Abstract: Cervical cancer is one of the most common gynecologically malignancies worldwide. Although vaccine and cervical cancer screening including human papillomavirus testing, cytology testing, and colposcopy have developed rapidly in recent years, effectively reducing cervical cancer mortality, cervical cancer remains a malignancy with higher female fatality rates worldwide and has a high risk for socioeconomically disadvantaged groups. The combination of platinum-paclitaxel and chemotherapy, possibly with the addition of bevacizumab, is currently the treatment of choice for advanced cervical cancer. Here, we make a preliminary analysis of cervical cancer immunotherapy.

Key Words: cervical cancer, immune checkpoint, vaccine, immune checkpoint inhibitors

BACKGROUND

Cervical cancer is one of the most common gynecologically malignancies worldwide, with nearly 570,000 new cervical cancer cases and more than 300,000 deaths every year. In 2018, there were about 570,000 new cases and about 310,000 deaths per year worldwide, an increase from 2012.1 Although vaccine and cervical cancer screening, including human papillomavirus (HPV) testing, cytology testing, and colposcopy, have developed rapidly in recent years, effectively reducing cervical cancer mortality, cervical cancer remains a malignancy with higher female fatality rates worldwide and has a high risk for socioeconomically disadvantaged groups. Advanced disease has a poor prognosis.2 Currently, the treatment of cervical cancer depends on the stage of the disease. According to The International Federation of Gynecology and Obstetrics stage, the treatment of cancers confined to the uterus is based on surgery (from tization to hysterectomy), and radiotherapy/chemotherapy is the standard of treatment for locally advanced cancer, and the recurrence rate of locally advanced tumors with chemotherapy and radiotherapy still reaches 20%.3 The combination of platinum-paclitaxel and chemotherapy, possibly with the addition of bevacizumab, is currently the treatment of choice for advanced cervical cancer, but it only has remission purposes.4-6 Therefore, new therapeutic strategies are needed for both locally advanced and metastatic cervical cancer.

Immune Checkpoint

Currently, many immunomodulatory therapies are being investigated in various clinical trials with different potential targets, including programmed cell death-1 (PD-1), CTLA-4, T-cell immunoglobulin mucin molecule-3 (Tim-3), and induced costimulatory molecules, 4-1BB, and OX-40, etc. Among these targets, induced costimulatory molecules, 4-1BB, and OX-40 are costimulatory receptors.7-9 However, PD-1, CTLA-4, and Tim-3 are the inhibitory receptors for T-cell immunity. In addition, the newly discovered inhibitory receptors, including T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain protein (TIGIT), killer cell lectin-like receptor G1, and 2B4, have also gradually attracted public attention.

PD

The programmed death-ligand 1 (PD-L1)/PD-1 axis is a key determinant of physiological immune homeostasis and pathologic immune destabilization. In the context of chronic antigen continuous stimulation and presence, T cells gradually lose their effector-killing function, and eventually develop a state of effector (or dysfunctional) depletion. It was recently shown that high PD-1 expression is one of the features of effector killing of depleted T cells.10 PD-1 plays a role in causing an immune-dysfunctional state in depleted T cells. In cancer, a significant enrichment of PD-1-positive T cells in the tumor tissue and peripheral blood was detected.11,12 Tumor cells in the tumor microenvironment (TME) are subjected to immune surveillance from both innate and adaptive immunity. Many inflammatory cytokines are present in this region and coordinate the balance of antitumor immunity. However, cancer cells can also hijack inflammatory pathways to create favorable conditions for tumor progression by suppressing antitumor immunity. TME induces PD-L1 expression by increasing proinflammatory cytokines (eg, interferon [IFN], tumor necrosis factor, and interleukin [IL-6]), weakens the activation of immune cells, defends against T-cell attack, and further enhances the immune escape of cancer cells.13 IFN is a proinflammatory cytokine produced by T cells and natural killer (NK) cells that promotes the presentation of neontigens on tumor cells by enhancing major histocompatibility complex expression. Binding of the IFN to its receptor results in the activation of the classical JAK-STAT signaling pathway that induces an increased expression of a range of transcription factors.14,15 By controlling the IFN/JAKSTAT1 pathway, PD-L1 expressed by cancer cells can inactivate CTLs and attenuate immune surveillance in the TME. Lipopolysaccharide also leads to increased PD-L1 expression. Lipopolysaccharide activates NF-kB and induces, via TLR4, the secretion of type I IFN.16

