Genetic and epigenetic heterogeneity of epithelial ovarian cancer and the clinical implications for molecular targeted therapy

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Abstract

Epithelial ovarian cancer (EOC) is the most lethal gynaecological malignancy, and tumoural heterogeneity (TH) has been blamed for treatment failure. The genomic and epigenomic atlas of EOC varies significantly with tumour histotype, grade, stage, sensitivity to chemotherapy and prognosis. Rapidly accumulating knowledge about the genetic and epigenetic events that control TH in EOC has facilitated the development of molecular-targeted therapy. Poly (ADP-ribose) polymerase (PARP) inhibitors, designed to target homologous recombination, are poised to change how breast cancer susceptibility gene (BRCA)-related ovarian cancer is treated. Epigenetic treatment regimens being tested in clinical or preclinical studies could provide promising novel treatment approaches and hope for improving patient survival.

Keywords: epithelial ovarian cancer – EOC – tumoural heterogeneity – TH – genetic and epigenetic alterations – molecular targeted treatment

Introduction

Human epithelial ovarian cancer (EOC) is the most common cause of death from gynaecological malignancy [1]. The standard treatment for EOC involves cytoreductive surgery followed by chemotherapy consisting of platinum and taxol. For high-grade serous ovarian cancer (HGSOC), the most prevalent and aggressive form of EOC, relapse is nearly the norm due to the development of resistance, although approximately 80% of patients initially respond to treatment [2]. Tumoural heterogeneity (TH) has been blamed for this treatment failure [3]. Gerlinger and Swanton [4] reported that genetic TH fosters the development of cancer drug resistance through Darwinian evolution, which points to a promising therapeutic target for preventing the evolution of more aggressive or resistant clones.

With the advent of next-generation sequencing in recent years, EOC has been found to consist of a complex set of diseases. Diverse genetic or epigenetic alterations that are of fundamental importance in tumorigenesis and progression have been identified in heterogeneous subsets of patients [5]. For example, breast cancer susceptibility gene (BRCA) mutations are most commonly associated with HGSOC [6]. Determining the molecular events that control this tumour trait might advance our understanding of tumorigenesis and facilitate individualized treatment strategies for this lethal disease.

Molecular portraits underlying TH of EOC

Underlying the hallmarks of cancers is genome instability, which can generate genetic diversity [7]. Genetic alterations can potentially...
upset the balance between proto-oncogenes and tumour suppressor genes, leading to tumorigenesis. The existence of extensive cytogenetic, genetic and epigenetic variations has been reported in EOC cell populations.

Numerical or structural chromosomal abnormalities are frequently observed in almost all human tumours [7]. Rearrangement of 19q has been identified in 61.6% of patients with ovarian cancer; such rearrangements have been significantly correlated with high-grade tumours, predicting shorter disease-free survival and worse overall survival (OS) [8] (Table 1). Underrepresentation of 11p and 19q and overrepresentation of 8q and 7p have been significantly correlated with undifferentiated ovarian carcinomas [9]. Underrepresentation of 12p and overrepresentation of 18p are frequently identified in well-and moderately differentiated ovarian tumours. Patients showing loss of D6S1581 are more likely to be resistant to platinum-based chemotherapy [10]. Gains of 14q32.33 have been associated with platinum resistance and reduced progression-free survival (PFS) and OS for patients with EOC [11]. Tumours exhibiting gain of 2p22-p25, 19p12-q13.1, and 20q12-q13 and loss of 5q14-q22 present a high risk of recurrence. The OS of patients is inversely correlated with the number of chromosomal alterations found in their tumours [12]. Gains at 5p are adversely associated with tumour recurrence [13], and gains at 1p and losses at 5q are associated with a significant decrease in recurrence. Loss at 6q24.2-26 is independently associated with a cluster of patients with HGSOc showing longer survival [14].

