Olaparib, Pembrolizumab, and Carboplatin as First-Line Treatment of Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: A Phase II Trial

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ABSTRACT

PURPOSE Impaired homologous recombination–mediated DNA repair is common in head and neck squamous cell carcinoma (HNSCC) and in preclinical models and sensitizes HNSCC to poly (ADP-ribose) polymerase (PARP) inhibitors and platinum therapy. PARP inhibitors and anti–PD-1 antibodies have synergistic antitumor activity. The primary hypothesis of this phase II trial was that olaparib, a PARP inhibitor, given with pembrolizumab and carboplatin as first-line treatment for biomarker-unselected recurrent or metastatic (RM)-HNSCC, would result in a higher objective response rate (ORR) than that historically reported with fluorouracil, pembrolizumab, and platinum therapy.

METHODS Patients received up to six 21-day cycles of olaparib (200 mg twice daily orally on days 1-10), pembrolizumab, and carboplatin followed by 29 cycles of olaparib (300 mg twice a day on days 1-21) and pembrolizumab. The primary end point was independent radiologist-assessed confirmed objective response per RECIST v1.1. A Simon optimal two-stage design tested the null (H_0: ORR ≤36%) versus the alternative hypothesis (ORR ≥62%) at a type I error rate of 10% and a power of 90%. H_0 would be rejected if ≥14 responses occurred among 29 patients. Secondary end points included duration of response (DoR), progression-free survival (PFS), and overall survival (OS).

RESULTS Between July 08, 2021, and October 11, 2023, 30 patients were enrolled. Among the 29 evaluable patients, the ORR was 51.7% (90% CI, 35.2 to 68.0; v H_0, one-sided $P = .04$). The median DoR was 14.1 months (IQR, 6.8 to 21.2), and the median PFS and OS were 7.8 (95% CI, 4.1 to 15.4) and 24.5 months (95% CI, 8.8 to 25.3), respectively. The most common study drug-related grade 3 to 4 adverse events included neutropenia (50%) and anemia (23%). Febrile neutropenia and treatment-related deaths did not occur.

CONCLUSION Olaparib, pembrolizumab, and carboplatin given as first-line treatment of RM-HNSCC resulted in a higher ORR than that historically reported with fluorouracil, pembrolizumab, and platinum therapy.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Over a million new cases of head and neck squamous cell carcinoma (HNSCC) occur each year. One half will develop recurrent or metastatic (RM) disease after curatively intended therapy.[1,2] The KEYNOTE-048 trial showed that pembrolizumab and chemotherapy improved overall survival (OS) of patients with previously untreated RM-HNSCC compared with cetuximab and chemotherapy.[3] With pembrolizumab and chemotherapy, the objective response rate (ORR) was 36%, the median duration of response (DoR) was 6.7 months, the median progression-free survival (PFS) was 4.9 months, and the median OS was 13.0 months. The best outcomes occurred in the tumor PD-L1 combined positive score (CPS) ≥20 subset.

In the KEYNOTE-048 trial, the chemotherapy given with pembrolizumab included platinum therapy and fluorouracil. Pembrolizumab and platinum are critical components of this regimen; however, the independent contribution of fluorouracil is unclear. In the preimmunotherapy era, fluorouracil added to platinum improved ORR, but not OS, of patients with previously untreated RM-HNSCC.[4] Antimetabolites like fluorouracil are immunosuppressive and thereby may impair the efficacy of pembrolizumab.[5] By contrast, platinum has a limited immunosuppressive effect

CONTEXT

Key Objective

Does olaparib, a selective poly (ADP-ribose) polymerase (PARP) inhibitor, given with pembrolizumab and carboplatin as first-line treatment for recurrent or metastatic (RM) head and neck squamous cell carcinoma result in a higher objective response rate (ORR) than that historically reported with fluorouracil, pembrolizumab, and platinum therapy (H_0 ORR 36%)?

Knowledge Generated

The confirmed ORR with olaparib, pembrolizumab, and carboplatin was 51.7% (90% CI, 35.2 to 68.0; *v* H_0, one-sided $P = .04$). The median duration of response was 14.1 months (IQR, 6.8-21.2), and the median progression-free survival (PFS) and overall survival (OS) were 7.8 (95% CI, 4.1 to 15.4) and 24.5 months (95% CI, 8.8 to 25.3), respectively.

Relevance *(F. Rubagumya)*

RM head and neck squamous-cell carcinoma (HNSCC) carries a poor prognosis, and current first-line regimens yield ORR of approximately 36%. By combining olaparib, a PARP inhibitor that impairs DNA repair, with pembrolizumab and carboplatin, this study demonstrates a significant improvement in tumor response (ORR, 51.7% *v* historic 36%, one-sided $P = .04$), with durable responses (median duration 14.1 months) and encouraging PFS (7.8 months) and OS (24.5 months) outcomes. These findings support further investigation of this triplet regimen as a potential new standard first-line treatment for RM-HNSCC.*

Plain Language Summary *(F. Rubagumya)*

Head and neck cancers often return after initial treatment or spread to other parts of the body, and existing therapies help only a minority of patients. In this Phase II trial, authors tested a three-drug combination, olaparib (which blocks cancer cells' ability to repair their DNA), pembrolizumab (an immunotherapy that helps the immune system attack tumors), and carboplatin (a chemotherapy drug), as the first treatment for patients whose head and neck cancer had come back or spread. Over half of the patients (52 out of 100) experienced a clear shrinkage of their tumors, compared to about 36 out of 100 with standard therapy. When tumors did respond, they stayed under control for more than a year on average. Patients lived without disease progression for about 8 months and overall lived for just over 2 years. These results suggest that adding olaparib to immunotherapy and chemotherapy could offer better benefits for people facing advanced head and neck cancer.†

*Relevance section written by *JCO Oncology Advances* Associate Editor Fidel Rubagumya, MD, MMed, MPH.
†Plain Language Summary written by *JCO Oncology Advances* Associate Editor Fidel Rubagumya, MD, MMed, MPH.

and induces tumor neoantigen expression.[5,6] Alternatives to fluorouracil are needed to increase the proportion of patients who experience durable benefit with pembrolizumab and platinum.

