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Review

Translational genomics of ovarian clear cell carcinoma

Saira Khalique[a,b], Christopher J. Lord[a,c], Susana Banerjee[d,e], Rachael Natrajan[a,b,*]

[a] The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, UK
[b] Division of Molecular Pathology, The Institute of Cancer Research, London, UK
[c] The CRUK Gene Function Laboratory, The Institute of Cancer Research, London, UK
[d] Gynaecology Unit, The Royal Marsden NHS Foundation Trust, London, UK
[e] Division of Clinical Studies, The Institute of Cancer Research, London, UK

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ABSTRACT

Ovarian clear cell carcinomas (OCCC) are rare aggressive, chemo-resistant tumours comprising approximately 13% of all epithelial ovarian cancers, which have distinct clinical and molecular features, when compared to other gynaecological malignancies. At present, there are no specific licensed targeted therapies for OCCC, although a number of candidate targets have been identified. This review focuses on recent knowledge underpinning our understanding of the pathogenesis of OCCC including direct and synthetic-lethal therapeutic strategies in particular focussing on *ARID1A* deficiency. We also discuss current targeted clinical trials and immunotherapeutic approaches.

1. Introduction

Epithelial ovarian carcinoma is the commonest cause of gynaecological cancer-associated death [1]. Worldwide, there were 239,000 new cases diagnosed in 2012 alongside 152,000 deaths [2]. Survival figures have not significantly changed since the 1980's, (European 5-year survival remains around 40% [3]), mainly due to the insidious onset of most cases, which are usually at advanced stages at presentation. Part of the lack of improvement is thought to be due to the fact that ovarian cancer subtypes are treated as a single disease, even in large-scale clinical trials, despite the existence of different histological subtypes and molecular drivers. Ovarian clear cell carcinoma (OCCC) was formally described in the World Health Classification in 1973 as "tumours composed of clear cells containing glycogen and resembling those of the renal cell carcinoma and/or with the presence of hobnail cells" [4]. They are traditionally considered high-grade carcinomas [5].

A SEER registry analysis of 28,082 women with epithelial ovarian cancer identified 5% had clear cell, 13% endometrioid with 49% having papillary serous cancer [6]. Women with a clear cell diagnosis were younger, with a median age of 55 years compared to 64 years in serous carcinoma and were associated with a significantly worse five-year survival, ($p < 0.001$) compared to endometrioid, serous and mucinous histological subtypes, across all stages [6]. OCCC has a variable worldwide distribution with the highest prevalence in Japan (25%) [6], although the reasons for this are unknown, but perhaps are related to the elevated incidence of endometriosis. The majority of OCCC patients are diagnosed at an early stage, with studies showing between 49–81% of patients are diagnosed at stage I and II [6,7], often presenting with large unilocular cysts [8]. A retrospective Japanese OCCC study assessed 254 OCCC's and found that stage I and II overall survival was 88% and 70% respectively, with stage III and IV being 33% and 0% respectively, highlighting that outcomes in advanced stages of OCCC are particularly poor [9].

The main risk factors for OCCC include nulliparity, endometriosis and tubal ligation [10]. Endometriosis has been associated with 33%–37% of OCCC's [10], and the presence of endometriosis has a relative risk of 3.37 (1.24–9.14) for OCCC [11,10]. Endometriotic cysts (the precursors for OCCC and endometroid carcinomas) contain free iron, which have been shown to lead to increased oxidative stress and frequent DNA mutations. Gene expression analysis of cell lines that had exposure to cyst contents showed similar patterns of gene expression to OCCC, suggesting there may be a correlation with the endometriotic environment [12]. As such this accumulation during a woman's reproductive period may thus be a possible cause for the malignant

Abbreviations: CR, Complete Response; PR, Partial Response; DPR, Time from study entry to change in response from CR to PR to stable disease (SD) or progressive disease (PD) as assessed by RECIST v1.1; DOR, Duration of Response; PFS, Progression-Free Survival; OS, Overall Survival; ORR, Overall Response Rate; CBR, Clinical Benefit Rate; AE, Adverse Event; DLT, Dose limiting Toxicity; pCR, Pathological Complete Response; RR, Response Rate; QOL, Quality of Life; BOR, Best Overall Response; CA125, Cancer antigen 125; MS-NIV, Oncolytic measles virus encoding thyroidal sodium iodide symporter; DCR, Disease Control Rate

* Corresponding author at: The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, SW3 6JB, UK.
E-mail address: rachael.natrajan@icr.ac.uk (R. Natrajan).

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chances in the cysts. Unlike high grade serous ovarian cancers (HGSOC) or endometrioid cancers however, OCCC's show no family history [13] and as such *BRCA1* and *BRCA2* germline mutations are rare [14].

Immunohistochemically, OCCCs are CK7 + /CK20- [15], tend to be negative for hormone receptors ER (oestrogen receptor) and PR (progesterone receptor), Wilms Tumour 1 (WT1) and p53 [16]. Hepatocyte nuclear factor 1-β (HNF1-β) is over-expressed in OCCC and useful in cases of diagnostic uncertainty (82.5% sensitivity and 95.2% specificity for OCCC vs. HGSOC) [17]. An IHC research tool has been devised to predict ovarian histological subtypes and includes WT1, p16, DKK1, vimentin, p53, PR, TFF3, HNF1B and MDM2 and ARID1A and gives a probability based on the expression statuses [18]. In 2010, Kurman and Shih proposed a classification system of ovarian cancers into two types based on molecular features [19]. Type I tumours are low-grade and underpinned by *KRAS, BRAF* and *PTEN* mutations with microsatellite instability. Type II tumours, such as high grade serous, are genetically unstable with mutations in *TP53, BRCA1 and BRCA2* and are aggressive in nature. OCCC and endometrioid carcinomas are considered as Type 1 endometriosis related tumours with similar molecular features and are considered genetically stable (other subsets being LGSOC and germ cell or transitional cell-related (Mucinous and Brenner tumours) [20].

The standard of care treatments for OCCC patients involves major debulking surgery followed by six cycles of 3 weekly post-operative chemotherapy of paclitaxel combined with carboplatin, as per all epithelial ovarian cancers [21]. In advanced cases, no residual disease after chemotherapy is associated with improved overall survival (OS) [9], however overall the response rates to chemotherapy are lower in OCCC than in, for example, serous ovarian cancers; with overall survival times of 21.3 months compared to 40.8 months for HGSOC and progression free survival times of 9.6 months in OCCC compared to 16.1 months in serous ovarian carcinomas [22]. A retrospective cohort study of OCCC patients showed that 50% with stage III/IV disease had chemotherapy refractory or resistant disease compared to 9.7% of women with early stage disease [23]. Chemotherapy response rates in the recurrent setting range between 1–9% [24,25]. These studies highlight that other therapeutic strategies involving novel targeted agents would offer improvements over current chemotherapeutic regimens.

The advent of the availability of targeted therapies, widespread genetic testing, increase in clinical trials and international collaboration and working groups have significantly altered the treatment landscape for patients with ovarian cancer. However, this focus has mainly been on HGSOC and no specific OCCC therapies have been licensed to date. There have been limited targeted therapeutic studies specifically focussing on OCCC, in part due to the rarity of the disease and the fact that OCCC have a low frequency of *BRCA1/2* mutations, and although new agents such as Poly (ADP-ribose) Polymerase (PARP) inhibitors are approved for HGSOC, current clinical evidence for efficacy in OCCC is lacking. Increasingly, a greater understanding of the molecular pathogenesis and heterogeneity of cancer has led to the development of more effective treatment strategies in various tumour types. In this article, the recent advances in our understanding of the molecular characteristics and pathogenesis of OCCCs and how they may facilitate the development of targeted therapeutic strategies are reviewed.

2. Actionable alterations in OCCC

Molecular profiling of ovarian cancers has highlighted that the different histological subtypes of ovarian cancer are underpinned by distinct molecular profiles. In particular, non-epithelial histological ovarian cancers are underpinned by pathognomonic driver mutations i.e. *DICER1* mutations in Sertoli-Leydig tumours, *FOXL2* mutations in Granulosa cell tumours of the ovary and *SMARCA4* mutations in Small Cell tumours of the Ovary [105–110]. These studies have also shown that epithelial ovarian cancers are underpinned by different repertoires of mutations. For instance, HGSOC invariably harbours *TP53* mutations and immunohistochemistry of p53 is now used clinically to aid diagnosis [110]. Moreover, these HGSOC's harbour DNA repair related defects including *BRCA1* and *BRCA2* germline and somatic mutations. Low grade and mucinous serous ovarian cancers tend to harbour more frequent mutations in *BRAF* and *KRAS* and exhibit *ERBB2* amplifications. Ovarian clear cell and endometrioid tumours, whilst histologically distinct, harbour a similar mutational profile, with high frequencies of *ARID1A* mutations (around 40–57% in OCCC and 30% in endometrioid ovarian tumours) [41,42] (Table 1).

Table 1
Published frequency of common ovarian clear cell cancer (OCCC) mutations.

Gene	Reported frequency	Reference
ARID1A	35-57%	[41,42,84]
PIK3CA	20-51%	[43,47,100]
PTEN	5-13%	[47,48]
KRAS	9-20%	[48,100]
TP53	11-13%	[48,101]
CTNBB1	11%	[101]

Although the number of OCCC specific trials are low, a recent report of a 115 patient series in which some had received targeted therapies such as bevacizumab, nintedanib, PARP inhibitors or PI3K/MTOR inhibitors in the second line resulted in an objective response rate (ORR) of 30% for the whole cohort, suggesting that access to experimental therapy could improve response rates in recurrent disease [26]. The majority of recent efforts to target recurrent genetic alterations in OCCC have focussed on targeting ARID1A deficiencies, given the high frequency of mutations in the disease, however other studies have focussed on targeting angiogenesis and more recently the use of immunotherapeutic agents, (Table 2 and 3).

3. Targeting angiogenesis in OCCC

Anti-angiogenic agents inhibit the formation of blood vessels (angiogenesis) through inhibition of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) [27,28]. Gene expression profiling studies have highlighted the similarities between OCCC and with clear cell carcinoma (RCCC) of the kidney, where anti-angiogenic treatments are licensed for clinical use. In particular OCCC's show upregulation of the IL6-STAT3-HIF signalling pathway, which is involved in angiogenesis, in up to 49% of cases and as such, OCCC may

Table 2
Summary of published targets and pathways in OCCC.

Pathway	Target	Drug	Reference
ARID1A Synthetic lethality	ATR	AZD6738, VX-970	[69]
	BCR/ABL/SRC	dasatinib	[71]
	ROS induction	elesclomol	[102]
	BET (BRD2)	JQ1	[66]
	EZH2	GSK126	[60]
	HDAC	NK84, SAHA, vorinostat (pan-HDAC inhibitor), ACY1215 and anti-PD-L1 antibody	[63,64,65,103]
	PARP	talazoparib, olaparib	[68,104]
PI3K/AKT/mTOR	PI3K	buparlisib	[105]
	AKT	MK-2206	[105]
	mTORC1/2	AZD8055	[82]
Proteosome	Ubiquitin-proteasome system	bortezomib	[103]
Glutathione	Glutathione metabolism	APR-246	[73]

Table 3
Currently recruiting OCCC international clinical trials.

