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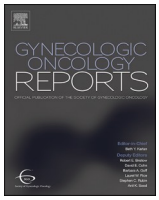

Immune checkpoint inhibitor therapy in advanced cervical cancer: Deepened response with prolonged treatment and repeat response to re-initiation of therapy

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ABSTRACT

Immune checkpoint inhibitors (ICI) were approved in June 2018 for second line treatment of metastatic cervical cancer after progression on platinum-based chemotherapy. A cohort of 10 patients who received single agent ICI as second line treatment was examined, with an initial analysis published in July 2021. We performed an updated review of the duration of treatment response, outcome off treatment after 2 years of therapy, and outcome after re-initiation of ICI. Excluding 4 patients from the original report who subsequently experienced progression of disease and/or death, 6 patients were followed for 40 months (range, 39.2–50.8 months), and all achieved complete response (CR) as their best response after prolonged treatment, including 3 with initial partial response (PR). Four patients discontinued treatment, and two developed asymptomatic recurrence, were both re-initiated on ICI, and reached a CR and PR. The combined positive score (CPS) was variable among responders and non-responders, but levels were highest among the 2 patients off treatment who remained without evidence of disease. This update on prolonged follow up demonstrates that patients who respond to immune checkpoint inhibitors may deepen their response with prolonged treatment, have durable response off treatment and respond again to re-treatment in the event of recurrent disease. A higher CPS score may predict prolonged remission off treatment.

1. Introduction

Management of recurrent cervical cancer has been transformed by the addition of immune checkpoint inhibitors, and multiple agents have shown activity, including pembrolizumab and nivolumab. Pembrolizumab is a monoclonal antibody that targets programmed death receptor-1 (PD-1) (Frenel et al., 2017; Marabelle et al., 2020; Borcoman and Le Tourneau, 2020) and nivolumab is a monoclonal antibody that targets the ligand PDL-1 (Santin et al., 2020). Both inhibit the suppression of T-cell activity and allow for normal immune induction of apoptosis. The phase Ib and II studies, KEYNOTE-028 and KEYNOTE-158, demonstrated activity for single agent pembrolizumab in advanced and recurrent cervical cancer (Frenel et al., 2017; Marabelle et al., 2020). Based on these studies, pembrolizumab has received approval as a single agent for second line use as of June 12, 2018. NRG-GY002 is a phase II trial for nivolumab in recurrent cervical cancer that demonstrated 4% partial response rate and 36% stable disease rate for single agent use. Results from the nivolumab-only arm of the phase I/II CheckMate 358 trial demonstrated objective response rate of 26.3% for cervical cancer (Naumann et al., 2019). The duration of therapy with immune checkpoint inhibitor in responding patients is under debate. These trials limited treatment to a maximum of 2 years, with the potential to restart pembrolizumab in KEYNOTE-028 for disease recurrence if diagnosed within 1 year after achieving at least stable disease (Frenel et al., 2017; Marabelle et al., 2020; Santin et al., 2020; Naumann et al., 2019).

We previously reported on 10 patients with metastatic cervical cancer treated with pembrolizumab or nivolumab monotherapy and reported on a response rate of 70% in this cohort of patients (Shieh et al., 2021). At this time, six patients have been treated for over 2 years. We aim to report their updated best response rate, outcome off immune checkpoint inhibitor therapy, patterns of recurrence, and response to re-initiation of immunotherapy.

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2. Methods

This is a retrospective study including all patients with recurrent/progressive cervical cancer who were treated at Maimonides Cancer Center and whose start date of receiving pembrolizumab or nivolumab treatment was before September 31, 2019. The patients were followed through December 6, 2022. The study protocol was approved by the Institutional Review Board. Electronic medical records were searched to collect demographics, tumor characteristics, treatment history and response. Tumor response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). PD-L1 expression was performed by Foundation Medicine (Cambridge, MA, USA) or Pathline Emerge (Ramsey, NJ, USA). Seven out of 10 patients had data on tumor molecular testing through next-generation sequencing (NGS) performed by Foundation Medicine. Progression free survival was defined as time from beginning of treatment until radiographic progression or death. We correlated clinical factors including PD-L1 CPS and sites of metastatic disease with clinical response.

3. Results

At the time of previous publication in April 2021, after a median duration of treatment of 26 cycles over 20.7 months, the response rate was 70%. The mean PFS was 22.6 months in the 7 responders and 20.7 months in those CPS $>$ 10 (Shieh et al., 2021).

At the current update, four patients have since died of disease, including 3 of the previously noted non-responders and 1 of the previous responders, whose partial response lasted 8.3 months when she died of immunotherapy-related side effects. Clinical courses are detailed in Table 1.

