Precision medicine for cervical cancer

Erica N. Manrriquez, Mae Zakhour, and Ritu Salani

Purpose of review
To summarize the data on precision medicine for cervical cancer including the use of potential biomarkers. We also review ongoing areas of research in cervical cancer therapeutics.

Recent findings
In the current clinical practice, programmed death ligand 1 (PD-L1) expression is used to select patients with cervical cancer for treatment with checkpoint inhibitors. However, more recently presented data suggest that PD-L1 may not be a fully accurate biomarker for selection and further analysis is warranted. With the publication of the molecular landscape of cervical cancer, tumor profile-based therapy selection is of greater interest (i.e. targeting PI3K and HER2).

Summary
In this review, we discuss the role of potential biomarkers for cervical cancer that may assist with the selection of precision therapies. Enrolling patients on active clinical trials will help clarify the role of targeting specific mutations.

Keywords
biomarkers, immunotherapy, precision medicine, targeted therapy

INTRODUCTION

Over the past 50 years, there has been a steady decline in the number of cervical cancer cases in the United States. This is in large part due to cervical cancer screening, treatment of preinvasive disease and human papillomavirus (HPV) vaccination. However, over this same time frame, the rate of cervical cancer-related death has remained relatively stable [1]. This lack of improvement in mortality rate corresponds to those who present with advanced and/or recurrent disease where limited therapies fail to result in curative outcomes.

In the past decade, cervical cancer management has evolved rapidly. In 2014, the addition of bevacizumab to chemotherapy demonstrated improvement in progression free and overall survival (OS) for recurrent, metastatic or persistent disease [2]. More recently, checkpoint inhibitors (CPIs) have become a common choice of treatment after progression on chemotherapy in select patients. On the contrary, though notable response rates (RRs) have been observed, cure rates continue to be extremely low.

In 2017, the cancer genome atlas (TCGA) was published, improving our understanding of the molecular profile in cervical cancer. Novel mutated genes, including ERBB2, CASP8, HLA-A and TGFBR2, and amplifications in immune targets, such as programmed death ligand 1 (PD-L1), PD-L2 and BCAR4, were identified [3]. With insight into potential targets and biomarkers, the future includes precision medicine for patients with cervical cancer. Though targeted therapy for cervical cancer remains in its infancy, we have summarized the current literature and ongoing studies to date.

Programmed cell death protein 1 inhibitors

Immunotherapy, such as CPIs and tumor infiltrating lymphocyte therapy, has revolutionized cervical cancer therapeutics over the last several years. As a virally mediated process, cervical cancer should elicit an immune response in immunocompetent patients, forming the rationale behind the use of immunotherapy in its management. While immunotherapy has demonstrated benefit in patients with a variety of biomarkers, all of which signify immunogenicity and/or genetic instability, a few

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA

Correspondence to Ritu Salani, MD, UCLA Center for Health Sciences, Room 24-126, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA. Tel: +1 310 794 3639; e-mail: RSalani@mednet.ucla.edu

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KEY POINTS

- Increasing evidence supports a role for checkpoint inhibitors (in particular, antiprogrammed cell death protein 1/anti-PD-L1) in recurrent/metastatic cervical cancer regardless of PD-L1 status, although response may be best in PD-L1+ tumors (combined positivity score $\geq$1).
- Alterations in the PIK3CA pathway, including HER2 derangements, have been identified in approximately half of cervical tumors although their role as therapeutic targets is not yet clear.
- Future studies within cervical cancer therapeutics should be developed with precision medicine in mind.

agents have emerged as stand-out treatment options.

Thus far, the primary target of interest has been the programmed cell death protein 1 (PD-1)/PD-L1 pathway. PD-1 is a receptor expressed on activated T cells while PD-L1 is expressed mainly on tumor cell surfaces. The binding of PD-L1 to PD-1 produces an inhibitory signal, limiting tumor cell recognition by the host immune system and inhibiting apoptosis and T-cell activation [4]. Genomic analyses of cervical cancer specimens demonstrate varying, albeit high, rates of PD-L1 amplification [3,5,6]. The combined positivity score (CPS), the ratio of PD-L1 positive cells to total viable tumor cells, was subsequently developed as a clinical scoring system with PD-L1 positivity defined as a score at least 1 [7].