Impaired homologous recombination (HR)–mediated DNA repair is common in HNSCC and occurs by several mechanisms. HR gene alterations occur in up to 27% of HNSCCs and include mutations in *BRCA1* (6%), *BRCA2* (7%), *ATM* (1%-16%), and *ATR* (4%-10%) and inactivation of the Fanconi anemia/BRCA1 pathway via promoter methylation of *FANCF* (15%).[7-11] These genomic alterations result in a HR deficiency (HRD) phenotype that sensitizes HNSCC cells to poly (ADP-ribose) polymerase (PARP) inhibition.[12,13] Homozygous deletion of *PTEN* occurs in 12% and sensitizes cell lines and xenografts to PARP inhibitors.[14] Preclinical studies showed that PARP inhibitors sensitized HRD HNSCC to platinum.[15] Furthermore, p16 overexpression, present in all human papillomavirus (HPV)–positive and 11% HPV-negative HNSCCs, impaired HR-mediated DNA repair by decreased recruitment of RAD50 to chromatin and increased sensitivity to genotoxic stressors.[16,17] PARP inhibitors had synergistic antitumor activity when combined with anti–PD-1 antibodies.[18-21] These data pointed to PARP inhibition as a rational therapeutic strategy to partner with pembrolizumab and platinum to treat patients with RM-HNSCC.

Olaparib, a highly selective PARP inhibitor, was safely combined with pembrolizumab or carboplatin in patients with other cancers.[22,23] The primary aim of this single-arm, phase II trial was to determine the ORR of olaparib, pembrolizumab, and carboplatin given as first-line treatment for biomarker-unselected RM-HNSCC.

METHODS

Study Design and Participants

We performed a single-center, single-arm, phase II trial, approved by the Washington University (St Louis, MO)

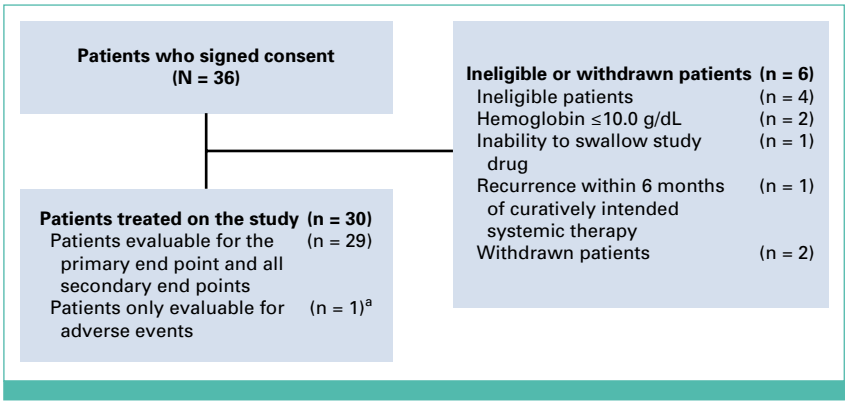

FIG 1. Trial profile. [a]This patient was removed from the trial during cycle 1 of therapy because of a change in diagnosis that made the patient ineligible for the trial.

Human Research Protection Office. All study participants provided written, signed, informed consent to participate. The trial was conducted in accordance with Good Clinical Practice guidelines. The Washington University Quality Assurance and Scientific Monitoring committee performed independent data monitoring. The trial used Simon optimal two-stage design to assess ORR with olaparib, pembrolizumab, and carboplatin given as first-line treatment for RM-HNSCC. Null hypothesis was based on the historical ORR with fluorouracil, pembrolizumab, and platinum given as first-line treatment for RM-HNSCC.[3] The full protocol is given in the Appendix.

Eligible patients were 18 years or older with RM-HNSCC of the oral cavity, oropharynx, larynx, or hypopharynx. Patients had measurable disease per RECIST v1.1.[24] Biomarker selection was not used for inclusion. Other inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0-1 and adequate marrow and organ function.

Key exclusion criteria included RM disease within 6 months of curatively intended systemic therapy, previous PD-(L)1 therapy, previous systemic therapy for RM disease, immunosuppressive therapy, immunodeficiency disease, or inability to swallow pills.

Procedures

Before treatment, patients underwent physical examination, laboratory studies, and computed tomography (CT) scans. Patients were scheduled to receive six 21-day cycles of olaparib (200 mg tablet formulation twice a day, orally, days 1-10), pembrolizumab (200 mg intravenously [IV] once on day 1), and carboplatin (area-under-the-curve 5 IV once on day 1) followed by 29 cycles of olaparib (300 mg twice a day orally on days 1-21) and pembrolizumab. Criteria for dose modifications, and dose reduction levels, are provided in the protocol. Olaparib-related grade 3 or 4 adverse events (AEs) were managed with dose reductions, delays, or discontinuation. If study drug was held or discontinued, the other study drug(s) could be given. Treatment continued until completion of 35 cycles of therapy, disease progression, unacceptable toxicity, or other discontinuation criteria were met. After treatment discontinuation, patients were followed to monitor for AEs (for at least 30 days), disease status, subsequent anticancer treatment, and survival.

Physical examination and laboratory studies were performed on day 1 of each cycle. CT scans were performed after cycles 2, 4, and 6 and then every four cycles.

Tumor response was assessed by an independent radiologist using RECIST v1.1.[24] AEs were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events v5.0. The investigator assessed the relationship of AEs to study drugs.

PD-L1 CPS status was assessed by immunohistochemistry (IHC: DAKO 22C3 clone). p16 was assessed by IHC: strong (≥70%) and diffuse staining was scored as positive; otherwise, tumors were scored as negative. HPV was defined as HPV-positive (p16-positive oropharynx squamous cell carcinoma [SCC]) or HPV-negative (p16-negative oropharynx SCC and tumors of other primary sites independent of p16).

Archived tumor tissue was collected and subjected to tumor analysis by targeted next-generation DNA sequencing for assessment of alterations in HR genes and *PTEN* performed in a Clinical Laboratory Improvement Amendments–certified laboratory (Tempus xT, Chicago, IL).

Outcomes

The primary end point was ORR: the proportion of patients with a complete or partial best overall response. Secondary

TABLE 1. Baseline Patient and Tumor Characteristics

Characteristic	Outcome (N = 30 patients)
Age, years	
Median (IQR)	66 (61-70)
Sex,[a] No. (%)	
Male	24 (80)
Female	6 (20)
Race,[a] No. (%)	
White	27 (90)
Black or African American	3 (10)
Performance status,[a,b] No. (%)	
0	25 (83)
1	5 (17)
Smoking history,[a] No. (%)	
Yes	17 (57)
No	13 (43)
HPV status and primary site,[a] No. (%)	
HPV-positive (oropharynx)	12 (40)
HPV-negative	18 (60)
Oral cavity	10
Oropharynx	3[c]
Larynx	5
Site of recurrence or presentation,[a] No. (%)	
Recurrence	22 (73)
Local/regional	7
Distant	9
Both	6
Metastatic at diagnosis	5 (17)
Second primary HNSCC	3 (10)
PD-L1 CPS,[a] No. (%)	
≥1	27 (90)
≥20	17
1-19	10
0	2 (7)
Not known	1 (3)

Abbreviations: CPS, combined positive score; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.
[a]No. (%) of patients with characteristic.
[b]Eastern Cooperative Oncology Group.
[c]One patient with HPV-negative oropharynx cancer was removed from the trial during cycle 1 of therapy when a genome sequencing test result unexpectedly showed a *MYB-NFIB* chromosomal rearrangement that changed the diagnosis from poorly differentiated SCC to poorly differentiated adenoid cystic carcinoma (an ineligible diagnosis).

end points included DoR (first date of response until the date of progression or the last date of follow-up without progression), proportion of patients with (any grade, grade 1/2, and grade 3/4/5) AEs, PFS (time from study enrollment until the date of progression or death, whichever occurred first. Alive patients without progression were censored at the date of last follow-up), OS (time from the date of first study treatment to death. Alive patients were censored at the date of last follow-up), HR and *PTEN* gene status (altered [presence of an alteration in one or more HR genes or *PTEN*] or not altered), p16 expression (positive or negative), and PD-L1 CPS (0-19 and ≥20).

