



Endometriosis-associated ovarian carcinomas: insights into pathogenesis, diagnostics, and therapeutic targets – a narrative review

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Abstract: Endometriosis is a benign gynecologic condition affecting up to one woman out of ten of reproductive age. It is defined by the presence of endometrial-like tissue in localizations outside of the uterine cavity. It often causes symptoms such as chronic pain, most frequently associated with the menstrual cycle, and infertility, but may also be oligo- or asymptomatic. There is evidence that some ovarian carcinoma (OC) histotypes, mainly the ovarian clear cell (OCCC) and endometrioid (EnOC) carcinoma, may arise from endometriosis. The most frequent genomic alterations in these carcinomas are mutations in the AT-rich interacting domain containing protein 1A (*ARID1A*) gene, a subunit of the SWI/SNF chromatin remodeling complex, and alterations in the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway, which frequently co-occur. In *ARID1A* deficient cancers preclinical experimental data suggest different targetable mechanisms including epigenetic regulation, cell cycle, genomic instability, the PI3K/AKT/mTOR pathway, inflammatory pathways, immune modulation, or metabolic alterations as potential precision oncology approaches. Most of these strategies are relying on the concept of synthetic lethality in which tumors deficient in *ARID1A* are more sensitive to the different compounds. Some of these approaches are currently being or have recently been investigated in early clinical trials. The remarkably frequent occurrence of these mutations in endometriosis-associated ovarian cancer, the occurrence in a relatively young population, and the high proportion of platinum-resistant disease certainly warrants further investigation of precision oncology opportunities in this population. Furthermore, advanced knowledge about oncogenic mutations involved in endometriosis-associated ovarian carcinomas may be potentially useful for early cancer detection. However, this approach may be complicated by the frequent occurrence of somatic mutations in benign endometriotic tissue as recent studies suggest. In this narrative review of the current literature, we will discuss the data available on endometriosis-associated ovarian carcinoma, with special emphasis on epidemiology, diagnosis and molecular changes that could have therapeutic implications and clinical applicability in the future.

Keywords: Ovarian cancer; endometriosis; clear cell ovarian carcinoma; endometrioid ovarian carcinoma; *ARID1A* mutations; PI3K/AKT/mTOR pathway; synthetic lethality; treatment; SWI/SNF transcription complex
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Introduction

Endometriosis is a benign gynecologic condition affecting up to one woman out of ten of reproductive age. It is characterized by pain associated with the menstrual cycle such as dysmenorrhea, dyspareunia, dyschezia, chronic pelvic pain and/or infertility. The prevalence of endometriosis in women affected by infertility is particularly high, up to 50%. It is an estrogen-dependent disease; therefore, it mainly affects women of reproductive age and manifestations of endometriosis in the postmenopausal age are rare. Nevertheless, certain residues of endometriosis may be found incidentally during surgical procedures (1-4).

There are three clinically distinct forms of endometriosis that may occur in combination: peritoneal endometriosis, which is characterized by endometriotic implants on the surface of the peritoneum and the ovaries, endometriotic ovarian cysts (endometrioma) and deep-infiltrating endometriosis, which is characterized by a complex solid mass comprised of endometriotic and fibromuscular tissue and frequently occurs in the rectovaginal septum. In severe cases of deep-infiltrating endometriosis, possible intestinal or urological complications such as obstruction of the rectosigmoid, bowel infiltration, bladder invasion or ureters' stenosis can occur and often require extensive surgical intervention (5). Laparoscopy represents the gold standard for diagnosis and surgical treatment of endometriosis; however, repeated laparoscopies should be avoided when possible.

Although most women with endometriosis will never suffer from cancer related to this benign disease, evidence suggested that certain epithelial ovarian cancer (EOC) subtypes, specifically ovarian clear cell (OCCC) and endometrioid ovarian (EnOC) carcinoma are directly related to endometriosis. This link between endometriosis and these EOC subtypes has been confirmed at the molecular pathology level through the presence of common mutations in cancer-associated genes (6,7). Atypical endometriosis may be the precursor of these cancers, but is not systematically found in all cases of endometriosis-associated ovarian cancer (EAOC).

The challenges raised by these cancers are: (I) they often affect younger women, to a considerable extent in the age span between 35 and 55 years; (II) sonographic differentiation between benign endometriotic cysts,

also called endometrioma or chocolate cysts, and early-stage cystic OCCC or EnOC may be very challenging. A carcinoma may arise from a limited atypical epithelial spot in the interior of an endometrioma and is difficult to recognize by sonography in its early stage. EnOC represent about 10% of EOC, whereas OCCC, with a prevalence of 5–12%, is geographically more variable and more frequent in some Asian countries. EnOC may be low or high grade, but OCCC is per definition high-grade ovarian carcinoma and has poor prognosis in advanced stages due to early platinum-resistance (8-12).

Benign endometrioma are usually managed surgically while preserving the ovary, either by excision of the cyst or, in cases where a maximum of ovarian tissue has to be preserved to maintain fertility, by fenestration and laser ablation of the inside of the endometrioma, for instance (*Figure 1*). In contrast, EAOC must obviously be managed surgically by complete salpingo-oophorectomy without opening the cystic lesions to avoid intra-abdominal spillage of malignant cells (*Figure 2*). These cases necessitate a referral to a center specialized in gynecologic oncology and usually require median laparotomy for staging and resection of any detectable tumor masses, hysterectomy and bilateral salpingo-oophorectomy, omentectomy, and a stage-dependent adequate pelvic and para-aortic lymph node assessment (13-15). In patients with presumable endometriotic cysts, it is crucial to detect the rare cases with increased risk of malignant transformation preoperatively in order to avoid the intraoperative dissemination of malignant cells. This requires a high degree of expertise in transvaginal sonography, which is the most useful and accessible method in preoperative assessment. Magnetic resonance tomography may have additional value in certain cases, but is not a standard procedure for preoperative assessment of endometrioma. Tumor marker CA-125 may be helpful, but its usefulness in the diagnosis of early EAOC is limited due to lack of specificity. Indeed, moderate elevations of CA-125 often occur in women with benign endometriosis without any evidence of EOC (16-22).

