Uterine Serous Carcinoma and Uterine Carcinosarcoma: Molecular Features, Clinical Advances, and Emerging Therapies

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Abstract: Endometrial cancer, including high-grade subtypes, has a rising incidence and mortality. Uterine serous carcinoma (USC) and uterine carcinosarcoma (UCS) make up a small but increasing proportion of endometrial cancer cases and account for a significant portion of endometrial cancer mortality. Despite being molecularly and clinically distinct, both USC and UCS have a poor prognosis. Thus far, there have been few therapeutic strategies directed at these endometrial cancer subtypes. This review summarizes the genomic and molecular features of USC and UCS, clinical advances in the treatment of primary advanced and recurrent endometrial cancer, and novel molecularly-driven treatment strategies.

Introduction

Endometrial cancer is the only gynecologic cancer in the United States with a rising incidence and mortality.[1] High-grade endometrial cancers, including uterine serous carcinoma (USC) and uterine carcinosarcoma (UCS), are also increasing in incidence.[2] Falling within the historical designation of type 2 endometrial cancers, high-grade endometrial cancers include high-grade (grade 3) endometrioid endometrial carcinoma, USC, UCS, and clear cell endometrial carcinoma. The Cancer Genome Atlas Program (TCGA) analysis of endometrial cancers established a now widely-used prognostic, genomically-based categorization to complement histologic grading. The TCGA identified 4 categories: polymerase ε–mutated, microsatellite instability–high, *TP53*-mutant, and no specific molecular profile. Of these, high-grade endometrial cancers are found to be almost entirely of the *TP53*-mutant (copy number–high) subtype. However, genomic analysis has also demonstrated that histologic subtypes of endometrial cancer, such as high-grade endometrioid endometrial carcinoma, may be comprised of several TCGA genomic categories within one histologic designation.[3] Given the heterogeneity seen

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Table. Molecular Characteristics of Uterine Serous Carcinoma and Uterine Carcinosarcoma

	Uterine Serous Carcinoma	Uterine Carcinosarcoma
TMB	Low (<10 mut/Mb), 96%[7] Median TMB 2.5 mut/Mb[7]	—
Microsatellite/mismatch repair status	Microsatellite stable (99%)[7]	pMMR 90%-95%[8-10]
LOH-high or HRD signature	HRD signature 30%-50%[11,12] LOH-positive 22%[7]	HRD signature 25%[11,13]
PD-L1 TPS positive (TPS ≥1)	26%[7]	20%[8]
TP53 mutations	87%-92%[7,14,15]	89%-91%[10,14,16]
PI3K pathway alterations	*PIK3CA* 35%-48%[7,14,15] *PTEN* 11%[14,15] *PIK3R1* 14%[14,15]	*PIK3CA* 35%-40%[10,16] *PTEN* 19%-27%[10,16] *PIK3R1* 11%-17%[10,16]
CCNE1 amplification	19%-26%[7,14,15]	41%[14,16]
FBXW7 mutation	17%-25%[7,14,15]	20%-28%[10,16]
PPP2R1A mutation	25%-39%[7,14,15]	13%-28%[10,16]
MYC amplification	12%-24%[7,14,15]	25%[14,15]
ERBB2 amplification	17%-19%[7,14,15,17]	11%[14,15]
HER2 IHC expressing	20%-60%[18,19]	40%-65%[20-22]

HER2, human epidermal growth receptor 2; HRD, homologous recombination deficiency; HRR, homologous recombination repair; IHC, immunohistochemistry; LOH, loss of heterozygosity; mut, mutated; pMMR, mismatch repair–proficient; PD-L1, programmed death ligand 1; PI3K, phosphoinositide 3-kinase; TMB, tumor mutational burden; TPS, tumor proportion score.

within high-grade endometrioid endometrial carcinoma and the rarity of clear cell endometrial carcinoma, the remainder of this review focuses on USC and UCS.

USC and UCS are rare but clinically aggressive subtypes of endometrial cancer, accounting for 5% to 10% and less than 5% of endometrial cancers, respectively. The prognosis for USC and UCS is poor, with a 5-year overall survival (OS) of 10% to 20% for patients diagnosed at advanced stages.[4-6] The poor outcomes of women with USC and UCS underscore the unmet need for more effective therapies in these clinically and molecularly distinct subtypes of endometrial cancer.

