The Hallmarks of Ovarian Cancer: Actionable Genetics, Targetable Pathways, and Predictive Biomarkers

3

Khalid El Bairi, Ouissam Al Jarroudi, and Said Afqir

Abstract

The development of the conceptual cancer hallmarks has deeply changed our understanding of cancer initiation, progression, and metastasis. Moreover, this pivotal effort is a milestone that provided the scientific rationale for developing new cancer biomarkers and anticancer drugs. In ovarian cancer (OC), the ten cancer hallmarks described by *Hanahan and Weinberg* were investigated in translational studies for prognostic and predictive biomarker discovery. In addition, several interventional clinical trials used these principles to explore the clinical efficacy of several chemotherapeutic and targeted agents such as antiangiogenics and PARP inhibitors. Promisingly, survival outcomes in women with OC were improved with the arrival of novel single agents and combinatorial approaches. In this chapter, the clinical impact of genetics, biomarkers, and therapy in OC is reviewed based on the hallmarks of cancer. We particularly present a special emphasis on druggable targets investigated in phase II/III clinical trials for OC.

Keywords

Ovarian cancer · Hallmarks · Genetics · Therapy · Biomarkers · Outcomes

K. El Bairi (✉) · O. Al Jarroudi · S. Afqir
Department of Medical Oncology, Mohammed VI University Hospital, Oujda, Morocco

Faculty of Medicine and Pharmacy, Mohammed Ist University, Oujda, Morocco
e-mail: k.elbairi@ump.ac.ma

K. El Bairi (ed.), *Ovarian Cancer Biomarkers*,
https://doi.org/10.1007/978-981-16-1873-4_3

3.1 Introduction

With the advent of next-generation sequencing platforms, emerging ovarian cancer (OC) genomic data illustrated important druggable pathways that enabled the successful development of various novel anticancer molecules such as PARP inhibitors (PARPi) and antiangiogenics. Until this time, the dualistic origins and pathogenesis of OC are still debated because of the changing evidence reported in the literature every year (Klotz and Wimberger 2017; Soong et al. 2018). OC is widely regarded as a genetic disease in which the accumulation of mutations is a key driver of its pathogenesis. Targetable genetic alterations reported in OC (Petrillo et al. 2016) might be classified according to the next-generation hallmarks of cancer as previously defined by Hanahan and Weinberg's influential manuscripts (Hanahan and Weinberg 2000, 2011; De Palma and Hanahan 2012; Hanahan and Coussens 2012; Lambert et al. 2017). These hallmarks are defined as "*acquired functional capabilities that allow cancer cells to survive, proliferate, and disseminate; these functions are acquired in different tumor types via distinct mechanisms and at various times during the course of multistep tumorigenesis*" (Hanahan and Weinberg 2011). In this perspective, the present chapter will be discussed according to this promising model. Moreover, a special and central spotlight will be given to the translation of these alterations in cancer drug discovery and biomarkers development based on recent observational and interventional human trials.

3.2 Actionable Hallmarks of Ovarian Cancer

3.2.1 Synthetic Lethality Beyond Genomic Instability

DNA damages and subsequent alterations in cell repair mechanisms are the principal causes that favor tumorigenesis. These are notable results of tumor mutational instability enabling proliferative properties to cancer cells. Genomic instability is the most studied cancer hallmark until today. Repair pathways of DNA damages are complex and encompass several genes of the family of homologous recombination repair (HRR), non-homologous end-joining, and single-strand annealing (De Picciotto et al. 2016). In OC, BReast CAncer (*BRCA*), RAD51 recombinase (*RAD51*), and partner and localizer of BRCA2 (*PALB2*) orchestrate HRR and are found mutated particularly in patients with high-grade serous histology (Lord and Ashworth 2012). Mutations in these tumor suppressor genes drive genomic instability which is a well-known characteristic that predicts outcomes in several cancers including OC. Remarkably, mutations in these genes—namely pathogenic actionable *BRCA1* and *BRCA2* variants—render women with OC particularly sensitive to chemotherapy (see Chaps. 4 and 7) and also PARPi (Le Page et al. 2020), a recently emerged concept known as synthetic lethality. Of note, synthetic lethality induced by PARPi followed by senolytic agents has proven to be synergistic preclinically and therefore, combinatorial approaches using this approach seem to be promising (Topatana et al. 2020). Furthermore, a durable response to immune-checkpoint

blockade can be achieved based on genomics. OC patients with HRR deficiency have a notable infiltration of immune infiltrates which correlate with greater improvement in overall survival (OS) (Keenan et al. 2019; Morse et al. 2019).

The development of PARPi based on this hallmark is a milestone in OC therapy. Various PARPi were approved worldwide for treating OC as a treatment and/or maintenance therapy based on landmark studies (Mirza et al. 2020). PARPi were initially investigated in three randomized phase III trials (NOVA, SOLO-2, and ARIEL-3) as maintenance treatment for patients with recurrent OC after platinum-based chemotherapy (Mirza et al. 2018). NOVA was a double-blind phase III trial that randomized OC patients with platinum-sensitive and recurrent disease to receive niraparib as monotherapy or placebo in a 2:1 fashion with progression-free survival (PFS) as a primary endpoint (Mirza et al. 2016). In this trial, 553 women were enrolled including 203 participants with germline mutated *BRCA* and other 350 participants with non-mutated *BRCA*. Median PFS in niraparib arm was significantly longer as compared to the placebo group ($p < 0.001$) with a manageable bone-marrow toxicity profile by dose reduction. In the germline mutated *BRCA* cohort, women treated with niraparib had 21 months of PFS as compared to 5.5 months in those treated with placebo (HR: 0.27; 95% CI: 0.17–0.41). Furthermore, patients with HRR deficiency (HRD) beyond *BRCA* also benefited from niraparib treatment within an increase of median duration of PFS by 9 months (HR: 0.38; 95% CI: 0.24–0.59) (Mirza et al. 2016). Following these promising findings for niraparib which is the only PARPi approved as maintenance therapy regardless of *BRCA* status, olaparib, another PARPi given as tablets was investigated in the SOLO-2/ENGOT-Ov21 phase III trial (Pujade-Lauraine et al. 2017). This study was a randomized, placebo-controlled and enrolled 295 platinum-sensitive and recurrent OC with *BRCA1* or *BRCA2* mutations to receive olaparib or placebo (2:1 ratio). Median PFS was significantly longer in the arm treated with olaparib than the placebo arm (19.1 vs 5.5 months, HR: 0.30, CI: 0.22–0.41, $p < 0.0001$) (Pujade-Lauraine et al. 2017). Long-term benefit from this oral therapy as a maintenance therapy for relapsed OC was markedly noticed as demonstrated by the latest updated OS data presented at ASCO20 virtual meeting (Poveda et al. 2020). Final OS in this trial showed that maintenance olaparib provided an improved median OS of 12.9 months as compared to placebo after a median follow-up of 65 months (Poveda et al. 2020). Rucaparib was studied in the randomized and placebo-controlled ARIEL-3 phase III trial ($n = 564$, 2:1 ratio) as a maintenance therapy for patients with recurrent platinum-sensitive who had received two regimens of platinum-based chemotherapy (Coleman et al. 2017a, b). Patients with mutated *BRCA* OC had superior median PFS (22.9 vs 5.4 months; HR: 0.23, 95% CI: 0.16–0.34, $p < 0.0001$). In addition, patients with HRD carcinoma also benefited from recuparib (13.6 vs 5.4 months; HR: 0.32, 0.24–0.42, $p < 0.0001$). With a hazard ratio of 0.36, clinically meaningful benefits of recuparib was also noticed in the intention-to-treat population ($p < 0.0001$) (Coleman et al. 2017a, b).

