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GYNECOLOGIC CANCERS (NS REED, SECTION EDITOR)

Targeted Agents in Cervical Cancer: Beyond Bevacizumab

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Abstract
Cervical cancer constitutes a leading cause of morbidity and cancer deaths in women throughout the world. Approximately two thirds of the patients are diagnosed with locally advanced cervical cancer, showing disappointing survival rates despite correct multidisciplinary management. Metastatic disease implies a poor prognosis itself since diagnosis. Platinum-based chemotherapy has been the backbone treatment of metastatic cervical cancer for years with no major outstanding improvements on survival. The addition of new molecules, such as antiangiogenic agents, dramatically changed the treatment of this disease. Bevacizumab, an antiangiogenic agent that targets vascular endothelial growth factor 2 (VEGF-2), added to standard chemotherapy in cervical cancer showed significant improvement on survival; therefore, the combination of carboplatin, paclitaxel, and bevacizumab is currently the standard frontline treatment in cervical cancer. Other antiangiogenic agents have been tested in this disease with no further development nor approvals. New compounds are currently being under development with promising results in this disease as well as a number of new strategies that could potentially fulfill the unmet need of establishing effective therapeutic approaches in cervical cancer.

Keywords Cervical carcinoma · Advanced disease · Bevacizumab · Antiangiogenic · Targeted therapy · Targeted agents · Immunotherapy · Novel agents

Introduction

Although largely preventable, cervix cancer continues to be a leading cause of morbidity and cancer deaths throughout the world. Cervix cancer accounts for more than 274,000 deaths each year [1, 2]. Most patients with early disease present as stage IB or IIA and are treated with surgery or radical radiotherapy. However, locally advanced cervical cancer (stage IIB-IVA according to the FIGO staging system) accounts for almost 32% of all stages with a 5-year overall survival rates of approximately 40–50% despite conventional treatment approach. Finally, some patients debut with metastasis and have a poor prognosis [3]. Although some relatively new drugs have been tested in recent years, the current treatment for relapsed or advanced carcinoma of the cervix has generally proved disappointing. Recent data has suggested that newer combinations may offer an increased response, progression-free survival, and overall survival. New compounds and strategies are currently in place or being planned in the context of recently generated genomic knowledge and immunotherapy advances. Cervix cancer patients can also be entered into some newly designed and innovative umbrella and basket trials.

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Biology of Cervical Cancer

Specific subtypes of human papillomaviruses (HPVs) are the etiological factor in cervix cancer. HPV are involved in more than 90% of cervical cancer cases [4–6]. To date, 15 of HPV subtypes identified are oncogenic, being HPV 16 and 18 the subtypes that account for the most oncogenic potential [7]. Distribution of HPV subtypes slightly varies between squamous and adenocarcinoma cervical cancer [8].

Persistent HPV infection leads to HPV's DNA integration into the host DNA upregulating E6 and E7 oncoproteins. Both oncoproteins are essential in HPV oncogenic process of replication, host cell immortalization, and transformation. E7

oncoprotein inactivates retinoblastoma gene product (Rb), leading to a release of transcription factors [5]. E6 oncoprotein of HPV 16 and 18 has high affinity for the tumor suppressor gene p53, inducing both its inactivation and degradation. This downregulation of p53 leads to stabilization of the hypoxia-inducible factor 1 (HIF-1), therefore promoting the expression of vascular endothelial growth factor (VEGF). Nonetheless, VEGF overexpression in cervical cancer is considered multifactorial.

Cervical cancer is also associated with tumor hypoxia, a strong stimulus of HIF-1 which also leads to an increasing production of VEGF, independently of p53 regulation [9, 10]. Several studies have shown the important role of VEGF expression in cervical carcinogenesis and its implications in poor prognosis of the disease [11, 12].

Medical Treatment (Advanced Disease)

Chemotherapy in Cervical Cancer

Chemotherapy in cervical cancer has a well-defined role in two situations: primary therapy in the management of advanced/recurrent disease, and in conjunction with radiation in the management of locally advanced disease.

Carcinoma of the cervix is considered a relatively chemotherapy-resistant disease. The vast majority of patients with recurrent disease are treated with palliative intent. Responses to chemotherapy are limited, and this may be secondary to compromised vascularity from previous treatments, renal impairment from obstructive uropathy, or due to the aggressive nature of recurrent tumors. Responses are particularly uncommon in previously irradiated sites and the duration of response is usually short, lasting approximately 4 to 6 months. According to series published a few years ago, the mean overall survival is usually not superior to 13 months.

