SAFETY AND EFFICACY IN PATIENTS WITH LONG-TERM EXPOSURE (LTE) TO TISLELIZUMAB, AN INVESTIGATIONAL ANTI-PD-1 ANTIBODY, IN A FIRST-IN-HUMAN PHASE 1 STUDY

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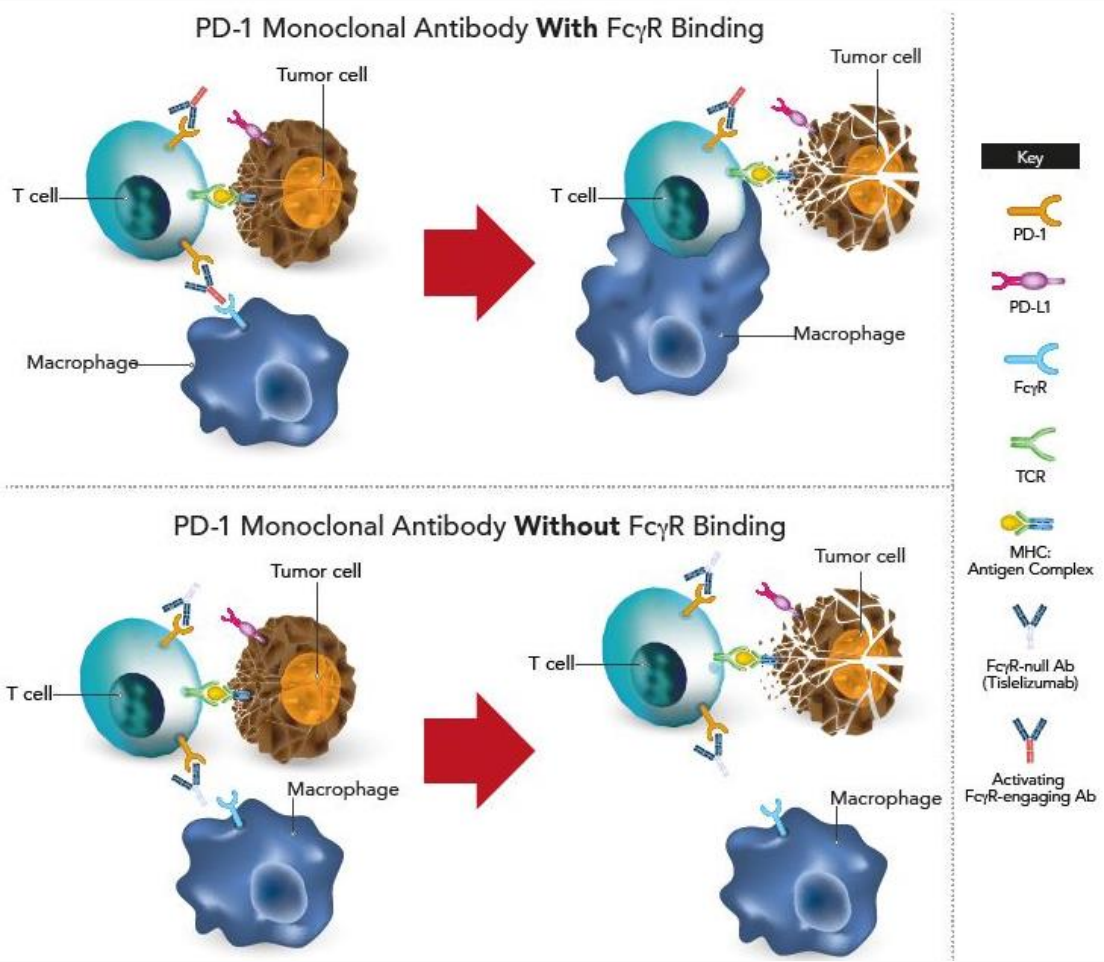
Tislelizumab: A Uniquely Engineered Anti-PD-1 Monoclonal Antibody

