original reports

Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial

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abstract

PURPOSE Nivolumab was assessed in patients with virus-associated tumors in the phase I/II CheckMate 358 trial (ClinicalTrials.gov identifier: NCT02488759). We report on patients with recurrent/metastatic cervical, vaginal, or vulvar cancers.

PATIENTS AND METHODS Patients received nivolumab 240 mg every 2 weeks. Although patients with unknown human papillomavirus status were enrolled, patients known to have human papillomavirus–negative tumors were ineligible. The primary end point was objective response rate. Duration of response (DOR), progression-free survival, and overall survival were secondary end points. Safety and patient-reported outcomes were exploratory end points.

RESULTS Twenty-four patients (cervical, n = 19; vaginal/vulvar, n = 5) were enrolled. Most patients had received prior systemic therapy for metastatic disease (cervical, 78.9%; vaginal/vulvar, 80.0%). Objective response rates were 26.3% (95% CI, 9.1 to 51.2) for cervical cancer and 20.0% (95% CI, 0.5 to 71.6) for vaginal/vulvar cancers. At a median follow-up of 19.2 months, median DOR was not reached (range, 23.3 to 29.5+ months; + indicates a censored observation) in the five responding patients in the cervical cohort; the DOR was 5.0 months in the single responding patient in the vaginal/vulvar cohort. Median overall survival was 21.9 months (95% CI, 15.1 months to not reached) among patients with cervical cancer. Any-grade treatment-related adverse events were reported in 12 of 19 patients (63.2%) in the cervical cohort and all five patients in the vaginal/vulvar cohort; there were no treatment-related deaths. In the cervical cohort, nivolumab treatment generally resulted in stabilization of patient-reported outcomes associated with health status and health-related quality of life.

CONCLUSION The efficacy of nivolumab in patients with recurrent/metastatic cervical and vaginal or vulvar cancers is promising and warrants additional investigation. No new safety signals were identified with nivolumab treatment in this population.

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INTRODUCTION

Almost all cervical cancers[1] and many vaginal[2] and vulvar[3] cancers are the result of human papillomavirus (HPV) infection. Despite the availability of cytologic screening, cervical cancer remains a significant cause of morbidity and mortality.[4] First-line treatment of patients with recurrent/metastatic cervical cancer and those presenting with stage IVB disease includes platinum-based chemotherapy or paclitaxel/topotecan[5]; adding bevacizumab to these chemotherapy regimens has been shown to improve survival.[6,7] Response rates associated with first-line treatment of recurrent/metastatic cervical cancer ranged from 13% to 46% for chemotherapy alone[6,8-10] to approximately 50% for bevacizumab-containing regimens.[6] Median overall survival (OS) values ranged from 6.5 to 13.3 months for chemotherapy-only regimens[6,8-10] to 16.8 months for bevacizumab-containing regimens.[6] Responses to second-line treatments for recurrent/metastatic cervical cancer are infrequent and transient, and there is no established standard of care.[5,11] Vaginal and vulvar cancers are rare, and there are no effective chemotherapy regimens for recurrent vaginal or vulvar cancer[12,13]; few clinical trials include these patient populations.

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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Virus-induced cancers are attractive targets for immunotherapy because viral proteins are strong immune stimulants.[14] In June 2018, pembrolizumab received accelerated approval for the treatment of patients with recurrent/metastatic cervical cancers expressing programmed death-ligand 1 (PD-L1) postchemotherapy.[15] Nivolumab is a fully human immunoglobulin G4 programmed death-1 immune checkpoint inhibitor that is approved for the treatment of various cancers.[16] CheckMate 358 (ClinicalTrials.gov identifier: NCT02488759) is an ongoing phase I/II study evaluating nivolumab-based therapy in virus-associated tumors. We report on a cohort of 24 patients with recurrent/metastatic cervical, vaginal, or vulvar cancers receiving nivolumab monotherapy in CheckMate 358.

PATIENTS AND METHODS

Study Design, Patients, and Treatment

CheckMate 358 is a multicenter, open-label, multicohort phase I/II trial investigating nivolumab-based therapies in patients with virus-associated solid tumors in the neoadjuvant or recurrent/metastatic setting. In the recurrent/metastatic cervical and vaginal/vulvar carcinoma cohorts, patients received nivolumab monotherapy (240 mg intravenously every 2 weeks for $\leq$ 2 years) until disease progression, unacceptable toxicity, or withdrawal of consent.

Eligible patients were nonpregnant, nonbreastfeeding women 18 years of age and older with an Eastern Cooperative Oncology Group performance status of 0 or 1 and a histologically confirmed diagnosis of squamous cell carcinoma of the cervix, vagina, or vulva measurable by computed tomography, magnetic resonance imaging, and/or physical examination, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients had recurrent/metastatic disease with two or fewer prior systemic therapies in the metastatic setting. For patients with accessible lesions, submission of fresh or archival tumor tissue was required. Whereas patients with unknown HPV status could be enrolled, patients with known HPV-negative tumors were not eligible for inclusion. Other key exclusion criteria were active brain or leptomeningeal metastases, another invasive malignancy active within the previous 3 years, active autoimmune disease, or needing systemic treatment with immunosuppressive medications within 2 weeks of study drug administration.

Study End Points

The primary end point was investigator-assessed objective response rate (ORR), defined as the proportion of patients with a best overall response of complete response (CR) or partial response, per RECIST version 1.1. Secondary end points included duration of response (DOR; defined for confirmed responses as the time from first documented response to first documented tumor progression or death from any cause), OS (time from first dose to death from any cause), and progression-free survival (PFS; time from first dose to first documented tumor progression or death from any cause). Exploratory end points included safety and patient-reported outcomes (PROs) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30; to assess cancer-specific health-related quality of life) and EuroQoL five dimensions (EQ-5D; to assess overall health status).

Physical examination was performed within 14 days before the first study dose and every 2 weeks thereafter. Tumor assessments by computed tomography or magnetic resonance imaging were conducted within 35 days before the first study dose, every 8 weeks during the first year, and every 12 weeks thereafter until disease progression or treatment discontinuation. Survival was monitored at the first follow-up assessment 35 days after the last dose, 80 days after the first follow-up assessment, and every 3 months thereafter. Safety was monitored throughout the study and until 100 days after the last dose. Patients were observed for ongoing treatment-related adverse events (TRAEs) until resolved, returned to baseline/deemed irreversible, or lost to follow-up, withdrawal of study consent, or start of a subsequent anticancer therapy. Adverse events were assessed using worst grade per National Cancer Institute Common Terminology Criteria for Adverse Events version 4 by system organ class and Medical Dictionary for Regulatory Activities preferred terms. PROs were assessed before dosing, on day 1 of week 1, every 8 weeks until week 34, and every 12 weeks thereafter.