Statistical Analysis

The primary hypothesis was that olaparib, pembrolizumab, and carboplatin would result in a higher ORR than the historical ORR reported with fluorouracil, pembrolizumab, and platinum.[3] An ORR of 36% or lower was deemed unacceptable (null hypothesis), and an ORR of 62% or higher was of clinical interest (alternative hypothesis). Based on Simon's optimal two-stage design, 13 patients would be enrolled in the first stage, and if six or more objective responses were observed, an additional 16 patients would be enrolled. Five or fewer responses during the first stage would prompt early trial closure. Fourteen or more responses among 29 patients would be sufficient evidence that this regimen was worthy of further investigation. The regimen was not worthy of further investigation if 13 or fewer objective responses occurred. This design would detect the difference in ORRs between the alternative and null hypotheses, with a power of 90% at a one-sided 0.10 significance level. The ORR was estimated with 90% CIs and compared with the null hypothesis using a binomial distribution.

After enrollment of 13 patients, an assessment of dose delivery of olaparib was performed. The target was for 80% or more patients to receive the planned 10 days of olaparib per cycle during the first two cycles.[22] If this target was met, enrollment continued. If not, the study would be paused to determine next steps.

AEs were summarized by type and grade. DoR was summarized using median and IQR values. PFS and OS were estimated using the Kaplan-Meier method. The relationship between HR and/or *PTEN* gene status, PD-L1 CPS status, or HPV status with ORR was investigated by chi-square test and with PFS or OS by log-rank test.

Patients who received at least one dose of treatment were evaluable for response, AEs, DoR, PFS, and OS. Patients who received at least one dose of treatment and had not undergone a response assessment before withdrawal, removal, or death were considered to have progressive disease.

Statistical analysis was performed using SAS v9.4 (SAS Institute, Cary, NC) and R v4.3.3. This study is registered (ClinicalTrials.gov identifier: NCT04643379).

RESULTS

The trial profile is shown in Figure 1. Between July 8, 2021, and October 11, 2023, 30 patients were enrolled and received study drugs. Twenty-nine patients were evaluable for the primary and secondary end points. One patient was removed from the trial during cycle 1 when a genomic test

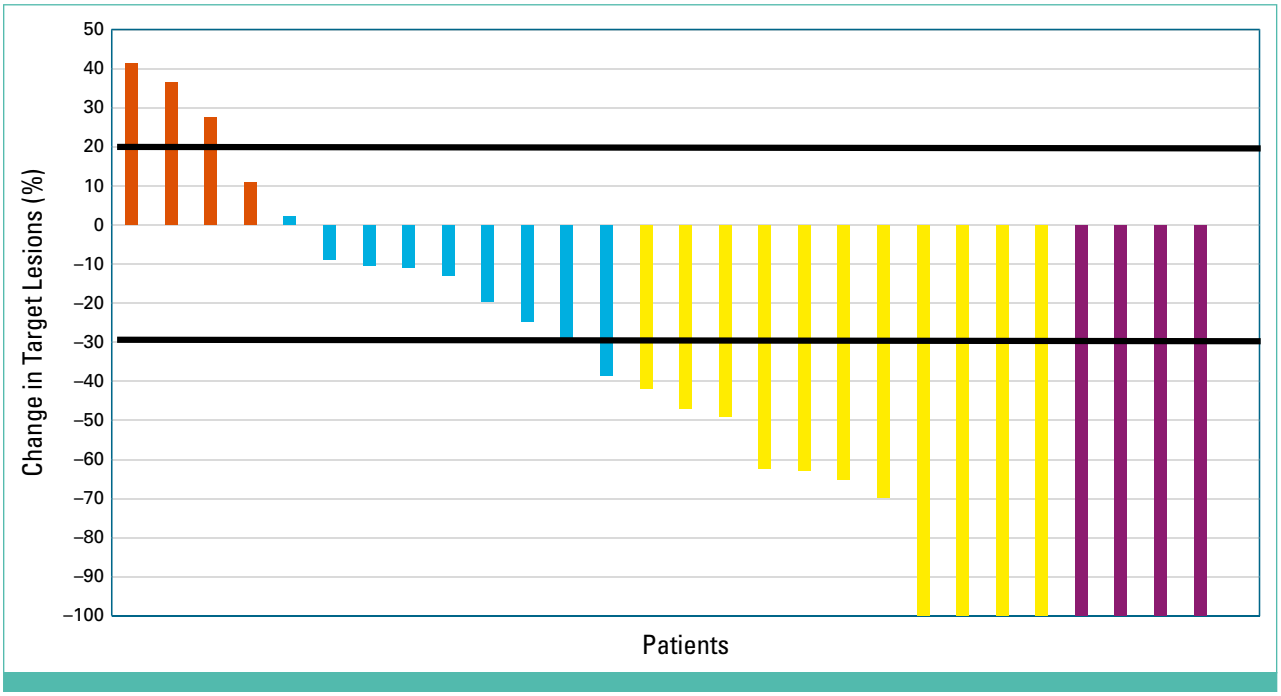

FIG 2. Waterfall plot showing the best response (percent change) in target lesions.

unexpectedly resulted in a change of diagnosis to adenoid cystic carcinoma. This patient was deemed nonevaluable for the primary end point and for all secondary end points except AEs and was replaced. The cutoff for data analysis presented here was October 29, 2024. The median follow-up was 14.7 months (IQR, 7.0-24.8).

Baseline patient and tumor characteristics for all 30 patients are shown in Table 1. Twenty-four (80%) patients were male, 27 (90%) were White, and 3 (10%) were Black or African American. HPV status was positive in 12 patients (40%) and negative in 18 (60%). PD-L1 status was CPS ≥1 in 27 patients (90%). Eleven patients (36.7%) had received previous platinum therapy as a component of a curative-intent regimen.