The following analysis focuses on the six alive responders. The median follow up was 45 months, with a range of 39.2 to 50.8 months. All 6 patients achieved CR by RECIST criteria as their best response. The mean time to PR was 3.0 months (range, 1.8–6.0 months) and mean time to CR was 16.0 months (range, 6.7–24.4 months). Of note, four of the six patients had a greater than 4 cm pelvic mass or distant visceral metastases at presentation and still achieved CR and a prolonged response.

After 2 years of pembrolizumab treatment, four patients made the joint decision with their oncologist to discontinue treatment. These patients had achieved CR on multiple CT scans, and 2 patients also had a negative PET CT. Subsequently, two patients were later found to have asymptomatic recurrence on surveillance CT at 9.0 and 11.7 months. Patient 2 had a CT scan with enlarged right retroperitoneal lymph node that was noted to be FDG-avid on subsequent PET CT. Her previous recurrence had included left retroperitoneal lymphadenopathy. She restarted pembrolizumab, had PR on repeat CT scan 3 months later, and has been recommended for proton radiation. She has been on treatment for 3.5 months at the time of this report. Patient 7 had a negative PET CT prior to pelvic exenteration procedure with no residual disease on pathology. Subsequent CT scans were NED until 11 months after surgery, when CT identified an area of suspicious new retroperitoneal lymphadenopathy that was FDG-avid on PET CT. She restarted pembrolizumab, had a CR on CT 6 months later, and remains on treatment for 11.7 months at the time of this report. Clinical course with response to treatment and disease characteristics are depicted for all six responders in Table 1 and Fig. 1.

During the prolonged follow up period, three patients experienced fatigue and were found to have low random cortisol levels, two of whom were managed with hydrocortisone replacement with symptomatic improvement. None of these mild endocrine effects required treatment delays.

In an exploratory analysis, the patients who decided to stop treatment and remained NED had the highest CPS (100and65), compared to those who discontinued treatment and experienced re-recurrence (CPS 5 and 10). TMB was not available for all patients and did not appear to correlate with treatment response.

4. Discussion

This retrospective updated report on a prolonged follow up of six patients with metastatic cervical cancer who received second line single agent ICI treatment attempted to address the questions of duration of response off therapy, pattern of recurrence, and treatment response to re-initiation of the same immunotherapy treatment. Our analysis showed that 50% of the patients who discontinued therapy recurred. The recurrences were asymptomatic, local (mainly in the previously involved lymph nodes sites, and both patients demonstrated another treatment response with re-initiation of single agent immunotherapy. In the initial report, 4 of the 7 responders had a partial response as their best response. With longer duration of therapy, the responses deepened from partial to complete, with all 6 of the responders experiencing CR and 1 of the previous partial responders progressing.

Our patients' response rates are much higher than that seen in trials, with 15% of cervical cancer patients with PD-L1-positive tumors in KEYNOTE-158 experiencing CR or PR compared to our population's 70% at median follow up close to the 2 years of allowed treatment on trial. Two differences that might account for this are the CPS and

Table 1
Clinical characteristics and response to treatment and re-treatment of recurrent/progressive cervical cancer with immune checkpoint inhibitors.

Serial number	CPS	TMB	Duration of treatment (months)	Site of recurrent disease	Initial response	Best response	PFS (months)	Duration off treatment (months)	Response to re-treatment	Duration on re-treatment
Responders continuing on treatment										
3	3	9	49.9	2	PR	CR	48.4	–	–	
10	30	14	48.0	4		PR	36.1	–	–	
Responders off treatment and NED										
1	100	n/a	24.0	1	PR	CR	39.4	17.5	–	
4	65	n/a	31.0	1, 4	PR	CR	50.4	19.8	–	
Responders off treatment with recurrence and re-treatment										
2	5	16	29.5	1, 3	PR	CR	38.5	9.0	PR	3.5
7	10	n/a	24.0	1, 2, 4	PR	CR	35.7	11.7	CR	11.7
Non-responders and 1 with short PR										
5	2	40	1.8	4	PD	PD	2.6	–	–	
6	60	15	7.1	2, 4	PR	PR	6.0	–	–	
8	50	6	14.6*	2	SD	SD	8.4	–	–	
9	0	9	1.4	4	PD	PD	1.7	–	–	

CPS- combined positive score; TMB: tumor mutational burden; n/a- not available; Sites of disease: 1 Pelvic lesion, 2 Pelvic lymph nodes, 3 Retroperitoneal lymph nodes, 4 Distant lymph nodes or visceral organs; PFS- progression free survival; NED- no evidence of disease; CR- complete response; PR- partial response; PD- progressive disease; SD- stable disease. *Patient was off treatment for 5 months after initially stable disease before restarting due to hospitalization and preference for treatment holiday, subsequently with stable disease to progression of disease.