Historically, single agent cisplatin has been considered the most active treatment for recurrent/advanced cervical cancer showing a 21–44% response rate (RR) and a median overall survival (OS) of 6.1–7.1 months [13, 14]. Several phase III studies of cisplatin-based combinations have attempted to improve those results, but only the combinations with ifosfamide or paclitaxel (GOG 169) showed better results in terms of RR (ifosfamide 17.8 to 31.1%; paclitaxel 19 to 36%) and progression-free survival (PFS) (ifosfamide 3.2 to 4.6 months; paclitaxel 2.8 to 4.8 months) but without a significant OS advantage compared to single agent cisplatin (ifosfamide 8 versus 8.3 months; paclitaxel 8.8 versus 9.7 months) [15, 16], compared to single-agent cisplatin. In the GOG-169, grade 3 to 4 anemia and neutropenia were more common in the combination arm. However, there was no significant difference in quality of life scores [16].

GOG-179 was the first study that showed a significant improvement in OS of a cisplatin-based combination containing topotecan over single-agent cisplatin (9.4 versus 6.5 months, HR 0.76, 95% CI, 0.593 to 0.979; $p = 0.017$) with a 27 versus 13% RR and PFS of 4.6 versus 2.9 months favoring the combination arm [17]. These results established cisplatin-based combination chemotherapy as standard of care in the treatment of recurrent or metastatic cervical cancer. GOG-204 compared four cisplatin-based combination regimens, cisplatin-paclitaxel, cisplatin-vinorelbine, cisplatin-gemcitabine, and cisplatin-topotecan, showing no significant differences in RR (29.1, 25.9, 22.3, and 23.4%, respectively), PFS (5.82, 3.98, 4.70, and 4.57 months, respectively), and OS (12.87, 9.99, 10.28, and 10.25 months, respectively) within the four regimens but with a trend favoring cisplatin 50 mg/m^2 plus paclitaxel 135 mg/m^2 24 h infusion over the other combinations. The toxicity profile was similar among the treatments except for hematological toxicity and infection [18].

Cisplatin combined with paclitaxel is less convenient and more toxic than carboplatin and paclitaxel combination. A number of phase II trials and retrospective analyses suggested the benefit and advantages of carboplatin-paclitaxel over cisplatin-paclitaxel. The randomized JCOG-0505 phase III trial showed that carboplatin AUC5 plus paclitaxel 175 mg/m^2 in 3 h was not inferior to cisplatin plus paclitaxel with the advantages of a more convenient and better tolerated regimen [19•, 20••].

Antiangiogenic Agents

Angiogenesis plays a key role in cervical cancer carcinogenesis. Further investigations focused their efforts on compounds that targeted VEGF and angiogenesis pathway confirming the activity of antiangiogenic agents in advanced and recurrent cervical cancer.

Bevacizumab binding and subsequent inactivation of VEGF leads to cervical tumors shrinkage and delays progression with generally low toxicity. Bevacizumab was the first antiangiogenic agent that showed efficacy in cervical cancer. GOG-227C tested 3-weekly bevacizumab 15 mg/kg in monotherapy in persistent/recurrent disease. The results were compared with single-agent compounds tested in prior GOG phase 2 trials in this setting, favoring bevacizumab with PFS and OS of 3.40 months (95% CI, 2.53 to 4.53) and 7.29 months (95% CI, 6.11 to 10.41), respectively. This study reached its primary endpoints with a PFS at 6 months of 23.9% (90%CI, 14 to 37%; 11/46 patients) and toxicities including grade 3 hypertension (7/46 patients), grade 3 hematologic toxicity (8/46 patients), and deep venous thrombosis (5/46 patients) with no arterial thrombosis events reported. In addition, two grade 4 events (urinary fistula and vaginal bleeding) were reported in patients treated with bevacizumab [21].