Many oncogenic signaling pathways may promote tumor growth by driving the expression of PD-L1, thus leading to immune escape. Overexpression of the MYC oncogene occurs in ~70% of all cancers. MYC gene knockdown or...
pharmacological inhibition inhibited PD-L1 expression, and MYC was able to directly bind to the PD-L1 promoter, suggesting that PD-L1 can be directly regulated by MYC at the transcriptional level.\textsuperscript{11} Binding to the PD-L1 promoter suggests that PD-L1 can be directly regulated in by MYC at the transcriptional level. Another driver of PD-L1 upregulation is anaplastic lymphoma kinase (ALK), which promotes PD-L1 expression through STAT3 after hyperactivation of ALK signaling caused by NPM-ALK gene fusion.\textsuperscript{18} In addition to MYC and ALK, HIF1/2 also binds to the hypoxia response element of the PD-L1 promoter region, resulting in increased PD-L1 transcript expression.\textsuperscript{19,20} Posttranslational modifications, including glycosylation, phosphorylation, and ubiquitination play an important role in the regulation of the protein stability, translocation, and protein-protein interactions of PD-L1. In the study of epidermal growth factor/epidermal growth factor receptor signaling, the B3GNT3-mediated poly-N-acetyl lactosamine glycosylation at both PD-L1 N192 and N200 is required for the PD-L1/PD-1 interaction.\textsuperscript{21} These findings support an important role for PD-L1 glycosylation in suppressing antitumor immunity in T cells.

**CTLA-4**

CTLA-4, also known as CD152, is one of the important costimulatory molecules on the T-cell surface. The CTLA-4 gene is located at the location of 2 on band 33 (2q33) of chromosome long, which belongs to the same family as CD28 molecules, can be combined with B7 receptor molecules on the surface of antigen-presenting cells (APCs).\textsuperscript{22} However, CTLA-4 has a strong binding force with B7 molecules and can competitively bind B7 molecules with CD28 molecules, blocking the signaling pathway produced by CD28 and B7 molecules, and play a role in negatively regulating the proliferation and differentiation of T cells. Meanwhile, the binding of CTLA-4 to B7 molecule inhibited cytokine secretion and cell cycle progression. At present, scholars have done a lot of research on the polymorphism of CTLA-4 gene.\textsuperscript{23} The polymorphisms of CTLA-4-318, CT60, and + 49 AA genes were related to the development of cervical cancer and affected the differentiated function of T cells. Another study showed that the ratio of regulatory T cells (Tregs) to CD4 + T cells and CTLA-4 expression on the Tregs cells. Tregs cell surface showed significantly higher expression rates in advanced non–small cell lung cancer patients than in adjacent tissues.\textsuperscript{24} In view of the above studies, to effectively help patients with antitumor immunotherapy, some scholars will fuse the T-cell antigen CTLA-4 with HPV16 E7 and E6 into a fusion therapy DNA vaccine (pcctl4-e76e), further verified in mice, with high antitumor specificity and relatively strong specific CTL response, the development of the vaccine may provide a new idea for cervical cancer patients.\textsuperscript{25} A recent clinical trial reported the safety and antitumor activity of anti-CTLA-4 monoclonal antibody Ipilimumab in recurrent cervical cancer showed that Ipilimumab could be tolerated in the population and can mediate anti-CTLA-4-specific immune response, but the promotion of this drug requires extensive and long-term clinical observation.\textsuperscript{26}