In this narrative review of the present literature, we will discuss the data available on EAOC, with special emphasis on epidemiology, diagnosis and molecular changes that have therapeutical implications. As especially OCCC are

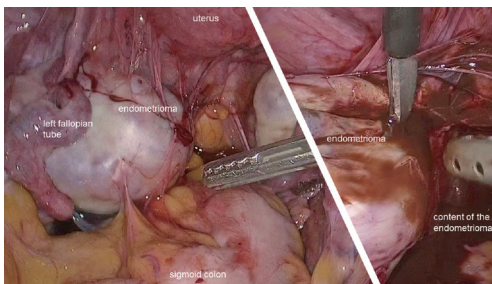


Figure 1 Endometrioma of the left ovary. Endometrioma typically contain brown viscous content resembling to melted chocolate, reason why they are sometimes also called “chocolate cysts”. The surgical treatment of choice consists in the laparoscopic excision or fenestration and laser therapy of the cyst with preservation of the ovary (Image credits: with special thanks to Dr. Markus Eberhard, Schaffhausen, Switzerland).

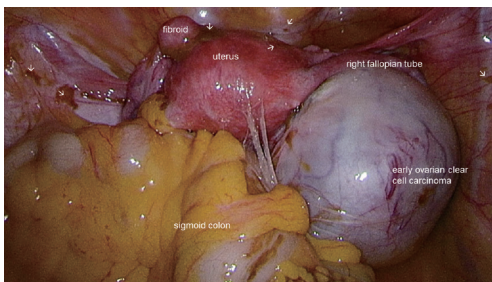


Figure 2 Early ovarian clear cell carcinoma (OCC). Clear cell carcinoma of the right ovary, most probably originating from endometriosis. The macroscopic picture in the very early stage may be difficult to distinguish from a benign endometrioma or another benign ovarian tumor. The preoperative assessment including transvaginal sonography and tumor marker CA-125 is important in the risk assessment (e.g. according to the IOTA criteria) and crucial for the correct surgical therapy of the patient. Arrows: various peritoneal endometriotic lesions and old blood deposits.

often associated with early occurring resistance to platinum-based chemotherapy regimen the rationale is to identify targetable molecular key-mechanisms that provide potential new opportunities in a precision oncology approach. As many of these mechanisms seem to be involved early in the pathogenesis of endometriosis-related ovarian cancer a better understanding may in future also be an opportunity for early cancer detection in these patients.

The objective of the present review is to provide an overview of these key-mechanisms in the development of endometriosis-related ovarian cancer and to discuss them

in a possible clinical context based on recent preclinical and early clinical observations.

Scientific articles with relevance for the discussion of the topic were searched using PubMed with emphasis on articles published over the last decade. The data in this review were all obtained from published studies and/or publicly available study information. Only articles published in English language were included. Written general consent of the patients was available for all intraoperative images reproduced in this review article. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3022a>).

Pathogenesis of endometriosis

Different theories have been proposed regarding pathogenesis of endometriosis since its first modern description by Sampson almost one century ago. There are probably various reasons for the development of endometriosis, such as anatomical variations leading to increased retrograde menstruation, environmental toxins or potent estrogens, especially in case of an *in utero* exposure, genetic factors as well as inflammatory mediators such as cytokines (3). Most theories regarding pathogenesis of endometriosis consider retrograde menstruation as being one of the principle factors connected to the development of endometriosis. However, retrograde menstruation through the natural orifice of the fallopian tubes is found in most women and is not sufficient to explain why only some women having retrograde menstruation will develop endometriosis. Nor does it explain why endometriosis can develop in patients without patency of the fallopian tubes or after hysterectomy and even in some women with congenital absence of uterus such as the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome (23).

Although endometriosis is regarded as a benign disease, it shares some features that are classic hallmarks of cancer, such as migration and tissue invasion, but in contrast to cancer, the misplaced tissue is morphologically resembling to normal endometrium. Endometriosis can also lead to lymph-angiogenesis and endometriotic tissue has been found in lymphatic nodes (24,25). Nevertheless, endometriosis is not lethal and does not metastasize or progress in the form of an expansile tumor mass like cancer (26).

Treatment modalities of endometriosis include surgical excision of endometriotic implants, through laparoscopic approach, and hormonal therapies, mainly progestins

(e.g., dienogest), GnRH analogs (e.g., goserelin) or GnRH antagonists (e.g., elagolix). Because endometriosis is a chronic disease, a prolonged hormonal recurrence prophylaxis is necessary, especially in cases with more severe endometriosis and/or associated pain (2,27). The risk for developing ovarian cancer is generally low for women with endometriosis, with a lifetime risk of about 1.9%, but it is relatively increased compared to the general population (lifetime risk of approximately 1.4%) (21,28).

Recent findings indicate that somatic cancer driver mutations in the *ARID1A* gene are present in a subset of endometriosis cases and may be involved in its pathogenesis (29–32). Endometriosis is an estrogen-dependent disease. The role of *ARID1A* mutations in regulating estrogen receptor signaling may further support its relevance in the pathogenesis of endometriosis, as it was recently reported in the context of estrogen-receptor-positive breast cancer (33,34).

Epidemiology of endometriosis-associated ovarian carcinoma

A possible link between endometriosis and EOC in certain cases has been suggested for a long time. It was Sampson who described for the first time in 1925 an endometriosis-associated ovarian endometrioid carcinoma (35). Multiple studies have since assessed the incidence of EAO (36–46). In a large register study of 20,686 Swedish women hospitalized for endometriosis, the standardized incidence ratio for developing ovarian cancer during a mean follow-up of 11.4 years was 1.9 (95% CI: 1.3–2.8). The risk of ovarian cancer was higher in patients with a long history of endometriosis (47). In another Swedish register study including 64,492 women with endometriosis, the standardized incidence ratio was 1.43 (95% CI: 1.19–1.71), again with a higher incidence in women with early diagnosis and a long history of endometriosis (48). In a pooled meta-analysis of 13 case-control studies including 7,911 women with ovarian cancer and 13,226 controls, the frequency of self-reported endometriosis was significantly higher in the group with ovarian cancer. This group had an odds ratio (OR) of 1.46 (95% CI: 1.31–1.63, $P < 0.0001$) after adjustment for the duration of oral contraceptive use as well as parity and stratification for age and ethnic origin. The OR were significantly increased in the histotypes OCCC (OR 3.05, 95% CI: 2.43–3.84, $P < 0.0001$), EnOC (OR 2.04, 95% CI: 1.67–2.48, $P < 0.0001$) and low-grade serous carcinoma (OR 2.11, 95% CI: 1.39–3.20, $P < 0.0001$). No association