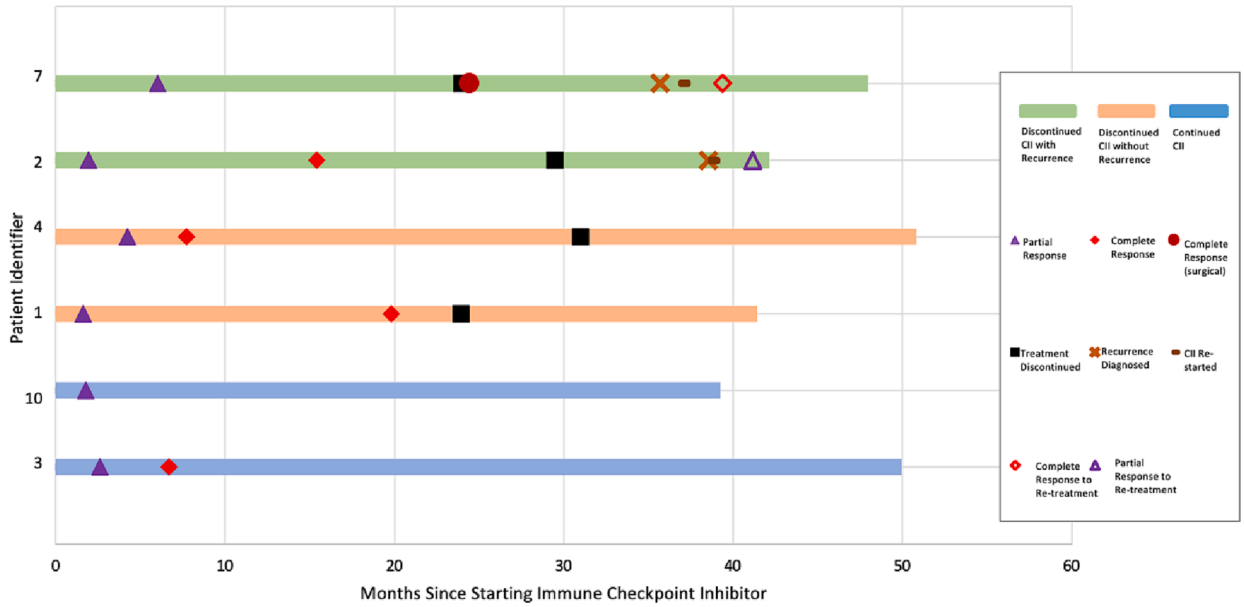

Fig. 1. Treatment Course of Six Patients with Response to Immune Checkpoint Inhibitor Six patients experienced partial and complete response to an immune checkpoint inhibitor. Time (in months) from start of immunotherapy to partial and complete response, durable response, and re-retreatment with another partial or complete response are demarcated. Responses are grouped based on decision to stop treatment with recurrence diagnosed, decision to continue treatment, and decision to stop treatment with continued response.

previous treatments. KEYNOTE-158 did not distinguish between CPS $\geq$ 1 and CPS $\geq$ 10, but 90% of our patient population had a CPS $\geq$ 1 and 60% $\geq$10. 50% of our patients had only received 1 line of systemic therapy prior to starting ICI, compared to 30% in KEYNOTE-158. In addition, the ethnicities of our patients were predominantly Asian and Caribbean (Shieh et al., 2021). Due to the small study size, this result should not be considered generalizable. On the other hand, similar to our patient population, KEYNOTE-158 demonstrated durable and deepened responses, with 50% of responses ongoing at $\geq$ 24 months of follow up and, in the updated analysis, 2 PRs converted to CRs and two additional patients converted to PR (Chung et al., 2021).

Immunotherapy is at the forefront of the treatment landscape for advanced and recurrent cervical cancer. The treatment options have changed since our first report was published in 2021, and the current standard upfront treatment is combination therapy with chemotherapy and immunotherapy with and without bevacizumab based on the KEYNOTE-826 trial, which showed improvement in disease free and overall survival (Colombo et al., 2021). More studies are ongoing, such as a randomized phase III study testing atezolizumab and bevacizumab in combination with chemotherapy in the first line (Grau et al., 2020), or exploring immunotherapy (PD-1 inhibition) with immunotherapy (CTLA-4 inhibition), such as RaPiDS/GOG 3028 for balstilimab with zalifrelimab (O'Malley et al., 2021) and CheckMate 358 for nivolumab with ipilimumab (Naumann et al., 2019). In the face of these advances, clinicians are left with the decisions about transitioning to maintenance immunotherapy, when to discontinue, and whether or not to re-treat with little prospective trial guidance. Single agent immunotherapy is usually safe with low chance of severe side effects and can be continued as maintenance therapy even when it is initially administered in combination with chemotherapy in the first line; however, patients and providers may be reluctant to change course. While we focused on patients who had been treated with single agent therapy, this decision is one we are continuously faced with, now in the upfront as well as recurrent setting. Of note, all our patients who discontinued treatment did so after reaching CR by CT or PET CT criteria. Six of the 10 recurrences described were biopsy-proven. Both of the recurrences requiring re-treatment with ICI were diagnosed based on lesion on a surveillance CT with subsequent increased FDG-avidity of those suspicious areas on PET CT. Although these recurrences were not biopsied, they appeared at the usual predictable sites of recurrence and were technically challenging for biopsy. However, considering the possibility of non-cancer-related hypermetabolic activity due to inflammation, another strategy could be a 3-month follow up with CT to document progression to confirm true recurrence. Our result showed that 50% of the patients who discontinued treatment did not have a recurrence. For those who had a recurrence, it occurred in same retroperitoneal lymph node region but the opposite side as the first recurrence, which led us to question whether longer duration could have prevented another recurrence.

