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Exploiting somatic alterations as therapeutic targets in advanced and metastatic cervical cancer

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Abstract

It is estimated that 604,127 patients were diagnosed with cervical cancer worldwide in 2020. While a small percentage of patients will have metastatic disease at diagnosis, a large percentage (15–61%) later develop advanced disease. For this cohort, treatment with systemic chemotherapy remains the standard of care, with a static 5-year survival rate over the last thirty years. Data on targetable molecular alterations in cervical cancer have lagged behind other more common tumor types thus stunting the development of targeted agents. In recent years, tumor genomic testing has been increasingly incorporated into our clinical practice, opening the door for a potential new era of personalized treatment for advanced cervical cancer. The interim results from the NCI-MATCH study reported an actionability rate of 28.4% for the cervical cancer cohort, suggesting a subset of patients may harbor mutations which that are targetable. This review sets out to summarize the key targeted agents currently under exploration either alone or in combination with existing treatments for cervical cancer.

Keywords

Cervical cancer; Mutation; Targeted therapy; Precision oncology

Introduction

Cervical cancer is the leading cause of gynecological cancer death worldwide [1]. It is the fourth most frequent cancer in women globally after breast cancer (2·1 million cases), colorectal cancer (0·8 million), and lung cancer (0·7 million) [2]. It is estimated that 604,127 patients were diagnosed with the disease worldwide in 2020 [1].

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Cervical cancer can be subclassified on the basis of pathological appearance: squamous (80%), glandular / adenocarcinoma and other epithelial tumors including adenosquamous carcinoma, neuroendocrine subtypes, and undifferentiated carcinoma [3]. Approximately half of patients are diagnosed with localized, early-stage cervical cancer [4]. A US study examining cases from 1998 to 2003 found that a further 31.5% of patients were diagnosed with locoregional spread and 9.1% of cervical carcinomas were diagnosed at the distant metastatic stage [4,5]. However, 15–61% of women with cervical cancer subsequently go on to develop metastatic disease, usually within the first 2 years of completing their upfront treatment [6]. Palliative systemic chemotherapy is the treatment of choice for patients with stage IVB, recurrent or persistent disease that is not amenable to curative treatment [7]. Over the past thirty years, the median overall survival (OS) of patients with stage IV or recurrent disease has not significantly improved, with a 5-year survival rate of 15–20% reported in the United States [8]. Paclitaxel plus cisplatin/carboplatin has remained the backbone of treatment for this subgroup since this regimen was established in the Gynecologic Oncology Group (GOG)-204 study [9]. In 2014, we saw the first major advance for the stage IVB group [9]. The US Food and Drug Administration (FDA) approved the anti-angiogenesis drug bevacizumab in combination with chemotherapy on the basis of an improved OS of 3.5 months over chemotherapy alone in the GOG-240 trial [10].

With the growing understanding of the molecular and genetic profiles of cancers, novel treatments are increasingly being explored to improve patient outcomes. In recent years there has been a paradigm shift towards the development of molecular-targeted and immunotherapeutic agents to prolong survival in subsets of patients with cancer. This has changed the treatment landscape of various cancers, most notably in non-small cell lung cancer and malignant melanoma [11–13]. Data on targetable genetic alterations in cervical cancer have lagged behind other more common tumor types, with a comprehensive genetic landscape analysis first published in 2014 [14]. Ojesina *et al* carried out whole-exome sequencing (WES) analysis of 115 cervical carcinoma–normal paired samples, transcriptome sequencing of 79 cases, and whole-genome sequencing (WGS) of 14 tumor–normal pairs. Variants in various oncogenic pathways were identified, including PI3K-Akt pathway (*PIK3CA* 14%, *PTEN* 6%) and MAPK pathway (E322K substitutions in the *MAPK1* gene 8%). Other variants in well-known tumor suppressor genes were also noted, including mutations in *STK11* (4%) and TP53 (5%). Among previously unknown cervical cancer somatic mutations, inactivating mutations in the *HLA-B* gene (9%), in addition to variants in *EP300* (16%), *FBXW7* (15%), *NFE2L2* (4%), and *ERBB2* (6%), were seen. Somatic *ELF3* (13%) and *CBFB* (8%) mutations in 24 adenocarcinomas were also observed [14]. Later, The Cancer Genome Atlas (TCGA) Research Network published comprehensive molecular and integrative profiling of 228 cervical cancers, which identified further novel genomic and proteomic characteristics [15]. The genes *ERBB3* (*HER3*), *CASP8*, *HLA-A*, *SHKBP1*, and *TGFBR2* showed significant variants for the first time in cervical cancer [15]. Amplifications and fusion events involving the *BCAR4* gene, which can be targeted indirectly by lapatinib, were also reported. Amplifications in *CD274* (PD-L1) and *PDCD1LG2* (PD-L2), two genes that encode well-known immunotherapy targets, were also identified [15]. It is worth noting that specimens used in these and many other studies were resected cervical cancers, indicating early-stage disease. It has been observed

that as cancers progress and metastasize, they can evolve, acquiring new mutations and subclonal variants. Thus, future sequencing should also seek to uncover targetable mutations within more advanced and metastatic cancers, taking into consideration the challenge of intra-tumoral genetic heterogeneity, or the genomic differences between different metastatic sites within the same patient.

The phase 2 clinical trials included in the National Cancer Institute (NCI)-MATCH study (NCT02465060), investigated the efficacy of anti-cancer treatment directed by tumor genomic testing. In this study, actionable molecular alterations were those that, at minimum, were associated with preclinical evidence linking the alteration with drug activity [16]. Eighty-eight cervical cancer patients were initially screened for inclusion, with 25 patients with cervical cancer enrolled [17]. Initial analysis of other cancer types demonstrated an expansive range of actionability rates, differing among histologies. Urothelial cancers had a greater than 35% actionability, whereas pancreatic and small-cell lung cancer revealed <6% actionability. In the MATCH study, 28.4% of patients with cervical cancer had an actionable molecular alteration, suggesting a promising future role for treatment directed by tumor genomic testing [17].

This review sets out to summarize the key targeted agents presently under exploration either alone or in combination with existing treatments for cervical cancer. Rigorous review of the literature and cervical cancer response rates to targeted, often variant-directed treatments will be essential in establishing the role for these agents in clinical practice. In the last few years we have seen a number of advances in immunotherapy in advanced cervical cancer; most recently, cemiplimab monotherapy demonstrated an improvement in OS in women with recurrent or metastatic cervical cancer following progression on platinum-based chemotherapy in a phase 3 trial [18]. For the purposes of clarity and brevity, immunotherapeutic and immunomodulatory agents which target PD-L1, PD-1, and CTLA-4 will not be discussed in this review. Instead we focus on biologic monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) against specific pathogenic variants. This review will include anti-angiogenic agents, in addition to the multitude of compounds that target EGFR, HER2, PI3K/Akt/mTOR pathways, and DNA damage repair pathways, as well as other promising early-phase investigational drugs Table 3 Fig. 1.