Gene copy number variations generally result in the abnormal expression of genes that are located within rearranged chromosomal regions. Nonrandom gains and deletions of DNA copy numbers and imbalances of alleles are frequently identified in ovarian tumours [15, 16]. Somatic copy number amplification is highly prevalent in high-grade ovarian cancer, whereas somatic mutational activation of oncogenes is a rare event, suggesting that the former is a common mechanism [17] of oncogene activation in this tumour type [15]. In addition, variations in gene copy number are specific to tumour histotypes, among which serous is the most prevalent, followed by endometrioid, clear cell and mucinous [17]. Mayr et al. [18] demonstrated that gains of FGFR3/4 and CCNE1 occur in all serous carcinomas. Endometrioid carcinomas most frequently show gains of JUNB, KRAS2, MYCN, ESR and CCND2. Among serous borderline tumours, 90% exhibit amplification of FGFR1 and MDM2, and 75% show gains of PIK3CA (Table 1). By applying an in silico hypothesis-driven approach to multiple datasets, Huang et al. [17] found 76 cancer genes to be significantly altered in EOC, several of which may be potential copy number drivers, such as ERBB2 in mucinous tumours and TPM3 in endometrioid histotypes. In addition, KRAS was observed to be significantly amplified in serous tumours, although mutations are rare in such high-grade tumours. Copy number variations can also predict a patient’s prognosis and response to treatment. Patients showing PIK3CA amplification generally respond well to treatment [19]. In contrast, amplification of 19q12 involving CCNE1 is the dominant structural variant associated with primary treatment failure of patients with HGSOc [20, 21]. Amplification of AKT2 is frequently identified in undifferentiated tumours and predicts a poor prognosis [22]. Ovarian cancer cells that either constitutively overexpress active Akt/AKT1 or exhibit AKT2 gene amplification are highly resistant to paclitaxel compared with cells with low AKT levels [23]. Overexpression of KLK6 [24], EGFR [25], LMX1B [26], BMP8B and ATP13A4 [27], because of gene amplification or high copy number gains, is associated with worse PFS and OS in patients with ovarian cancer. In contrast, an increased copy number of GAB2 is associated with improved PFS and OS and correlates with enhanced sensitivity to the dual PI3K/mTOR inhibitor PF-04691502 in vitro [27].

TP53 mutations are almost invariably present in HGSOc [15, 18, 20] (Table 1). The early loss of P53 function observed in sporadic cancers could create a permissive environment for the loss of BRCA1 or BRCA2 function (or other phenotypes of DNA repair deficiency), which would otherwise lead to apoptosis because of checkpoint activation [29]. Inactivation of BRCA1 and/or BRCA2 is detected in 67% of patients with HGSOc, which is markedly higher than in the other histotypes of EOC [6]. However, only 7–9% of sporadic ovarian carcinomas exhibit BRCA1 [30] mutations leading to inactivation of BRCA1, while 4% exhibit BRCA2 mutations [31]. HGSOc tumours only form in animal models when all three of the BRCA, TP53 and PTEN genes are altered, which suggests a synergistic role of these genes in tumorigenesis [32]. Mutation in other genes, including FAT3, CSND3, NF1, CDK12, RB1 and GABRA6, are also frequently identified in HGSOc tumours [15]. Mutations in BRAF are restricted to serous borderline tumours, indicating that the majority of serous borderline tumours do not progress to serous carcinomas [33]. Activating KRAS mutations are more common in mucinous tumours than in all other histological types [17, 34], while no mucinous tumours have been found to harbour a BRAF mutation [34]. Loss or dysfunction of mismatch repair of gain-of-function PTEN [35] and PIK3CA [36] mutations is common in endometrioid and clear cell carcinoma, but not in serous or mucinous ovarian cancer [37]. Deletion of LRP1B in HGSOc is associated with acquired resistance to liposomal doxorubicin [38]. In addition to their histological implications, tumours with BRCA mutations are more likely to be platinum-sensitive and associated with longer PFS and OS [39, 40]. Reversion of germline BRCA1 or BRCA2 mutations in individual patients or loss of BRCA1 promoter methylation predicts resistance to platinum [20] and may also predict resistance to PARP ((poly (ADP-ribose) polymerase) inhibitors [41, 42].

Epigenetics is defined as heritable changes in gene expression that do not alter the DNA sequence itself. The mechanisms responsible for such changes include DNA methylation, histone modification, and microRNAs, which are related to post-transcriptional gene regulation. Epigenetic alterations are increasingly being implicated in the development and progression of ovarian cancer, and the gradual accumulation of epigenetic alterations has been associated with an advancing grade and stage of disease [43] (Table 2).

