Genomic and Molecular Abnormalities in Gynecologic Clear Cell Carcinoma

Eric I. Marks, MD, Victoria S. Brown, MD, and Don S. Dizon, MD

Abstract: Gynecologic clear cell carcinoma is a rare histology, accounting for ~5% of all ovarian and endometrial cancers in the United States. Compared to other types of gynecologic cancer, they are generally less responsive to standard therapy and have an overall worse prognosis. In addition, mounting evidence suggests that the landscape of genetic and molecular abnormalities observed in these tumors is distinct from other cancers that arise from the same sites of origin. On a molecular level, these tumors characteristically display upregulation of the PI3K-AKT-mTOR and RAS-RAF-MAPK signaling axes, frequent loss of ARID1a, and overexpression of MDM2. Evidence also suggests that these tumors are more likely to express programmed death ligand 1 or demonstrate microsatellite instability than other gynecologic cancers. Despite these important differences, there has been relatively little investigation into histology-specific treatment of clear cell gynecologic cancers, representing an opportunity for new drug development. In this article, we review the unique genetic and molecular features of gynecologic clear cell cancers with an emphasis on potential therapeutic targets. The results of completed studies of treatment for clear cell carcinoma are also presented. We conclude with a discussion of ongoing clinical trials and potential avenues for future study.

Key Words: clear cell carcinoma, ovarian cancer, endometrial cancer, targeted therapy, immuno-oncology, personalized medicine

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Extrarenal clear cell carcinoma (CCC) is a rare malignancy that most frequently arises within the female reproductive system including the ovary (CCCO), endometrium (CCCE), vagina, and cervix. Rarely, CCC may also arise from other sites including the lung, gastrointestinal tract, pancreas, and bladder.

In the United States, ~5% of ovarian or endometrial cancers display clear cell histology.[1,2] In Asian populations, however, these rates are much higher. In Japan, for instance, the estimated rate of CCCO approaches 25%.[3] The biology underlying this geographic difference remains poorly understood. Additional risk factors for developing CCCO include endometriosis, obesity, and delayed menopause.[4] Prenatal exposure to diethylstilbestrol is a unique and strong risk factor for CCC of the vagina or cervix.[5]

This review will specifically address gynecologic CCC, as the most common extrarenal site of origin. It should be noted, however, that similar findings have been observed in case reports of CCC that arise from other sites.

From the Lifespan Cancer Institute, Warren Alpert Medical School of Brown University, Providence, RI.

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Reprints: Eric I. Marks, MD, Rhode Island Hospital, George Building Suite 310, 593 Eddy Street, Providence, RI 02903. E-mail: eric.marks@lifespan.org.

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DIAGNOSIS AND PATHOLOGY

Although certain clinical and radiographic findings may suggest the presence of this disease, the diagnosis of CCC is established through pathology review. These tumors have a unique histologic appearance that features cells with abundant, clear cytoplasm. The nuclei are often eccentric, rounded, and contain distinct nucleoli. CCC generally displays a mixture of glandular/tubular, papillary, cystic, and solid microscopic architectures.[6]

Since cells with clear cytoplasm may be seen in other, more common malignancies, immunohistochemistry is often helpful to confirm the diagnosis. CCC is differentiated from other types of ovarian or endometrial cancer on the basis of positive staining for hepatocyte nuclear factor 1-beta (HNF1β), and negativity for estrogen receptor, progesterone receptor, and Wilms tumor protein 1.[6] As will later be discussed in greater detail, these tumors are also far more likely than other types of epithelial ovarian cancer (EOC) to be TP53 *wild-type*. Absent staining for alpha-fetoprotein and CD10 can further narrow the differential diagnosis to exclude yolk cell tumors and renal cell carcinoma (RCC).[7,8]