Anti-Angiogenic agents

New blood vessel formation (tumor angiogenesis) is a fundamental hallmark of tumor growth and dissemination [19]. The vascular endothelial growth factor (VEGF) pathway is well established as one of the key regulators of this process [20]. Poor prognosis and early recurrence in cervical cancer has been associated with increased VEGF expression [21]. Direct VEGF stimulation may disable apoptosis and confer resistance to standard chemotherapy and radiotherapy. Therefore, its inhibition may improve treatment outcomes [22]. Moreover, agents that target angiogenic pathways have been shown to ‘normalize’ tumor vasculature, resulting in enhanced delivery of oxygen and drugs into the tumor microenvironment [23,24].

Bevacizumab is a recombinant humanized monoclonal immunoglobulin (Ig)-G1 antibody directed against VEGF-A. By inactivating VEGF-A, it blocks signal transduction through

VEGF receptor (VEGFR)-1-associated and VEGFR-2-associated pathways. The pivotal study GOG-240 established the survival benefit of bevacizumab with standard chemotherapy [10]. A statistically significant improvement in median OS of 16.8 months was seen in the chemotherapy plus bevacizumab groups versus 13.3 months in the chemotherapy alone groups (hazard ratio [HR] 0.77; 95% CI, 0.62–0.95; $p = 0.007$). The CECILIA phase 2 study evaluated the addition of bevacizumab to carboplatin and paclitaxel, and the findings were in line with GOG-240 [25]. At data cutoff, the median follow-up was 27.8 months. Objective response rate (ORR) was 61% (95% CI, 52–69%), including complete response in 14%. Median progression-free survival (PFS) was 10.9 months (95% CI, 10.1–13.7) and median OS was 25.0 months (95% CI, 20.9–30.4).

Future investigational directions of bevacizumab include combinations with other novel agents including antibody drug conjugates (ADCs) such as tisotumab vedotin (NCT03786081), polyADP-ribose polymerase (PARP) inhibitors (NCT03476798), and immune checkpoint inhibitors (NCT03367871). While a recent phase 2 study of atezolizumab (an anti-PD-L1 inhibitor) with bevacizumab failed to meet its primary endpoint, with a 0% ORR [26], ongoing studies such as BEATcc with atezolizumab [27], BCD-100 (anti-PD-1) /bevacizumab/platinum-based chemotherapy combination (NCT03912415), and a pembrolizumab/bevacizumab/ chemotherapy combination (NCT03367871) will permit a better understanding of whether these strategies should be pursued further. These are summarised along with reported studies investigating bevacizumab in Table 1.

The small-molecule anti-angiogenic TKI cediranib (AZD2171) is a potent oral inhibitor of VEGFR 1, 2 & 3, platelet-derived growth factor receptor (PDGFR), and c-kit. In the CIRCCa trial, cediranib 20 mg oral once daily was added to standard chemotherapy (3-weekly carboplatin AUC5 plus paclitaxel 175 mg/m^2) in a randomized, double-blind, placebo-controlled phase 2 study that enrolled 69 patients with first-line metastatic or recurrent cervical carcinoma [28]. The primary endpoint of PFS was significantly longer in the experimental arm (8.1 vs 6.7 months; HR 0.58; 80% CI, 0.40 to 0.85; $p = 0.032$), but the secondary endpoint of OS did not differ significantly between the arms (13.6 vs 14.8 months; HR 0.94; 80% CI, 0.65 to 1.36; $p = 0.52$). As expected from an antiangiogenic agent, grade 2–3 hypertension was higher in the experimental arm (34 vs 11%). Of note, no fistula events were reported with cediranib despite 91% of patients in the cediranib group having had prior radiotherapy [28]. The phase 2 COMICE trial of olaparib (PARP inhibitor) and cediranib for advanced cervical cancer is currently recruiting (NCT04487587).

Other anti-angiogenic TKIs are also being investigated, with varying results. Sunitinib, a multi-kinase inhibitor of VEGFR, PDGFR, c-KIT, and FLT-3 was studied in a phase 2 trial in the treatment of locally advanced or metastatic cervical cancer [29]. Of 19 evaluable patients, the median time to progression was 3.5 months (range, 2.7–7.0 months). The ORR was 0%, although 16 patients had stable disease with a median duration of 4.4 months (range, 2.3–17.0 months). Five of 19 patients (26.3%) developed a fistula, and thus, it was concluded that as a single agent, sunitinib demonstrated minimal benefit and an unacceptable high rate of fistulization and did not warrant additional study. The TKI pazopanib targets VEGFR, PDGFR, and c-Kit. A phase 2 study comparing oral pazopanib

with oral lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2/neu), found both agents as monotherapy were tolerable, with an equal number of grade 3/4 toxicities in each arm. Median PFS was 18.1 vs 17.1 weeks with pazopanib and lapatinib, respectively. OS was increased by 11.6 weeks with pazopanib compared to lapatinib (50.7 weeks vs 39.1 weeks). The combination of both drugs caused a greater number of serious adverse events (SAEs) and treatment discontinuation in 17% compared with lapatinib alone (5%) and pazopanib alone (12%) [30]. Despite this study demonstrating a prolonged PFS and acceptable toxicity profile, pazopanib has not been further developed for cervical cancer, and there are no current registered trials.

Finally, apatinib showed activity in a phase 2 study as a single agent, with a 15% ORR and 35% disease control rate. Median PFS in this pretreated population was 5.1 months (95% CI, 2.9–7.3 months), and the median OS was 12.3 months (95% CI, 10.1–14.5 months) [31]. In the CLAP study, 45 patients with previously treated metastatic cervical cancer were enrolled to the combination of apatinib and camrelizumab (PD-1 inhibitor). The ORR was 55.6% (95% CI, 40.0% to 70.4%), with two complete and 23 partial responses. Median PFS was 8.8 months (95% CI, 5.6 months to not estimable). Median duration of response (DOR) and median OS were not reached. Treatment-related grade 3 or 4 AEs occurred in 71.1% of patients. The most common AEs were hypertension (24.4%), anemia (20.0%), and fatigue (15.6%) [32]. The response rate and survival results for this combination are very promising, but significant toxicity was observed. Nevertheless, the combination of anti-angiogenic agents and other compounds such as immune checkpoint inhibitors or ADCs may lend themselves to improved efficacy. These agents do not have overlapping toxicities for the most part and may synergistically enhance activity when given together.

