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Novel therapeutics for recurrent cervical cancer: Moving towards personalized therapy

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Abstract

While screening programs and HPV vaccination have decreased the incidence of cervical cancer, still over 13,000 cases occur in the United States annually. Early stage cervical cancer has an excellent long-term prognosis, with 5-year survival for localized disease being >90%. Survival decreases markedly for both locally advanced and metastatic disease, and both are associated with a higher risk of recurrence. Few effective treatment options exist for persistent, recurrent, or metastatic cervical cancer. In 2014, the anti-VEGF antibody bevacizumab was approved in combination with chemotherapy based on the results of the phase III GOG-240 study. As the majority of cervical cancers have a viral etiology, which impairs the immune system, immunotherapy using checkpoint inhibitors and other agents, appears to be a promising approach. In June 2018, the US FDA approved the anti-PD1 antibody pembrolizumab for recurrent or metastatic cervical cancer with PD-L1 expression that progressed after one or more lines of chemotherapy. Another anti-PD1 antibody, cemiplimab also shows potential in this setting, either as monotherapy or combined with radiotherapy, and it is currently being evaluated in a phase III trial. Additional checkpoint inhibitors including nivolumab, durvalumab, atezolizumab, and camrelizumab are in different stages of clinical development for the disease. Finally, an additional targeted approach being pursued are PARP inhibitors (rucaparib and olaparib are both in phase II) based on earlier study results.

1. Epidemiology

Cervical cancer is both the fourth most commonly diagnosed and the deadliest cancer in women worldwide [1]. In the United States, improved screening augmented by implementation of HPV testing in the last two decades has led to a decreased incidence of cervical cancer [2]. Nonetheless, over 4000 women are estimated to die from cervical cancer in the United States in 2019 [3]. Unfortunately, this number has largely been stagnant since

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Conflicts of Interest

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1999, and while screening practices have demonstrated that cervical cancer is largely preventable, this trend suggests a recent lack of progress in the treatment of advanced and/or recurrent disease [4]. Indeed, platinum-based chemotherapy in combination with radiation was deemed highly active in the treatment of advanced cervical cancer in late 1990s [5]. Moreover, nearly three decades passed before the FDA approved a new, targeted therapy for cervical cancer, bevacizumab, to be utilized in addition to a traditional platinum chemotherapy doublet [6].

Fortunately, the understanding of cervical cancer biology and oncogenesis has evolved. Persistent HPV infection has been recognized as a prerequisite for the development of invasive cervical cancer for over twenty years [7]. The high-risk HPV E6 and E7 oncoproteins bind natural tumor suppressors – *p53* and *Rb* – to propagate malignant transformation [8]. In addition to screening, the development of highly effective vaccinations targeting high risk HPV genotypes, are predicted to be effective at preventing the vast majority of cervical cancer in immunized women in the future [9,10]. However, in the recurrent, progressive, or metastatic setting, there remains an absence of curative therapies. Novel therapies have been developed and are currently being studied in clinical trials to increase options for management in this patient population. This review aims to characterize the most recent targeted and biologic therapies currently being evaluated in the treatment of advanced cervical cancer.

2. Current Standard Therapy for Recurrent Cervical Cancer

In spite of effective screening programs in the United States and other countries, women with either lack of access to health care and/or those failing to participate in screening are at increased risk for the development of this disease [11]. Management of early stage cervical cancer has remained fairly consistent over the last several decades and is largely surgical based on trials by the Gynecologic Oncology Group (GOG)/NRG Oncology [12]. While minimally invasive radical hysterectomy has been preferred for appropriate patients, a recent randomized controlled trial demonstrated decreased overall survival (OS) among patients treated with a minimally invasive approach compared to an open approach for early stage disease [13].

Historically, recurrent cervical cancer has been treated with platinum-based chemotherapy, which until recently was the combination of cisplatin and paclitaxel [12,14]. However, there are a select group of patients, where surgery is an option for management. These patients are characterized by a centrally located recurrence without evidence of sidewall or distant disease. Total pelvic exenteration – the en bloc resection of reproductive organs along with the rectum, sigmoid colon, and lower urinary tract, currently represents the only surgical option with curative intent in recurrent cervical cancer patients. Improvements in surgical techniques have led to a 5 year survival rate of approximately 50% in these patients [15].

