

JASPER: Phase 2 Trial of First-Line Niraparib Plus Pembrolizumab in Patients With Advanced Non–Small Cell Lung Cancer

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Background: Poly(ADP-ribose) polymerase (PARP) inhibitors may synergize with programmed cell death receptor-1 (PD-1) inhibitors to enhance adaptive and innate antitumor immune responses. In the phase 2 JASPER study (NCT04475939), the PARP inhibitor niraparib was evaluated in combination with the PD-1 inhibitor pembrolizumab in patients with metastatic and/or locally advanced non–small cell lung cancer (NSCLC). **Methods:** Patients whose tumors had programmed cell death ligand 1 (PD-L1) tumor proportion scores (TPS) \geq 50% (cohort 1) or 1%-49% (cohort 2) received first-line niraparib (200 mg once daily) plus pembrolizumab (200 mg every 3 weeks). The primary end point was investigator-assessed objective response rate (ORR). Secondary end points included duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety, and pharmacokinetics. **Results:** Thirty-eight patients were enrolled in cohorts 1 and 2. In cohort 1, ORR (95% confidence interval [CI]) was 56.3% (9 of 16 patients; 29.9%-80.2%); 2 of 16 patients had complete responses and 7 of 16 had partial responses (PRs). In cohort 2, ORR was 20.0% (5.7%-43.7%) with 4 of 20 PRs. In cohorts 1 and 2, the median DoR was 19.7 months (95% CI, 4.2 months to not estimable [NE]) and 9.4 months (95% CI, 4.2 months to NE), the median PFS was 8.4 months (95% CI, 3.9-22.1 months) and 4.2 months (95% CI, 2.0-6.2 months), and the median OS was NE (95% CI, 6.0 months to NE) and 7.7 months (95% CI, 4.0-12.5 months), respectively. Grade \geq 3 treatment-emergent adverse events occurred in 88.2% and 85.7% of patients in cohorts 1 and 2, respectively. Safety was consistent with known profiles of single-agent niraparib and pembrolizumab. **Conclusions:** Niraparib plus pembrolizumab showed clinical activity in patients with advanced and/or metastatic NSCLC. **Cancer 2022;128:65-74.** © 2021 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Lay Summary:

- The JASPER clinical trial studied a new combination treatment for advanced or metastatic non–small cell lung cancer (NSCLC).
- Pembrolizumab, a drug approved for NSCLC, was given with niraparib.
- Previous research showed that these 2 drugs together might work better than either drug alone.
- This study found that more than half of patients with high levels of a tumor marker responded to the combination, and one-fifth of patients with lower levels of the marker responded.
- The types of side effects from the combination were similar to side effects from both drugs alone.
- These results support more research on this combination.

KEYWORDS: clinical study, combination drug therapy, lung neoplasms, niraparib, non–small cell lung carcinoma, pembrolizumab, poly(ADP-ribose) polymerase inhibitors.

INTRODUCTION

The programmed cell death receptor 1 (PD-1) pathway has emerged as a therapeutic target in advanced non–small cell lung cancer (NSCLC), with several PD-1 or programmed cell death ligand 1 (PD-L1) inhibitors approved for the treatment of NSCLC.^{1,2} Pembrolizumab is a PD-1 inhibitor approved as a single agent for the treatment of patients with advanced or

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This trial is registered at ClinicalTrials.gov (NCT04475939).

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metastatic NSCLC and a PD-L1 tumor proportion score (TPS) $\geq 1\%$ in first-line therapy or following progression on platinum-based chemotherapy and as first-line treatment in combination with chemotherapy with or without pemetrexed for metastatic NSCLC.³⁻⁵ However, responses to first-line PD-(L)1 inhibitor monotherapy are seen in only a subset of patients, with objective response rates (ORRs) ranging from 22% to 27% in patients with PD-L1 TPS $\geq 1\%$ or $\geq 5\%$.^{1,6-8} Furthermore, many patients who initially respond to PD-(L)1 inhibitors ultimately relapse and become resistant to these therapies.⁹ The combination of pembrolizumab with pemetrexed and/or chemotherapy is also associated with substantial toxicity, indicating a significant unmet need for patients with PD-L1 TPS $\geq 1\%$.^{4,5}

Poly(ADP-ribose) polymerases (PARPs) are a family of proteins involved in DNA repair, genomic stability, and apoptosis. Inhibition of PARP prevents single-strand DNA break repair and, in the presence of mutations in DNA repair genes or homologous recombination deficiency (HRd), leads to cancer cell death.¹⁰ HRd cancers are particularly sensitive to certain PARP inhibitors, such as niraparib, although efficacy has also been observed with niraparib in patients with homologous recombination proficient tumors.^{11,12} Data from The Cancer Genome Atlas show that squamous cell carcinoma and lung adenocarcinoma exhibit high levels of HRd.¹³ Consistently, a phase 2 study of veliparib plus chemotherapy suggested antitumor activity of PARP inhibitors in NSCLC.