between a history of endometriosis and risk for high-grade serous or mucinous carcinoma were found (49). Consistent observations were reported by a Danish register study (OR 1.34, 95% CI: 1.16–1.55), confirming the association with the two histotypes EnOC (OR 1.64, 95% CI: 1.09–2.37) and OCCC (OR 3.64, 95% CI: 2.36–5.38) (50). In the ENOCA population-based cohort study using the Dutch nationwide registry of histopathology and cytopathology, the incidence of endometrioid and clear-cell ovarian cancer in a cohort of 131,450 women with a histological diagnosis of endometriosis was compared to an age-matched control cohort of 132,654 women with a benign dermal nevus. The age-adjusted incidence rate ratio (IRR) was 7.18 (95% CI: 6.17–8.46) for ovarian cancer in women with endometriosis, and there was a strong association with the two subtypes of OCCC (with an IRR of 21.34, 95% CI: 14.01–32.51) and EnOC (with an IRR of 29.06, 95% CI: 20.66–40.87), all of them age adjusted. However, an important subset of these patients had a simultaneous diagnosis of endometriosis and ovarian cancer in the same surgery, which represented a potential bias in the study. Therefore, the authors excluded women with diagnosis of endometriosis less than one year before diagnosis of ovarian cancer in a subsequent analysis. Overall, the recalculated age-adjusted IRR was estimated to be 1.08 (95% CI: 0.87–1.35) for ovarian cancer, with still a significantly increased risk for the two subtypes of OCCC and EnOC. An important observation in this study was that the median age at diagnosis of ovarian cancer was earlier, with 56 years (IQR 49–63) for women with endometriosis compared to 60 years in the control cohort (IQR 53–67). This observation suggests that women with endometriosis still have an increased risk for developing ovarian cancer even if the activity and symptoms of endometriosis drop after the onset of menopause (51). In contrast to the evident link between endometriosis and ovarian carcinoma, women with endometriosis do not seem to be at increased risk for endometrial cancer, as reported by a large prospective cohort of U.S. nurses (52). The present literature generally does not support an increased risk for cancers other than EOC in women with endometriosis (53).

In summary, the lifetime risk for developing ovarian cancer is low with approximately 1.9% (as compared to 1.4% for the general population) since ovarian cancer is not frequent when compared to other cancers (breast, lung, colon, etc...). Nevertheless, the risk for a woman with endometriosis to develop ovarian cancer is up to 50% higher than in the general population. This is particularly true regarding the risk for developing the clear cell or endometrioid histotype,

Table 1 Prevalence of ARID1A mutations in different cancers

Tumor origin	Histologic subtype	ARID1A mutations frequency	References
Ovarian carcinoma	clear cell (OCCC)	~60%	(6,7,81)
	endometrioid (EnOC)	~30%	
Endometrial carcinoma	endometrioid	29%	(68,69,82)
	clear cell	26%	
	serous	18%	
Breast cancer (luminal types)		4–35%	(33,78,79)
Hepatobiliary carcinoma		10–17%	(75-77)
Pancreatic carcinoma		8–45%	(70,71)
Gastric carcinoma		8–29%	(72-74)

where the risk is tripled or doubled, respectively (21).

Diagnosics in endometriosis and issues for early cancer detection

Transvaginal sonography is one of the most valuable diagnostic tools in the routine diagnosis of endometrioma and suspicious ovarian masses. It is usually complemented by serum measurement of the tumor marker CA-125 and, in certain circumstances, may be supplemented by other imaging techniques such as magnetic resonance tomography or computer tomography. The sensitivity and specificity of transvaginal sonography is overall comparable to magnetic resonance tomography, and it is usually sufficient for the preoperative assessment of endometrioma and/or suspicious ovarian masses (21).

Recently, the diagnostic possibilities of ultrasound imaging have improved considerably, both regarding technology and assessment expertise of the sonographer. Clinical research collaborations such as the International Ovarian Tumour Analysis (IOTA) group and others have permitted results that were not possible before for ultrasound assessment of suspicious ovarian masses (54-56).

The description of all sonographic criteria that allow preoperative assessment of the risk of malignancy in endometrioma and other masses of the ovary is beyond the scope of this review. It is important to note that a typical endometrioma is mostly a unilocular (or multilocular with up to four locules) cyst containing a homogeneous “ground-glass” echogenicity without detectable solid or vascularized papillary parts, whereas borderline tumors and carcinoma arising from endometrioma generally show a vascularized

solid component (54). An increased age of 45 years or more as well as increased endometrioma size (≥ 8 cm) were independent predictors for the development of ovarian cancer in women with endometrioma (43,57,58).

Recent studies have proposed mutation analyses in endocervical or preferably intrauterine cell samples for a potential early detection of endometrial and ovarian cancer. These methods must be further studied regarding their clinical validity. However, even if some of these concepts should prove to be valid for a peri-/postmenopausal population in future, this may likely not be the same for a younger population of patients with endometriosis as somatic mutations occur more frequently in eutopic and ectopic endometrium than previously thought (30,59-62). At present, there is no useful screening possibility for EOC and this also applies to patients with endometriosis (63-66).

Common pathogenic features of endometriosis and associated ovarian carcinoma

Since the discovery in 2010 that mutations in the *AT-rich interacting domain 1A* (*ARID1A*), encoding an accessory subunit of the SWI/SNF chromatin remodeling complex, are frequent in OCCC, EnOC and their endometriotic precursor lesions, there has been substantial emphasis on EAO and the epigenetic role of the SWI/SNF chromatin remodeling complex in carcinogenesis (6,7). Overall, SWI/SNF-associated genes are mutated in about 20% of all human cancers. Mutations in *ARID1A* have been found in a multitude of different cancers, with the highest frequency in OCCC (up to 60%) and EnOC (approx. 30%) (6,7,33,34,67-81) (Table 1).