CLINICAL CHARACTERISTICS

The clinical behavior of CCC often differs from that of other cancers which arise from the same site. Compared to other types of EOC, CCCO is more likely to present with unilateral,[1] early-stage disease.[9] When presenting as advanced disease, however, clear cell histology is prognostic of reduced stage-adjusted overall survival (OS).[9] This is largely attributable to the tendency to respond poorly to standard treatment with a platinum and taxane-containing regimen. In a retrospective review of >600 women with EOC, patients with CCCO had a significantly lower response rate to first-line platinum-based chemotherapy than those with serous histology (11% vs. 72.5%, respectively, $P<0.001$).[9] A similar lack of response to standard chemotherapy and poor survival has also been reported in CCC arising from the lung[10] and endometrium.[11]

Patients with CCCO[1] and CCCE[12] are also at particularly high risk of developing hypercalcemia or venous thromboembolism. The high incidence of hypercalcemia is believed to be partially due to increased rates of parathyroid hormone related protein (PTHRP) expression and IL-6 mediated activation of stanniocalcin-1 signaling.[13] The increased risk for thromboses may also be related to increased IL-6 expression,[13] in addition to frequent alteration of tissue factor pathway inhibitor-2.[14,15]

PATHOGENESIS

As is the case with other rare tumors, there are many gaps in our understanding of the pathogenesis of CCC. Even certain fundamental points, such as the cell of origin, remain a matter of some controversy.

For CCCO, there is evidence of an intimate relationship with endometriosis that begins at the earliest stages of tumor development. Endometriosis provides abundant oxidative stress and an iron-rich environment, which in turn alter gene expression[16] and promote the accumulation of DNA damage.[17]

This was illustrated in a study that bathed immortalized ovarian cell lines in the contents of endometriotic cysts.[16] In a time-dependant manner, this induced a gene expression profile similar to that which is commonly observed in CCCO, including increased expression of HIF1α, STAT3, HNF1β, p21, and IL-6.[16] In addition, it is common for CCCO and adjacent areas of endometriosis to harbor identical somatic mutations of ARID1A[18] and PIK3CA.[19] This may be interpreted as circumstantial evidence that CCC may in fact arise from endometriosis.

These observations have been combined by Oda et al[20] to generate a proposed model of CCCO carcinogenesis. The model posits that these tumors develop along a continuum from endometriosis to atypical endometriosis, and finally CCCO. Mutations of ARID1A, PIK3CA, and KRAS are thought to be important early events. The subsequent loss of regulation over chromatin remodeling and induction of the CCCO gene expression signature occurs in atypical endometriosis. Later events include the development of stereotyped copy number alterations (CNA), which are typically observed only in carcinomas.

MOLECULAR CHARACTERIZATION OF GYNECOLOGIC CCC

As oncology progresses toward the goal of personalized cancer care, there has been increasing effort to characterize CCC on a genetic and molecular level. Unfortunately, there are inherent difficulties in the study of this disease that include—but extend beyond—its rarity. There is often an element of diagnostic uncertainty. This is particularly true in cases of mixed histology CCC, where interobserver reliability among pathologists is rather low.[21] In addition, CCC is a molecularly heterogenous disease. These caveats must be considered when interpreting studies that attempt to characterize this disease.

The concept that gynecologic CCC is a distinct entity rather than another histologic subtype of ovarian or endometrial cancer was introduced in a 2005 study by Zorn et al.[22] This study subjected 75 cancers of the ovary (9 CCCO) and endometrium (5 CCCE), as well as 5 renal CCCs to immunohistochemistry and RNA-based gene expression profiling. This revealed substantial similarity among all of the clear cell tumors, including RCC, regardless of the site of origin. There was notably less resemblance between CCC and other tumors that arose from the same anatomic location, with a set of 50 genes consistently differentiating CCC from other histologies.[22] These findings were echoed in a second study of 113 ovarian epithelial tumors, which identified a distinct gene expression profile that was specific to the 8 CCCO specimens.[23]

Copy Number Alterations

At the most broad level of genomic analysis, gynecologic CCC is a disease that is characterized by frequent and stereotyped chromosomal imbalances. In 1 study of 20 CCCO specimens, 85% had at least 1 CNA and there was an average of just over 4 CNA per tumor.[24] Common sites of copy number gain (CNG) include segments of 17q and 20q that contain the oncogenes PPM1D and ZF217, respectively.[25,26] Copy number loss, meanwhile, is frequent on chromosome 9q. This includes loci that are home to the tumor suppressor genes CDKN2A/2B.[25]