Confirmed tumor response occurred in 15 of 29 evaluable patients. The ORR was 51.7% (90% CI, 35.2 to 68.0 versus H_0 ORR 36%, one-sided $P = 0.04$). Best tumor response included complete response in four patients (13.8%), partial response in 11 (37.9%), stable in nine (31%), and progressive disease in five (17.2%). A waterfall plot displaying the best response (percent change) in target lesions is shown in Figure 2. The median DoR was 14.1 months (IQR, 6.8-21.2).

Tumor response occurred in 10 of 17 patients (58.8%) with PD-L1 CPS ≥20 and in five of 11 (45.5%) with PD-L1 CPS 0-19 disease. Tumor response occurred in seven of 12 patients (58.3%) with HPV-positive and in eight of 17 (47.1%) with HPV-negative disease. A post hoc analysis showed that tumor response occurred in nine of 20 patients (45%) with locoregional recurrence or second primary HNSCC with or without distant metastases and in six of nine patients (66.7%) with only distant metastases.

Among 29 evaluable patients, the median PFS was 7.8 months (95% CI, 4.1 to 15.4) and the median OS was 24.5 months (95% CI, 8.8 to 25.3; Fig 3). Survival analyses of subgroups based on the status of HPV, PD-L1 CPS, and HR and *PTEN* genes are shown in the Appendix (Figs A1-A3). Among 22 evaluable patients removed from the trial, subsequent lines of systemic treatment were administered to 16 patients and included one line in seven and two or more lines in 9.

At last follow-up, 12 of 29 evaluable patients were alive and 17 expired. Of the 12 living patients, four had disease control and continued with study therapy, two had disease control after completing study therapy and were in follow-up, one had disease control and discontinued study therapy (patient decision) but remained in follow-up, and five discontinued study therapy (because of disease progression) and were removed from the study. Of the 17 patients who expired, causes of death included disease progression in 15 and comorbidity in 2 (both had acute myocardial infarction [AMI], attributed to known underlying vascular disease and unrelated to study drugs). Further details of these two patients are provided in the Appendix.

AEs that occurred among the 30 evaluable patients are shown in Table 2. Grade 3 AEs of any cause occurred in 26 patients (86.7%), grade 4 in 6 (20%), and grade 5 in 2 (6.7%). Treatment-related deaths did not occur. Most of the grade 3 AEs were unrelated to the study drug(s). Five of the grade 4 AEs (3-neutropenia and 2-thrombocytopenia) were related to study drug(s). Febrile neutropenia and thrombocytopenia-related bleeding did not occur. The two grade 5 AEs (AMI) were attributed to comorbidity. The most common AEs of any grade and cause were anemia (86.6%), fatigue (83.3%),

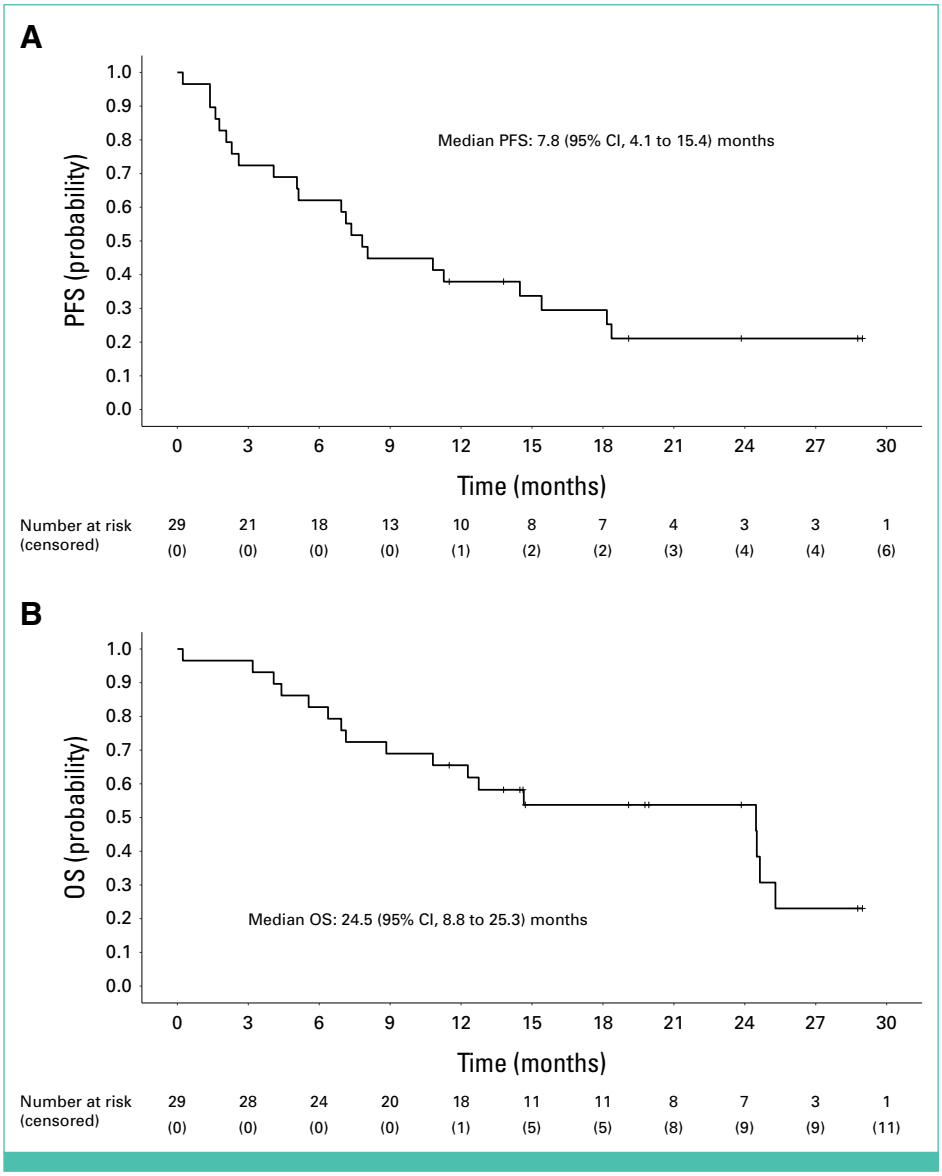

FIG 3. PFS and OS. OS, overall survival; PFS, progression-free survival.

lymphopenia (73.3%), thrombocytopenia (70%), neutropenia (66.7%), and hyponatremia (66.7%). Nonthyroid, immune-related AEs occurred in two patients (6.7%).

Olaparib dose delivery during cycles 1 and 2 was 100% (target: ≥80%) for all evaluable patients in the first stage of the trial. Overall, the median number of cycles administered to the 29 evaluable patients was 10 (IQR, 3-20). Across all cycles of therapy, eight (27.6%) of 29 patients received olaparib, pembrolizumab, and carboplatin without dose modification or hold, whereas 21 (72.4%) required dose modification or hold of olaparib (10), pembrolizumab (1), and/or carboplatin (17; Appendix Table A1).

