

## PD-1/PD-L1 Inhibitors in Cervical Cancer

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*Submitted to Journal:*  
Frontiers in Pharmacology

*Specialty Section:*  
Cancer Molecular Targets and Therapeutics

*ISSN:*  
1663-9812

*Article type:*  
Review Article

*Received on:*  
27 Nov 2018

*Accepted on:*  
18 Jan 2019

*Provisional PDF published on:*  
18 Jan 2019

*Frontiers website link:*  
[www.frontiersin.org](http://www.frontiersin.org)

*Citation:*  
Liu Y, Wu L, Tong R, Yang F, Yin L, Xue J and Lu Y (2018) PD-1/PD-L1 Inhibitors in Cervical Cancer. *Front. Pharmacol.* 10:65. doi:10.3389/fphar.2019.00065

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# PD-1/PD-L1 Inhibitors in Cervical Cancer–

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**Key words:** Cervical cancer, Programmed cell death-1/Programmed cell death-ligand 1 (PD-1/PD-L1), Immune checkpoint inhibitors, Immunotherapy, Human papillomavirus (HPV)

## Abstract

As a Cervical cancer is one of the most common gynecological tumors, and the a majority of early-stage cervical cancer patients in the early stage can recover well achieve good recovery through surgical treatment and concurrent chemoradiotherapy (CCRT). However, for patients with recurrent, persistent, metastatic cervical cancer, effective treatment is rare, except for aside from bevacizumab combined with chemotherapy. To this end, pProgrammed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors might be a novel choice to improve for improving the clinical outcomes of these patients. Thus far, some pivotal trials, including Keynote 028, Keynote 158 and Checkmate 358, have indicated established some clinical benefit of PD-1/PD-L1 inhibitors in cervical cancer. In light of these data, the FDA has approved pembrolizumab for patients with recurrent or metastatic cervical cancer with disease progression during or after chemotherapy. There are also some ongoing studies that may provide more evidence for the PD-1/PD-L1 pathway as a therapeutic target in cervical cancer. In this review, we have summarized the status and application of PD-1/PD-L1 inhibitors in clinical trials for the treatment of cervical cancer and suggested some future directions in this field.

## Introduction

Cervical cancer is one of the most common gynecological tumors. More than

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569,847 women ~~worldwide~~ are diagnosed with cervical cancer annually ~~worldwide~~, ~~accounting for~~ ~~resulting in~~ over 311,365 deaths (Bray et al., 2018). Although the incidence of cervical cancer has been greatly reduced by the use of ~~the human papillomavirus (HPV) vaccines and cervical cancer the screening of cervical cancer~~ (Goodman, 2015), ~~the morbidity of~~ cervical cancer is second ~~in terms of morbidity~~ among gynecological tumors in developing countries (Sahasrabudde et al., 2012). ~~Over 70% cervical cancer diagnosed in developing countries are locally invasive or metastatic~~ Over 70% of cervical cancer cases diagnosed in developing countries ~~is~~are locally invasive or metastatic, ~~which contributes~~contributing to the high mortality ~~rate~~ of cervical cancer. The 5-year overall survival (OS) rate of local cervical cancer can achieve approximately 75-85% through effective treatments such as ~~surgical treatments~~surgery, concurrent chemoradiotherapy (CCRT), etc. (Chen et al., 2015). Nevertheless, the 5-year OS of recurrent, persistent, metastatic cervical cancer is only approximately 15%. The poor prognosis is mainly due to limited therapeutic options (Guitarte et al., 2014). ~~The~~A majority of these patients can only be treated with palliative chemotherapy (Boussios et al., 2016), in which platinum-based ~~chemo~~combination therapies were the prior choice ~~of treatment~~ (Monk et al., 2009). ~~Until~~In 2014, the GOG 240 ~~trial~~ indicated that when bevacizumab was added to ~~the~~ chemotherapy, the objective response rate (ORR) was improved from 36% to 48% (Tewari et al., 2014), ~~while and~~ the OS could be prolonged from 13 months to 17 months for recurrent, persistent, metastatic cervical cancer, thus laying the foundation for the first-line choice of combining bevacizumab with chemotherapy for this population (Tewari et al., 2017). However, for those who progress during ~~the~~ first-line treatment, the lack of effective second-line treatment remains ~~to be~~ the main reason for the high mortality rate ~~of patients with recurrent, persistent, metastatic cervical cancer~~ (Minion and Tewari, 2018). Currently, immune checkpoint inhibitors (Schumacher and Schreiber, 2015), especially PD-1/PD-L1 inhibitors (Constantinidou et al., 2018), have achieved favorable efficacy in treating multiple solid tumors (Gettinger et al., 2018), including cervical cancer (Borcoman and Le Tourneau, 2017). Accumulating evidence has demonstrated that PD-1/PD-L1 inhibitors may be a promising approach for cervical cancer treatment.