PI3K-AKT-mTOR Pathway

The PI3K-AKT-mTOR pathway is among the most commonly altered pathways in gynecologic CCC. A recent multiplatform analysis of 521 CCCO identified abnormalities of this pathway in 50% of pure CCCO.[27] Increased activation of the terminal member, mTOR is observed in 86.6% of CCCO compared with 50% of serous tumors.[28] This may hold prognostic significance. In a study of 55 patients with CCCO, the 3-year OS rate was significantly higher among patients whose tumors displayed PI3K-AKT-mTOR overactivation (91% vs. 40%).[29]

The first component of this pathway, phosphoinositide 3-kinase (PI3K) is mutated in 33% to 40% of gynecologic CCC.[30–32] Most are activating mutations involving exons 9 or 20 of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), which result in increased immunostaining of phosphorylated AKT.[30] As described previously, PI3K mutations are also observed in tumor-associated endometriosis and are thought to be early events in carcinogenesis.[31]

Another common finding in this disease is loss of phosphatase and tensin homolog (PTEN) expression. This phosphatase ordinarily functions as a tumor suppressor that negatively regulates the PI3K-AKT-mTOR pathway. In CCCO, absent or substantially reduced expression of PTEN occurs in 10% to 37.5% of cases.[33–35] The mechanisms by which its expression is lost, however, remain incompletely characterized. Mutations involving PTEN are observed in only 5% to 8.3% of CCCO.[30,33] Although LOH at the PTEN locus of 10q23.3 and promoter methylation are both common, neither reliably correlates with protein expression.[33,36] Investigation into alternative mechanisms of PTEN loss is ongoing.

Other, less common abnormalities of this pathway that have been documented in CCC include amplifications at 19q13.2, which is the locus of AKT2.[37] It remains unclear whether this finding has clinical or therapeutic implications, however.

RAS-RAF-MAPK Pathway

A second canonical signaling axis that is often altered in extrarenal CCC is the RAS-RAF-MAPK pathway. Most mutations affecting this pathway arise within the first signaling element, KRAS. Activating mutations of KRAS are observed in 0% to 16% of CCCO.[30,32,38,39] Although data are too sparse to calculate the frequency, KRAS mutations have also been documented in CCC arising from sites outside of the female reproductive system, such as the colon[40] and lung.[41] It is additionally interesting that this is an area where the genetics of extrarenal and renal CCC appear to diverge, since KRAS mutations are seldom observed in RCC.[42]

Mutations also arise within several downstream members of this signaling pathway. BRAF mutations are observed in ~1% of CCCO,[30,38] and a BRAF V600E mutation has been identified in a colorectal clear cell cancer.[40] Further downstream, mutations of MAP3K5/ASK1 have also been observed, although the frequency has not been defined.[22]

ARID1A

Another common finding in gynecologic CCC is the absence of AT-rich interaction domain 1A (ARID1A) expression. This gene encodes BAF250a, which is a component of the SWI/SNF chromatin remodeling complex. It functions as a tumor suppressor through regulation of transcription. Loss of ARID1A is believed to contribute to the pathophysiology of many malignancies, including gastric and pancreatic adenocarcinomas. In CCCO, loss of ARID1A expression is believed to be an important "hit" in the stepwise progression to carcinogenesis. Study of mouse models has revealed that ARID1A loss is not independently sufficient to induce tumor formation. When combined with an activating mutation of PIK3CA, however, clear cell tumors develop rapidly.[43] As described previously, loss of this gene is also believed to be an early step in tumor development since absent BAF250a expression and identical ARID1A mutations have been identified in CCC and associated areas of atypical endometriosis.[18]

Loss of ARID1A expression occurs in 15% to 46% of clear cell gynecologic cancers[18,44] but is decidedly less common in other types of EOC.[18] The mechanisms by which this occurs