PD-1/PD-L1 inhibition has since gained traction in cervical cancer therapeutics. In the phase II basket trial KEYNOTE-158, 98 patients with previously treated advanced cervical cancer, 77 of whom had PD-L1+ tumors, were evaluated for response to the PD-1 inhibitor pembrolizumab. An objective RR (ORR) of 14% was documented with three complete and nine partial responses (PRs), all of which were in PD-L1+ tumors. The median OS was 9.4 months in the entire cohort and 11 months in PD-L1+ patients. Median duration of response (DoR) was not reached, but 91% had response durations of at least 6 months, and the drug was well tolerated with only 12% experiencing grade 3 or 4 toxicity [8]. Following the clinical activity exhibited in KEYNOTE-158, pembrolizumab was FDA-approved for advanced cervical cancer patients with PD-L1 expression (CPS $\geq$ 1) and progression during or after chemotherapy [9].

CheckMate 358 is an ongoing multicohort phase I/II trial of PD-1 inhibitor nivolumab in recurrent/metastatic virus-associated gynecologic cancers. Of the 24 patients with metastatic disease (19 cervical, 5 vaginal/vulvar), 63% had PD-L1+ tumors. The authors reported an ORR of 26% in the cervical cohort, regardless of PD-L1 status. The median OS was 21.9 months and, after 19.2 months of follow-up, the median DoR was not reached [10].

Another PD-1 inhibitor, balstilimab, was evaluated in a phase II study of recurrent or metastatic disease. One hundred sixty-one patients were treated after one prior line of platinum-based therapy, of which 61.5% were noted to have PD-L1 expression. The ORR was 20% in PD-L1+ patients and 7.9% in PD-L1− patients with a median DoR of 15.4 months. Notably, RRs in cervical adenocarcinoma were 12.5% [11▪].

Recently, the results of a randomized phase III trial evaluating PD-1 inhibitor cemiplimab compared with chemotherapy (pemetrexed, topotecan and gemcitabine) in second-line or greater metastatic disease with progression following platinum-based chemotherapy were presented. Final results revealed a significant improvement in OS (12 vs. 8.5 months) favoring cemiplimab. Similar to balstilimab, cemiplimab also demonstrated an improved median OS in adenocarcinoma when compared with chemotherapy (13.3 vs. 7.0 months). These results were independent of PD-L1 status, though RRs to cemiplimab were higher in those with PD-L1 expression (18.3 vs. 11.4%) and comparable in chemotherapy (7.5 vs. 8.3%). Most importantly, patients receiving cemiplimab experienced lower rates of adverse events and improved quality-of-life outcomes [12▪▪].

The excitement of CPI in the recurrent setting has led to studies in the frontline treatment of advanced/recurrent ovarian cancer. The phase III randomized controlled trial KEYNOTE-826 evaluated the addition of pembrolizumab to platinum-based chemotherapy with or without bevacizumab in 617 patients [13▪▪]. Though PD-L1 expression was not required for enrollment, prespecified analysis based on CPS (<1, $\geq$1 or >10) are planned. In June 2021, a press release reported that the addition of pembrolizumab to chemotherapy improved progression free and OS regardless of PD-L1 status [13▪▪]. Details, including the proportion of patients receiving bevacizumab and the outcomes based on CPS, have yet to be described. However, this is the first phase III trial to demonstrate positive results using CPI in the frontline setting, expanding the role of immunotherapy in the treatment of gynecologic malignancies.

Additional ongoing studies reflect similar themes around the use of PD-1/PD-L1 inhibition in combination with chemotherapy as well as in conjunction with chemoradiation with maintenance use in patients with locally advanced cervical cancer (Table 1). Ideally, these studies, which are performing survival analysis based on CPS/PD-L1

Table 1. Ongoing immunotherapy trials

Trial	Design	Primary endpoint	Status
CALLA	CRT vs. CRT + durvalumab + maintenance durvalumab	PFS	Active, not recruiting
KEYNOTE A18 (GOG 3047)	CRT vs. CRT + pembrolizumab + maintenance pembrolizumab	PFS, OS	Recruiting
BEATcc (GOG 3030)	C/T/bevacizumab vs. C/T/bevacizumab + atezolizumab	OS	Recruiting
FERMATA	C/T ± bevacizumab vs. C/T ± bevacizumab + BCD-100 (PD-1 inhibitor)	OS	Recruiting
SKYSCRAPER-04	Atezolizumab vs. atezolizumab + tiragolumab (TIGIT inhibitor)	ORR	Active, not recruiting
RaPiDS	Balstilimab ± zalifrelimab	ORR	Recruiting

CRT, chemoradiation; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression free survival.

expression, will help clarify the role of CPI in the treatment of cervical cancer.

