LONG-TERM EXPOSURE TO TISLELIZUMAB, AN INVESTIGATIONAL ANTI-PD-1 ANTIBODY, IN A FIRST-IN-HUMAN PHASE 1 STUDY

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BACKGROUND

- The programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axis plays a central role in suppressing antitumor immunity; dysregulation of the PD-1/ PD-L1 axis can be used by cancer cells to evade the immune system^{1,2}
- Antibodies against PD-1 can block the binding of PD-L1 to PD-1, which then allows activated T cells to induce tumor cells to undergo programmed cell death^{2,3}
- Monoclonal antibodies (mAb) against PD-1 have demonstrated antitumor activity in a multitude of tumor types⁴ and patients receiving PD-(L)1 therapy for less than 12 months have been associated with higher rates of relapse⁵
- A long-term safety analysis of patients treated with the PD-1 inhibitor nivolumab reported no cumulative toxicities with prolonged exposure and that most adverse events (AEs) occurred within the first 6 months of therapy 6
- Tislelizumab (BGB-A317) is an investigational mAb 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 therapy¹
- Previous reports from this first-in-human study (FIH; NCT02407990)⁸⁻¹⁰ 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

METHODS

Overall Design and Study Objectives

- This FIH study was a dose-escalation/indication-expansion study of tislelizumab in patients with advanced tumors
- In phase 1A, 10 mg/kg IV Q2W was the maximum administered dose; maximum tolerated dose was not reached
- All patients in phase 1B received tislelizumab as a 5 mg/kg IV infusion Q3W
- Radiographic assessment was performed approximately every 9 weeks
- PD-L1 expression was retrospectively assessed with the VENTANA PD-L1 (SP263) assay
- Tumors were considered PD-L1-positive (PD-L1+) if there was $\geq 1\%$ expression on tumor cells
- Response rates were defined as follows: objective response rate (ORR) = complete response (CR) + partial response (PR); disease control rate (DCR) = CR + PR +stable disease (SD); clinical benefit rate (CBR) = CR + PR + SD with a duration of ≥24 weeks
- Safety and tolerability were assessed by monitoring AEs (NCI-CTCAE v4.03 grade) and severity) and by evaluating results from physical examinations, ophthalmologic examinations, electrocardiograms, and laboratory investigations

Patient Population

- Adult patients (aged \geq 18 years) with histologically/cytologically confirmed advanced or metastatic solid tumors who have at least one measurable lesion, have not received prior anti-PD-1 or PD-L1 treatment, and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 were enrolled; patients were excluded if they had a history of severe hypersensitivity reactions to other mAbs or if they had a prior malignancy active within the previous 2 years
- This analysis focuses on a subgroup of patients who received tislelizumab for >12 months

Table 1: Demographics and Baseline Disease Characteristics

Median age, years (ra

Sex, n (%)

ECOG status, n (%)

Tumor type (occurring ≥2 patients), n (%)

Prior systemic anticar therapy regimens,

Median duration of Prior anticancer radio Prior surgery related

nismatch repair deficient (dMMR), one patients 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.

RESULTS

Patient Demographics and Baseline Disease Characteristics

- Twenty-five patients with LTE were enrolled as part of phase 1A: - Two patients received 2 mg/kg Q2W and nine received 2 mg/kg Q3W Five received 5 mg/kg Q2W and six received 5 mg/kg Q3W Three received 200 mg Q3W
- The remaining 40 patients were part of phase 1B and received 5 mg/kg Q3W
- In the 65 patients in the LTE cohort, the median age was 64 years, 51% had received prior anticancer radiotherapy, and 75% had prior anticancer surgery (Table 1)