Title	Phase	Treatment	Primary Aims	Secondary Aims	Patients (n)	Molecular target	Trial Identifier
A Study of PLX2853 in Advanced Malignancies.	IB/IIA	PLX2853	PK, PD, DLT, AE	ORR, DOR, PFS, OS	166	BRD4	NCT03297424
Safety Study of MGD009 in B7-H3-expressing Tumors	I	MDG009	MTD	PK, Immunogenicity, change in tumour volume	200	DART	NCT02628535
Tazemetostat in Treating Patients with Recurrent Ovarian, Primary Peritoneal, or Endometrial Cancer	II	EPZ-6438 (Tazemetostat)	ORR	Response in ARID1A mutated cases, AE, PFS, OS	43	EZH2	NCT03348631
Ruxolitinib Phosphate, Paclitaxel, and Carboplatin in Treating Patients With Stage III-IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	I/II	carboplatin and paclitaxel +/- ruxolitinib	PFS, DLT	AE, Resection margins, pCR, OS	147	JAK-STAT	NCT02713386
Paclitaxel Albumin-Stabilized Nanoparticle Formulation and Bevacizumab in Treating Patients With Stage IV Melanoma That Cannot Be Removed by Surgery or Gynecological Cancers	I	Abraxane and bevacizumab	MTD	PFS, RR	36	microtubule inhibitor and VEGF-A	NCT02020707
Dual mTorc Inhibition in advanced/Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer (of Clear Cell, Endometrioid and High-Grade Serous Type, and Carcinosarcoma)	II	paclitaxel +/- TAK228	PFS	PFS, ORR, DOR	126	mTOR	NCT03648489
MV-NIS Infected Mesenchymal Stem Cells in Treating Patients With Recurrent Ovarian Cancer	I/II	oncolytic measles virus +/- infected mesenchymal stem cells (MV-NIS)	MTD, PFS	AE, OS	54	oncolytic virus	NCT02068794
MV-NIS or Investigator's Choice Chemotherapy in Treating Patients With Ovarian, Fallopian, or Peritoneal Cancer	II	MV-NIS vs. standard cytotoxic chemotherapy	OS	PFS, safety, AE, QOL	134	oncolytic virus	NCT02364713
Cediranib Maleate and Olaparib or Standard Chemotherapy in Treating Patients With Recurrent Platinum-Resistant or -Refractory Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	II/III	cediranib and olaparib	PFS, OS	ORR, AE, QOL	680	PARP, VEGF (1,2,3)	NCT02502266
BrUOG 354 Nivolumab +/- Ipilimumab for Ovarian and Extra-renal Clear Cell Carcinomas	II	nivolumab +/- ipilimumab	PFS	PFS	62	PD-1 and CTLA4	NCT03355976
Nivolumab and Ipilimumab in Treating Patients With Rare Tumors	II	Nivolumab and Ipilimumab	ORR	AE, BOR, CBR, OS, PFS	707	PD-1 and CTLA4	NCT02834013
A Multicentre Phase II Trial of Durvalumab Versus Physician's Choice Chemotherapy in Recurrent Ovarian Clear Cell Adenocarcinomas	II	Durvalumab vs standard cytotoxic chemotherapy	PFS	ORR, OS, AE, QOL	46	PD-L1	NCT03405454
Metformin and Chemotherapy in Treating Patients With Stage III-IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	II	metformin and standard chemotherapy with metformin continuation for 2 years	PFS	CA125 response, AE	160	Respiratory chain complex	NCT02122185
Use of Regorafenib in Recurrent Epithelial Ovarian Cancer	II	regorafenib	PFS	OS, ORR, AE	43	VEGFR, Kit, RET, BRAF, PDGFR, FGFR	NCT02736305
Study Of Nintedanib Compared To Chemotherapy in Patients With Recurrent Clear Cell Carcinoma Of The Ovary Or Endometrium (NiCCC)	II	nintedanib (BIBF1120) vs. standard cytotoxic chemotherapy	PFS	OS, DCR, QOL, RR, AE	120	VEGFR, PDGFR, FGFR	NCT02866370

preferentially benefit from targeted anti-angiogenic therapy [29,30]. A number of studies have therefore tried anti-angiogenics in OCCC, however the majority of these have showed limited efficacy. The GOG-254 study investigating sunitinib (a VEGFR and PDGFR inhibitor) demonstrated limited activity with an ORR of 6.7% in a phase II trial of 35 patients with recurrent OCCC setting, with a median PFS of 2.7 months and median overall survival of 12.8 months (GOG-254) [31]. The NRG-GY001 phase II study of single agent Cabozantinib, (a VEGFR, MET and RET kinase inhibitor) in patients with recurrent OCCC assessed 13 patients and resulted in a median PFS of 3.6 months and an overall survival of 8.1 months. Toxicities included a grade 5 thromboembolic event and no objective tumour responses were seen; although one patient received Cabozantinib for 23 cycles and remained on treatment at the point of data cut off [32]. The international phase II trial investigating ENMD-2076, an oral multi-target kinase inhibitor against Aurora kinase-A and potent anti-angiogenic activity against VEGFR, in unselected OCCC, did not meet its pre-set alternative hypothesis of a 6-month PFS rate of 40% compared to a null hypothesis of 20%, reaching a PFS rate of 22% at 6 months [33]. Of note however a subgroup analysis identified that patients with ARID1A protein loss correlated with a better PFS on ENMD-2076, with ARID1A loss of expression patients showing a 33% PFS rate compared with a 12% PFS rate in the ARID1A IHC positive population, $p = 0.023$). The mechanistic basis behind this finding is however unknown. A number of other trials in ovarian cancer are investigating angiogenesis (Table 3) including a randomised Phase II multi-centre international study of nintedanib (BIBF 1120), versus chemotherapy in recurrent OCCC or the endometrium [34] (Table 3). Nintedanib is a novel, orally available, potent triple angiokinesis inhibitor that mainly blocks VEGFR 1–3, FGFR 1–3 and PDGF receptor α and β. The assessment of plasma levels of CRP, IL-6, soluble VEGF and soluble VEGFR, and associated correlation with response, PFS and OS will be studied within the NiCCC (ENGOT-GYN1) trial [34].

There are perhaps a number of reasons why there has been no real response seen with these anti-angiogenic drugs to date in OCCC. The patient characteristics and differences in biology (increased frequency in ARID1A/ PI3K pathway alterations in OCCC and lack of VHL mutations compared to RCC) may explain the limited efficacy as single agent treatment. The regimens e.g. sunitinib (4:2) 4 weeks on and 2 weeks off (GOG-254) may not have been optimally tolerated. For example in RCC, clinicians initially used this scheduling but can now opt for a variation in scheduling 2:1, with better tolerance. None of these trials had pre-selected stratification of anti-angiogenic markers and their translational work is still awaited. Detailed genomic information from these patient biopsies is critical to understanding responses and resistance mechanisms and for the Identification of predictive biomarkers specifically for nintedanib or for other VEGR pathway inhibitors, of which have not yet been established for use in clinical practice. Soluble VEGFR2 however has been shown to decrease over the first 4 weeks of nintedanib treatment, highlighting a potentially useful blood biomarker of response [34].

4. Targeting the copy number landscape of OCCC

On the whole, unlike HGSOC, OCCC are not characterised by high levels of genomic instability in agreement with the lower frequency of germline *BRCA1/2* mutations seen in these cancers [35]. Copy number profiling of a series of 50 OCCC's using microarray comparative genomic hybridisation, found that OCCC's could be classified into two distinct clusters, according to their pattern of copy number alterations, a surrogate of the degree of genomic instability. These clusters were identified with different clinical outcomes, with cluster 1 having a higher prevalence of 'complex-sawtooth' (multiple focal gains and losses) and 'firestorm' (i.e. high-level amplification) patterns [36], and a shorter median progression-free survival compared to cluster 2, comprising of simple genomic patterns (whole chromosomal arm gains and losses), (11 vs. 65 months, $p = 0.009$). Of note, cluster 1 was found to have recurrent amplifications of the human epidermal growth factor receptor 2 (*ERBB2HER2)* [37].

Indeed, amplification of certain genomic loci, make these attractive as potential therapeutic targets [37]. These include recurrent amplifications of the 17q12 locus which encompasses HER2 seen in 14% of OCCC, suggestive that HER2 amplified patients could be treated with HER2 targeted therapies akin to breast cancer. Previous phase II studies have examined the effectiveness of trastuzumab monotherapy in recurrent EOC with HER2 overexpression, however an overall response rate of only 7% was observed [38]. Single agents targeting HER2 are however often ineffective, whereas further benefit has been seen in combination therapies (targeting multiple HER receptors) or antibody drug conjugates, such as trastuzumab emtansine (T-DM1) in breast cancer [39]. Future studies are however warranted to test the effectiveness of such combinations of anti-HER2 agents in combination with chemotherapy or other targeted agents in OCCC.

Amplification and overexpression of the anti-apoptotic protein, *PPM1D* at 17q23, has also been documented in around 10% of OCCC [40]. PPM1D is an oncogenic phosphatase which functions by negatively regulating p53, Chk2 and ATM. In cell line models PPM1D has been shown to be selectively required for the growth of *PPM1D* amplified OCCC cell lines, highlighting its potential as a novel target [40]. However, to date no clinically available inhibitors against *PPM1D* have been successfully developed despite considerable effort.

5. Targeting the mutational landscape of OCCC

Genetically, 85% of OCCCs have wild-type *TP53* and a lower frequency of *BRCA1* and *BRCA2* germline mutations [35] compared to HGSOC, meaning newly approved strategies such as PARP inhibitors in the context of germline *BRCA1/2* mutations may be limited clinically use for these patients. The most significant finding to come from the molecular characterisation of OCCC is the identification of *ARID1A* truncating mutations in 40–57% of this disease, making it the highest frequency recurrent alteration in OCCC [41–43].

Although *ARID1A* mutations are the most frequent molecular alteration in OCCC, there are a number of additional recurrent alterations that also occur in patients (Table 1). These may thus represent excellent targets for combinatorial therapies for patients, (Table 2) and may highlight the underlying biology of this disease. PI3-kinase pathway alterations are known to be common in OCCC, with a number of studies identifying a mutation rate between 29–40% involving *PIK3CA* [41,43,44], often co-occurring with *ARID1A* loss in up to 71% of cases and in adjacent endometriosis [45]. This is consistent with an in vivo genetically engineered mouse model (GEMM) that was developed by Chandler et al, where both *ARID1A* and *PIK3CA* mutations were required to initiate tumour formation [46]. In addition, *PTEN* mutations have been described in 5–13% of OCCC cases [47,48], although at the protein level, loss of PTEN expression has been seen in up to 37.5% of cases [49]. *KRAS* mutations have been reported in 9–20% of OCCC cases [47,48].