Alterations in HR and *PTEN* genes occurred in six of 29 evaluable patients (20.7%). p16 status was positive in 13 of 28 evaluable patients (46.4%; unavailable in 1; Appendix Table A2). Tumor response was observed in five of six patients (83.3%) with and 10 of 23 patients (43.5%) without tumor HR and/or *PTEN* gene alterations. No significant association was observed between status of HR and/or *PTEN* genes, PD-L1 CPS, or HPV and ORR, PFS, or OS (Appendix Table A3).

DISCUSSION

In this phase II trial, the ORR with olaparib, pembrolizumab, and carboplatin given as first-line treatment for biomarker-unselected RM-HNSCC was significantly higher than the ORR reported with the prespecified historical control of fluorouracil, pembrolizumab, and platinum (51.7% [90% CI, 35.2 to 68.0] versus 36%, one-sided $P = .04$).[3] In the pre-immunotherapy era, the ORR with fluorouracil and platinum was higher than that with platinum alone.[4] If olaparib was an inactive drug, deletion of fluorouracil from our regimen would have been expected to result in a lower ORR than the historical control. Yet, we observed a higher ORR with our

TABLE 2. Summary of Adverse Events (N = 30 patients)

	Grade, No. (%)			
Adverse Event	1 + 2	3	4	5
Abdominal pain	3 (10)	0	0	0
Acute kidney injury	0	1[a] (3)	0	0
Alanine aminotransferase increased	4 (13)	3[a] (10)	1[a] (3)	0
Alkaline phosphatase increased	9 (30)	0	0	0
Anemia	19 (63)	7[b] (23)	0	0
Anorexia	8 (27)	5[a] (17)	0	0
Anxiety	3 (10)	0	0	0
Aspartate aminotransferase increased	5 (17)	2[a] (7)	1[a] (3)	0
Atrial flutter	0	1[a] (3)	0	0
Back pain	2 (7)	1[a] (3)	0	0
Blood bilirubin increased	4 (13)	0	0	0
Bone pain	3 (10)	0	0	0
Chills	3 (10)	0	0	0
Confusion	1 (3)	1[a] (3)	0	0
Constipation	11 (37)	0	0	0
Cough	5 (17)	0	0	0
Creatinine increased	10 (33)	0	0	0
Diarrhea	8 (27)	1[a] (3)	0	0
Dizziness	9 (30)	0	0	0
Dry skin	9 (30)	0	0	0
Dysarthria	4 (13)	0	0	0
Dysgeusia	4 (13)	0	0	0
Dysphagia	9 (30)	3[a] (10)	0	0
Dyspnea	8 (27)	2[a] (7)	0	0
Edema limbs	8 (27)	0	0	0
Esophageal fistula	0	1[a] (3)	0	0
Fatigue	22 (73)	3[b] (10)	0	0
Fever	3 (10)	0	0	0
Headache	3 (10)	0	0	0
Hypercalcemia	8 (27)	0	0	0
Hyperkalemia	8 (27)	0	0	0
Hypertension	5 (17)	1[a] (3)	0	0
Hypoalbuminemia	8 (27)	0	0	0
Hypocalcemia	6 (20)	0	0	0
Hypoglycemia	5 (17)	0	0	0
Hypokalemia	4 (13)	2[a] (7)	0	0
Hyponatremia	20 (67)	0	0	0
Hypophosphatemia	3 (10)	0	0	0
Hypotension	4 (13)	1[a] (3)	0	0
Hypothyroidism	5 (17)	0	0	0
Hypoxia	0	1[a] (3)	0	0
Lymphedema	1 (3)	1[a] (3)	0	0
Lymphocyte count decreased	6 (20)	16[a] (53)	0	0
Mucosal infection	0	1[a] (3)	0	0
Mucositis oral	6 (20)	1[a] (3)	0	0
Myocardial infarction	0	0	0	2[a] (7)
Nasal congestion	5 (17)	0	0	0
Nausea	13 (43)	1[b] (3)	0	0
Neck pain	4 (13)	0	0	0
Neutrophil count decreased	5 (17)	12[b] (40)	3[b] (10)	0
Oral pain	1 (3)	1[a] (3)	0	0
Other—mandibular infection	1 (3)	1[a] (3)	0	0
Peripheral sensory neuropathy	3 (10)	0	0	0
Platelet count decreased	16 (53)	3[b] (10)	2[b] (7)	0
Sinus bradycardia	3 (10)	0	0	0
Sinus tachycardia	4 (13)	0	0	0
Soft tissue infection	1 (3)	1[a] (3)	0	0
Stoma site infection	0	1[a] (3)	0	0
Syncope	0	2[a] (7)	0	0
Tooth infection	1 (3)	1[a] (3)	0	0
Upper respiratory infection	3 (10)	0	0	0
Urinary tract infection	1 (3)	1[a] (3)	0	0
Vomiting	9 (30)	0	0	0
Weight gain	4 (13)	0	0	0
Weight loss	4 (13)	3[a] (10)	0	0

(continued in next column)

TABLE 2. Summary of Adverse Events (N = 30 patients) (continued)

NOTE. Grade 1 to 2 AEs with an incidence of ≥10% are shown. All grade 3 to 5 events are shown.
Abbreviation: AEs, adverse events.
Attribution to olaparib:
[a]Unrelated.
[b]Related.

regimen compared with the historical control. A previous report of patients with RM-HNSCC showed that the ORR with carboplatin and fluorouracil was lower than that with cisplatin and fluorouracil although the carboplatin-based regimen was better tolerated.[25] All patients in our trial received carboplatin, whereas 43% in KEYNOTE-048 received cisplatin and 57% received carboplatin. A higher ORR might have been observed in our trial with cisplatin versus carboplatin. In KEYNOTE-048, the ORR with pembrolizumab and chemotherapy was higher in patients with PD-L1 CPS ≥20 disease than the total population.[3] The higher ORR observed in our trial may in part be due to the higher proportion of patients with PD-L1 CPS ≥20 disease (58.6% *v* 45% in KEYNOTE-048).[3] However, the ORR with olaparib, pembrolizumab, and carboplatin in PD-L1 CPS ≥20 and 1-19 disease was higher than that historically reported with pembrolizumab and chemotherapy (CPS ≥20: 58.8% *v* 43% and CPS 1-19: 50.0% *v* 33%, respectively).[3,26]

Increasing the durability of response is a key objective when combining therapeutic agents with pembrolizumab and chemotherapy. In our trial, the median DoR with olaparib, pembrolizumab, and carboplatin was 14.1 months (IQR: 6.8-21.2). Among the total population in KEYNOTE-048 treated with pembrolizumab, fluorouracil, and platinum, the median DoR was 6.7 months.[3] Cross-trial comparisons are limited by many factors but may yield valuable insights

worthy of further pursuit. The 2.1-fold longer median DoR with olaparib, pembrolizumab, and carboplatin compared with pembrolizumab, fluorouracil, and platinum may be due to the incorporation of olaparib into and/or deletion of fluorouracil from the pembrolizumab/platinum backbone.