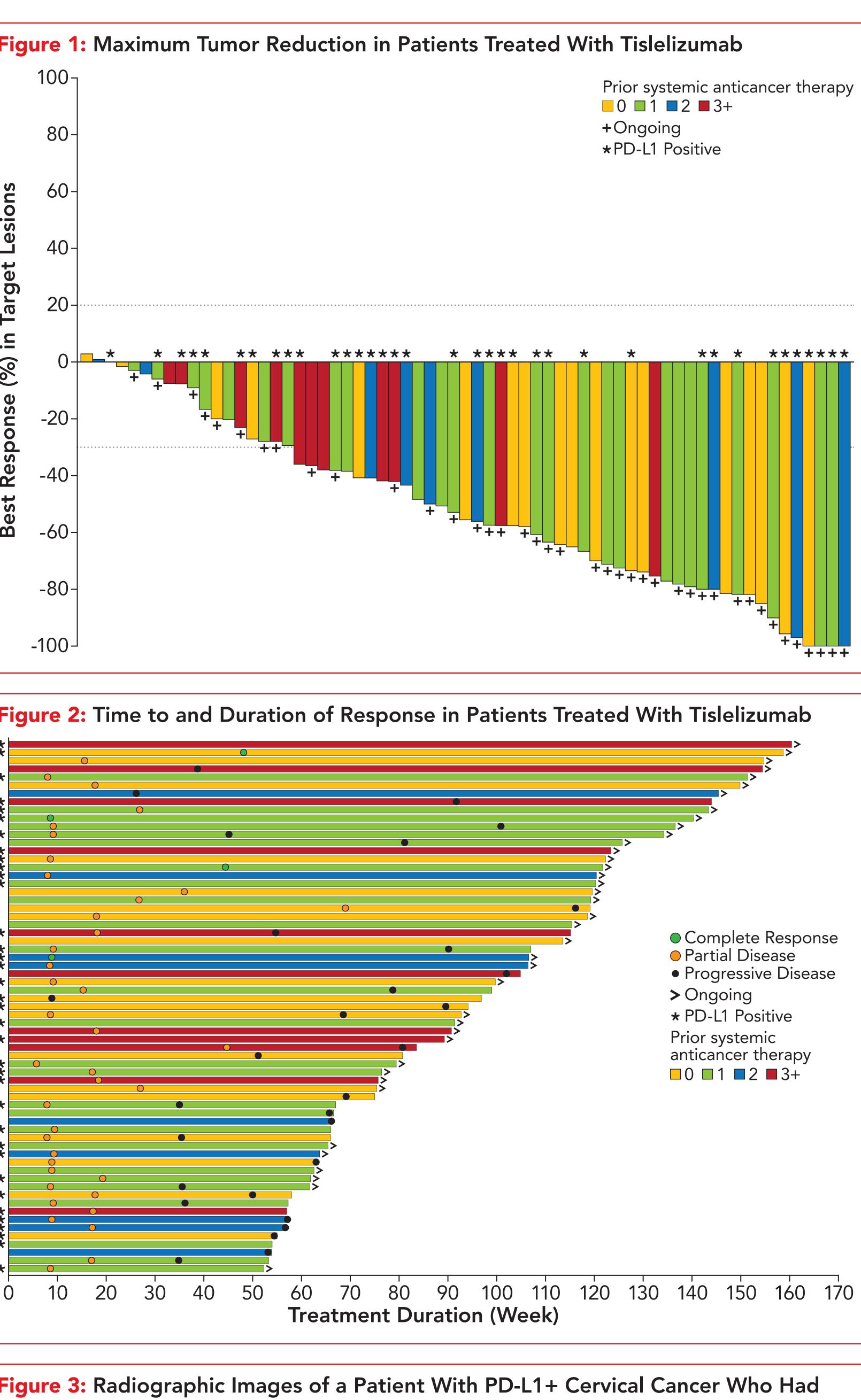
Antitumor Activity

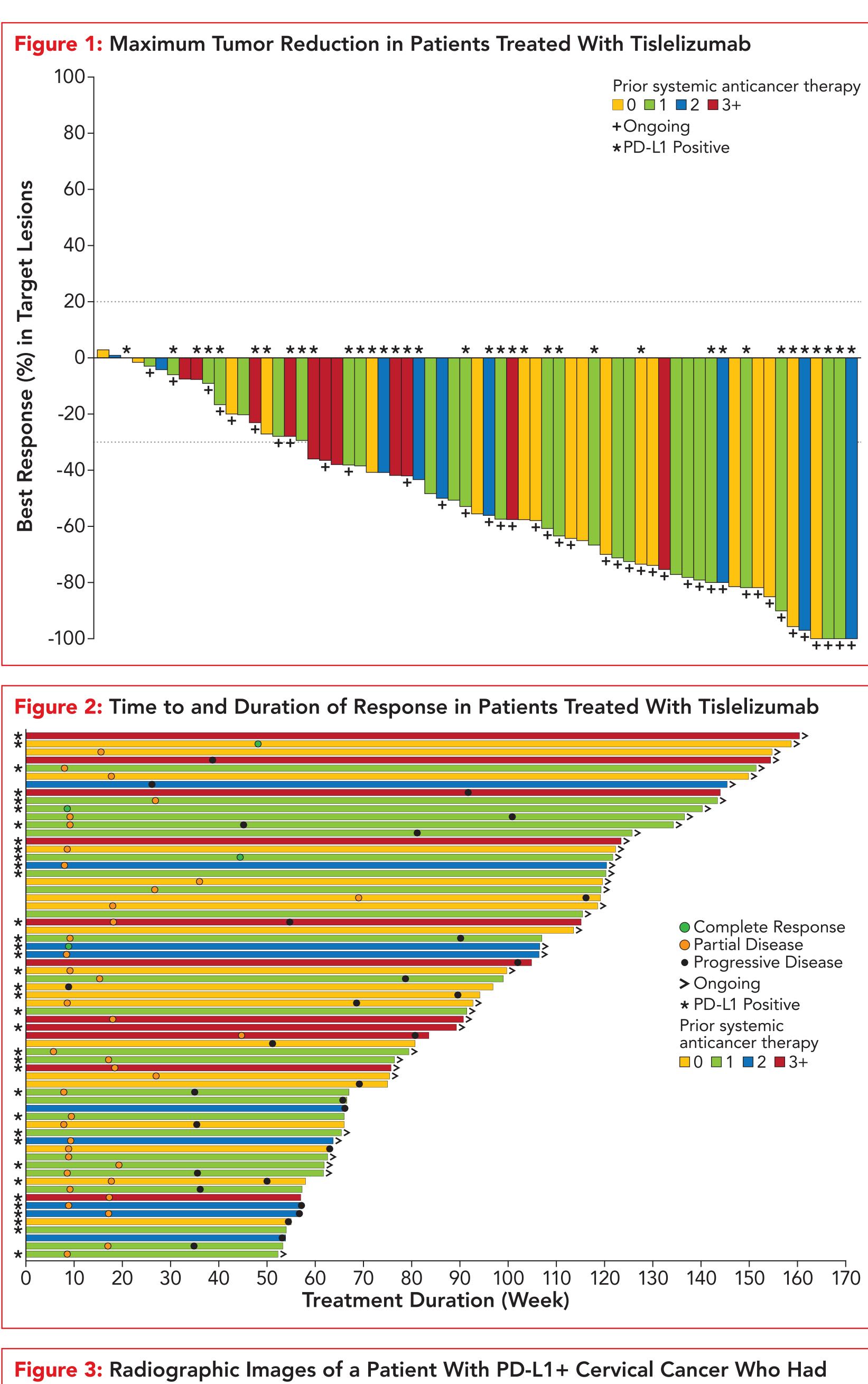
- Four LTE patients achieved CR (Table 2) - These included cutaneous squamous cell carcinoma, and endometrial, bladder, and esophageal cancers (n=1 each)
- All four patients were PD-L1+
- Partial responses and SD were observed in both PD-L1+ and PD-L1-negative tumors (Table 2 and Figure 2) • A 61-year-old female with PD-L1+ cervical cancer, previously treated with cisplatin
- and radiation, had pseudo-progression during Cycle 4 (Figure 3)
- In patients with objective responses, the median duration of CR/PR was 21.1 months in those with LTE (n=44) and 6.3 months in those who responded but did not remain on treatment for >12 months (n=16)

		Patients With LTE (N=65)			
range)		64 (24–81)			
	Male	39 (60)			
	Female	26 (40)			
	0	32 (49)			
	1	33 (51)			
ng in	NSCLC	9 (14)			
	HCC	8 (12)			
	Ovarian cancer	5 (8)			
	Bladder cancer	5 (8)			
	Colorectal cancer*	4 (6)			
	Gastric cancer	4 (6)			
	Head and neck squamous cell carcinoma	4 (6)			
	Renal cell carcinoma	4 (6)			
	Merkel cell carcinoma	4 (6)			
	Esophageal carcinoma	3 (5)			
	Endometrial cancer	3 (5)			
	Cutaneous squamous cell carcinoma	2 (3)			
	Sarcoma	2 (3)			
ancer n (%)	Neoadjuvant	3 (5)			
	Adjuvant	20 (31)			
	Metastatic	20 (31)			
	Locally advanced	5 (8)			
	Palliative	26 (40)			
prior treatment, months (range)		21.7 (12.0–36.9)			
iotherapy		33 (51)			
d to current cancer		49 (75)			
psatellite instability-high (MSI-H) and mismatch repair deficient (dMMR), one patients was MSI-H					