Niraparib is an oral, selective PARP-1/2 inhibitor approved for the treatment of advanced or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.^{11,14,15} Preclinical evidence suggests that PARP inhibitors may synergize with PD-(L)1 inhibitors by enhancing immune surveillance in the tumor microenvironment via activation of the stimulator of interferon genes pathway and by overcoming PD-L1-mediated resistance mechanisms induced by PARP inhibition, such as PD-L1 upregulation.¹⁶⁻²⁰ The phase 1/2 TOPACIO/KEYNOTE-162 trial demonstrated that niraparib plus pembrolizumab had a tolerable safety profile and promising antitumor activity in patients with advanced triple-negative breast cancer or platinum-resistant ovarian cancer.²¹ Given the preclinical evidence for synergistic mechanisms of action between these 2 classes of drugs and the promising clinical activity of niraparib and pembrolizumab in other cancer types, niraparib plus pembrolizumab is a logical combination in NSCLC.²²

Here, we report the results of the phase 2 JASPER study (NCT04475939) evaluating clinical outcomes

with niraparib plus pembrolizumab as first-line therapy in patients with locally advanced or metastatic NSCLC.

MATERIALS AND METHODS

Study Design

JASPER was a phase 2, multicenter, open-label, 2-stage trial. Eligible patients were ≥ 18 years of age with measurable (by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1²³) histologically or cytologically proven advanced (unresectable) or metastatic NSCLC (stage 3B/4). Patients had an Eastern Cooperative Oncology Group performance status of 0 to 1, had not received a prior PARP inhibitor, anti-PD-(L)1, or anti-programmed cell death ligand 2 therapy, and had adequate organ function. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines following approval by ethics committees and institutional review boards at each study site. All patients provided written informed consent.

Cohorts

In stage 1, patients in cohorts 1 and 2 received niraparib plus pembrolizumab. If predefined responder criteria were met in stage 1, the study would progress to stage 2. In stage 2, cohorts 1A and 2A were to assess niraparib plus the PD-1 inhibitor dostarlimab, and cohort 3 was to assess niraparib monotherapy for patients who progressed on prior platinum-based chemotherapy and PD-(L)1 inhibitor treatment. Results of cohorts 1 and 2 are reported in this article.

PD-L1 status was assessed by immunohistochemistry (IHC) testing performed locally on either archival or fresh tumor tissue. PD-L1 status was also assessed centrally when possible using a Food and Drug Administration-approved in vitro companion diagnostic assay; 22C3 antibody was used for all central and most local testing. Patients with all histological subtypes of NSCLC and no known epidermal growth factor receptor-sensitizing mutation and/or *ROS1* or *ALK* translocations were eligible for cohorts 1 or 2. Patients in cohort 1 had tumors with PD-L1 TPS $\geq 50\%$; patients in cohort 2 had tumors with PD-L1 TPS 1% to 49%. Patients who received previous first-line systemic therapy for the treatment of advanced-stage NSCLC were excluded. Neoadjuvant and/or adjuvant therapy must have been completed at least 6 months before the diagnosis of metastatic disease.

Treatments

Patients in cohorts 1 and 2 received 200 mg of oral niraparib once daily with 200 mg of intravenous pembrolizumab every 3 weeks. Treatment with niraparib continued until disease progression, and treatment with pembrolizumab continued until unacceptable toxicity or disease progression (maximum of 24 months). Niraparib treatment was interrupted for any niraparib-related nonhematologic adverse event (AE) of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 and was restarted (with dose reduction if required) on resolution to a grade ≤ 1 event. Niraparib dose modifications were also permitted for specific hematologic AEs. Pembrolizumab treatment could be interrupted or discontinued for pembrolizumab-related toxicities, but dose reductions were not permitted.

End Points and Assessments

The primary efficacy end point was investigator-assessed ORR, defined as the proportion of patients with \geq partial response (PR) per RECIST v1.1. Secondary efficacy end points included duration of response (DoR), disease control rate (DCR; proportion of patients with complete response [CR], PR, or stable disease), progression-free survival (PFS), and overall survival (OS). Other secondary end points were the safety and tolerability of niraparib in combination with pembrolizumab (treatment-emergent AEs [TEAEs], treatment-related TEAEs, and discontinuations due to AEs).

Efficacy and safety end points were assessed every 3 weeks. Tumor assessments were performed at baseline by computed tomography (CT) or magnetic resonance imaging (MRI). Follow-up imaging assessments for tumor response were conducted every 9 weeks up to week 72 and every 12 weeks thereafter. Stable disease was recorded if documented on CT/MRI assessment >4 weeks from baseline. A safety follow-up visit occurred 30 (+7) days after the last dose of study medication and follow-up visits occurred every 90 (± 14) days until death or end of study (≥ 6 months after the enrollment of the last patient). AE data were collected through 30 days after the last dose of study treatment, and serious AEs were collected through 90 days after last dose of study treatment.

Pharmacokinetic Assessments

Pharmacokinetic (PK) assessments of niraparib were performed on day 1 of cycles 1, 2, 4, and 8 on blood collected 30 minutes pre-dose and 4 hours post-dose of niraparib. Niraparib plasma concentrations were determined using

K3EDTA and developed and validated using a protein precipitation extraction procedure and liquid chromatography with tandem mass spectrometry (Charles River Laboratory, Worcester, Massachusetts).