HPV Testing

HPV positivity was defined by a US Food and Drug Administration–approved test or other well-validated commercially available test comprising in situ hybridization (ISH), real-time polymerase chain reaction, or immunohistochemistry. HPV status per institutional testing before enrollment was documented. If not available, HPV testing was performed retrospectively on a fresh tumor biopsy obtained at study screening, using ISH, for the following subtypes: 6, 11, 16, 18, and 33.

PD-L1 Expression

Tumor cell PD-L1 expression was assessed in pretreatment (archival or fresh) tumor biopsy specimens with the use of a validated, automated immunohistochemical assay (PD-L1 IHC 28-8 pharmDx; Dako–Agilent Technologies, Santa Clara, CA) using the rabbit antihuman PD-L1 clone 28-8.[17] Tumor cell PD-L1 expression was defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity. PD-L1 expression by tumor cells plus tumor-associated immune cells was determined using a combined positive score (defined as the number of PD-L1$^+$ cells, including tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells $\times$ 100) for a post hoc analysis.[18]

Study Oversight

The protocol was approved by an institutional review board or independent ethics committee at each site before study activation. The study was conducted in accordance with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation, and in accordance with the ethical principles of the European Union Directive and US Code of Federal Regulations. All patients provided written informed consent in accordance with the Declaration of Helsinki. Bristol-Meyers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

Statistical Analysis

An enrollment of 23 patients was planned for the cohort of patients with recurrent/metastatic cervical, vaginal, or vulvar carcinoma. If the true ORR is 20%, the probability of detecting three or more responses among 23 patients would be 86.7%; if the true ORR is 30%, the probability would be 98.4%. Tumor responses were evaluated in patients who received one or more doses of the study drug and who had either one or more in-study time point with all baseline target lesion(s) assessed, or clinical progression or death before any in-study tumor assessment. ORR was summarized by binomial response rates and their corresponding 95% exact CIs by the Clopper-Pearson method.[19] DOR, OS, and PFS were estimated using Kaplan-Meier techniques.[20] DOR was summarized for all treated patients who achieved confirmed partial response or CR using the Kaplan-Meier product-limit method. Median DOR, along with two-sided 95% CIs using the Brookmeyer and Crowley method,[21] was also calculated. Median PFS or OS and corresponding 95% CIs were constructed based on a log-log transformed CI for the survivor function. Rates at fixed time points were derived from the Kaplan-Meier estimate, and corresponding CIs were derived based on the Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.[22] Safety was summarized for all treated patients using descriptive statistics. PRO data were summarized using descriptive statistics. The database lock for this analysis was July 13, 2018.

RESULTS

Patient, Tumor, and Treatment Characteristics

Twenty-four patients with squamous cell carcinomas were enrolled in the gynecologic cancer cohort of CheckMate 358, 19 with cervical carcinoma and five with vaginal/vulvar carcinoma. The median age was 51.0 years (range, 28 to 75 years) in the cervical cohort and 59.0 years (range, 40 to 78 years) in the vaginal/vulvar cohort (Table 1). Most patients had stage IV disease at enrollment (cervical, 84.2%; vaginal/vulvar, 60.0%) and had received prior systemic therapy for metastatic disease (78.9% and 80.0%, respectively).The most common sites of metastatic disease seen in 40% or more of patients were lymph node and lung in the cervical cohort and lymph node, skin/soft tissue, and lung in the vaginal/vulvar cohort.

Among patients with evaluable HPV status (cervical, 18 of 19 patients; vaginal/vulvar, five of five patients), 15 (83.3%) and two (40.0%) patients, respectively, had tumors positive for HPV subtypes 6, 11, 16, 18, or 33 (Table 1). Among patients with quantifiable tumor cell PD-L1 expression (cervical, 16 of 19 patients; vaginal/vulvar, four of five patients), 10 (62.5%) and four (100.0%), respectively, had 1% or more tumor cell PD-L1 expression. When PD-L1 expression was assessed on tumor cells plus tumor-associated immune cells, all patients with quantifiable PD-L1 expression had a combined positive score of 1 or greater (not shown).

The median duration of nivolumab treatment was 5.6 months (range, 0.5 to 31.4+ months; + indicates patient still receiving therapy) in the cervical cohort and 6.7 months (range, 2.1 to 7.5 months) in the vaginal/vulvar cohort. The median follow-up was 19.2 months (range, 1.4 to 31.4 months) and 10.3 months (range, 3.9 to 23.7 months), respectively. At the time of the database lock, three patients (15.8%) in the cervical cohort and none in the vaginal/vulvar cohort continued to receive treatment (Appendix Table A1; Appendix Fig A1, online only).

Efficacy

ORRs were 26.3% (95% CI, 9.1% to 51.2%) in the cervical cohort and 20.0% (95% CI, 0.5% to 71.6%) in the vaginal/vulvar cohort (Table 2). The disease control rates were 68.4% (95% CI, 43.4% to 87.4%) and 80.0% (95% CI, 28.4% to 99.5%) in the cervical and vaginal/vulvar cohorts, respectively. Of the five responding patients in the cervical cohort, three patients continued to receive treatment and remain in response as of database lock. These three patients were white, ranged in age from 33 to 75 years, had HPV-positive tumors, and had undergone prior surgery and radiotherapy; two patients had received prior systemic therapies for recurrent/metastatic disease. One patient had tumor cell PD-L1 expression of 1% or greater, one had tumor cell PD-L1 expression less than 1%, and one patient was not evaluable. Median DOR was not reached (range, 23.3 to 29.5+ months; + indicates a censored observation) in the cervical cohort; DOR was 5.0 months in the single responding patient in the vaginal/vulvar cohort. Subgroup analyses in the cervical cohort by tumor cell PD-L1 expression and prior systemic therapy for metastatic disease are listed in Appendix Table A2 (online only). Owing to small patient numbers, response rates were not analyzed within these subgroups in the vaginal/vulvar cohort. Best change from baseline in tumor burden and changes in tumor burden over time for individual patients are presented in Figure 1. Time to response and DOR are presented in Appendix Figure A1. An example of a CR observed in a patient with recurrent stage IIB cervical cancer is shown in Figure 2.