Molecular Features

Advancements in genomic and molecular testing, and increased adoption of molecular profiling techniques, reveal characteristic features of USC and UCS that distinguish these high-grade endometrial cancers (Table). Evidence of cell cycle dysregulation is common, typified by a high frequency of mutations in *TP53*, *FBXW7*, and *PPP2R1A*, and amplification of *CCNE1* and *MYC*. Alterations in the phosphoinositide 3-kinase pathway are common in both UCS and USC, typically involving mutually exclusive mutations in *PIK3CA*, *PTEN*, and *PIK3R1*. Loss of heterozygosity (LOH), homologous recombination deficiency (HRD), and alterations in homologous recombination repair (HRR)-related genes can occur, although the designation of LOH or a genetic HRD signature may result from epigenetic silencing of HRR-related genes in addition to loss-of-function mutations.[7] Features associated with response to immune checkpoint inhibition are uncommon, as the majority of USC and UCS display microsatellite stability, low tumor mutational burden, and a programmed death ligand 1 (PD-L1) tumor proportion score of less than 1.[7]

Advances in the Treatment of Primary Advanced or Recurrent Endometrial Cancer

The combination of pembrolizumab (Keytruda, Merck) and lenvatinib (Lenvima, Eisai) has become a new standard of care for the treatment of recurrent mismatch repair–proficient (pMMR) endometrial cancer. The single-arm phase 1b/2 KEYNOTE-146 trial of pembrolizumab and lenvatinib in recurrent endometrial cancer showed preliminary evidence of activity regardless of MMR status, notably demonstrating an overall response rate (ORR) of 36.2% in patients with pMMR disease.[23] In the confirmatory phase 3 KEYNOTE-775 trial, patients were randomized to receive a combination of pembrolizumab and lenvatinib or the physician's choice of doxorubicin or weekly paclitaxel.[24] In a final updated analysis, median progression-free survival (PFS) in the pMMR group was 6.7 months with pembrolizumab and lenvatinib vs 3.8 months with chemotherapy. There was a 40% reduction in the risk of progression or death (hazard ratio [HR], 0.60) in the pMMR group.[24] Clinical benefit also extended to improved OS: median OS was 18.0 months with pembrolizumab and lenvatinib vs 12.2 months with chemotherapy, with a 30% reduction in the risk of death (HR, 0.70) in the pMMR group.[24] In a supplemental analysis of the response by histologic subtype, 37.4% of patients with pMMR USC receiving pembrolizumab and lenvatinib achieved a response vs 13.4% of patients treated with chemotherapy.[24] As UCS was excluded from KEYNOTE-146 and KEYNOTE-775, the activity of pembrolizumab and lenvatinib in UCS is derived from a small case series with variable activity reported. For example, in a small single-institution series of 7 women with UCS, no responses were observed following treatment with pembrolizumab and lenvatinib.[25] In another single-institution report including 12 women with UCS, an ORR of 25% and a clinical benefit rate of 58.3% were reported.[26]

The treatment landscape of recurrent and newly diagnosed advanced endometrial cancer and the role and timing of immune checkpoint inhibition continues to evolve with results from the phase 3 RUBY and NRG-GY018 trials reported in 2023, which evaluated the addition of immune checkpoint inhibition to carboplatin and paclitaxel. In the RUBY trial, women with primary stage III or IV or first recurrent endometrial cancer, including USC and UCS, were randomized to receive carboplatin/paclitaxel with or without dostarlimab (Jemperli, GSK), given concurrently and continued as maintenance therapy.[27] In the pMMR group, which comprised the majority of patients with USC and UCS, the addition of dostarlimab led to a 24% reduction in the risk of progression or death (HR, 0.76; 95% CI, 0.59-0.98), and PFS at 24 months was 28.4% in those receiving dostarlimab compared with 18.8% receiving placebo. Similarly, a 27% reduction in the risk of death was seen with the addition of dostarlimab (HR, 0.73; 95% CI, 0.52-1.02), yielding a 24-month OS rate of 67.7% compared with 55.1% in those receiving placebo in preliminary OS results.[27] Subsequent exploratory histologic and molecular subgroup analysis suggests that the addition of dostarlimab may be associated with improved PFS in both USC (HR, 0.65; 95% CI, 0.403-1.035) and UCS (HR, 0.56; 95% CI, 0.278-1.138); however, both hazard ratios crossed neutrality.[28]