Methylation, which primarily consists of dimethylation of oncogenes and hypermethylation of tumour suppressing genes, is frequently identified in ovarian cancer [44, 45]. Gene hypermethylation and satellite and global DNA hypomethylation in ovarian tumours are both independently associated with the degree of malignancy [46]. Satellite DNA hypomethylation is significantly more prevalent in advanced-stage and high-grade ovarian cancers and is an independent marker of poor prognosis [47]. In addition to repetitive elements and DNA satellites, hypomethylation of promoter CpG islands and gene overexpression have been reported in ovarian cancer. CpG islands are DNA sequences
containing CpG sites at an atypically high frequency [48] and are usually, but not exclusively, associated with gene promoters [49]. Demethylation of CpG islands in gene promoters generally allows active gene transcription to occur [50]. As a result of hypomethylation, re-expression of MCL1, SNCG, and BORIS and overexpression of CLDN4, MAL, BORIS [45] and TUBB3 [44] have been associated with chemoresistance in patients with EOC. As a result of promoter hypomethylation [51], HOXA10 is overexpressed in ovarian clear cell adenocarcinomas, but not in ovarian serous adenocarcinomas, normal ovarian epithelia or endometrial cysts [53]. In addition, this overexpression in ovarian clear cell adenocarcinomas [52, 53] is associated with poor survival [53]. DNA hypomethylation-mediated activation of the LINE-1 [54] and CT45 [55] genes is correlated with high-grade and advanced-stage EOC and associated with poorer PFS and OS.

Aberrant methylation of CpG islands in ovarian tumours is associated with silencing of genes involved in the control of the cell cycle, apoptosis and drug sensitivity as well as tumour suppressor genes [56]. Hypermethylation of the MLH1 gene, accompanied by loss of gene expression, and methylation of hmSH2 are correlated with a higher histological grade and lymph node metastasis of EOC [57]. In addition, methylation of the hMLH1 promoter has been identified in 56% of EOC patients with acquired resistance to platinum-based chemotherapy [58-60], predicting a high risk of relapse and poor OS [59]. The methylation rate of hMSh2 is significantly higher in endometrioid adenocarcinoma tissues compared with other histological types of the disease [57]. Epigenetic silencing of ARMCK2, COLI1A1, MOK and MEST due to promoter hypermethylation at CpG sites has also been linked to the development of platinum-based resistance in ovarian cancer [60]. Methylation of DLEC1 is associated with recurrence of HGSOC, independent of tumour stage and suboptimal surgical debulking [61]. Chou et al. [62] reported that hypermethylation of the FBXO32 promoter is more commonly observed in advanced-stage ovarian tumours, and patients showing FBXO32 methylation exhibit significantly shorter PFS. Re-expression of FBXO32 was demonstrated to markedly reduce proliferation, increase apoptosis, and restore sensitivity to cisplatin in a platinum-resistant ovarian cancer cell line both in vitro and in vivo.

BRCA1 and BRCA2 germline mutations are present in the majority of patients with hereditary ovarian carcinoma [63], in contrast to the frequency of these mutations detected in unselected patients, which is only 15.3% [64]. The majority of ovarian cancers arise independently of mutations in the BRCA1/2 genes [65]. BRCA1/2 alterations of all kinds, including mutations, have been reported in up to 82% of ovarian tumours [31]. The term ‘BRCAness’ has been used to describe the phenotypic traits that some sporadic ovarian tumours share with tumours found in BRCA1/2 germline mutation carriers and reflects similar causative molecular abnormalities [86]. BRCAness appears to be the result of different epigenetic processes. Recent data suggest that hypermethylation of the BRCA1 promoter occurs in 10-15% of sporadic cases and is associated with the serous histotype [67, 68]. BRCA2 can also be down-regulated through silencing of its upstream regulator, FANCF, by promoter methylation [69, 70]. Although patients with BRCA1/2 mutations and low protein/mRNA expression of BRCA1 tend to show a favourable response to treatment [20] and a better outcome [40], BRCA1 promoter methylation is significantly correlated with resistance to treatment [20] and a poorer prognosis [68] in patients with EOC. Thus, methylation is not functionally equivalent to a germline mutation in mediating chemotherapy sensitivity. While methylation of BRCA1 is common in sporadic ovarian cancer, it has not been reported in the hereditary form of the disease or in samples from women with germ-line BRCA1 mutations [71]. BRCA2 does not present a similar methylation profile in ovarian cancer [72].