TABLE 1. Baseline Patient and Tumor Characteristics

Characteristic	Cervical Cancer (n = 19)	Vaginal/Vulvar Cancers[a] (n = 5)
Median age (range), years	51.0 (28-75)	59.0 (40-78)
Region		
United States/Canada	1 (5.3)	0
Europe	18 (94.7)	5 (100.0)
Race		
White	17 (89.5)	5 (100.0)
American Indian or Alaska Native	1 (5.3)	0
Other	1 (5.3)	0
AJCC stage,[b]		
IIB	1 (5.3)	1 (20.0)
IIIB or IIIC	2 (10.5)	1 (20.0)
IVA or IVB	16 (84.2)	3 (60.0)
ECOG performance status		
0	10 (52.6)	1 (20.0)
1	8 (42.1)	4 (80.0)
Not reported	1 (5.3)	0
HPV status,[c]		
Evaluable	18 (94.7)	5 (100.0)
Positive	15 (83.3)	2 (40.0)
Negative	3 (16.7)	3 (60.0)
Not tested	1 (5.3)	0
Tumor cell PD-L1 expression[d]		
Quantifiable	16 (84.2)	4 (80.0)
≥ 1%	10 (62.5)	4 (100.0)
< 1%	6 (37.5)	0
Not tested[e]/not evaluable[f]	3 (15.8)	1 (20.0)
Sites of metastatic disease[g]		
Lymph node	12 (63.2)	3 (60.0)
Lung	8 (42.1)	2 (40.0)
Pelvis	5 (26.3)	1 (20.0)
Other	5 (26.3)	0
Uterus	3 (15.8)	0
Peritoneum	2 (10.5)	0
Bone with no soft tissue component	2 (10.5)	0
Bone with soft tissue component	1 (5.3)	0
Chest wall	1 (5.3)	1 (20.0)
Skin/soft tissue	1 (5.3)	3 (60.0)
Gastric	0	1 (20.0)
Liver	0	1 (20.0)
Time from initial diagnosis to study entry		
≤ 1 year	5 (26.3)	3 (60.0)
> 1 year	14 (73.7)	2 (40.0)
Prior radiotherapy	17 (89.5)	4 (80.0)
Prior lines of systemic therapy		
0	0	1 (20.0)
1	8 (42.1)	3 (60.0)
2	8 (42.1)	1 (20.0)
3	3 (15.8)	0
Prior systemic therapy in the metastatic setting or with radiation in the neoadjuvant or adjuvant setting[h]		
Platinum	19 (100.0)	4 (80.0)
Cisplatin	15 (78.9)	3 (60.0)
Carboplatin	11 (57.9)	1 (20.0)
Paclitaxel	12 (63.2)	0
Bevacizumab	6 (31.6)	0
Topotecan	5 (26.3)	0
Capecitabine	1 (5.3)	1 (20.0)
Other	1 (5.3)	0
Mitomycin	0	1 (20.0)
Fluorouracil	0	1 (20.0)
Docetaxel	0	1 (20.0)
Prior lines of systemic therapy for metastatic disease		
0	4 (21.1)	1 (20.0)
1	8 (42.1)	3 (60.0)
2	7 (36.8)	1 (20.0)
Time from completion of most recent prior therapy to study entry		
≤ 6 months	12 (63.2)	3 (60.0)
> 6 to ≤ 12 months	1 (5.3)	1 (20.0)
> 12 months	2 (10.5)	1 (20.0)
Unknown/not reported	4 (21.1)	0

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PD-L1, programmed death ligand-1.

[a]Two patients had vaginal cancer and three patients had vulvar cancer.

[b]Aligned with Fédération Internationale de Gynécologie et d'Obstétrique staging.

[c]Retrospective HPV testing included the following subtypes: 6, 11, 16, 18, and 33.

[d]Tumor cell PD-L1 expression was defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity.

[e]Sample not available.

[f]Less than 100 viable tumor cells present on the stained slide.

[g]Twelve patients with cervical cancer and three patients with vaginal/vulvar cancer had lesions at more than one site, including target and nontarget lesions.

[h]Some patients received more than one type of therapy.

TABLE 2. Tumor Responses According to RECIST, version 1.1

Response	Cervical Cancer (n = 19)	Vaginal/Vulvar Cancers (n = 5)
Best overall response (assessed by investigator)*		
Complete response	3 (15.8)	0
Partial response	2 (10.5)	1 (20.0)
Stable disease	8 (42.1)	3 (60.0)
Progressive disease	6 (31.6)	1 (20.0)
ORR, No. (%; 95% CI)†	5 (26.3; 9.1 to 51.2)	1 (20.0; 0.5 to 71.6)
Disease control rate,‡ No. (%; 95% CI)†	13 (68.4; 43.4 to 87.4)	4 (80.; 28.4 to 99.5)
Median time to response (range), months	1.7 (1.6-1.9)	2.0 (2.0-2.0)
Median duration of response (range), months§	NR (23.3-29.5‖)	5.0 (5.0-5.0)

NOTE. Data are No. (%) unless otherwise indicated.
Abbreviations: NR, not reached; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1.
*Assessed by investigators per RECIST.
†On the basis of the Clopper and Pearson method.
‡Proportion of patients with a complete response, a partial response, or stable disease.
§Median computed using Kaplan-Meier method.
‖Censored observation.

In the cervical cohort, median OS was 21.9 months (95% CI, 15.1 months to not reached) and the 12-month and 24-month OS rates were 77.5% (95% CI, 50.5% to 91.0%) and 49.8% (95% CI, 23.6% to 71.3%; Fig 3A), respectively. Median PFS was 5.1 months (95% CI, 1.9 to 9.1 months) and 26.3% (95% CI, 9.6% to 46.8%) of patients were progression free at 12 months (Fig 3B). Owing to the small size of the vaginal/vulvar cohort, median OS and PFS were not calculated. At 12 months and 18 months, 40.0% (95% CI, 5.2% to 75.3%) and 20.0% (95% CI, 0.8% to 58.2%) of patients with vaginal/vulvar cancers, respectively, were alive; at 6 months, 40.0% (95% CI, 5.2% to 75.3%) of patients were progression free. On the basis of a subgroup analysis, OS was not considerably affected by PD-L1 status or prior systemic cancer therapy for metastatic disease in the cervical cohort (Appendix Fig A2, online only).