Bevacizumab was added to chemotherapy in cervical cancer in a phase III trial, GOG240. Four hundred fifty-two women diagnosed with metastatic or persistent/recurrent cervical carcinoma were randomized to one of the four following treatment arms: 3-weekly cisplatin 50 mg/m^2 plus paclitaxel 175 mg/m^2 (control arm), 3-weekly topotecan 0.75 mg/m^2 on days 1–3 plus paclitaxel 175 mg/m^2 on day 1 and bevacizumab 15 mg/kg added to each of the arms mentioned. The addition of bevacizumab significantly improved OS (16.8 versus 13.3 months; HR 0.77; 95%CI 0.62-0.95, p = 0.007) 0.84 to 0.82, $p = 0.002$) without a significant reduction in quality of life. Bevacizumab also showed superiority in terms of RR (48% with bevacizumab versus 36%, without bevacizumab, $p = 0.008$), achieving a greater number of complete responses (14/225 patients versus 28/227 patients, respectively). Bevacizumab class toxicity included grade ≥ 2 hypertension (25%), genitourinary fistula (7%), and grade >3 thromboembolic events (8%) [22••]. This was the first phase III trial that showed significant OS advantage of the addition of bevacizumab to a platinum-based regimen in this disease, establishing carboplatin plus paclitaxel plus bevacizumab as the standard of care of frontline treatment of cervical cancer.

Pazopanib, an oral vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and C-kit inhibitor, has been tested in second-line treatment of cervical cancer. Two hundred thirty patients VEGF inhibitor-naive were randomized to receive pazopanib 800 mg daily or an EGFR and Her2/neu inhibitor, lapatinib (1500 mg daily) [23]. In cervical cancer, EGFR, HER2/neu overexpression and high microvascular density correlate with survival.

The combination arms of the trial (pazopanib 400 mg daily plus lapatinib 1000 mg daily and pazopanib 800 mg daily plus lapatinib 1500 mg daily) were discontinued after the first interim analysis due to futility; patients treated in those arms were switched to one of the monotherapy arms, but their outcomes did not count in the survival analysis. Pazopanib improved PFS compared to lapatinib (18.1 versus 17.1 weeks, HR 0.66; 90% CI, 0.48 to 0.91; $p = 0.013$) with no differences in the updated OS analysis (49.7 versus 44.1 weeks, HR 0.96; 90% CI, 0.71 to 1.30; $p = 0.407$); however, the study was not powered for OS [24]. RRs were 9 and 5% for pazopanib and lapatinib, respectively. Diarrhea was the only grade 3 toxicity (11% pazopanib and 13% lapatinib) reported. This study demonstrated the benefit of pazopanib based on the prolonged PFS and favorable toxicity profile in advanced and recurrent cervical cancer. In spite of this interesting data and the convenience of the oral route, pazopanib has not been further developed in cervical cancer.

Cediranib is a potent oral tyrosine kinase inhibitor of VEGFR 1–3 and C-kit. Cediranib 20 mg added to standard chemotherapy (3-weekly carboplatin AUC5 plus paclitaxel 175 mg/m^2) was studied in a randomized, double-blind, placebo-controlled phase 2 study enrolling 69 patients diagnosed with metastatic or recurrent cervical carcinoma. Cediranib was continued beyond 6 cycles of chemotherapy until disease progression or unacceptable toxicity. PFS (primary endpoint) was significantly greater in the experimental arm (8.1 versus 6.7 months, HR 0.58; 80% CI, 0.40 to 0.85; $p = 0.032$). Sixty-four percent of patients had an overall response in the cediranib group, the highest reported to date for any agent in this disease. Grade 3 diarrhea, fatigue, leucopenia, neutropenia, and febrile neutropenia were more prevalent in the cediranib arm (16, 13, 16, 31, and 16%, respectively). No deterioration in overall quality of life occurred except from diarrhea in the cediranib group ($p = 0.030$). As expected, grade 2–3 hypertensions were higher in the experimental arm (34 versus 11%). Of note, no fistula events were reported in the experimental arm [25, 26].

Nintedanib (BIBF 1120), a VEGFR1–3, αPDGFR, βPDGFR, and fibroblast growth factor receptor (FGFR) 1 and 3, is currently being studied in the frontline setting of cervical cancer (BGOG-cx1/ENGOT-cx1 trial). In this phase II randomized trial, patients are randomly allocated to receive nintedanib or placebo in combination with 6 cycles of 3-weekly carboplatin AUC5 plus paclitaxel 175 mg/m^2 followed by nintedanib versus placebo maintenance [27]. No data is available yet.