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## Immune checkpoint inhibitors

Numerous immunomodulatory ~~therapy~~therapies are being investigated in clinical trials with diverse potential targets, including PD-1/PD-L1, CTLA-4, Tim-3, ICOS, 4-1BB, ~~and~~ OX-40, ~~etc.~~ Among these novel targets, ICOS (Amatore et al., 2018), 4-1BB (~~Amatore et al., 2018~~ ~~Compte et al., 2018~~) and OX-40 (Polesso et al., 2018) ~~belongs to~~belong to ~~the~~are costimulatory receptors, while PD-1/PD-L1 (Raedler, 2015), CTLA-4 (Lheureux et al., 2018) and Tim-3 (Gorris et al., 2018) are negative immune regulators of T cells. Currently, only ~~inhibitors of~~CTLA-4 ~~inhibitors~~ (Hodi et al., 2010) and PD-1/PD-L1 ~~inhibitors~~ (Bagchi, 2014) have been approved by ~~the~~ FDA. ~~Among the immune checkpoint inhibitors (Chen and Mellman, 2013), inhibitors of cytotoxic~~

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T lymphocyte associated protein 4 (CTLA-4) and PD-1/PD-L1 were the most widely studied. CTLA-4 and PD-1/PD-L1 are negative immune regulators of T cells (Fife and Bluestone, 2008). CTLA-4 integrates with the costimulatory ~~receptor molecules~~ CD80 (B7-1) and CD86 (B7-2) that ~~are expressed~~ on the surfaces of antigen-presenting cells (APCs) (Fife and Bluestone, 2008), while PD-L1 is expressed on a wide variety of cell types, including tumor-associated fibroblasts, tumor cells, APCs, etc. (Boussiotis, 2016). As a result, CTLA-4 inhibits T cell activation within secondary lymphoid organs (Kurup et al., 2017), but PD-1/PD-L1 chiefly regulates T cell function within peripheral tissues and the tumor microenvironment (Pardoll, 2012). Therefore, PD-1/PD-L1 ~~has signaling is more specific to tumor than CTLA-4 signaling~~ stronger tumor specificity, and inhibitors of PD-1/PD-L1 may cause less damage to healthy tissue (Boussiotis, 2016;Minion and Tewari, 2018)- (Fig. 1).

Based on the above mechanism, ipilimumab (monoclonal anti-CTLA-4), the first immune checkpoint inhibitor, ~~which was~~ approved for melanoma, had little clinical ~~benefit~~ progress until the emergence of pembrolizumab, and the combination of the two drugs further improved treatment efficacy in malignant melanoma (Boreman and Le Tourneau, 2017;Wang et al., 2017). To date, another monoclonal antibody (mAb) for CTLA-4, tremelimumab, has not been approved for ~~the~~ treatment in any type of cancer. However, mAbs targeting PD-1 (pembrolizumab (Paz-Ares et al., 2018), nivolumab (Long et al., 2018) ~~and~~ cemiplimab (Sidaway, 2018)) and PD-L1 (atezolizumab (Hsu et al., 2018), durvalumab (Siu et al., 2018) ~~and~~ avelumab (Le Tourneau et al., 2018)) have presented clinical advantages in malignant melanoma, advanced non-small cell lung cancer (NSCLC), urothelial cancer (Zhang and Li, 2018) and other tumors (Lim et al., 2018) ~~(Table 1)~~ Table 1). In addition, extensive research has been carried out on gynecological tumors, such as ovarian cancer (Liu and Zamarin, 2018) and breast cancer (Julia et al., 2018), and clinical researches on cervical cancer ~~is are~~ ongoing. At present, some initial results have been achieved.