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remain poorly understood. Nearly all tumors that harbor somatic mutations of ARID1A retain 1 *wild-type* allele that continues to be expressed.[18] Despite ongoing production of the *wild-type* transcript, BAF250a is curiously absent in most ARID1A mutated cells.[18] For this reason, it is thought that posttranscriptional or posttranslational processes may play a role. Regardless of the mechanism, absence of ARID1A is an ominous prognostic sign. In a study of 60 patients with CCCO, loss of ARID1A correlated with higher stage disease, increased CA-125, and shorter PFS in patients treated with platinum-based chemotherapy.[44]

Inactivation of TP53

Mutations of TP53 are nearly ubiquitous in non–clear cell EOC, reaching as high as 80% in 1 study.[45] In CCCO, however, TP53 mutations occur in <15% of cases.[30,39] Despite the low mutational rate, inactivation of the p53 gene product is observed in the vast majority of clear cell tumors. This is thought to occur mostly through abnormalities of several associated proteins.

MDM2 encodes an E3 ubiquitin-protein ligase that negatively regulates p53 activity by promoting its degradation. Expression of MDM2 is significantly increased in CCCO relative to both normal ovarian tissue and other types of EOC.[46] In a retrospective analysis of 75 patients with CCCO, those with the highest levels of MDM2 expression exhibited significantly worse PFS and OS.[46] Similar findings have also been reported in clear cell RCC, where expression of MDM2 is seen in 19% of tumors and correlates with both increased tumor grade and disease progression.[47]

Another mechanism by which *wild-type* TP53 is silenced in CCC is through amplification of protein phosphatase magnesium-dependent 1 delta (PPM1D). This gene, which resides at a frequent site of CNG on 17q, is an oncogene that encodes wild-type p53 induced phosphatase (WIP1). WIP1 inactivates p53 through several mechanisms, including direct dephosphorylation and indirect action through p38.[48] It additionally functions as a negative regulator of CHEK1, which is involved in regulation of the cell cycle and DNA repair.[48] There is preclinical evidence suggesting that it could also eventually become a therapeutic target, as the introduction of a targeted inhibitor was shown to reduce growth in PPM1D overexpressing CCCO cell lines.[26]

Cell Surface Receptors

Although mutations or altered expression of several cell surface receptors may be observed in CCC, 2 may be of therapeutic significance. Human epidermal growth factor receptor-2 (HER-2) overexpression and amplification have been reported. In 1 study of 50 CCCO specimens, CISH analysis detected HER-2 amplification in 14%.[37] A separate, smaller study identified overexpression HER-2 in 43% of resected CCCO compared with <30% in other types of EOC.[49] Unfortunately, given the rarity of the subset of CCCO that express HER-2, there have been no attempts to study anti-HER-2 directed treatment in a prospective clinical trial.

The hepatocyte growth factor receptor, MET, is also commonly altered in this disease. While there is limited data regarding the frequency of gain of function mutations, such as exon 14 skipping, CNG of some degree is seen in roughly half of CCCO.[50,51] While this is mostly due to polysomy, 6% demonstrate true amplification of MET,[51] which is a marker for crizotinib sensitivity in non–small cell lung cancer. In CCCO, MET amplification is also indicative of poor prognosis.[51] Overexpression of the MET ligand has also been reported in CCCO, although the clinical significance of this finding is less clear.[13]

HNF1β

Perhaps the most specific molecular marker for gynecologic CCC is HNF1β. The product of this gene is a transcription factor that stimulates transcription of genes involved in hepatic protein synthesis and glucose homeostasis. While its role in malignancy is unclear, HNF1β expression is nearly universal in CCC.[52] In 1 study, nuclear staining for HNF1β was identified in 100% of 30 CCCO specimens[53] compared with <2% of other EOC subtypes.[53] Staining was also observed in areas of endometriosis associated with CCC in 75% of cases.[53] Epigenetics are believed to play a role in the overexpression of HNF1β in this disease, as hypomethylation is frequently identified in clear cell lines.[16] Preclinical evidence also supports HNF1β as a potential therapeutic target. Treatment of CCCO lines with RNA interference against HNF1β has been shown to induce apoptosis.[54]