In the recurrent setting, ARIEL-2 was an open-label multicenter phase II trial that investigated rucaparib in 206 women with recurrent and platinum-sensitive high-grade serous OC (Swisher et al. 2017). The median PFS of patients in the *BRCA*

mutant cohort after treatment with rucaparib was 12.8 months. In the other cohorts, median PFS was 5.7 months and 5.2 months in patients with high and low loss of heterozygosity, respectively (Swisher et al. 2017). QUADRA is another phase II trial ($n = 463$) that was planned to investigate the clinical efficacy of niraparib as a single agent in the fourth or later line of treating recurrent OC (Moore et al. 2019a). Enrolled heavily pretreated patients were mainly resistant or refractory to platinum-based chemotherapy ($n = 151$ and $n = 161$, respectively). Median follow-up for OS exceeds 1 year with a manageable hematological toxicity profile, as expected (Moore et al. 2019a). More recently, SOLO-3 randomized FDA-mandated confirmatory phase III was designed to look at response rates for PARP inhibitor olaparib versus one of the non-platinum drugs used in this setting including pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan (Penson et al. 2020). This study randomly assigned 266 recurrent OC patients with platinum-sensitive disease and *BRCA* mutant tumors to receive olaparib or single non-platinum chemotherapy and the objective response rate (ORR) was its primary endpoint. ORR in this population was significantly higher (72.2%) compared to chemotherapy (51.4%). In heavily pretreated women who had received at least two prior lines of chemotherapy, ORR was also superior in the olaparib arm (84.6% vs 61.5%). Median PFS also favored olaparib, which resulted in significantly improved outcomes (HR: 0.62; $p = 0.013$; 13.4 vs 9.2 months) (Penson et al. 2020). However, as mentioned above, this phase III compared a PARPi versus non-platinum drugs in a platinum-sensitive setting without a control using platinum-based chemotherapy. Therefore, this strategy should be reserved for OC patients who are not candidates for platinum-based chemotherapy.

Four randomized phase III clinical trials using PARPi have been conducted for newly diagnosed OC in the first-line setting (SOLO-1, PAOLA-1, PRIMA, and VELIA) (for review, see: Franzese et al. 2020; Mirza et al. 2020; Lee and Matulonis 2020). These trials were all in the front-line setting and had PFS as the primary endpoint but with differences in terms of the composition of their control arms, the timing of the use of PARP inhibition, and platinum-resistance status (Mirza et al. 2020). SOLO-1 was a double-blind phase III trial that randomly allocated patients with newly diagnosed OC and *BRCA* mutant tumors to receive olaparib as a maintenance treatment or placebo in a 2:1 fashion after clinical response platinum-based chemotherapy (Moore et al. 2018c). After a median follow-up of 41 months of the 391 enrolled participants, a reduction of risk of disease progression or death by 70% was noticed in the olaparib arm as compared to placebo (HR: 0.30; 95% CI: 0.23–0.41; $p < 0.001$) (Moore et al. 2018c). Of note, this study excluded all patients without *BRCA* mutant tumors and also not permitted a prior exposure to bevacizumab. Niraparib was studied as monotherapy for maintenance after response to first-line chemotherapy in the randomized and placebo-controlled PRIMA phase III trial ($n = 733$) (González-Martín et al. 2019). Half of the enrolled participants had homologous recombination deficient tumors in which PFS was statistically and clinically meaningful as compared to the placebo arm (21.9 vs 10.4 months; HR: 0.43; 95% CI: 0.31–0.59; $p < 0.001$). Moreover, PFS in the intention-to-treat population was also improved (13.8 vs 8.2 months; HR: 0.62; 95% CI: 0.50–0.76;

$p < 0.001$) (González-Martín et al. 2019). The efficacy of veliparib in the first-line induction treatment was assessed in the VELIA study (Coleman et al. 2019). 1140 patients with previously untreated OC received carboplatin and paclitaxel in combination with veliparib followed by veliparib for maintenance or without veliparib as maintenance in the experimental arm and the standard of care plus placebo and placebo maintenance in the control arm (1:1:1 ratio). Median PFS in *BRCA*-mutated women was significantly superior to the control group and achieved 34.7 vs 22 months (HR: 0.44; 95% CI: 0.28–0.68; $p < 0.001$). Notably, the population of patients with homologous recombination deficiency also benefited from veliparib (HR: 0.68; 95% CI: 0.56–0.83; $p < 0.001$). The findings of this study suggest that first-line induction therapy using carboplatin, paclitaxel, and veliparib followed by veliparib maintenance is superior in terms of PFS as compared to the classical doublet protocol alone (Coleman et al. 2019). PAOLA-1 examined the clinical benefits of adding olaparib to bevacizumab in the first-line maintenance after response to chemotherapy plus bevacizumab in OC patients *BRCA* mutation status (Ray-Coquard et al. 2019). 806 eligible patients received either olaparib or placebo in a randomized fashion (2:1). Median PFS was increased with the use of olaparib in combination with bevacizumab as compared to bevacizumab and placebo (HR: 0.59; 95% CI: 0.49–0.72; $p < 0.001$). The hazard ratio for progression or death in women with positive tumors for homologous recombination deficiency (including *BRCA*) treated with olaparib was 0.33 suggesting a substantial benefit from this combination (Ray-Coquard et al. 2019). Currently, this doublet is considered as the standard of care for first-line maintenance regardless of *BRCA* and HRR deficiency.

Building on this, these landmark studies were successful in providing evidence supporting the use of PARPi in various OC treatment settings. This is further supported by recent multiple meta-analyses of randomized and controlled trials discussed in this section (Tomao et al. 2019; Ruscito et al. 2020; Lin et al. 2021; Hao et al. 2021). Future head-to-head comparisons of PARPi and combinatorial approaches with other anticancer drugs including antiangiogenics and immune-checkpoint blockers will be promising to improve OC care (Veneris et al. 2020) and are a research priority. Moreover, synthetic lethality appears to play a principal role in selecting patients to benefit from the development of PARPi. Knowledge on HRR including *BRCA* mutations seems to be important in conferring sensitivity to these agents. The accuracy of currently available genetic testing procedures needs to be improved in the future. More details on this hallmark can be found in the other chapters of this book.