## Theoretical basis for PD-1/PD-L1 inhibitors in cervical cancer

The expression of PD-L1 on tumor surface has been identified relevant with objective responses to PD-1/PD-L1 inhibitors. To date, numerous studies have investigated the expression of PD-L1 in cervical cancer (Y et al., 2013; N et al., 2016). Expression of PD-L1 has been reported in a range of 34.4%–96% of cervical carcinoma tissues, while expression of PD-L1 in histologically normal cervical tissues was rarely found (EN et al., 2017). Opal L. et al. showed that PD-L1 was positive in 32 of 93 (34.4%) cervical carcinoma sample, subcategorically, 28 of 74 (37.8%) in squamous cell carcinomas, 2 of 7 (28.6%) in adenosquamous carcinomas, and 2 of 12 (16.7%) in endocervical adenocarcinomas (PI and NA, 2017), while in another study, PD-L1 expression was found in 96% of samples (EN et al., 2017). Specifically, for cervical squamous cell cancers (SCCs), PD-L1 expression was found in 80% (56/70) of cases (B et al., 2015). In the TCGA data for cervical SCCs, the amplification or gain of PD-

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L1 was found in 28 of 129 (22%) cases (Dijkstra et al., 2016). Additionally, Feng YC et al. showed that for cervical SCCS samples, the expression rates of PD-L1 in cancer cells and in tumor infiltrating lymphocytes (TILs) were 59.1% and 47.0%, respectively (Wu et al., 2018). Collectively, as a key role of PD-L1 in immune escape, PD-L1 was widely observed in cervical cancer, providing a potential therapeutic target for PD-1/PD-L1 inhibitors.

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The PD-L1/PD-1 axis is one of the most well-known immune-checkpoint pathways with a mechanism of immune ~~evading~~ evasion for cancer cells and thus inhibiting the immune response in various kinds of solid tumors, including cervical cancer (2017). In brief, PD-L1 ~~were~~ ~~was~~ expressed on the surface of cervical tumor cells, ~~antigen-presenting cells~~ APCs and tumor infiltrating leukocytes (TILs), while the PD-1-positive cells were mostly ~~identified~~ identified in ~~as~~ T cells in the stroma of cervical tumors. For the expression of PD-1 in the tumor stroma of cervical cancer, Meng Y, et al. ~~has~~ reported that ~~is~~ 60.82% (59/97) of the patients (59/97) ~~had~~ exhibited PD-1 expression (Meng et al., 2018), while another study showed ~~a result of~~ PD-1 expression in 46.97% (31/66) of the patients (31/66) (Feng et al., 2018).

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To date, numerous studies have investigated the expression of PD-L1 in cervical cancer (Yang et al., 2013; Chen et al., 2016). The expression of PD-L1 has been reported in ~~a range of~~ 34.4%-96% of cervical carcinoma tissues, while expression of PD-L1 in histologically normal cervical tissues was rarely found (Enwere et al., 2017). Opal L. Reddy et al. showed that PD-L1 expression was positive in 32 of 93 (34.4%) cervical carcinoma samples, subcategorically ~~in~~ 28 of 74 (37.8%) ~~in~~ squamous cell carcinomas (SCCs), 2 of 7 (28.6%) ~~in~~ adenosquamous carcinomas, and 2 of 12 (16.7%) ~~in~~ endocervical adenocarcinomas (Reddy et al., 2017). In another study, PD-L1 expression was found in 96% of the samples (Enwere et al., 2017). Specifically, for cervical ~~squamous cell cancers~~ (SCCs), PD-L1 expression was found in 80% (56/70) ~~of~~ cases (Mezache et al., 2015). In the TCGA database for cervical SCCs, the amplification or gain of PD-L1 was found in 28 of 129 (22%) cases (Dijkstra et al., 2016). In addition, PD-L1 can also be expressed on TILs, which plays a role in anti-tumor response inhibition. A study found that for cervical SCCs samples, the expression rates of PD-L1 ~~in~~ on cancer cells and ~~in~~ TILs were 59.1% and 47.0%, respectively (Feng et al., 2018). Collectively, these data suggested that both PD-L1 and PD-1 ~~were~~ ~~are~~ widely ~~observed~~ ~~expressed~~ in cervical cancer tumor cells and stroma, providing ~~the~~ potential therapeutic targets for PD-1/PD-L1 inhibitors.