Similar results were seen with the use of pembrolizumab in combination with chemotherapy in the phase 3 NRG-GY018 trial.[29] Women with primary advanced stage (measurable stage III to IVA), primary stage IVB, or recurrent endometrial cancer were randomized to receive carboplatin/paclitaxel with or without pembrolizumab. UCS was excluded from this trial; however, patients with USC were enrolled. In patients with pMMR endometrial cancer, the addition of pembrolizumab demonstrated a 46% reduction in the risk of progression or death (HR, 0.54; 95% CI, 0.41-0.71), resulting in a median PFS of 13.1 months compared with 8.7 months in those receiving placebo.[29] An exploratory subgroup analysis showed persistence of benefit in women with USC (HR, 0.59; 95% CI, 0.36-0.96).[29] Together, these studies suggest that there may be a benefit to adding immune checkpoint inhibition in the first-line management of advanced/recurrent USC and UCS, despite pMMR status and a low incidence of PD-L1 positivity. A greater understanding of how immune checkpoint inhibition should be included in our treatment paradigms will continue to evolve as the data from these studies mature and more biomarker data become available.

The potential role of poly(ADP-ribose) polymerase (PARP) inhibitors in endometrial cancer has also been of interest, especially given molecular features suggestive of genomic instability in a subset of USC and UCS histologic subtypes.[7] The recent phase 3 DUO-E trial investigated whether combining PARP inhibition with anti–PD-L1 therapy has clinical benefit in pMMR endometrial cancer.[30] Women with primary measurable stage III, newly diagnosed stage IV, or recurrent endometrial cancer, including women with USC and UCS, were randomized to receive treatment with carboplatin/paclitaxel, carboplatin/paclitaxel + durvalumab followed by durvalumab maintenance, or carboplatin/paclitaxel + durvalumab followed by combined durvalumab and olaparib (Lynparza, AstraZeneca) maintenance. At 12 months, 59.4% of women with pMMR disease treated with durvalumab/olaparib were alive and progression-free compared with 44.4% of women receiving durvalumab (HR, 0.76) and 40.8% of women receiving placebo (HR, 0.57). The molecular and histologic analysis of women benefiting from the addition of a PARP inhibitor has not yet been reported but will be of high interest. The role of immune checkpoint inhibition and PARP inhibitor maintenance is under further investigation in the RUBY Part 2 trial, in which women with advanced or recurrent endometrial cancer, including UCS, will be randomized to receive carboplatin/paclitaxel, carboplatin/paclitaxel plus dostarlimab followed by dostarlimab maintenance therapy, or carboplatin/paclitaxel plus dostarlimab and niraparib (Zejula, GSK) maintenance therapy.[31] The role of maintenance olaparib following adjuvant chemotherapy and radiation is being evaluated in the RAINBO subtrial p53abn-RED, which will enroll patients with primary stage III endometrial cancer.[32]

The use of maintenance therapy is an opportunity to maintain control of cancer and potentially prolong the duration of remission. The phase 3 SIENDO trial assessed the use of selinexor (Xpovio, Karyopharm), an exportin-1

(XPO1) inhibitor, as maintenance therapy in advanced or recurrent endometrial cancer, including USC and UCS.[33] Patients were randomized to receive maintenance selinexor or placebo. In a subgroup analysis, patients with *TP53* wild-type cancers derived the greatest degree of benefit from selinexor with a median PFS of 13.7 months compared with 3.7 months with placebo (HR, 0.41; 95% CI, 0.23-0.72).[33] In contrast, patients with *TP53*-mutant cancers receiving selinexor had a median PFS of 3.7 months compared with 5.6 months with placebo (HR, 1.34; 95% CI, 0.82-2.21).[33] The significant difference in outcomes between patients with wild-type *TP53* vs mutant *TP53* cancers could be related to the mechanism of action of selinexor, which causes nuclear retention and reactivation of tumor suppressors such as p53, meaning that a nonmutated, functionally active p53 is needed for efficacy. Thus, although XPO1 remains a target of interest in *TP53* wild-type endometrial cancer, XPO1 inhibitors appear to have limited activity as monotherapy in high-grade *TP53*-mutant endometrial cancers, which comprise the majority of USC and UCS.