First-line treatment of RM-HNSCC with olaparib, pembrolizumab, and carboplatin resulted in a median PFS of 7.8 months (95% CI, 4.1 to 15.4) and a median OS of 24.5 months (95% CI, 8.8-25.3). Among the total population treated with pembrolizumab, fluorouracil, and platinum in KEYNOTE-048, the median PFS was 4.9 months and the median OS was 13.0 months.[3] The proportion of patients with HPV-positive disease and those who received subsequent lines of systemic therapy were higher in our trial than in KEYNOTE-48 (40% *v* 21% and 55.2% *v* 41%, respectively). These differences may, in part, explain the more favorable PFS and OS seen in our trial.

Olaparib, pembrolizumab, and carboplatin were safe to administer. The types and frequencies of AEs observed were those expected for each drug and for patients with RM-HNSCC. Treatment-related deaths did not occur. Hematologic AEs were common but manageable with dose delays or modifications. Although grade 3 or greater neutropenia occurred more frequently with this regimen than with pembrolizumab, fluorouracil, and platinum (50% *v* 18%), no patients developed febrile neutropenia.[3] The proportion of patients who discontinued any or all study drugs because of AEs was lower in our trial than with pembrolizumab, fluorouracil, and platinum (any: 10% *v* 33% and all: 0% *v* 8%).[3] However, most patients (72.4%) in our trial did require dose modification or hold of study drug(s) because of AEs, usually during cycles 3-6 of therapy. Two patients expired because of AMI, which was attributed to comorbidity. A meta-analysis found that PARP inhibitors did not increase the risk of high-grade cardiac events such as fatal AMI.[27] Randomized trials will be required to directly compare the AE profile and tolerance of the olaparib, pembrolizumab, and carboplatin and the pembrolizumab, fluorouracil, and platinum regimens.[3]

The proportion of patients with tumor HR gene alterations in our trial was similar to that reported in the literature.[7-11] *PTEN* alterations were less common, and p16 expression was more common.[3,14] Status of HR and *PTEN* genes, PD-L1 CPS, and HPV did not significantly correlate with activity end points. However, this analysis was limited by the small number of patients in each subset.

Other investigations of PARP inhibitors have been or are being conducted in HNSCC. Ophelia, a window-of-opportunity randomized trial of patients with newly diagnosed, biomarker-unselected locally advanced HNSCC, showed that olaparib given alone or with durvalumab or cisplatin before surgery decreased Ki67 and increased PD-L1 levels, but upregulated M2 macrophages.[28] Olaparib has been given as a potential radiosensitizer with definitive radiation therapy alone or with cetuximab in patients with locally advanced HNSCC.[29] The combination of niraparib and dostarlimab is under evaluation in patients with platinum therapy– and/or immunotherapy-pretreated RM-HNSCC (ClinicalTrials.gov identifier: NCT04313504).

Several limitations were observed in this trial. The trial was conducted at a single center and had a small sample size that resulted in activity results with wide CIs. The primary hypothesis used a one-sided, type I (alpha) error rate of 10%. A concurrent control group treated with fluorouracil, pembrolizumab, and platinum was not part of the study design. Most participating patients were White, and all were American, so the results may or may not apply to other races or geographic zones. However, the proportion of patients who were Black or African American (10%) approximates that of the large metropolitan community where the trial was conducted. Patients were excluded from the trial if they could not swallow medication. The proportion of patients with PD-L1 CPS ≥20 and/or HPV-positive disease were different from the prespecified historical control.[3] The proportion of patients (36.7%) who had received previous platinum therapy as a component of a curative-intent regimen was somewhat low, which might have led to more favorable efficacy outcomes. Selection bias may limit the generalizability of these results to other populations. Because of these limitations, the results of this trial are exploratory and randomized trials are required to effectively compare the olaparib, pembrolizumab, and carboplatin regimen with the historical control regimen.[3]

We conclude that olaparib, pembrolizumab, and carboplatin given as first-line treatment of RM-HNSCC resulted in a higher ORR than that historically reported with fluorouracil, pembrolizumab, and platinum.[3] The median DoR, PFS, and OS were favorable. Olaparib may be a better partner than fluorouracil when combined with pembrolizumab and platinum as first-line treatment of RM-HNSCC. Future studies should be designed to assess whether the candidate biomarkers of HR and *PTEN* gene status and HPV status predict the efficacy of PARP inhibition in patients with RM-HNSCC. In addition, further studies that directly compare the activity of these two regimens in patients with RM-HNSCC are warranted.

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DISCLAIMER

Neither had a role in the study design, data collection, data analysis, data interpretation, or writing of the report. Data analysis and interpretation were performed by the authors. All authors had full access to all data. The corresponding author had final responsibility for the decision to submit the article for publication.

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DATA SHARING STATEMENT

Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices), and the study protocol will be shared, beginning 9 months and ending 24 months following article publication, with investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose. Types of acceptable analyses include approved proposal(s) or individual participant data for meta-analyses. Proposals may be submitted up to 24 months following article publication. Information regarding submitting proposals and accessing data may be submitted to jcley@wustl.edu.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX 1. RESULTS

One of the two patients who expired from acute myocardial infarction was a 75-year-old with a history of smoking, symptomatic peripheral vascular disease, and abdominal aortic aneurysm who presented on cycle 1 day 8 of study therapy with syncope and cardiac arrest. The second patient was a 75-year-old with a history of a stroke who presented on cycle 10 day 2 of study therapy with acute chest pain and cardiac arrest.

