

A First-in-Human, Phase 1 Study of BGB-15025 (Hematopoietic Progenitor Kinase 1 [HPK1] inhibitor) as Monotherapy and in Combination With Tislelizumab (anti-PD-1 Antibody) in Patients With Advanced Solid Tumors

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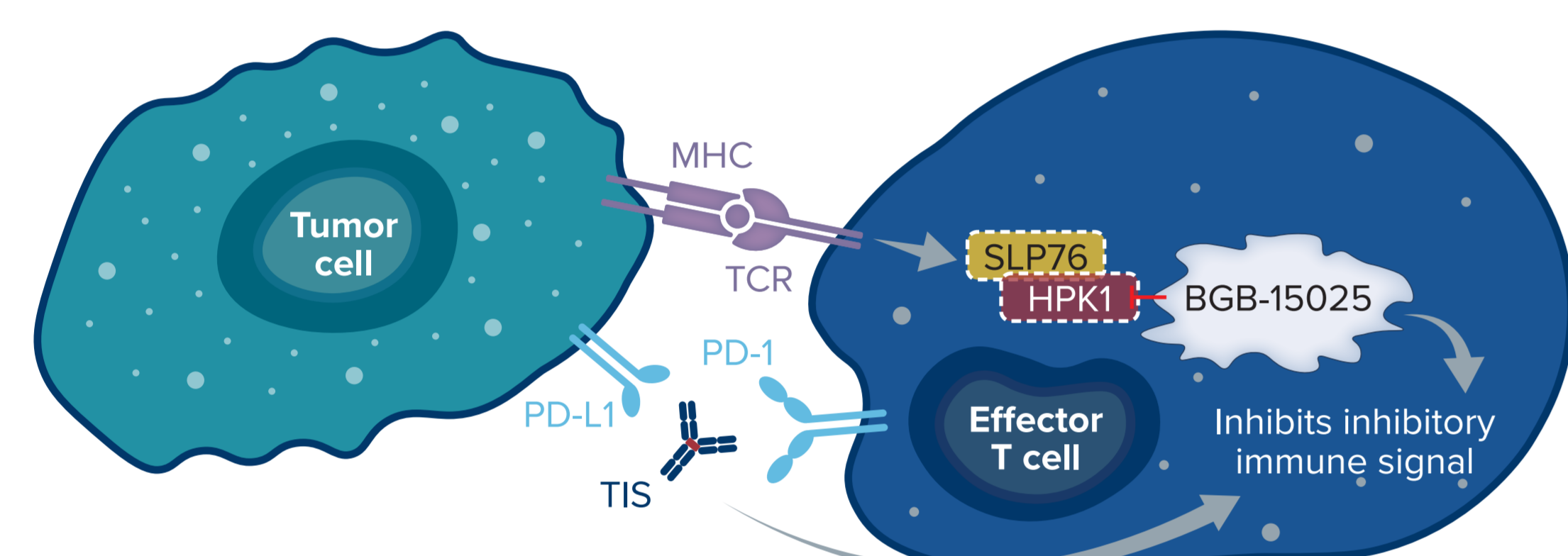
CONCLUSIONS

- BGB-15025 in combination with tislelizumab and chemotherapy demonstrated promising antitumor activity in treatment-naïve gastric and gastroesophageal junction (G/GEJ) adenocarcinoma and non-small cell lung cancer (NSCLC)
- The combination was generally well tolerated across these advanced solid tumor cohorts

INTRODUCTION

- Hematopoietic progenitor kinase 1 (HPK1) is a hematopoietic cell-restricted serine/threonine protein kinase that is expressed on T cells, B cells, and dendritic cells¹
- HPK1 acts as a negative feedback regulator of T lymphocyte and dendritic cell activation^{2,3} and is involved in antitumor immune surveillance⁴
- BGB-15025, a potent, selective, small-molecule HPK1 inhibitor, has shown preclinical antitumor effects in combination with the anti-programmed cell death protein 1 (PD-1) antibody tislelizumab (Figure 1)
- Results from the dose-escalation part of the phase 1, open-label, multicenter, non-randomized, dose-escalation/dose-expansion trial of BGB-15025 in patients with advanced solid tumors (NCT04649385) were presented previously⁵
 - BGB-15025 ± tislelizumab was generally tolerable; BGB-15025 showed greater antitumor activity when combined with tislelizumab⁵
- Here we present results from the dose-expansion phase of BGB-15025 and tislelizumab with or without chemotherapy