Emerging Therapeutic Strategies

Expanding the Use of Antibody-Drug Conjugates to Endometrial Cancer

Human Epidermal Growth Factor Receptor 2. HER2, encoded by *ERBB2*, is a transmembrane tyrosine kinase receptor that heterodimerizes with other HER family receptors, including epidermal growth factor receptor (HER1), HER3, and HER4. Dimerization initiates transphosphorylation of their intracellular domains and subsequent activation of numerous downstream intracellular signaling pathways involved in growth, survival, and proliferation.[34,35] Overexpression of HER2 is linked with the pathogenesis of several types of cancer, and HER2 overexpression has been described in both USC and UCS.[18-22,34,35] In a phase 2 trial, the addition of trastuzumab to carboplatin/paclitaxel in HER2-positive advanced or recurrent USC, defined as having HER2 IHC 3+ or 2+ with confirmatory fluorescence in situ hybridization, scored by American Society of Clinical Oncology/College of American Pathologists breast cancer guidelines, was associated with prolongation of PFS and OS. The greatest degree of benefit was observed in those with primary advanced disease: median PFS was 17.7 months in patients receiving trastuzumab compared with 9.3 months with placebo (HR, 0.44; 90% CI, 0.23-0.83), and the median OS was not reached in the trastuzumab arm compared with 25.4 months in those receiving placebo (HR, 0.49; 90% CI, 0.25-0.97).[36] These results are being further confirmed in a phase 3 study of the HER2-targeting therapy, NRG-GY026 (NCT05256225), and provide a basis for further expanding strategies to target HER2 in high-grade endometrial cancers.

Trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), is an antibody-drug conjugate (ADC) comprised of a humanized immunoglobulin G (IgG) antibody targeting HER2, conjugated via a protease-cleavable linker to a topoisomerase I inhibitor exatecan-derivative payload (DXd). In the phase 2 DESTINY PanTumor-02 trial of T-DXd in various solid tumor types, an ORR of 57.5% was observed among the 40 endometrial cancer patients enrolled.[37] In endometrial cancer patients with HER2 IHC 3+ by central testing, an ORR of 84.6% was seen, the median PFS was not reached (7.3 months to not reached), and the median OS was 26.0 months (18.9 months to not reached). In endometrial cancer patients with centrally-determined HER2 IHC 2+, a benefit was still observed although potentially to a lesser degree, with an ORR of 47.1%, median PFS of 8.5 months (4.6-15.1 months), and median OS of 16.4 months (8.0 months to not reached).[37] Twenty-two percent of endometrial cancer patients had received prior HER2-directed therapy, including HER2-directed monoclonal antibodies and ADCs, suggesting that properties of T-DXd may help offset resistance to other HER2-directed therapies, including a high drug-to-antibody ratio and a potent bystander effect to overcome intratumoral heterogeneity of HER2 expression.[37,38,39]

T-DXd also demonstrated efficacy in 32 patients with UCS in the STATICE trial, which enrolled women with UCS and HER2 IHC of at least 1+.[39] Treatment with T-DXd yielded an investigator-assessed ORR of 68.2%, median PFS of 6.2 months, and median OS of 13.3 months in the group with HER2 IHC of at least 2+. Within this group, the majority (n=15/22) had expression of HER2 IHC 2+. In a subgroup analysis, there was no difference in response rate between the IHC 2+ and IHC 3+ groups.[39] In the group with HER2 IHC 1+, T-DXd yielded an investigator-assessed ORR of 60.0% and median PFS of 6.7 months, and median OS was not reached. In contrast to results of the DESTINY PanTumor-02 trial, response rates in STATICE did not differ by HER2 expression. Based on these cumulative data, T-DXd was incorporated into National Comprehensive Cancer Network guidelines for IHC 2+ or 3+ recurrent endometrial carcinoma.[40]