While the role of PD-L1/CPS as a biomarker for cervix cancer is still under investigation, tumor agnostic biomarkers for CPI use have been identified. First, the presence of mismatch repair deficiency (MMRd) and/or microsatellite instability (MSI), defined as genetic instability that impairs DNA repair processes, received FDA approval for pembrolizumab in May 2017 [14]. Rates of MMRd in cervix cancer are low with a rate of 2.6% in squamous cell cervical cancer [15]. In regards to MSI status, a series of 50 cases reported 14% of cervical cancer cases had MSI, and two additional MSI-low cases were noted to be MMRd [16]. The second tumor agnostic biomarker is tumor mutational burden (TMB) which is the total number of mutations in a coding area of a tumor genome. Typically, 10 mutations per million base pairs are defined as TMB-high, and pembrolizumab received FDA approval for this indication in June 2020 [17]. In cervical cancer, the rate of TMB-high tumors is approximately 6% [18]. Therefore, though rare, these biomarkers may play a role in selecting patients and should be evaluated to ensure all therapeutic options are considered.

CTLA4 inhibitors

In addition to PD-1/PD-L1 blockade, a secondary target of interest is CTLA4 (cytotoxic T-lymphocyte-associated protein 4), which is expressed on regulatory T cells and functions similarly in immune response downregulation. Inhibition of CTLA4 enhances tumor-specific CD8+ T-cell responses providing another opportunity for therapeutic target [4].

In a separate cohort of CheckMate 358, 91 cervical cancer patients, 65% with PD-L1+ tumors, were evaluated for response to nivolumab (PD-1 inhibitor) in combination with ipilimumab (CTLA4 inhibitor). Two combinations of drug dosages and schedules were studied, and outcomes were reported with or without prior systemic therapy. PD-L1 expression was similar in both groups (62.2% combination A, 67.6% combination B). Response was demonstrated with both regimens in patients with and without prior systemic therapy (combination A ORR: 36 vs. 23%; combination B ORR: 46 vs. 32%, respectively). Median progression free survival (PFS), with and without prior systemic therapy, was 3.6 and 13.8 months for combination A and 5.8 and 8.5 months for combination B, respectively. Responses were noted regardless of PD-L1 status but tended to be higher in those with PD-L1+ tumors [19].

Along these same lines, balstilimab and zalifrelimab (CTLA4 inhibitor) are being evaluated in a phase II study. CPS at least 1% was present in 51% of the 143 evaluable patients. The combination demonstrated an ORR 22%, and DoR was not reached at the time of the analysis. Responses were most common in PD-L1+ tumors (27%) but were seen in PD-L1− disease as well (11%) [20].

T-cell therapy

T-cell therapy has been effective in the treatment of hematologic cancers but limited in solid tumors. Targeting the uniformly expressed E7 epitope in HPV-associated malignancies has been identified as a target for T-cell therapy. In a proof of principal study, Nagarsheth *et al.* developed a T-cell receptor that targets HPV 16 E7 through recognition of the E7 epitope complexed with HLA-A*02:01. In a study of 12 patients with HPV 16-positive malignancies – five with cervical cancer – using the T-cell receptor therapy, they reported objective clinical RRs in 50% of patients, including four of eight with CPI-refractory disease [21]. This presents a potential new target for patients with HPV 16 as a biomarker.

OTHER PATHWAYS

In addition to immunotherapy targets, the TCGA also identified other somatic mutations including PIK3CA, PTEN, MAPK1, KRAS, ERBB3, HLA-A and

BCAR4. Though these have not been validated as biomarkers, several are targetable mutations. We have summarized the data, to date, below.

As an upstream regulator of the PIK3CA/AKT/mTOR signal transduction pathway, HER2 has been an oncogene of interest in several cancer types. While HER2 overexpression has been recognized as a prognostic factor and a therapeutic target in breast cancer for over 2 decades, its use as a molecular target in gynecologic cancer, particularly in uterine serous carcinoma, has only recently been established [22]. Significantly, HER2 amplification in cervical cancer was described in 1994 but did not gain traction as a therapeutic target due to a relatively low incidence of HER2 amplification in this malignancy [23–25].