Molecular profiling of one of the largest cohorts to date of 125 OCCC cases using the FoundationOne® panel identified a number of potentially actionable genomic alterations. Forty five percent of samples originated from primary sites and 13.6% from regional metastatic sites (peritoneum, fallopian tube, pelvis or uterus) and 40.8% distant metastatic sites [50]. The most frequent mutation was *PIK3CA* (52.8%) followed by *ARID1A* (51.2%) with 69% of the samples having an alteration in at least one component of the mTOR pathway, (including *PIK3CA, AKT2* (7.2%), *PTEN* (5.6%), *FBXW7* (5.6%), *PIK3R1* (4.8%), *STK11* (3.2%), *MTOR* (1.6%), *AKT1* (1.6%), *AKT3* (1.6%), *TSC2* (1.6%), *TSC1* (0.8%), *NF1* (0.8%) and *RICTOR* (0.8%). In cases with *ARID1A* loss 56% had co-occurring *PIK3CA* mutations. These results highlight the potential benefit of targeting the mTOR pathway in patients with OCCC.

6. Synthetic lethal approaches for targeting *ARID1A* loss of function mutations

ARID1A mutations were first identified from the seminal study from Wiegand *et al*, who analysed the transcriptome of endometriosis-associated ovarian carcinomas using RNA-sequencing and identified *ARID1A* mutations in 55 out of 119 OCCCs (46%), 10 out of 33 endometrioid (30%) and none in 76 HGSOC cases [42]. In two cases, the presence of the mutation and the loss of expression of the encoded ARID1A protein were found in the tumour, contiguous atypical endometriosis but not in the distal endometriosis lesions, suggesting that *ARID1A* mutations may be an early event in endometriosis associated cancer. The vast majority of *ARID1A* mutations are inactivating; i.e. either a frameshift mutation or the introduction of a premature stop codon, leading to early protein termination and as a result lead to protein truncations and loss of protein expression. The majority of ARID1A mutations in OCCC are not associated with tumour loss of heterozygosity (LOH) suggesting that ARID1A is haploinsufficient [42]. OCCCs that are *ARID1A* mutant often have co-existing mutations in the PI3K/AKT signalling pathway by having gain of function mutations in the *PIK3CA* oncogene or loss of function mutations in *PTEN* [45].

The *ARID1A* gene is located on chromosome 1p35.11 and encodes for a protein (ARID1A, aka BAF250A) that forms a key DNA binding subunit in the ATP dependent BAF SWI/SNF chromatin-remodeling complex [51]. BAF modulates nucleosomes, allowing the winding of DNA around histone cores providing access to the DNA to enable transcription, DNA repair and replication [41,52,53]. Loss of function of ARID1A leads to aberrant cell cycle and loss of proliferation control [54]. In a study analysing 18 tumour types, nearly 20% of human cancers have mutations in the genes encoding the SWI/SNF complex [55] making it the most commonly mutated chromatin remodeling complex in cancer.

As mutations in *ARID1A* are loss of function, the rationale to target ARID1A defective OCCC lies on synthetic-lethal approaches. This is where a defect in either one of two genes has little deleterious effect on a cell but a combination of defects in both genes causes cell death [56]. The archetypal example of synthetic lethality is that of *BRCA1/2* deficient tumours, which leads to a deficiency in the homologous recombination (HR) DNA double-strand break (DSB) repair pathway. By losing HR, cells are unable to repair the DNA lesions caused by Poly (ADP-Ribose) Polymerase (PARP) inhibitors [57].

Synthetic lethal approaches have been used to identify genetic and drug synthetic lethal effects associated with *ARID1A* defects (Fig. 1). Project Achilles utilised a broad screening approach to identify essential genes in a large cohort of cancer cell lines. *ARID1B,* an *ARID1A* homolog whose gene product is mutually exclusive with ARID1A in SWI/SNF complexes, was identified as the number one gene preferentially required for the survival of *ARID1A*-mutant cell lines [58]. *ARID1A*-deficient cancers were found to retain at least one functional *ARID1B* allele [59], and by using shRNA knockdown of *ARID1B* in *ARID1A*-deficient cells, Helming et al. showed that loss of ARID1B destabilised the SWI/SNF complex and impaired the proliferative rate of ARID1A defective tumour cells. However, to date no therapies have been developed that target ARID1B.

6.1. Epigenetic targeting of ARID1A deficiency

Using a small molecule screen of epigenetic inhibitors, Bitler et al. highlighted the potential of targeting the antagonistic activity between SWI/SNF and the enhancer of zeste homolog 2 (EZH2) methyltransferase with the EZH2 small molecule inhibitor GSK126, which triggers apoptosis in *ARID1A* mutated cells [60]. EZH2, is the catalytic subunit of the polycomb repressive complex 2, and silences gene expression through the trimethylation of histone H3 lysine 27 (H3K27me3) [61]. This synthetic-lethal association, was found to be mediated via upregulation of *PIK3IP1*, a direct target of EZH2, and selectivity was further enhanced upon inhibition of PI3K-AKT signaling [60]. Interestingly, identification of SWI/SNF catalytic subunit switching has been shown to drive resistance to EZH2 inhibitors in *ARID1A* mutated cells, specifically the switch of the mutually exclusive catalytic subunits SMARCA4 to SMARCA2. Consequently, this subunit switching leads to upregulation of the direct SMARCA4 target BCL2 (also an ARID1A target gene), leading to hypersensitisation of EZH2 resistant *ARID1A* mutant cells to the BCL2 inhibitor (ABT263). Combination treatment with both EZH2 (GSK126) and BCL2 inhibitors (ABT263) led to significant tumour regression in an in vivo *GEMM* model (*Arid1a*$^{fl/fl}$*;(Gt) Rosa26Pik3ca*H1047R*) [62].

Further work has indicated that pre-clinically, *ARID1A* mutant OCCC are selectively sensitive to HDAC2 inhibition. HDAC2 co-represses EZH2 leading to downregulation of the tumour supressor PIK3IP1, thus inhibiting proliferation and promoting apoptosis [63]. As a result, ARID1A defective cells are selectively sensitive to the pan HDAC inhibitor vorinostat. Subsequent work by Bitler et al. has shown that *ARID1A*-mutated ovarian cancer models are selectively dependent on HDAC6 activity, due to HDAC6 upregulation in *ARID1A* mutant cells that mechanistically inactivates the apoptosis-promoting function of *TP53* due to deacetylation of histone lysine 120 [64]. This work showed that treating *ARID1A*-mutated tumours with the small molecule HDAC6 inhibitor, ACY1215, had a significant survival benefit in vivo. Inhibition of HDAC6, with ACY1215 has been shown to synergise with anti-PD-L1 immune checkpoint blockade in ARID1A inactivated ovarian cancer.

Fukumoto et al identified that ARID1A directly repressed transcription of *CD274*, with combination treatment in an OCCC GEMM model showing reduction in tumour burden and improved survival as a result of activation and stability of interferon-gamma positive CD8 T cells [65]. The NRG-GY-014 phase II clinical trial, assessing the EZH2 inhibitor tazemetostat in recurrent endometrioid/clear cell carcinoma

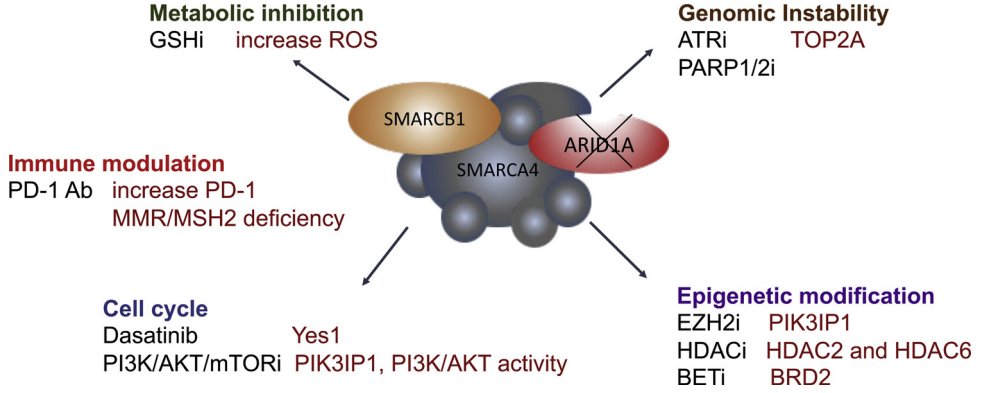

Fig. 1. Summary of synthetic lethal targeting strategies of ARID1A deficiency. Inhibitors are listed and specific target or mechanistic rationale in red.

of the ovary or peritoneum, and recurrent low grade endometrioid endometrial adenocarcinoma has recently opened (Table 3) and combination strategies are likely to follow.

Recent high-throughput siRNA screens focussing on the kinome in a large panel of OCCC tumour cell lines identified the bromodomain protein BRD2, that functions to bind to acetylated histone tails and promote gene transcription, as essential for survival of *ARID1A* mutant cells [66]. As predicted *ARID1A* mutant cells showed enhanced sensitivity to the BET domain (bromodomain and extra terminal domain) inhibitors JQ1 and iBET-762, that work by blocking binding of BRD proteins to acetylated lysine recognition motifs on acetylated histones [66]. Interestingly inhibition of BRD2 specifically led to a reduction in ARID1B and SMARCC2 and SMARCE1 suggesting that BRD inhibition can interfere with SWI/SNF function by affecting the transcription of multiple components of this multi-protein complex.

Taken together the studies outlined above suggest that epigenetic targeting of ARID1A defective OCCC could be of clinical benefit. Currently EZH2 inhibitors are in clinical trials (Table 3) [67] and HDAC inhibitors such as vorinostat have been approved for T-cell lymphoma and in clinical trials in many other tumour types. Equally several BET inhibitors are currently in phase II trials.

6.2. Targeting DNA damage response pathways in ARID1A defective tumours

ARID1A is recruited to double strand DNA breaks, (DSBs), via its interaction with Ataxia telangiectasia and RAD3-related protein (ATR) [68]. ATR is involved in DNA repair, specifically where the DNA damage caused results in tracts of single stranded DNA, such as occurs at stalled or collapsed replication forks. In addition to initiating the DNA repair processes that repair and restart replication forks, ATR also prevents the firing of latent replication forks (that would otherwise enhance replication fork stress) and causes cell cycle arrest, thus preventing cells from progressing into mitosis in the presence of damaged DNA. Shen and collegues identified that ARID1A helps DSB processing to create replication protein A (RPA)-coated single strand DNA (ssDNA) and sustains ATR activation in response to DSBs. Therefore, cells that are ARID1A deficient have impaired DNA damage checkpoint regulation [68]. As a result, this impaired G_2/M DNA damage checkpoint activation and defect in the repair of DSB causes sensitivity to the PARP inhibitor talozaparib, both in vitro and in vivo [68].