Sunitinib is an oral VEGFR1–3, PDGFR α and β, C-kit, and FLT3 receptor tyrosine kinase inhibitor. Sunitinib 50 mg daily was studied in a phase II study showing no objective response and a concerning rate of fistula formation (26.3%) among the 19 patients enrolled. Sixteen patients (84%) had stable disease as their best response with a median time to progression of 3.5 months (95% CI, 2.6 to 7 months) [28]. No further investigations of this agent have been developed in cervical cancer as it showed insufficient activity with a high toxicity profile [29].

Other antiangiogenic agents such as aflibercept, sorafenib, and trebananib have not been tested in phase II or III studies in cervical cancer.

A summary of the phase II/III clinical trials of antiangiogenic therapies in cervical cancer is shown in Table 1.

New Therapies and Strategies

Immunotherapy

Different treatment options beyond antiangiogenic compounds have been explored in advanced cervical carcinoma. Immunotherapy outstands as an attractive approach as for the impressive results in other solid malignancies such as melanoma or lung cancer. This approach could potentially be more

Table 1 Phase II/III clinical trials of antiangiogenic compounds in cervical cancer

Study	Number	Phase	Eligible patients	Drugs and schedule	PFS	OS	ORR
Bevacizumab							
GOG 227C [21]	46	II	Persistent/recurrent squamous cervical carcinoma (adenosquamous included)	Bevacizumab 15 mg/kg D1 every 21 days	3.40 months 95% CI, 2.53 to 4.53	7.29 months 95% CI, 6.11 to 10.41	No data
GOG 240 [22••]	452	III	Metastatic, persistent, recurrent cervical carcinoma. *Excluded patients amenable to curative pelvic exenteration	A. Cisplatin 50 mg/m^2 D1 + paclitaxel 175 mg/m^2 D1 (control arm) B. Topotecan 0.75 mg/m^2 D1–3 + paclitaxel 175 mg/m^2 D1 C. Cisplatin 50 mg/m^2 D1 + paclitaxel 175 mg/m^2 D1 + bevacizumab 15 mg/kg D1 D. Topotecan 0.75 mg/m^2 D1–3 + paclitaxel 175 mg/m^2 D1 + bevacizumab 15 mg/kg D1	5.2 months HR 0.67; 95% CI, 0.54 to 0.82 8.2 months	13.3 months HR 0.71; 98% CI, 0.54 to 0.95 17 months	36% 14/225 Complete response (CR) 48% 28/227 CR
Pazopanib							
NCT00430781 [23]	228	II	Stage IVB, recurrent/persistent squamous cell carcinoma, adenosquamous, or adenocarcinoma of the cervix	A. Lapatinib 1500 mg/day. B. Pazopanib 800 mg/day C. Lapatinib 1000 mg/day + lapatinib 400 mg/day D. Lapatinib 1500 mg/day + lapatinib 800 mg/day	4.25 months 4.5 months HR 0.66; 90% CI, 0.48 to 0.91, $p < 0.013$	11 months 12.42 months HR 0.96; 90% CI, 0.71 to 1.30, $p = 0.407$ *Study not powered for OS	9% 19%
Cediranib							
CIRCCa [25]	69	II	Metastatic/persistent or locally recurrent cervical cancer *Excluded patients amenable to curative pelvic exenteration	A. Carboplatin AUC5 D1 + paclitaxel 175 mg/m^2 D1 every 3 weeks + placebo/day B. Carboplatin AUC5 D1 + paclitaxel 175 mg/m^2 D1 every 3 weeks + cediranib 20 mg/day	6.7 months HR 0.58; 80% CI, 0.40 to 0.85, $p = 0.032$ 8.1 months	35.2 months HR 1.027 (0.79–1.33) 33.3 months	45% 0 CR 64% 3/33 CR (9%)
Sunitinib							
NCIC CTG 184 [28]	19	II	Metastatic/unresectable locally advanced squamous cell, adenosquamous, or adenocarcinoma of the cervix	Sunitinib 50 mg/day	No data	No data	No objective response

PFS progression-free survival, *OS* overall survival, *ORR* overall response rate, *D1* day 1, *D1–3* days 1 to 3, *HR* hazard ratio, *CI* confidence interval, *CR* complete response

efficient than current standard chemotherapy with a far more tolerable toxicity profile.

HPVs are known to be highly immunogenic viruses that need the host's immune system deregulation for tumor progression. HPV integrates its DNA into the host's genome, thus generating non-self neoantigens. Interestingly, there are several immunoevasion mechanisms that have been described following HPV DNA integration. MHC class I downregulation, immune-mediated resistance to apoptosis, and the presence of an immunosuppressive microenvironment are examples of immunoevasion mechanisms used by HPV which give a rational for the use of immunotherapy in cervical cancer [30].