Traditionally, patients with recurrent cervical cancer have been evaluated in clinical trials that also include both primary Stage IVB disease as well as persistent cervical cancer following chemoradiation therapy. Importantly, the relative composition of this heterogenous mix of cervical cancer patients, which could include both women naive to platinum-based

chemotherapy as well as those with a recent completion of platinum based chemoradiation whose predicted response to additional therapy is less robust than either those with a late recurrence or those treated with surgical management alone, may impact trial outcomes.

Through a series of clinical trials, it was determined that the combination of paclitaxel with cisplatin was the preferred chemotherapy backbone especially in women that had not received prior cisplatin-based therapy [16–18]. Specifically, the GOG evaluated four platinum doublets consisting of cisplatin with either paclitaxel, gemcitabine, topotecan, or vinorelbine [17]. The response rate (29.1%) and survival trends, both progression-free (5.82 months, 95% CI 4.53–7.59) and overall (12.87 months, 95% CI 10.02–16.76), favored the paclitaxel and cisplatin combination [17].

Until recently, limited success had been observed when using non-cytotoxic systemic therapy. In general, the use of non-cytotoxic systemic therapy had been reserved for patients that had already experienced disease progression following both primary therapy - often with chemoradiation, as well as at least one line of cytotoxic chemotherapy. Preclinical work initially identified the potential impact of anti-angiogenic therapy in the treatment of cervical cancer [19]. Since then, clinical trials have shown efficacy of various anti-angiogenic therapies as well as activity with other targeted agents such as PARP inhibitors, immunotherapy, and other immune modulating therapeutics (Tables 1–4).

2.1 Anti-Angiogenic Therapy

Angiogenesis plays an integral role in cancer invasion, metastasis, and progression [20]. This physiologic process is excessively activated due to upregulation of a variety of proangiogenic factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) [21]. VEGF has been identified as a key pro-angiogenic factor in a variety of cancerous tumors including cervical cancer [22]. As a marker of poor prognosis in cervical cancer, VEGF has been a focus of targeted anti-angiogenic therapy [23]. Bevacizumab, a humanized, monoclonal antibody that specifically targets VEGF-A [24], is the most widely studied and most commonly used anti-angiogenic therapy in patients with cervical cancer [25]. A two stage trial evaluated the use of single agent bevacizumab in women that had received one-two prior lines of chemotherapy for recurrence [26]. GOG227C was the first targeted therapy trial that demonstrated sufficient activity to proceed to the second stage of accrual. As reported, of 46 patients enrolled 11 patients (23.9%, 90% CI 14–37%) remained progression free at six months with a median OS of 7.29 months (95% CI 6.11–10.41). Importantly, based on the observation of the exciting activity of bevacizumab in these heavily pretreated patients, a randomized phase III trial combining bevacizumab with cytotoxic therapy (cisplatin and paclitaxel, or topotecan and paclitaxel) was undertaken [6,26]. The GOG Trial 240 demonstrated an improvement in both progression free survival (PFS) (8.2 vs 5.9 months; HR = 0.67; CI, 0.54 – 0.82) and OS (17.0 vs 13.3 months; HR 0.71; CI, 0.54 – 0.95) [6]. In 2014, the US Food and Drug Administration (FDA) approved bevacizumab in combination with chemotherapy for patients with metastatic, persistent, or recurrent cervical cancer [27].

Following the results of GOG 240, additional studies have explored bevacizumab in combination with other therapies in cervical cancer patients. The CECILIA study is

evaluating the addition of bevacizumab to the another commonly used platinum doublet - carboplatin and paclitaxel. Trial enrollment has been completed and interim results suggest that this combination is well tolerated with comparable adverse events to those documented in GOG 240. Outcomes results from this trial are expected in the near future [28].