A high throughput RNAi screen in the normal breast epithelial cell line MCF12A and triple-negative breast cancer cell line HCC1143, demonstrated that loss of *ARID1A* caused sensitivity to ATR inhibitors [69]. ATR inhibition caused increased anaphase bridges, DNA double strand breaks and apoptosis in *ARID1A*–deficient cells [69]. The drug sensitivity was also validated in in vivo models of ARID1A defective cancers [69]. Loss of function of ARID1A results in the inability to recruit topoisomerase II (TOP2A) to chromatin [107] and delayed cell cycle progression [69]. The normal role of TOP2A is in decatenating complex DNA structures prior to the division of the nuclear material at mitosis. Targeting ARID1A defective cells with an ATR inhibitor, in the absence of this normal TOP2A function, caused cells to progress into mitosis prior to the resolution of DNA damage [69].

Given that ARID1A loss results in TOP2A deficiency and cell cycle defects also leads to an increased reliance on the ATR checkpoint, by combining ATR inhibitors together with PARP inhibitors is thought to increase the number of cells entering mitosis prematurely with defective DNA, resulting in mitotic catastrophe. This approach may also halt the onset of therapy resistance. Phase I and early phase II trials have already been initiated investigating this combination and identification of a cohort that may do particularly well with the combination is of great interest. An international academic phase II trial of ATR inhibition in combination with a PARP inhibitor in ARID1A-stratified gynaecological cancers (ENGOT-GYN1/NCRI/ATARI) will test the hypothesis that ATR inhibition alone will be efficacious in ARID1A mutant tumours. More recently, combination treatment with low-dose radiation and the PARP inhibitor olaparib greatly improved anti-tumour efficacy, resulting in long-term remission in mice bearing ARID1A-deficient tumours [70].

Taken together, these studies highlight that perturbations of the DNA repair balance associated with ARID1A-deficiency can be exploited to develop highly specific anticancer treatments [70], and highlight the fact that PARP inhibitors that are already approved for platinum-sensitive HGSOC, may be able to be repurposed for OCCC, either as single agent or in combination with other therapies.

6.3. Additional ARID1A synthetic-lethal approaches

Miller et al used a focused high throughput drug screen in 12 OCCC cell lines looking for *ARID1A* synthetic lethality, with dasatinib, a multi-target kinase inhibitor, identified as selective for *ARID1A* mutant OCCC cell lines [71]. Both short-term and long-term drug sensitivity assays and isogenic model cell line work showed significant selectivity for *ARID1A* mutant cells. Proteomic assessment using sepharose-linked dasatinib beads identified YES1, (a target of dasatinib) to be significantly enriched in the *ARID1A* mutant cells. *ARID1A* mutant models were found to have a significant increase in G_1 arrest compared to wild-type models and dasatinib sensitivity in *ARID1A* mutant OCCC cell lines was found to be p21 and Rb dependent and characterized by an apoptotic response. On the basis of this data, a phase two trial looking at dasatinib in recurrent ovarian (including OCCC) and endometrial clear cell carcinoma characterising retention or loss of ARID1A expression opened in 2014 with an aim to recruit 35 patients (NCT02059265, Table 3).

A recent study has highlighted the role of altered cellular metabolism as an effective therapeutic strategy in ARID1A deficient cells. In particular, *ARID1A*-mutant OCCC cells were shown to have lower levels of SLC7A11, one component of cystine/glutamate transporter XCT thus rendering basal levels of glutathione (GSH) low. The XCT complex imports cystine into the cell in exchange for glutamate, and the cystine is reduced to cysteine and used by glutamate cysteine ligase (GCL) to produce reduced glutathione (GSH). Within the cell there is an intricate balance between GSH and reactive oxygen species (ROS) levels in order to maintain cellular homeostasis. Disruption of this balance via reduced GSH leads to higher ROS levels and further perturbation of this balance with GSH specific inhibitors such as APR-246 causes cell death, due to unbearable levels of ROS accumulation [72,73].

7. PPP2R1A mutations in OCCC

Although *ARID1A* mutations are the most prevalent mutations in OCCC, there are a number of other mutations that have been identified as potential drivers, including *PPP2R1A* seen in 7.1% of OCCC [41]. *PPP2R1A* codes for Protein phosphatase 2A (protein phosphatase 2, regulatory subunit A), which is a serine-threonine phosphatase that is highly conserved and ubiquitously expressed in human tissue [74]. PP2A is formed of three subunits, all of which have at least two isoforms [75]. Subunit A contains one of two isoforms, α encoded by *PPP2R1A* and β encoded by *PPP2R1B* and forms the structural subunit, which stabilises the whole complex. PP2A maintains cellular homeostasis by negatively regulating signalling pathways that have been initiated by protein-kinases. Specifically, PP2A is required for chromosome segregation through its interactions with Bub1 and Sgo1 [76]. *PPP2R1A* mutations are heterozygous and cluster at particular hotspots: p. R183W, p. R183 G and p. R182W, suggesting that it may function as an oncogene. The two arginine residues that are mutated in OCCC are highly conserved and reside within one of the Huntington, elongation factor 3, PP2A, TOR (HEAT) domains of *PPP2R1A* that are involved in binding regulatory subunits [41]. Mutations affecting both isoforms of *PP2A* subunit A, have been identified in a variety of tumours: *PPP2R1A* (breast, lung, melanoma) and *PPP2R1B* (breast), albeit at a low

frequency [77]. Although *PPP2R1A* displays the mutation profile that would impart oncogenic function, its role is not established in OCCC. However, in uterine cancers *PPP2R1A* hotspot mutations have been shown to trigger hyperphosphorylation of oncogenic PP2A-B56/B' substrates in the GSK3β, AKT, and mTOR/p70S6K signalling pathways, suggesting that PI3K pathway inhibition may be a useful therapeutic strategy, however this hasn't been formally tested to date [78]. Interestingly in haematological malignancies, such as chronic myeloid leukaemia, *PPP2R1A* is postulated to be a tumour suppressor, with restoration of functional PP2A possible with PP2A activating drugs such as forskolin [79].

8. Targeting the PI3K pathway

Activation of the phosphatidylinositol 3-kinase (PI3K)/AKT/ mammalian target of rapamycin (mTOR) pathway is known to play an important role in the pathogenesis of OCCC, and is involved in a number of cellular functions required for cancer cells to sustain proliferation, cell adhesion and apoptosis, and regulates G1 cell cycle progression in ovarian cancer cells [80]. Overall as the PI3K/AKT/mTOR signalling pathway is more frequently activated in OCCCs [81], it would suggest that therapeutic inhibition of the pathway would be a viable targeted approach to treatment. Although a significant enrichment of co-existing *PIK3CA* and *PTEN* mutations have been associated with *ARID1A* mutations in OCCC (Table 1), suggesting there may be a synthetic-lethal relationship between PI3K pathway activation and ARID1A loss, this has not been substantiated in patient derived models [82]. However, it is clear from the use of orthotopic genetically engineered mouse models (GEMMs), that *PIK3CA* activation is needed concurrently with inactivation of *ARID1A* to give rise to highly penetrant tumours with OCCC histopathology [46]. In this GEMM model, the animals had a base-line median survival of around 7.5 weeks and treatment with BKM120, a pan-PI3K inhibitor led to improved survival of 11 weeks, demonstrating efficacy with this targeted approach [46]. In the context of clinical trials in human OCCC patients, the GOG268 Japanese phase II study assessing first-line carboplatin and paclitaxel with the addition the mTOR inhibitor temsirolimus in patients with Stage III-IV OCCC, was a well-tolerated regimen with 54% of optimally debulked patients having a PFS greater than 12 months, however, this was not statistically significant compared to historical controls. A recently published case report described a 36-year-old relapsed OCCC patient, who had 3 alterations in *PTEN* and *PIK3CA* who derived 27 months of benefit from everolimus, in the 4th line setting after genomic profiling of her liver metastatectomy [50]. A Japanese study had one relapsed OCCC patient out of 6 treated with temsirolimus who managed a partial response for 14 months [83]. There are now a number of trials in ovarian cancer (not OCCC specific) looking at AKT inhibitors (single agent AZD5364, NCT01226316; MK2206, NCT01283035), PI3K inhibitor and MEK inhibitor combinations (BKM120 and MEK162, NCT01363232), PI3K inhibitor and PARP inhibitor (BKM120 or BYL719 and Olaparib, NCT01623349) and a PI3K/HDAC inhibitor (CUDC-907, NCT02307240). However, these studies and trails have not correlated findings to ARID1A status to date.

9. ARID1A alterations as patient selection biomarkers for clinical trials

Given the high frequency of *ARID1A* defects in multiple tumour types that may be eligible for treatment, translation of the synthetic-lethal findings into clinical trials highlights that *ARID1A* assessment for patient stratification is an area of unmet need. One obvious way to do this, is through targeted sequencing approaches, however *ARID1A* mutational analysis alone is not straightforward as there are no "hotspot mutations" and the entire gene will need to be sequenced. Furthermore, mutational analysis will not incorporate post-translational modifications that may impact on the functionality of *ARID1A*. Therefore, a surrogate biomarker of mutational status such as IHC is needed. Although IHC has been shown to be a useful tool in predicting *ARID1A* mutational status in the research setting there is no uniform scoring system or specific antibody that is recommended for clinical use to date. Work from our lab has systematically assessed a number of commercially available antibodies and identified EPR13501 as a robust biomarker of *ARID1A* status with a cut-off of < 8 identifying mutated cases, using our optimised scoring system [84]. This will be useful for recruiting patients for clinical trials based on *ARID1A* mutational status. The ENGOT-GYN1/NCRI/ATARI that utilises our findings is planned to open in 2019 using this approach, allowing validation and evaluation of the IHC scoring system in the context of a prospective clinical trial.

Currently there are no clinical trials recruiting patients that prospectively assess *ARID1A* mutational status. However, there are a number of early phase trials investigating *ARID1A* mutational status and response to therapy, the first of which allocates treatment to patients with advanced solid tumours whose biopsies are sequenced as part of ongoing clinical sequencing programmes outside of the remit of the clinical trial [85]. Patients with *PIK3CA*, *AKT* or *ARID1A* mutations will receive olaparib with the AKT inhibitor AZD5363. Table 3 highlights a number of current clinical OCCC trials including a randomised phase II study of nintedanib compared to chemotherapy in patients with clear cell carcinoma of the ovary or endometrium, which will assess *ARID1A* mutational status retrospectively and correlate with outcome [34] and a trial assessing dasatinib in patients with recurrent or persistent ovarian, fallopian tube, endometrial or peritoneal carcinoma which will retrospectively compare ARID1A mutational and IHC status [86]. These trials highlight that prospectively assessing *ARID1A* mutational status is potentially cost-prohibitive and the turnaround time can make it difficult for trial recruitment. Upfront sequencing costs are still expensive and time-consuming for the majority of academic trials, whereas the costs and practicalities of IHC are more realistic, in particular given the need for many of these patients to start therapy soon due to the rapid nature of disease progression and limited life expectancy.

10. Emerging role of the immune landscape in OCCC

The immune microenvironment is now considered to be of importance in both tumour development and pathogenesis. The ability of a tumour to evade immune destruction has led to it being described as an emerging hallmark of cancer [87]. Immuno-oncology is a new approach to cancer treatment enabling the body's immune system (T cells) to detect and attack cancer cells with the potential to deliver long-term responses, via the enhancement of T cell activation or reversal of tumour-induced T cell inhibition. Several of these agents, such as antibodies targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor 1 (PD-1) have already demonstrated significant promise in other tumour types in clinical trials [88].