Statistical Analysis

Sample size for stage 1 was based on Simon's 2-stage design. Sample size was calculated for each cohort based on ORR and with the assumption of a 1-sided α level of 0.10 and 80% power. For cohort 1, the target ORR was 65% (standard-of-care ORR, 45%) for a sample size of 16, and for cohort 2, the target ORR was 50% (standard-of-care ORR, 33.5%) for a sample size of 20.

Efficacy was evaluated in the modified intent-to-treat (mITT) population, which included all patients who received any study drug and did not withdraw consent before having ≥ 1 post-baseline tumor assessment. Response was evaluated in patients who received any study drug, did not withdraw consent, and had ≥ 1 post-baseline tumor assessment. Safety was evaluated in patients who received ≥ 1 dose of study drug. The number of responders, ORR, DCR, and 95% CIs were reported by cohort. Kaplan-Meier estimates, including median and 95% CI, were calculated for DoR, PFS, and OS. All analyses for safety end points were descriptive, AEs were coded using Medical Dictionary for Regulatory Activities v23.0, and CTCAE v4.03 was used to grade the severity of AEs and laboratory abnormalities. All other statistical analyses were performed using SAS software, version 9.4 (Cary, North Carolina).

RESULTS

Patient Population

As of the May 4, 2020, data cutoff, a total of 38 patients had been enrolled into cohorts 1 and 2 (Fig. 1). Seventeen patients were assigned to cohort 1 (PD-L1 TPS $\geq 50\%$) and 21 were assigned to cohort 2 (PD-L1 TPS 1%–49%). In cohorts 1 and 2, 16 of 17 patients and 20 of 21 patients, respectively, were included in the mITT population and were efficacy evaluable. A total of 14 and 18 patients in cohorts 1 and 2, respectively, were evaluable for response.

The median age of patients was 72.0 years (range, 50–81 years) in cohort 1 and 72.0 years (range, 53–91 years) in cohort 2 (Table 1). Almost all patients in each cohort had stage 4 NSCLC at the time of randomization. Most patients ($>58\%$) in cohorts 1 and 2 had adenocarcinoma and approximately 25% of patients had squamous cell carcinoma.

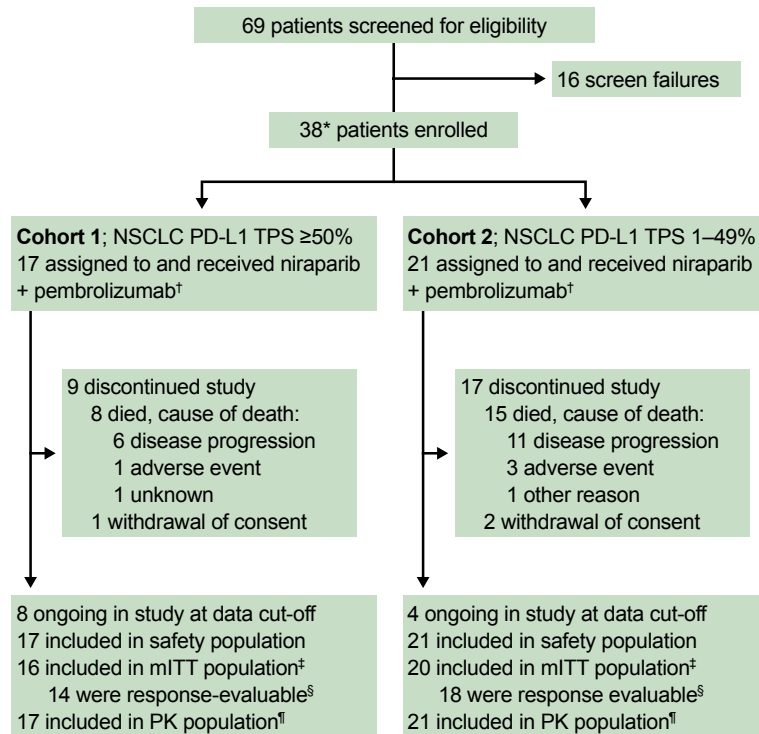


Figure 1. Consolidated Standards of Reporting Trials diagram. *A total of 53 patients were enrolled across all cohorts in the study; 38 patients were enrolled and assigned to cohorts 1 and 2. †In cohort 1, 15 of 17 patients discontinued niraparib treatment (10 adverse event, 3 disease progression, 1 physician decision, 1 protocol noncompliance) and 17 of 17 patients discontinued pembrolizumab treatment (5 disease progression, 4 adverse event, 4 other reason, 1 physician decision, 1 protocol noncompliance, 1 patient withdrawal of consent, 1 died). In cohort 2, 21 of 21 patients discontinued niraparib treatment (7 adverse event, 6 disease progression, 4 died, 2 physician decision, 1 protocol noncompliance, 1 patient withdrawal of consent), and 21 of 21 discontinued pembrolizumab treatment (9 disease progression, 4 adverse event, 3 died, 2 physician decision, 2 patient withdrawal of consent, 1 other reason). ‡mITT (efficacy-evaluable) population included all patients who received any study drug and did not withdraw consent before having ≥ 1 post-baseline tumor assessment. §Response-evaluable patients were those who received any study drug, did not withdraw consent, and had ≥ 1 post-baseline tumor assessment. ¶PK population included patients who received niraparib and had sufficient evaluable samples to determine PK parameters. mITT, indicates modified intent-to-treat; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death receptor ligand 1; PK, pharmacokinetics; TPS, tumor proportion score.