Safety

TRAEs are listed in Table 3. The most common TRAE was diarrhea in the cervical cohort (four of 19 patients; 21.1%) and decreased appetite in the vaginal/vulvar cohort (two of five patients; 40.0%). One patient (5.3%) in the cervical cohort discontinued treatment owing to a TRAE (grade 3 pneumonitis), which occurred 2 days after the last (25th) dose of nivolumab and resolved 14 days later with intravenous corticosteroids. No treatment-related deaths were reported in either cohort. Three patients (15.8%) reported serious grade 3 to 4 TRAEs in the cervical cohort (one each: diarrhea, hepatocellular injury, and pneumonitis); these were reported on study days 16, 267, and 367, respectively. No serious TRAEs were reported in the vaginal/vulvar cohort. Most select TRAEs (defined as adverse events with potential immunologic causes) were grade 1 to 2 in severity. The most common select TRAEs of any grade in the cervical cohort were GI (21.1%) and skin (21.1%) reactions; in the vaginal/vulvar cohort, skin-related and endocrine reactions reported in one of five patients each (20.0%) were most common. Grade 3 to 4 select TRAEs reported in the cervical cohort included GI and pulmonary events in 1 patient each; none were reported in the vaginal/vulvar cohort.

Patient-Reported Outcomes

In the cervical cohort, 18 of 19 patients (94.7%) at baseline and all 14 patients (100%) at week 9 answered the EORTC QLQ-C30 and EQ-5D questionnaires. For EORTC QLQ-C30, complete data in 10 or more patients were available at baseline (n = 16) and week 9 (n = 13). On the basis of EORTC QLQ-C30 scores, global health status was stable at week 9 compared with baseline, as were physical functioning, emotional functioning, and social functioning; however, clinically meaningful deterioration was noted in role functioning and cognitive functioning. Patients reported clinically meaningful improvement in pain and constipation, clinically meaningful deterioration in fatigue, and stability with regard to nausea and vomiting, dyspnea, insomnia, appetite loss, diarrhea, and financial difficulties. For EQ-5D, complete data in 10 or more patients were available at baseline (n = 18) and week 9 (n = 13). Patients were stable at week 9 compared with baseline on the basis of EQ-5D utility scores and EQ-5D visual analog scale scores. PRO data were not reported for the vaginal/vulvar cohort owing to small patient numbers.

DISCUSSION

There is currently no standard of care for recurrent/metastatic cervical cancer that has progressed on systemic chemotherapy and bevacizumab. In CheckMate 358,

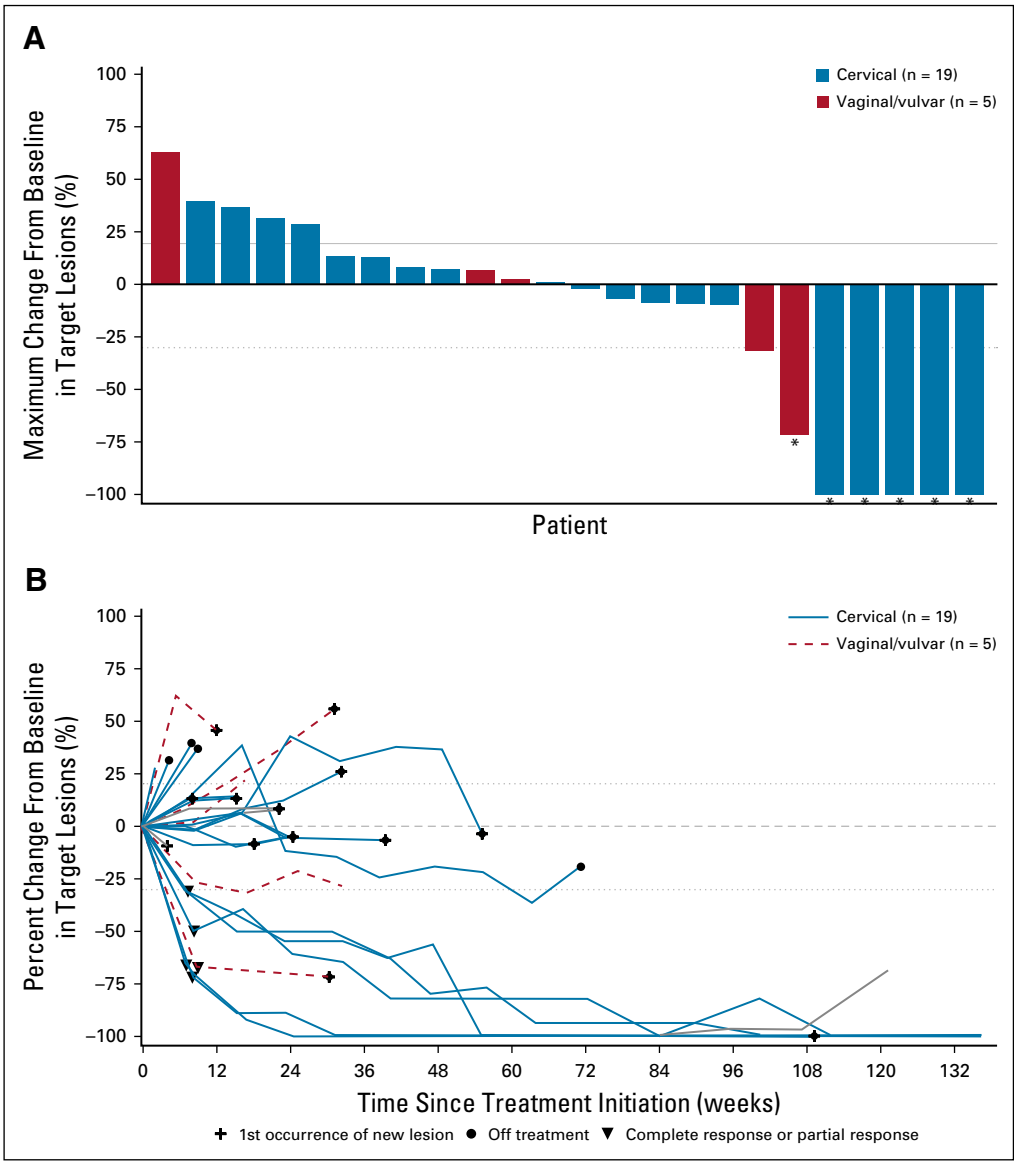

FIG 1. Characteristics of treatment response. (A) Maximum change from baseline in the sum of tumor target lesion diameters, according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST). Tumor reduction data (bars) correspond to maximum change from baseline in only target lesions and not to best overall response. (B) Kinetics of change in tumor burden over time on therapy. Dotted horizontal lines in panels A and B indicate 30% target lesion reduction (consistent with a response in the absence of new lesions) and 20% increase (consistent with progressive disease), per RECIST. (*) Bars with asterisks represent confirmed responses (complete response or partial response). Bars without asterisks represent unconfirmed responses.