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Notoriously, persistent ~~human papillomavirus~~ (HPV) infection is involved in the pathogenesis of cervical cancer and is related to ~~the~~ ~~its~~ prognosis ~~of cervical cancer~~. Several teams have interrogated whether HPV infection could affect PD-L1 expression in cervical cancer and found that HPV positivity was positively correlated with increased PD-L1 expression (Mezache et al., 2015; Liu et al., 2017). ~~The underlying mechanism may be that HPV-induced somatic mutations generate a multitude of neoantigens, which play a crucial role in the inhibitory tumor microenvironment, thus leading to the release of immune suppressor molecules such as PD-L1 (S et al., 2017)~~

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Considerable effort has ~~gone into~~ ~~been made to~~ dissecting the underlying mechanism of the association between HPV status and PD-L1 expression in HPV-related solid tumors, mainly head and neck squamous cell carcinoma (HNSCC) and cervical cancer. In HPV-HNSCCs, membranous expression of PD-L1 ~~and significant increased levels of mRNA of IFN- $\gamma$  were found~~ in the tonsillar crypts, ~~As tonsillar crypts witnesses the initial HPV infection, and IFN- $\gamma$  induces PD-L1 expression, this evidence~~ ~~the site of initial HPV infection, as well as and significant levels of mRNA for IFN- $\gamma$ , a major cytokine inducer of PD-L1 expression, were found, which~~ might support the role of the PD-1/PD-L1 interaction in creating an "immune-privileged" site for initial viral infection and subsequent adaptive immune resistance (Franzen et al., 2018). In another study, DNA methylation of PD-L1 was ~~found correlated to be~~ inversely correlated with PD-L1 mRNA expression ( $p \leq 0.002$ ) and was further significantly associated with HPV infection in the TCGA cohort, indicating that DNA methylation of PD-L1 is associated with transcriptional silencing and HPV infection in HNSCCs (Balermipas et al., 2017). In cervical cancer, Qin Y et al. ~~indicted~~ ~~indicated~~ that HPV-induced somatic mutations and a multitude of neoantigens, which played a crucial role in the inhibitory tumor microenvironment ~~and~~, could lead to notable ~~alteration~~ ~~alterations~~ ~~between~~ ~~among~~ checkpoint-related genes such as CTLA-4, PD-1 and PD-L1. Specifically, PD-L1 showed a positive correlation with ENO1, PRDM1, OVOL1, and MNT, ~~all of which are related master regulators of all HPV16 E6 and E7-oncoprotein related master regulators~~ (Qin et al., 2017). Of note, a single-arm, phase II study investigated durvalumab in patients ~~of with~~ recurrent/metastatic HNSCCs ( $n=112$ ) and found that HPV-positive patients had a ~~numerically~~ higher response rate and ~~better~~ survival than ~~that of the~~ HPV-negative ~~patient~~ ~~patients did~~ (Zandberg et al., 2018). Nevertheless, for cervical cancer, the association of HPV status and the efficacy ~~to of~~ PD-1/PD-L1 inhibitors is not ~~yet unveiled~~ ~~certain~~ ~~yet~~ due to the paucity of available data.

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Several studies have probed the role of PD-L1 expression in the prognosis and therapeutic efficacy of cervical cancer. These ~~results separately~~ ~~proved~~ ~~separately~~ that an increase in PD-L1 expression was positively associated with tumor metastasis (Yang et al., 2017), tumor progression (Hsu et al., 2018) and poor prognosis in cervical cancer (Heeren et al., 2016). In this regard, the negative relationship between HPV infection and the clinical outcomes of cervical cancer may be partially attributed to ~~the~~ PD-L1 expression induced by HPV infection (Yang et al., 2017). For patients with locally advanced cervical adenocarcinoma and adenosquamous carcinoma treated with chemoradiotherapy (CRT), the underexpression of PD-L1 was a prognostic factor ~~for~~ ~~of~~ tumor relapse ( $p=0.041$ ), indicating that PD-L1 expression might be a novel biomarker ~~for~~ ~~of~~ CRT outcome (Lai et al., 2017).—

