20.0)	1 (16.7)	0	4 (7.4)

Data presented as n (%). *One patient had a fatal AE resulting from myocarditis/myositis.

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

Data cut-off: 5 June 2018

Adverse Events Reported as Related to Tislelizumab and Occurring in ≥2 Patients per Cohort

- A total of 37 (68.5%) patients had AEs that were reported to be related to tislelizumab
  - Five (9.3%) patients experienced at least 1 grade ≥3 AE
    - Polymyositis, dyspnea, rhabdomyolysis, myocarditis/myositis, and myasthenia gravis were considered to be at least possibly related to tislelizumab

	NSQ Tislelizumab + pemetrexed + P (n=16)		SQ-A Tislelizumab + paclitaxel + P (n=15)		SQ-B Tislelizumab + gemcitabine + P (n=6)		SCLC Tislelizumab + etolposide + P (n=17)		Total (N=54)	
CTCAE Grade AE	**≤2**	**≥3**	**≤2**	**≥3**	**≤2**	**≥3**	**≤2**	**≥3**	**≤2**	**≥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	2 (11.8)	0	5 (9.3)	0
Increased AST	0	0	2 (13.3)	0	1 (16.7)	0	2 (11.8)	0	5 (9.3)	0
Pyrexia	0	0	0	0	1 (16.7)	0	2 (11.8)	0	3 (5.6)	0
Decreased T3	2 (12.5)	0	0	0	0	0	0	0	2 (3.7)	0
Pruritus	0	0	0	0	0	0	2 (11.8)	0	2 (3.7)	0

Data presented as n (%).

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; P, platinum therapy; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B; T3, tri-iodothyronine.

Data cut-off: 5 June 2018

Immune-related Adverse Events Occurring in ≥2 Patients Across Cohorts

- A total of 13 patients experienced ≥1 immune-related AEs (irAEs)
  - Across the study, hypothyroidism (n=3), hyperthyroidism, decreased tri-iodothyronine, pneumonitis, pyrexia, and rash (n=2 each) were irAEs occurring in ≥2 patients

	NSQ (n=16)	SQ-A (n=15)	SQ-B (n=6)	SCLC (n=17)	Total (N=54)
Hypothyroidism	0	1 (6.7)	1 (16.7)	1 (5.9)	3 (5.6)
Decreased T3	*2 (12.5)*	*0*	*0*	*0*	*2 (3.7)*
Hyperthyroidism	0	0	1 (16.7)	1 (5.9)	2 (3.7)
Pneumonitis	0	1 (6.7)	0	1 (5.9)	2 (3.7)
Pyrexia	0	0	1 (16.7)	1 (5.9)	2 (3.7)
Rash	1 (6.3)	0	0	1 (5.9)	2 (3.7)

Data presented as n (%).

Abbreviations: NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; SCLC, small cell lung cancer; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B; T3, tri-iodothyronine.

Safety and Tolerability of Tislelizumab

- All AEs were manageable and reversible, with chemotherapy dose modifications or tislelizumab dose holds, except for one fatal event of myocarditis/myositis
  - 76.5% of patients had chemotherapy dose modifications
  - 35.2% of patients had tislelizumab dose holds
  - Fatal myocarditis/myositis: patient, who experienced both myocarditis and rhabdomyolysis, had an onset of AEs on Day 10 and died on Day 19 of treatment administration