Therapeutic vaccines, inducing a cytotoxic T-cell response to tumor specific antigens, and immune checkpoint inhibitors are the two main immunotherapy approaches that have been tested in cervical cancer within the last years.

HPV infection induces the presence of E6 and E7 oncoproteins; consequently, these antigens have been tested as potential targets for therapeutic vaccines [31••]. The vast majority of vaccines developed so far in advanced cervical carcinoma are live-vector (bacterial or viral-vector) vaccines providing high immunogenicity and efficient infection rates.

Several bacterial-vectors have been studied for HPV therapeutic vaccines: *Lactobacillus lactis*, *Lactobacillus platarum*, *Salmonella enterica*, and *Listeria monocytogenes* [32–34]. *Listeria monocytogenes* is, by far, the most promising vector to date. ADXS11-001 is a live attenuated *Listeria monocytogenes* vector vaccine that secretes a fusion protein, Lm-LLO-E7, which is currently being tested in phase III trials.

The development of ADXS11-001 is outstanding. In the phase I trial three dose levels of ADXS11-001 (1×10^9 CFU, 3.3×10^9 CFU, and 1×10^{10} CFU) were tested in two intravenous doses every 21 days. Fifteen heavily pretreated cervical cancer patients were enrolled. The vaccine was generally well tolerated with mild grade 2 adverse events such as pyrexia, vomiting and flu-like symptoms occurring within 12 h of treatment infusion. Hemodynamic instability was the dose limiting toxicity at 1×10^{10} CFU dose. ADXS11-001 showed a clinical response rate of 61.5%, mainly stable disease [35]. Data of safety and OS from the stage 1 of an international phase I/II trial (GOG/NRG0265 Study, NCT01266460) were reported in the 2016 *American Society of Clinical Oncology Congress* (ASCO), confirming the good tolerability and showing a 12-month OS of 38.5% (median OS 7.7 months) with a median PFS of 3.1 months.

ADXS11-001 has also been tested combined with cisplatin in a phase 2 trial. One hundred ten patients were included. ADXS11-001 showed a disease control rate (DCR) of 43%, a RR of 11%, and 18-month OS of 28%. Despite the combination was well tolerated, adding cisplatin to ADXS11-001 did not show any additional benefit [36].

A phase III trial (NCT02853604) is currently testing the activity of ADXS11-001 (axalimogene filolisbac) in the adjuvant setting following cisplatin-based chemoradiotherapy in high-risk, locally advanced cervical carcinoma. Trials as a single agent and in combination with other immunotherapy approaches are on the verge of being launched in recurrent, metastatic cervix cancer patients.

Viral-vector vaccine TA-HPV (recombinant virus-vector vaccine expressing both E6 and E7 oncoproteins) has been tested in early stage (IB-IIA) cervical cancer following surgery patients, with promising results [37]. Protein, peptide, and DNA vaccines have low immunogenicity compared to live-vector vaccines, thus requiring adjuvant proteins to enhance efficacy [38].

DNA vaccines have advantages over traditional vaccines and are usually well tolerated. VGX-3100 is a therapeutic vaccine that includes DNA plasmids for expression of E6 and E7 proteins of both HPV subtypes 16 and 18. Phase I and II studies have shown no significant safety findings. E6 and E7 proteins represent tumor-specific antigens in HPV-associated carcinomas, and they are currently being tested for the treatment of HPV-related cervical high-grade squamous intraepithelial lesions (NCT03185013). INO-9012 is a synthetic DNA plasmid for expression of two human IL-2 subunit proteins, p53 and p40. Preclinical studies have shown that the immunogenicity of DNA vaccines could be increased by the use of IL-12 DNA as an adjuvant [39]. In addition, radiotherapy can contribute to antigen-cross presentation by promoting death of tumor cells and releasing antigens, eliciting tumor-specific T cells and cytokines in the context of inflammatory response. Therefore, there is a clear rationale for open-label phase I/II trial in HPV 16/18-positive patients to examine INO-9012, VGX-3100 vaccine against HPV 16/18 combined with a DNA plasmid for IL-2 as immune activator, administered following chemoradiotherapy in locally advanced cervical carcinoma. However, this coherent strategy has not been incorporated in comprehensive clinical trials so far.