3.2.2 Tumor Promoting Inflammation

It is well established that inflammation substantially contributes to the supply of protumoral state as well as in the progression of malignancies (Diakos et al. 2014; Taniguchi and Karin 2018). During cancer progression and metastasis, a large number of tumor cells undergo necrotic cell death which drives the recruitment of immune inflammatory cells that can actively promote cancer invasiveness by acting

on angiogenesis and cell proliferation mechanisms (Hanahan and Weinberg 2011). In the ovaries, several events that majorly delay inflammation such as parity (Fortner et al. 2018), oral contraceptives use (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2008; Cibula et al. 2011; Havrilesky et al. 2013), and non-steroidal anti-inflammatory drugs are associated with a reduced risk of OC (Trabert et al. 2018) and improved outcomes in OC patients (Verdoodt et al. 2018). On the other hand, events causing inflammation such as endometriosis have been suggested to increase OC risk (Pearce et al. 2012; Wendel et al. 2018). The link between cancer and inflammation has been investigated in both epidemiological and experimental studies and it was subsequently confirmed through anti-inflammatory therapies that were relatively effective in chemopreventive approaches as suggested by numerous recent meta-analyses (Qiao et al. 2018; Zhang et al. 2016a; Wang et al. 2015; Huang et al. 2014a). Inflammation can damage DNA by releasing reactive oxygen species (ROS) which may cause considerable structural and functional changes such as somatic mutations during the multistep carcinogenesis (Kawanishi et al. 2017). Oxidative stress has been linked to cancer initiation and progression by inducing genome instability through DNA damage or by its mutagenic effects (Aguilera and García-Muse 2013). High concentrations of ROS at the site of damage cause DNA DSBs, mutations in tumor suppressor genes and proto-oncogenes which promote carcinogenesis (Kruk and Aboul-Enein 2017; Kawanishi et al. 2017). Interestingly, various molecular changes associated with repeated hemorrhage-associated oxidative stress during carcinogenesis of high-grade serous OC may explain some pieces of the puzzle (Kobayashi et al. 2017). Retrograde menstruations were proposed as a possible driver of high-grade serous OC by accumulation of genetic alterations in some key genes such as *CCNE1* (Kroeger and Drapkin 2016), *EZH2* (Li and Zhang 2013), *ALDH1A1* (Chui et al. 2014), and *PAX2* (Song et al. 2013) that have key roles in tissue differentiation and carcinogenesis (reviewed by Kobayashi et al. 2017). In addition, fimbrial cells of the fallopian tube may also be a target of ROS (Kobayashi et al. 2017) and are currently considered as a possible origin of high-grade serous OC (Karnezis et al. 2017). Mature ovarian follicles and their fluids (a rich source of ROS) during ovulation were also recently emerged as another probable inflammatory factor that may affect ovarian malignant transformation by causing DNA double-strand breaks and upregulation of inflammatory pathways (Bahar-Shany et al. 2014; Huang et al. 2015). Moreover, cyclooxygenase 2 (COX-2) was found to be highly expressed in OC and correlated with tumor grade (Zhang et al. 2019a). Moreover, COX-2 seems to enhance the capability of cancer cells for proliferation and invasiveness and also confers cisplatin-resistance (Zhang et al. 2019a; Deng et al. 2020). In animal studies, COX-2 inhibition by celecoxib was found to reduce the invasion and growth of OC cells (Li et al. 2012; Wang et al. 2018). This concept was introduced into interventional clinical trials for OC with two published randomized phase II studies using the COX-2 inhibitor celecoxib in combination with carboplatin. Heavily pretreated OC patients were enrolled in a single-arm phase II study to evaluate the clinical activity of oral celecoxib combined with carboplatin (NCT01124435) (Legge et al. 2011). ORR was 28.9% including three complete and ten partial responses with median PFS and OS of 5 and

13 months, respectively, and a well-tolerated toxicity profile (Legge et al. 2011). DoCaCel study was another randomized phase II clinical trial that investigated celecoxib as a combination with docetaxel and carboplatin compared to up-front chemotherapy alone in the first-line setting for stage IC to IV OC (Reyners et al. 2012). After a median follow-up of 32.2 months, median PFS and OS were similar in both arms (14.3 and 34 months respectively). However, no conclusions can be drawn as most patients discontinued celecoxib earlier because of skin reactions (Reyners et al. 2012). Recently, celecoxib was given with metronomic chemotherapy using oral cyclophosphamide for patients with recurrent epithelial OC (Gupta et al. 2019). No difference in terms of medial OS was noticed between the combination group compared to cyclophosphamide alone ($p = 0.95$) (Gupta et al. 2019). Celecoxib is currently investigated in combination with chemotherapy in other ongoing clinical trials for OC (NCT02432378, NCT00538031). Moreover, acetylsalicylic acid (aspirin), another COX-2 inhibitor is being explored for preventing venous thromboembolism among women with OC receiving neoadjuvant chemotherapy (NCT04352439). Aspirin is also used in a randomized phase II study of atezolizumab, bevacizumab, and aspirin for recurrent platinum-resistant OC in the ongoing EORTC-1508 ($n = 122$) (NCT02659384).

3.2.3 Sustaining Proliferative Signaling

3.2.3.1 PI3K/AKT/mTOR Pathway

Phosphoinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway is implicated in various required cell functions such as cell growth, vesicle trafficking, metabolism control, survival, mobility, and angiogenesis and is triggered by cell surface tyrosine kinase receptors (RTKs) (Bilanges et al. 2019; Li et al. 2014; Ghigo et al. 2012). This central signaling axis involves PI3K, the major downstream transducer RTKs, and allows activation of AKT by phosphorylation, which in turn activates downstream effector serine/threonine-protein kinase mTOR. PI3K is composed of eight isoforms divided into class I, class II, and class III PI3Ks that generate lipid messengers involved in signal transduction of intracellular trafficking (Vanhaesebroeck et al. 2010). Oncogenic *PIK3CA* is one of the most commonly mutated genes in human cancers and encodes for enzymatic PI3K protein activated by extracellular signals essentially growth factors (Fruman and Rommel 2014). The negative regulation of PI3K signaling is mainly driven by phosphatase and tensin homolog (*PTEN*) and inositol polyphosphate 4-phosphatase type II (*INPP4B*) tumor suppressor genes (LoRusso 2016). Notably, Loss of *PTEN* or *INPP4B* leads to prolonged activation of AKT which directly activates mTOR complex (mTORC) by phosphorylation. Therefore, this leads to activation of eukaryote translation initiation factor 4E binding protein-1 (4EBP-1) and ribosomal S6 kinase-1 (S6K-1) with protein synthesis as a result which is required for cell-cycle progression and growth (Laplante and Sabatini 2012; Mabuchi et al. 2015).

Upregulation of PI3K/AKT/mTOR pathway can occur as a result of over-activation, modifications in the downstream targets of PI3K and mutations in their regulatory and/or catalytic domains (Mabuchi et al. 2015). Notably, PI3K/AKT/mTOR axis plays a central function in the proliferation and progression of OC (Petrillo et al. 2016; Aziz et al. 2018a). According to the TCGA study, genetic aberrations in PI3K pathway suggested that 45% of OC cases harbor this alteration (Cancer Genome Atlas Research Network 2011). These aberrations include incident mutations and amplifications in key oncogenes *PIK3CA* (12%, 46% in clear cell OC), *PIK3R1* (3.8%), *AKT1* (2%), *AKT2* (13.3%), and *mTOR* (1.9%) (reviewed by Mabuchi et al. 2015). Mutations in *PIK3CA* are frequent (51%) especially in ovarian clear cell carcinomas (a distinct and relatively rare histopathologic subtype of epithelial OC) as found by a recent study using whole-exome sequencing technology (Murakami et al. 2017). Not previously reported *PIK3R1* mutations (8%) in the same tumor histology were also found which suggest that integrated genomic profiling using NGS may be useful in understanding the molecular genetics of this aggressive subtype of OC (Murakami et al. 2017). Similarly, in another NGS report enrolling more clear cell OC patients ($n = 48$), *PIK3CA* mutations were found in 50% of cases (Shibuya et al. 2018). Importantly, *PIK3CA* missense mutations were found significantly associated with improved OS in OC patients with clear cell histology (Rahman et al. 2012). In addition, clear cell ovarian tumors with mutated *PIK3CA* are likely to have hyalinized/mucoid stroma which is a potential risk of paraneoplastic thromboembolism (Kato et al. 2018). Amplification of *PIK3CA* is also seen in recurrent OC suggesting maintained alteration of this pathway during progression and metastasis (Li et al. 2019a). Taken together this high mutation frequency of *PIK3CA* gene in clear cell OC, this signature is of great significance as a biomarker for diagnosis and prognosis and should be investigated in further studies. Alterations in tumor suppressor genes *PTEN* (protein loss or downregulation) and *INPP4B* have also been reported in OC and account for 77% (Martins et al. 2014) and 79% (protein loss) (Salmena et al. 2015), respectively. Importantly, *PTEN* loss was found as an early event in OC and it induces fallopian tube tumor initiation and invasion via a mechanism involving upregulation of *WNT4*, a key gene in cell migration (Russo et al. 2018). Moreover, INPP4B and PTEN loss were found significantly associated with worse outcomes in OC (Gewinner et al. 2009; Skírnisdóttir and Seidal 2011; Salmena et al. 2015; Patch et al. 2015), however, data from other reports were not in line with these findings (McCormick et al. 2016; Bakkar et al. 2015).