Figure 1. Proposed Mechanism of Action of BGB-15025 Plus Tislelizumab



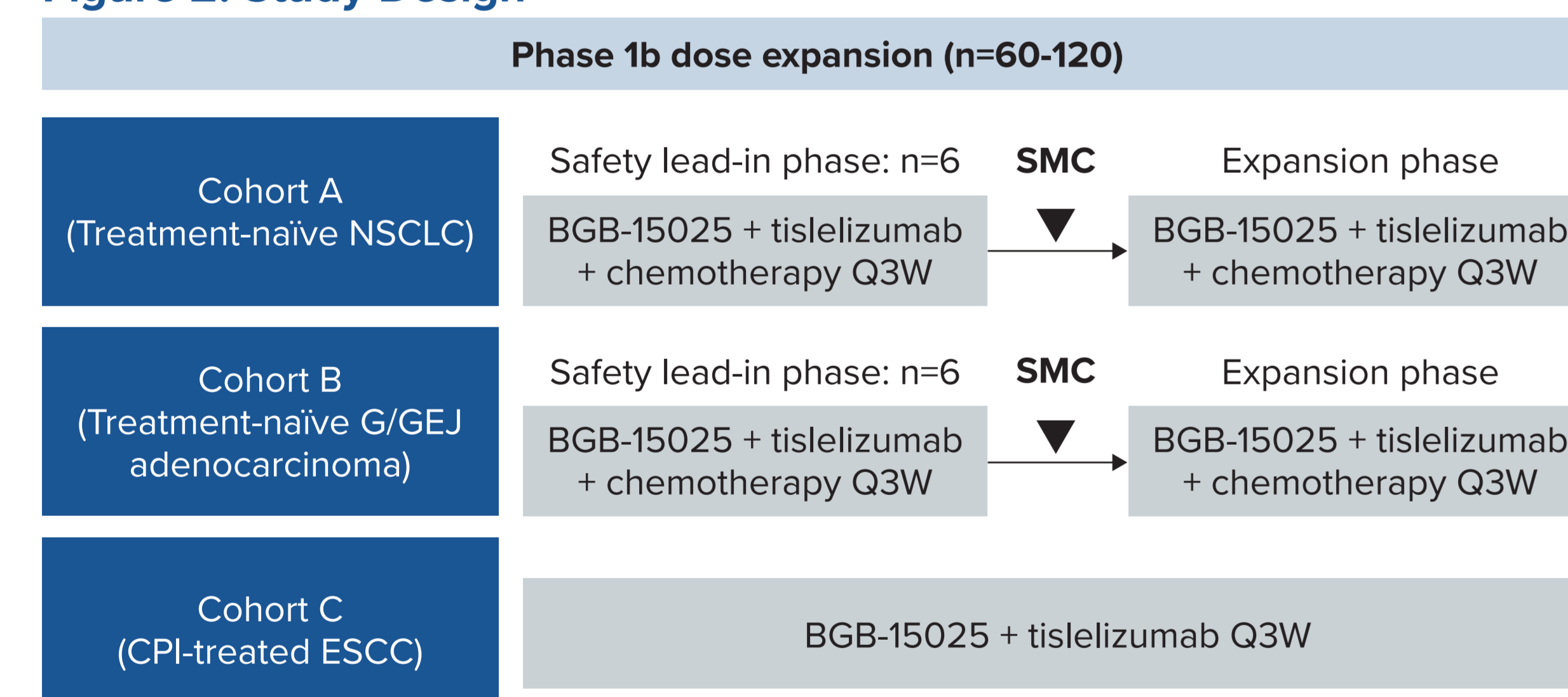
Abbreviations: MHC, major histocompatibility complex; PD-L1, programmed death-ligand 1; SLP76, SH2-domain-containing leukocyte protein of 76 kDa; TCR, T-cell receptor; TIS, tislelizumab.