While bevacizumab has been incorporated into the standard of care in the management of metastatic and recurrent cervical cancer, other pro-angiogenic factors have been studied as potential targets for additional therapy. EGFR and HER2/neu have been associated with poor outcomes in patients with cervical cancer [29,30]. Pazopanib is an oral multi-targeted antivascular agent targeting VEGFR, and lapatinib is a dual anti-EGFR and anti-Her2/neu tyrosine kinase inhibitor [31]. These two agents were studied in a phase II trial in metastatic cervical cancer. Originally patients were randomized to pazopanib vs lapatinib vs the combination of the two; however, at the time of interim analysis, the combination arm was closed due to futility. As monotherapy, both agents were deemed tolerable with an equal number of grade 3/4 toxicities experienced in each arm. Median PFS was 18.1 vs 17.1 weeks in pazopanib and lapatinib respectively. OS was increased by 11.6 weeks in pazopanib compared to lapatinib (50.7 weeks vs 39.1 weeks). The conclusion from this study was that, as monotherapy, both pazopanib and lapatinib are well tolerated therapies with modest activity in patients with advanced and recurrent cervical cancer [31].

Neratinib, another tyrosine kinase inhibitor, has also recently demonstrated activity against cervical cancer. The SUMMIT Trial is an open-label Phase 2 study evaluating the safety and efficacy of neratinib in patients with solid tumors with a variety of mutations, including Her2 (). Interim results of the cervical cancer arm were presented at the 2019 SGO annual meeting. Of nine eligible patients (eight with adenocarcinoma) who had undergone prior chemotherapy for cervical cancer, four achieved an objective response (ORR 44%), including one complete response. The most common adverse event was diarrhea; however, the drug was well-tolerated and no patient discontinued the therapy due to side effects [32].

The CIRCCa trial studied the combination of cediranib, a potent inhibitor of VEGFR 1, 2, and 3, with carboplatin and paclitaxel. This small double-blind placebo controlled phase II trial included 69 patients. The addition of cediranib to carboplatin/paclitaxel, increased PFS from 6.7 months to 8.1 months compared to placebo (HR 0.58, 80% CI 0.40–0.85, p=0.032). Not surprisingly, the addition of cediranib to cytotoxic therapy resulted in significantly increased grade 3/4 adverse events including diarrhea, fatigue, leukopenia, neutropenia, and febrile neutropenia. This study demonstrated that cediranib provided some benefit when added to carboplatin/paclitaxel in patients with advanced and metastatic cervical cancer at the expense of increased toxicities [33].

Cetuximab is an antibody that targets EGFR and was studied in combination with cisplatin in women with advanced, persistent, or recurrent cervical cancer. The combination therapy was well tolerated. PFS with cetuximab and cisplatin was compared to historical controls in patients treated with cisplatin alone in GOG 169 and GOG 179. The response to cisplatin plus cetuximab was similar to response to cisplatin alone demonstrated in those studies [34].

Sunitinib, another multi-target VEGF tyrosine kinase inhibitor, was studied in a phase II trial in the treatment of locally advanced or metastatic cervical cancer patients. Nineteen patients were evaluated, with a median time to progression of 3.5 months (range 2.7–7.0 months). There were no objective responses observed in these 19 patients, although 16 of them had stable disease with a median duration of 4.4 months (range 2.3–17.0 months). Five out of 19 patients (26.3%) developed a fistula and thus it was concluded that as a single agent, sunitinib shows minimal benefit with a higher rate of fistulalization and did not warrant additional study [35].

Other non-bevacizumab anti-angiogenic therapies currently being evaluated include nimotuzumab in combination with concurrent chemoradiation therapy [36,37], nintedanib with carboplatin and paclitaxel [38], and apatinib with a platinum doublet [39]. Additional summary information regarding anti-angiogenic therapy from clinical trials is provided in Table 1.