Efficacy

At the time of data analysis, 9 patients in cohort 1 and 17 patients in cohort 2 had discontinued the study (Fig. 1). A total of 2 patients were still receiving niraparib (cohort 1, $n = 2$); no patient in either cohort remained on pembrolizumab treatment. The median treatment duration for any study drug was 8.5 months (range, 1-29 months) for cohort 1 and 3.4 months (range, 1-17 months) for cohort 2.

In cohort 1, the confirmed ORR was 56.3% (95% CI, 29.9%-80.2%) with responses in 9 of 16 patients (CR, $n = 2$; PR, $n = 7$) (Fig. 2A). In cohort 2, the confirmed ORR was 20.0% (95% CI, 5.7%-43.7%); 4 of 20 patients had a PR and 4 patients had disease progression (Fig. 2B). The DCR (response \geq stable disease) was 87.5% (95% CI, 61.7%-98.4%) and 70.0% (95% CI, 45.7%-88.1%) in cohorts 1 and 2, respectively. The median DoR

was 19.7 months (95% CI, 4.2 months to not estimable [NE]) in cohort 1 and 9.4 months (95% CI, 4.2 months to NE) in cohort 2.

The median best percent decrease in target tumor lesion dimensions from baseline was 55.9% (range, 8%-100% decrease) in cohort 1 (Fig. 3A) and 9.4% (range, 24.1% increase to 78.4% decrease) in cohort 2 (Fig. 3B).

In cohorts 1 and 2, the median PFS was 8.4 months (95% CI, 3.9-22.1 months) and 4.2 months (95% CI, 2.0-6.2 months), respectively. At the time of data analysis, median OS for cohort 1 had not been reached (NE; 95% CI, 6.0 months to NE). In cohort 2, median OS was 7.7 months (95% CI, 4.0-12.5 months).

Safety

All patients in the safety populations for cohorts 1 ($n = 17$) and 2 ($n = 21$) experienced ≥ 1 any-grade

TABLE 1. Patient Demographics and Baseline Disease Characteristics

Parameter	Cohort 1, PD-L1, TPS \geq 50% (Niraparib + Pembrolizumab) (N = 17)	Cohort 2, PD-L1, TPS 1%-49% (Niraparib + Pembrolizumab) (N = 21)
Age, median (range), years	72.0 (50-81)	72.0 (53-91)
Sex, n (%)		
Female	6 (35.3)	12 (57.1)
Race, n (%)		
White	14 (82.4)	19 (90.5)
Black or African American	1 (5.9)	0
Asian	0	1 (4.8)
American Indian or Alaska Native	0	0
Other	2 (11.8)	1 (4.8)
ECOG PS, n (%)		
0	5 (29.4)	6 (28.6)
1	10 (58.8)	15 (71.4)
2	2 (11.8) ^a	0
Disease stage at randomization, n (%)		
Stage 3B	1 (5.9)	0
Stage 4	16 (94.1)	21 (100)
Histology at diagnosis, n (%)		
Adenocarcinoma	11 (64.7)	14 (66.7)
Squamous cell carcinoma	5 (29.4)	5 (23.8)
Other (not otherwise specified)	1 (5.9)	2 (9.5)
Unknown	0	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death receptor ligand 1; TPS, tumor proportion score.

^aTwo patients had ECOG PS 1 at screening and worsened to ECOG PS 2 on cycle 1 day 1, which was documented as the baseline ECOG PS. Inclusion criteria were verified on the basis of screening ECOG PS, and patients were deemed eligible.

TEAE (Table 2). The most frequently reported any-grade treatment-related TEAEs in cohorts 1 and 2 were fatigue (41.2% and 33.3%, respectively), nausea (35.3% and 42.9%, respectively), and decreased appetite (35.3% and 38.1%, respectively). Occurrence of any-grade treatment-related thrombocytopenia was low: 1 patient (5.9%) had niraparib-related and pembrolizumab-related thrombocytopenia, and 2 patients (11.8%) had niraparib-related platelet count decrease in cohort 1. In cohort 2, 5 patients (23.8%) had niraparib-related platelet count decrease, and 2 patients (9.5%) had pembrolizumab-related platelet count decrease.

A total of 15 (88.2%) and 18 (85.7%) patients had \geq 1 grade \geq 3 TEAE in cohorts 1 and 2, respectively (Table 3). Eleven (64.7%) and 13 (61.9%) patients in cohorts 1 and 2, respectively, experienced \geq 1 grade \geq 3 treatment-related TEAE, the most common of which were anemia (cohort 1, 23.5%; cohort 2, 14.3%) and platelet count decrease (cohort 1, 5.9%; cohort 2, 14.3%). Serious treatment-related TEAEs occurred in 6 patients (35.3%) in cohort 1 (including anemia, pneumonia, facial paralysis, hemoptysis, encephalopathy, and dyspnea) and 5 patients (23.8%) in cohort 2 (pneumonia, respiratory failure, diarrhea, atrial fibrillation, and pneumonitis). Of these 6 patients, only 1 serious treatment-related TEAE of encephalopathy resulted in death (cohort 1) and was deemed possibly related to

pembrolizumab by the investigator and study sponsor. The patient received 8 cycles of study treatment before the event occurred. Four patients (19.0%) in cohort 2 had TEAEs that led to death (cardiac arrest, intestinal obstruction, sepsis, and dyspnea [n = 1 each]); all were deemed unlikely to be related to either study treatment by investigators or the study sponsor. These patients in cohort 2 received anywhere from 2 to 6 cycles of treatment before the events occurred.