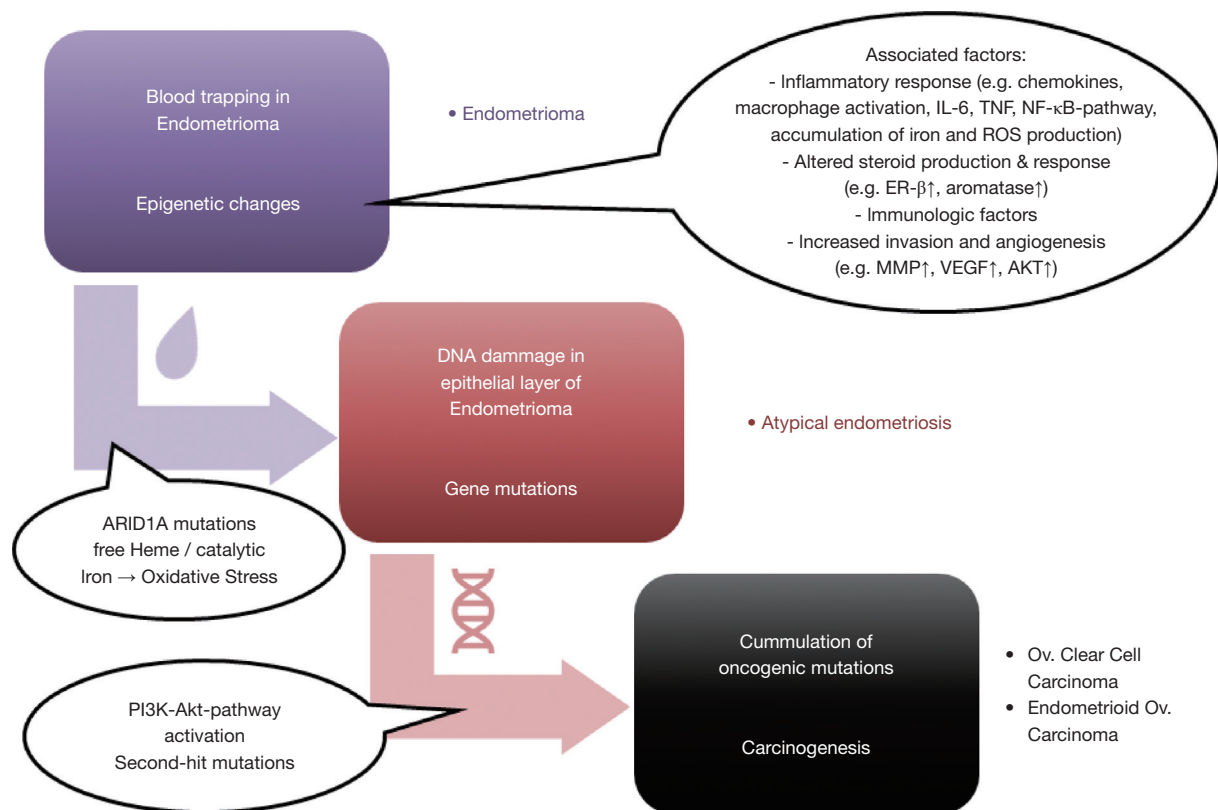


Figure 3 Hypothetic model of pathogenesis of endometriosis-associated ovarian carcinoma. Reactive oxygen species (ROS) due to free heme and catalytic iron contained in the trapped blood in endometriomas may lead to increased oxidative stress and DNA damage in the epithelial layer of endometriomas. This may result in mutations and epigenetic changes, including mutations in the tumor suppressor gene *ARID1A* and possible second-hit mutations as well as activation of the PI3K-AKT-mTOR pathway to escape apoptosis caused by increased oxidative stress. The accumulation of oncogenic mutations in atypical endometriosis may ultimately lead to the development of endometriosis-associated ovarian clear cell (OCC) and endometrioid (EnOC) carcinomas (adapted from Vercellini *et al.*, Hum Reprod, 2011 and Samartzis *et al.*, GYNÄKOLOGIE, 2018).

The *ARID1A* gene encodes the protein BRG1-associated factor 250a (BAF250a or p270), which is part of a family of 15 human proteins that contain a typical 100-amino-acid DNA-binding ARID domain (83). The SWI/SNF complexes bind to DNA regions via *ARID1A* or *ARID1B*, which are two mutually exclusive, nonselective DNA binding accessory subunits of the complex, and/or through interaction with general or specific transcription factors (84,85). Mutations in *ARID1A* are in general loss-of-function mutations, including nonsense, frameshift and large deletions that lead to a loss of BAF250a protein expression (6). Importantly, endometriosis is the first and only benign disease in which a loss of *ARID1A* expression has been observed in cases without any evidence for cancer (29,30,86-88). Mutations in *ARID1A* are considered as an

early event but *ARID1A* inactivation alone is not sufficient for the oncogenic transformation of either the endometrium or ovarian surface epithelium. Several other mechanisms such as *PIK3CA*-activating mutations in cooperation with loss of *ARID1A* expression seem to be necessary to initiating cancer development (*Figure 3*) (80,89-94).

Due to its large size (20 exons) and the distribution of mutations across the whole gene, detection of mutations in *ARID1A* by sequencing is quite challenging, especially when only a very limited amount of tissue is available, which is the case for the epithelial fraction of endometriosis (6,30). *ARID1A* immunohistochemistry has been shown to be an excellent surrogate marker for *ARID1A* mutations (95).

Interestingly there are no known mutually exclusive mutations that clearly distinguish OCC and EnOC,