Targeting EGFR/ HER2

EGFR and *HER2/neu* have been associated with poor outcomes in patients with cervical cancer [33,34]. In one study, the 5-year OS rates of patients with HER2-positive and -negative cervical cancer were 41% vs 61%, respectively ($p = 0.022$) [35]. High EGFR levels have also been predictive of poor OS (HR 1.40; 95% CI, 1.10–1.78) and disease-free survival (DFS) (HR 1.84; 95% CI, 1.51–2.24) [36]. It has been estimated that between 54% and 71% of cervical cancers, in particular the squamous subtype, overexpresses EGFR [37]. EGFR overexpression has been shown to correlate with resistance to cytotoxic chemotherapy and radiation in squamous cervical cancer [38]. Unfortunately, monotherapy studies with gefitinib and erlotinib, both oral reversible EGFR TKIs, in the treatment of recurrent cervical cancer have shown minimal activity [39,40]. Cetuximab is a monoclonal antibody that targets EGFR and was studied in combination with cisplatin in women with advanced, persistent, or recurrent cervical cancer [41]. The combination of cetuximab with cisplatin was adequately tolerated but did not indicate additional benefit beyond cisplatin therapy alone. The MITO CERV-2 trial, a phase 2 study of carboplatin and paclitaxel with or without cetuximab in unselected advanced or recurrent cervical cancer, found that the addition of cetuximab to the chemotherapy combination did not lead to increased OS (17.7 vs 17 months) [42]. Biomarker analysis of 20 tumor samples noted an interesting and significant interaction between treatment effect and PIK3CA mutational status, suggesting

a benefit of cetuximab in the PIK3CA wild-type subgroup (HR 0.09; 95% CI, 0.01–0.87) but not in the PIK3CA mutant cohort (HR 1.69; 95% CI, 0.46–6.47; $p = 0.001$) [42]. The phase 2 NCI-MATCH trial (NCT02465060), mentioned previously in this article, includes the EGFR inhibitors afatinib and osimertinib.

HER2 gene amplification or HER2 protein expression are most commonly associated with breast cancer but are also dysregulated in a variety of other cancer types. Overexpression of HER2/neu is seen in 1% to 12% of cervical cancers [14,43], with *HER2* mutations estimated at 3–6% [14,44,45]. There is evidence of acquiring HER2 overexpression or variants over time as the cervical cancer progresses, and therefore, this evolving HER2 immunoprofile could be a therapeutic target in more advanced disease and potentially in more heavily pretreated cancers [46–48].

Neratinib is an irreversible pan-HER TKI that has single-agent clinical activity in multiple *HER2*–mutant cancers, including cervical cancer. The SUMMIT trial is an international, open-label, phase 2 study evaluating the safety and efficacy of neratinib in patients with solid tumors with a variety of HER2 mutations (NCT01953926). At data cutoff in February 2020, 16 eligible cervical cancer patients were enrolled, with 10 (62.5%) of the adenocarcinoma subtype. The most frequent *HER2* mutation was *S310F* (63%). Three of 12 RECIST-measurable patients in the cervical cancer cohort had confirmed partial response (ORR 25%; 95% CI, 5.5–57.2%); 3 had stable disease ≥ 16 weeks [49]. DOR for these 3 stable patients was 5.6, 5.9, and 12.3 months. Median PFS was 7.0 months (95% CI, 0.7–18.3 months) and median OS was 16.8 months (95%, CI 4.1–NE months). Diarrhea (75%), nausea (44%), and decreased appetite (38%) were the most common AEs. There were no grade 4 events and no diarrhea-related treatment discontinuations[49].

Other EGFR and HER2/neu targeted compounds previously tested or undergoing investigation in advanced cervical cancer are summarized in Table 2. As mentioned previously, in combination with the anti-angiogenic agent pazopanib, lapatinib showed little single-agent activity in a phase 2 trial [30]. Despite relatively disappointing results thus far, HER-targeted therapies continue to be investigated in cervical cancer for their potential value in biomarker selected patients. A novel anti-HER2 ADC, A166, is being explored in an ongoing phase 1–2 study of patients with relapsed/refractory cancers expressing HER2 antigen or having amplified *HER2* gene, including cervical cancer (NCT03602079). PRS-343, a bispecific agent that targets HER2 and the immune receptor CD137 (also known as 4-1BB), is being studied in a phase 1 trial for patients with HER2-positive advanced solid tumors (NCT03330561). Trastuzumab deruxtecan is an ADC composed of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and potent topoisomerase I inhibitor payload [50]. A phase 2 study examining trastuzumab deruxtecan in solid tumors, including cervical cancer, is also currently recruiting (NCT04482309). Results from this trial in breast cancer and gastric cancer have been promising [51,52]. A basket study of tucatinib, a small-molecule TKI that is highly selective for HER2, in combination with trastuzumab in solid tumors with HER2 alterations is currently recruiting (NCT04579380). These well-tolerated agents will likely have a future role in selected subsets of cervical cancer with *EGFR* or *HER2/neu* variants or overexpression.

Targeting phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway

The PI3K/AKT/mTOR pathway is often dysregulated in gynecological cancers, particularly in human papillomavirus (HPV)-associated tumors, such as cervical cancer [53]. Activating mutations and amplification reported in 23–36% of cervical cancer specimens [54–57]. AKT phosphorylation (p-AKT) has also been demonstrated in cervical cancer, signifying constitutive activation of the PI3K/AKT pathway in this tumor type [58]. *PIK3CA* mutation rates are not significantly different in adenocarcinoma and squamous cell carcinomas (25.0% vs. 37.5%, respectively; $p = 0.33$) [56]. *PIK3CA* mutations have been associated with shorter OS; 67.1 vs. 90.3 months (HR 9.1; 95% CI, 2.8–29.5; $p < 0.001$) in an observational study [56]. Similarly, AKT and mTOR have been found to be indicators of poorer prognosis in a study on the predictive and prognostic role of molecular overexpression in cervical cancer treated with cisplatin-based neoadjuvant chemotherapy [59]. The same authors also investigated the expression of activated AKT (p-AKT) and mTOR (p-mTOR) in patients with cervical adenocarcinoma, identifying 50% p-AKT expression and 53% p-mTOR expression, the latter being an independent significant prognostic marker [60]. Radiation activates the PI3K/AKT pathway, and mTOR inhibitors may sensitize tumor and endothelial cells to cisplatin and radiotherapy effects *in vitro* [61]. Temsirolimus (CCI-779) is an example of an mTOR inhibitor. A phase 2 study of temsirolimus in recurrent, unresectable, locally advanced or metastatic carcinoma of the cervix found that single-agent temsirolimus had modest activity, with about two-thirds of 33 patients exhibiting stable disease [62]. One patient experienced a partial response (ORR 3.0%). Nineteen patients had stable disease (57.6%) for a median duration of 6.5 months (range, 2.4–12.0 months). The median PFS was 3.52 months (95% CI, 1.81–4.70). A phase 1 study of temsirolimus and bevacizumab in advanced gynecological malignancies included 6 patients with advanced cervical cancer [63]. Among the 4 patients with squamous cell carcinoma of the cervix, half achieved a partial response [63]. A phase I study of weekly temsirolimus and topotecan in the treatment of advanced and/or recurrent gynecologic malignancies, which included 2 patients with cervical cancer found myelosuppression to be a dose-limiting toxicity [64]. The disappointing results thus far may be related to feedback loop and compensatory activation of RAS pathway [65]. The previously mentioned NCI-MATCH study (NCT02465060) includes one mTOR-targeted arm of the drug sapanisertib (TAK-228). This compound is an oral and highly selective adenosine triphosphate (ATP)-competitive mTOR kinase inhibitor that suppresses both mTORC1 and mTORC2. The NCI-MATCH PIK3CA arm investigates both taselisib (GDC-0032), an oral, selective PI3K inhibitor with enhanced activity against PIK3CA-mutant cancer cells, and copanlisib, an intravenous PI3K inhibitor. In The NCI-MATCH AKT arm includes both capivasertib (AZD5363), an oral, selective ATP-competitive pan-AKT kinase inhibitor, and ipatasertib (RG7440), an oral ATP-competitive selective inhibitor of AKT1/2/3. These trials are summarized in Table 3.