DNA-associated histone proteins are subject to extensive modifications that mediate the assembly of transcriptionally permissive or repressive (i.e., open or closed) chromatin. Chromatin modifiers regulate the expression of different sets of genes involved in tumorigenesis [73]. DNA methylation and histone deacetylation often coordinateably inhibit gene transcription [74]. However, histone modification is an independent mechanism of epigenetic gene regulation under some conditions [75, 76]. H3K27me3 is a transcription-suppressive histone mark found in chromatin in association with EZH2, a component of the Polycomb (PcG) complex [77]. In ovarian cancer, decreased expression of H3K27me3 is significantly associated with high-grade and advanced-stage tumours, but not with the histological type [78], predicting resistance to chemotherapy [79] and a poor clinical outcome in ovarian cancer and other malignancies [78]. Removal of H3K27 methylation was shown to lead to re-expression of the RASS1 tumour suppressor and resensitize drug-resistant ovarian cancer cells to cisplatin; this increased platinum access to DNA was likely due to relaxation of condensed chromatin [80]. Sirtuin1 (SIRT1) is a nicotinamide adenine dinucleotide-dependent deacytleyase and a class III histone deacetyltransferase. The proportion of SIRT1 expression is significantly higher in serous carcinoma compared with mucinous tumours. SIRT1 overexpression is more common in early-stage serous carcinomas and is correlated with longer OS compared with late-stage disease [81]. SIRT1 also facilitates the acquisition of drug resistance through its influence on the tumour microenvironment, function in DNA repair and promotion of cancer stem cell survival [82]. Thus, SIRT1 is being considered as a possible target for overcoming drug resistance in many malignancies.

Having been implicated in the initiation and progression of human cancers, microRNAs regulate processes such as cell growth, differentiation and apoptosis [83]. A variety of miRNAs are associated with tumour subtype, stage, grade, therapy resistance and prognosis in ovarian cancer [84] (Table 2). Up-regulation of miR-205 [85] and miR-200a [86] and down-regulation of miR-101 [87] are significantly associated with a high pathological grade and advanced stage of EOC in patients. In addition, patients with lymph node metastasis show significant elevation of miR-200c [86]. Reduced expression of miR-34a* [88], hsa-miR-200a, hsa-miR-34a and hsa-miR-449b [89] is frequently identified in advanced-stage tumours. Hsa-miR-378 [89] and hsa-let-7i [90] are up-regulated in patients who are sensitive to platinum; in contrast, miR-101, [87] miR-30c, miR-130a and miR-335 [91] are down-regulated in several resistant ovarian cancer cell lines, suggesting direct involvement in the development of chemoresistance. MiR-214 induces cell survival and cisplatin resistance through targeting the
3'-UTR of the PTEN gene, which leads to reduced expression of PTEN and activation of the Akt pathway [92]. Down-regulation of miRNA-149 decreases the sensitivity of ovarian cancer cells to paclitaxel treatment by increasing MyD88 expression [93]. MIR-197 is significantly increased in Taxol-resistant ovarian cancer cells [94]. In addition, decreased expression of let-7i [90] and overexpression of miR-200a and miR-200c [86] are associated with shorter PFS, suggesting their potential for predicting relapse. Overexpression of miR-200, miR-141, miR-18a, miR-93 and miR-429 [95] is associated with improved OS, whereas high levels of hsa-miR-27a, [89] let-7b and miR-199a [96] are potentially correlated with a poor prognosis in patients with EOC.

**Molecular targeted treatment**

The rapid development of genetics and epigenetics has facilitated the study of the molecular mechanisms of TH in EOC. This knowledge has led to the introduction of novel treatments that are rationally designed to target specific molecular factors implicated in tumour growth (Table 3).

Dysfunction of BRCA1 and BRCA2 is associated with ovarian cancer tumorigenesis, due to an inability to repair DNA double-strand breaks (DSBs) [96]. The PARPs are a family of enzymes involved in base excision repair, a key pathway in the repair of DNA single-strand breaks (SSBs). PARP inhibition leads to the persistence of spontaneously occurring SSBs and subsequent formation of DSBs, as the SSBs stall and collapse replication forks. These DSBs cannot be repaired by the defective HR pathway in BRCA-mutated cells, resulting in cell death.