Additional HER2-directed ADCs are in development. DB-1303 is an anti-HER2 ADC consisting of an IgG1 monoclonal antibody carrying a topoisomerase I inhibitor payload (P1003) via a maleimide tetrapeptide-based cleavable linker, which has received US Food and Drug Administration (FDA) fast-track designation for the treatment of advanced or recurrent HER2-expressing malignant solid tumors.[41] In preliminary findings reporting the results from endometrial cancer patients in a phase 1a/2 trial of DB-1303 (NCT05150691), 17 of 32 endometrial cancer patients were evaluable for response; within these patients, an ORR of 58.8% (10/17) was seen.[42] Patients with USC achieved an ORR of 87.5% (n=7/8), and 50% of UCS patients (n=1/2) achieved a response.[42] Final results from this clinical trial are awaited. Another ADC, disitamab vedotin, which comprises a novel anti-HER2 antibody conjugated to monomethyl auristatin E via a cleavable valine-citrulline linker, is currently in development across solid tumors, including endometrial cancer (NCT06003231).

Folate Receptor Alpha. Folate receptor alpha (FRα) is a cell surface glycoprotein encoded by *FOLR1*, with high-affinity binding to folates and folic acid, and subsequent internalization as part of folate-dependent intracellular processes.[43] Following embryogenesis, FRα is minimally expressed on normal tissues but is overexpressed in many cancer types, including endometrial, ovarian, breast, and lung, presenting an opportunity for FRα-directed therapeutics.[43]

Mirvetuximab soravtansine (Elahere, ImmunoGen) is an anti-FRα ADC carrying a tubulin-disrupting DM4 maytansinoid payload. Mirvetuximab soravtansine received accelerated FDA approval in November 2022 for the treatment of platinum-resistant epithelial ovarian cancer with FRα expression of 75% or greater at 2+ IHC staining intensity.[44] Early evidence of clinical activity of mirvetuximab soravtansine in endometrial cancer was seen in the phase 1 dose escalation trial of mirvetuximab soravtansine in 2017. A total of 11 patients with endometrial cancer (25%) were enrolled, of whom 2 patients derived clinical benefit, with one achieving a CA125 response and another staying in the study for 28 weeks.[45] A phase 2 trial evaluating mirvetuximab soravtansine in FRα-positive USC, UCS, and grade 3 endometrial adenocarcinoma is ongoing (NCT03832361). Augmentation of antitumor activity with regimens combining mirvetuximab soravtansine with PARP inhibitors, chemotherapy, and immune checkpoint inhibition are underway, with preliminary results reporting responses in 2 of 3 USC patients receiving mirvetuximab and rucaparib (Rubraca, Clovis Oncology) in a phase 1 trial, and in 2 of 4 evaluable patients receiving combination mirvetuximab and gemcitabine in a separate phase 1 trial.[46,47] Combined mirvetuximab soravtansine and pembrolizumab is also under investigation in a phase 2 study in microsatellite-stable FRα-positive USC (NCT03835819).[48]

Newer FRα-targeting ADCs are in development, including luveltamab tazevibulin (STRO-002), which carries a novel tubulin polymerization-inhibiting hemiasterlin derivative payload (SC209, DAR 4) conjugated via a protease cleavable linker.[49] Results from the endometrial cancer dose expansion cohort of the STRO-002-GM1 phase 1 clinical trial were reported at the European Society for Medical Oncology conference in 2023.[50] Endometrial carcinomas, excluding UCS, were enrolled and were required to have FRα expression of at least 1% by IHC. Of the 44 patients screened, 30 patients (68%) were found to have FRα expression of at least 1%. USC accounted for 29% of the endometrial cancer patients (5/17). Of 16 efficacy-evaluable patients, 3 patients (19%) achieved a response; 1 response occurred in a patient with FRα expression of less than 25% and 2 occurred in patients with FRα expression of 25% or greater.[50]

Trophoblast Cell-Surface Antigen 2. Trophoblast cell-surface antigen 2 (TROP2) is a glycoprotein typically found on the cell surface as a transmembrane calcium signal transducer. TROP2-mediated intracellular signals may confer the ability for proliferation, transformation, and invasion.[51] Overexpression of TROP2 has been demonstrated in several cancer types, including endometrial cancers, and is associated with a worse prognosis.[51,52] Expression of TROP2 has been reported in 65% to 95% of USC samples, with 60% of cases graded as moderate to strong expressors in one report.[53,54]