Mediators of Antitumor Immune Response

There is mixed data regarding the immunogenicity of CCC. Without pharmacologic manipulation, these tumors do not intrinsically evoke a strong immune response. In 1 study of nearly 300 ovarian cancer specimens, fewer infiltrating immune cells were observed in the 132 clear cell specimens than other types of EOC.[55] Despite this, there is reason to believe in the potential for these tumors to respond to immunotherapy. First, the rate of microsatellite instability (MSI) in CCCO is nearly double that of other EOC histologies. One study of 42 CCCO specimens found 7.2% to be MSI-low and 14.3% MSI-high.[56] In addition, the percentage of ovarian cancers that are clear cell histology in patients with Lynch syndrome is roughly 17%—nearly triple the frequency observed in an unselected population.[57] Furthermore, at least low-level expression of programmed death ligand 1 (PD-L1) is observed in >40% of CCCO and 75% of CCCE.[58]

While the rarity of this disease arising from other sites precludes a systematic analysis, these statistics are consistent with observations of patients with CCC of the colon. In a series of 2 cases of colorectal CCC, 1 of the 2 tumors was MSI-high.[40] For comparison, only 15% of non–clear cell colorectal cancers are MSI-high.

TOWARD A HISTOLOGY-DIRECTED TREATMENT STRATEGY

With accumulating evidence suggesting that CCC are molecularly distinct from other cancers that arise from the female reproductive system, the present challenge is leveraging this knowledge into more effective treatments. The current standard of first-line care for patients with metastatic CCCO consists of optimal debulking surgery and combination chemotherapy with a platinum and taxane—a protocol that was established in studies that included just 2% to 5% clear cell cancers, and in which response rates are significantly lower compared with serous and endometrioid ovarian cancers. In addition, no progress has been made toward identifying a more effective chemotherapeutic regimen.[59] It seems, therefore, that the treatment of this disease is an area that is ripe for clinical investigation.

Because of the molecular similarity between these diseases, most research has attempted to translate the gains made in treating clear cell RCC to extrarenal CCC. A bevy of targeted therapies and immune checkpoint inhibitors have now been trialed in this disease, with varying degrees of success. Other treatment modalities, including conventional chemotherapies and novel targeted agents are also being explored.

Molecular-targeted Therapy

Because of the success of targeted therapies in revolutionizing the treatment of RCC, there has been tremendous interest

TABLE 1. Completed Trials of VEGF and mTOR Inhibition in Clear Cell Carcinoma

Treatment Regimen	Therapeutic Targets	Results Summary	References
Bevacizumab+Carboplatin +Paclitaxel	VEGF	Subgroup analysis of CCCO patients showed response rate of 63.6% (n = 11), which compares favorably to historical control (20%-50%) Minimal bevacizumab-associated toxicity	60
Sunitinib	VEGF-R, PDGF-R	Response rate of 6.7% and median PFS 2.7 mo (n = 30) Well tolerated	61
Cabozantinib	VEGF-R, MET	Response rate of 0% (n = 13) Single patient with lethal thromboembolic event, possibly treatment related	62
Temsirolimus+Carboplatin +Paclitaxel	mTOR	12 mo PFS rate 54% (n = 90) not significantly different than historical controls Most common grade 3-4 AE were cytopenias. Otherwise well tolerated	63

CCCO indicates clear cell carcinoma of ovary; mTOR, mammalian target of rapamycin; PDGF-R, platelet-derived growth factor receptor; PFS, progression-free survival; VEGF, vascular endothelial growth factor; VEGF-R, vascular endothelial growth factor receptor.

in deploying these drugs against extrarenal CCC. To date, clinical trials of bevacizumab,[60] sunitinib,[61] cabozantinib,[62] temsirolimus[63] have been completed. Unfortunately, each has failed to appreciably improve upon the existing standard of care. The results of these trials are summarized in Table 1.