Targeting the DNA damage repair pathways

Cellular DNA constantly suffers both endogenous and exogenous insults that result in crosslinks, mutations, and single- and double-stranded breaks. In response, cells have evolved DNA damage and repair response (DDR) pathways to correct the above errors

[66]. The DDR consists of sensors that detect the above irregularities and recruit Ataxia telangiectasia mutated (ATM) and Ataxia telangiectasia and Rad3 related (ATR) transducer kinases to the site of damage [66]. Following the latter recruitment, a signaling cascade is initiated through the effector kinases, checkpoint kinase (Chk) 1 and Chk2, activating cell cycle check points and preventing cell cycle progression while recruiting the DNA damage machinery to damaged DNA [67]. DDR-proficient tumor cells repair chemo/radiotherapy-induced DNA damage and are more resistant to therapy compared to tumor cells in which DNA repair components are inactivated [68–70]. The tumor suppressor gene *TP53* is an integral part of the DDR. As previously mentioned, the viral oncogene HPV-E6 promotes ubiquitin mediated degradation of p53 [71]. HPV-positive cervical cancer cells display a significantly impaired ability to activate cell cycle checkpoints and induce apoptosis following DNA damage [70]. In a cancer that is almost always caused by HPV infection, and where the treatment response is limited by tumor DNA repair capacity, targeting residual cell cycle checkpoint components or DNA repair factors appears to be a promising therapeutic venture.

PARP is an intracellular protein involved in the repair of errors of DNA replication, in particular in repairing single-stranded DNA breaks [72–74]. PARP1 has multiple functions in DNA repair and is a key player in base excision repair and single-stranded breaks [75]. If unrepaired, these lesions can lead to double-stranded breaks through replication fork breakdown, and therefore, loss of PARP1 function can lead to increased requirement for homologous recombination repair (HRR). Inhibition of PARP1 in cells with HRR defects leads to synthetic lethality [76,77]. In a study from the 1980s, PARP activity was twice as high in cervical cancer cells compared to normal cells, representing a potential target for therapy in these patients [78]. More recently, immunohistochemical staining found PARP1 was easily detected in 86%, 77.5%, and 94% of patients with low-grade squamous intraepithelial lesion (SIL), high-grade SIL, and invasive squamous cell carcinoma, respectively, with no or minimal staining in normal cervical tissue [79]. The phase 1 trial combining paclitaxel, cisplatin, and veliparib (ABT-888) in the treatment of persistent or recurrent carcinoma of the cervix found the combination to be safe and feasible [80]. Objective responses were achieved in 34% (95% CI, 20–53%). Median PFS was 6.2 months (95% CI, 2.9–10.1 months), with an OS of 14.5 months (95% CI, 8.2–19.4 months) [80]. A second phase 1 study looked at the combination of veliparib with topotecan [81]. Clinical activity of the combination was minimal in patients with persistent or recurrent cervical cancer, but it was hypothesized that cervical tumors with low levels of PARP1 may respond to PARP inhibitors when combined with cytotoxic therapies, suggesting further study of PARP expression as an important biomarker for this treatment approach [81]. Limitations to combining PARP inhibitors with chemotherapy include overlapping toxicities of anemia, leukopenia, and thrombocytopenia, in addition to non-hematological adverse events such as nausea, vomiting, and renal dysfunction. Finding complementary dosing or innovative scheduling strategies as well as PARP inhibitor combinations with non-cytotoxic, immunotherapy, or anti-angiogenic compounds will help overcome these challenges.

A number of phase 1/2 clinical trials are currently investigating various PARP inhibitors in advanced cervical cancer. A phase 2 study of olaparib in combination with the immune checkpoint inhibitor pembrolizumab in cervical cancer is currently recruiting patients. This

combination has been shown to be effective in prostate cancer (NCT04483544) [82]. A phase 2 study investigating rucaparib, an oral small molecule inhibitor of PARP1, PARP2 and PARP3, in combination with bevacizumab in recurrent carcinoma of the cervix or endometrium, is active but not yet recruiting (NCT03476798). Finally, a phase 1/2 study investigating niraparib with radiotherapy for treatment of metastatic cervical cancer is also currently recruiting (NCT03644342). Additional studies will help determine if PARP inhibitors, alone or in combination, have a role in the treatment of cervical cancer and perhaps identify biomarkers of response to this strategy.

Other agents targeting the DNA damage repair pathways, including Wee1 inhibitors, are also under scrutiny. As previously mentioned, cervical cancer development involves functional p53 inactivation by HPV infection [83,84]. p53 is well known as a cell cycle regulator at the G1 checkpoint that arrests cell cycle and subsequently provides time for DNA damage repair. It is also an activator of other critical DDR genes [85]. For tumors in which the G1 checkpoint is bypassed by p53 inactivation, DDR may become solely dependent on the G2 checkpoints [86]. It has been shown that Wee1, the G2 checkpoint kinase, is upregulated in p53-mutated cancer cells [86]. As greater than 90% of patients with cervical cancer showed HPV E6-mediated inactivation of p53 in their primary tumors, Wee1 inhibitors may be a potential therapeutic target for cervical cancer [83,84]. Recently reported results with adavosertib (AZD1775) in combination with gemcitabine in platinum-resistant ovarian cancer revealed a modest increase in PFS with the addition of adavosertib (4.6 months vs 3.0 months; HR 0.55; 95% CI, 0.35–0.90) [87]. A phase 1 trial of adavosertib, external beam radiation therapy, and cisplatin in treating patients with cervical, vaginal, or uterine cancer is currently recruiting (NCT03345784). These novel DDR targeting compounds show promise.