Sacituzumab govitecan (Trodelvy, Gilead) is an anti-TROP2 ADC comprised of a humanized IgG conjugated to SN-38, a topoisomerase I inhibitor and the active metabolite of irinotecan, via an acid-cleavable linker. Sacituzumab govitecan is FDA-approved for use in urothelial and metastatic triple-negative breast cancers; investigation in gynecologic cancers, including endometrial cancers, is ongoing.[55] The antitumor activity of sacituzumab govitecan was demonstrated preclinically against TROP2-expressing USC cell lines and xenograft models.[53,56] In the phase 1/2 IMMU-132-01 basket trial, the highest ORR was seen in endometrial cancer patients (ORR, 22%; 4/18), in whom the median PFS was 3.2 months and the median OS was 11.9 months.[56] Similar results were shown in the subsequent multicohort phase 2 TROPiCS-03 trial.[57] In a preliminary analysis of the endometrial cohort, which enrolled patients with endometrial cancer who had previously received platinum-based chemotherapy and anti–programmed death 1/PD-L1 therapy, an ORR of 22% was seen in 41 evaluable patients; all of these responses were partial responses. The median duration of response was 8.8 months, and the median PFS was 4.8 months.[57] Patients with USC made up 41.5% (17/41) of the enrolled endometrial cancer patients. Of note, this was a biomarker-unselected trial and the correlation of TROP2 expression to clinical outcome has not yet been reported. In an ongoing phase 2 trial of sacituzumab govitecan in endometrial carcinoma (NCT04251416), patients enrolled in stage 1 of the trial had tumors with TROP2 staining in at least 50% of cancer cells.[58] In preliminary results from this stage, 48% (10/21) of patients had USC and 14% (3/21) had UCS. Seven of 21 evaluable patients achieved a response (ORR, 33%; 1 CR and 6 PR), with a median PFS of 5.7 months and a median OS of 22.5 months.[58] Enrollment to stage 2 is now ongoing and agnostic of TROP2 expression level.[60]

Datopotamab deruxtecan (Dato-DXd) is a newer-generation TROP2-targeting ADC utilizing a humanized IgG1 conjugated to a topoisomerase I–inhibiting DXd via a cleavable tetrapeptide linker.[59] In the ongoing TROPION-PanTumor03 trial (NCT05489211), biomarker-unselected endometrial cancer patients will receive Dato-DXd alone, with durvalumab, with the PARP1-selective inhibitor saruparib (AZD5305), or in combination with durvalumab and saruparib.[60]

Targeting TP53

A tantalizing therapeutic strategy is to capitalize on the near-universal *TP53* mutations seen in USC and UCS. p53 forms tetramers and enacts transcription-dependent effects by binding DNA at specific p53 response elements as well as transcription-independent effects through interactions with various proteins, such as BCL2 and the MRN complex, allowing p53 to regulate numerous processes including cell cycle control, DNA repair, and apoptosis.[61-63] The type and location of a *TP53* mutation impacts whether transcription-dependent and/or -independent functions are lost and whether some wild-type functions are retained.[61,62] Most *TP53* mutations lie within the DNA-binding domain, thus altering transcription-dependent functions. Strategies to target p53 include further destabilizing or depleting mutant p53, preventing degradation of wild-type p53, and restoration (reactivation) of wild-type function in mutant p53.[64]

The strategy of restoring wild-type *TP53* function is the mechanism of action of PC14586, a first-in-class p53 Y220C-selective reactivator. Upon binding a crevice formed by the mutant p53 Y220C protein, PC14586 restores the wild-type protein conformation and thus wild-type tumor suppressor functions. In updated preliminary results from the tumor-agnostic phase 1/2 PYNNACLE trial, an ORR of 38% (6/16) was seen in patients treated at the recommended phase 2 dose, and 34% (13/38) for those treated in the efficacious dose range.[65] Responses occurred across multiple tumor types and included patients with endometrial cancer, demonstrating the potential promise of this therapeutic approach.