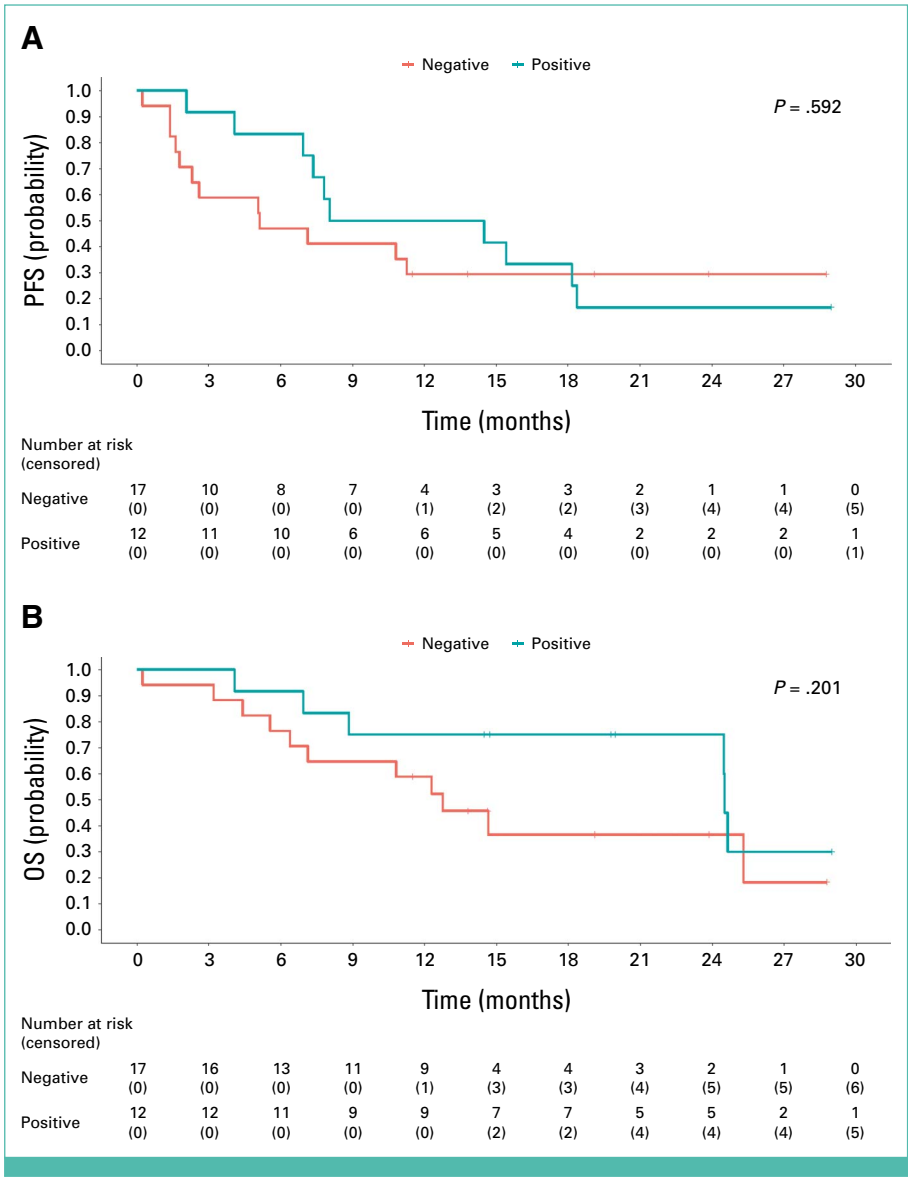

FIG A1. (A) PFS and (B) OS by HPV status. HPV, human papillomavirus; OS, overall survival; PFS, progression-free survival.

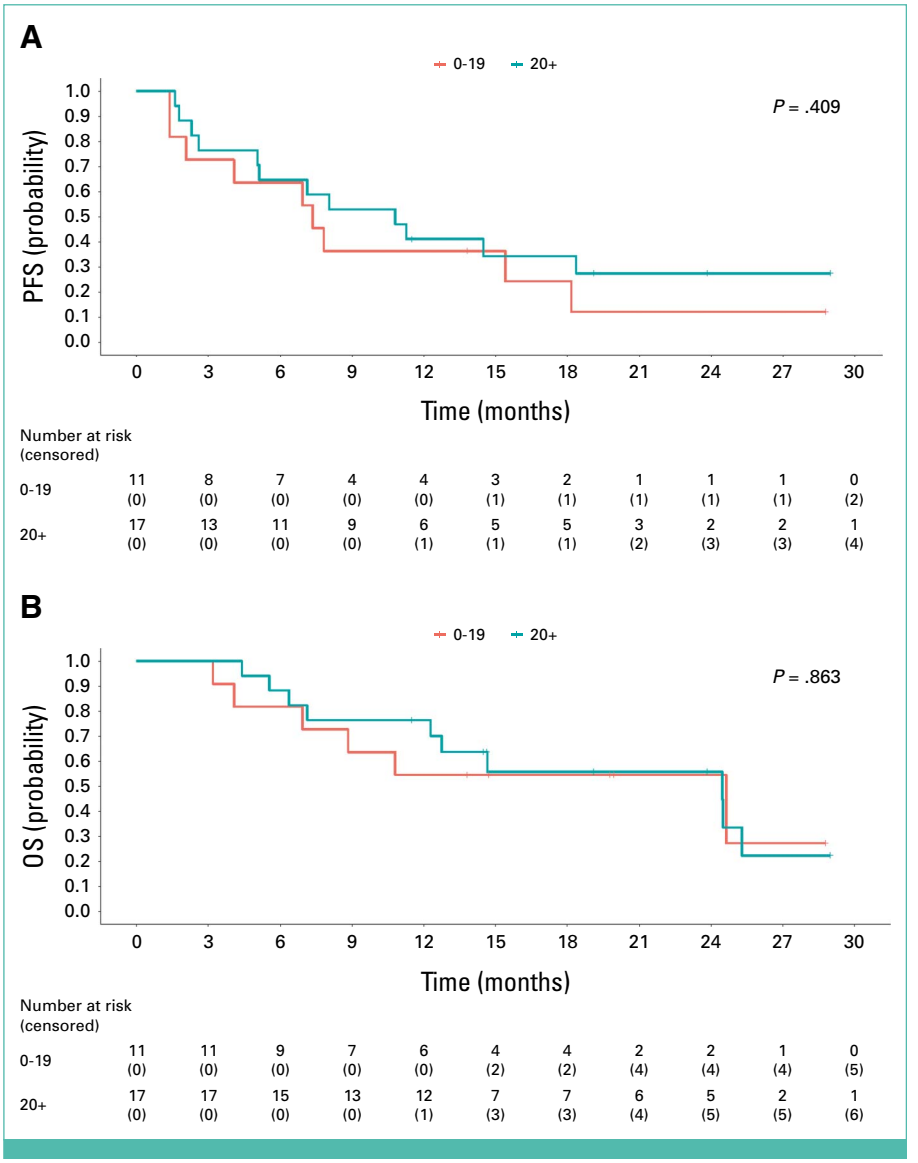

FIG A2. (A) PFS and (B) OS by PD-L1 status. OS, overall survival; PFS, progression-free survival.