Notably, Cai et al. assessed the clinical significance of this pathway in OC based on a meta-analytic approach that included 20 eligible studies (PTEN: 11, PI3K: 5, AKT: 11) and 2499 patients with epithelial OC (Cai et al. 2014). High PI3K and protein AKT expressions were found associated with reduced OS (PI3K—HR: 1.44, 95% CI: 1.08–1.91; AKT—HR: 1.60, 95% CI: 1.26–2.04) (Cai et al. 2014). In terms of PFS, OC patients with high PI3K and protein AKT expressions were related to poor outcomes (PI3K—HR: 3.35, 95% CI: 1.14–9.82; AKT—HR: 1.65, 95% CI: 1.07–2.55) (Cai et al. 2014). Accordingly, the currently available evidence is insufficient to recommend these biomarkers as predictors of prognosis and additional updated meta-analyses and translational prospective studies are warranted.

Drugging the components of the PI3K/AKT/mTOR signaling cascade has been extensively investigated in various human clinical trials according to the U.S. National Library of Medicine database (http://www.clinicaltrials.gov). mTOR inhibition using temsirolimus alone or combined with other anticancer drugs tested in early dose-finding phase I trials showed manageable toxicity profile as well as some signals of clinical activities in gynecological cancers including OC (Temkin et al. 2010; Boers-Sonderen et al. 2014; Piha-Paul et al. 2014; Kyriakopoulos et al. 2016). Previously, Behbakht et al. conducted a phase II trial to study the efficacy of weekly intravenous temsirolimus in 60 patients with persistent and recurrent epithelial OC and other peritoneal carcinomas that have received at least 1–3 chemotherapy regimens (Behbakht et al. 2011). The modest activity was seen in this setting including 24.1% of patients that had a PFS $\geq$ 6 months and 9.3% with partial response (Behbakht et al. 2011). Moreover, Emons et al. enrolled women ($n = 22$) with platinum-refractory/resistant OC to receive weekly intravenous temsirolimus in a phase II trial (AGO-GYN8; NCT01460979) but unfortunately, it didn't meet its predefined efficacy endpoint (Emons et al. 2016). Recently, everolimus, an oral mTOR inhibitor, was combined in another phase II trial with the aromatase inhibitor letrozole in relapsed estrogen receptor-positive high-grade OC in both platinum-resistant and sensitive settings (Colon-Otero et al. 2017). Promisingly, this study enrolling 20 OC patients found a 47% 12-week PFS rate with this combination (median PFS: 3.9 months; 95% CI: 2.8–11.0 and median OS: 13 months) (Colon-Otero et al. 2017). More recently, Tew et al. randomized 150 OC patients in a phase II trial (GOG186-G; NCT00886691) with a recurrent or persistent disease to receive bevacizumab combined with oral everolimus versus bevacizumab alone (Tew et al. 2018). In this study, PFS was the primary endpoint and was not significantly improved in the everolimus arm compared to bevacizumab alone (5.9 vs 4.5 months, HR: 0.95; 95% CI: 0.66–1.37, $p = 0.39$) (Tew et al. 2018). Furthermore, similar findings were noted for median OS (16.6 vs 17.3 months, respectively, HR: 1.16; 95% CI: 0.72–1.87, $p = 0.55$) (Tew et al. 2018). Unfortunately, this combination associating mTOR inhibitor everolimus and bevacizumab demonstrated higher rates of serious adverse events ($\geq$ grade 3) including gastrointestinal perforation and it was not effective in this indication (Tew et al. 2018). Therefore, it is not recommended for further clinical exploration in patients with recurrent OC. Biological rationale and additional clinical data about mTOR inhibition in gynecologic cancers can be found in a recent review (Kassem and Abdel-Rahman 2016).

Preliminary evidence of targeting this pathway by inhibiting AKT has also shown some anticipation in developing new therapeutics for high-grade OC (Fu et al. 2012). Perifosine, a small-molecule AKT inhibitor developed by AEterna Zentaris, was previously tested in platinum and taxane resistant or refractory high-grade OC in combination with docetaxel and showed some signals of activity as well as a good tolerability profile in this phase I trial (Fu et al. 2012). Perifosine monotherapy was also tested in a phase II trial based on a basket design using *PIK3CA* mutational status for recurrent OC patients' stratification (Hasegawa et al. 2017). The modest activity was seen in OC patients with mutated *PIK3CA* including disease control

rates (40%) compared with wild-type status (12.5%) (Hasegawa et al. 2017). Therapeutic advances regarding AKT axis blockade using small molecules and biologics are reviewed elsewhere (in general, by Mattmann et al. 2011 and in gynecologic malignancies, by Bregar and Growdon 2016). Antitumor activity of PI3K inhibition using the Genentech's pictilisib (GDC-0941) designed to be used orally was initially found to have some clinical signs of efficacy in patients with platinum-refractory OC exhibiting PTEN loss and *PIK3CA* amplification (Sarker et al. 2014). When combined with MEK1/2 inhibitor trametinib, PI3K inhibition by buparlisib (BKM120, Array BioPharma and Novartis) given daily has shown promising response in OC patients with mutated *KRAS* (Bedard et al. 2015). However, these positive results were invalidated by the serious toxicity profile found in this phase Ib (NCT01155453) trial including grade 3/4 adverse events (Bedard et al. 2015). Furthermore, combined inhibition of PI3K and PARP in vitro (Wang et al. 2016a) provided the first evidence of synergistic activity that was tested in a phase I trial (Matulonis et al. 2016). Remarkably, the association of PI3K inhibitor buparlisib with PARP inhibitor olaparib demonstrated clinical benefits in breast and OC subjects with both germline mutated and wild-type *BRCA* (Matulonis et al. 2016). Recently, the use of olaparib with the PI3K inhibitor alpelisib confirmed the synergistic effects of this combination (Konstantinopoulos et al. 2019). In this dose-escalation and dose-expansion phase Ib trial (NCT01623349), the authors observed preliminary clinical evidence of the efficacy of this association with 36% of patients having a partial response and 50% with stable disease, which merits further investigation in epithelial OC (Konstantinopoulos et al. 2019). To date, clinical data on this topic are not mature enough to conduct large randomized phase III trials. As a final point, until to date, most sequencing reports have provided discordant mutation frequencies in genes related to this pathway which makes developing targeted drugs difficult as they play an important role in drug resistance. Therapeutic interventions in this OC pathway showed some promise that should be evaluated in future clinical trials with potential predictive biomarkers for better patients' selection.