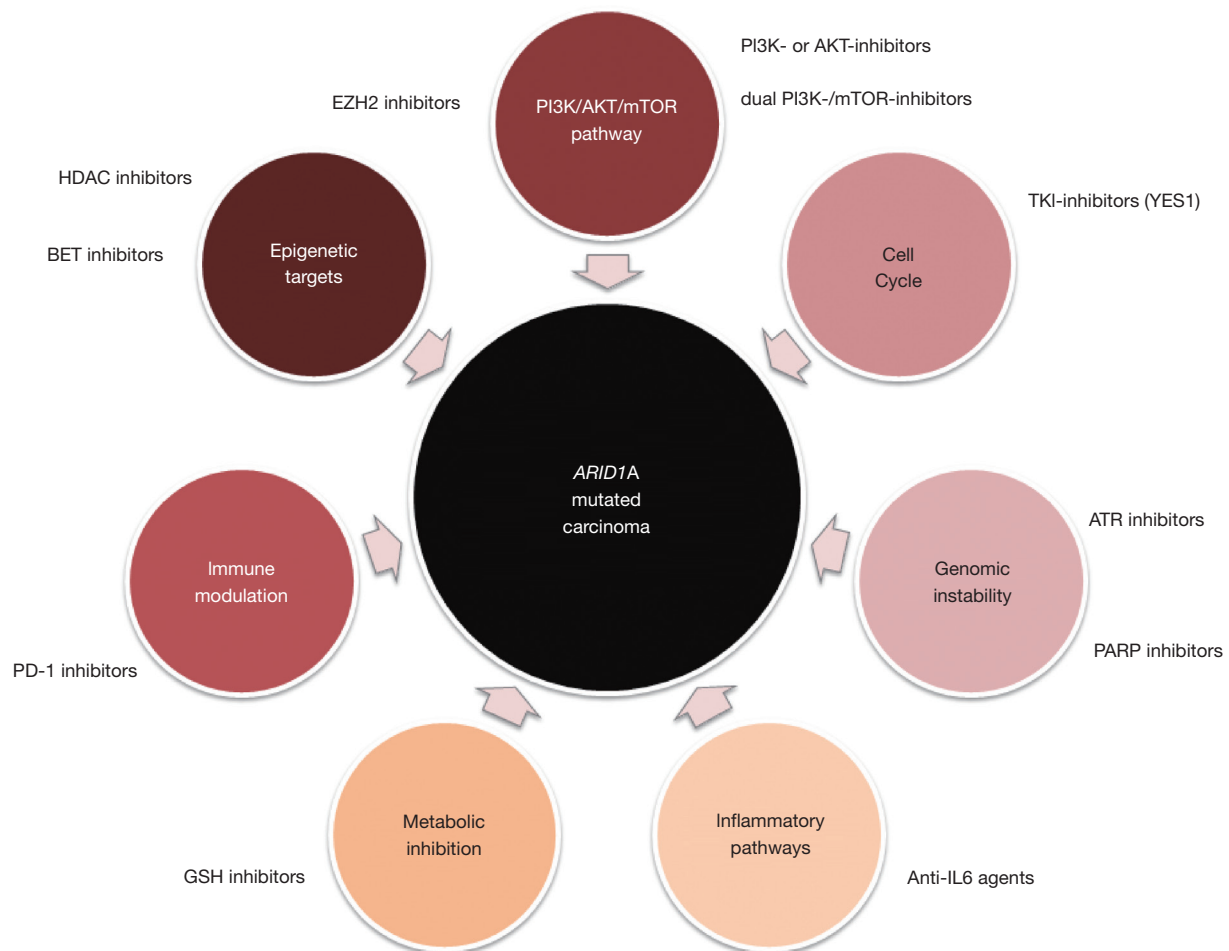


Figure 4 Therapeutic targeting strategies in *ARID1A* deficient tumors. Since *ARID1A* mutations lead to a deficiency in the encoded protein, the strategies to target *ARID1A* mutated tumors use the principle of synthetic lethality. The main approaches are stated in circles and the examples of inhibitor families are listed next to the main groups.

even though these two histotypes are distinct in their morphological and clinical presentation. However, some genomic features such as the APOBEC (apolipoprotein B mRNA editing enzyme catalytic polypeptide-like) signature are found in 26% of OCCC, whereas microsatellite instability is more frequent (28%) in EnOC (80,96).

Preclinical studies targeting *ARID1A*-mutated tumors

Since *ARID1A* mutations cause loss of functions in a tumor-suppressing mechanism, there is no possibility of directly targeting the mutations with a therapeutic intent (97). Various preclinical studies suggest the possibility of using the synthetic lethality approach, a concept that is best

known in PARP-inhibitors, to target *ARID1A*-deficient tumors (Figure 4) (98-101). A general overview of different preclinically identified therapeutic targets related to *ARID1A* deficiency is provided in Table 2.

In OCCC, *ARID1A* mutations frequently co-occur with mutations that lead to the activation of the PI3K/AKT signaling pathway, such as loss of *PTEN* (phosphatase and tensin homolog) or gain-of-function mutations of the *PIK3CA* gene, encoding the catalytic subunit, p110 α , of PI3K (91,119). These changes have also been observed in benign and atypical endometriosis adjacent to OCCC (6,29,61,120). These observations suggest a cooperative role of *ARID1A* inactivation and PI3K/AKT activation in the malignant transformation of the endometriotic precursor lesion. A conditional *ARID1A* knockout was combined

Table 2 Potential targets in ARID1A-mutated tumors in preclinical studies

Pathway	Target	Drug class	Drugs investigated	Ref.
Epigenetic	HDAC2	HDAC inhibitor	Vorinostat	(102)
	HDAC6	HDAC inhibitor	Ricolinostat (ACY1215)	(103)
	BRD2	BET inhibitor	iBET-762	(104)
	HDAC1, BRD4	BET inhibitor (BRD4-i)	Pexidartinib (PLX2853)	(34)
	ARID1B	ARID1B knockout	Non targetable <i>in vivo</i>	(105)
	PIK3IP1	EZH2 inhibitor	Tazemetostat	(106,107)
PI3K/AKT/mTOR	PI3K	PI3K-inhibitor	Buparlisib	(100,106)
	AKT	AKT-inhibitor	Perifosine, MK-2206	(100)
	mTOR	mTORC1/2 inhibitor	AZD8055 (in OCCC, ARID1A-independent)	(108)
	mTOR + PI3K	Dual-PI3K-/mTOR-i	Dactolisib (BEZ235), DS-7423	(109,110)
Cell cycle	YES1 (SRC family)	Tyrosine kinase inhibitor	Dasatinib	(99,111,112)
Genomic instability	TOP2A	ATR inhibitor	Berzosertib (VX-970)	(113)
	PARP	PARP inhibitor	Olaparib, Rucaparib, Veliparib, Talazoparib (BMN673)	(114)
Inflammatory	IL-6/IL-6-receptor	Anti-IL-6 agents	Tocilizumab (anti-IL-6-receptor ab), Siltuximab (anti-IL-6 ab)	(115)
Metabolic inhibition	Increase of ROS	GSH inhibitor GCLC inhibition	APR-246 buthionine sulfoximine	(116)
Immune modulation	PD-1	PD-1 inhibitor	Pembrolizumab, Nivolumab	(117)
	MMR/MSH2 deficiency			(118)

with insertion of a mutant PIK3CA allele in a transgenic mouse model, leading to the expression of a constitutively active catalytic subunit of PI3K and the development of highly penetrant ovarian tumors with OCCC-like histopathology (115). These results affirmed that ARID1A loss and activation of PI3K/AKT functionally cooperate in ovarian carcinogenesis, and suggest that ARID1A-deficient tumors may be “addicted” to PI3K/AKT oncogenic signaling. As a consequence, elements of the PI3K/AKT signaling pathway may be good candidate targets for the induction of synthetic lethality in tumors with ARID1A loss-of-function mutations. *In vitro* studies have shown increased sensitivity and induced apoptosis towards the AKT-inhibitors MK-2206 and perifosine, as well as the Pan-PI3K-inhibitor buparlisib, in ARID1A-depleted breast cancer and OCCC cell lines (100,106). The mTORC1/2 inhibitor AZD8055 showed a significant sensitivity in OCCC cell lines and patient-derived xenografts which however was independent of the ARID1A mutation

status and PI3K/AKT/mTOR alterations (108). EZH2 inhibition led to synthetic lethality in ARID1A-mutated tumors, in which PIK3IP1, an inhibitor of PI3K/Akt, plays a major role (106,107). As another epigenetic target, a lethal relationship was identified between ARID1A loss and inhibition of HDAC6 using the HDAC6-inhibitor ACY1215 (103).