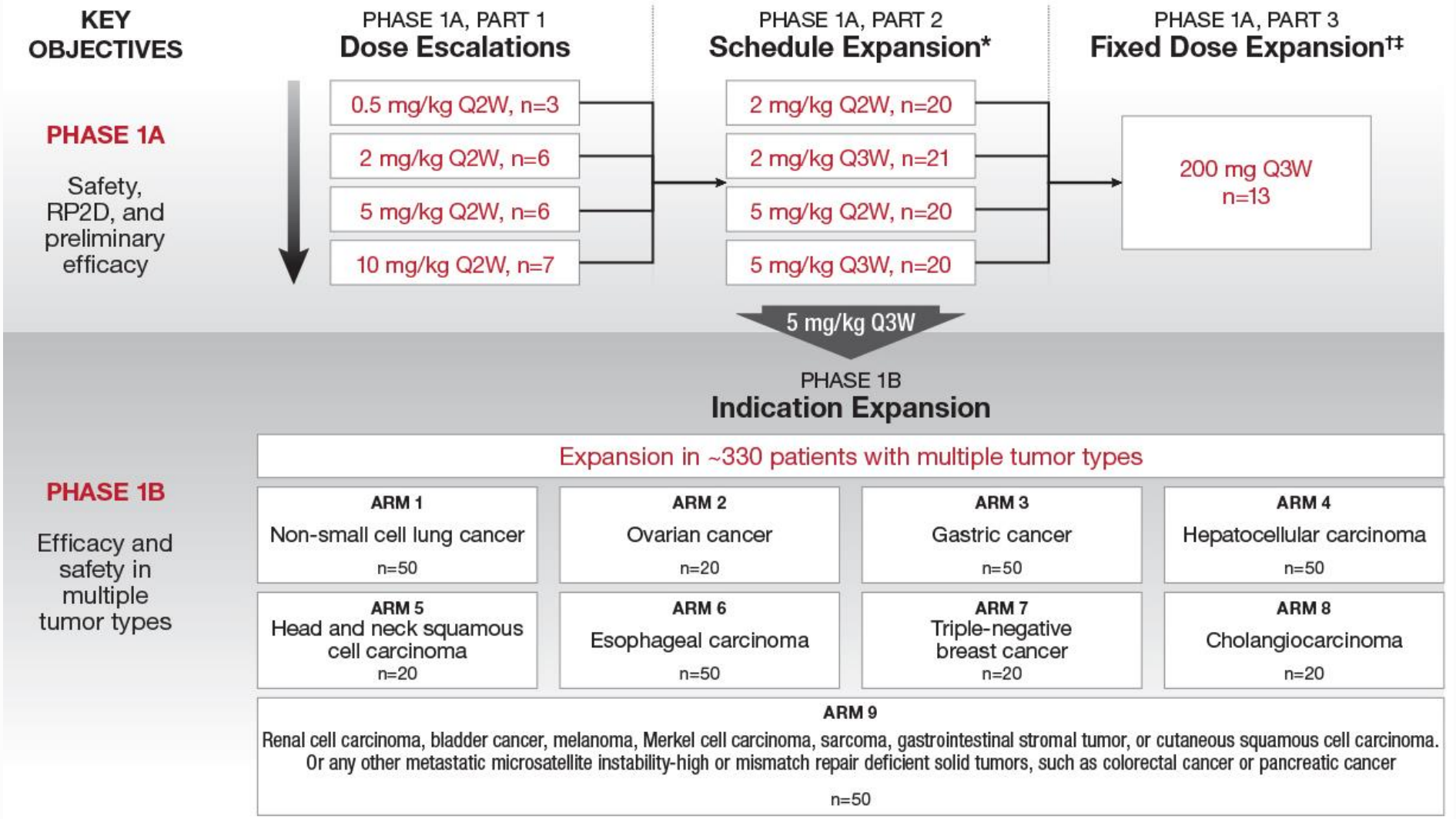
- Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1 that was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy[1,2]



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 et al. *Cancer Cell*. 2015;28(3):285-295.

Study Design (N=451)



*In select tumors for RP2D determination and preliminary differentiation. †In select tumors at fixed doses that do not exceed the exposure of minimum tolerated dose. ‡Conducted in parallel with Phase 1B.

Abbreviations: Q2W, once every 2 weeks; Q3W, once every 3 weeks; RP2D, recommended Phase 2 dose.