In cohorts 1 and 2, TEAEs led to niraparib dose interruptions in 11 (64.7%) and 10 (47.6%) patients and pembrolizumab dose interruptions in 5 (29.4%) and 7 (33.3%) patients, respectively. TEAEs led to niraparib dose reductions in 5 (29.4%) and 7 (33.3%) patients in cohorts 1 and 2, respectively. Niraparib was discontinued due to TEAEs in 10 (58.8%) and 8 (38.1%) patients, and pembrolizumab was discontinued due to TEAEs in 4 (23.5%) and 5 (23.8%) patients in cohorts 1 and 2, respectively.

Pharmacokinetics

Supporting Table 1 shows PK data for niraparib (200 mg) in both cohorts. The mean (\pm SD) niraparib plasma concentration at 4 hours after the first dose of niraparib (200 mg) was 335 (\pm 233) and 345 (\pm 188) ng/mL for cohorts 1 and 2, respectively. The accumulation ratio following 21 days of repeated daily dosing was 2- to 3-fold.

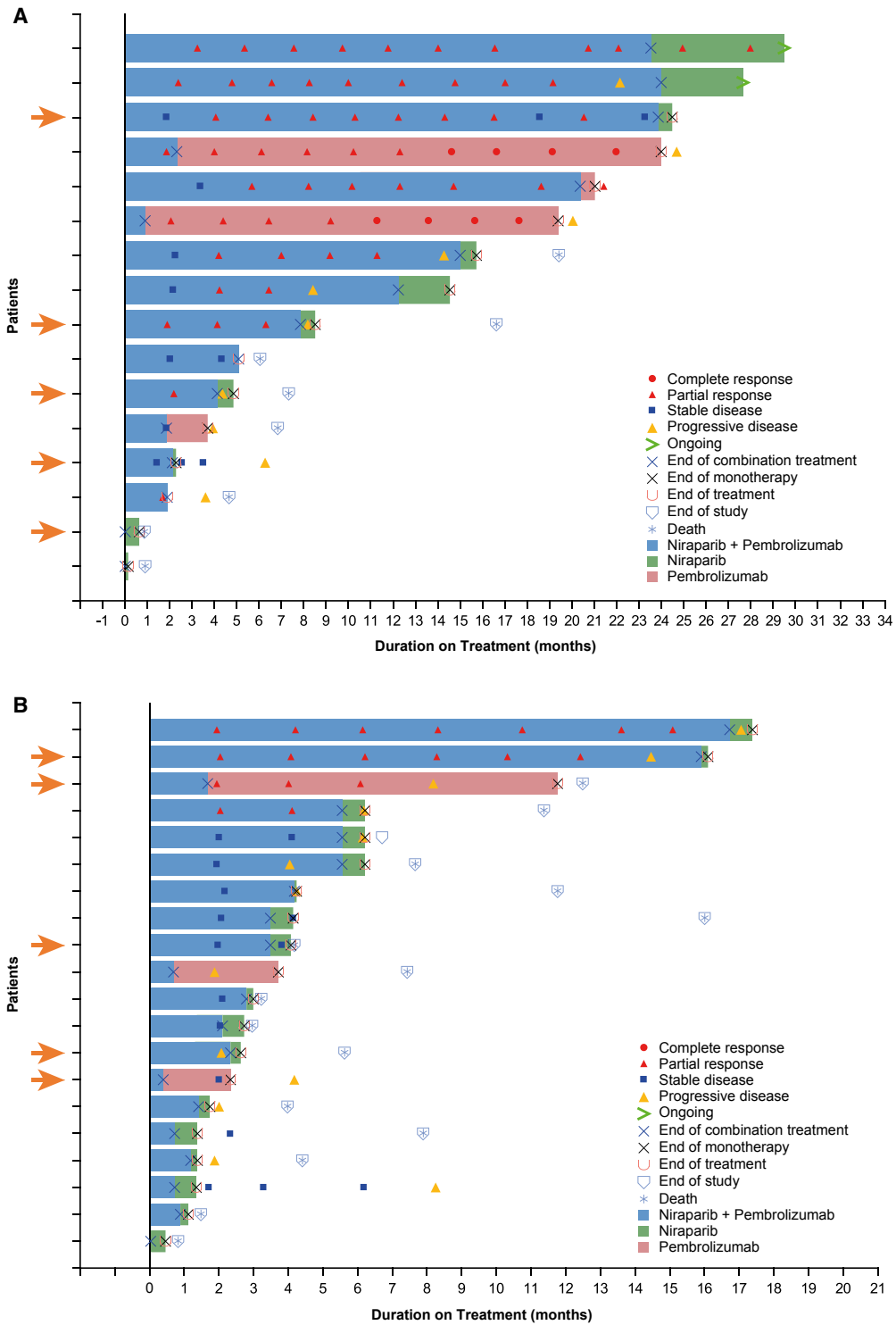