As noted above, ATR is activated in response to single-stranded breaks as well as abnormal DNA structures that arise as a result of stalled or collapsed replication forks [88]. In absence of external DNA damage signals, HPV induces activation of the ATR pathway, and inhibition of ATR activation leads to suppression of HPV genome maintenance and amplification [89,90]. Treatment of HPV-positive cells with the ATR inhibitor VE-822, *in vitro*, triggers DNA breaks and the fragmentation of viral episomes [91]. A trial looking at AZD6738, an orally active and selective ATR kinase inhibitor, with the PARP inhibitor olaparib in gynecological cancers with or without ARID1A loss is currently recruiting (NCT04065269). Another ATR inhibitor, BAY1895344, is being trialed as an addition to the chemotherapy backbone of cisplatin or cisplatin with gemcitabine in solid tumors, including cervical cancer (NCT04491942). This latter trial is not yet recruiting.

In a similar vein to other cancers, such as ovarian and breast cancer, identifying biomarkers of potential sensitivity to targeting the DDR pathways will remain critical in fully realizing the potential benefits in cervical cancer. Biomarkers for consideration include platinum sensitivity, evaluation of tumor HRR status, identification of somatic BRCA1/2 mutations and alterations in PALB2 and RAD51, and loss of other tumor suppressors such as ARID1A.

To repair damaged DNA, cells increase synthesis of deoxyribonu-cleotide triphosphates through the rate-limiting, p53-regulated ribonu-cleotide reductase (RNR) enzyme [92]. Triapine is a small-molecule inhibitor of RNR. Overactive RNR is a hallmark molecular

driver in greater than 80% of cervical cancers, leading to efficient DNA damage repair, which has a limiting effect on chemoradiation treatment [93–95]. The phase 2 study evaluating triapine's use in combination with cisplatin during radiation therapy for patients with advanced-stage cervical and vaginal cancer did not include any stage IVA patients in the treatment group despite being open to this cohort [95]. Results for stage II-III patients showed that the addition of triapine improved the rate of metabolic complete response from 69% to 92% ($p = 0.32$) and increased the 3-year PFS rate estimate from 77% to 92% (HR for progression, 0.30; $p = 0.27$) [95]. The phase 3 clinical trial, which includes stage IVA disease, is currently recruiting (NCT02466971).

Other targets

Tisotumab vedotin is an ADC directed against tissue factor (TF), which is expressed across multiple solid tumor types and is associated with poor clinical outcomes [96]. Tisotumab vedotin is composed of a fully human monoclonal antibody specific for TF conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable valine-citrulline linker [96]. TF is a transmembrane glycoprotein and is the main initiator of the extrinsic coagulation pathway, with its overexpression contributing to a variety of pathologic processes, such as thrombosis, metastasis, tumor growth, and tumor angiogenesis [97]. The mechanisms of action of tisotumab vedotin are illustrated in Fig. 2. The results from the cervical cancer arm of innovaTV 201, a phase 1–2 study evaluating tisotumab vedotin use in solid tumors, were presented in 2020 and reported an ORR of 22% (95% CI, 12%–35%), median DOR of 6.0 months (range, 1.0 ± 0.7), and 6-month PFS rate of 40% (95% CI, 24%–55%) [98]. Results from the innovaTV 204 study, a phase 2 multi-center study of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer, was recently published and included 102 patients [99]. The most common AEs were alopecia (38%), epistaxis (30%), and nausea (27%). Grade 3 or worse treatment-related AEs were reported in 28% of patients and included neutropenia (3%), fatigue (2%), ulcerative keratitis (2%), and peripheral neuropathies (2%) [99]. Of the 101 patients with recurrent or metastatic cervical cancer, an ORR of 24% (95% CI, 16%–33%) was observed, including 7% with a complete response. The disease control rate was 72% (95% CI, 63%−81%). At a median follow-up of 10 months, the median DOR was 8.3 months (95% CI, 4.2-not reached), the median PFS was 4.2 months (95% CI, 3–4.4), and the median OS was 12.1 months (95% CI, 9.6–13.9) [99]. The 12-month OS rate was 51%. Clinically meaningful responses were observed, irrespective of histology subtype, tissue factor expression level, or prior therapy. It is hoped that the positive results achieved with monotherapy may be built upon by combining tisotumab vedotin with other agents to improve outcomes further [99]. Results of phase 1b/2 trials of tisotumab vedotin alone or in combination with bevacizumab, pembrolizumab, or carboplatin in recurrent or metastatic cervical cancer (innovaTV 205/ENGOT-cx8/GOG-3024) are pending [100]. This ADC as a single agent is also being randomized against investigators choice of chemotherapy in the second- and third-line setting for metastatic cervical cancer in an ongoing phase 3 trial (NCT04697628).

Enapotamab vedotin, an ADC targeted to AXL, is another drug currently being tested in clinical trials in patients with solid tumors, including cervical cancer. A phase 1–2 study of enapotamab vedotin is currently recruiting (NCT02988817). AXL is a unique receptor

tyrosine kinase that is aberrantly expressed in many solid tumor types and is implicated in tumor cell proliferation, migration, and invasion [101].

A novel bifunctional fusion protein, bintrafusp alfa, targets both transforming growth factor β (TGF-β) and PD-L1. It has shown promising clinical activity in HPV-associated malignancies [102]. TGF-β, a pleio-tropic cytokine, is associated with tumor growth, evasion of immune surveillance, invasion, and metastasis in advanced cancer [103]. Dys-regulated *TGF-β* signaling is a key process common to multiple HPV-related cancers [102]. The results from a phase 1/2 trial in HPV-associated malignancies included 33 patients with advanced cervical cancer and demonstrated an ORR of 30.5% (95% CI, 19.2 to 43.9). Two cervical cancer patients had complete responses and 8 achieved partial responses [102]. The dedicated cervical cancer phase 2 study has finished recruitment, with results expected shortly (NCT04246489). A phase 1 study combining bintrafusp alfa with standard chemotherapy regimes in locally advanced and advanced cervical cancer is currently recruiting (NCT04551950).