**TIM-3**

The Tim gene family was discovered in 2001 by Mcntire and colleagues and was named Tim for its containing immunoglobulin IgV-like and mucin domains.\textsuperscript{27} Tim-3 is mainly expressed on the differentiating mature Th1 surface and, which, upon binding to its corresponding ligand, acts as a negative regulator and negatively regulates the immune response. The presence of Tim-3 with these coexpressing cells can affect the cell cycle and cell proliferation, as well as the secretion of cytokines such as IL2, tumor necrosis factor- and IFN, induced incompetence, or depletion of CD8 + T cells. Tim-3 was upregulated in hepatocellular carcinoma immune microenvironment and further promoted hepatocellular carcinoma cell proliferation.\textsuperscript{28} In cervical cancer patients, Tim-3 is in a high expression state, and the degree of its expression is related to cancer progression and metastasis. The multivariate analysis shows that Tim-3 expression is an independent factor in predicting cervical cancer prognosis, and it is closely related to the metastasis of cervical cancer.\textsuperscript{29} Related studies have found that, CD8 + T cells Tim-3 can restore secretory cytokine function and effectively control the tumor growth after blocking the Tim-3/PD-1 signaling pathway in tumor patients.\textsuperscript{28} Tim-3 is also highly expressed on the surface of tumor-infiltrating dendritic cells (DCs), and Tim-3 can reduce the entry of nucleic acid from tumor dead cells into the DCs by interacting with B1 protein, and subsequently inhibit the antitumor immune response caused by nucleic acid.\textsuperscript{30} Alternatively, promoting the production of Tregs during tumor progression further influences the tumor patient prognosis, a process that is correlated with Tim-3–mediated downregulation of NK cells.\textsuperscript{31} On the basis of the above mechanistic studies, the Tim-3 blocker Ipilimumab has been studied in tumor patients in recent years, and the results show that some patients benefit from it.

**TIGIT**

However, in recent years, another type is specifically expressed in activated T cells, regulatory T cells, and NK cells. The inhibitory receptor TIGIT on the surface of immune cells has received much attention.\textsuperscript{32} TIGIT is a T-cell immunoglobulin and ITIM domain protein, also known as Vsig9, Vstn3, or WUCAM. TIGIT is a type I transmembrane protein containing both Ig and ITIM domains, including the IgV extracellular segment and the immunoglobulin tyrosine tail-like phosphorylated fragment. TIGIT binds to the adhesion molecules, CD155, and CD122 and is essential for T cells, as well as for NK cell-mediated cytotoxic anti-tumor resistance.\textsuperscript{33} CD155 and CD122 also associate with other ligands, including CD226, the costimulatory molecule of TIGIT, which interacts with CD132 to form a low-affinity complex and effectively enhances the IL-10 secretion by binding to CD155, thereby inhibiting the proliferation and differentiation of CD8 + T lymphocytes. Additional studies have shown that TIGIT suppresses T-cell function through competitive effects with CD226. Moreover, studies have shown that tumor-infiltrating T lymphocytes have high surface expression of TIGIT in non–small cell lung cancer, colon cancer tissues, which is associated with the inactivation of PD-1–expressing tumor antigen-specific CTLs.\textsuperscript{34} CD226 is a cytokine receptor subunit that binds to CD112 to form a low-affinity IL-2 receptor; CD25 (IL-2R) and CD112 to form a high-affinity IL-2 receptor; and IL-2 to promote lymphocytes. Proliferation, differentiation, and participation in the regulation of peripheral immune tolerance.\textsuperscript{35}
Immune Checkpoint Inhibitors