Other *in vitro* approaches such as the depletion of ARID1B in ARID1A-mutated tumor cells demonstrated strong synthetic lethality, since ARID1A and ARID1B are mutually exclusive subunits of the SWI/SNF complex and the survival of ARID1A-deficient cells depends on the presence of ARID1B in the residual SWI/SNF complex (105).

Without a doubt, chronic inflammation is a central process in EAO, with proinflammatory cytokines playing an important role in benign endometriosis. ARID1A has been shown to protect against inflammation-driven tumorigenesis. The combination of ARID1A loss and

PIK3CA activating mutations led to the development of OCCC through sustained IL-6 production. Knockdown of *IL6* led to significantly smaller tumors. High levels of IL-6, measured in the serum or by IHC are associated with poor outcome in OCCC (121,122). Thus, anti-IL-6 therapies, which are already used in the clinics for rheumatologic disease, may show a potential activity in *ARID1A*-mutated ovarian cancer (115).

There is evidence suggesting a role of immune checkpoint inhibitors in tumors harboring mutations in components of the SWI/SNF complex. Recent treatment successes have been reported in small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), which is a highly aggressive monogenic cancer driven by *SMARCA4* mutations, affecting the catalytic ATPase subunit *SMARCA4/BRG1* of the SWI-SNF complex. These tumors responded well to treatment with anti-PD1 immunotherapy despite a low mutation burden (117). In clear cell renal cell carcinoma, clinical benefit from anti-PD1 was associated with loss-of-function mutations in the *PBRM1* gene, which encodes a subunit of the PBAF form of the SWI-SNF complex (123). In the early clinical trials with anti-PD1 in EOC, the highest response rates were observed in OCCC (124,125). Together, these observations support further investigation of immune checkpoint inhibitors in OCCC and the predictive value of *ARID1A* mutations (117).

Besides genes' regulation, the SWI/SNF complex has a role in the DNA damage repair processes. The complex often localizes to sites of DNA double-strand breaks and facilitates the phosphorylation of histone H2AX via ATM/ATR (126). Treatment with the ATR-inhibitor berzosertib (VX-970) resulted in more than three times effective response in various *ARID1A*-deficient cell lines including OCCC, and sensitivity towards ATR-inhibition was observed in *ARID1A* mutant xenograft mouse models. *ARID1A* loss was shown to result in accumulation of cells in G2/M. Treatment with ATR inhibitors reversed cells accumulation in G2/M and resulted in an increased chromosomal instability and apoptosis (113). It is important to note that *ARID1A*-deficient tumors counterintuitively typically display less copy number alterations than *ARID1A* wild-type tumors across various cancer types. This seemingly increased genomic stability is the result of defects in telomere cohesion in *ARID1A*-deficient tumors leading to a continuous selection process against genetically unstable cancer cells and this mechanism amongst others significantly relies on the ATR checkpoint (127).

A drug screening study of 68 clinically approved or late-stage

clinically developed inhibitors identified dasatinib, a SRC, ABL and C-KIT inhibitor, as being a specific inhibitor in *ARID1A*-mutated OCCC cell lines. This was confirmed in *ARID1A* knockout cell lines. The study identified YES1, an SRC family protein, as being the most selective target in *ARID1A*-deficient OCCC tumor cells. Dasatinib induced cell cycle arrest in G1 and caspase activity in *ARID1A*-mutant tumor cells (99).

Last but not least, it has been shown that SWI/SNF function is required for oxidative stress resistance (128,129). Oxidative stress induced by reactive oxygen species (ROS) plays an important role through the abundance of free heme and catalytic iron in endometrioma and probably plays a central role in the pathogenesis of EAOC (130). *ARID1A*-mutant OCCC and endometrial cancer cell lines were five to six times more sensitive towards the ROS-inducing agent elesclomol compared to *ARID1A*-wildtype cancer cell lines, resulting in increased ROS-levels and apoptosis (131). Ogiwara *et al.* demonstrated a link between *ARID1A* and glutathione metabolism that is mediated by the regulation of the cystine/glutamate transporter XCT, revealing that decreased glutathione synthesis is a metabolic dependency of cancers with *ARID1A*-inactivating mutations (116). This complex interaction between epigenetics and the glutathione synthesis metabolic pathway opens new insights into the mechanisms of tumor initiation, progression and drug resistance. This may open great therapeutic opportunities, but the complexity of these interactions will have to be better understood in order to develop properly tailored glutathione synthesis inhibitors (132,133).

Current clinical trials

Targeting of sustained proliferative pathways, such as the PI3K/AKT/mTOR pathway and the YES1/SRC tyrosine kinase pathway, or metabolic alterations, such as the glutathione biogenesis pathway, in *ARID1A*-deficient CCOC may be interesting options for future clinical trials (134). Various agents showing synthetic lethality in the *ARID1A* mutant context are currently in clinical development. An overview of current clinical trials mainly regarding OCCC or relevant for EAOC is available in *Table 3*. In addition to its potential role as a predictive biomarker in cancer treatments, *ARID1A* mutations have also been investigated for other purposes such as e.g., early cancer detection or in other biomarker studies (*Table 4*). Some studies have also assessed *ARID1A* as a potential prognostic marker in ovarian cancer correlating it to the overall survival and resistance to platinum-

Table 3 Current clinical trials in gynecological cancer using an ARID1A-related treatment approach (www.clinicaltrials.gov)