Figure 2. Tumor response in patients treated with niraparib plus pembrolizumab with (A) PD-L1 TPS $\geq 50\%$ (cohort 1) and (B) PD-L1 TPS 1% to 49% (cohort 2). Cohort 1 enrolled 17 patients; 1 patient withdrew consent before the first dose (mITT n = 16). Cohort 2 enrolled 21 patients; 1 patient withdrew consent before the first dose (mITT n = 20). Orange arrows indicate patients with squamous cell carcinoma. mITT, indicates modified intent-to-treat; PD-L1, programmed cell death receptor ligand 1.

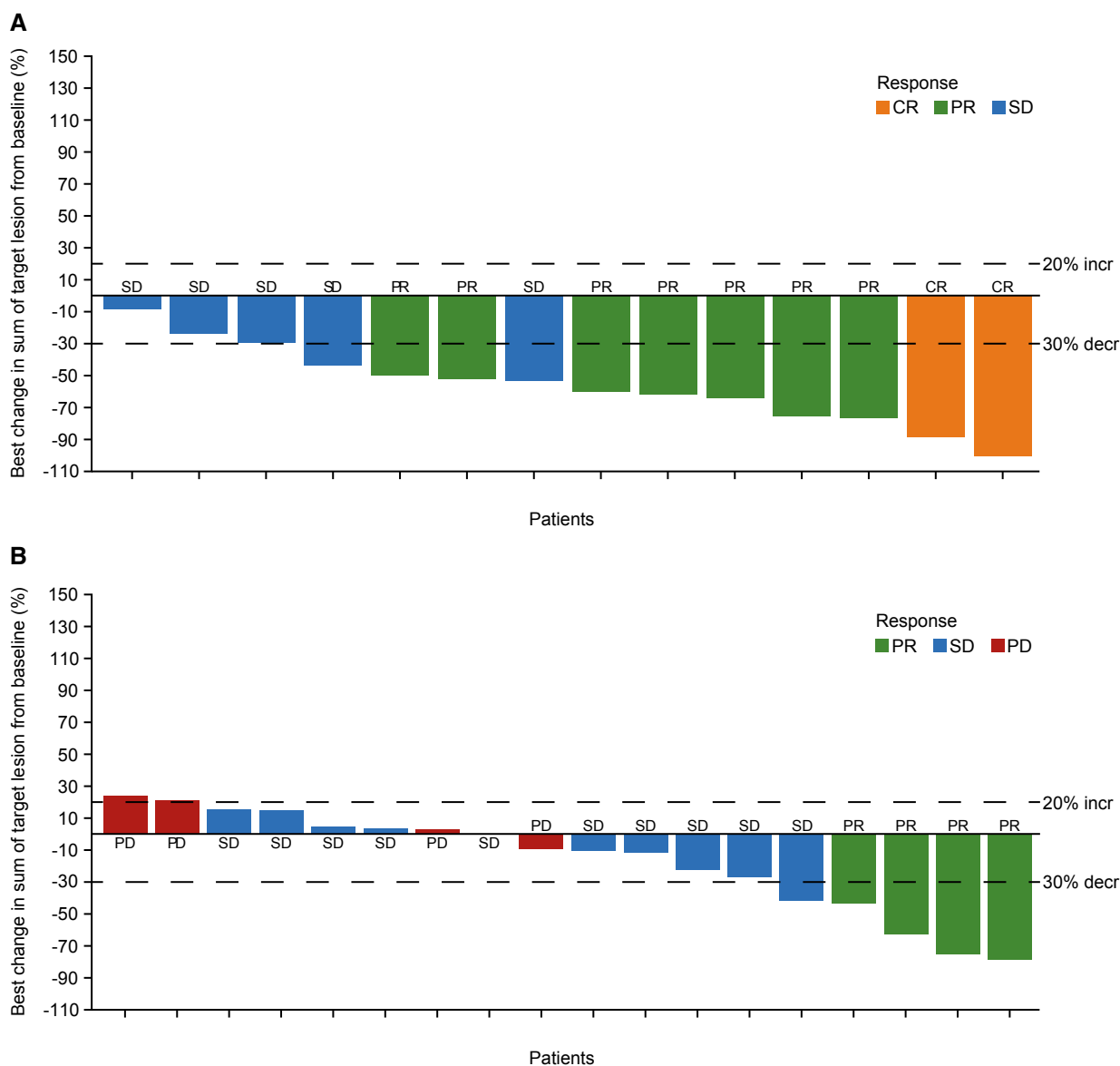


Figure 3. Best percent change in target tumor lesion in patients treated with niraparib plus pembrolizumab with (A) PD-L1 TPS $\geq 50\%$ (cohort 1) and (B) PD-L1 TPS 1% to 49% (cohort 2). Patients who withdrew consent or died before having at least 1 post-baseline assessment were not included. Confirmed best overall response was determined based on change in sum of target lesion dimensions and the appearance of new lesions based on RECIST v1.1. 2 patients died in cohort 1 and 2 patients in cohort 2 before post-baseline tumor assessment scan. PD-L1 indicates programmed cell death receptor ligand 1.