METHODS

Trial Design

- The dose-expansion part of the phase 1, open-label, dose-escalation/dose-expansion trial consisted of a safety lead-in to establish tolerability, followed by a dose-expansion phase to ensure safety and preliminary antitumor activity (Figure 2)

Figure 2. Study Design



Key eligibility criteria for phase 1b

- Locally advanced, unresectable or metastatic NSCLC, G/GEJ adenocarcinoma or ESCC
- ECOG PS ≤1
- Cohorts A and B: No prior systemic treatment for patients with NSCLC and G/GEJ adenocarcinoma
 - Prior systemic therapy in the neoadjuvant/adjuvant setting for non-metastatic disease permitted
- Cohort C: Patients received one to two lines of prior standard systemic therapy and must have investigator-confirmed disease progression from prior anti-PD(L1) treatment

Endpoints for phase 1b

- Primary: ORR
- Secondary: PFS; DoR; DCR; safety/tolerability; PK of BGB-15025
- Exploratory: OS; predictive, prognostic, and/or pharmacodynamic biomarkers; PK of tislelizumab; host immunogenicity to tislelizumab

Enrollment in each cohort was designed to be 20-40 patients per protocol and varied depending on study status and discussion. Tislelizumab was given at 200 mg IV Q3W. The chemotherapy regimen was cohort A: carboplatin + paclitaxel or nab-paclitaxel for squamous NSCLC and cisplatin or carboplatin + gemtuzumab for non-squamous NSCLC; cohort B: oxaliplatin + capecitabine. The dosage and modification followed local guidance and practice.

Abbreviations: CPI, checkpoint inhibitor; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q3W, once every 3 weeks; SMC, Safety Monitoring Committee.

Analysis and Statistical Methods

- Data from phase 1b were summarized by cohort

RESULTS

Baseline Characteristics and Patient Disposition

- As of July 24, 2025, 45 patients (12 in Cohort A; 20 in Cohort B; 13 in Cohort C) were treated
- Median study follow-up in the overall population was 10.9 months (range 0.7-24.8)
- Baseline characteristics are shown in Table 1

Table 1. Baseline Characteristics (Safety Analysis Set)

	Cohort A* (N=12)	Cohort B (N=20)	Cohort C (N=13)
Age, median (range), years	69.0 (41-78)	60.5 (28-76)	65.0 (39-75)
Sex, n (%)			
Male	10 (83.3)	11 (55.0)	11 (84.6)
Race			
Asian	10 (83.3)	15 (75.0)	13 (100.0)
Native Hawaiian or Other Pacific Island	0 (0.0)	1 (5.0)	0 (0.0)
White	0 (0.0)	2 (10.0)	0 (0.0)
Other	0 (0.0)	2 (10.0)	0 (0.0)
Multiple	2 (16.7)	0 (0.0)	0 (0.0)
ECOG PS, n (%)			
0	2 (16.7)	7 (35.0)	5 (38.5)
1	10 (83.3)	13 (65.0)	8 (61.5)
Time from diagnosis to first dose, median (range), months	0.67 (0.3-14.7)	1.13 (0.1-73.1)	13.7 (6.5-102.8)

*n=8 non-squamous NSCLC, n=4 squamous NSCLC.