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

In the LTE cohort, the ORR was 68% with a median follow-up of 27.2 months





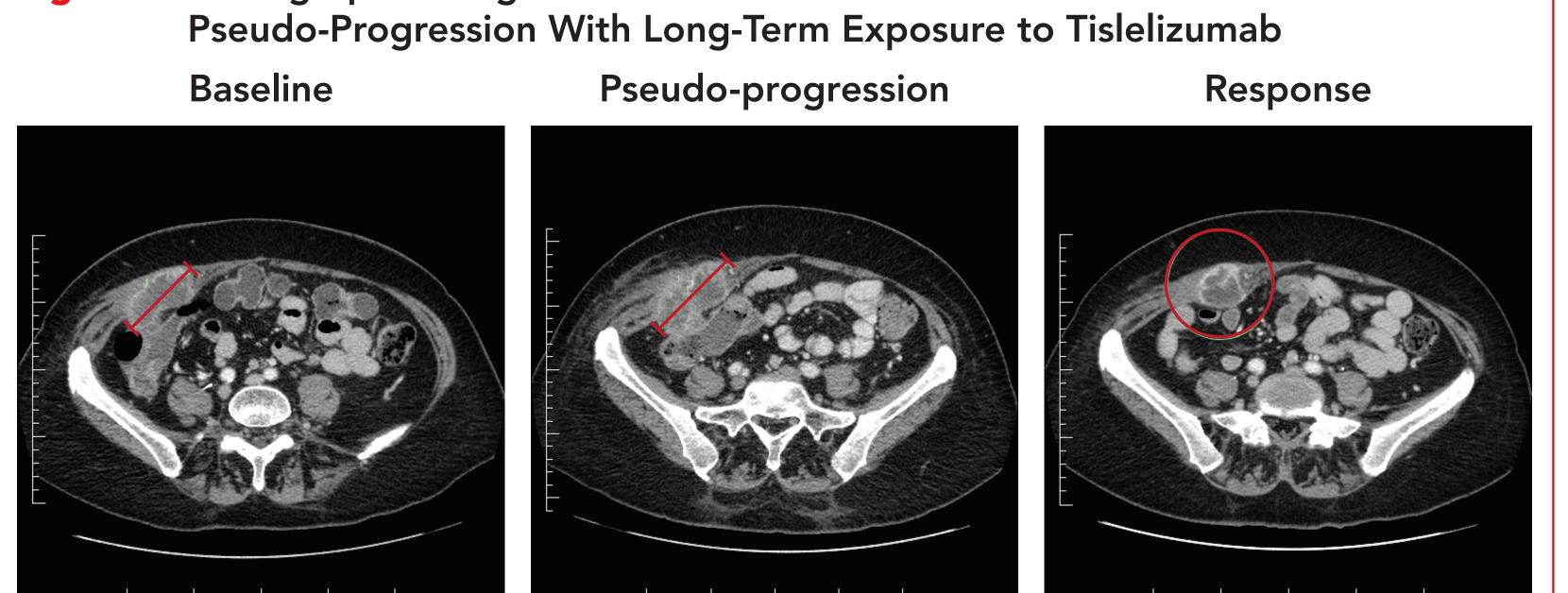


Table 2: Confirmed Best Overall Response by PD-L1 Status (Safety Analysis Set)

		PD-L1 Positive (n=36)	PD-L1 Negative (n=23)	Missing (n=6)	Total (N=65)
	CR	4	0	0	4 (6)
Best overall response per	PR	22	14	4	40 (62)
RECIST v1.1 (confirmed), n (%)	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)

. 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.

Safety and Tolerability

- Long-term exposure to tislelizumab was generally well tolerated
- As of 27 October 2018, 52 of the 65 patients with LTE (80%) experienced ≥ 1 treatment-related AE (TRAE), most of which were mild to moderate in severity (Table 3)
- Rash was the only TRAE reported in \geq 15% of patients; no rash event was grade \geq 3 - The only grade ≥ 3 TRAEs reported with tislelizumab LTE were arthritis, diarrhea, fatigue, granuloma, hyperglycemia, increased alanine aminotransferase, rash papular, and lichenoid keratosis (n=1 each)
- Serious TRAEs occurred in 3 patients (pyrexia, n=2 and arthritis, n=1); all serious TRAEs resolved
- In patients in the LTE cohort, three patients experienced AEs that eventually led to discontinuation
- After approximately 23 months, one patient developed grade 3 arthritis
- After approximately 14 months, one patient developed grade 2 non-serious pneumonitis
- After approximately one year, one patient experienced grade 2 dyspnea
- No fatal AEs occurred

Table 3: Treatment-Related Adverse Events in ≥5% of LTE Patients

	LTE Patients (N=65)
	Any Grade
Any TRAE ^a	52 (80)
Rash	15 (23)
Hypothyroidism	10 (15)
Diarrhea	9 (14)
Rash, maculopapular	9 (14)
Fatigue	9 (14)
Pruritus	7 (11)
Infusion-related reaction	6 (9)
Nausea	5 (8)
Generalized pruritus	5 (8)
Dry eye	5 (8)
Hyperthyroidism	4 (6)
Dry mouth	4 (6)
Peripheral edema	4 (6)
Arthralgia	4 (6)
Alopecia	4 (6)
Dry skin	4 (6)

^aPatients may have had more than one TRAE.

Abbreviations: LTE, long-term exposure; TRAE, treatment-related adverse event.

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Grade ≥3 7 (11)

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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