Study title (acronym)	Phase	Pat (n)	Description	Population, experimental design	Primary outcome measure	Trial, status
ATR Inhibitor in Combination With Olaparib in Gynaecological Cancers With ARID1A Loss or no Loss (ATARI)	II	40	AZD6738 (ATR inhibitor) Olaparib	<p>Experimental: 1A: AZD6738 Women with relapsed ovarian (fallopian tube/primary peritoneal) and endometrial (uterus) clear cell carcinomas with loss of ARID1A expression treated with single agent AZD6738</p> <p>Experimental: 1B: AZD6738 + olaparib. In second stage of trial, opening of this cohort depends on response rate in cohort 1A during first stage of trial. Women with relapsed ovarian (fallopian tube/primary peritoneal) and endometrial (uterus) clear cell carcinomas with loss of ARID1A expression treated with AZD6738 in combination with olaparib</p> <p>Experimental: 2: AZD6738 + olaparib. Women with relapsed ovarian (fallopian tube/primary peritoneal) and endometrial (uterus) clear cell carcinomas with NO loss of ARID1A expression treated with AZD6738 in combination with olaparib</p> <p>Experimental: 3: AZD6738 + olaparib. Women with other rare relapsed gynaecological cancers (endometrioid ovarian carcinoma, endometrioid endometrial carcinoma, cervical adenocarcinoma, cervical squamous, ovarian carcinosarcoma and endometrial carcinosarcoma) irrespective of ARID1A status, treated with AZD6738 in combination with olaparib</p>	ORR	NCT04065269, recruiting
Dasatinib in Treating Patients With Recurrent or Persistent Ovarian, Fallopian Tube, Endometrial or Peritoneal Cancer	II	35	Dasatinib	<ul style="list-style-type: none"> - Endometrial clear cell adenocarcinoma - Ovarian clear cell cystadenocarcinoma - Recurrent fallopian tube carcinoma - Recurrent ovarian carcinoma - Recurrent primary peritoneal carcinoma - Recurrent uterine corpus carcinoma <p>Patients receive dasatinib PO QD on days 1-28. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity</p>	ORR	NCT02059265, active, not recruiting

Table 3 (continued)

Table 3 (continued)

Study title (acronym)	Phase	Pat (n)	Description	Population, experimental design	Primary outcome measure	Trial, status
A Study of PLX2853 in Advanced Malignancies	I/II	166	PLX2853 (BRD4 inhibitor)	<ul style="list-style-type: none"> • Small cell lung cancer • Uveal melanoma • Ovarian clear cell carcinoma • Non-Hodgkin lymphoma • Advanced malignancies • Solid tumor • Diffuse large B cell lymphoma • Follicular lymphoma <p>Phase 1b (dose escalation): up to 30 subjects with advanced malignancies</p> <p>Phase 2a (dose expansion): there will be 5 total expansion cohorts. Either 10 or 29 subjects per cohort in each of 4 expansion cohorts: advanced SCLC, uveal melanoma, OCCC, and any other advanced malignancy with a known ARID1A mutation (between 40 to 116 subjects total for the solid tumor expansion phase). For the 5th expansion cohort, up to 20 subjects may be enrolled for NHL</p>	<ul style="list-style-type: none"> • Number of participants with treatment-related AE • Area under the concentration-time curve (AUC) • Maximum observed concentration (C_{max}) • Time to peak concentration (T_{max}) • Half life (t_{1/2}) • Number of participants who experience dose limiting toxicity • Change in disease burden using RECIST 1.1 (solid tumors) or Lugano criteria (NHL) 	NCT03297424, recruiting
Tazemetostat in Treating Patients With Recurrent Ovarian or Endometrial Cancer	II	86	Tazemetostat (EZH2-inhibitor)	<ul style="list-style-type: none"> • FIGO Grade 1 Endometrial Endometrioid Adenocarcinoma • FIGO Grade 2 Endometrial Endometrioid Adenocarcinoma • Recurrent endometrial endometrioid adenocarcinoma • Recurrent ovarian carcinoma • Recurrent ovarian clear cell adenocarcinoma • Recurrent ovarian endometrioid adenocarcinoma • Recurrent uterine corpus carcinoma <p>Patients receive tazemetostat PO BID on days 1–28. Cycles repeat every 28 days in the absence of disease progression or unacceptable</p>	ORR	NCT03348631, suspended

Table 3 (continued)

Table 3 (continued)

Study title (acronym)	Phase	Pat (n)	Description	Population, experimental design	Primary outcome measure	Trial, status
A Study of ENMD-2076 in Ovarian Clear Cell Cancers	II	40	ENMD-2076 (oral anti-angiogenic and anti-proliferative kinase inhibitor)	ENMD-2067 will be taken orally at a dose of 275 mg, once a day, everyday. Patients with a body surface area of less than 1.65 m ² will receive a starting dose of 250 mg, once a day, everyday	Six-month progression free survival rate Complete or partial response rate	NCT01914510, completed

OC, ovarian cancer; ORR, overall response rate; MTD, maximum tolerated dose; PFS, progression free survival; OS, overall survival.

based chemotherapies, but the results of the different mainly retrospective studies are conflicting and a possible association remains to be elucidated (135-139).

Besides the very intensively and successfully investigated PARP inhibitors, which have led to a dramatic improvement in the treatment of ovarian cancer and beyond, several clinical trials investigating ATR inhibitors and inhibitors of the PI3K/Akt/mTOR-pathway are currently ongoing in gynecologic cancers, some of them with molecular subanalyses or stratification including ARID1A (Table 3).

In a Phase II trial of everolimus plus bevacizumab in advanced non-clear cell renal cell carcinoma there was a net benefit in tumors with papillary features with an ORR of 43% *vs.* 11%, a median PFS of 12.9 *vs.* 1.9 months, and an overall survival of 28.2 *vs.* 9.3 months ($P < 0.001$) compared to non-clear cell renal cell carcinoma without papillary features. Of note, five of the fourteen tumors with papillary features harbored somatic mutations in ARID1A and all five patients achieved treatment benefit (140). In a recently published Phase II trial of everolimus and bevacizumab in recurrent ovarian, peritoneal, and fallopian tube cancer, two of the nine responders were OCCC cases which both harbored mutations in ARID1A and PI3K-mediated activations of the mTOR-pathway. Three other responders had serous ovarian cancer with mutations in the homologous recombination pathway. It was noted that the two OCCC were among the patients staying on treatment for the longest with 11 and 15 cycles of treatment respectively (141). Although the combination of bevacizumab plus everolimus, compared to bevacizumab alone, did not improve PFS or OS in recurrent or persistent ovarian, fallopian tube or peritoneal carcinoma in a randomized Phase II trial (142), these observations indicate a possible benefit in certain subgroups such as ARID1A mutated OCCC.