Antitumor Activity

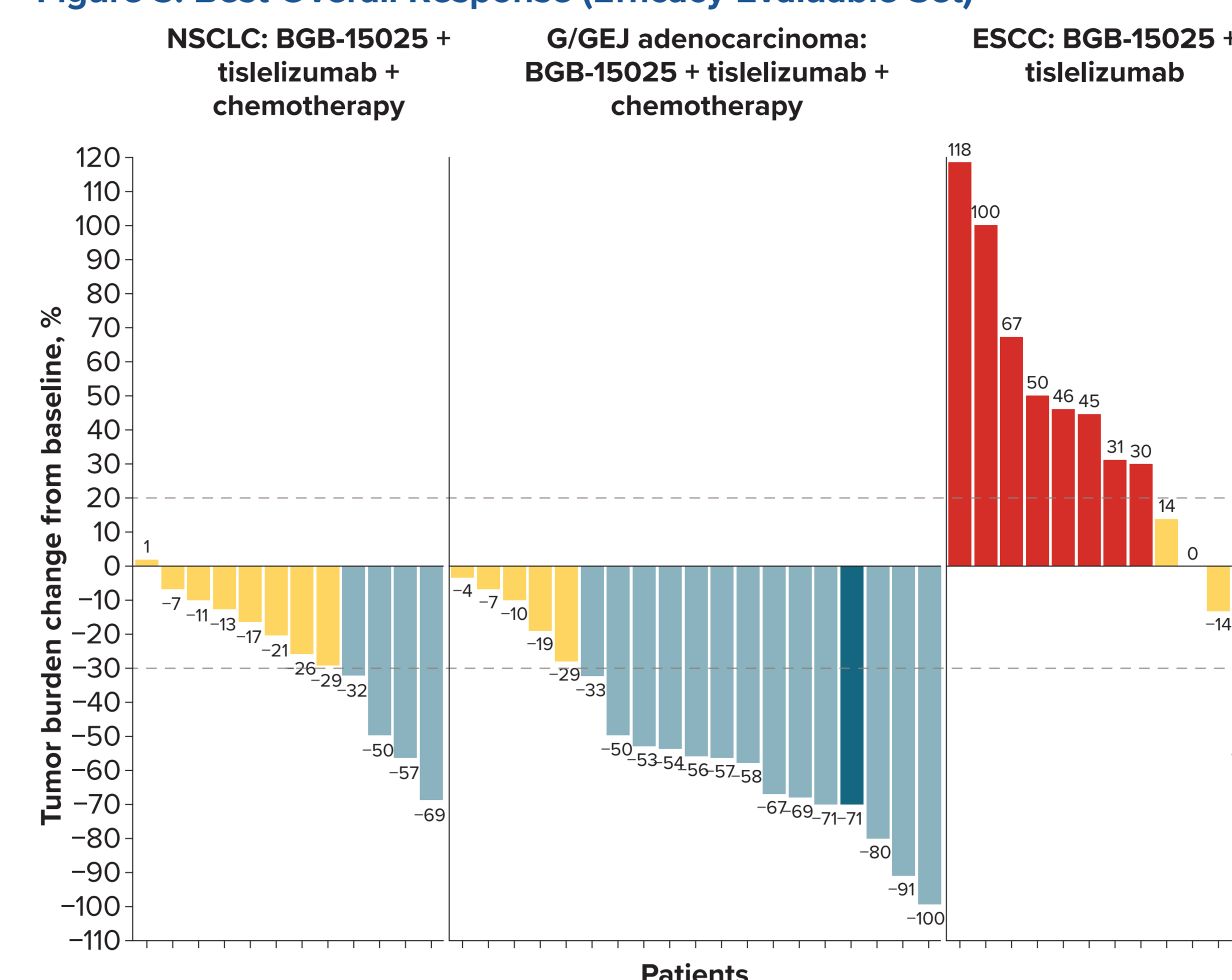
- Antitumor activity data are summarized in Figures 3, 4, and 5
- Confirmed ORR (95% confidence interval [CI]) was 25.0% (5.5-57.2) in Cohort A (3 partial responses [PRs]), 60.0% (36.1-80.9) in Cohort B (1 complete response [CR] and 11 PR), and 0% (0-24.7) in Cohort C (Table 2, Figure 3)
 - Median DoR (95% CI) was 7.0 months (6.0-not evaluable [NE]) in Cohort A and not reached (NR) (3.0-NR) in Cohort B because 66.7% of the data were censored
 - Median PFS (95% CI) was 7.7 months (4.1-8.3) in Cohort A, 8.4 months (4.3-NE) in Cohort B, and 1.3 months (0.8-2.1) in Cohort C