Targeting the downstream effects of *TP53* mutations is an indirect treatment strategy. Angiogenic inhibition with bevacizumab maintenance may be effective in *TP53*-mutant endometrial cancer based on retrospective exploratory analysis of the GOG-86P phase 2 trial, in which women were randomized to receive carboplatin/paclitaxel + bevacizumab, carboplatin/paclitaxel + temsirolimus, or carboplatin/ixabepilone + bevacizumab.[66,67] In patients with *TP53*-mutant cancers receiving bevacizumab-containing regimens, the median PFS was 12.5 months compared with 8.2 months for those receiving temsirolimus, with a 52% reduction in the risk of progression or death (PFS HR, 0.48; 95% CI, 0.31-0.75) and a 39% reduction in the risk of death (OS HR, 0.61; 95% CI, 0.38-0.98).[66] There was no significant difference in PFS in patients with wild-type *TP53* receiving bevacizumab compared with temsirolimus. Derepressed transcription of vascular endothelial growth factor A (VEGF-A) from loss of normal p53 function may explain, in part, the benefit of bevacizumab (anti-VEGF receptor) in the *TP53*-mutant group.[68,69]

Targeting Cell Cycle Dysregulation and Replication Stress

USC and UCS have molecular alterations consistent with ongoing cell cycle dysregulation and high replication stress, including *TP53* mutations in almost all cases, *FBXW7* mutations, and frequent amplification of *CCNE1* and *c-MYC*. Loss of p53 function impairs the G1/S and G2/M cell cycle checkpoints, resulting in altered replication fork progression and DNA replication. Cyclin E1 (encoded by *CCNE1*) interacts with cyclin dependent kinase 2 (CDK2) at the G1/S checkpoint to promote entry into S phase; downstream processes regulated by the cyclin E1/CDK2 complex includes histone synthesis, origin firing, initiation of DNA replication, and centrosome duplication.[70] Oncogenic hyperactivation of cyclin E1/CDK2 processes, for example through *CCNE1* amplification, generates replication stress, including by impairing replication fork dynamics, promoting fork collapse, and generating double strand DNA breaks.[70] Amplification of c-*MYC* (encoding c-MYC) stimulates cell cycle progression through the G1/S and G2/M checkpoints by inducing expression of cell cycle–promoting factors, including cyclins and E2F transcription factors, and antagonizes inhibitors of cell cycle progression.[71] Overexpression of c-MYC induces genomic instability by impairing the repair of double-strand DNA breaks, generation of extrachromosomal elements, and chromosome-level alterations, including chromatid breaks and aneuploidy.[72–74] FBXW7, a ubiquitinase, regulates key proteins of the G1/S checkpoint, including cyclin E1 and c-MYC by targeting them for degradation; loss of function of FBXW7 increases levels of cyclin E1 and c-MYC.[75] Studies also suggest that FBXW7 regulates DNA repair through interactions with PARP and XRCC4, and, through regulation of AURKA, facilitates the appropriate duplication of centrosomes and formation of mitotic spindles.[75,76] Therefore, loss of FBXW7 may contribute to chromosomal instability and abnormal mitotic spindle assembly. Taken together, these characteristic genomic alterations in USC and UCS cumulatively produce an abnormal cell cycle with increased replication stress and present an opportunity for synthetic lethality with novel therapeutics.

WEE1. WEE1 is a tyrosine kinase with multiple roles in cell cycle regulation via its interaction with CDK1, which is active at the G2/M checkpoint, and CDK2, which is active at the intra-S phase and G1/S checkpoints. WEE1 exerts its effect by phosphorylating, and thus deactivating, CDK1 and CDK2 to halt the cell cycle.[77] Through its action on CDK2, WEE1 also assists in regulating DNA replication in S phase. Therefore, inhibiting WEE1 leads to dysregulation of the cell cycle and generation of genomic instability via abnormal origin firing, exhaustion of the deoxyribonucleotide pool, and degradation of replication forks. Cells with intrinsically high replication stress, such as in USC and UCS, may have increased dependence on cell cycle checkpoints and susceptibility to WEE1 inhibition.