Dasatinib is already approved for leukemia treatment and is currently under investigation for various solid tumors. A

phase-II trial evaluating dasatinib in recurrent or persistent EOC showed limited efficacy but this study did not assess ARID1A status in the tumors (111).

After the first generation of EZH2 inhibitors have shown toxicity *in vivo*, novel EZH2 inhibitors are currently the subject of clinical trials (143). Meanwhile, the NRG-GY-014 phase II clinical trial assessing the EZH2-inhibitor tazemetostat in recurrent EnOC or OCC, as well as recurrent low-grade endometrioid endometrial carcinoma, is currently recruiting (144).

Other alternatives for epigenetic targeting agents include HDAC2 inhibition, e.g., with vorinostat, or the HDAC6 inhibitor ricolinostat (ACY-1215), which has been well tolerated by patients with relapsed or refractory multiple myeloma in a phase-1b trial (102,145). Furthermore, there is preclinical evidence of synergies between HDAC-inhibitors and anti-PD-L1 immune checkpoint blockade in ARID1A-deficient ovarian cancer which may be a promising combination to be evaluated in future clinical trials (146,147).

Inhibitors of the BET (bromodomain and extra terminal domain) family of proteins have been shown to inhibit the proliferation of ARID1A-mutated cancer cell lines *in vitro* as well as in patient-derived xenograft models (104). Several BET inhibitors such as iBET-762 are currently under evaluation in phase I-II trials (148).

Besides target therapies and immunotherapies, the assessment of ARID1A in OCCC patients may also be helpful in the choice of chemotherapy. Gemcitabine appears the most effective chemotherapy agent in platinum-resistant OCCC with response rate estimated to 66% ($n=12$) in a sub-group analysis of the MITO-9 study (149). This was confirmed in another small retrospective cohort from Japan ($n=7$) that showed that three ARID1A-deficient OCCC patients had a significantly longer progression-free survival with gemcitabine compared to four OCCC patients ($P=0.02$)

Table 4 Some examples of recent or ongoing studies in benign gynecologic disease and cancer including the detection of ARID1A mutations (www.clinicaltrials.gov)

Study title, acronym	Pat n	Description	Population, experimental design	Primary outcome measure	Trial, status
Cancer Driving Mutations in Endometriosis Lesions and Development of Progesterone Resistance	135	Observational, case-control, prospective	<ul style="list-style-type: none"> • Case Group: clinical or surgical diagnosis of Endometriosis, patients undergoing surgical management (n=100) • Control Group: no Endometriosis (Pat. undergoing Laparoscopic Tubal Ligation) (n=35) 	<ul style="list-style-type: none"> • Somatic cancer driver mutations in progesterone-resistant vs. -sensitive endometriosis lesions • Cancer driver mutations in eutopic versus ectopic endometrial tissue (cases vs. controls) • Difference in DNA methylation PCR profile of endometriotic lesions in ectopic versus eutopic endometrium (cases vs. controls) 	NCT03756480, not yet recruiting
Lavage of the Uterine Cavity for the Diagnosis of Ovarian and Tubal Carcinoma and their Premalignant Changes (LUDOC)	50	Interventional	<ul style="list-style-type: none"> • Procedure: lavage of the Cavum uteri and proximal fallopian tubes • Procedure: liquid-PAP smear 	<ul style="list-style-type: none"> • Detection of EOCs by mutation analysis in the lavage of the uterine cavity • Detection of EOCs by mutation analysis of the liquid-based Pap smear 	NCT02062697, completed
Lavage of the Uterine Cavity for the Diagnosis of Ovarian and Tubal Carcinoma - Study of Sensitivity and Specificity (LUDOC II)	540	Interventional	<p>Ovarian epithelial cancer</p> <ul style="list-style-type: none"> • Procedure: lavage of the Cavum uteri and proximal fallopian tubes 	Detection of somatic mutation analysis in at least one of the analyzed genes in cells found in the lavage of the uterine cavity and proximal tubes	NCT02518256, recruiting
Diagnosing Ovarian and Endometrial Cancer Early Using Genomics (DOvEEgene)	1200	Observational, case-control, prospective	<ul style="list-style-type: none"> • Case Group: cases undergoing surgery for endometrial or ovarian cancer • Control Group: cases undergoing hysterectomy and/or salpingectomy, oophorectomy for benign gynecologic conditions 	Detection of cancer-related mutations: diagnosis ovarian and endometrial cancers by detection of cancer-related mutation taken by brush sample of uterus with high sensitivity and specificity	NCT02288676, recruiting
Preoperative Olaparib Endometrial Carcinoma Study (POLEN)	36	Preoperative "Window of opportunity" Study Treatment with Olaparib	Evaluate the Inhibitory Effects of Single Agent AZD2281 (Olaparib), in Patients with Early-stage Endometrial Carcinoma	Expression of cell cycle-related proteins	NCT02506816, completed

who were not (150).

Conclusions and future implications

Despite being one of the most frequent benign disease in women of reproductive age, endometriosis remains fairly enigmatic in its cause and even more concerning the factors

that in rare cases may lead to malignant transformation. Many unresolved aspects in endometriosis-associated ovarian cancer remain to be addressed. This includes diagnosis and early detection of malignant transformation of endometriosis, identification of risk factors associated with development of ovarian cancer and stratification of women at increased risk.

Recent knowledge advances about alterations involving the SWI/SNF complex and its subunit ARID1A lead to a better picture of the processes involved in endometriosis and the carcinogenesis of EAOC. The dramatic improvement in ovarian cancer therapy achieved through intensive investigation of PARP inhibitors has undoubtedly boosted the research of new target therapies in ovarian cancer. New approaches are likely to soon translate into clinical research. Since inflammatory and epigenetic processes seem to play a predominant role in the pathogenesis of endometriosis-associated ovarian carcinomas, which mainly account for the subtypes OCCC and EnOC, immune checkpoint inhibitors and targeting the PI3K pathway as well as epigenetic treatment approaches may play an important role in the treatment of these tumor entities. Further clinical research based on the specific molecular features of these tumor subtypes, such as e.g., umbrella or basket trials, will be crucial to elucidate the potential role of these treatment approaches.

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