Table 2. Efficacy Data (Safety Analysis Set)

	Cohort A (N=12)	Cohort B (N=20)	Cohort C (N=13)
ORR, n (%)	3 (25.0)	12 (60.0)	0 (0.0)
95% CI ^a	5.5-57.2	36.1-80.9	0.0-24.7
BOR, n (%)			
CR	0 (0.0)	1 (5.0)	0 (0.0)
PR	3 (25.0)	11 (55.0)	0 (0.0)
SD	9 (75.0)	7 (35.0)	3 (23.1)
PD	0 (0.0)	0 (0.0)	8 (61.5)
NE/NA	0 (0.0)	1 (5.0)	2 (15.4)
DCR, n (%)	12 (100.0)	19 (95.0)	3 (23.1)
95% CI ^a	73.5-100.0	75.1-99.9	5.0-53.8
CBR, n (%)	8 (66.7)	14 (70.0)	1 (7.7)
95% CI ^a	34.9-90.1	45.7-88.1	0.2-36.0

Response was assessed per investigator by RECIST v1.1. All responses are confirmed. CBR was the proportion of patients who achieved a CR or PR or had SD maintained for at least 24 weeks. ^a95% CI was estimated using the Clopper-Pearson method. Abbreviations: BOR, best overall response; CBR, clinical benefit rate; NA, not assessed; PD, progressive disease; SD, stable disease.

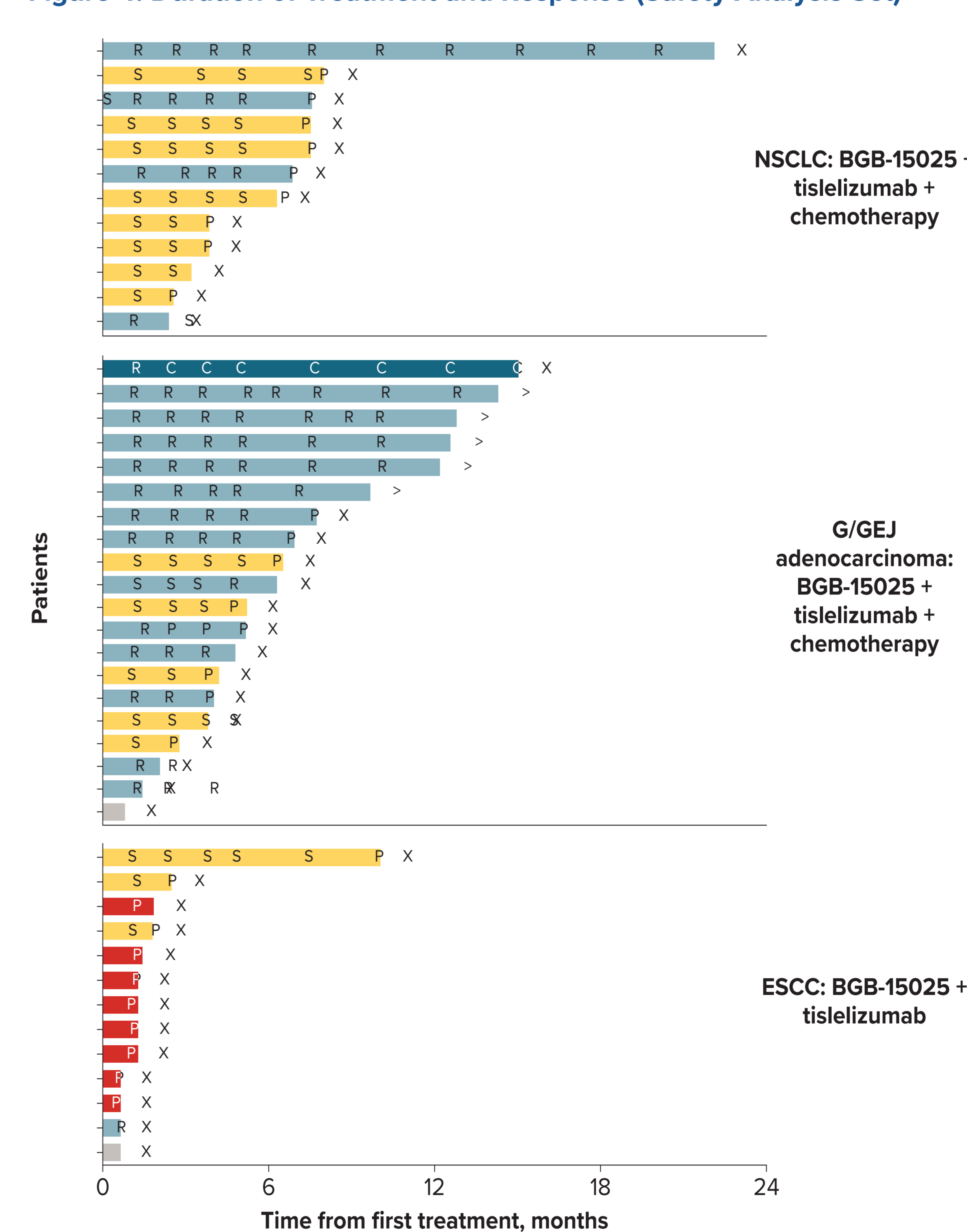
Figure 3. Best Overall Response (Efficacy Evaluable Set)