Limitations in drug development in cervical cancer—Drug development in patients with advanced cervical cancer presents its own unique challenges. These patients are heavily pretreated with chemotherapy, most have received prior pelvic radiation, and many have experienced treatment- or disease-related morbidities, which excludes them from clinical trials. Patients with stage IVA disease frequently develop vesicovaginal and or rectovaginal fistulae after radiotherapy, with some studies suggesting this occurs in up to 48% of patients in this setting [104]. Hydronephrosis and subsequent renal impairment also limits inclusion in clinical trials. The incidence of obstructive uropathy in cervical cancer ranges from 14% to 44.2% [105]. These are in addition to long-term treatment morbidities associated with standard chemotherapy. Baseline peripheral neuropathy grade >2 is a common exclusion criterion for studies of new promising ADCs. Inequity and healthcare disparity remain global issues posing many challenges in the delivery of cancer care. This divide is starkly illustrated in cervical cancer, as the greatest number of cases occur in developing countries, with many of these women presenting with advanced disease due to a lack of access to HPV vaccination, screening, and early treatment. The agents mentioned in this review are unlikely to ever reach these patients. In the US, we also see persistent healthcare disparities. A study assessing socioeconomic disparities in cervical cancer in the US from 1975 to 2000 found that incidence and mortality rates increased with increasing poverty and decreasing education levels for the total population [106]. It also found that those from lower socioeconomic census tracts had higher rates of late-stage cancer diagnosis and lower rates of survival [106]. A recent NCI-funded study found that clinical trial participants from areas with the highest socioeconomic deprivation had worse OS (HR 1.28; 95% CI, 1.20 to 1.37; $P < 0.001$), PFS (HR 1.20; 95% CI, 1.13 to 1.28; $P < 0.001$), and cancer-specific survival (HR 1.27; 95% CI, 1.18 to 1.37; $P < 0.001$) compared to participants from affluent areas [107]. With the rapid expansion of costly immunotherapeutic options for patients with recurrent cervical cancer, we will need to judiciously determine how best to incorporate novel targeted therapies into that rapidly evolving landscape.

Conclusion

The prognosis of advanced cervical cancer remains poor, with the backbone of treatment remaining paclitaxel with platinum-based chemotherapy with or without bevacizumab. Across all cancers, there is now a paradigm shift towards developing targeted treatment agents and personalizing cancer treatment. As evident from the above review, we have a number of promising drugs targeting a large number of cervical cancer gene targets currently in development. This is in addition to the substantial number of immunotherapy agents currently being investigated in cervical cancer, which have not been reviewed here. The future of targeted cervical cancer treatment will undoubtedly involve a number of therapeutic options alone or in combination with chemotherapy, other targeted agents, and/or immunotherapy compounds. This approach will be supported by ongoing research to identify novel gene targets for this cancer type both at early and late stages of disease evolution. As noted above, evidence suggests cervical cancer can develop potentially actionable variants as it becomes more advanced, and future treatment strategies will involve capitalizing on these changes as they occur. Moreover, improved biomarker identification, novel combinations, and innovative scheduling will maximize tumor response to targeted therapeutic strategies while minimizing toxicity.

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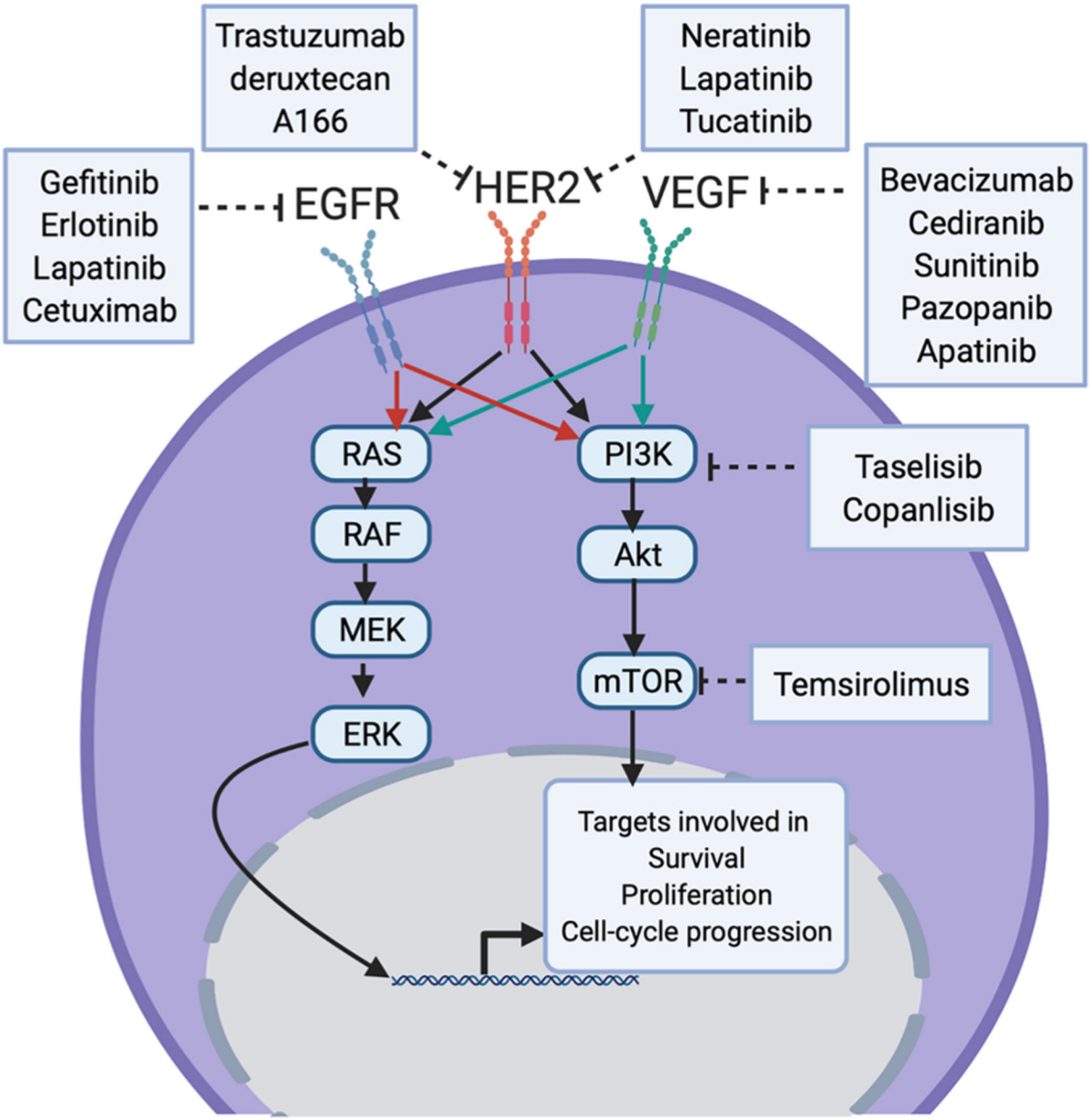

Fig. 1.