3.2.3.2 RAS Pathway

The RAS/RAF/MEK/ERK cascade is a receptor tyrosine kinase-dependent signaling axis that links intracellular gene expression pathways to extracellular stimuli (De Luca et al. 2012). It enhances key cellular activities including proliferation, survival, migration, cell-cycle regulation, and other cell functions by phosphorylation/dephosphorylation mechanisms. The dysfunction of this pathway by genetic alterations has been linked to several human malignancies including type I epithelial OC (Spreafico et al. 2017; Della Pepa et al. 2015) and contributes to the hallmarks of cancer by sustaining proliferative signaling. The canonical RAS/RAF/MEK/ERK cascade is initiated by signals such as binding ligands (growth factors, cytokines, etc.) to the corresponding receptor at the cell membrane level. The RAS family of proteins includes three important members, KRAS, NRAS, and HRAS which are located downstream of receptors. The downstream mediators RAF isoforms are protein kinases activated by the binding of small G proteins of the RAS family to

their N-terminal region. Basically, activated RAS recruits and activates RAF which in turn phosphorylates MEK1/2 leading to ERK activation. Activated ERK1/2 has a wide variety of cytosolic and nuclear targets that induce inappropriate cell proliferation and metabolism, survival, and mobility (Papa et al. 2018; Liu et al. 2018). Deregulation of this pathway mainly by constitutive activation of RAS and RAF proteins has been well studied in most solid cancers (reviewed elsewhere: Khan et al. 2018).

Recent studies suggest that *KRAS* mutations are found in clear cell OC with a prevalence ranging from 13% to 16.7% (Shibuya et al. 2018; Zannoni et al. 2014, 2016). *KRAS* and *BRAF* mutations are rare in high-grade serous OC but are proposed to be an important driver of its cancer biology (Cancer Genome Atlas Research Network 2011). In low-grade serous OC, *BRAF* mutations are less common and represent 5% (Turashvili et al. 2018), which is contradictory with the previous data suggesting 33% prevalence (Singer et al. 2003). Based on targeted exome and whole-genome sequencing, Moujaber et al. find that 13.8% of low-grade serous OC patients had somatic mutations in the *BRAF* gene (Moujaber et al. 2018). However, this difference in mutation frequency may be due to the difference in the enrollment of patients with this relatively rare OC subtype as well as the variability of clinical stages of included samples. Moreover, low-grade serous OC is known for remarkable mutated *KRAS* (35%) (Singer et al. 2003). In summary, *KRAS* and *BRAF* mutations are more likely to be associated with low-grade serous and clear cell OC (Prat et al. 2018; DeFazio et al. 2016; Kaldawy et al. 2016; Russel and McCluggage 2004). Very few reports have investigated the prognostic value of these genetic alterations in OC. Earlier, Wong et al. found based on a cohort of 91 OC samples that low-grade serous tumors with mutant-*BRAF* and *KRAS* are likely to have improved clinical outcomes (Wong et al. 2010). In addition, patients with this chemoresistant disease harboring mutated *BRAF* had better OS as compared to patients with wild-type *KRAS* and *BRAF* status (Grisham et al. 2012). Recently, it was reported that low-grade serous OC patients with mutated *BRAF* or *KRAS* have significantly improved OS compared with wild-type patients (106.7 vs 66.8 months, respectively; $p = 0.018$) (Gershenson et al. 2015). Unexpectedly, these findings are conflicting with the recent results in the Chinese patients in which neither *KRAS* nor *BRAF* mutations were found to be prognostic biomarkers (Xu et al. 2017). In addition, mutated *KRAS* was found to predict chemosensitivity to anticancer drug decitabine (an FDA approved DNA methyltransferase inhibitor) (Stewart et al. 2015) but the real clinical impact of these two mutated signatures (*KRAS* and *BRAF*) is still inconclusive because of the small number of enrolled cases and therefore, should be replicated in larger cohorts.

The blockade of the components of this pathway by the recently developed inhibitors, trametinib (mekinist®, Novartis), dabrafenib (tafinlar®, GlaxoSmithKline), and vemurafenib (zelboraf®, Plexxikon and Hoffmann-La Roche) has demonstrated significant clinical benefits in various cancers such as advanced melanoma (Luther et al. 2019; Dhillon 2016) and lung cancer (Kelly 2018) especially when combined with other anticancer agents. In OC, preclinical findings indicating the efficacy of MEK inhibitors in cancer cell lines (Simpkins

et al. 2018; Pétigny-Lechartier et al. 2017; Fernández et al. 2016, 2019; Gruosso et al. 2015; Cossa et al. 2014; Sheppard et al. 2013; Katagiri et al. 2010) have provided biological rationale of using MEK blockade in human clinical trials. In this perspective, selumetinib (AZD6244; Array BioPharma and AstraZeneca), a potent orally available small molecule that inhibits MEK1/2 enzymes, was recently granted orphan drug designation by the FDA for treating uveal melanoma, thyroid cancer, and neurofibromatosis (AdisInsight (Springer) website, https://adisinsight.springer.com/drugs/800019504, accessed 25/01/2019). It was investigated in OC in a single-arm phase II trial (NCT00551070) enrolling women with recurrent low-grade serous ovarian or peritoneal tumors (Farley et al. 2013). This pretreated population experienced a PFS of 11 months and 63% of patients had PFS $>$ 6 months which merit further development of this drug in this chemoresistant OC (Farley et al. 2013). Interestingly, a dramatic response to selumetinib was seen in a patient with mutated *KRAS* recurrent low-grade serous OC who showed a durable response for more than 7 years (Takekuma et al. 2016). Selumetinib is being investigated by M.D. Anderson Cancer Center and AstraZeneca in a phase I trial (NCT03162627) combined with PARP inhibitor olaparib for patients with advanced endometrial, ovarian, and other solid malignancies with altered RAS pathway and is still recruiting (estimated study completion date: 2026). In addition, selumetinib combined with fulvestrant (Faslodex®), an estrogen receptor antagonist developed by AstraZeneca, showed potential for this association in reversing resistance in positive estrogen receptor OC (Hew et al. 2015) which illustrates a promising use in upcoming early human studies. MEK blockade by binimetinib (MEK162; Array BioPharma), another inhibitor of this pathway, has shown an interesting prolongation of response duration (31 months) in a woman with advanced/recurrent low-grade serous OC that was enrolled in the MILO phase III trial (NCT01849874) and having mutated *KRAS* (Han et al. 2018). Additionally, evidence of binimetinib activity in OC has been achieved in a phase Ib trial (NCT01649336) combining this drug with paclitaxel particularly in patients with known altered MEK pathway (Grisham et al. 2018). MILO phase III randomized and parallel-assignment clinical trial is currently being conducted to assess the efficacy of binimetinib as monotherapy versus best physician choice (paclitaxel, topotecan, or PLD) in women ($n = 360$, estimated) with recurrent or persistent low-grade serous OC in North America, Europe, and Australia (NCT01849874). MILO study completion date is estimated in September 2019. Trametinib is another potential oral inhibitor of MEK enzymes that have exhibited impressive response rates with dabrafenib combo in treating solid cancers especially unresectable or metastatic melanoma with *BRAF* $^{V600E/K}$ mutations (Long et al. 2017a, b; Abdel-Rahman et al. 2016). In OC, doublet PI3K/MEK inhibition using buparlisib in combination with trametinib has been studied in phase Ib trial (NCT01155453) and demonstrated promising clinical signals of activity (76% of disease control rate) in patients with mutated *KRAS* (Bedard et al. 2015). To date, only two case reports have reported dramatic response to trametinib combined with dabrafenib or metformin in selected patients with low grade and clear cell histology harboring *KRAS* and *BRAF* mutations and therefore, highlighting the need for clinical trials with predefined basket designs (Mendivil et al. 2018; Castro et al.