Best overall response by investigator

- Complete response
- Partial response
- Stable disease
- Progressive disease

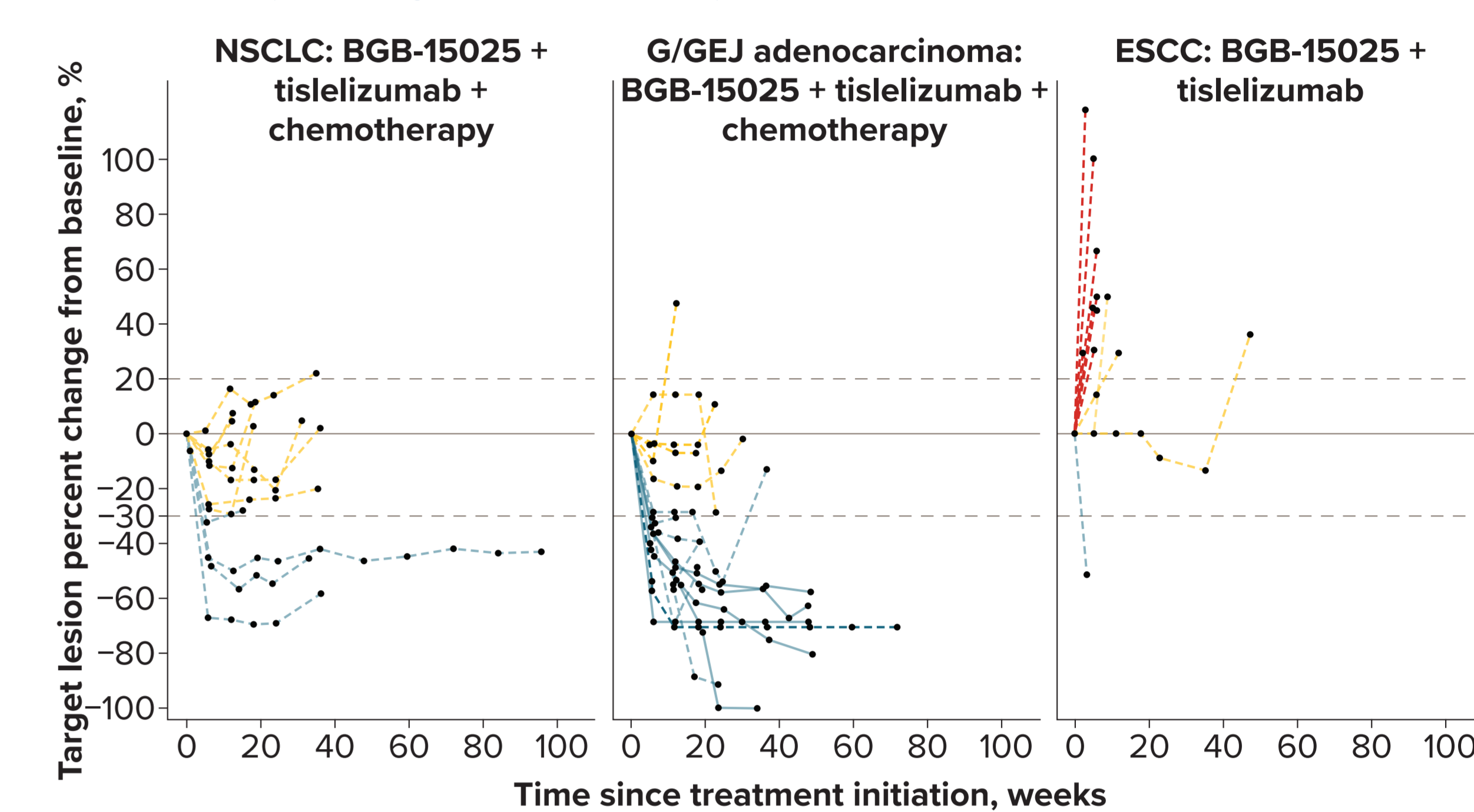
Figure 4. Duration of Treatment and Response (Safety Analysis Set)