nivolumab resulted in an ORR of 26.3% among patients with recurrent/metastatic cervical cancer. Responses were durable; at a median follow-up of 19.2 months, median DOR was not reached. Median OS was 21.9 months, with 12-month and 24-month OS rates of 77.5% and 49.8%, respectively. Median PFS was 5.1 months, and the 12-month PFS rate was 26.3% without regard to PD-L1 status. All five patients who responded had an unconfirmed CR, with three of the five CRs confirmed on subsequent evaluation. For most PRO measures, nivolumab treatment was associated with stabilization with regard to overall health status and cancer-specific health-related quality of life. To our knowledge, this study provides the longest reported follow-up for patients with advanced cervical cancer treated with a programmed death-1 or PD-L1 inhibitor.

Pembrolizumab was recently approved for the treatment of PD-L1–expressing recurrent/metastatic cervical cancer postchemotherapy on the basis of results from the phase II KEYNOTE-158 trial (ClinicalTrials.gov identifier: NCT02628067), in which an ORR of 14.3% was reported in PD-L1–positive cervical cancers.[15,23] In an earlier phase Ib study (KEYNOTE-028; ClinicalTrials.gov identifier: NCT02054806) that evaluated pembrolizumab in patients with similar eligibility, ORR was 17% and median OS was 11 months.[24] In the NRG-GY002 (ClinicalTrials.gov identifier: NCT02257528) study, nivolumab treatment resulted in an ORR of 4% in a patient population (n = 25) similar to that of CheckMate 358.[25]

The current standard for the management of metastatic vaginal/vulvar cancers is driven by the approach taken for cervical cancer, owing to the lack of robust data or clinical trials evaluating novel treatments. The majority of patients with recurrent/metastatic vaginal/vulvar cancers are typically treated with platinum combinations;

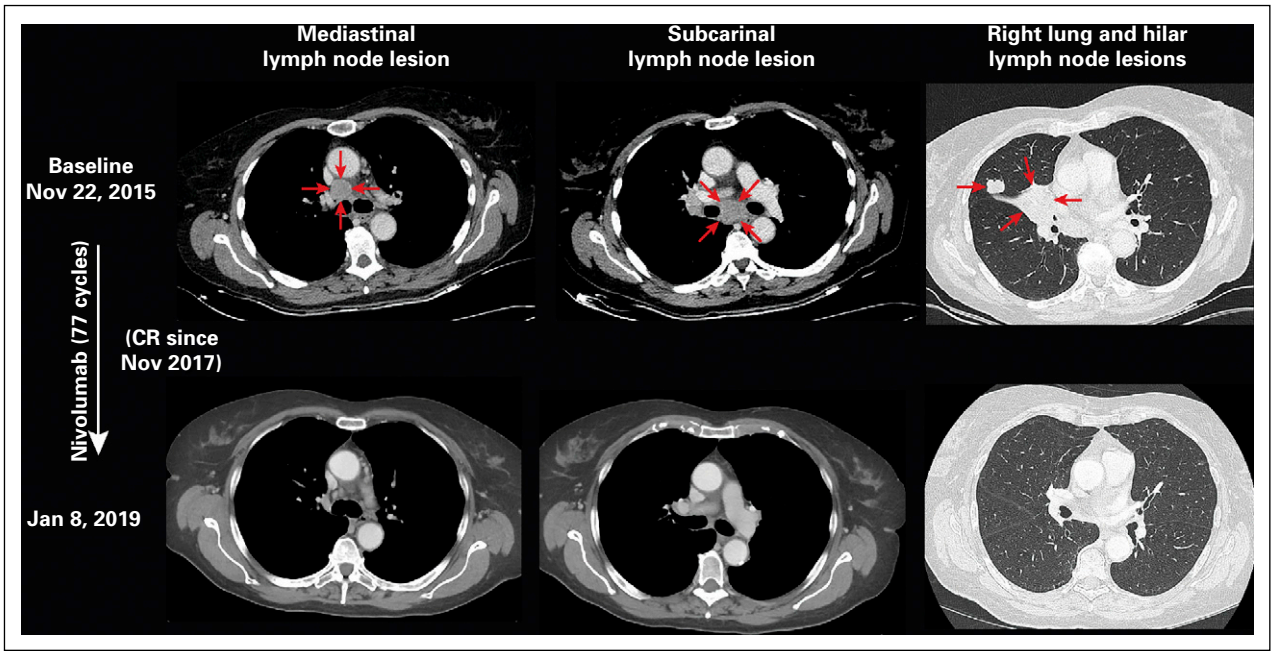

FIG 2. Computed tomography scans at baseline and cycle 77 are shown for a 75-year-old white woman with human papillomavirus–positive metastatic cervical cancer with tumor cell programmed death-ligand 1 expression of 1% or greater. This patient was initially diagnosed in April 2014 with stage IIB disease (per Fédération Internationale de Gynécologie et d'Obstétrique staging) and underwent chemoradiotherapy with cisplatin. She was diagnosed with recurrent metastatic disease in October 2015 and enrolled in CheckMate 358 in November 2015 with stage IV disease and an Eastern Cooperative Oncology Group performance status of 0. Target lesions at baseline included mediastinal lymph node lesion (20 mm), subcarinal lymph node lesion (25 mm), and right lung lesion (19 mm). The patient received her first dose of nivolumab on December 3, 2015. Her best overall response was complete response (CR), documented in November 2017 after 50 cycles of treatment. She was cancer-free as of January 8, 2019, and is continuing in this study.

however, the efficacy of platinum-based treatments in this patient population has not been demonstrated, and there are no approved systemic therapies. In CheckMate 358, nivolumab showed promising activity in a small cohort of five patients with recurrent/metastatic vaginal/vulvar cancers, with one partial responder (patient with HPV-negative vulvar cancer), 12-month and 18-month OS rates of 40.0% and 20.0%, respectively, and a 6-month PFS rate of 40.0%. CheckMate 358 is the only immunotherapy trial to report outcomes of patients with metastatic vaginal/vulvar cancers.