Programme death 1 (PD-1) and programmed death ligand 1 (PD-L1) monoclonal antibodies have been trialled in the recurrent ovarian cancer setting with only modest response rates of up to 15%, although no specific biomarkers have been identified [89]. Findings from various cancer types highlight that mechanisms underlying the tumour immune response are extremely complex and involve many different aspects of the host immune system, tumour microenvironment, tumour genomics, and cytokine/vascular milieu [90]. PD-L1 expression is associated with poorer prognosis in ovarian cancer patients [91] and promotes peritoneal dissemination of ovarian cancer [92]. Interestingly, a Phase II study investigating best overall response using Nivolumab (an anti-PD-1 antibody that blocks PD-1 signalling) in 20 platinum resistant ovarian cancers had two patients with a durable complete response, of which one was an OCCC patient who had a maintained complete response for more than a year and ongoing at time of publication, although PD-L1 expression was not described [93].

Studies have shown that mismatch repair deficiency (MSI), caused

by defects in the DNA of mis-match repair (MMR) genes, is independently predicative of response to PD-1 blockade. Pembrolizumab has been approved as a single agent for cancers with microsatellite instability regardless of tumour site of origin based on five clinical trials as part of the KEYNOTE trial series (this is the first FDA tissue/site-agnostic approval [94]). Indeed, MSI is seen in around 14% of OCCC's with strong correlation between alterations in the protein expression of hMLH1 and hMSH2 [95]. Given that immunohistochemical testing is routine in diagnostic laboratories this may be a practical upfront test that may guide treatment and could change the landscape of access to immuno-oncology drugs. Recent work has demonstrated that *ARID1A* deficiency is related to a mis-match repair phenotype with *ARID1A* mutant tumours showing an increase in CD8 + TILS and activation of the immune checkpoint via upregulation of *Pdcd1* (which encodes for PD-1) and sensitization to PD-L1 checkpoint blockade therapy in vivo compared to *ARID1A* wild-type tumours in an ID-8 *ARID1A* deficient ovarian orthotopic model. A proteomic screen identified an interaction between MSH2 and ARID1A, with ARID1A recruiting MSH2 to chromatin during DNA replication, promoting MMR. In the ARID1A deficient setting, MMR was compromised and a C > T mutation pattern (seen commonly in MMR-deficient tumours [96]) and increased mutational load was observed [97]. A phase II study (NCT01876511) evaluated the efficacy of pembrolizumab, a PD-1 inhibitor, in 86 patients with advanced MMR-deficient cancers encompassing 12 tumour types. Disease control was achieved in 77% of patients and complete responses were seen in 21% of patients. This is likely related to the large number of mutation-associated neoantigens (MANAs) seen in MMR deficient cancers, which predicts response of solid tumours to PD-1 blockade [98].

11. Discussion

There is a clear unmet clinical need for OCCC patients that show poor responses to chemotherapy. There have been a number of advances in the understanding of the molecular background of OCCC in the last decade, especially with *ARID1A* synthetic lethal approaches. Being able to robustly identify patients who may benefit from targeted therapy will be of the paramount importance. The use of robust biomarkers such as ARID1A IHC will allow patients to be easily streamlined into appropriate trials. The upcoming ENGOT-GYN1/NCRI/ATARI phase II trial (NCT04065269), looking at the ATR inhibitor, AZD6738 + /- olaparib in the recurrent OCCC setting, will use this approach to select patients with ARID1A deficiency upfront to direct treatment. There is a role for smaller proof of concept phase II studies specifically in OCCC due to the rarity of the disease, which will require international collaboration in order to accrue patients and obtain results in a timely fashion. Changing how we approach clinical trials means strategic designs including use of basket trials will help the field move forward. These are a novel approach to clinical trial design based on the hypothesis that the presence of a molecular marker (independent of tumour histological subtype) is predictive of response to therapy [99]. Therefore, patients will be enrolled based on a molecular diagnostic test rather than tumour type. A recent example of this type of approach is testing of PD-1 status in patients with deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) tumours, based on the above clinical trial, NCT01876511) which confirmed that dMMR is predictive of response to PD-1 blockade in solid tumours and has led to the approval of pembrolizumab for dMMR patients, irrespective of histology [98]. The upcoming NRG-GY-014 trial, in the recurrent ovarian cancer setting assessing the EZH2 inhibitor tazemetostat will be eagerly awaited. There is also great interest in PARP inhibitors, angiogenic and immunotherapy approaches. Combination treatments are likely to be required to circumvent the emergence of resistance and to improve on response rates. In the context of OCCC immunotherapy trials, retrospective assessment of the response with tumour mutational burden, MSI and *ARID1A* status will be needed to evaluate which patient populations are likely to benefit from these therapies.

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References

[1] G.C. Jayson, E.C. Kohn, H.C. Kitchener, J.A. Ledermann, Ovarian cancer, Lancet 384 (9951) (2014) 1376–1388.
[2] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, Int. J. Cancer 136 (5) (2015) E359–86.
[3] M. Sant, M.D. Chirlaque Lopez, R. Agresti, M.J. Sanchez Perez, B. Holleczek, M. Bielska-Lasota, N. Dimitrova, K. Innos, A. Katalinic, H. Langseth, N. Larranaga, S. Rossi, S. Siesling, P. Minicozzi, E.-W. Group, Survival of women with cancers of breast and genital organs in Europe 1999-2007: results of the EUROCARE-5 study, Eur. J. Cancer 51 (15) (2015) 2191–2205.
[4] S.F. Serov, R.E. Scully, L.H. Sobin, International Histologic Classification of Tumours. No. 9. Histologic Typing of Ovarian Tumours, World Health Organisation, Geneva, 1973.
[5] W.G. McCluggage, My approach to and thoughts on the typing of ovarian carcinomas, J. Clin. Pathol. 61 (2) (2008) 152–163.
[6] J.K. Chan, D. Teoh, J.M. Hu, J.Y. Shin, K. Osann, D.S. Kapp, Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers, Gynecol. Oncol. 109 (3) (2008) 370–376.
[7] M. Kobel, S.E. Kalloger, D.G. Huntsman, J.L. Santos, K.D. Swenerton, J.D. Seidman, C.B. Gilks, V.B.C. Cheryl, Brown Ovarian Cancer Outcomes Unit of the British Columbia Cancer Agency, Differences in tumor type in low-stage versus high-stage ovarian carcinomas, Int. J. Gynecol. Pathol. 29 (3) (2010) 203–211.
[8] S. Saito, H. Kajiyama, Y. Miwa, M. Mizuno, F. Kikkawa, S. Tanaka, T. Okamoto, Unexpected ovarian malignancy found after laparoscopic surgery in patients with adnexal masses–a single institutional experience, Nagoya J. Med. Sci. 76 (1-2) (2014) 83–90.
[9] M. Takano, Y. Kikuchi, N. Yaegashi, K. Kuzuya, M. Ueki, H. Tsuda, M. Suzuki, J. Kigawa, S. Takeuchi, H. Tsuda, T. Moriya, T. Sugiyama, Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging, Br. J. Cancer 94 (10) (2006) 1369–1374.
[10] A.G. Montag, E.L. Jenison, C.T. Griffiths, W.R. Welch, P.T. Lavin, R.C. Knapp, Ovarian clear cell carcinoma. A clinicopathologic analysis of 44 cases, Int. J. Gynecol. Pathol. 8 (2) (1989) 85–96.
[11] L.A. Brinton, L.C. Sakoda, M.E. Sherman, K. Frederiksen, S.K. Kjaer, B.I. Graubard, J.H. Olsen, L. Mellemkjaer, Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors, Cancer Epidemiol. Biomarkers Prev. 14 (12) (2005) 2929–2935.
[12] K. Yamaguchi, M. Mandai, S. Toyokuni, J. Hamanishi, T. Higuchi, K. Takakura, S. Fujii, Contents of endometriotic cysts, especially the high concentration of free iron, are a possible cause of carcinogenesis in the cysts through the iron-induced persistent oxidative stress, Clin. Cancer Res. 14 (1) (2008) 32–40.
[13] A.W. Kurian, R.R. Balise, V. McGuire, A.S. Whittemore, Histologic types of epithelial ovarian cancer: have they different risk factors? Gynecol. Oncol. 96 (2) (2005) 520–530.
[14] B.M. Norquist, M.I. Harrell, M.F. Brady, T. Walsh, M.K. Lee, S. Gulsuner, S.S. Bernards, S. Casadei, Q. Yi, R.A. Burger, J.K. Chan, S.A. Davidson, R.S. Mannel, P.A. DiSilvestro, H.A. Lankes, N.C. Ramirez, M.C. King, E.M. Swisher, M.J. Birrer, Inherited mutations in women with ovarian carcinoma, JAMA Oncol. 2 (4) (2016) 482–490.
[15] W.G. McCluggage, Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis, Pathology 43 (5) (2011) 420–432.
[16] M. Kobel, A.M. Piskorz, S. Lee, S. Lui, C. LePage, F. Marass, N. Rosenfeld, A.M. Mes Masson, J.D. Brenton, optimized p53 immunohistochemistry is an accurate predictor of TP53 mutation in ovarian carcinoma, J. Pathol. Clin. Res. 2 (4) (2016)