PARP inhibitors induce synthetic lethality in BRCA-deficient tissues. BRCA1/2-deficient cancers are now recognized as the target of a class of drugs known as PARP inhibitors. Deficiency of either PARP or BRCA alone has no impact, but deficiency in both leads to a lethal effect [97, 98]. Clinical investigation of the use of PARP inhibitors for the treatment of EOC evolved rapidly from the observations of single-agent activity conducted in vitro in BRCA-deficient cancer cells in 2005 to the initiation of multiple phase 3 studies in 2013. Ledermann et al. [99] retrospectively analysed the data from a randomized, double-blind, phase 2 study [100] and showed that patients with recurrent, platinum-sensitive serous ovarian cancer with a BRCA mutation exhibit the highest likelihood of benefiting from olaparib, the first human PARP inhibitor. Two phase III studies have been carried out to test olaparib versus placebo as maintenance therapy for both newly diagnosed and platinum-sensitive recurrent BRCA-associated ovarian cancer [101]. In December 2014, olaparib was approved for the treatment of patients with germline BRCA1/2-associated advanced ovarian cancer who have received three or more lines of chemotherapy. This approval represents the first ‘personalized’ therapy for ovarian cancer [102]. Other PARP inhibitors that have been tested or are currently being tested in clinical trials for ovarian cancer include veliparib, niraparib, rucaparib and BMN673 [101]. In addition to ovarian cancer, PARP inhibitors have shown encouraging in for other BRCA1/2 mutation-related cancers, such as breast cancer [103], endometrial cancer [104], prostate cancer [105] and pancreatic cancer [106]. Future and ongoing trials will identify the most effective role of these agents for use in human cancer treatment.

The signalling cascade involving PI3K, Akt and mTOR plays a key role in mediating cell proliferation and survival and is one of the pathways that is frequently affected in human cancer [107]. Various genetic alterations that activate PI3K/Akt/mTOR signalling have been identified in ovarian cancer [108]. In a previous study, we demonstrated that PI3K/Akt/mTOR pathway activation is associated with significantly higher migratory and invasive capacities in subpopulations of human ovarian cancer cell lines [109]. Thus, this pathway is regarded as an attractive candidate for therapeutic interventions against EOC, and inhibitors targeting different components of the pathway are in various stages of clinical development. Thus far, results have been published only for a phase I trial of an AKT inhibitor, perifosine [110], and a phase II trial of an mTORC1 inhibitor, temsirolimus [111]. Perifosine plus docetaxel appears to be effective in patients with mutational activation of the PI3K/AKT pathway [110]. A phase II clinical trial is currently being conducted to investigate the efficacy of perifosine as well as the association between PIK3CA status and the response to treatment in patients with recurrent gynaecological malignancies, including ovarian cancer. In a GOG phase II trial, [111] temsirolimus monotherapy showed modest activity in persistent or recurrent EOC and primary peritoneal cancer, and PFS was just below that required to warrant the inclusion of unsellected patients in phase III studies. Based on these results, a phase II trial is currently being conducted specifically targeting ovarian clear cell carcinoma, which often exhibits PI3K/AKT/mTOR activation [108]. This trial is aimed at examining the use of temsirolimus in combination with carboplatin and paclitaxel, followed by temsirolimus consolidation, as a first-line therapy for patients with ovarian cancer, and its results appear promising.

Because genetic alterations are almost impossible to reverse, the potential reversibility of epigenetic mechanisms makes them more attractive candidates for the prevention and treatment of ovarian carcinoma [112]. There are two types of DNA methylation inhibitors (DNMTIs): nucleoside and non-nucleoside analogues [44]. Nucleoside analogues, such as cytarabine and decitabine, can inhibit methylation when they are integrated into DNA and block the release of DNA methyltransferases by forming a covalent complex with these enzymes [113]. Cytarabine has been reported to induce re-expression of hMLH1 and reverse drug resistance in human tumour xenografts through demethylation of the hMLH1 promoter [114]. Zebularine can also induce demethylation of hMLH1 and RASSF1A and sensitize drug-resistant cell lines to cisplatin [115]. The ability of azacitidine and decitabine to reverse platinum resistance in ovarian cancer patients has been preliminarily confirmed in two clinical trials [116, 117].