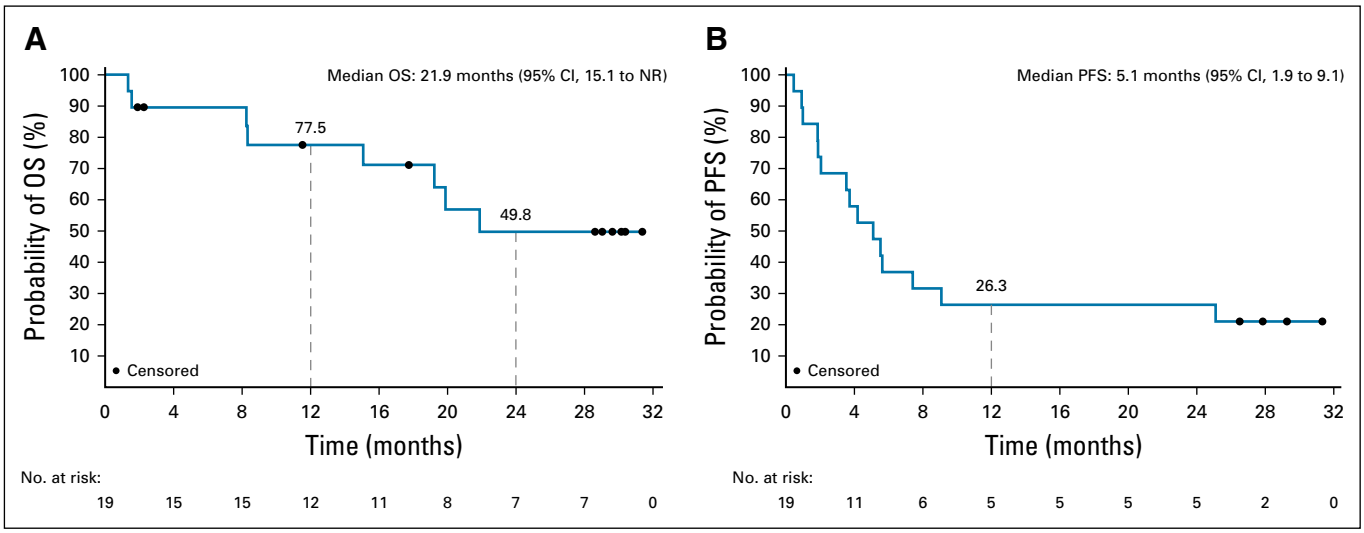

FIG 3. (A) Overall survival (OS) and (B) progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST) in patients with cervical cancer. Owing to the high percentage of censored responses, median and rate estimators may be misleading. NR, not reached.

TABLE 3. TRAEs (in ≥ 10% of patients) and Select Treatment-Related Adverse Events

	Cervical Cancer (n = 19)		Vaginal/Vulvar Cancers (n = 5)	
Event	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Any TRAE	12 (63.2)	4 (21.1)	5 (100.0)	0
TRAEs leading to discontinuation	1 (5.3)*	1 (5.3)*	0	0
TRAEs reported in ≥ 10% of patients†				
Diarrhea	4 (21.1)	1 (5.3)	0	0
Fatigue	3 (15.8)	0	1 (20.0)	0
Pneumonitis	2 (10.5)	1 (5.3)	0	0
Abdominal pain	2 (10.5)	0	1 (20.0)	0
Stomatitis	2 (10.5)	0	0	0
Dry eye	2 (10.5)	0	0	0
Arthralgia	2 (10.5)	0	1 (20.0)	0
Decreased appetite	1 (5.3)	0	2 (40.0)	0
Any serious TRAE	3 (15.8)	3 (15.8)	0	0
Diarrhea	1 (5.3)	1 (5.3)	0	0
Hepatocellular injury	1 (5.3)	1 (5.3)	0	0
Pneumonitis	1 (5.3)	1 (5.3)	0	0
Any serious TRAE leading to discontinuation	1 (5.3)*	1 (5.3)*	0	0
Select TRAEs				
GI	4 (21.1)	1 (5.3)	0	0
Skin	4 (21.1)	0	1 (20.0)	0
Pulmonary	2 (10.5)	1 (5.3)	0	0
Endocrine	1 (5.3)	0	1 (20.0)	0
Hepatic	1 (5.3)	0	0	0
Renal	1 (5.3)	0	0	0
Hypersensitivity/infusion reactions	0	0	0	0

NOTE. Data are No. (%). Includes events reported from the time of the first dose of study drug to 100 days after the last dose.
Abbreviation: TRAE, treatment-related adverse event.
*Discontinuation because of treatment-related pneumonitis.
†Events are listed in order of frequency for any-grade TRAEs in patients with cervical cancer. Individual patients may have had more than one TRAE.

Nivolumab demonstrated a manageable safety profile in patients with cervical, vaginal, or vulvar cancers. Any-grade TRAEs were reported in 12 of 19 patients (63.2%) in the cervical cohort and all five patients in the vaginal/vulvar cohort; grade 3 to 4 TRAEs were reported in four patients (21.1%) and 0 patients, respectively. There were no treatment-related mortalities, and no new safety signals for nivolumab were observed. This experience compares favorably with adverse effects typically observed with chemotherapies used in this patient population.[8-11]

In this study, 18 of 19 patients (83.3%) with cervical cancer, both patients with vaginal cancer, and no patients among the three patients with vulvar cancer tested positive for HPV. However, it is known that almost all cervical cancers[1] and a proportion of vulvar (40%)[3] and vaginal cancers (75%)[2] are caused by HPV infection. The lower-than-expected rate of HPV positivity in this study might be attributed to the varied sensitivity of different HPV tests at different sites and the low coverage of HPV subtypes by the ISH assay used.[26] Additional studies in larger cohorts will be needed to examine the influence that the presence/genotype of HPV and other factors might have on the efficacy of nivolumab in gynecologic cancers.