Since 2015, relevant clinical trials of cervical cancer treatment have been conducted against various ICIs. KEYNOTE-028 is a phase I study of pembrolizumab in advanced solid tumors, where the CC cohort contained 24 patients with stage IB or recurrent cervical cancer with PD-L1 expression > 1%, all had previous systemic chemotherapy, 63% had 2 or more regimens, and 42% had previous bevacizumab treatment. The enrolled patients were treated with 10 mg/kg of PD-1 antibody pembrolizumab every 2 weeks for 24 months. The results showed an overall objective response rate (ORR) of 17% (4/24), a case fatality rate of 12.5% (3/24), a 6-month progression-free survival (PFS) of 13%, and an overall survival rate of 66.7%. A more interesting is the KEYNOTE-158 phase II clinical study, also for previously treated patients with advanced cervical cancer, unlike KEYNOTE-028, where the enrolled patients no longer limit their PD-L1 status. Preliminary results from the first 47 patients showed an ORR of 17%. Although the ORR was not associated with PD-L1 status, 87% of the patients were PD-L1 positive (> 1%). As 91% of patients were effective and responded for > 6 months, the US Food and Drug Administration has accelerated the approval of apolizumab for the treatment of recurrent or metastatic cervical cancer. Like pembrolizumab, nivolumab is also an antibody directed against PD-1 and was first used for the treatment of CC patients in the NRG-GY002 II study. All patients in this study received 1 chemotherapy in relapse, and 77% of patients expressed PD-L1. Of the 25 evaluable responses, although only 1 patient had a PR, the right rate was 4%. But the median survival period in this group was 14.5 months (95% CI, 8.3 to 26.8). CheckMate 358 is a single-arm clinical trial evaluating Nivolumab in HPV-positive recurrent or metastatic cervical, vulvar, or vaginal cancer, enrolling 24 patients with 19 cervical and 5 exceptional vaginal or vaginal cancers. The treatment regimen is 240 mg intravenous infusion every 2 weeks with a median follow-up of 31 weeks. The results showed an objective response rate of 26.5% and was not associated with PD-L1 or HPV status. A clinical trial evaluating the efficacy and safety of the CTLA-4 inhibitor Iplimunab enrolled 42 subjects with metastatic or recurrent cervical cancer with an intravenous dose of Iplimunab at 10 mg/kg every 3 weeks, and 1 course every 12 weeks thereafter. One out of 34 patients that could be used for efficacy assessment had a partial remission, 10 were stable, and 23 progressed, with a right rate of only 3%. The patient had a median PFS of 2.5 months, and the median overall survival was 8.5 months. Several other checkpoint inhibitors are currently under development. The targets of these antibodies include TIM-3, LAG-3, killer cell lectin-like receptor G1, and TIGIT. It remains to be determined whether they are more active than the currently available cervical cancer drugs.

Vaccine

Vaccines With Bacteria as Carriers

Listeria monocytogenes is the bacterial carrier that has attracted the most attention. The vaccine Lm-LO-E7 (a therapeutic HPV vaccine based on a listeria vector) produces an immune response against the E7 oncoprotein by expressing the HPV 16 E7 antigen. A peptide-based vaccine is stable, safe, and easy to produce. Long overlapping peptide (SLP) regimen containing E6/E7 peptide synthesis has been shown to be effective in some preclinical models, can increase the innate immunity and adaptive immunity, to 20 advanced or recurrent cervical cancer patients vaccinated by E6 and E7 overlapping peptide and 51 HPV16 synthetic 5 peptide adjuvant (Montanide ISA-51), 9 cases of HPV16-specific T-cell response. In addition, the long peptide vaccine (ISA101/ISA101b), consisting of the E6 and E7 genes of HPV 16, is in phase II clinical trials to evaluate the safety and efficacy of its combination with palitaxel and carboplatin (plus or without bevacizumab) for advanced or recurrent cervical cancer.

Protein-based Vaccines

E6/E7 or HPV fusion proteins have been used as a source of antigen in early therapeutic vaccines with the advantage of including many CD4 + and CD8 + T epitopes and therefore not restricted by major histocompatibility complex; however, the potential disadvantage of protein vaccines is that they may induce antibody responses rather than CTL responses, antigen targeting of fusion proteins of DC, and the use of adjuvants can enhance immunogenicity. TA-CIN, a fusion protein subunit vaccine consisting of HPV 16 L2, E6, and E7, showed 63% of patients with increased CD4 + and CD8 + T cells in phase II trials (VIN2-3) 1 year after TA-CIN vaccination, and vaginal intraepithelial neoplasia completely subsided.

Nucleic Acid Vaccine

DNA vaccines are mostly bacterial-derived plasmids engineered genetically to encode immunogens under the control of promoters, thereby promoting stable DNA expression in cells and inducing adaptive immunity. Despite the advantages of DNA vaccines, easy production, and reproducible administration of DNA vaccines, they lack relative immunogenicity, and the delivery of vaccines such as electroporation, encapsulation, gene guns, or laser therapy has been identified as methods to enhance immunogenicity. At present, DC is a key element in DNA vaccine development, because DC is an important APC capable of initiating naive T cells. RNA-based vaccines are derived from RNA replicon systems of positive and negative single-stranded RNA viruses. The obvious advantage of RNA replicon vaccines is that their ability to self-replicate in a variety of cells and can help maintain cellular
antigen expression, allowing them to produce more target proteins than conventional DNA vaccines, but they are limited by poor stability and poor cell-to-cell diffusion.