Immune checkpoint inhibitors can help to overcome cancer-associated immune suppression and are currently approved by health authorities in a growing list of indications in several solid tumors. There is not robust data to date about the efficacy of checkpoint inhibition in cervical carcinoma.

Ipilimumab, an anti-CTLA4, is currently being tested in a phase I trial following chemoradiation therapy in locally advanced tumors, including a cervical carcinoma cohort (NCT01711515) as well as in a phase II trial in recurrent/advanced cervical carcinoma (NCT01693783).

Other immune checkpoints, such as PD1 and PDL1, are upregulated in HPV-positive cervical cancer cells. Preliminary results of the cervical carcinoma cohort of the phase 1b in KEYNOTE 028 study, testing pembrolizumab in PDL1-positive advanced solid tumors

were first reported at *ASCO 2016*. The median OS of the cervical carcinoma cohort reached 9 months and, interestingly, PDL1-positive tumors showed a durable antitumor activity with long-lasting responses. The clinical benefit of pembrolizumab in recurrent or advanced cervical cancer is being currently studied in the phase II Keynote-158 trial (NCT02628067).

Pembrolizumab is also being tested combined with concurrent chemoradiotherapy in locally advanced cervical carcinoma (NCT02635360).

Finally, another anti-PD1 antibody, nivolumab, is being tested in recurrent or advanced disease (NCT02257528).

In addition to the two approaches previously described, adoptive T-cell therapy has also been tested in this disease with promising results. The infusion of tumor-infiltrating T-cells selected for HPV E6 and E7 oncoproteins induced durable and complete responses in a small study of nine heavily pretreated cervical cancer patients [40••]. Further studies are awaited.

A summary of the main immunotherapy clinical trials in cervical carcinoma and of the immunotherapy clinical trials currently ongoing in cervical cancer are shown in Tables 2 and 3, respectively.

Targeted Therapies

The growing knowledge on cancer genetics thanks to the development of new technologies for molecular analysis could potentially guide at the time of selecting new targets for cancer treatment.

Whole exome sequencing (WES) studies have confirmed that the main mutated oncogenic genes implicated in this tumor are PI3KCA, PTEN, PT53, and KRAS. Furthermore, WES identified novel mutations in other oncogenic pathways such as interferon gamma signaling pathway, MAPK or ErbB2 pathway activation [41••].

These findings have already been used as new approaches for cervical carcinoma. Of note, adding interferon-alpha to standard chemotherapy has showed no survival advantage in a clinical trial enrolling patients with advanced/recurrent cervical carcinoma but with interesting efficacy outcomes: RR 30% and disease control rate 51% [42, 43].

EGFR is expressed in the majority of cervical cancer samples (85–100%) and implies a worse prognosis. EGFR inhibitors such as cetuximab, gefitinib, erlotinib, or lapatinib have failed to show efficacy in cervical cancer patients [44–47].

The apparent resistance to EGFR inhibitors could be explained owing to mTOR pathway is overactivated/overexpressed in these patients. Activation of mTOR signaling pathway contributes to survival of cervical cancer cells. mTOR inhibitors have also been tested in preclinical studies and clinical trials in cervical carcinoma. A phase II trial enrolling 38 patients with advanced cervical carcinoma treated with weekly temsirolimus showed a 6-month PFS of 28% with long-lasting stabilizations (57.6%). No biomarkers of response were identified [48]. Targeted inhibition of PI3k/Akt may improve response to chemoradiation [49].

Poly(ADP-ribose) polymerase (PARP) family is implicated in DNA repair systems, and PARP inhibitors have gained massive interest within the last years mainly in ovarian carcinoma. PARP activity is known to be higher in cervical cells [50]. Veliparib, a PARP inhibitor, has been tested administered with chemotherapy in advanced cervical carcinoma. Two phase I trials combining veliparib with topotecan or cisplatin plus paclitaxel have shown activity although the correct schedule and treatment dose needs further research.

Interestingly, low PARP-2 expression in tumor could be associated with longer PFS [51, 52].