Anticancer targets in cervical cancer: focus on EGFR, HER2, VEGF pathways. Made with Biorender.com.

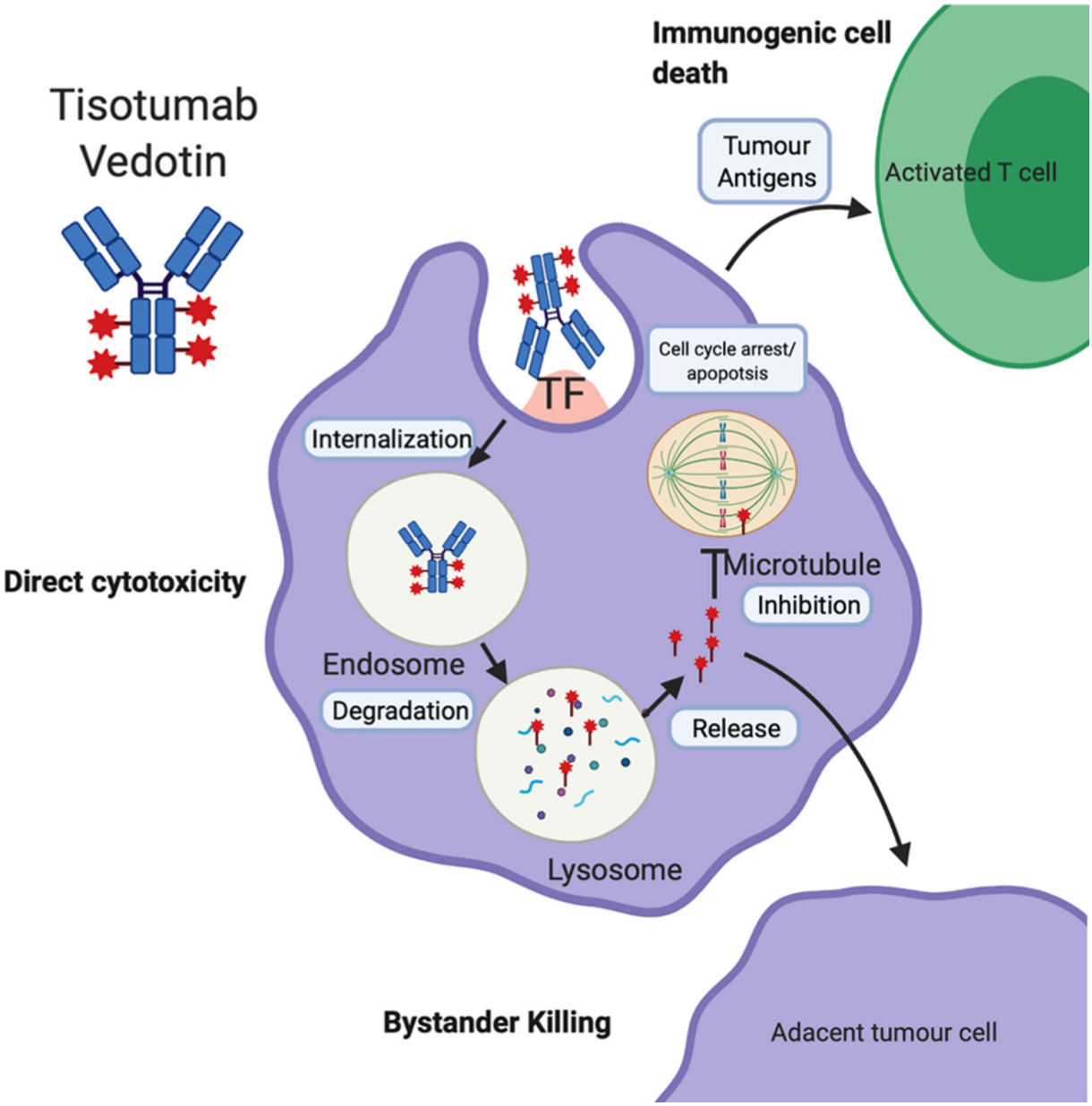

Fig. 2.
Mechanism of action of tisotumab vedotin. Made with Biorender.com.

Table 1

Summary of clinical trials with anti-VEGF agents.

	Drug	Phase	Results	Reference
Bevacizumab	Bevacizumab plus paclitaxel with cisplatin or topotecan (GOG-240)	Phase 3	• Median OS 16.8 mos (chemo + bevacizumab) vs 13.3 mos (chemo alone) (HR 0.77 [95% CI 0.62–0.95]; p = 0.007).	NCT00803062 [10]
	Bevacizumab in combination with carboplatin and paclitaxel (CECILIA)	Phase 2	• ORR 61% (95% CI 52–69%) • Median PFS 10.9 mos (95% CI 10.1–13.7 mos) • Median OS 25.0 mos (20.9–30.4 mos)	NCT02467907 [26]
	Tisotumab vedotin (HuMax®-TF-ADC) monotherapy and in combination with bevacizumab, pembrolizumab, or carboplatin	Phase 1/2	Active, not recruiting	NCT03786081
	Bevacizumab and rucaparib	Phase 2	Active, not recruiting	NCT03476798
	Atezolizumab in combination with bevacizumab	Phase 2	• N = 10. • ORR of 0% (2 unconfirmed PR) • Median PFS 2.9 mos (95% CI, 1.8 to 6) • Median OS 8.9 mos (95% CI, 3.4 to 21.9)	NCT02921269
	Standard chemotherapy with bevacizumab with pembrolizumab	Phase 2	Recruiting	NCT03367871
	First line pembrolizumab plus chemotherapy +/− bevacizumab (KEYNOTE-826)	Phase 3	Active, not recruiting	NCT03635567
	Cisplatin or carboplatin/paclitaxel/ bevacizumab plus atezolizumab (BEATcc)	Phase 3	Active, not recruiting	NCT03556839
	Temsirolimus (CCI-779) and bevacizumab	Phase 1	• N = 6 • ORR 50% achieved a PR	NCT00610493
Cediranib	Cediranib (CirCCa)	Phase 2	• ORR 64% (cediranib group) compared with 45% (placebo group) • PFS 8.1 mos (exp arm) vs 6.7 mos (HR 0.58; 80% CI, 0.40 to 0.85; $p = 0.032$) • OS 13.6 vs 14.8 mos (HR 0.94 (80% CI, 0.65 to 1.36), p = 0.52)	NCT01229930 [29]
	Olaparib and cediranib (COMICE)	Phase 2	Recruiting	NCT04487587
Sunitinib	Sunitinib	Phase 2	• N = 19 • ORR 0% • Median PFS 3.5 mos (range 2.7–7.0 months),	NCT00389974 [30]