2.2 Poly ADP-Ribose Polymerase Inhibitors

Poly ADP-ribose polymerase (PARP) is an intracellular protein involved in the repair of single stranded DNA breaks. This enzyme is utilized by tumor cells to repair errors in DNA replication in the setting of high mutational burden that is a hallmark of malignancy [40,41]. PARP inhibitors are a class of anti-cancer drugs aimed at blocking the DNA repair mechanism in tumor cells, and they are particularly efficacious in patients with inherent errors already present in their DNA repair pathways, known as homologous recombination deficiency [42]. These drugs have been studied in a variety of cancers including gynecologic malignancies, most notably in ovarian cancer [43]. In cervical cancer cells, PARP is found at higher levels compared to normal cells representing a potential target for therapy in these patients [44].

Two studies from the GOG/NRG Oncology have evaluated PARP inhibitor use in advanced stage cervical cancer [45,46]. In a phase I trial, veliparib was combined with paclitaxel and cisplatin in the treatment of 34 patients with advanced, persistent, or recurrent cervical cancer including 29 with measurable disease [45]. Maximum tolerated dose was not reached and the only grade 3 and 4 adverse events were one patient with dyspnea and another patient with persistent neutropenia. Objective responses were achieved in 34% (95% CI, 20% to 53%) of patients with measurable disease at the time of trial enrollment. Median PFS was 6.2 months (95% CI, 2.9 to 10.1 months) with an OS of 14.5 months (95% CI, 8.2 to 19.4 months). These results led the investigators to conclude that veliparib in combination with cisplatin and paclitaxel in persistent and recurrent cervical cancer was safe and feasible [45].

A second study investigating veliparib activity combined veliparib with topotecan in combination with granulocyte colony stimulating factor for bone marrow support in patients with persistent or recurrent cervical cancer. Twenty-seven patients were evaluated and a significant proportion of women experienced grade 3 and 4 toxicities including over 50% with severe anemia. Only 2 women (7%) demonstrated a partial response and 4 had progression of disease beyond 6 months of therapy. Overall, this trial demonstrated minimal activity with significant toxicity when using veliparib and topotecan. However, a subset of women with low levels of PARP-1 on immunohistochemistry staining demonstrated

statistically significant higher PFS and OS, suggesting that PARP-1 may be a potential biomarker, identifying patients who may receive benefit from this therapy [46].

There are additional ongoing trials further investigating PARP inhibitor therapies in cervical cancer patients. Rucaparib combined with bevacizumab is being studied in women with metastatic, recurrent, or persistent cervical or endometrial cancer [47]. Another phase I/II trial for patients with advanced cervical cancer has been approved and is anticipated to start in 2019. Patients will be randomized to two different doses of niraparib (100mg and 200mg) while receiving concurrent radiation therapy following completion of systemic chemotherapy via carboplatin and paclitaxel in stage IVB cervical cancer. The study aims to determine the maximum tolerated dose of niraparib given with radiation and the difference in local and PFS in these patients [48].

With somewhat limited data on the efficacy of PARP inhibitors in cervical cancer, additional studies will help determine if PARP inhibition has a role in the treatment of cervical cancer and perhaps if we are able to identify patients who may have a predisposition to responding to this therapy. Currently available information from completed and ongoing trials utilizing PARP inhibitors are referenced in Table 2.

2.3 Immune Checkpoint Inhibitors

In recent years, there has been increasing focus on understanding the role of the immune system in the recognition and control of cancer progression [49]. Intrinsic signaling via immune checkpoint receptors leads to suppression of anti-tumor immunity and contributes to tumor progression. These signals are essentially a quiescence of the immune response, which can be inhibited leading to increased tumor recognition and subsequent improved control or even remission of tumor growth [50]. Two different pathways are explicitly targeted with monoclonal antibody therapy to block the immunosuppression signaling. Anti-programed cell death (PD-1) and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are two targets for therapy being studied in a variety of malignancies including cervical cancer [51,52].