2015). This underscores the need for predictive biomarkers for this pathway blockade to identify OC patients who are most likely to derive durable clinical benefit. A phase III randomized trial (NCT02101788) is being conducted by the NCI (National Cancer Institute) that will enroll an estimated number of 260 recurrent or progressive low-grade OC patients with cross-over assignment. In this trial, PFS is the primary endpoint with intention-to-treat analysis and patients will be randomized to receive trametinib or clinician's choice (topotecan, paclitaxel, letrozole, tamoxifen, or PLD). Importantly, this trial will also assess various genetic testing by NGS for various genes related to this pathway such as KRAS in addition to circulating cell-free tumor DNA and their correlation with tumor response. Patient recruitment with this rare histological subtype is the major challenging barrier. Taken together, targeting this pathway in this subtype of OC is at the beginning and promising treatments are to come in the near future (for a detailed review in this topic, see: McLachlan et al. 2016a, b).

3.2.3.3 Cyclin E1

Cyclin 1 protein is encoded by the *CCNE1* gene and constitutes a core signaling that accelerates G1/S transition by binding cyclin-dependent kinases (CDK) (Kanska et al. 2016). Principally, CDK2 is the main partner of CCNE1 and plays a key role in various cell functions such as cell-cycle progression, DNA replication, transcription, and repair (Wood and Endicott 2018; Kanska et al. 2016). Interactions of CCNE1 and their associated CDK can provoke modifications in their ATP-binding pockets which enables access of target substrates. Briefly, CDK enzymes are activated by Cdc25 which in turn phosphorylates Cdc25 by positive feedback to generate active CDK/cyclins required for cell-cycle control (Kanska et al. 2016). Negative regulation of this signaling is ensured by cell-cycle inhibitors p21 and p27, key mediators of *TP53*-mediated damage response as well as TGF-β/SMAD pathway (reviewed in detail elsewhere: Kanska et al. 2016).

Increased oncogenic CCNE1/CDK2 kinase activity is involved in the mitogenic transformation of various cancers such as hepatocellular carcinoma (Bayard et al. 2018; Sonntag et al. 2018), lung cancer (Huang et al. 2012), breast cancer (Lundgren et al. 2015), endometrial and uterine cancers (Kuhn et al. 2014), and OC (Kuhn et al. 2016). *CCNE1* genetic deregulation by amplification is an early event in the genesis of fallopian tube-derived high-grade serous OCs (Karst et al. 2014; Kuhn et al. 2016). Genetically altered *CCNE1* is found in about 20% of OCs (Nakayama et al. 2010). Notably, OC patients with *CCNE1* amplifications tend to have poor survival (Nakayama et al. 2010; Cancer Genome Atlas Research Network 2011; Ayhan et al. 2017; Zhao et al. 2018) and are chemoresistant to standard chemotherapy (Patch et al. 2015; Etemadmoghadam et al. 2009). Recently, various reports have confirmed this association which supports the use of altered *CCNE1* as a prognosticator and predictive biomarker of treatment failure in OC management. In this perspective, an early study by Etemadmoghadam et al. found that *CCNE1* copy number gain is significantly associated with poor PFS and OS in a cohort of 43 advanced serous ovarian tumors (Etemadmoghadam et al. 2010). Similarly and based on primary tumors data, another study by the previous team showed that high-grade OC patients

with amplified *CCNE1* showed short OS and their tumors were associated with polyploidy (Etemadmoghadam et al. 2013a), a substantial driver of chemotherapy resistance (Kuznetsova et al. 2015; Mittal et al. 2017). Moreover, this study has also demonstrated that cell polyploidy drives resistance to inhibition of CCNE1 partner CDK2 and therefore may be used to identify a subset of OC patients that are likely to benefit from anti-CDK agents under development (Etemadmoghadam et al. 2013a). Of note, polyploidy arises from genome doubling, early during cancer evolution and is highly common across various cancers with poor prognosis (Bielski et al. 2018). Likewise, another recent study suggests that tumors from high-grade serous OC patients ($n = 41$) with short survival are characterized by focal copy number gain of *CCNE1* in addition to wild-type *BRCA* status (Yang et al. 2018). In a relatively large cohort that enrolled 262 high-grade serous OC, amplified-*CCNE1* tumors were found associated with genome instability as well as poor clinical outcomes as compared with the non-amplified group (Aziz et al. 2018b). Unlike previously discussed reports and contrary to the expectations, Pils et al. demonstrated in a cohort of 172 serous epithelial OC tissues that amplified-*CCNE1* has no impact on clinical outcomes (Pils et al. 2014). Surprisingly, based on Cox model, high *CCNE1* gene expression was found to be significantly an independent predictive biomarker of prolonged OS in stage III/IV OC patients (Pils et al. 2014). One possible explanation is that ovarian tumors harboring *CCNE1* alterations may have other important genetic signatures that influence survival and therapy response and have to be considered as well because of the substantial heterogeneity within and between OC patients. More recently, co-amplification of *CCNE1* and *BRD4* (bromodomain and extraterminal 4) was found in OC patients with worse OS (Petersen et al. 2020). In addition, this report also confirmed the role of high protein expression of cyclin E in conferring platinum-resistance ($p = 0.016$) (Petersen et al. 2020). These discordant results came from small study cohorts which limit definitive answers to the prognostic and predictive value of this oncogene in OC. Hopefully, more conclusive data are awaited especially from randomized and controlled trials that are investigating *CCNE1* in OC as a biomarker for patients' stratification. Based on promising anticancer activity of bortezomib (a proteasome inhibitor) in *CCNE1*-amplified high-grade serous OC (Etemadmoghadam et al. 2013b), this amplification is being used as a predictor of response rate in a currently recruiting phase II trial (NCT03509246) that will evaluate the efficacy of bortezomib combined with PLD for platinum-resistant OC patients with wild-type *BRCA* status. In addition, two other phase I/II trials (NCT02797977; NCT02797964) conducted by Sierra Oncology, Inc. are recruiting patients with advanced cancers including OC and will investigate SRA737 agent (a checkpoint kinase 1 inhibitor) based on various genetic signatures including altered *CCNE1* and *BRCA* to predict sensitivity to this new anticancer drug.

Remarkable advances regarding pharmacological inhibition of the kinase components of this pathway were recently achieved especially in breast cancer with the promising results from phase III trials (NCT01958021, NCT01942135) testing inhibitors of cyclin-dependent kinases (CDK) 4/6 including palbociclib (Ibrance®, Pfizer) (Verma et al. 2016) and ribociclib (Kisqali®, Novartis)

(Hortobagyi et al. 2016). In OC, preclinical investigation of dinaciclib (MK-7965, Merck & Co), a CDK2 inhibitor, showed synergistic anticancer activity when combined with AKT inhibitors in CCNE1-amplified tumors (Au-Yeung et al. 2016). In addition, a combination of ribociclib and cisplatin followed by ribociclib maintenance demonstrated potential antitumor response in both in vitro and in vivo high-grade serous OC model (Iyengar et al. 2018). Currently, there is one phase I clinical trial (NCT02897375) recruiting patients with advanced cancers including OC and will assess the safety of palbociclib combined with cisplatin or carboplatin. Ribociclib is also being evaluated in OC in combination with immunotherapy (PDR001) and hormone therapy (fulvestrant) in a phase I trial (NCT03294694) as well as in another phase I trial (NCT03056833) in combination with paclitaxel/carboplatin and is still currently recruiting patients. Until this time, only one phase II trial (NCT03673124, $n = 51$) by the Gynecologic Oncology Group (GOG—http://www.gog.org) in collaboration with Pfizer is planned to evaluate the efficacy of palbociclib combined with letrozole in women with recurrent low-grade serous OC and it is estimated to provide first results in July 2021. Promisingly, these recent signs of progress in understanding this proliferative signaling have illuminated potential targets and biomarkers to guide drug selection and are currently used in developing novel targeted agents for OC.