Cell Immunotherapy

The DC-based HPV vaccine has emerged as a potential therapeutic vaccine against HPV-related malignancies because of it. Not only are they the main APCs, but they can also serve as natural adjuvants to enhance the effectiveness of antigen-specific immunotherapies against cancer. Although can use small interference with prosapoptotic molecules of RNA (small interfering RNA), DC, there are still because of technical requirements lead to mass production, effective route of vaccine drug delivery is not certain, need patients to provide enough autologous DC, low transduction efficiency, terminal differentiation DC cannot in vitro amplification and DC life is limited. 49 Adoptive cell therapy (ACT) or T-cell therapy based on T cells has made a breakthrough in the era of precision medicine. ACT is a highly personalized approach to specifically kill tumor cells by using autologous or allogeneic tumor-specific T cells after mass in vitro expansion or modified and amplified by genetic engineering techniques. They mainly include tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor T cells (CAR-T), and T-cell receptor-modified T cells (TCR-T). TILs are a heterogeneous group of lymphocytes that infiltrate primary tumors, metastatic tissues, and lymph nodes bearing tumors to control tumor growth. A higher proportion of tumor-specific T cells of TILs compared with peripheral lymphocytes. It has been shown that IL-7 and IL-15 can maximize tumor-reactive TIL amplification in vitro as compared with IL-2. Studies have found that the infusion of TIL (mainly CD8 +) can transport, infiltrate, and destroy tumor cells, leading to most patients with cancer regression and produce tumor antigen-specific memory T cells, and can circulate in patients and play a sustained role in cancer, thus confirming the feasibility of ACT therapy in patients with advanced cervical cancer treatment. 50

CONCLUSIONS

With the development of immunotherapy in cancer, which has shown strong clinical efficacy in many malignancies, including prolonged patient PFS or overall survival in many cancer patients, whereas targeting monoclonal antibodies against immune checkpoint proteins have been successful. However, most patients initially fail to respond to therapy or have limited efficacy, so they need to further enhance the clinical benefits of single immunotherapy by combining relevant traditional therapies or developing drugs with synergistic mechanisms, thus making immunotherapy more widely available for common malignancies. The combination of immunotherapy and chemotherapy has a high response rate in triple-negative breast cancer and HPV-positive head and neck squamous cell carcinoma patients compared with previous treatments, including immunotherapy combined with radiotherapy in advanced lung cancer treatment and nanoscale drugs in enhanced immunotherapy. Collaborative combination of immunotherapy agents and new tricombinations of immunotherapy and targeted therapy are being studied, all of which will enhance the potential for the clinical success of immunotherapy. Although cancer immunotherapy has been successfully used in a variety of human cancers, relevant evidence-based medical evidence suggests that only a few patients with advanced tumors achieve durable survival in these therapies, that cancer presents differently in different patients, and that specific human tumors may differ. All of these indicate the complexity and predictability of the interaction between the human immune system and cancer, meaning that cancer immunotherapy still faces many challenges.

ACKNOWLEDGMENTS

The authors thank all those who have helped in researching and writing this paper. The authors thank Professor AiZen Fu, from whose lectures have benefited greatly. The authors particularly indebted to Zou who gave kind encouragement and useful instruction all through the writing. Sincere gratitude should also go to all the learned professors and warm-hearted teachers who have greatly helped in the study. And the authors also thank friends and family who gave much encouragement and financial support, respectively. Moreover, the authors also extend the thanks to the library and the electronic reading room for providing much useful information for the thesis.