Currently, data is limited but increasing in the utilization of immune checkpoint inhibitors in cervical cancer [53]. Importantly it has been demonstrated that there is an upregulation of PD-1 and PD-L1 in cervical cancer tumor cells [54]. Accordingly, early phase clinical trials have evaluated the potential efficacy in the utilization of this class of immunotherapy. Keynote 158 is a multi-cohort phase II clinic trial that evaluated the safety and efficacy of pembrolizumab, a humanized monoclonal antibody that interacts with PD-1, preventing interaction with its ligands and resultant T-cell exhaustion. The trial was designed as a basket trial for multiple tumor types including previously treated cervical cancer patients. The subset of cervical cancer patients received pembrolizumab as monotherapy every 3 weeks for 2 years or until progression or intolerable toxicities were encountered. Interim results an ORR of 12.2% (95% CI, 6.5 −20.4%) including 3 complete and 9 partial responses from 97 evaluable patients. All 12 responses were seen in patients with PD-L1 positive tumors for an ORR of 14.3% among these 77 patients [55]. These results led to FDA approval of pembrolizumab in the treatment of recurrent or metastatic cervical cancer

patients with disease progression during or after chemotherapy treatment and who have at least 1 % of PD-L1 positive staining cells on IHC [56].

Both PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab) as well as PD-L1 inhibitors (atezolizumab, avelumab, durvalumab) are being evaluated in other cervical cancer trials. An ongoing phase III randomized trial is comparing PFS and OS among patients receiving standard platinum-based chemotherapy plus pembrolizumab compared to standard therapy plus placebo [57]. Another phase II randomized trial is examining changes in immunologic markers and dose limiting toxicities among patients receiving pembrolizumab with concurrent chemoradiation compared to pembrolizumab following chemoradiation [58]. Nivolumab is a PD-1 inhibitor that gained FDA approval in 2014 for use in melanoma patients, and subsequently has been approved for use in a wide variety of malignancies [59]. Checkmate 358 is an ongoing phase I/II trial evaluating monotherapy nivolumab in recurrent and metastatic cervical, vulvar, and vaginal cancer. Results from a cohort of 24 patients, including 19 cervical cancer patients, were recently published [60]. For the cervical cancer patients specifically, the ORR was 26.3% (95% CI, 9.1 to 51.2%). An additional 8 patients had stable disease for a disease control rate of 68.4% (95% CI, 43.4 to 87.4%). Additional investigation into nivolumab-based therapy continued in Checkmate 358 with the addition of ipilimumab. Recently presented data showed durable clinical activity in patients with recurrent or metastatic cervical cancer who had not received prior systemic therapy. At 12 months, 53% of patients were progression free on the combination of the two immune checkpoint inhibitors [61]. The National Cancer Institute (NCI) is conducting a phase II single-group trial assessing the effect of nivolumab on objective tumor response rate in patients with previously-treated progressive cervical cancer [62]. Cemiplimab is being studied in a phase III randomized trial comparing cemiplimab monotherapy as first-line therapy for patients with incurable cervical cancer compared to a chemotherapy of the investigator’s choice [63].

The PD-L1 inhibitor atezolizumab is being evaluated in a phase III clinical trial in patients with stage IVB who are treated with cisplatin, paclitaxel, and bevacizumab with and without atezolizumab [64]. In addition, a phase II study is evaluating the benefit of adding atezolizumab to standard chemoradiation in the treatment of locally advanced cervical cancer [65]. In a trial conducted by the NRG, GY017, atezolizumab is being studied in two different ways as an addition to chemoradiation in patients specifically with para aortic node positive disease [66].

Other studies involving PD-L1 inhibitors include two trials that are studying the effects of avelumab in cervical cancer patients [67,68] and two additional trials, including one phase III randomized trial [69], are studying durvalumab [69,70].

Ipilimumab is the most commonly studied anti-CTLA-4 therapy in cervical cancer patients. Five phase I or II trials are now evaluating its safety and efficacy in the treatment of advanced cervical cancer. Trials involving ipilimumab therapy in cervical cancer patients include treating with ipilimumab following standard chemoradiation [71]. Other phase I trials are evaluating experimental immunotherapy in combination with ipilimumab [72,73].

To date, there is limited outcomes data on immune checkpoint therapy in cervical cancer patients; however, current investigations are underway which should help shed light on the efficacy of this therapy in these patients. Summary information for both completed as well as ongoing clinical trials utilizing immune checkpoint inhibitors both as monotherapy and in various combinations is depicted in Table 3.