247–258.
[17] M. Kobel, S.E. Kalloger, J. Carrick, D. Huntsman, H. Asad, E. Oliva, C.A. Ewanowich, R.A. Soslow, C.B. Gilks, A limited panel of immunomarkers can reliably distinguish between clear cell and high-grade serous carcinoma of the ovary, Am. J. Surg. Pathol. 33 (1) (2009) 14–21.
[18] M. Kobel, S.E. Kalloger, S. Lee, M.A. Duggan, L.E. Kelemen, L. Prentice, K.R. Kalli, B.L. Fridley, D.W. Visscher, G.L. Keeney, R.A. Vierkant, J.M. Cunningham, C. Chow, R.B. Ness, K. Moysich, R. Edwards, F. Modugno, C. Bunker, E.L. Wozniak, E. Benjamin, S.A. Gayther, A. Gentry-Maharaj, U. Menon, C.B. Gilks, D.G. Huntsman, S.J. Ramus, E.L. Goode, Ovarian Tumor Tissue Analysis, Biomarker-based ovarian carcinoma typing: a histologic investigation in the ovarian tumor tissue analysis consortium, Cancer Epidemiol. Biomarkers Prev. 22 (10) (2013) 1677–1686.
[19] R.J. Kurman, M. Shih Ie, The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory, Am. J. Surg. Pathol. 34 (3) (2010) 433–443.
[20] R.J. Kurman, M. Shih Ie, The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded, Am. J. Pathol. 186 (4) (2016) 733–747.
[21] E.A. du Bois, A, consensus statements on the management of ovarian cancer: final document of the third International Gynaecologic Cancer intergroup Ovarian Cancer consensus Conference (GCIG OCCC 2004), Ann. Oncol. 6 (Suppl. 8) (2004) viii7–12.
[22] H.J. Mackay, M.F. Brady, A.M. Oza, A. Reuss, E. Pujade-Lauraine, A.M. Swart, N. Siddiqui, N. Colombo, M.A. Bookman, J. Pfisterer, A. du Bois, I. Gynecologic Cancer, Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer, Int. J. Gynecol. Cancer 20 (6) (2010) 945–952.
[23] C.A. Shu, Q. Zhou, A.R. Jotwani, A. Iasonos, M.M. Leitao Jr, J.A. Konner, C.A. Aghajanian, Ovarian clear cell carcinoma, outcomes by stage: the MSK experience, Gynecol. Oncol. 139 (2) (2015) 236–241.
[24] M. Takano, T. Sugiyama, N. Yaegashi, M. Sakuma, M. Suzuki, Y. Saga, K. Kuzuya, J. Kigawa, M. Shimada, H. Tsuda, T. Moriya, A. Yoshizaki, T. Kita, Y. Kikuchi, Low response rate of second-line chemotherapy for recurrent or refractory clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study, Int. J. Gynecol. Cancer 18 (5) (2008) 937–942.
[25] D.R. Crotzer, C.C. Sun, R.L. Coleman, J.K. Wolf, C.F. Levenback, D.M. Gershenson, Lack of effective systemic therapy for recurrent clear cell carcinoma of the ovary, Gynecol. Oncol. 105 (2) (2007) 404–408.
[26] C.D. Devlin Michael-John, Singh Naveena, A. Ledermann Jonathan, Lockley Michelle, Mc Cormack Mary, Wilkinson Nafisa, Miller Rowan, Kristeleit Rebecca Sophie, Clear cell ovarian cancer (CCOC): 115 patient (pt) series showing access to experimental therapy may improve response rates in recurrent disease, ASCO Annual Meeting, Chicago, USA, 2018.
[27] K.K. Zorn, T. Bonome, L. Gangi, G.V. Chandramouli, C.S. Awtrey, G.J. Gardner, J.C. Barrett, J. Boyd, M.J. Birrer, Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer, Clin. Cancer Res. 11 (18) (2005) 6422–6430.
[28] S. Khalique, S. Banerjee, Nintedanib in ovarian cancer, Expert Opin. Investig. Drugs 26 (9) (2017) 1073–1081.
[29] M.S. Anglesio, J. George, H. Kulbe, M. Friedlander, D. Rischin, C. Lemech, J. Power, J. Coward, P.A. Cowin, C.M. House, P. Chakravarty, K.L. Gorringe, I.G. Campbell, A. Okamoto, M.J. Birrer, D.G. Huntsman, A. de Fazio, S.E. Kalloger, F. Balkwill, C.B. Gilks, D.D. Bowtell, IL6-STAT3-HIF signaling and therapeutic response to the angiogenesis inhibitor sunitinib in ovarian clear cell cancer, Clin. Cancer Res. 17 (8) (2011) 2538–2548.
[30] J. Coward, H. Kulbe, P. Chakravarty, D. Leader, V. Vassileva, D.A. Leinster, R. Thompson, T. Schioppa, J. Nemeth, J. Vermeulen, N. Singh, N. Avril, J. Cummings, E. Rexhepaj, K. Jirstrom, W.M. Gallagher, D.J. Brennan, I.A. McNeish, F.R. Balkwill, Interleukin-6 as a therapeutic target in human ovarian cancer, Clin. Cancer Res. 17 (18) (2011) 6083–6096.
[31] J.K. Chan, W. Brady, B.J. Monk, J. Brown, M.S. Shahin, P.G. Rose, J.H. Kim, A.A. Secord, J.L. Walker, D.M. Gershenson, A phase II evaluation of sunitinib in the treatment of persistent or recurrent clear cell ovarian carcinoma: an NRG Oncology/Gynecologic Oncology Group Study (GOG-254), Gynecol. Oncol. 150 (2) (2018) 247–252.
[32] P.A. Konstantinopoulos, W.E. Brady, J. Farley, A. Armstrong, D.S. Uyar, D.M. Gershenson, Phase II study of single-agent cabozantinib in patients with recurrent clear cell ovarian, primary peritoneal or fallopian tube cancer (NRG-GY001), Gynecol. Oncol. 150 (1) (2018) 9–13.
[33] S. Lheureux, A. Tinker, B. Clarke, P. Ghatage, S. Welch, J.I. Weberpals, N.C. Dhani, M.O. Butler, K. Tonkin, Q. Tan, D.S.P. Tan, K. Brooks, J. Ramsahai, L. Wang, N.A. Pham, P.A. Shaw, M.S. Tsao, S. Garg, T. Stockley, A.M. Oza, A clinical and molecular phase II trial of oral ENMD-2076 in ovarian clear cell carcinoma (OCCC): a study of the princess Margaret Phase II consortium, Clin. Cancer Res. (2018).
[34] R.M. Glasspool, I.A. McNeish, J. Paul, C.A. Lawless, D. Taggart, D.W.M. Millan, W.G. McCluggage, N. Wilkinson, C.S. Barlow, G. Hall, J.S. Waters, S.N. Banerjee, J. Alexandre, N.L. Fur, A.M. Westermann, C. Coens, C. Jederud, M.R. Mirza, NiCCC (ENGOT-GYN1): a randomized phase II study of nintedanib (BIBF1120) compared to chemotherapy in patients with recurrent clear-cell carcinoma of the ovary or endometrium, J. Clin. Oncol. 34 (15_suppl) (2016) TPS5603-TPS5603.
[35] M. Kobel, D. Huntsman, C.B. Gilks, Critical molecular abnormalities in high-grade serous carcinoma of the ovary, Expert Rev. Mol. Med. 10 (2008) e22.
[36] J. Hicks, A. Krasnitz, B. Lakshmi, N.E. Navin, M. Riggs, E. Leibu, D. Esposito, J. Alexander, J. Troge, V. Grubor, S. Yoon, M. Wigler, K. Ye, A.L. Borresen-Dale, B. Naume, E. Schlicting, L. Norton, T. Hagerstrom, L. Skoog, G. Auer, S. Maner, P. Lundin, A. Zetterberg, Novel patterns of genome rearrangement and their association with survival in breast cancer, Genome Res. 16 (12) (2006) 1465–1479.
[37] D.S. Tan, M. Iravani, W.G. McCluggage, M.B. Lambros, F. Milanezi, A. Mackay, C. Gourley, F.C. Geyer, R. Vatcheva, J. Millar, K. Thomas, R. Natrajan, K. Savage, K. Fenwick, A. Williams, C. Jameson, M. El-Bahrawy, M.E. Gore, H. Gabra, S.B. Kaye, A. Ashworth, J.S. Reis-Filho, Genomic analysis reveals the molecular heterogeneity of ovarian clear cell carcinomas, Clin. Cancer Res. 17 (6) (2011) 1521–1534.
[38] M.A. Bookman, K.M. Darcy, D. Clarke-Pearson, R.A. Boothby, I.R. Horowitz, Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: a phase II trial of the Gynecologic Oncology Group, J. Clin. Oncol. 21 (2) (2003) 283–290.
[39] A. Ruiz-Saenz, M.M. Moasser, Targeting HER2 by combination therapies, J. Clin. Oncol. 36 (8) (2018) 808–811.
[40] D.S. Tan, M.B. Lambros, S. Rayter, R. Natrajan, R. Vatcheva, Q. Gao, C. Marchio, F.C. Geyer, K. Savage, S. Parry, K. Fenwick, N. Tamber, A. Mackay, T. Dexter, C. Jameson, W.G. McCluggage, A. Williams, A. Graham, D. Faratian, M. El-Bahrawy, A.J. Paige, H. Gabra, M.E. Gore, M. Zvelebil, C.J. Lord, S.B. Kaye, A. Ashworth, J.S. Reis-Filho, PPM1D is a potential therapeutic target in ovarian clear cell carcinomas, Clin. Cancer Res. 15 (7) (2009) 2269–2280.
[41] S. Jones, T.L. Wang, M. Shih Ie, T.L. Mao, K. Nakayama, R. Roden, R. Glas, D. Slamon, L.A. Diaz Jr, B. Vogelstein, K.W. Kinzler, V.E. Velculescu, N. Papadopoulos, Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma, Science 330 (6001) (2010) 228–231.
[42] K.C. Wiegand, S.P. Shah, O.M. Al-Agha, Y. Zhao, K. Tse, T. Zeng, J. Senz, M.K. McConechy, M.S. Anglesio, S.E. Kalloger, W. Yang, A. Heravi-Moussavi, R. Giuliany, C. Chow, J. Fee, A. Zayed, L. Prentice, N. Melnyk, G. Turashvili, A.D. Delaney, J. Madore, S. Yip, A.W. McPherson, G. Ha, L. Bell, S. Fereday, A. Tam, L. Galletta, P.N. Tonin, D. Provencher, D. Miller, S.J. Jones, R.A. Moore, G.B. Morin, A. Oloumi, N. Boyd, S.A. Aparicio, M. Shih Ie, A.M. Mes-Masson, D.D. Bowtell, M. Hirst, B. Gilks, M.A. Marra, D.G. Huntsman, ARID1A mutations in endometriosis-associated ovarian carcinomas, N. Engl. J. Med. 363 (16) (2010) 1532–1543.
[43] K.T. Kuo, T.L. Mao, S. Jones, E. Veras, A. Ayhan, T.L. Wang, R. Glas, D. Slamon, V.E. Velculescu, R.J. Kuman, M. Shih Ie, Frequent activating mutations of PIK3CA in ovarian clear cell carcinoma, Am. J. Pathol. 174 (5) (2009) 1597–1601.
[44] S. Yamamoto, H. Tsuda, M. Takano, S. Tamai, O. Matsubara, PIK3CA mutations and loss of ARID1A protein expression are early events in the development of cystic ovarian clear cell adenocarcinoma, Virchows Arch. 460 (1) (2012) 77–87.
[45] S. Yamamoto, H. Tsuda, M. Takano, S. Tamai, O. Matsubara, Loss of ARID1A protein expression occurs as an early event in ovarian clear-cell carcinoma development and frequently coexists with PIK3CA mutations, Mod. Pathol. 25 (4) (2012) 615–624.
[46] R.L. Chandler, J.S. Damrauer, J.R. Raab, J.C. Schisler, M.D. Wilkerson, J.P. Didion, J. Starmer, D. Serber, D. Yee, J. Xiong, D.B. Darr, F. Pardo-Manuel de Villena, W.Y. Kim, T. Magnuson, Coexistent ARID1A-PIK3CA mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signalling, Nat. Commun. 6 (2015) 6118.
[47] R. Murakami, N. Matsumura, J.B. Brown, K. Higasa, T. Tsutsumi, M. Kamada, H. Abou-Taleb, Y. Hosoe, S. Kitamura, K. Yamaguchi, K. Abiko, J. Hamanishi, T. Baba, M. Koshiyama, Y. Okuno, R. Yamada, F. Matsuda, I. Konishi, M. Mandai, Exome sequencing landscape analysis in ovarian clear cell carcinoma shed light on key chromosomal regions and mutation gene networks, Am. J. Pathol. 187 (10) (2017) 2246–2258.
[48] S.I. Kim, J.W. Lee, M. Lee, H.S. Kim, H.H. Chung, J.W. Kim, N.H. Park, Y.S. Song, J.S. Seo, Genomic landscape of ovarian clear cell carcinoma via whole exome sequencing, Gynecol. Oncol. 148 (2) (2018) 375–382.
[49] Y. Hashiguchi, H. Tsuda, T. Inoue, R.S. Berkowitz, S.C. Mok, PTEN expression in clear cell adenocarcinoma of the ovary, Gynecol. Oncol. 101 (1) (2006) 71–75.
[50] J.A. Elvin, J. Chura, L.M. Gay, M. Markman, Comprehensive genomic profiling (CGP) of ovarian clear cell carcinomas (OCCC) identifies clinically relevant genomic alterations (CRGA) and targeted therapy options, Gynecol. Oncol. Rep. 20 (2017) 62–66.
[51] B. Weissman, K.E. Knudsen, Hijacking the chromatin remodeling machinery: impact of SWI/SNF perturbations in cancer, Cancer Res. 69 (21) (2009) 8223–8230.
[52] H. Kwon, A.N. Imbalzano, P.A. Khavari, R.E. Kingston, M.R. Green, Nucleosome disruption and enhancement of activator binding by a human SW1/SNF complex, Nature 370 (6489) (1994) 477–481.
[53] A.N. Imbalzano, H. Kwon, M.R. Green, R.E. Kingston, Facilitated binding of TATA-binding protein to nucleosomal DNA, Nature 370 (6489) (1994) 481–485.
[54] N.G. Nagl Jr, A. Patsialou, D.S. Haines, P.B. Dallas, G.R. Beck Jr, E. Moran, The p270 (ARID1A/SMARCF1) subunit of mammalian SWI/SNF-related complexes is essential for normal cell cycle arrest, Cancer Res. 65 (20) (2005) 9236–9244.
[55] A.H. Shain, J.R. Pollack, The spectrum of SWI/SNF mutations, ubiquitous in human cancers, PLoS One 8 (1) (2013) e55119.
[56] A. Ashworth, C.J. Lord, J.S. Reis-Filho, Genetic interactions in cancer progression and treatment, Cell 145 (1) (2011) 30–38.
[57] C.J. Lord, A. Ashworth, PARP inhibitors: synthetic lethality in the clinic, Science 355 (6330) (2017) 1152–1158.
[58] H.W. Cheung, G.S. Cowley, B.A. Weir, J.S. Boehm, S. Rusin, J.A. Scott, A. East, L.D. Ali, P.H. Lizotte, T.C. Wong, G. Jiang, J. Hsiao, C.H. Mermel, G. Getz, J. Barretina, S. Gopal, P. Tamayo, J. Gould, A. Tsherniak, N. Stransky, B. Luo, Y. Ren, R. Drapkin, S.N. Bhatia, J.P. Mesirov, L.A. Garraway, M. Meyerson, E.S. Lander, D.E. Root, W.C. Hahn, Systematic investigation of genetic vulnerabilities across cancer cell lines reveals lineage-specific dependencies in ovarian cancer, Proc Natl Acad Sci U S A 108 (30) (2011) 12372–12377.
[59] K.C. Helming, X. Wang, B.G. Wilson, F. Vazquez, J.R. Haswell, H.E. Manchester,