Whole-exome sequencing has identified frequent molecular alterations along the HER2/PIK3/AKT/mTOR pathway [26,27]. Zammataro *et al*. identified genomic alterations in the oncogene PIK3CA or the PIK3CA pathway, including derangements in HER2 expression, in 52% of cervical tumors, primarily consisting of missense mutations and amplifications. Despite the high frequency of PIK3CA alteration, the selective PI3K inhibitor copanlisib demonstrated limited in-vitro activity in these tumors. However, when combined with the pan-HER kinase inhibitor neratinib, copanlisib worked synergistically to durably control both in-vitro tumor growth as well as in-vivo cervical cancer xenografts with aberrations in this pathway [26]. This suggests that a multifaceted approach to targeting this pathway may be required to achieve tumor response.

In the recent phase II SUMMIT basket trial, 16 patients with HER2-mutated cervical cancer were evaluated for response to neratinib, an oral tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), HER2 and HER4. Of the 12 patients with measurable disease, three PRs and three stable diseases were noted for an ORR of 25% and a clinical benefit rate of 50%. Median PFS was 7 months, and median OS was 16.8 months [28▪▪]. Although HER2 amplification appears to be rare in cervical cancer, the era of personalized medicine and routine implementation of next-generation sequencing may help identify those who might benefit from HER inhibition. Certainly, phase III data is needed to better evaluate the efficacy of this therapeutic approach compared with other standard of care options.

Along the same signal transduction pathway, mTOR inhibition has been described in the treatment of cervical cancer. A phase II trial utilizing mTOR inhibitor temsirolimus in 33 cases of recurrent, unresectable or metastatic cervical cancer demonstrated modest activity. While 58% of patients had stable disease for a median duration of 6.5 months, only one patient demonstrated a PR [29]. Recent in-vitro and in-vivo experiments, including a mouse xenograft model, utilizing the new mTOR inhibitor CZ415 in cervical cancer cell lines demonstrated significant inhibition of tumor growth via induction of apoptosis [30]. The role of mTOR inhibition in cervical cancer treatment needs to be better characterized; however, with several of these drugs already in use for other malignancies, it is assuredly a target of interest.

The Ras/Raf/MEK/ERK signal transduction pathway has also been extensively studied in a broad range of malignancies, and several regulators and inhibitors of different molecules along this pathway have been developed. In cervical cancer, limited data are available on the efficacy of these drugs in the advanced or recurrent setting. A recent study utilizing organotypic epithelial tissue demonstrated that high-risk HPV oncogene transcription is governed by MEK/ERK signaling, which suggests that this is an important pathway in HPV-driven cancers such as cervical cancer [31▪]. A small phase II trial combining the MEK inhibitor trametinib and the AKT inhibitor GSK2141795 only enrolled 14 patients but had no responses [32]. Further in-vivo and human studies are required to understand the implications of disrupting the Ras/Raf/MEK/ERK pathway in cervical tumors.

BCAR4 copy number gains were noted in the TCGA analysis. BCAR4's involvement in metastases and activation of the HER2/3 pathway suggests this as a potential target. In a phase II study of stage IVb persistent/recurrent cervical cancer, patients were randomized to receive pazopanib (angiogenic inhibitor targeting vascular endothelial growth factor, platelet derived growth factor receptor and c-Kit), lapatinib (EGFR/HER2 inhibitor) or a combination of the two agents. Pazopanib was noted to have improved PFS (18.1 vs. 17.1 weeks), OS (50.7 vs. 39.1 weeks) and RR (19 vs. 9%) when compared with lapatinib, and the combination arm was deemed futile [33]. Though lapatinib, which would target BCAR4, did not demonstrate favorable results, the patients were not selected based on EGFR expression or HER2 amplification in their tumor, and further evaluation should be considered.

CONCLUSION

As a deeper understanding of potential targets and driver mutations are being evaluated, we hope this will translate to better survival outcomes. Prior negative studies should not be discounted as they may have been affected by lack of selection based on tumor profile. In addition, novel agents such as

tisotumab vedotin, which are not biomarker driven, are being studied, and understanding how to best sequence these therapies will be important. Regardless, enrollment in clinical trials with translational endpoints and biomarker analysis is critical to advancing the care of patients with metastatic/recurrent cervical cancer.

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Conflicts of interest

M.Z. reports advisory board participation for Seagen (formerly Seattle Genetics). R.S. reports advisory board participation for GSK, Merck, Instil Bio, Seagen and Arcus Biologics.

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