REFERENCES

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3:524–548.
2. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020;8:e191–e203.
3. Gupta S, Maheshwari A, Parab P, et al. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IB squamous cervical cancer: a randomized controlled trial. J Clin Oncol. 2018;36:1548–1555.
4. Stolnicu S, Hoang L, Soslow RA. Recent advances in invasive adenosquamous carcinoma of the cervix. Virchows Arch. 2019;475:537–549.
5. Tewari KS, Sill MW, Long HJ III, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370:734–743.
6. Bermudez A, Bhatia N, Leung E. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2015;131(suppl 2):S88–S95.
7. Amatore F, Gorvel L, Olive D. Inducible co-stimulator (ICOS) as a potential therapeutic target for anti-cancer therapy. Expert Opin Ther Targets. 2018;22:343–351.
8. Compte M, Harwood SL, Muñoz IG, et al. A tumor-targeted trimeric 4-1BB-agonist antibody induces potent anti-tumor immunity without systemic toxicity. Nat Commun. 2018;9:4809.
9. Polleso F, Weinberg AD, Moran AE. Late-stage tumor regression after PD-L1 blockade plus a concurrent OX40 agonist. Cancer Immunol Res. 2019;7:269–281.
10. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol. 2015;15:486–499.
11. Gros A, Parkhurst MR, Tran E, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med. 2016;22:433–438.
12. Gros A, Robbins PF, Yao X, et al. PD-1 identifies the patient-specific CD8 tumor-reactive repertoire infiltrating human tumors. J Clin Invest. 2014;124:2246–2259.
13. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002;8:793–800.
14. Platania LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat Rev Immunol. 2005;5:375–386.
15. Lee SJ, Jang BC, Lee SW, et al. Interferon regulatory factor-1 is prerequisite to the constitutive expression and IFN-gamma-induced upregulation of B7-H1 (CD274). FEBS Lett. 2006;580:755–762.
16. Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway. Cytokine. 2008;42:145–151.
17. Assaves V, Tesmetzis N, Chioureas D, et al. PD-L1 is commonly expressed and transcriptionally regulated by STAT3 and MYC in
ALK-negative anaplastic large-cell lymphoma. *Leukemia*. 2017;31:1633–1637.

18. Marzec M, Zhang Q, Goradia A, et al. Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1). *Proc Natl Acad Sci USA*. 2008;105:20852–20857.

19. Barsoum IB, Smallwood CA, Siemens DR, et al. A mechanism of hypoxia-mediated escape from adaptive immunity in cancer cells. *Cancer Res*. 2014;74:665–674.

20. Messay Y, Gad S, Noman MZ, et al. Renal Cell Carcinoma Programmed Death-ligand 1, a New Direct Target of Hypoxia-inducible Factor-2 Alpha, is Regulated by von Hippel-Lindau Gene Mutation Status. *Eur Urol*. 2016;70:623–632.

21. Li CW, Lim SO, Chung EM, et al. Eradication of triple-negative breast cancer cells by targeting glycosylated PD-L1. *Cancer Cell*. 2018;33:187–201.e10.

22. Condomines M, Arnason J, Benjamin R, et al. Tumor-targeted human T cells expressing CD28-based chimeric antigen receptors circumvent CTLA-4 inhibition. *PLoS One*. 2015;10:e0130518.

23. Lee YH, Song GG. A meta-analysis of the association between gene polymorphisms in patients with HBV-related hepatocellular neoplasia. *Mediators Inflamm*. 2016;2016:6891482.

24. Long M, Beckwith K, Do P, et al. Ibrutinib treatment improves T cell number and function in CLL patients. *Oncotarget*. 2017;12:3052–3064.

25. Gan L, Jia R, Zhou L, et al. Fusion of CTLA-4 with HPV16 E7 and E6 enhanced the potency of therapeutic HPV DNA vaccine. *PLoS One*. 2014;9:e108892.

26. Chen Z, Pang N, Du R, et al. Elevated Expression of Programmed Death-1 and Programmed Death Ligand-1 Negatively Regulates Immune Response against Cervical Cancer Cells. *Mediators Inflamm*. 2016;2016:6891482.

27. Wang S, Zhu X, Xu Y, et al. Programmed cell death-1 (PD-1) and T-cell immunoglobulin mucin-3 (Tim-3) regulate CD4+ T cells to induce Type 2 helper T cell (Th2) bias at the maternal-fetal interface. *Hum Reprod*. 2016;31:700–711.