2.4 Therapeutic Vaccines, Antibody Drug Conjugates, and Tumor Infiltrating Lymphocyte Therapy

Given that the majority of cervical cancer is related to HPV infection, therapeutic vaccines have been studied as treatment options in this patient population [74]. A variety of strategies to enhance innate immune responses to target and eliminate tumor cells have been studied or are currently under investigation [75,76]. Therapeutic live vaccines targeting HPV have been developed using bacterial vectors from a variety of bacterial species [77–79]. *Listeria* is a particularly promising vector due to its ability to avoid phagocytosis by macrophages and it is presented on both MHC class I to cytotoxic T cells and MHC class II to helper T cells [80]. Axalimogene filolisbac (ADXS11–001 or AXAL) is a *Listeria monocytogenes* derived, live attenuated vaccine that targets HPV-16 E7 protein. In a phase II trial, this vaccine was studied in cervical cancer patients with recurrent or refractory disease following chemotherapy or radiation therapy. The vaccine was administered as monotherapy or in combination with cisplatin. Sixty-nine patients were evaluated for tumor response. The median OS was 8.3 months vs. 8.8 months in patients treated with vaccine alone versus with the addition of cisplatin respectively. Additionally, 12- and 18- months survival rates were 35% and 25% respectively. The vaccine was well tolerated, even in combination with cisplatin. The results of this trial were encouraging given the moderate response in a patient population with an extremely poor overall prognosis [81].

The GOG has conducted a single arm, phase II trial investigating AXAL and its use in women with recurrent or progressive cervical cancer. Fifty patients were treated and OS at 12 months was 38% (range 12.02–40.6 months). This study used a logistic model-based approach to calculate expected survival based on historical data from prior phase II GOG cervical cancer trials. Based on these calculations, the expected 12-month survival rate was predicted to be approximately 24.5%. There was one patient who had a complete response up to 18.5 months and was still disease free at 40.6 months. Out of the 50 patients, 30% experienced stable disease. Similar survival rates were achieved regardless of HPV 16 or 18 positivity [82]. There is another phase I/II trial evaluating high dose AXAL in metastatic, persistent, and recurrent cervical cancer patients that has just been completed and results are pending [83].

Additional studies investigating alternative vaccine strategies are underway in cervical cancer patients. GX-188E is a naked vector vaccine targeting E6 and E7 proteins in HPV 16/18 cancers. This vaccine has been shown to generate an HPV-specific CD8 T-cell response in patients with CIN3. In a small study evaluating 9 patients with high grade dysplasia treated with the GX-188E vaccine at 3 different doses, 7 demonstrated resolution of cervical neoplasia with clearance of HPV within 20 weeks [84]. This vaccine is currently

being given in addition to pembrolizumab in a phase I/II trial to determine dose limiting toxicities of the combination and objective response rates (ORR) at 24 months [85].

Antibody drug conjugates (ADCs) are a class of targeted therapy where an antibody is linked to active anti-cancer agent with the antibody targeting a specific tumor antigen, delivering the drug to the tumor cells and avoiding non-malignant cells [86,87]. Tisotumab vedotin is an ADC that targets tissue factor which is highly expressed in many malignancies including cervical cancer [88,89]. This specific ADC has been studied in a variety of solid tumors in the recurrent, advanced, and metastatic setting and is a part of two other ongoing trials specifically focused on cervical cancer [90–92]. Results from a phase I/II trial have been published investigating the safety and efficacy of tisotumab in recurrent, advanced, or metastatic cancer in different tumor sites including 34 patients with cervical cancer. The cervical cancer patients had a 26.5% ORR (95% CI, 12.9 to 44.4 %), representing the second highest response rate behind only bladder cancer patients. Dose limiting toxicities (DLTs) experienced in this study included mucositis, neutropenic fever, and type 2 diabetes mellitus, all of which occurred at the 2.2 mg/kg dose, making the 2.0m mg/kg every 3 weeks the maximum tolerated dose [93]. This study demonstrated that tisotumab appears to have an acceptable safety profile with encouraging activity in certain tumor types including cervical cancer [90].