## Clinical research outcomes of PD-1/PD-L1 inhibitors in cervical cancer

Since 2015, ~~multiple~~ ~~wealth of~~ clinical trials have been conducted to explore the application of PD-1/PD-L1 antibodies in cervical cancer. To date, four studies have



yielded preliminary results (Table 2). Keynote 028 (a phase Ib study) and Keynote 158 (a phase II study) evaluated pembrolizumab at the doses of 10 mg/kg and 200 mg/kg, respectively, in recurrent, metastatic cervical cancer. In Keynote 028 (Frenel et al., 2017), 24 patients were enrolled, and the overall response rate (RECIST v1.1) was 17% (95% CI: 5% to 37%). In terms of toxicity, 5 patients experienced grade 3 adverse events (AEs, NCI-CTCAE 3.0), while no grade 4 AEs ~~were was~~ observed. In Keynote 158 (Schellens et al., 2017), 98 patients with recurrent or metastatic cervical cancer were enrolled. With a median follow-up time of 11.7 months, the ORR in 77 patients was 14.3% (95% CI: 7.4% to 24.1%), including 2.6% of the patients with complete responses (CR) and 11.7% of patients with partial responses (PR), whereas no responses ~~were was~~ observed in patients ~~without whose tumors did not have exhibit~~ PD-L1 expression in tumor cells. The most frequent serious adverse reactions ~~reported~~ included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infection (4.1%). Based on Keynote 158, the FDA approved pembrolizumab on June 12, 2018, for advanced cervical cancer with disease progression during or after chemotherapy (<https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm610572.htm>). Checkmate 358 (Hollebecque et al., 2017) (phase I-II studies) adopted nivolumab (200 mg/kg q2w) for the treatment of recurrent, metastatic cervical cancer and resulted in an ORR of 26.3%. The disease control rate was 70.8%. The related grade 3-4 toxic effects included hyponatremia, syncope, diarrhea and hepatocellular injury. From these three studies, pembrolizumab and nivolumab showed promising ~~activities-antitumor effects~~ and were well tolerated in patients with recurrent or metastatic cervical cancer. However, due to a limited follow-up time, progression-free survival (PFS) and OS were not reported. Additionally, the REGN2810 study (Papadopoulos et al., 2016), a phase I multicenter study, assessed REGN2810 (a PD-1 mAb) as a monotherapy and in combination with hyperfraction radiotherapy (hfRT), in combination ~~or~~ with cyclophosphamide (CTX) or with CTX + hfRT in patients with advanced solid tumors, including cervical cancer. This study adopted a dose escalation design, and as of Feb 2016, no dose-limiting toxicity (DLT) was observed. The most common treatment-related AEs were fatigue (n=14, 24.1%), arthralgia (n=7, 12.1%), and nausea (n=6, 10.3%). Additionally, 4 patients experienced grade  $\geq 3$  ~~adverse event~~ AEs. ~~For 9/22-Nine of twenty-two~~ (40.9%) patients who received REGN2810 + hfRT and 2/21 (9.5%) patients who received REGN2810 monotherapy, they were ~~evaluated as having determined to have~~ partial/unconfirmed partial responses (uPR), suggesting that the treatment responses ~~appear was~~ augmented ~~when by REGN2810 was combined with the addition of~~ hfRT.

#### Ongoing clinical research on PD-1/PD-L1 in cervical cancer

As of September 2018, eleven clinical trials have been conducted, mainly in patients with persistent, recurrent, or metastatic cervical cancer, with only three studies on patients with locally advanced cervical cancer. Twenty to thirty cases were intended to be included in the majority of these studies, while there were only 3 studies (Keynote 826, GOG 3016/ENGOT-cx9 and NCT03556839) in which more than 200 cases were intended to be included. Except for the two studies (IMMUVIX, GHR002) aimed at