It should be noted that patient numbers were small in this study, thus limiting subgroup analyses. Furthermore, tumor response was not assessed by independent radiologic review. Nonetheless, the tumor response rate, durability of response, and OS results are encouraging, especially considering that approximately 80% of patients had undergone prior systemic therapies for recurrent/metastatic disease.

In conclusion, the efficacy of nivolumab monotherapy in CheckMate 358 in patients with recurrent/metastatic cervical cancer was promising. Responses were durable; at a median follow-up of 19.2 months, three of 19 (16%) patients were continuing to receive treatment, and median DOR was not reached. The activity noted in vulvar/vaginal cancer also warrants additional investigation. Given the lack of effective therapy and low survival rates for patients with metastatic disease in these gynecologic cancers, the results reported here are of strong clinical interest and underscore the growing role of immune checkpoint inhibitors in this patient population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial

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APPENDIX

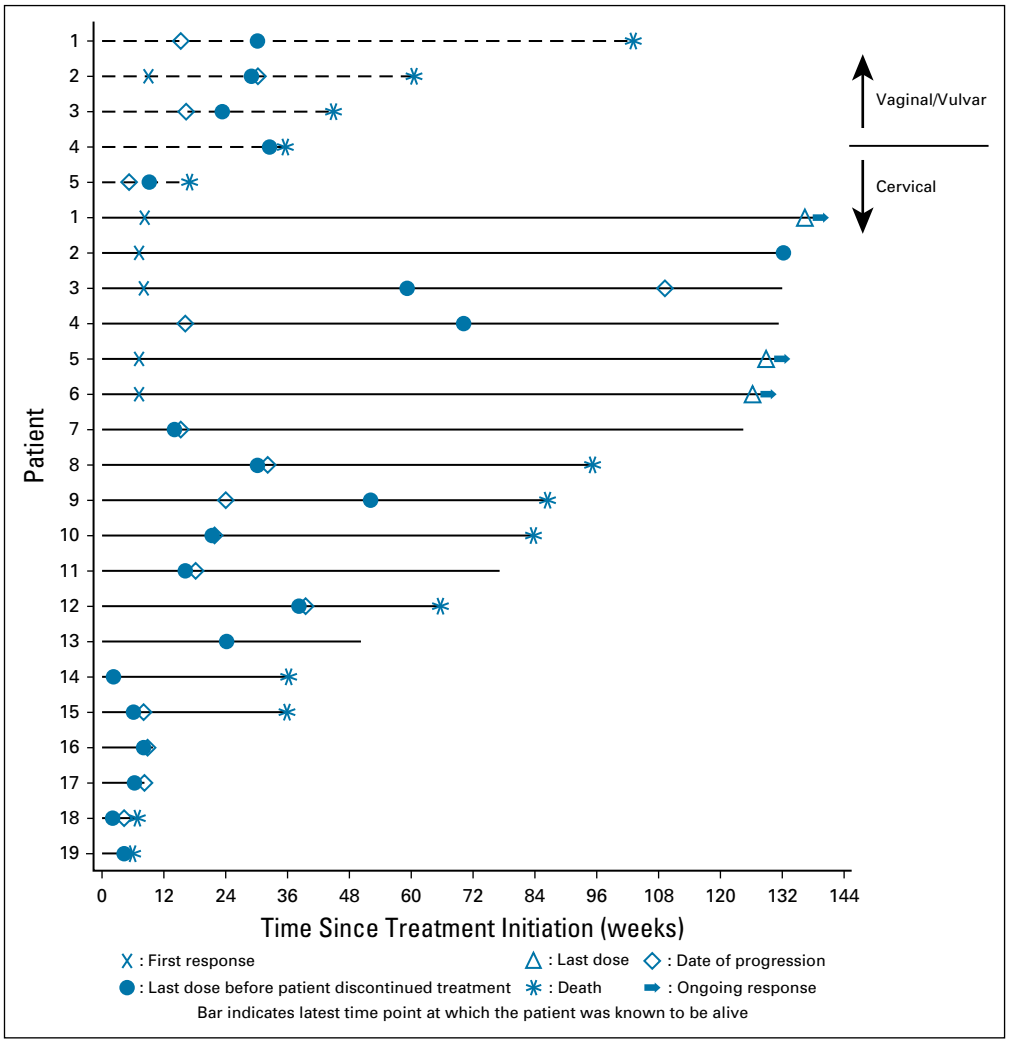

FIG A1. Treatment exposure, time to response, and duration of response in all patients. Patient 2 in the cervical cohort was documented as having progressive disease 5 days after last nivolumab dose; this information is not included in the figure as it was not captured in the data cut reported in the manuscript.