Given the results demonstrated in the subset of cervical cancer patients in the aforementioned clinical trial, two different studies are investigating tisotumab in cervical cancer patients exclusively. A phase II trial has just been completed evaluating this ADC as monotherapy in recurrent or metastatic cervix cancer; results are pending [91]. Moreover, an ongoing study is combining tisotumab with carboplatin, bevacizumab, or pembrolizumab in recurrent and stage IVB cervical cancer. This study will evaluate both DLTs with planned dose escalation as well as antitumor activity [92].

Through emerging technologies, tumor infiltrating lymphocytes (TILs) have been harvested from solid tumors, and activated and expanded ex vivo [94]. An open-label phase II clinical trial has investigated LN-145, a TIL therapy developed to target cervical cancer. Preliminary trial data was recently presented at the 2019 ASCO annual meeting. The trial followed 27 patients with advanced cervical cancer who had undergone at least one line of prior chemotherapy. Following lymphodepletion, patients received a single infusion of LN-145 followed by several doses of interleukin-2. ORR at a median 3.5 month follow up assessment was 44%, including one complete response. In February 2019, the US FDA granted Fast T rack designation to LN-145 for the treatment of patients with recurrent, metastatic, or persistent cervical cancer who have progressed on or after prior therapy.

Targeted therapy aimed at unique tumor antigens appears to be promising and well tolerated in cervical cancer patients and are depicted in Table 4. Therapeutic vaccination or antibody drug conjugates provide a tumor specific treatment option that warrants further investigation in cervical cancer patients.

3. Conclusions

Patients with recurrent, progressive, and metastatic cervical cancer have a poor overall prognosis. The estimated OS for these patients is approximately 1 year with about 1/3 of patients responding to systemic therapy [26]. Bevacizumab and pembrolizumab represent two approved and vetted therapies that have been added to the standard of care for these patients after decades of somewhat limited progress in identifying effective therapy. Preliminary studies and clinical trials with newer and novel therapies have been published and are currently underway that show potential for possible therapies. As we continue to gain further understanding into the molecular biology of cervical cancer, biomarkers may play an important role in the prediction of early recurrence and can lead to alternative treatment options, while other markers may help tailor therapy and attenuate the response to these novel therapies. In a patient population with such a poor prognosis, enrollment in clinical trials is key to help determine if these investigative treatments can provide benefit and improve outcomes.

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Key points:

- Recurrent and metastatic cervical cancer carries a poor prognosis, and progress in treatment had been limited prior to the use of bevacizumab in combination with chemotherapy.
- Targeted immunotherapy provides other treatment options, and some agents have shown activity in patients with recurrent and advanced cervical cancer.
- Health care providers should encourage patients to enroll in clinical trials to bolster research and further progress in the treatment of recurrent advanced cervical cancer.

Table 1:

Summary of anti-angiogenic therapeutic agents studied in the treatment of cervical cancer.

Drug	Additional Therapy	Mechanism of Action	Trial	Potential Toxicities
Bevacizumab	cisplatin/paclitaxel or topotecan/paclitaxel	Anti-VEGF-A	GOG 240[6]	Hypertension, thrombosis, nephrotic syndrome, rash, bowel perforation, headache
	carboplatin/paclitaxel		CECILIA[28]	
Pazopanib	*[monotherapy]*	Anti-VEGFR-1,2,3	Monk et al[31]	
Lapatinib	*[monotherapy]*	Anti-EGFR Anti-Her2/neu		
Neratinib	*[monotherapy]*	Anti-Her2/neu	SUMMIT[32]	
Cediranib	carboplatin/paclitaxel	Anti-VEGFR-1,2,3	CIRCCa[33]	
Cetuximab	cisplatin	Anti-EGFR	GOG-0076D[34]	
Sunitinib	*[monotherapy]*	Anti-VEGFR-1,2,3	NCIC CTG Trial IND.184[35]	
Nimotuzumab	cisplatin/vinorelbine	Anti-EGFR	[36]	
	concurrent chemoradiation		[37]	
Nintedanib	carboplatin/paclitaxel	Anti-VEGFR, FGFR, PDGFR	[38]	
Apatinib	paclitaxel + cisplatin or carboplatin	Anti-VEGFR 2	[39]	