Y. Kim, G.V. Kryukov, M. Ghandi, A.J. Aguirre, Z. Jagani, Z. Wang, L.A. Garraway, W.C. Hahn, C.W. Roberts, ARID1B is a specific vulnerability in ARID1A-mutant cancers, Nat. Med. 20 (3) (2014) 251–254.
[60] B.G. Bitler, K.M. Aird, A. Garipov, H. Li, M. Amatangelo, A.V. Kossenkov, D.C. Schultz, Q. Liu, M. Shih Ie, J.R. Conejo-Garcia, D.W. Speicher, R. Zhang, Synthetic lethality by targeting EZH2 methyltransferase activity in ARID1A-mutated cancers, Nat. Med. 21 (3) (2015) 231–238.
[61] M. Sauvageau, G. Sauvageau, Polycomb group proteins: multi-faceted regulators of somatic stem cells and cancer, Cell Stem Cell 7 (3) (2010) 299–313.
[62] S. Wu, N. Fatkhutdinov, T. Fukumoto, B.G. Bitler, P.H. Park, A.V. Kossenkov, M. Trizzino, H.Y. Tang, L. Zhang, A. Gardini, D.W. Speicher, R. Zhang, SWI/SNF catalytic subunits' switch drives resistance to EZH2 inhibitors in ARID1A-mutated cells, Nat. Commun. 9 (1) (2018) 4116.
[63] T. Fukumoto, P.H. Park, S. Wu, N. Fatkhutdinov, S. Karakashev, T. Nacarelli, A.V. Kossenkov, D.W. Speicher, S. Jean, L. Zhang, T.L. Wang, I.M. Shih, J.R. Conejo-Garcia, B.G. Bitler, R. Zhang, Repurposing Pan-HDAC inhibitors for ARID1A-Mutated ovarian Cancer, Cell Rep. 22 (13) (2018) 3393–3400.
[64] B.G. Bitler, S. Wu, P.H. Park, Y. Hai, K.M. Aird, Y. Wang, Y. Zhai, A.V. Kossenkov, A. Vara-Ailor, F.J. Rauscher III, W. Zou, D.W. Speicher, D.G. Huntsman, J.R. Conejo-Garcia, K.R. Cho, D.W. Christianson, R. Zhang, ARID1A-mutated ovarian cancers depend on HDAC6 activity, Nat. Cell Biol. 19 (8) (2017) 962–973.
[65] T. Fukumoto, N. Fatkhutdinov, J.A. Zundell, E.N. Tcyganov, T. Nacarelli, S. Karakashev, S. Wu, Q. Liu, D.I. Gabrilovich, R. Zhang, HDAC6 inhibition synergizes with anti-PD-L1 therapy in ARID1A-inactivated ovarian cancer, Cancer Res. (2019).
[66] K. Berns, J.J. Caumanns, E.M. Hijmans, A.M.C. Gennissen, T.M. Severson, B. Evers, G.B.A. Wisman, G. Jan Meersma, C. Lieftink, R.L. Beijersbergen, H. Itamochi, A.G.J. van der Zee, S. de Jong, R. Bernards, ARID1A mutation sensitizes most ovarian clear cell carcinomas to BET inhibitors, Oncogene 37 (33) (2018) 4611–4625.
[67] K.H. Kim, C.W. Roberts, Targeting EZH2 in cancer, Nat. Med. 22 (2) (2016) 128–134.
[68] J. Shen, Y. Peng, L. Wei, W. Zhang, L. Yang, L. Lan, P. Kapoor, Z. Ju, Q. Mo, M. Shih Ie, I.P. Uray, X. Wu, P.H. Brown, X. Shen, G.B. Mills, G. Peng, ARID1A deficiency impairs the DNA damage checkpoint and sensitizes cells to PARP inhibitors, Cancer Discov. 5 (7) (2015) 752–767.
[69] C.T. Williamson, R. Miller, H.N. Pemberton, S.E. Jones, J. Campbell, A. Konde, N. Badham, R. Rafiq, R. Brough, A. Gulati, C.J. Ryan, J. Francis, P.B. Vermulen, A.R. Reynolds, P.M. Reaper, J.R. Pollard, A. Ashworth, C.J. Lord, ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A, Nat. Commun. 7 (2016) 13837.
[70] Y. Park, M.H. Chui, Y. Suryo Rahmanto, Z.C. Yu, R.A. Shamanna, M.A. Bellani, S. Gaillard, A. Ayhan, A. Viswanathan, M.M. Seidman, S. Franco, A. Leung, V.A. Bohr, I.M. Shih, T.L. Wang, Loss of ARID1A in tumor cells renders selective vulnerability to combined ionizing radiation and PARP inhibitor therapy, Clin. Cancer Res. (2019).
[71] R.E. Miller, R. Brough, I. Bajrami, C.T. Williamson, S. McDade, J. Campbell, A. Kigozi, R. Rafiq, H. Pemberton, R. Natrajan, J. Joel, H. Astley, C. Mahoney, J.D. Moore, C. Torrance, J.D. Gordan, J.T. Webber, R.S. Levin, K.M. Shokat, S. Bandyopadhyay, C.J. Lord, A. Ashworth, Synthetic lethal targeting of ARID1A-Mutant ovarian clear cell tumors with dasatinib, Mol. Cancer Ther. 15 (7) (2016) 1472–1484.
[72] C. Gorrini, T.W. Mak, Glutathione Metabolism: An Achilles' Heel of ARID1A-Deficient Tumors, Cancer Cell 35 (2) (2019) 161–163.
[73] H. Ogiwara, K. Takahashi, M. Sasaki, T. Kuroda, H. Yoshida, R. Watanabe, A. Maruyama, H. Makinoshima, F. Chiwaki, H. Sasaki, T. Kato, A. Okamoto, T. Kohno, Targeting the vulnerability of glutathione metabolism in ARID1A-Deficient cancers, Cancer Cell 35 (2) (2019) 177–190 e8.
[74] A. Bononi, C. Agnoletto, E. De Marchi, S. Marchi, S. Patergnani, M. Bonora, C. Giorgi, S. Missiroli, F. Poletti, A. Rimessi, P. Pinton, Protein kinases and phosphatases in the control of cell fate, Enzyme Res. 2011 (2011) 329098.
[75] C. Van Hoof, J. Goris, PP2A fulfills its promises as tumor suppressor: which subunits are important? Cancer Cell 5 (2) (2004) 105–106.
[76] X. Tang, Y. Wang, Pds1/Esp1-dependent and -independent sister chromatid separation in mutants defective for protein phosphatase 2A, Proc Natl Acad Sci U S A 103 (44) (2006) 16290–16295.
[77] G.A. Calin, M.G. di Iasio, E. Caprini, I. Vorechovsky, P.G. Natali, G. Sozzi, C.M. Croce, G. Barbanti-Brodano, G. Russo, M. Negrini, Low frequency of alterations of the alpha (PPP2R1A) and beta (PPP2R1B) isoforms of the subunit A of the serine-threonine phosphatase 2A in human neoplasms, Oncogene 19 (9) (2000) 1191–1195.
[78] D. Haesen, L. Abbasi Asbagh, R. Derua, A. Hubert, S. Schrauwen, Y. Hoorne, F. Amant, E. Waelkens, A. Sablina, V. Janssens, Recurrent PPP2R1A mutations in uterine Cancer act through a dominant-negative mechanism to promote malignant cell growth, Cancer Res. 76 (19) (2016) 5719–5731.
[79] D. Perrotti, P. Neviani, Protein phosphatase 2A: a target for anticancer therapy, the Lancet, Oncology 14 (6) (2013) e229–38.
[80] J.A. Engelman, Targeting PI3K signalling in cancer: opportunities, challenges and limitations, Nat. Rev. Cancer 9 (8) (2009) 550–562.
[81] S. Mabuchi, C. Kawase, D.A. Altomare, K. Morishige, K. Sawada, M. Hayashi, M. Tsujimoto, M. Yamoto, A.J. Klein-Szanto, R.J. Schilder, M. Ohmichi, J.R. Testa, T. Kimura, mTOR is a promising therapeutic target both in cisplatin-sensitive and cisplatin-resistant clear cell carcinoma of the ovary, Clin. Cancer Res. 15 (17) (2009) 5404–5413.
[82] J.J. Caumanns, K. Berns, G.B.A. Wisman, R.S.N. Fehrmann, T. Tomar, H. Klip, G.J. Meersma, E.M. Hijmans, A.M.C. Gennissen, E.W. Duiker, D. Weening, H. Itamochi, R.J.C. Kluin, A.K.L. Reyners, M.J. Birrer, H.B. Salvesen, I. Vergote, E. van Nieuwenhuysen, J. Brenton, E.I. Braicu, J. Kupryjanczyk, B. Spiewankiewicz, L. Mittempergher, R. Bernards, A.G.J. van der Zee, S. de Jong, Integrative kinome profiling identifies mTORC1/2 inhibition as treatment strategy in ovarian clear cell carcinoma, Clin. Cancer Res. 24 (16) (2018) 3928–3940.
[83] M. Takano, Y. Kikuchi, K. Kudoh, T. Goto, K. Furuya, R. Kikuchi, T. Kita, K. Fujiwara, T. Shiozawa, D. Aoki, Weekly administration of temsirolimus for heavily pretreated patients with clear cell carcinoma of the ovary: a report of six cases, Int. J. Clin. Oncol. 16 (5) (2011) 605–609.
[84] S. Khalique, K. Naidoo, A.D. Attygalle, D. Kriplani, F. Daley, A. Lowe, J. Campbell, T. Jones, M. Hubank, K. Fenwick, N. Matthews, A.G. Rust, C.J. Lord, S. Banerjee, R. Natrajan, Optimised ARID1A immunohistochemistry is an accurate predictor of ARID1A mutational status in gynaecological cancers, J. Pathol. Clin. Res. (2018).
[85] NCT02576444, OLAParib COmbinations (2015).
[86] NCT02059265, Dasatinib in Treating Patients With Recurrent or Persistent Ovarian, Fallopian Tube, Endometrial or Peritoneal Cancer (2014).
[87] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (5) (2011) 646–674.
[88] D. Zamarin, M.A. Postow, Immune checkpoint modulation: rational design of combination strategies, Pharmacol. Ther. 150 (2015) 23–32.
[89] U.A. Matulonis, Management of newly diagnosed or recurrent ovarian cancer, Clin. Adv. Hematol. Oncol. 16 (6) (2018) 426–437.
[90] A.P. Cogdill, M.C. Andrews, J.A. Wargo, Hallmarks of response to immune checkpoint blockade, Br. J. Cancer 117 (1) (2017) 1–7.
[91] J. Hamanishi, M. Mandai, M. Iwasaki, T. Okazaki, Y. Tanaka, K. Yamaguchi, T. Higuchi, H. Yagi, K. Takakura, N. Minato, T. Honjo, S. Fujii, Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer, Proc Natl Acad Sci U S A 104 (9) (2007) 3360–3365.
[92] K. Abiko, M. Mandai, J. Hamanishi, Y. Yoshioka, N. Matsumura, T. Baba, K. Yamaguchi, R. Murakami, A. Yamamoto, B. Kharma, K. Kosaka, I. Konishi, PD-L1 on tumor cells is induced in ascites and promotes peritoneal dissemination of ovarian cancer through CTL dysfunction, Clin. Cancer Res. 19 (6) (2013) 1363–1374.
[93] J. Hamanishi, M. Mandai, T. Ikeda, M. Minami, A. Kawaguchi, T. Murayama, M. Kanai, Y. Mori, S. Matsumoto, S. Chikuma, N. Matsumura, K. Abiko, T. Baba, K. Yamaguchi, A. Ueda, Y. Hosoe, S. Morita, M. Yokode, A. Shimizu, T. Honjo, I. Konishi, Safety and antitumor activity of Anti-PD-1 antibody, Nivolumab, in patients with platinum-resistant ovarian Cancer, J. Clin. Oncol. 33 (34) (2015) 4015–4022.
[94] FDA.gov, FDA Grants Accelerated Approval to Pembrolizumab for First tissue/site Agnostic Indication, (2017) https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm.
[95] K.Q. Cai, C. Albarracin, D. Rosen, R. Zhong, W. Zheng, R. Luthra, R. Broaddus, J. Liu, Microsatellite instability and alteration of the expression of hMLH1 and hMSH2 in ovarian clear cell carcinoma, Hum. Pathol. 35 (5) (2004) 552–559.
[96] C. Kandoth, M.D. McLellan, F. Vandin, K. Ye, B. Niu, C. Lu, M. Xie, Q. Zhang, J.F. McMichael, M.A. Wyczalkowski, M.D.M. Leiserson, C.A. Miller, J.S. Welch, M.J. Walter, M.C. Wendl, T.J. Ley, R.K. Wilson, B.J. Raphael, L. Ding, Mutational landscape and significance across 12 major cancer types, Nature 502 (7471) (2013) 333–339.
[97] J. Shen, Z. Ju, W. Zhao, L. Wang, Y. Peng, Z. Ge, Z.D. Nagel, J. Zou, C. Wang, P. Kapoor, X. Ma, D. Ma, J. Liang, S. Song, J. Liu, L.D. Samson, J.A. Ajani, G.M. Li, H. Liang, X. Shen, G.B. Mills, G. Peng, ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade, Nat. Med. (2018).
[98] D.T. Le, J.N. Durham, K.N. Smith, H. Wang, B.R. Bartlett, L.K. Aulakh, S. Lu, H. Kemberling, C. Wilt, B.S. Luber, F. Wong, N.S. Azad, A.A. Rucki, D. Laheru, R. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, T.F. Greten, A.G. Duffy, K.K. Ciombor, A.D. Eyring, B.H. Lam, A. Joe, S.P. Kang, M. Holdhoff, L. Danilova, L. Cope, C. Meyer, S. Zhou, R.M. Goldberg, D.K. Armstrong, K.M. Bever, A.N. Fader, J. Taube, F. Housseau, D. Spetzler, N. Xiao, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, J.R. Eshleman, B. Vogelstein, R.A. Anders, L.A. Diaz Jr, Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade, Science 357 (6349) (2017) 409–413.
[99] A.J. Redig, P.A. Janne, Basket trials and the evolution of clinical trial design in an era of genomic medicine, J. Clin. Oncol. 33 (9) (2015) 975–977.
[100] H. Itamochi, T. Oishi, N. Oumi, S. Takeuchi, K. Yoshihara, M. Mikami, N. Yaegashi, Y. Terao, K. Takehara, K. Ushijima, H. Watari, D. Aoki, T. Kimura, T. Nakamura, Y. Yokoyama, J. Kigawa, T. Sugiyama, Whole-genome sequencing revealed novel prognostic biomarkers and promising targets for therapy of ovarian clear cell carcinoma, Br. J. Cancer 117 (5) (2017) 717–724.
[101] Y. Maru, N. Tanaka, M. Ohira, M. Itami, Y. Hippo, H. Nagase, Identification of novel mutations in Japanese ovarian clear cell carcinoma patients using optimized targeted NGS for clinical diagnosis, Gynecol. Oncol. 144 (2) (2017) 377–383.
[102] S.Y. Kwan, X. Cheng, Y.T. Tsang, J.S. Choi, S.Y. Kwan, D.I. Izaguirre, H.S. Kwan, D.M. Gershenson, K.K. Wong, Loss of ARID1A expression leads to sensitivity to ROS-inducing agent elesclomol in gynecologic cancer cells, Oncotarget 7 (35) (2016) 56933–56943.
[103] M. Bazzaro, Z. Lin, A. Santillan, M.K. Lee, M.C. Wang, K.C. Chan, R.E. Bristow, R. Mazitschek, J. Bradner, R.B. Roden, Ubiquitin proteasome system stress underlies synergistic killing of ovarian cancer cells by bortezomib and a novel HDAC6 inhibitor, Clin. Cancer Res. 14 (22) (2008) 7340–7347.
[104] E. George, H. Kim, J. Tanyi, R. Ragland, R.G. Zhang, P. Bradford, C. Krepler, K. Nathanson, B. Wenz, Y.L. Lu, G. Mills, M. Morgan, F. Simpkins, Targeting the ATR/CHK1 axis in combination with PARP inhibition is more effective than PARP inhibition alone in BRCA mutant models, Cancer Res. 76 (2016).