3.2.3.4 EGFR Pathway

Historically, epidermal growth factor receptor (EGFR) and its related proteins including human epidermal receptor (HER2) have been extensively studied for more than three decades and their critical role in epithelial cell development and cancer has been elucidated since 1978 (for review see: Mitsudomi and Yatabe 2010; Arteaga and Engelman 2014). Moreover, family members of EGFR proteins are important targets of multiple anticancer drugs such as monoclonal antibodies and small-molecule tyrosine kinase inhibitors that were successfully developed for treating various epithelial cancers including gynecological cancers (Reyes et al. 2014). The interaction between the four EGFR family transmembrane protein receptors through homodimerization and heterodimerization, as a result of ligand binding and/or receptor mutations, directly affects downstream key cell signaling pathways by activating many genes responsible for tumor cell proliferation, survival, and invasion (Sigismund et al. 2017). Studies reporting overexpression of EGFR in epithelial OC suggest a range of 4–100% of cases (Teplinsky and Muggia 2015). Importantly, EGFR and HER protein (or gene) members, especially HER2, are suggested to have an impact on the prognosis of OC as demonstrated by recent studies (Despierre et al. 2015; Demir et al. 2014; Shang et al. 2017a) and an up-to-date meta-analysis (Luo et al. 2018). However, blockade of EGFR in randomized controlled trials (RCTs) comparing targeted anti-EGFR drugs with or without standard chemotherapy in epithelial OC patients as first-line or as maintenance has demonstrated a marginal gain in survival outcomes (Morrison et al. 2018).

3.2.3.5 Folate Receptor Pathway

Folate is a vitamin with fundamental roles in DNA synthesis and methylation, and also recombination repair (Rizzo et al. 2018). Cellular intake of folates is achieved throughout its contact with the reduced folate carrier transporter or by endocytosis facilitated by folate receptor alpha (FR-α) glycoprotein (Zhao et al. 2011). FR-α is encoded by the FOLR1 gene located on chromosome 11 (11q13.4). FR-α is a high affinity glycosylphosphatidylinositol membrane-anchored protein that binds and transports physiological levels of folate into cells (Rizzo et al. 2018). FR-α is suggested to affect chemoresistance via regulating the expression of apoptosis-related signaling proteins, Bcl-2 and Bax (Chen et al. 2012). A higher FR-α expression was found to be an important biomarker for prognosis and response to therapy in several aggressive solid cancers such as pancreatic ductal adenocarcinoma (Cai et al. 2017), triple-negative breast cancer (Ginter et al. 2017), and recurrent, platinum-resistant and refractory OC (Martin et al. 2017; Rubinsak et al. 2018). Furthermore, OC patients who express an increased level of FR-α have poor response to chemotherapy ($p = 0.021$) as well as poor disease-free interval (HR: 2.45; 95% CI: 1.16–5.18, $p = 0.02$) and OS (HR: 3.6; 95% CI: 0.93–13.29, $p = 0.03$) (Chen et al. 2012). Promisingly, recent studies provided rational therapeutic targeting of FR-α in OC as showed by several human clinical trials using monoclonal antibodies (Armstrong et al. 2013), vaccines (Kalli et al. 2018), and novel class antibody-drug conjugates (ADC) (Stewart and Cristea 2019). Recently, Armstrong et al. enrolled 54 OC patients with platinum-sensitive disease in phase II open-label trial comparing the anti-FR-α farletuzumab (MORAb-003) weekly as monotherapy versus in combination with standard carboplatin and taxanes (paclitaxel 175 mg/m^2 or docetaxel 75 mg/m^2) every 3 weeks (six cycles) followed by farletuzumab as maintenance (Armstrong et al. 2013). Notably, adding farletuzumab to carboplatin and taxanes improved the response rate and duration of response in this setting (Armstrong et al. 2013). Following these promising results, a phase III randomized and controlled trial (NCT00849667) was conducted to evaluate treatment with farletuzumab versus placebo in 1100 recurrent and sensitive OC but it didn't show any statistically significant difference between the arms (Vergote et al. 2016). Interestingly, attempts to develop immunity against FR-α in OC based on peptide vaccines were also investigated and showed motivating results (Kalli et al. 2018). In this perspective, a phase I trial (NCT01606241) that tested the safety of FR-α peptide vaccine and enrolled OC patients with no evidence of disease after completed standard therapy found that this strategy is well-tolerated and that FR-α T-cell immunogenic response was developed over the vaccination course which was observed and persisted for at least 12 months (Kalli et al. 2018). In addition, Yeku et al. assessed this strategy in a phase II trial (NCT02764333) using TPIV200 vaccine (Tapimmune Inc.), a polypeptide multi-epitope against FR-α, in combination with anti-PD-L1 durvalumab (Imfinzi®, AstraZeneca) for patients with platinum-resistant or refractory OC (Yeku et al. 2018). This promising combination with an immune-checkpoint inhibitor was found safe and opened a new era for OC vaccines. FR-α-based therapeutic targeting in OC has benefited from the innovative ADC as well (Moore et al. 2018a). Briefly, ADC are newly developed anticancer

drugs and are based on engineered complexes composed of a monoclonal antibody directed against cancer cell antigens such as (FR-α and CD30), a biologically active cytotoxic drug and a linker (Moore et al. 2018a; Beck et al. 2017). This method enables a targeted delivery and cancer-killing ability with reduced toxicity by allowing discrimination between healthy and cancer tissues (Beck et al. 2017). There are currently various randomized and controlled trials investigating ADCs in human cancers such as brentuximab vedotin (Adcetris®, Seattle Genetics) and ado-trastuzumab emtansine (Kadcyla®, Genentech) as well as mirvetuximab soravtansine (IMGN853, ImmunoGen) for OC particularly for platinum-resistant patients. Mirvetuximab soravtansine is an ADC that binds to FR-α to deliver a powerful anti-microtubule (maytansinoid) drug into cancer cells (Moore et al. 2018a). Phase I dose-finding and safety trials demonstrated manageable toxicity (grade 1 or 2 fatigue, blurred vision, and diarrhea) and encouraging preliminary clinical activity in OC (Moore et al. 2017, 2018b). Recently, results of FORWARD II (expansion cohort, NCT02606305) phase Ib trial combining mirvetuximab soravtansine with immune-checkpoint inhibitor pembrolizumab (Keytruda®, Merck) were presented at ESMO 2018 meeting and showed potential signals of clinical activity in recurrent platinum-resistant setting (Matulonis et al. 2018). Promisingly, FORWARD I phase III multicenter trial conducted by ImmunoGen, Inc. in collaboration with Gynecologic Oncology Group is enrolling 333 women with platinum-resistant advanced OC in a randomized fashion (NCT02631876). This trial compared the efficacy of mirvetuximab soravtansine versus the investigator's choice of chemotherapy (paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan) in FR-α-positive patients and with PFS as a primary endpoint (study design reviewed by Moore et al. 2018a). Recently, the findings of this pivotal trial showed significant improvements in the arm treated with mirvetuximab soravtansine in terms of ORR (24% vs 10% in the controlled arm; $p = 0.014$) but without improved PFS in the intention to treat population (HR: 0.981; $p = 0.897$) (Moore et al. 2019b). The data on OS (as of August 2019) showed a benefice for this antibody-drug conjugate in patients selected based on high expression of FR-α (16.4 vs 12.0 months; HR: 0.678, $p = 0.048$) (Moore et al. 2019b). Two additional phase III trials (MIRASOL/NCT04209855, SORAYA/NCT04296890) with a large sample size for this setting are currently ongoing. Moreover, approaches using combinations such as mirvetuximab soravtansine and bevacizumab yielded promising findings for this difficult-to-treat population (O'Malley et al. 2020; Fowler 2020). Furthermore, academic clinical trials are also currently ongoing to study the early efficacy of mirvetuximab soravtansine in combination with PARP inhibitors and chemotherapy (NCT02996825/cohort C; NCT03552471).