CIRCCa = Cediranib combined with carboplatin and paclitaxel in patients with metastatic or Recurrent Cervical Cancer; EGFR - Epidermal Growth Factor Receptor; GOG = Gynecologic Oncology Group; Her2 = Human Epidermal Growth Factor; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; NCT = National Clinical Trials; VEGF = Vascular Endothelial Growth Factor (R = Receptor);

Table 2:

Summary of Poly ADP-Ribose Polymerase (PARP) Inhibitors studied in the treatment of cervical cancer.

Drug	Additional Therapy	Mechanism of Action	Trial	Potential Toxicities
Veliparib	cisplatin/paclitaxel	PARP inhibitor	GOG-0076HH[45]	GI distress, bone marrow suppression, fatigue
	topotecan		GOG-0127W[46]	
Rucaparib	bevacizumab		[47]	
Niraparib	concurrent radiation therapy		[48]	

GOG = Gynecologic Oncology Group; NCT = National Clinical Trials

Table 3:

Summary of immune checkpoint inhibitors studied in the treatment of cervical cancer.

Drug	Additional Therapy	Mechanism of Action	Trial	Potential Toxicities
Pembrolizumab	*[monotherapy]*	Anti-PD1	KEYNOTE-158[55]	Immune-related side effects: hypophysitis, hepatitis, pneumonitis. Endocrine-related side effects: hypo/ hyperthyoridi sm, T1DM
	carbo/cisplatin		MK-3475–826/ KEYNOTE-826[57]	
	concurrent chemoradiation		[58]	
Nivolumab	*[monotherapy]*		CHECKMATE 358[60]	
	Ipilimumab		CHECKMATE 358[61]	
	[monotherapy]		[62]	
Cemiplimab	*[monotherapy]*		REGN2810[63]	
Atezolizumab	cisplatin/paclitaxel/ bevacizumab	Anti-PDL1	[64]	
	concurrent chemoradiation		[65]	
	[monotherapy]		NRG - GY017[66]	
Avelumab	valproic acid		[67]	
	axitinib		[68]	
Durvalumab	cisplatin/carboplatin		CALLA[69]	
	tremelimumab + SBRT		[70]	
Ipilimumab	concurrent chemoradiation	Anti-CTLA-4	[71]	
	GITR receptor agonist		[72]	

CTLA-4 = Cytotoxic T-lymphocyte-Associated Antigen-4; GITR = Glucocorticoid-Induced TNFR family Related; NCT = National Clinical Trials; PD1 = Programmed Death-1; PDL1 = Programmed Death Ligand-1; SBRT = Stereotatic Body Radiation Therapy; T1DM = Type-1 Diabetes Mellitus; T2DM: Type-2 Diabetes Mellitus.

Table 4:

Summary of targeted therapies including vaccines, antibody drug conjugates, and tumor infiltrating lymphocytes studied in the treatment of cervical cancer.

Drug	Additional Therapy	Mechanism of Action	Trial	Potential Toxicities
ADXS11–001 (AXAL)	cisplatin	*Listeria monocytogenes* derived live vaccine	Basu et al[81]	pyrexia, flushing
	[monotherapy]		Huh et al[82]	
	[monotherapy]		[83]	
GX-188E	pembrolizumab	Naked vector targeting E6/E7 proteins	[85]	Rash, swelling
Tisotumab	*[monotherapy]*	Antibody drug conjugate	[90]	Mucositis, neutropenia, T2DM
	[monotherapy]		[91]	
	bevacizumab or pembrolizumab or carboplatin		[92]	
LN-145	*[monotherapy]*	Tumor Infiltrating Lymphocytes	[94]	Rash, swelling

NCT = National Clinical Trials; T2DM: Type-2 Diabetes Mellitus