Data cut-off: 5 June 2018

Best Tumor Response Following Tislelizumab in Combination With Chemotherapy

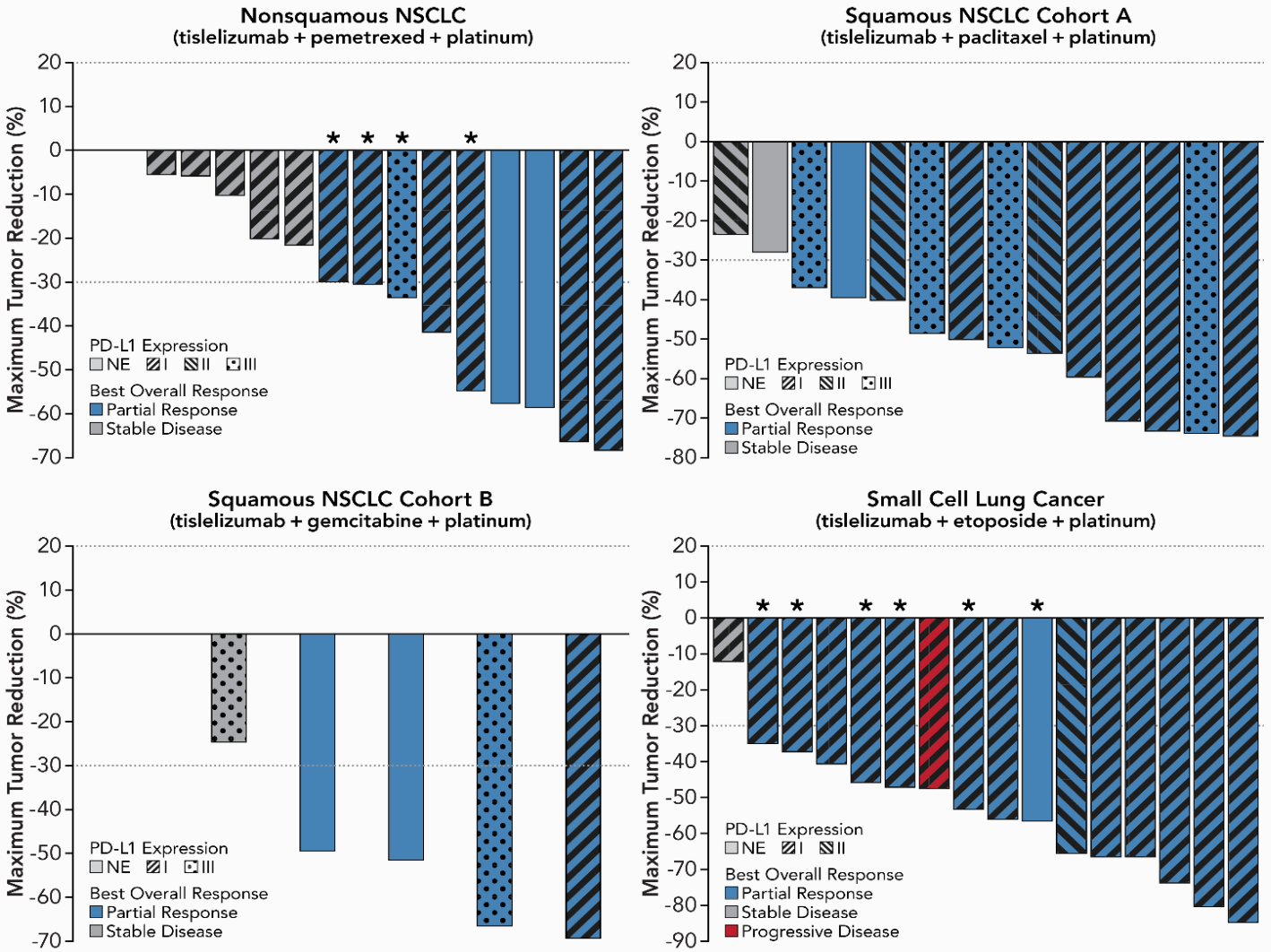
- All 54 patients had baseline assessment; 51 patients were evaluated for response post-treatment
- Clinical response to treatment was observed across all cohorts

Responses	NSQ Tislelizumab + pemetrexed + P (n=16)	SQ-A Tislelizumab + paclitaxel + P (n=15)	SQ-B Tislelizumab + gemcitabine + P (n=6)	SCLC Tislelizumab + etoposide + P (n=17)	Total (N=54)
BOR, n (%)					
CR	0	0	0	0	0
PR	5 (31.3)	12 (80.0)	4 (66.7)	8 (47.1)	29 (53.7)
UPR	4 (25.0)	0	0	6 (35.3)	10 (18.5)
SD	5 (31.3)	2 (13.3)	1 (16.7)	1 (5.9)	9 (16.7)
PD	2 (12.5)	0	0	1 (5.9)	3 (5.6)
Missing	0	1 (6.7)	1 (16.7)	1 (5.9)	3 (5.6)
Confirmed objective response rate, % (95% CI)	31.3 (11.0, 58.7)	80.0 (51.9, 95.7)	66.7 (22.3, 95.7)	47.1 (23.0, 72.2)	53.7 (39.6, 67.4)

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; PR, partial response; P, platinum therapy; SCLC, small cell lung cancer; SD, stable disease; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC cohort B.