In addition, there has been some preclinical investigation into the use of HER-2 targeted therapies. In EOC, inhibition of HER-2 has proven modestly efficacious[64] but is generally limited by a low rate of overexpression or amplification. Since HER-2 amplification is more common in CCCO than other types of EOC, this is a reasonable avenue for exploration. In preclinical studies, trastuzumab inhibited cell proliferation and induced apoptosis in CCCO lines that overexpress HER-2.[49] In mouse xenografts, trastuzumab also produced a dose-dependent decrease in tumor volume.[49] Ultimately, however, it seems unlikely that HER-2-targeted therapy will be a paradigm-shifting treatment in this disease.

Poly-ADP Ribose Polymerase (PARP) Inhibitors

PARP plays an integral role in the repair of single-strand DNA breaks through base excision repair. In the absence of PARP, these single-strand breaks persist and can become a nidus for double-strand break (DSB) formation. For this reason, PARP inhibition can be synthetically lethal in cells with deficient mechanisms of DSB-repair such as BRCA mutations. While BRCA mutations are uncommon in CCC,[65] this disease often harbors other abnormalities that impair DSB-repair and may confer synthetic lethality to PARP inhibition. In endometrioid endometrial cancer, PTEN deficiency has been shown to predict response to these agents.[66] This notion is further supported by a preclinical study of CCCO cell lines, which found PTEN mutation to confer sensitivity to cisplatin and talazoparib similar to other deficiencies in DSB-repair.[34] In addition, ARID1A contributes to DSB-repair and preclinical evidence suggests that PARP inhibitors are synthetically lethal in BRCA *wild-type* but ARID1A depleted cells.[67]

There are not yet any clinical trials investigating the use of PARP inhibitors in patients with CCC, but the high rates of ARID1A and PTEN loss make this a promising area for future exploration.

Synthetic Lethality With ARID1A Loss

A novel and particularly intriguing treatment approach seeks to capitalize on the high rates of ARID1A loss in extrarenal CCC through synthetic lethality. While there are several candidate synthetic lethality partners, among the most promising are Aurora Kinase A and Enhancer of Zeste 2 Polycomb Repressive Complex 2 subunit (EZH2). Clinical trials of several of these agents are presently underway.

Aurora Kinase A is a serine/threonine kinase that serves several integral roles in cell division. It is ordinarily under strict control by ARID1A, which serves as transcriptional repressor. In tumors that lack ARID1A, however, Aurora Kinase A becomes overexpressed and drives unchecked cell growth. It is therefore not surprising that increased Aurora Kinase A expression has been found to correlate with reduced OS in patients with stages III-IV CCCO.[68] The efficacy of targeting Aurora Kinase A in CCCO was evaluated in a phase II study of 40 patients who received ENMD2076, which is a potent inhibitor of Aurora Kinase A and several mediators of angiogenesis.[69] While this was a negative trial, there was evidence of benefit in the subset of patients whose tumors tested negative for ARID1A via immunohistochemistry. A 6-month PFS rate of 33% was seen in this group of patients.

The loss of ARID1A in CCC may also be exploited through inhibition of EZH2, which is a member of the polycomb complex. It works in opposition to ARID1A and the SWI/SNF chromatin remodeling complex to regulate transcription. Preclinical studies have demonstrated EZH2 inhibition to be synthetically lethal in ARID1A-mutated ovarian cancer cells and produce *in vivo* responses in mouse models.[70] There is an ongoing NCI-sponsored phase II study of tazemetostat in gynecologic carcinoma of any histology that should be completed in January 2025 (NCT03348631).

A third approach to capitalizing on high rates of ARID1A loss may be the use of dasatinib, a multikinase inhibitor that is most often used to treat hematologic malignancies. Dasatinib was first identified as a synthetic lethality partner for ARID1A-deficient CCCO in a drug screening study.[71] While the mechanism by which it induces cell death in this setting remains incompletely understood, there is presently a phase II trial of dasatinib in CCC underway (NCT02059265).