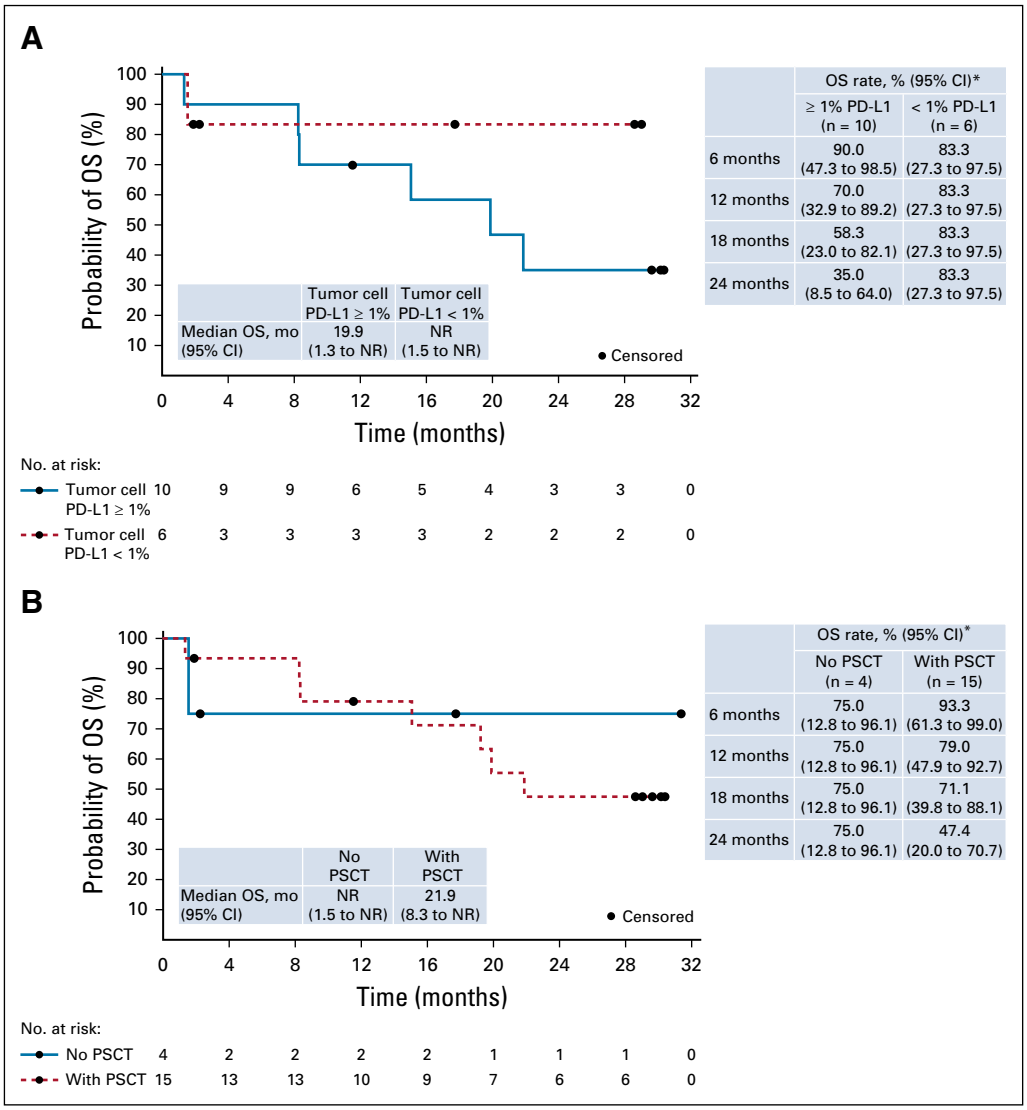

FIG A2. Overall survival (OS) in patients with cervical cancer by (A) Tumor cell programmed death ligand 1 (PD-L1) expression (defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity) and (B) prior systemic cancer therapy (PSCT) for metastatic disease. Owing to the high percentage of censored responses, median and rate estimators may be misleading. CI, confidence interval; NR, not reached. (*) Point estimates are derived from Kaplan-Meier analyses; 95% CIs are derived from Greenwood's formula.

TABLE A1. Patient Disposition

Outcome	Cervical Cancer (n = 19)	Vaginal/Vulvar Cancers (n = 5)
Patients continuing to receive study treatment	3 (15.8)	0
Patients not continuing to receive study treatment	16 (84.2)	5 (100.0)
Reason for treatment discontinuation		
Disease progression	14 (87.5)	4 (80.0)
Adverse event unrelated to study drug	1 (6.3)	1 (20.0)
Study drug toxicity	1 (6.3)	0

NOTE. Data are No. (%).

TABLE A2. Tumor Responses According to RECIST Version 1.1 by Tumor Cell PD-L1 Expression and Prior Therapy for Metastatic Disease in Patients With Cervical Cancer

	Cervical Cancer (n = 19)					
	Tumor Cell PD-L1 Expression[a]				Prior Systemic Therapy for Metastatic Disease	
	PD-L1 ≥ 1%	PD-L1 < 1%	PD-L1 Not Evaluable	PD-L1 Not Reported	No PSCT	PSCT
Response	(n = 10)	(n = 6)	(n = 1)	(n = 2)	(n = 4)	(n = 15)
Investigator-assessed ORR, No. (%; 95% CI)[b]	2 (20.0; 2.5 to 55.6)	1 (16.7; 0.4 to 64.1)	1 (100.0; 2.5 to 100.0)	1 (50.0; 1.3 to 98.7)	1 (25.0; 0.6 to 80.6)	4 (26.7; 7.8 to 55.1)
Best overall response[c]						
Complete response	2 (20.0)	0	1 (100.0)	0	1 (25.0)	2 (13.3)
Partial response	0	1 (16.7)	0	1 (50.0)	0	2 (13.3)
Stable disease	5 (50.0)	2 (33.3)	0	1 (50.0)	1 (25.0)	7 (46.7)
Progressive disease	3 (30.0)	3 (50.0)	0	0	2 (50.0)	4 (26.7)
Disease control rate,[d] No. (%; 95% CI)[b]	7 (70.0; 34.8 to 93.3)	3 (50.0; 11.8 to 88.2)	1 (100.0; 2.5 to 100.0)	2 (100.0; 15.8 to 100.0)	2 (50.0; 6.8 to 93.2)	11 (73.3; 44.9 to 92.2)
Median time to response (range), months	1.8	1.6	1.9	1.6	1.9	1.7
	(1.7-1.9)	(1.6-1.6)	(1.9-1.9)	(1.6-1.6)	(1.9-1.9)	(1.6-1.9)
Median duration of response (range), months[e]	NR	NR	NR	NR	NR	NR
	(23.3-27.6[f])	(24.9[f]-24.9[f])	(29.5[f]-29.5[f])	(26.3[f]-26.3[f])	(29.5[f]-29.5[f])	(23.3-27.6[f])
Duration of response, months[g]						
≥ 3	2 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	4 (100.0)
≥ 6	2 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	4 (100.0)
≥ 12	2 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	4 (100.0)
≥ 18	2 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	4 (100.0)
≥ 24	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	3 (75.0)
Patients with ongoing response of duration ≥ 12 months[g,h]	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	3 (75.0)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: NR, not reached; ORR, objective response rate; PD-L1, programmed death-ligand 1; PSCT, prior systemic cancer therapy; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

[a]Tumor cell PD-L1 expression was defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity.

[b]On the basis of the Clopper and Pearson method.

[c]Assessed by investigators per RECIST.

[d]Proportion of patients with a complete response, a partial response, or stable disease.

[e]Median computed using Kaplan-Meier method.

[f]Censored observation.

[g]Percentages are reported as a fraction of the number of responders.

[h]Responders who had neither progressed nor initiated subsequent therapy at the time of analysis were categorized as patients with ongoing response; responders censored before 9 weeks of the clinical data cutoff date (if the cutoff date was before or at week 48) or before 13 weeks of the cutoff date (if the cutoff date was after week 48) were excluded.