Data cut-off: 5 June 2018

Tumor Shrinkage Following Tislelizumab in Combination With Chemotherapy



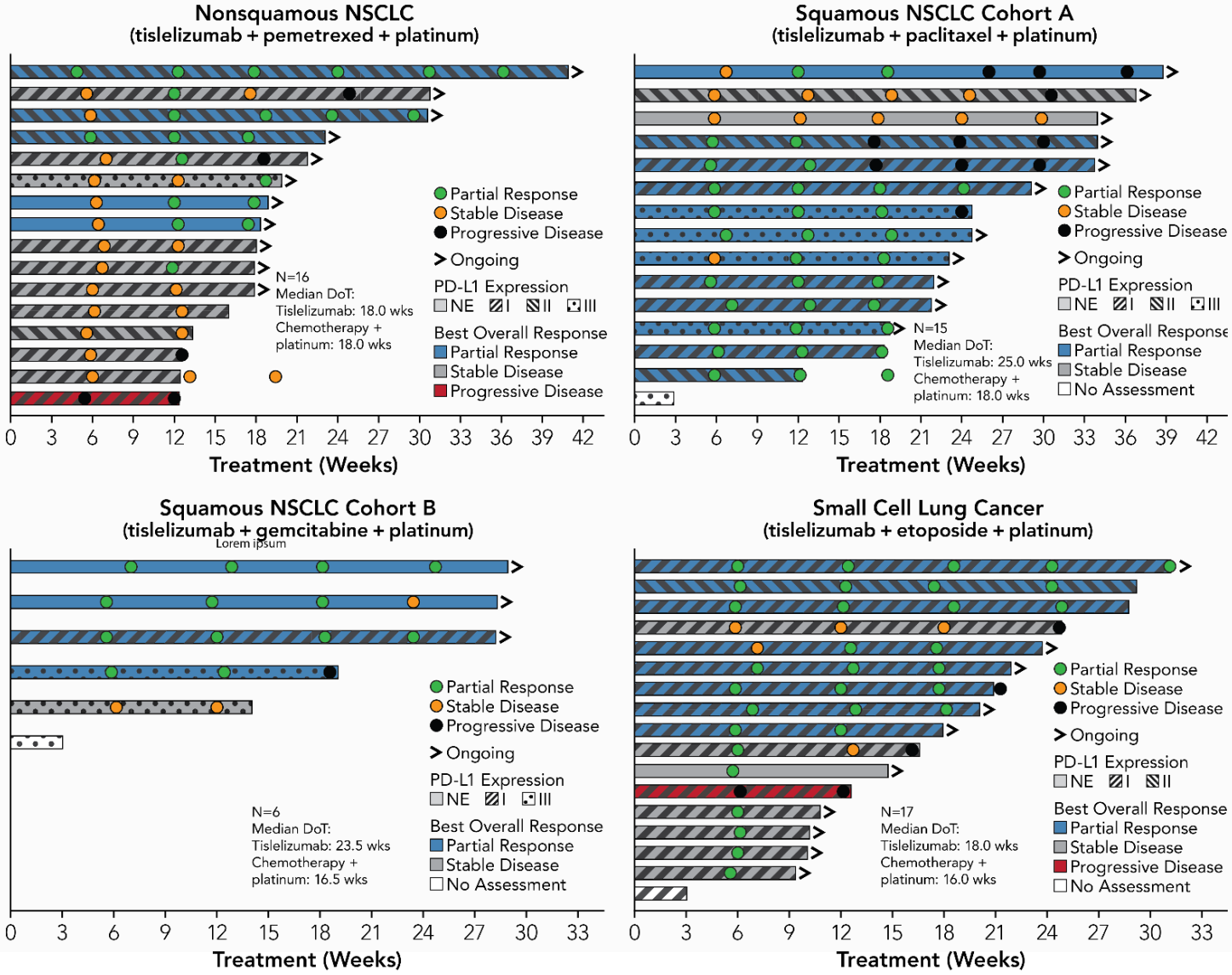
*Unconfirmed partial response

I, PD-L1 TC<10%; II, PD-L1 TC ≥10% and <50%; III, PD-L1 TC ≥50%.

Abbreviations: CR, complete response; NE, not evaluable; NSCLC, non-small cell lung cancer; NSQ, nonsquamous NSCLC; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; SQ-A, squamous NSCLC cohort A; SQ-B, squamous NSCLC

Data cut-off: 5 June 2018

Duration of Tislelizumab Treatment and Response



I, PD-L1 TC <10%; II, PD-L1 TC ≥10% and <50%; III, PD-L1 TC ≥50%.

Abbreviations: NE, not evaluable; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; SCLC, small cell lung cancer; UCR, unconfirmed complete response; UPR, unconfirmed partial response); PD-L1 TC, PD-L1 % expression on tumor cells.

Data cut-off: 5 June 2018

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 5 June, 2018, 35 (64.8%) patients remain on treatment
  - Most AEs were reported to be mild or moderate in severity
  - The rate of treatment discontinuation due to an AE was low (n=3/54)
- Adverse events reported across all cohorts were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy
- Across all cohorts, objective response rates ranged from 31.3% (NSQ) to 80% (SQ-A), with data being more mature among SQ cohorts
  - The majority of responses were observed within the first two tumor assessments
- The preliminary safety/tolerability profile and antitumor activity support continued development of tislelizumab in patients with advanced lung cancer
  - A phase 3 study has been initiated to evaluate tislelizumab as a single agent as second/third-line treatment (NCT03358875)
  - Three phase 3 studies have been initiated to evaluate tislelizumab in combination with chemotherapy as first-line treatment (NCT03594747, NCT03432598, NCT03663205)

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