Adavosertib (AZD1775) is a potent WEE1 inhibitor that demonstrated activity in USC in a proof-of-concept single center phase 2 trial (NCT03668340).[78] Of 34 efficacy-evaluable patients, an ORR of 29.4% (10/34) was seen and 47.1% of patients were alive and progression-free at 6 months. Of 32 patients with archival specimens tested by next-generation sequencing, all were found to have a *TP53* mutation and 31% of patients had gain or amplification of *CCNE1*, though no molecular alterations were found to be statistically correlated with clinical outcomes.[78] In the subsequent international phase 2b ADAGIO trial of adavosertib in USC, a similar ORR of 27% was observed, but with a disappointing duration of response of 4.7 months, and significant treatment-related adverse events which may have limited dosing and efficacy.[79]

Azenosertib (ZN-c3) is a newer-generation WEE1 inhibitor with similar potency to adavosertib.[80] In the phase 1 Zn-c3-001 trial dose expansion cohort of USC, preliminary results reported an ORR of 27.3% with a median duration of response of 5.55 months, 63.6% of patients had stable disease for at least 12 weeks, and the median PFS was 4.2 months.[81] In contrast to the safety profile of adavosertib, neutropenia was infrequent, noted in 6.3% of patients.[81] The safety, efficacy, and biomarkers related to clinical outcomes of azenosertib monotherapy in USC are under investigation in the international ZN-c3-004 phase 2 trial (NCT04814108). Additional WEE1 inhibitors are in development.

PKMYT1. Protein kinase, membrane-associated tyrosine/threonine 1 (PKMYT1) is a WEE1 family kinase that selectively phosphorylates threonine 14 on CDK1, thereby deactivating CDK1 and halting the cell cycle at the G2/M checkpoint. Unlike WEE1, which regulates both CDK1 and CDK2 and is essential for cell cycle progression, PKMYT1 regulates CDK1 and does not appear to be critical to the cell cycle.[82] However, in the setting of cell cycle dysregulation, such as from *CCNE1* amplification, cells may become more dependent on the G2/M checkpoint, and the loss of PKMYT1 in this setting leads to mitotic catastrophe and cell death.[83] Therefore, pharmacologic PKMYT1 inhibition in genetically susceptible cells is an attractive therapeutic strategy for synthetic lethality.

Lunresertib (RP-6306) is a first-in-class PKMYT1 inhibitor with in vivo activity against *CCNE1*-amplified xenograft models.[84] In preliminary results from the phase 1 MYTHIC trial, 67 patients with *CCNE1*-amplified, *FBXW7*-mutated, and *PPP2R1A*-mutated advanced solid cancers received lunresertib monotherapy, including 23 endometrial cancer patients.[85] In a case presentation from the MYTHIC trial, a patient with recurrent UCS with *FBXW7* and *PPP2R1A* mutations achieved a confirmed partial response and remained on lunresertib for more than 8 months.[85]

Combining PKMYT1 inhibition with ATR inhibition is also of interest in high-grade endometrial cancers. Sensitizing mutations in *FBXW7* and *PPP2R1A* and *CCNE1* amplification generate replication stress, which activates the ATR/CHK1 pathway. Subsequently, inhibition of the CDC25 phosphatase leads to deactivation of CDK1, thereby halting the cell cycle at the G2/M checkpoint. Inhibiting both PKMYT1 and ATR results in enhanced CDK1 activation, unscheduled progression through G2/M, and mitotic catastrophe. In preliminary results from a cohort in the MYTHIC trial, 59 patients with sensitizing mutations, including 17 with endometrial cancer, received the combination of lunresertib and the ATR inhibitor camonsertib.[85] In 26 patients with ovarian, endometrial, and cervical cancers receiving lunresertib and camonsertib combination therapy, an ORR of 38.5% was seen.[85] These data support further investigation of PKMYT1 inhibition as monotherapy or in combination with ATR inhibition in the context of specific genomic alterations commonly seen in USC and UCS.

Conclusion

Despite the poor prognosis of USC and UCS, advancements in targeted therapies hold promise for future improvement of clinical outcomes of women with these aggressive endometrial cancers. The role of immune checkpoint inhibition in USC and UCS continues to evolve, and significant advancements in the treatment of gynecologic cancers have emerged with the rapidly growing use of ADCs. Continued innovation in target discovery and linker and payload design have led to a large influx of novel ADCs under investigation. Lastly, small-molecule inhibitors seek to capitalize on key genomic features in USC and UCS, including *TP53* mutations and cumulative states of cell cycle dysregulation and replication stress. These therapeutic strategies underscore the possibility of tailored treatment options for USC and UCS.

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