Table 2 Main immunotherapy clinical trials in advanced/recurrent cervical carcinoma

	Drug/vaccine	Trial	Number	Response	PFS	OS
Live-vector vaccines	ADXS11–100 (bacterial vector)	Maciag et al. Phase I (dose escalating) [35]	15	1/15 PR 7/15 SD	–	–
		GOG/NRG0265 (ASCO2016) Phase I/II	29[a]	1/29 PR 9/20 SD	mPFS 3.1 m	12 m OS 38.5% OS 7.7 m
		Petit et al. Randomized phase II (ADXS11–100 ± cisplatin) [36]	110	DCR 43% (11% RR)	–	12 m OS 36% 18 m OS 22%
Adoptive T-cell therapy	HPV-targeted tumor-infiltrating T-cells	Stevanovic et al. [40••]	9	DCR 3/9 (2 complete responses)	–	–
Checkpoint inhibitors	Pembrolizumab	Frenel et al. (ASCO2016) KEYNOTE028 (cervical cohort PDL1+)	24	12.5% RR 12.5% SD	6 m PFS 13%	6 m OS 66.7%

PFS progression-free survival, *OS* overall survival, *PR* partial response, *SD* stable disease, DCR disease control rate

[a] Preliminary data of stage 1

Table 3 Ongoing immunotherapy clinical trials in cervical cancer

Trial	Phase	Drug/vaccine	Mechanism	Patient selection
NCT02172911	I-IIa	INO-3112	Viral-vector vaccine	After chemoradiation in locally advanced, persistent or recurrent cervical cancer
NCT02853604	III	ADXS11-100	Bacterial-vector	After chemoradiation in locally advanced cervical carcinoma
NCT02128126	I-II	ISA101	Long peptide vaccine	Advanced or recurrent disease concomitant with carboplatin plus paclitaxel (± IFN)
NCT01711515	I	Ipilimumab (GOG9929)	Checkpoint inhibitor	After chemoradiotherapy in locally advanced cervical carcinoma
NCT01693783	II	Ipilimumab	Checkpoint inhibitor	Recurrent or metastatic disease
NCT02635360	II	Pembrolizumab	Checkpoint inhibitor	Concomitant with chemoradiation in locally advanced disease
NCT02257528	II	Nivolumab	Checkpoint inhibitor	Persistent or recurrent disease

Referenced from www.clinicaltrials.gov, last accessed November 6, 2017

Finally, a maintenance study with rucaparib in cervical carcinoma FIGO stages III and IV following definitive chemoradiation has recently been planned by the NSGO (ENGOT-CX7/NSGO-CC1-MaRuC).

New Directions and Future Research

Taking apart the recent approval of bevacizumab in the first-line setting in advanced cervix cancer, no new compounds are envisaged in the short term for achieving commercial rights. In this scenario, the international community is fully aware of the unmet needs in cervical cancer and it has been developing initiatives aimed to reach consensus on a number of research areas for current and future clinical trials [20••]. The Gynecologic Cancer Intergroup (GCIG) and the European Network Gynecology Oncology Trials (ENGOT) are performing a number of studies in advanced cervical cancer with new compounds. Currently, the GOG/NRG is performing a randomized phase III trial in recurrent or metastatic platinum-refractory cervical cancer patients comparing REGN2810, a fully human monoclonal antibody against PD-1, with investigator's choice chemotherapy (NCT03257267). Preclinical data strongly suggest that REGN2810 is a potent and promising candidate for cancer immunotherapy [53].

Tissue factor (TF), also known as thromboplastin, factor III or CD142, is abnormally expressed in solid tumors and it is believed that it contributes to disease progression [54]. TF is the principal initiator of the extrinsic coagulation pathway and is widely expressed in different organs. TF-011-MMAE (Tisotumab Vedotin, HuMax-TF-ADC) is an antibody-drug conjugate composed of a human TF-monoclonal antibody and the cytotoxic agent MMAE. A number of studies in solid tumors are currently ongoing (NCT02001623) and planned in recurrent or advanced cervix cancer.

Therapies targeting the immune checkpoint molecules CTLA-4 and/or PD-1 have achieved objective responses in a variety of solid tumors such as melanoma, renal cancer, or lung cancer. However, a number of patients will not obtain benefit from these therapies. This has led interest to scrutinize the role of other novel immune checkpoint receptors with the objective of examining the potential of checkpoint blockade for treating cancer. Tumor-associated or infiltrating lymphocytes (TALs or TILs) coexpress multiple immune inhibitory receptor which may contribute to immunosuppression in the tumor microenvironment. Dual blockade of PD-1 along with lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin, and mucin protein 3 (TIM-3) or CTLA-4 has shown to synergistically enhance T-cell effector function in preclinical models [55].