	Drug	Phase	Results	Reference
			• DOR 4.4 mos (range 2.3–17.0 mos).	
Pazopanib	Pazopanib plus lapatinib compared to lapatinib alone and pazopanib alone	Phase 2	• Median PFS 18.1 (pazopanib) vs 17.1 wks (lapatinib) • Median OS 50.7 wks (pazopanib) vs 39.1 wks (lapatinib)	NCT00430781 [31]
Apatinib	Apatinib	Phase 2	• Median PFS 5.13 mos (95% CI, 2.94–7.32 mos) • Median OS 12.3 mos (95% CI, 10.13–14.47 mos)	[32]
	Apatinib in combination with camrelizumab	Phase 2	• N = 45 • ORR 55.6% (95% CI, 40.0% to 70.4%), with 2 CR + 23 PR. • Median PFS 8.8 mos (95% CI, 5.6 mos to not estimable). • Median DOR & median OS not reached.	NCT03816553 [33]
	Apatinib and Chemotherapy Sequential Treatment	Phase 2	Recruiting	NCT03029013
	SHR-1210 in combination with apatinib	Phase 2	Active, not recruiting	NCT03816553

Abbreviations: CBR: clinical benefit rate; CI: confidence interval; CR: complete response; DOR: duration of response; HR: hazard ratio; mos: months; ORR: objective response rate; OS: overall survival; PFS: progression free survival; PR: partial response; SD: stable disease; wks: weeks

Table 2

Summary of trials targeting EGFR and HER2.

	Drug	Phase	Result		Reference
EGFR	Gefitinib	Phase 2	•	N = 30	NCT00049556 [39]
			•	ORR 0%	
			•	20% (n = 6) SD with median DOR of 111.5 days.	
			•	Median PFS 37 days	
			•	Median OS 107 days	
	Erlotinib	Phase 2	•	N = 28.	NCT00031993 [40]
			•	ORR 0%	
			•	16% (n-4) SD	
			•	1 patient had PFS 6 mos (4%)	
	Cetuximab plus cisplatin	Phase 2	•	N = 69	NCT00101192 [41]
			•	ORR 9% in prior chemotherapy subgroup	
			•	ORR 16% in no chemotherapy subgroup	
	Cetuximab plus carboplatin and paclitaxel (MITO CERV2)	Phase 2	•	N = 108	NCT00997009 [42]
			•	ORR 38%	
			•	Median event free survival 6 mos	
			•	Median PFS 7.6 mos	
			•	Median OS 17 mos	
HER2	Neratinib (SUMMIT)	Phase 2	•	ORR 25% (95% CI 5.5–57.2%)	NCT01953926 [49]
			•	CBR 50% (95% CI 21.1–78.9%).	
			•	Median PFS	
			•	mos (95%CI 0.7–18.3 mos)	
			•	Median OS 16.8 mos (95%CI	
			•	-NE mos).	
	A166	Phase 1–2	•	Recruiting	NCT03602079
	Trastuzumab deruxtecan (T-DXd)	Phase 2	•	Recruiting	NCT04482309
	Tucatinib	Phase 2	•	Recruiting	NCT04579380

Abbreviations: CBR: clinical benefit rate; CI: confidence interval; CR: complete response; DOR: duration of response; mos: months; NE: not evaluable; ORR: objective response rate; OS: overall survival; PFS: progression free survival; PR: partial response; SD: stable disease

Table 3

Other trials of targeted agents in Cervical Cancer.

	Drug	Phase	Results	Reference
PI3K/AKT/mTOR pathway	Temsirolimus	Phase 2	• N = 33. • ORR 3% (1 PR) • 57.6% SD [median duration 6.5 mos (range 2.4–12.0 mos)]. • 6-month PFS rate 28% (95% CI: 14–43%). • Median PFS 3.52 mos [95% CI (1.81–4.70)].	NCT01026792 [62]
	Temsirolimus and Bevacizumab	Phase 1	• N = 6 • 2 of 4 squamous cell cervical carcinoma of achieved PR	[63]
	Temsirolimus and Topotecan	Phase 1	• N = 2 • DLT = neutropenia and thrombocytopenia	NCT00523432 [64]
DNA damage repair pathways	Paclitaxel, cisplatin and veliparib	Phase 1	• ORR 34% (95% CI 20–53%). • Median PFS 6.2 mos (95% CI 2.9–10.1 mos) • Median OS 14.5 mos (95% CI 8.2–19.4 mos)	NCT01281852 [80]
	Veliparib with topotecan	Phase 1	• N = 27. • ORR 7% (2 PR) • Four pts had PFS greater than 6 mos.	NCT01266447 [81]
	Pembrolizumab with Olaparib	Phase 2	Recruiting	NCT04483544
	Bevacizumab combined with rucaparib	Phase 2	Active, not recruiting	NCT03476798
	Niraparib with radiotherapy	Phase 1 –2	Recruiting	NCT03644342
	Adavosertib (AZD1775), External Beam Radiation Therapy, and Cisplatin	Phase 1	Active, not recruiting	NCT03345784
	AZD6738 with olaparib	Phase 2	Recruiting	NCT04065269
	BAY 1,895,344 with cisplatin or cisplatin with gemcitabine	Phase 2	Recruiting	NCT04491942
Other ADCs	Tisotumab Vedotin (HuMax®-TF-ADC) (innovaTV204)	Phase 2	• N = 102 • ORR 24% (7% CR) • DCR 72%. • Median PFS 4.2 mos	NCT02552121 [99]

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	Drug	Phase	Results	Reference
			• Median OS 12.1 mos	
	Tisotumab vedotin ± bevacizumab, pembrolizumab, or carboplatin (innovaTV 205/ENGOT-cx8/ GOG-3024)	Phase 1/2	Active, not recruiting	NCT03786081
	Tisotumab vedotin versus investigators choice of chemotherapy	Phase 3	Recruiting	NCT04697628
	Enapotamab vedotin (HuMax-AXL-ADC)	Phase 1–2	Recruiting	NCT02988817
	Bintrafusp alfa (bifunctional fusion protein TGF-β and PD-L1)	Phase 2	Active, not recruiting	NCT04246489
	Bintrafusp alfa + chemotherapy	Phase 1	Recruiting	NCT04551950

Abbreviations: CBR: clinical benefit rate; CI: confidence interval; CR: complete response; DCR: disease control rate; DLT: dose limiting toxicity; DOR: duration of response; mos: months; ORR: objective response rate; OS: overall survival; PFS: progression free survival; PR: partial response; pts: patients; SD: stable disease