An exploratory analysis of the CheckMate 153 trial addressed the question of duration of treatment in non-small-cell lung cancer (NSCLC) and found an improved PFS and OS for those receiving continuous nivolumab versus a fixed limit of 1 year (Waterhouse et al., 2020). As for the efficacy of re-initiation of immune checkpoint inhibitors a second time after progression, two studies were reviewed which showed conflicting results. In a study evaluating the outcomes of nivolumab re-treatment in NSCLC who previously responded to prior immune checkpoint inhibitors, objective response rate was only 8.5% with median PFS of 2.6 months. In the multivariate analysis, the immunotherapy-free interval was predictive of PFS (HR 2.02, $p = 0.02$) (Akamatsu et al., 2022). In an exploratory study of KEYNOTE-010, patients with NSCLC who were treated with pembrolizumab were evaluated for response to re-treatment as well. Among 79 patients who completed 2 years of treatment, 72.5% remained progression free and 98.7% were alive at 12 months. Of these, only 14 patients started a second course of pembrolizumab treatment. 6 (42.9%) had a PR and 5 (35.7%) had stable disease (Herbst et al., 2020). Our results appeared to align well with this latter study result.

There are other considerations favoring discontinuation of treatment, including financial and physical toxicity in the face of unknown therapeutic benefit (Marron et al., 2021). Significant adverse events were documented in the nivolumab re-treatment study, with nine grade 3 and three grade 4 events among 59 total patients (Akamatsu et al., 2022). In our study, only one patient had a severe adverse treatment-related reaction of immune-related thrombocytopenia during her short treatment duration, which led to her death (Shieh et al., 2021). Three

patients experienced fatigue and were found to have low cortisol in their workup. They were clinically thought to have mild adrenal insufficiency with improvement in symptoms after hydrocortisone replacement. According to NCCN guidelines, a workup with ACTH, renin, LH, FSH, and testosterone levels should be completed for concern for adrenal insufficiency, and an endocrinology consult should be obtained with replacement of corticosteroid and mineralocorticoid as indicated. While adrenal insufficiency has been found rarely in ICI trials, around 1% in single agent therapy (Arnaud-Coffin et al., 2019), it is potentially life-threatening in the event of adrenal crisis. Around 10% of patients on a PDL-1 or PD-1 inhibitor therapy are expected to experience a severe adverse event (Arnaud-Coffin et al., 2019). Discussion of these rare but serious side effects must be part of a provider's counseling on decision to continue ICI.

From a financial standpoint, though, continued treatment requires more frequent visits and financial cost to patients. The listed price of 200 mg of pembrolizumab is $8762, not including infusion center costs (Huang et al., 2017). If patients could be selected for potential to have continued response or potential for response to re-treatment, significant financial burden could be avoided. In that regard, the result from our small cohort on the pattern of recurrence and response to re-treatment is reassuring. Although achieving CR was not dependent on the CPS score, our 2 patients who remained NED off treatment for prolonged time had CPS scores of 65 and 100, raising a hypothesis that a high CPS score may be predictive of prolonged response, while a cut off value remains to be further studied. The possibility of achieving CR was not dependent on CPS, and a larger volume of disease or distant visceral metastases did not exclude patients from having a prolonged response. Our study re-demonstrated that the response to immunotherapy can be very durable, with complete responses lasting months to years.

5. Conclusion

Patients who respond to immune checkpoint inhibitors may deepen their response with prolonged treatment, have durable response off treatment, and may respond again to re-treatment in the event of recurrent disease. A higher CPS score may predict prolonged remission off treatment. However, this small dataset is only hypothesis-generating, and a larger prospective trial is needed to guide management decisions in this setting.

CRediT authorship contribution statement

Jennifer Wolf: Data curation, Writing – original draft, Writing – review & editing. **Yiquing Xu:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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