A number of antibodies targeting these novel receptors, TIM-3 and LAG-3, have recently been developed and are entering into early clinical trials. Combination of checkpoint inhibitors is a consolidated strategy against some cancers and remains exploratory in gynecological tumors. Dual blockage combining checkpoint inhibitors with anti-TIM-3 or anti-TIM-3 with anti-LAG-3 should be a priority in cervix cancer [55, 56]. In this way, the CheckMate-358 trial is a non-comparative, open-label, multiple cohort, phase 1/2 study of nivolumab monotherapy and nivolumab combination therapy in subjects with virus (+) and virus (−) solid tumors (NCT02488759). In this ongoing trial, patients with advanced cervical cancer are treated with a combination of nivolumab with ipilimumab, nivolumab with BMS-986016 (anti-LAG-3), or nivolumab with daratumumab (anti-CD38).

To make progress, a better understanding of the language between tumor cells and its immunological microenvironment is needed. In cervix cancer, tumor-associated macrophages (TAMs) may orchestrate immune suppression. TAMs promote angiogenesis and lymphangiogenesis, and it is thought that their presence in cervix tumors is associated with lymph node metastasis and worse prognosis [57, 58].

Prostaglandin E2 (PGE2) is commonly elevated in tumor microenvironment and its receptor signaling of PGE2, EP4,

leads to differentiation of TAM with myeloid derived suppressor cells (MDSCs), which are immunosuppressive. Targeting PGE2-EP4 signaling may reverse the immunosuppressive phenotype of TAM to a more immunosupportive TAMs and decrease MDSC activity. E7046 specifically inhibits PGE-EP4 signaling, and a phase I trial in solid tumors is currently being performed (NCT02540291).

Gene expression profiling has been applied to the study of cervix cancer. In particular, further research should be performed with targeted therapy focused on PI3k/AKT/mTOR pathway [49]. In a recent research focused on integrated genomic and extensive molecular characterization of cervical cancer, 228 primary cervical cancers samples were tested showing that more than 70% of cervical cancers exhibited genomic alterations in either one or both of PI3k/MAPK and TGF beta pathways [59••]. A number of novel significantly mutated genes in cervix cancer were identified: SHKBP1, ERBB3, CASP8, HLA-A, and TGFBR2. The authors also identified amplifications in CD274 and PDCD1LG2, two genes that encode for immunotherapy targets. Initiatives such as BIORAIDS (www.raids-fp7.eu/project-overview), a prospective multicenter European study currently recruiting patients, in which 700 patients (stages Ib2-IV) are planned to be enrolled with the main objectives of the discovery of predominant genetic aberrations, signaling pathway activation, and the study of tumor microenvironment regulation of tumor progression and metastasis (NCT02428842), could represent an important advance in the biological understanding of this disease with therapeutic implications.

There is some evidence to suggest that inducing DNA damage with PARP inhibitors and reducing VEGF signaling with antiangiogenic therapy may add antitumor activity to immune checkpoint blockade. A recent dose escalation, phase I study demonstrated that anti-PD-L1 plus olaparib or cediranib combination therapy was feasible and clinically active in gynecological cancers [60]. These combinations should be a major focus of research.

In addition, maintenance strategies among high-risk patients who are treated with definitive chemoradiation should be tested. In addition, new efforts should be directed to a limited state of metastatic disease, the oligometastases state, with preclinical models supporting this concept [61] which suggest that if primary site is controlled and the metastatic(s) site are treated with surgery or radiation, with or without systemic therapy, a sustained disease-free interval, and maybe cure could be achieved [62•].

Conclusions

Recurrent or advanced cervix cancer is an unmet medical need that requires urgent efforts to improve prognosis and to bring new strategies to more curable stages of the disease such as patients with high-risk locally advanced disease and in patients with oligometastatic or low volume disease. The academic world should continue coordinating efforts to discuss with private industry the benefits of research in cervix cancer. Preventive measures will have an impact on this disease, but it will be in the long term. In the meantime, many women will face dismal prognosis unless significant progress is achieved. The implementation and testing in cutting-edge clinical trials based on gene expression profile, vaccines, new immunotherapies approaches, and PARP inhibition-DNA damage are a must for the scientific community.

Compliance with Ethical Standards

Conflict of Interest Gloria Marquina, Arancha Manzano, and Antonio Casado declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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