Study Background

- Previous reports from this first-in-human study (NCT02407990)[1-3] indicated that tislelizumab was generally well tolerated and had antitumor activity in patients with advanced solid tumors
- Here we report the clinical effects of long-term exposure (LTE; >12 months) to tislelizumab in a subset of patients enrolled in the FIH study

1. Deva S, et al. Ann Oncol. 2018;29 (suppl 10):x24-x38.2. Desai J, et al. *J Immunother Cancer*. 2016;4(suppl 1):P154. 3. Desai J, et al. *Ann Oncol*. 2017;28(suppl 5):v122-v141..

Demographics and Baseline Disease Characteristics

- As of 27 October 2018, 65 of the 451 enrolled patients received tislelizumab for >12 months and were included in the LTE group

	Patients With LTE (N=65)
Median age, years (range)	64 (24–81)
Male/female, n (%)	39 (60)/26 (40)
ECOG PS, n (%)	
0	32 (49)
1	33 (51)
Tumor type (occurring in 5% of patients), n (%)	
NSCLC	9 (14)
HCC	8 (12)
Ovarian cancer	5 (8)
Bladder cancer	5 (8)
Colorectal cancer[a]	4 (6)
Gastric cancer	4 (6)
Head and neck squamous cell carcinoma	4 (6)
Renal cell carcinoma	4 (6)
Merkel cell carcinoma	4 (6)
Median number of prior systemic anticancer therapy regimens, n (range)	1.0 (0.0–5.0)
Median duration of prior treatment, months (range)	21.7 (12.0–36.9)
Prior anticancer radiotherapy, n (%)	33 (51)
Prior surgery related to current cancer, n (%)	49 (75)

[a]Two patients were microsatellite instability-high (MSI-H) and mismatch repair deficient (dMMR), one patient was MSI-H only, and one patient was dMMR only.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular cancer; LTE, long-term exposure; NSCLC, non-small cell lung cancer.

Antitumor Activity

- In the LTE cohort, the ORR was 68% with a median follow-up of 27.2 months
- Four LTE patients achieved CR
  - These included cutaneous squamous cell carcinoma (n=1), as well as endometrial, bladder, and esophageal cancer (n=1 each)
  - All four patients were PD-L1 positive

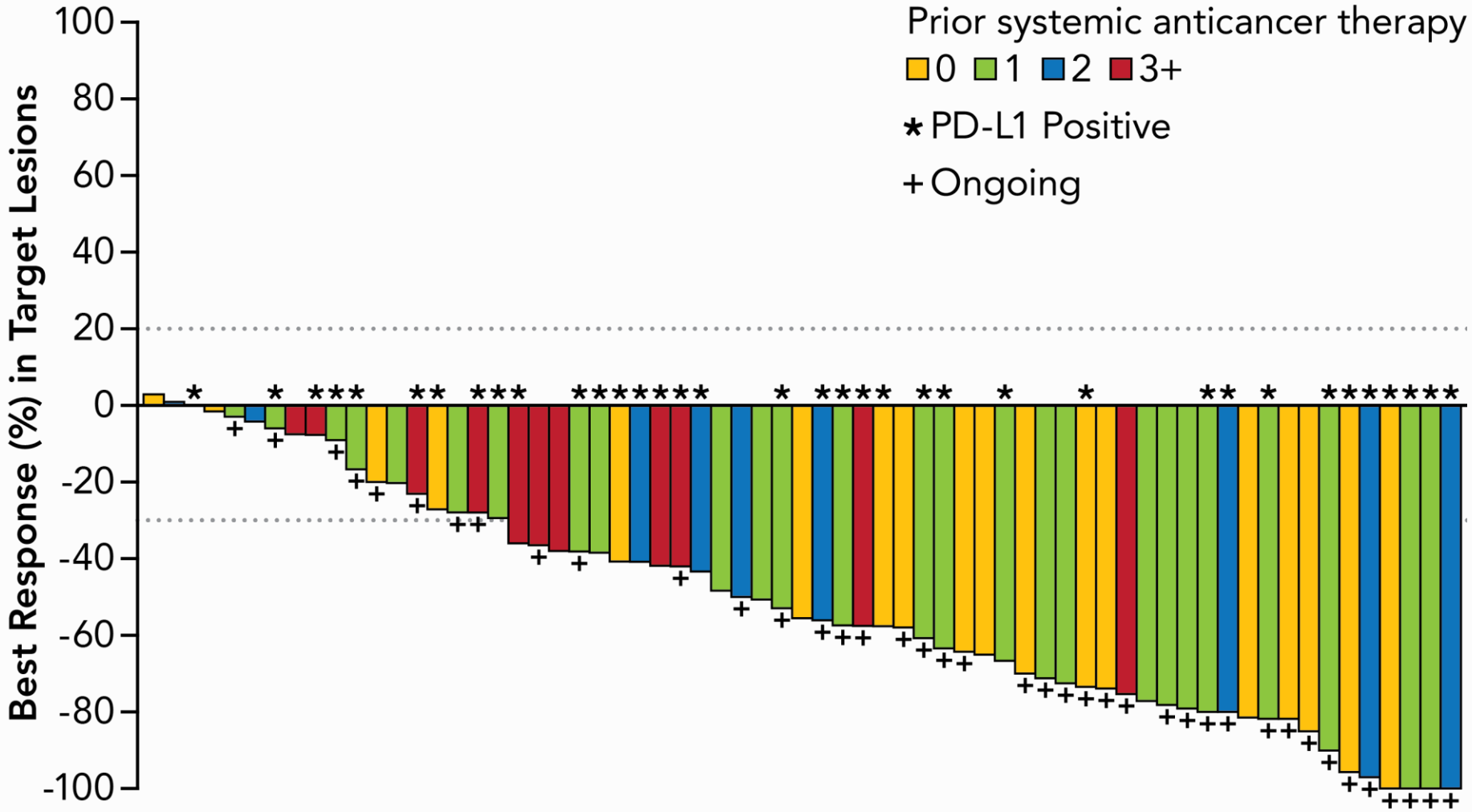
Confirmed Best Overall Response by PD-L1 Status (Safety Analysis Set)