exploring the immune status of PD-1/PD-L1 in patients with locally advanced cervical cancer, the remaining 12 studies all looked into the applicability of PD-1/PD-L1 inhibitors in cervical cancer. Of these 12 studies, there are 2 studies on nivolumab, 2 on pembrolizumab, 4 on durvalumab, 2 on atezolizumab, 1 on cemiplimab (REGN2810) and 1 on AGEN2034. For PD-1 inhibitors, the difference between the 2 studies on nivolumab is the study population. NRG-GYO-02 was conducted in patients with persistent, recurrent, or metastatic cervical cancer, while the NiCOL study enrolled a larger quantity of more patients with locally advanced cervical cancer. The main difference between the 2 studies on pembrolizumab is that KEYNOTE-826 adopted pembrolizumab in combination with chemotherapy versus placebo, while PAPAYA mainly adopted pembrolizumab in combination with platinum and radiotherapy. The GOG 3016/ENGOT-cx9 (EMPOWER-Cervical) study is an important phase III clinical study to advance the clinical application of cemiplimab (REGN2810) in advanced cervical cancer. NCT03104699 is a phase I/II clinical study on AGEN2034, another PD-1 inhibitor, in advanced solid tumors that includes 75 cases of cervical cancer. In terms of treatment combinations, tremelimumab (a fully human mAb against CTLA-4), Vigil vaccine for cervical cancer, bevacizumab and chemotherapy were paired with PD-1/PD-L1 inhibitors throughout these studies (Table 3).

## Conclusion

Although there are a few studies suggesting the potential feasibility of PD-1/PD-L1 inhibitors for the treatment of cervical cancer, a consideration should be made for the clinical application of PD-1/PD-L1 inhibitors. The inadequate number of cases included and the insufficient follow-up time are the main defects of all the studies, leading to the unavailability of data regarding OS, PFS, AEs, drug resistance and the treatment mechanism as well. These data are very pivotal not only for obtaining a more convincing result, but also for guiding physicians to select the appropriate patients for PD-1/PD-L1 inhibitors.

Currently, most of these studies, including the ongoing studies, are mostly limited to recurrent, persistent, metastatic cervical cancer, which accounts for only a minor portion of patients with cervical cancer. There are several future directions that can be paid given more attention to. First, the latest evidence suggests the a clinical benefit of PD-1/PD-L1 inhibitors as neoadjuvant therapy in lung cancer (Lommatzsch et al., 2018). For patients with early-early-stage cervical cancer, studies in a small sample size can be conducted to investigate PD-1/PD-L1 inhibitors with an attempted of surgical treatment or to prevent postoperative recurrence. Second, for patients with locally advanced cervical cancer who are not sensitive to CCRT or who relapse in the short term after initial treatment, PD-1/PD-L1 inhibitors may be a useful treatment, and we are looking forward to the research targeting this population. Third, for locally advanced cervical cancer patients, whether PD-1/PD-L1 inhibitors can achieve better therapy-therapeutic efficacy in tumors with higher PD-L1 expression before CCRT begins will provide a better understanding of the effects of these inhibitors. Finally,

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since the expression of PD-L1 is related to HPV, combining the level of HPV DNA with the expression of PD-L1 as a biomarker may be able to predict the efficacy of PD-1/PD-L1 inhibitors and the prognosis of patients with cervical cancer. Finally, since PD-L1 expression is correlated with HPV status, more studies are warranted ~~for~~ to provide further insights into the association of HPV status and the efficacy of PD-1/PD-L1 inhibitors in patients with cervical cancer. Combining the level of HPV DNA with the expression of PD-L1 may also ~~act as~~ provide a novel predictive biomarker ~~for~~ of the efficacy of PD-1/PD-L1 inhibitors and the prognosis ~~in~~ ~~for~~ of patients with cervical cancer.

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#### Conflict of interest statement

The authors declare no conflicts of interest.

#### Author Contributions

Jianxin Xue and You Lu conceived the review. Yuncong Liu searched the literature. Yuncong Liu, Limei Yin, Jianxin Xue, and Ruizhan Tong critically appraised the literature and wrote and approved the final version of the manuscript.

#### Abbreviations

~~c~~ervical cancer (CC)  
programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1)  
concurrent chemoradiotherapy (CCRT)  
chemoradiotherapy (CRT)  
cytotoxic T-lymphocyte-associated protein-4 (CTLA-4)  
monoclonal antibody (mAb)  
antigen-presenting cells (APC)  
squamous cell cancers (SCCs)  
non-small cell lung cancer (NSCLC)  
human papillomavirus (HPV)  
tumor infiltrating lymphocytes (TILs)  
hyperfraction radiotherapy (hfRT)  
adverse event (AE)  
objective response rate (ORR)  
overall survival rate (OS)  
progression-free survival (PFS)  
complete responses (CR)  
partial responses (PR)  
unconfirmed partial responses (uPR)  
head and neck squamous cell carcinoma (HNSCC)

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Figure 01.JPEG