Inhibitors of histone deacetylation (HDACIs) represent another promising new class of anticancer agents. Among the currently available HDACIs, four have been tested in ovarian cancer, including vorinostat, romidepsin, valproate and PXD101. Vorinostat and romidepsin have both been approved by the FDA for the treatment of cutaneous T-cell lymphoma. Both agents, in combination with cytotoxic agents, have shown significant activity in inhibiting ovarian cancer cell growth in preclinical studies [118–120]. However, in a phase II study, vorinostat displayed minimal activity as a single agent for treating persistent or recurrent epithelial ovarian or primary peritoneal carci-
Table 1 Cytogenetic and genetic tumour heterogeneity in EOC

| Molecular events | Heterogeneous clinicopathological characteristics |
|------------------|--------------------------------------------------|
|                  | Histology | Grade | Response to CT | Relapse risk | Survival |
| Chromosomal abnormalities |           |       |               |             |          |
| Rearrangement of 19q [8] | HGSOC |       |               |             |          |
| Underrepresentation of 11p and 13q; overrepresentation of 8q and 7p [9] | High |       |               |             |          |
| 12p underrepresentation and 18p overrepresentation [9] | Low |       |               |             |          |
| Loss of D6S1581 [10] |           |       |               |             |          |
| Gains of 14q32.33 [11] | Resistant |       |               |             |          |
| Gains of 2p22p25, 19p12q13.1 and 20q12q13 and loss of 5q14q22 [12] | High |       |               |             |          |
| Gain in 5p [13] |           |       |               |             |          |
| Gain in 1p and loss in 5q [13] | Low |       |               |             |          |
| Loss at 6q24.2-26 [14] |           |       |               |             |          |
| Gene copy number variation |           |       |               |             |          |
| Gains of FGF3/4 and CCNE1 [18] | Serous |       |               |             |          |
| KRAS amplification [17] | HGSOC, rare in mucinous tumour |       |               |             |          |
| Gain of JUNB, KRAS2, MYCN, ESR and CCND2 [18]; TPM3 amplification [17] | Endometrioid |       |               |             |          |
| ERBB2 amplification [17] | Mucinous |       |               |             |          |
| Amplification of FGFR1 and MDM2; gain of PIK3CA [18] | Borderline |       |               |             |          |
| PIK3CA amplification [20] |           |       |               |             |          |
| CCNE1 amplification [20, 21]; Akt/AKT1 overexpression [23] | Resistant |       |               |             |          |
| AKT2 amplification | High [22] |       | Resistant [23] |             | Adverse [22] |
| Molecular events                                                                 | Heterogeneous clinicopathological characteristics |
|---------------------------------------------------------------------------------|---------------------------------------------------|
|                                                                                | Histology | Grade | Response to CT | Relapse risk | Survival   |
| **Amplification of KLK6 [24], EGFR [25], LMX1B [26], BMP8B, and ATP13A4 [27]** |           |       |                | High         | Adverse    |
| GAB2 amplification [27]                                                         |           |       | Sensitive      | Low          | Favourable |
| **Somatic gene mutation**                                                       |           |       |                |              |            |
| TP53 [15, 20, 28]; FAT3, CSND3, NF1, CDK12, RB1, and GABRA6 [15]                | HGSOC     |       |                |              |            |
| BRCA1/2                                                                         | HGSOC [6] | Sensitive [39, 40] | Resistant | Adverse     |            |
| Reversions of germline BRCA1 or BRCA2 mutations or loss of BRCA1 promoter methylation [20, 41, 42] |           |       |                |              |            |
| BRAF                                                                            | Not mucinous [34]; Serous Borderline tumours [33] |       |                |              |            |
| KRAS [17, 34]                                                                   | Mucinous  | High   |                |              |            |
| PTEN loss [35]; PIK3CA mutation with gain of function [36]                      | Endometrioid and clear cell carcinoma             |       |                |              |            |
| LRP1B deletion [38]                                                             | HGSOC     |       |                | Resistant    |            |