28. Li Z, Li N, Li F, et al. Immune checkpoint proteins PD-1 and TIM-3 are both highly expressed in liver tissues and correlate with their gene polymorphisms in patients with HBV-related hepatocellular carcinoma. *Medicine (Baltimore)*. 2016;95:e5749.

29. Li F, Dang J, Jiang M, et al. Upregulation of Tim-3 expression at feto-maternal interface may explain embryo survival in the CBAXDBA/2 model of abortion. *Am J Reprod Immunol*. 2018;79.

30. Takano S, Saito H, Ikeguchi M. An increased number of PD-1+ and Tim-3+ CD8+ T cells is involved in immune evasion in gastric cancer. *Surg Today*. 2016;46:1341–1347.

31. Sarhan D, Hrippen KL, Lemire A, et al. Adaptive NK cells resist Tim-3 expression at feto-maternal interface may explain embryo survival in the CBAXDBA/2 model of abortion. *Am J Reprod Immunol*. 2018;79.

32. Fuhrman CA, Yeh WI, Seay HR, et al. Divergent Phenotypes of Human Regulatory T Cells Expressing the Receptors TIGIT and CD226. *J Immunol*. 2015;195:145–155.

33. Joller N, Haller JP, Bryndal B, et al. Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. *J Immunol*. 2011;186:1338–1342.

34. Kamran N, Takai Y, Miyoshi J, et al. Toll-like receptor ligands induce expression of the costimulatory molecule CD155 on antigen-presenting cells. *PLoS One*. 2013;8:e54406.

35. Yu X, Harden K, Gonzalez LC, et al. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. *Nat Immunol*. 2009;10:48–57.

36. Gao J, Zheng Q, Xin N, et al. CD155, an onco-immunologic molecule in human tumors. *Cancer Sci*. 2017;108:1934–1938.

37. Lozano E, Dominguez-Villar M, Kuchroo V, et al. The TIGIT/CD226 axis regulates human T cell function. *J Immunol*. 2012;188:3869–3875.

38. Johnston RJ, Comps-Agrar L, Hackney J, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. *Cancer Cell*. 2014;26:923–937.

39. Villarreal DO, Allegrezza MJ, Smith MA, et al. Targeting of CD122 enhances antitumor immunity by altering the tumor microenvironment. *Oncotarget*. 2017;8:109151–109160.

40. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-defective cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38:1–10.

41. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2021;398:759–771.

42. Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 538 Trial. *J Clin Oncol*. 2019;37:2825–2834.

43. Lheureux S, Butler MO, Clarke B, et al. Association of ipilimumab with safety and antitumor activity in women with metastatic or recurrent human papillomavirus-related cervical carcinoma. *JAMA Oncol*. 2018;4:e173776.

44. Menderes G, Black J, Schwab CL, et al. Immunotherapy and targeted therapy for cervical cancer: an update. *Expert Rev Anticancer Ther*. 2016;16:83–98.

45. Peter M, Kühnel F. Oncolytic adenovirus in cancer immunother-apy. *Cancers*. 2020;12.

46. Hasan Y, Furtado L, Tergas A, et al. A phase 1 trial assessing the safety and tolerability of a therapeutic DNA vaccination against HPV16 and HPV18 E6/E7 onecogenes after chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys*. 2020;107:487–498.

47. Arbyn M, Xu L, Simoens C, et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Syst Rev*. 2018;5:CD009069.

48. Östergård S, Vorbeck CS, Meinert M. Vulvar intraepithelial neoplasia. *Ugeskr Laeger*. 2018;180.

49. Schetters ST, Jong WSP, Horrevorts SK, et al. Outer membrane vesicles engineered to express membrane-bound antigen program dendritic cells for cross-presentation to CD8(+) T cells. *Acta Biomater*. 2019;91:248–257.

50. Zsíros E, Tsuji T, Odunsi K. Adoptive T-cell therapy is a promising salvage approach for advanced or recurrent metastatic cervical cancer. *J Clin Oncol*. 2015;33:1521–1522.