DISCUSSION

The primary strength of this study is that it represents one of the first investigations of a PARP inhibitor with a PD-1 inhibitor for the first-line treatment of NSCLC. Niraparib in combination with pembrolizumab showed clinical activity in patients with advanced or metastatic NSCLC whose tumors had PD-L1 TPS $\geq 50\%$, among whom 56.3% of patients responded to the combination treatment. The duration of response was greater than

1 year for some patients in both cohorts 1 and 2, with a median DoR of 19.7 and 9.4 months, respectively.

Pembrolizumab is the current standard-of-care first-line treatment for patients with advanced NSCLC and PD-L1 TPS $\geq 50\%$. The ORR with pembrolizumab monotherapy was 44.8% in the KEYNOTE-024 primary analysis of patients with PD-L1 TPS $\geq 50\%$.²⁴ Comparisons of the results from JASPER, in which the number of patients was very small, with large KEYNOTE

TABLE 2. Any Grade TEAEs Occurring in $\geq 20\%$ of Patients in Either Cohort 1 or 2

Preferred Term	Cohort 1, PD-L1, TPS $\geq 50\%$ (Niraparib + Pembrolizumab) (N = 17), No. (%)	Cohort 2, PD-L1, TPS 1%-49% (Niraparib + Pembrolizumab) (N = 21), No. (%)
Any TEAE	17 (100)	21 (100)
Fatigue	8 (47.1)	9 (42.9)
Nausea	7 (41.2)	12 (57.1)
Decreased appetite	7 (41.2)	11 (52.4)
Constipation	7 (41.2)	10 (47.6)
Cough	7 (41.2)	3 (14.3)
Anemia	5 (29.4)	11 (52.4)
Pneumonia	5 (29.4)	3 (14.3)
Dyspnea	4 (23.5)	10 (47.6)
Diarrhea	4 (23.5)	4 (19.0)
Insomnia	4 (23.5)	4 (19.0)
Upper respiratory tract infection	4 (23.5)	3 (14.3)
Anxiety	4 (23.5)	2 (9.5)
Vomiting	3 (17.6)	5 (23.8)
Peripheral edema	2 (11.8)	5 (23.8)
Platelet count decreased	2 (11.8)	5 (23.8)
Stomatitis	1 (5.9)	5 (23.8)
Any treatment-related TEAE	15 (88.2)	18 (85.7)
Fatigue	7 (41.2)	7 (33.3)
Nausea	6 (35.3)	9 (42.9)
Decreased appetite	6 (35.3)	8 (38.1)
Anemia	4 (23.5)	7 (33.3)
Constipation	4 (23.5)	2 (9.5)
Platelet count decreased	2 (11.8)	5 (23.8)
Any niraparib-related TEAE	15 (88.2)	16 (76.2)
Any pembrolizumab-related TEAE	14 (82.4)	15 (71.4)

Abbreviations: PD-L1, programmed cell death receptor ligand 1; TEAE, treatment-emergent adverse event; TPS, tumor proportion score. TEAEs are listed in descending order of incidence in cohort 1.

studies, should be made with caution. Nevertheless, these preliminary data may suggest a greater percentage of patients with PD-L1 TPS $\geq 50\%$ respond to niraparib plus pembrolizumab than pembrolizumab alone in the first-line setting. For patients with PD-L1 TPS 1%-49%, there appeared to be a similar or diminished response in cohort 2 (ORR, 20%) compared with pembrolizumab monotherapy (ORR, 27%).⁷ However, these results are not directly comparable; KEYNOTE-042 assessed pembrolizumab in patients with PD-L1 TPS $\geq 1\%$, which included 47% of patients who had TPS $\geq 50\%$ and had a higher ORR (39%).⁷ Therefore, it is possible that a greater proportion of patients with high PD-L1 tumor expression respond to niraparib plus pembrolizumab, consistent with higher response rates with pembrolizumab monotherapy in patients with high PD-L1 expression versus lower PD-L1 levels.^{7,24} The JASPER study was not powered to formally compare efficacy between cohorts 1 and 2.

The TEAEs observed with niraparib plus pembrolizumab were consistent with the safety profiles of niraparib and pembrolizumab alone as monotherapy seen in previous studies.^{7,25-27} Notably, thrombocytopenia was reported in few patients in this study (platelet count

decreased in 11.8% of patients in cohort 1 and in 23.8% of patients in cohort 2). The incidences of any-grade, grade ≥ 3 , and serious treatment-related TEAEs were similar to those observed with niraparib monotherapy and niraparib plus pembrolizumab combination therapy.^{12,21} However, the rate of discontinuations due to TEAEs was higher in JASPER than observed with niraparib or pembrolizumab as monotherapy.^{7,12,27} These results are not unexpected, based on the distinct, but somewhat overlapping, safety profiles of niraparib and pembrolizumab. Additional safety assessment of this combination in a larger number of patients is needed.