Immune Checkpoint Inhibitors

Perhaps the most meaningful advance in medical oncology in recent years, immune checkpoint inhibition has revolutionized the treatment of many cancers. There is reason to be optimistic about the potential that these agents hold in treating CCC. As described previously, MSI is more common in CCC than other types of EOC. This is particularly relevant following the recent site-agnostic approval of pembrolizumab for tumors with MSI.[72] In addition, PD-1/PD-L1-targeted therapy has single agent efficacy in both EOC[73] and RCC.[74] In fact, in an interim analysis of a small phase II study of 18 patients with

TABLE 2. Ongoing Clinical Trials in Gynecologic Clear Cell Carcinoma

Investigational Treatment	Type of Therapeutic Agent	Phase	Clinicaltrials.gov #
Nivolumab+/–Ipilimumab	PD-L1 inhibition CTLA-4 inhibition	Phase II	NCT03355976
Nintedanib	VEGFR, PDGFR, FGFR inhibition	Phase II	NCT02866370
Pembrolizumab+Epacadostat	PD-L1 inhibition IDO1 inhibition	Phase II/suspended	NCT03602586
Pembrolizumab	PD-L1 inhibition	Phase II	NCT03425565
Durvalumab	PD-L1 inhibition	Phase II	NCT03405454
AMG 337	c-MET inhibition	Phase II	NCT03132155
ENMD-2076	Aurora A kinase inhibition	Phase II	NCT01914510
Sunitinib	Multikinase inhibition	Phase II	NCT01824615
Dasatinib	Synthetic lethality ARID1A loss	Phase II	NCT02059265

c-MET indicates hepatocyte growth factor receptor; CTLA4, cytotoxic T-lymphocyte antigen 4; FGFR, fibroblast growth factor receptor; IDO1, indoleamine 2,3 dioxygenase 1; PDGFR, platelet-derived growth factor; PD-L1, programmed death ligand 1; VEGFR, vascular endothelial growth factor receptor.

heavily pretreated platinum-resistant ovarian cancer, 1 complete response was observed in a patient with CCC.[73] In RCC, even further gains have been realized by combining PD-1 blockade with the inhibitor of cytotoxic T-lymphocyte associated protein 4 (CTLA-4), ipilimumab.[75]

At this time, the data regarding checkpoint inhibition in CCC has been relatively sparse. In a subgroup analysis of the KeyNote 100 study, the response rate in CCC was 16%. While relatively low, this was nearly double the response rate in the overall study population of patients with any histology of EOC (8%) and several durable response rates were observed.[76] There are multiple trials of immune checkpoint inhibitors as both single agents and combination therapy that are presently underway.

Ongoing Clinical Trials

Table 2.

CONCLUSIONS AND FUTURE DIRECTIONS

Extrarenal CCC is a rare malignancy that is most often found within the female reproductive system, but can arise from epithelial tissue anywhere in the body. The prognosis associated with this disease is generally poor, due in part to a lack of sensitivity to standard platinum and taxane-based chemotherapy regimens. On a genetic and molecular level, these tumors bear little resemblance to other gynecologic cancers but are quite similar to clear cell RCC. For this reason, most efforts to introduce new therapies have focused on agents that have proven effective against kidney cancer. While major gains in the treatment of this disease have not yet been actualized, trials of several promising treatments are currently underway.

One potential treatment approach that has not yet been explored involves restoration of normal, *wild-type* p53 signaling through inhibition of MDM2. There is preclinical evidence to support this approach, as the MDM2 inhibitor RG7112 induced apoptosis in TP53 *wild-type* clear cell lines and reduced tumor volume in mouse xenografts.[46] MDM2 inhibition may also be useful in combination with a checkpoint inhibitor, considering the role of MDM2 amplification in hyperprogression in patients receiving PD-1/PD-L1-targeted therapy.[77]

There are also several obstacles which must be overcome if we are to make meaningful advances in the treatment of CCC. Although there is now a growing body of literature regarding common molecular abnormalities in this disease, additional research is needed to understand the roles that each play in tumor pathophysiology. This will facilitate rational selection of therapeutic targets. In addition, the rarity of this disease makes multicenter and even international collaboration a necessity to meet accrual for clinical trials.

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