	PD-L1 Positive (n=36)	PD-L1 Negative (n=23)	Missing (n=6)	Total (N=65)
Best overall response per RECIST v1.1 (confirmed), n (%)				
CR	4	0	0	4 (6)
PR	22	14	4	40 (62)
SD	9	9	2	20 (31)
PD	1	0	0	1 (2)
ORR, % (95% CI)	**72 (54.8, 85.8)**	**61 (38.5, 80.3)**	**67 (22.3, 95.7)**	**68 (55.0, 78.8)**

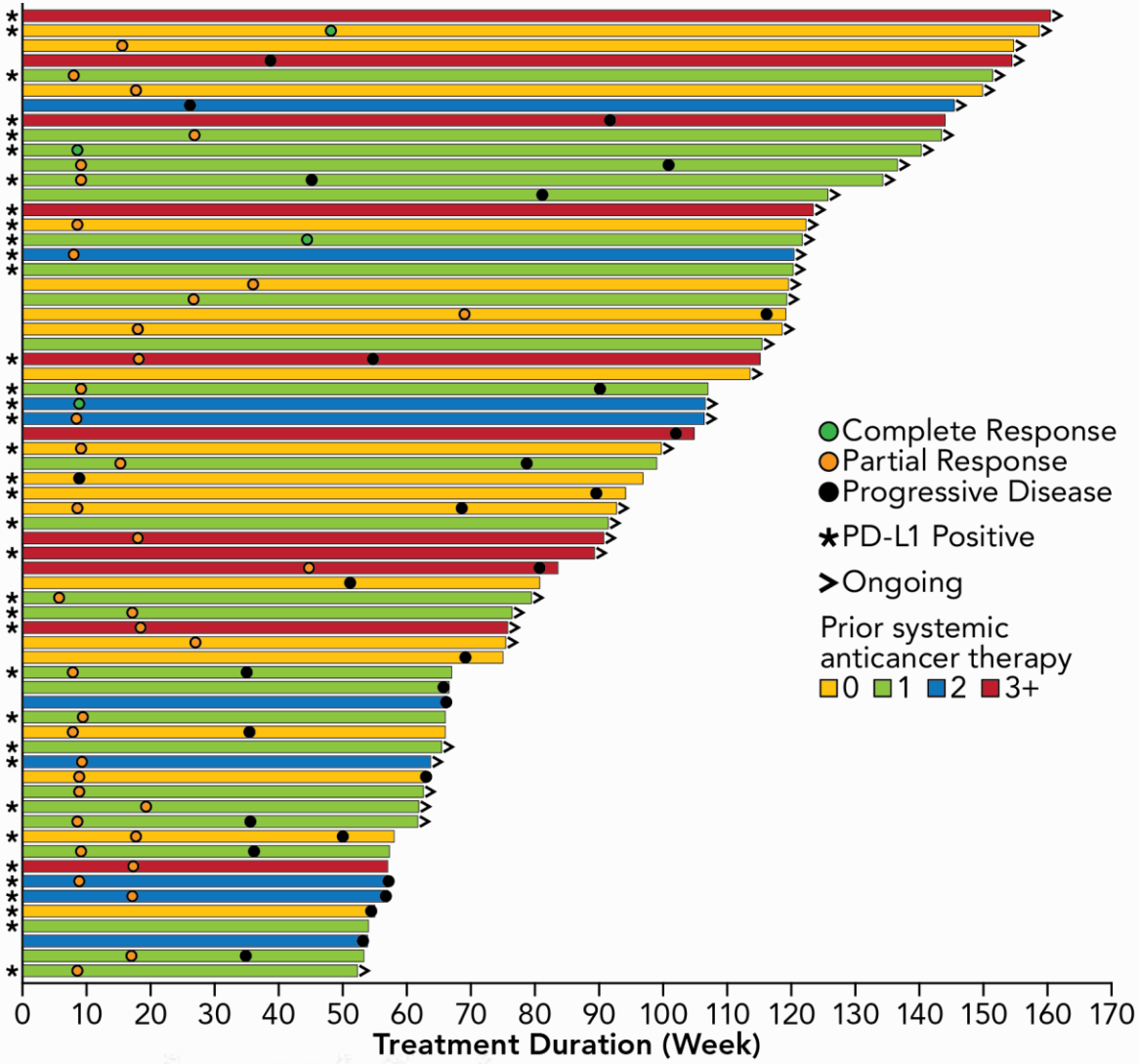
[a]PD-L1 expression was retrospectively assessed with the VENTANA™ PD-L1 (SP263) assay. Tumors were considered PD-L1-positive if there was ≥1% expression on tumor cells.

Abbreviations: CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; SD stable disease