CT: chemotherapy; HGSOC: high-grade serous ovarian cancer; EOC: epithelial ovarian cancer.
| Molecular events | Heterogeneous clinicopathological characteristics | Histology | Grade | Stage | Response to CT | Relapse risk | Survival |
|------------------|--------------------------------------------------|-----------|-------|-------|----------------|--------------|----------|
| **Hypomethylation** |                                                  |           |       |       |                |              |          |
| Satellite DNA hypomethylation [47] | High | Advanced |       |       |                |              |          |
| Re-expression of MCJ, SNGC, and BORIS [45]; overexpression of CLDN4, MALT, BORIS, and TUBB3 [44] |       |       |       |       | Resistant      |              |          |
| LINE-1 [54] and CT45 [55] | High | Advanced |       | High  | Adverse        |              |          |
| HOXA10 promoter hypomethylation | CCC [52, 53], rare in serous tumour [53] |       |       |       |                | Adverse [53] |          |
| **Hypermethylation or methylation** |                                                  |           |       |       |                |              |          |
| MLH1 Hypermethylation [57] | High |       |       |       | Resistant      |              |          |
| hMLH1 promoter methylation |       |       |       |       | Resistant [58–60] | High [59] | Adverse [59] |
| hMSH2 [57] | Endometrioid | High |       |       |                |              |          |
| DLEC1 methylation [60] | HGSOC | Advanced |       | High  |                |              |          |
| FBXO32 promoter hypermethylation or methylation [62] | Advanced |       |       |       | Resistant      | High         |          |
| Promoter hypermethylation of ARMCX2, COL1A1, MDK, and MEST [60] |       |       |       |       |                | Resistant    |          |
| BRCA1 promoter hypermethylation | Serous [67, 68] |       |       |       | Resistant [20] | Adverse [68] |          |
| **Histone modification** |                                                  |           |       |       |                |              |          |
| H3-K27 m3 loss | High [78] | Advanced [78] |       |       | Resistant [79, 80] | Adverse [78] |          |
| Proportion of SIRT1 expression [79] | Serous |       |       |       |                |              |          |
| SIRT1 overexpression [81] | Serous | Early |       |       |                | Favorable    |          |
| **MiRNAs** |                                                  |           |       |       |                |              |          |
| Up-regulation of miR-205 [85] | High | Advanced |       |       |                |              |          |
| Up-regulation of miR-200a [86] | High | Advanced |       |       | High            |              |          |
| Down-regulation of miR-101 [87] | High | Advanced |       |       | Resistant       |              |          |
### Table 2. Continued

| Molecular events | Heterogeneous clinicopathological characteristics |
|------------------|--------------------------------------------------|
|                  | Histology | Grade | Stage | Response to CT | Relapse risk | Survival |
| Reduced expression of miR-34b/c [88], hsa-miR-200a, hsa-miR-34a, and hsa-miR-449b [89] |  |  | Advanced |  |  |  |
| Up-regulation of Hsa-miR-378 [89] |  |  |  | Sensitive |  |  |
| Reduced expression of miR-30c, miR-130a, miR-335 [91], and miRNA-149 [94]; overexpression of MiR-214 [92] and MiR-197 [94] |  |  |  | Resistant |  |  |
| Overexpression of miR-200c [86] |  |  |  |  | High |  |
| Reduced expression of let-7i [90] |  |  |  | Resistant | High |  |
| Overexpression of miR-200, miR-141, miR-18a, miR-93, and miR-429 [95] |  |  |  |  |  | Favourable |
| Overexpression of hsa-miR-27a [89], let-7b, and miR-199a [95] |  |  |  |  |  | Adverse |

### Table 3. Molecular-targeted treatments for EOC

| Drug | Condition | Treatment regimen | Trial phase |
|------|-----------|-------------------|-------------|
| **Targeting homologous recombination (PARP inhibitors)** |  |  |  |
| Olaparib [101, 102] | BRCA-associated ovarian cancer in both newly diagnosed and platinum-sensitive recurrent settings | Combined with post-platinum based CT | Phase III |
| Veliparib [101] | Recurrent HGSC (both germline BRCA and sporadic allowed) | Combined with Temozolomide | Phase II |
| Niraparib [101] | Recurrent platinum-sensitive ovarian cancer | Combined with post-platinum based CT | Phase III |
| Rucaparib [101] | Recurrent platinum-sensitive ovarian cancer | Combined with post-platinum based CT | Phase III |
| BMN673 [101] | Advanced or recurrent EOC | Single agent | Phase I |
| **Targeting the PI3K/AKT/mTOR pathway** |  |  |  |
| Perifosine [110] | Recurrent EOC | Combined with docetaxel | Phase II |
| Temsirolimus [111] | Primary, persistent or recurrent EOC | Single agent | Phase II |
Conclusions

Epithelial ovarian cancer is a heterogeneous disease. As discussed above, the genomic and epigenomic atlas of EOC varies significantly with tumour histotypes, grades, stages as well as with a patient’s prognosis and sensitivity to chemotherapy. The rapidly increasing knowledge about the genetic and epigenetic events that control TH in EOC is facilitating the development of molecular targeted therapy. PARP inhibitors, which are designed to target HR, are poised to change how BRCA-related ovarian cancer is treated, representing the first ‘personalized’ therapy for ovarian cancer. Epigenetic treatments being tested in preclinical or clinical studies are giving rise to optimism regarding the improvement of patient survival and may also provide promising novel treatment approaches.

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Author contribution

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