[105] E.P. Samartzis, K. Gutsche, K.J. Dedes, D. Fink, M. Stucki, P. Imesch, Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition, Oncotarget 5 (14) (2014) 5295–5303.
[106] O.M. Al-Agha, H.F. Huwait, C. Chow, W. Yang, J. Senz, S.E. Kalloger, D.G. Huntsman, R.H. Young, C.B. Gilks, FOXL2 is a sensitive and specific marker for sex cord-stromal tumors of the ovary, Am. J. Surg. Pathol. 35 (4) (2011) 484–494.
[107] E.C. Dykhuizen, D.C. Hargreaves, E.L. Miller, K. Cui, A. Korshunov, M. Kool, S. Pfister, Y.J. Cho, K. Zhao, G.R. Crabtree, BAF complexes facilitate decatenation of DNA by topoisomerase IIalpha, Nature 497 (7451) (2013) 624–627.
[108] A. Heravi-Moussavi, M.S. Anglesio, S.W. Cheng, J. Senz, W. Yang, L. Prentice, A.P. Fejes, C. Chow, A. Tone, S.E. Kalloger, N. Hamel, A. Roth, G. Ha, A.N. Wan, S. Maines-Bandiera, C. Salamanca, B. Pasini, B.A. Clarke, A.F. Lee, C.H. Lee, C. Zhao, R.H. Young, S.A. Aparicio, P.H. Sorensen, M.M. Woo, N. Boyd, S.J. Jones, M. Hirst, M.A. Marra, B. Gilks, S.P. Shah, W.D. Foulkes, G.B. Morin, D.G. Huntsman, Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers, New England J. Med. 366 (3) (2012) 234–242.
[109] P. Jelinic, J.J. Mueller, N. Olvera, F. Dao, S.N. Scott, R. Shah, J. Gao, N. Schultz, M. Gonen, R.A. Soslow, M.F. Berger, D.A. Levine, Recurrent SMARCA4 mutations in small cell carcinoma of the ovary, Nat. Genet. 46 (5) (2014) 424–426.
[110] M. Kobel, A.M. Piskorz, S. Lee, S. Lui, C. LePage, F. Marass, N. Rosenfeld, A.M. Mes Masson, J.D. Brenton, Optimized p53 immunohistochemistry is an accurate predictor of TP53 mutation in ovarian carcinoma, J. Pathol. Clin. Res. 2 (4) (2016) 247–258.