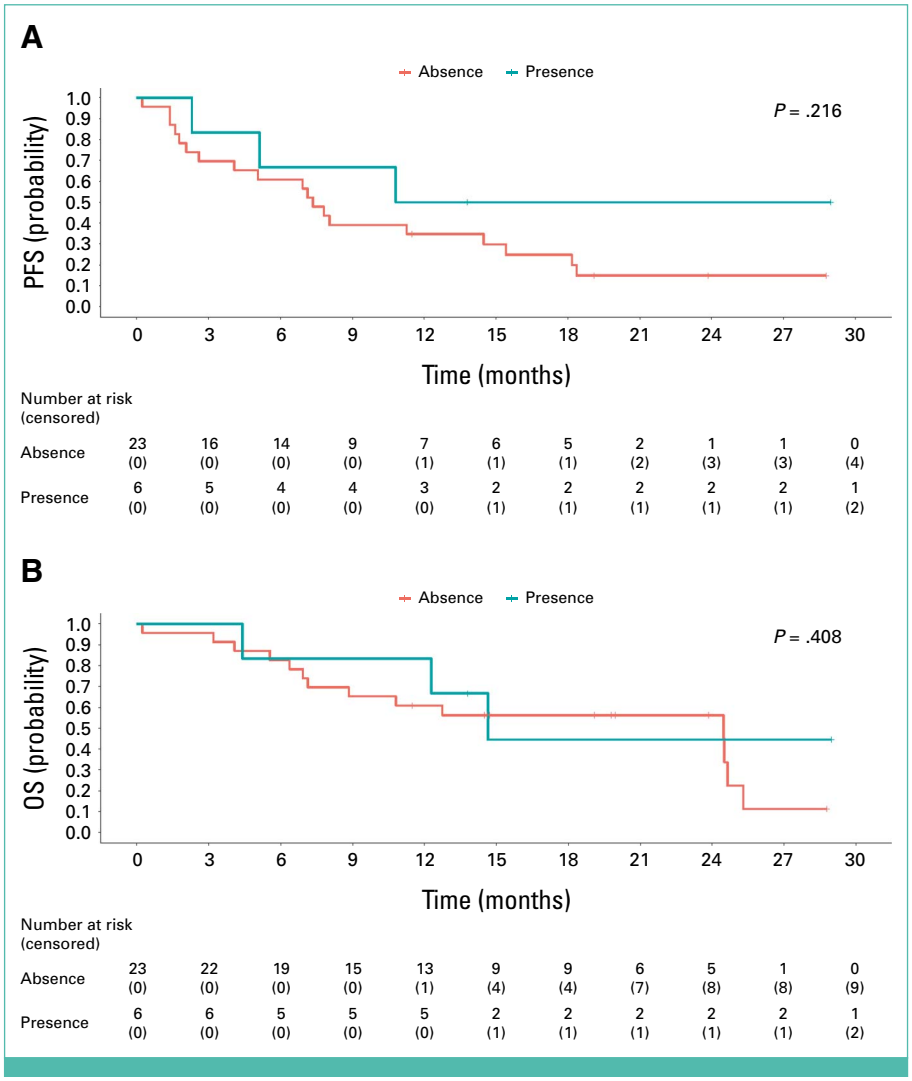

FIG A3. (A) PFS and (B) OS by HR and/or PTEN mutation status. HR, homologous recombination; OS, overall survival; PFS, progression-free survival.

TABLE A1. Number of Patients Who Required Dose Modification or Hold of Each Study Drug by Cycle of Treatment (N = 30 patients)

Cycle No.	1	2	3-6	1-6	7-35
Pembrolizumab	0	0	0	0	1
Olaparib	0	2	8	9	3
Carboplatin	0	8	15	17	NA

Abbreviation: NA, not yet reached.

TABLE A2. Baseline p16 Status, Tumor HR and *PTEN* Gene Status, and PD-L1 CPS Status Among the 29 Evaluable Patients

Patient ID	p16 Expression Status	HR or *PTEN* Gene Alteration	PD-L1 CPS	Best Response[a]	PFS (mos)	OS (mos)
1	Positive	FANCA p.R609fs	95	CR	37.3	37.3
2	Negative	—	50	SD	11.4	25.7
3	Positive	—	50	PR	8.2	24.9
4	Positive	—	10	SD	2.1	9.0
5	Negative	—	10	PD	1.4	3.2
6	Positive	—	0	SD	4.1	4.1
7	Negative	—	15	CR	29.2	29.2
8	Positive	ATM copy number loss PTEN copy number loss	99	CR	29.4	29.4
9	Negative	BARD1 p.Q176*	90	PR	11.0	12.5
10	Positive	—	15	PR	15.6	25
12	Negative	BAP1 p.E269fs	30	PR	5.2	14.9
13	Negative	—	25	PR	7.2	7.2
14	Positive	—	92	PR	18.6	24.8
15	Negative	—	65	CR	24.2	24.2
16	Not done	—	50	SD	5.1	12.9
17	Positive	—	5	SD	7.0	7.0
18	Positive	—	2	PR	18.4	20.1
19	Positive	—	1	PR	7.9	20.2
20	Negative	—	50	PR	19.4	19.4
21	Negative	BAP1 p.R385*	70	SD	2.3	4.5
22	Negative	—	45	PD	1.8	5.6
23	Negative	—	95	SD	2.6	6.5
24	Negative	—	ND	PD	0.2	0.2
25	Positive	—	5	SD	7.5	14.9
26	Negative	—	50	PD	1.6	14.8
27	Positive	—	95	SD	14.7	14.7
28	Negative	—	10	PD	1.4	11.0
29	Positive	BRCA2 p.L1091fs ATR c.3172-1G>C	10	PR	14	14
30	Negative	—	80	PR	11.7	11.7

Abbreviations: CPS, combined positive score; CR, complete response; HR, homologous recombination; ND, not done; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]RECIST.

TABLE A3. Correlation of Baseline Tumor HR and *PTEN* Gene Status, PD-L1 CPS Status, or HPV Status with ORR, PFS, and OS Among the 29 Evaluable Patients

	HR and PTEN Gene Status			PD-L1 CPS Status			HPV Status		
Activity End Point	Altered	Not Altered	*P*[a]	≥20	0-19	*P*[a]	Positive	Negative	*P*[a]
ORR (%)	83.3	43.5	.17	58.8	45.5	.49	58.3	47.1	.55
PFS, median months, (95% CI)	NA (2.3 to NA)	7.4 (2.6 to 14.5)	.22	10.8 (2.6 to 18.4)	7.4 (1.4 to 18.2)	.41	11.3 (4.1 to 18.4)	5.1 (1.6 to NA)	.59
OS, median months (95% CI)	14.7 (4.4 to NA)	24.5 (7.1 to 24.6)	.41	24.5 (7.1 to NA)	24.6 (4.1 to NA)	.86	24.5 (6.9 to NA)	12.7 (5.6 to NA)	.20

Abbreviations: CPS, combined positive score; HPV, human papillomavirus; HR, homologous recombination; NA, not yet reached; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.

[a]HR and *PTEN* gene status, PD-L1 CPS status, or HPV status with ORR were investigated by the chi-square test, and those with PFS or OS were investigated by the log-rank test.