Further research is needed to elucidate additional predictive biomarkers which may assist in targeting treatments to patients most likely to derive benefit from the combination of PARP and PD-(L)1 inhibitor therapy.²⁸ For PARP inhibitors, HRd status has utility for predicting response in patients with solid tumors displaying DNA repair dysfunction; although there are limited data on the predictive capability of HRd in NSCLC, several trials of PARP inhibitors in combination therapy for NSCLC are underway.^{10,29,30} Weaknesses of this study include the small number of enrolled patients in each cohort (which limits the generalizability of findings to the broader

TABLE 3. Grade ≥ 3 TEAEs (in ≥ 3 Patients) and Serious TEAEs (in ≥ 2 Patients) Occurring in Either Cohort 1 or 2

Preferred Term	Cohort 1, PD-L1, TPS $\geq 50\%$ (Niraparib + Pembrolizumab), (N = 17), No. (%)	Cohort 2, PD-L1, TPS 1%-49% (Niraparib + Pembrolizumab), (N = 21), No. (%)
Any grade ≥ 3 TEAE	15 (88.2)	18 (85.7)
Fatigue	2 (11.8)	3 (14.3)
Pneumonia	5 (29.4)	3 (14.3)
Anemia	4 (23.5)	6 (28.6)
Dyspnea	1 (5.9)	5 (23.8)
Platelet count decreased	1 (5.9)	3 (14.3)
Neutrophil count decreased	0	3 (14.3)
Any grade ≥ 3 treatment-related TEAE	11 (64.7)	13 (61.9)
Anemia	4 (23.5)	3 (14.3)
Platelet count decreased	1 (5.9)	3 (14.3)
Any grade ≥ 3 niraparib-related TEAE	10 (58.8)	11 (52.4)
Anemia	4 (23.5)	3 (14.3)
Platelet count decreased	1 (5.9)	3 (14.3)
Any grade ≥ 3 pembrolizumab-related TEAE ^a	7 (41.2)	7 (33.3)
Any serious TEAE	11 (64.7)	14 (66.7)
Pneumonia	3	3
Anemia	2	1
Mental status changes	2	0
Pleural effusion	1 ^b	2
Dyspnea	1	4 ^b
Atrial fibrillation	0	2
Any serious treatment-related TEAE	6 (35.3)	5 (23.8)
Anemia	2	0
Atrial fibrillation	0	2
Any serious niraparib-related TEAE	5 (29.4)	3 (14.3)
Anemia	2	0
Atrial fibrillation	0	2
Any serious pembrolizumab-related TEAE ^b	5 (29.4)	4 (19.0)

Abbreviations: PD-L1, programmed cell death receptor ligand 1; TEAE, treatment-emergent adverse event; TPS, tumor proportion score.

TEAEs are listed in descending order of incidence in cohort 1.

^aNo individual grade ≥ 3 pembrolizumab-related TEAE occurred in >2 patients in either cohort.

^bOne patient had >1 event.

^cNo individual serious pembrolizumab-related TEAE occurred in >1 patient in either cohort.

NSCLC patient population), and the trial was nonrandomized and did not include a comparator arm.

In conclusion, niraparib in combination with the PD-1 inhibitor pembrolizumab demonstrated clinical activity in patients with advanced or metastatic NSCLC. Despite the small number of patients in this study, these results suggest that niraparib plus pembrolizumab may be an active combination with no new safety signals and support further evaluation of this novel combination approach in advanced NSCLC. The combination of niraparib plus pembrolizumab is being studied as maintenance therapy in patients with advanced NSCLC who had stable disease or response to pembrolizumab plus platinum-based first-line induction chemotherapy in the ongoing phase 3 ZEAL-1L study (NCT04475939).

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AUTHOR CONTRIBUTIONS

Suresh S. Ramalingam: Conceptualization, investigation, methodology, resources, writing—original draft, writing—review and editing. **Eddie Thara:** Investigation, resources, writing—original draft, writing—review and editing. **Mark M. Awad:** Investigation, resources, writing—original draft, writing—review and editing. **Basir Haque:** Investigation, resources, writing—original draft, writing—review and editing. **Thomas E. Stinchcombe:** Investigation, resources, writing—original draft, writing—review and editing. **Grace K. Dy:** Investigation, resources, writing—original draft, writing—review and editing. **David R. Spigel:** Investigation, resources, writing—original draft, writing—review and editing. **Afshin Dowlati:** Conceptualization, investigation, methodology, resources, writing—original draft, writing—review and editing. **Sharon Lu:** Data curation, formal analysis, resources, validation, writing—original draft, writing—review and editing. **Nithya Iyer Singh:** Data curation, formal analysis, resources, writing—original draft, writing—review and editing. **Iryna Teslenko:** Data curation, formal analysis, resources, writing—original draft, writing—review and editing. **Yongqiang Tang:** Conceptualization, data curation, formal analysis, methodology, resources, validation, writing—original draft, writing—review and editing. **Nicholas Iannotti:** Investigation, data curation, formal analysis, resources, writing—original draft, writing—review and editing.

DATA AVAILABILITY

GlaxoSmithKline makes available anonymized individual participant data and associated documents from interventional clinical studies that evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com.

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