Maximum Tumor Reduction in Patients Treated With Tislelizumab



Time to and Duration of Response in Patients Treated With Tislelizumab

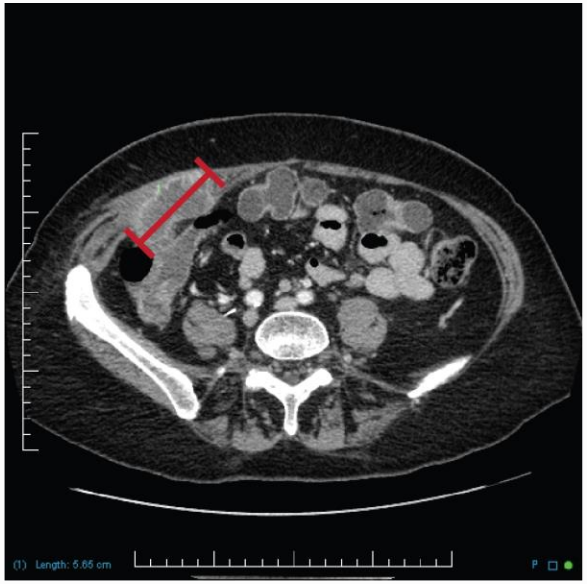


- Partial responses were observed in both PD-L1+ and PD-L1- negative tumors

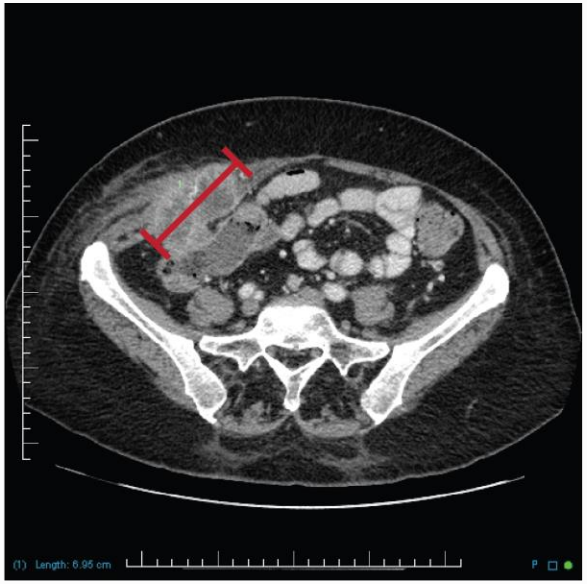
Radiographic Images of a Patient With PD-L1+ Cervical Cancer Who Had Pseudo-Progression With Long-Term Exposure to Tislelizumab

- A 61-year-old female with PD-L1+ cervical cancer, previously treated with cisplatin and radiation, had pseudo-progression during Cycle 4

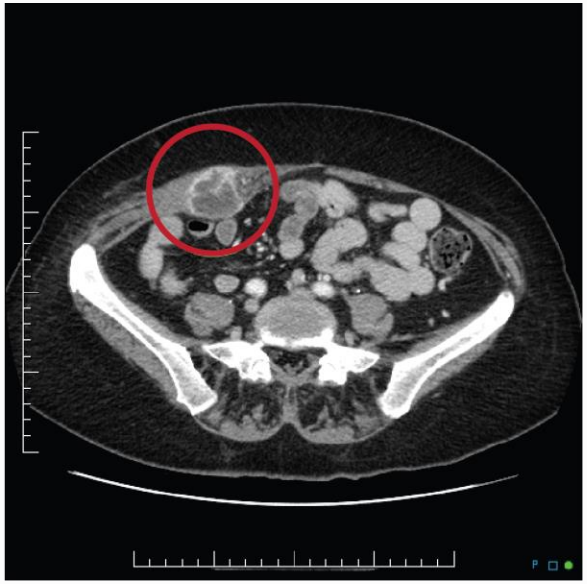
Baseline



Pseudo-progression



Response



Treatment-Related Adverse Events in ≥10% of LTE Patients

- Long-term exposure to tislelizumab was generally well tolerated
- As of 27 October 2018, 52 of the 65 patients with LTE (80%) experienced ≥1 TRAE, most of which were mild to moderate in severity

	All Grades	Grade ≥3
Any TRAE[a]	**52 (80)**	**7 (11)**
Rash	15 (23)	0
Hypothyroidism	10 (15)	0
Diarrhea	9 (14)	1 (2)
Rash, maculopapular	9 (14)	0
Fatigue	9 (14)	1 (2)
Pruritus	7 (11)	0

[a]Patients may have had more than one TRAE.
Abbreviations: LTE, long-term exposure; TRAE, treatment-related adverse event.

Serious TRAEs and AEs Leading to Discontinuation

- Serious TRAEs occurred in three patients (pyrexia, n=2; arthritis, n=1); all serious TRAEs resolved
- In patients in the LTE cohort, three patients experienced AEs that eventually led to permanent discontinuation
  - After approximately 23 months, one patient developed grade 3 arthritis
  - After approximately 14 months, one patient developed grade 2 nonserious pneumonitis
  - After approximately 1 year, one patient experienced grade 2 dyspnea
- No fatal AEs occurred

Conclusions

- Treatment with tislelizumab remained generally well tolerated when given for >12 months
  - Adverse events reported across these cohorts were generally of mild or moderate severity and were consistent with prior reports for tislelizumab monotherapy
- Single-agent tislelizumab elicited durable responses in patients with a variety of tumor types, regardless of PD-L1 status
- Tislelizumab, as monotherapy and in combination, is being further evaluated in multiple tumor types in phase 2 and phase 3 clinical studies
  - Phase 2: Esophageal, gastric, or gastroesophageal junction (GEJ) carcinoma (NCT03469557); HCC (NCT03419897); NSCLC/small cell lung cancer (NCT03432598); bladder cancer (CTR20170071)
  - Phase 3: Esophageal squamous cell carcinoma (NCT03430843); HCC (NCT03412773); NSCLC (NCT03358875, NCT03594747, NCT03663205); esophageal squamous cell carcinoma (NCT03783442); gastric or GEJ carcinoma (NCT03777657)

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