Best overall response by investigator

- Complete response
- Partial response
- Stable disease
- Progressive disease
- Not evaluable

Figure 5. Percent Change from Baseline in Target Lesion Sum of Diameters (Efficacy Evaluable Set)



Best overall response by investigator

- Complete response
- Partial response
- Stable disease
- Progressive disease

Safety and Tolerability

- Safety data are summarized in Table 3
- Most common treatment-related treatment-emergent adverse events (TEAEs) are shown in Table 4
- The most common immune-mediated AE (imAE) was skin rash, which occurred in 41.7%, 10.0%, and 15.4% of patients in Cohorts A, B, and C, respectively

Table 3. Overall Safety Summary (Safety Analysis Set)

	Cohort A (N=12)	Cohort B (N=20)	Cohort C (N=13)
Any TEAE, n (%)	12 (100.0)	20 (100.0)	12 (92.3)
Grade ≥3	8 (66.7)	15 (75.0)	5 (38.5)
Serious	7 (58.3)	8 (40.0)	5 (38.5)
Leading to death	0 (0.0)	0 (0.0)	2 (15.4)
Leading to treatment discontinuation	2 (16.7)	5 (25.0)	2 (15.4)
Any treatment-related TEAE, n (%)	12 (100.0)	20 (100.0)	8 (61.5)
Grade ≥3	8 (66.7)	13 (65.0)	2 (15.4)
Serious	3 (25.0)	3 (15.0)	1 (7.7)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	0 (0.0)	3 (15.0)	1 (7.7)
Any imAE, n (%)	6 (50.0)	5 (25.0)	3 (23.1)

AEs were graded for severity using CTCAE v5.0. Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship. Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Table 4. Treatment-related TEAEs by Preferred Term Occurring in ≥30% of Patients (Safety Analysis Set)

n (%)	Cohort A (N=12)	Cohort B (N=20)	Cohort C (N=13)
Anemia	12 (100.0)	7 (35.0)	1 (7.7)
Neutrophil count decreased	9 (75.0)	9 (45.0)	0 (0.0)
AST increased	6 (50.0)	10 (50.0)	1 (7.7)
Platelet count decreased	4 (33.3)	12 (60.0)	1 (7.7)
ALT increased	5 (41.7)	8 (40.0)	1 (7.7)
Nausea	2 (16.7)	10 (50.0)	2 (15.4)

AEs were classified based on MedDRA v27.0. Patients with multiple events for a given preferred term were counted once at preferred term level. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities.

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