In another effort for this setting, vintafolide (a folate-vinca (desacetylvinblastine hydrazide) conjugate; Endocyte®) that targets tumors with positive FR-α was tested in phase III trials (Ledermann et al. 2015; Assaraf et al. 2014). In this perspective, PRECEDENT is a phase II trial (NCT00722592) that has been conducted to randomize 149 women (intention to treat population) with platinum-resistant OC to receive intravenous vintafolide + PLD versus PLD alone (Naumann et al. 2013). Some marginal improvement in terms of PFS in the vintafolide arm was seen in this

difficult to treat setting (5.0 vs 2.7 months, HR: 0.63; 95% CI: 0.41–0.96, $p = 0.031$) (Naumann et al. 2013). However, the interim analysis of the following PROCEED phase III trial (NCT01170650) didn't provide significantly improved outcomes with this treatment and therefore, the study was stopped to enroll more patients (Oza et al. 2015b). This strategy particularly using mirvetuximab soravtansine may represent a promising hope for targeting this pathway in platinum-resistant OC (for further reading, see: Bergamini et al. 2016; Scaranti et al. 2020; El Bairi et al. 2021). This hallmark of OC and particularly this drug target seem to have a promising future as a therapeutic strategy for this aggressive gynecological cancer.

3.2.4 Evading Growth Suppressors

3.2.4.1 TP53 Network

Mutated *TP53* events are still by far the most prevalent in cancer since the discovery of this tumor suppressor gene in 1979 (Soussi 2010). Every year, thousands of papers are published and provided notable novel findings regarding p35 functions, genetic variants as well as possible therapeutic interventions. There are more than 70,000 articles recorded on PubMed/Medline until today along with 140 clinical trials on the US ClinicalTrials.gov database (accessed 25 February 2019). Moreover, there is a rich source of data related to this gene and important databases were created for this purpose such as the IARC TP53 Database (http://p53.iarc.fr/) and The UMD TP53 Database (https://p53.fr/tp53-database) providing updated information for the scientific community working on this hot subject (for review, see: Leroy et al. 2014; Bouaoun et al. 2016). The *TP53* gene encodes for p53 protein with suppressive cell functions and is the most studied anti-oncogene to date (Aubrey et al. 2016). P53 protein has binding transcription factor activity and can bind to various promoter elements of key human genes to regulate their expression. Particularly, *TP53* fundamentally controls cell proliferation and maintains the integrity of the human genome and is linked to all cancer hallmarks previously described by Hanahan and Weinberg in 2011 (Hanahan and Weinberg 2011; Aubrey et al. 2016). Briefly, in normal conditions, low p53 levels are maintained by negative regulation of MDM2 (murine double minute 2), an E3 ubiquitin ligase, that represses p53 transcriptional function and also enables its degradation by the proteasome (Vijayakumaran et al. 2015). Furthermore, p53 acts on several target genes that mediate cell-cycle arrest, DNA repair, apoptosis, and autophagy in the presence of activating stimuli such as oncogene expression and DNA damage.

While somatic *TP53* gene alterations are frequent in several cancers (Hainaut and Pfeifer 2016), germline mutations predispose to a wide spectrum of early-onset cancers such as Li-Fraumeni and Li-Fraumeni-like syndromes (Guha and Malkin 2017; Andrade et al. 2017). According to the TCGA project, OCs are characterized predominantly (96%) by mutated *TP53* in almost all sequenced tumors (Cancer Genome Atlas Research Network 2011). *TP53* gene alterations reported in cancer are represented mainly by point mutations and are dominated by missense mutations (exons 5–8) particularly in breast and OCs (Silwal-Pandit et al. 2017). Tumor cells

with mutated *TP53* can control the gene expression associated with tumorigenesis, including proliferation, migration, and invasiveness (Kang et al. 2013; Lee et al. 2015; Ren et al. 2016; Ahn et al. 2017; Xu et al. 2019). Mutated *TP53* upregulates the expression of several pro- and anti-apoptotic genes, such as *MYC*, *FAS*, *BCL2L*, *NFkB2*, and *ABCB1* (Brosh and Rotter 2009). Recent evidence from sequencing reports of low stage tumors suggests that deleterious *TP53* mutations alongside tetraploidy and homologous recombination repair defects are the earliest events in the pathogenesis of high-grade serous OC (Flesken-Nikitin et al. 2013; Chien et al. 2015; Huang et al. 2015; Labidi-Galy et al. 2017; Soong et al. 2019).

Based on previous studies that assessed the clinical relevance of linking *TP53* mutations with the prognosis of OC (Kang et al. 2013; Rechsteiner et al. 2013; Nadkarni et al. 2013; Wong et al. 2013; Wojnarowicz et al. 2012; McAlpine et al. 2012; Köbel et al. 2010; Bernardini et al. 2010), various recent studies have provided evidence regarding their impact on survival outcomes and response to treatments. In this regard, the $TP53^{K351N}$ variant was found to be associated with platinum-resistance to neoadjuvant chemotherapy in advanced OC (Zhang et al. 2014). Notably, this mutation independently predicted disease-free survival in this setting (Zhang et al. 2014). Mechanistically, it seems that mutated *TP53* induces genome instability and chromosome 7 accumulation in addition to *MDR1* gene amplification favors chemoresistance (Zhang et al. 2017). Recently, these findings were confirmed in a large prospective cohort (Ghezelayagh et al. 2020). In fact, *TP53* mutations, which account for 87.9% in high-grade OC, were found associated with platinum sensitivity even after adjusting for *BRCA*-mutated status (OR: 0.41, 95% CI: 0.17–0.99; $p = 0.048$) but not with survival outcomes (Ghezelayagh et al. 2020). However, several authors have recently demonstrated that *TP53* also impacts the survival of OC patients. Based on the Cancer Genome Atlas (TCGA) data, Seagle et al. demonstrated that *TP53* hot spot mutations in epithelial high-grade serous OC confer differential OS outcomes (Seagle et al. 2015). Patients with R248 codon had the worse OS, followed by those with any other codons, R175 codon, and R273 codon which had the highest OS ($p = 0.04$). Moreover, the authors also showed their in vitro experimentation that *TP53* mutations confer resistance to the antimicrotubules paclitaxel, epothilone B, and ixabepilone (Seagle et al. 2015). In another TCGA-based study, the co-occurrence of mutated *TP53* and *BRCA* in serous OC was found to be associated with improved survival as compared to *TP53* or *BRCA* alone (Li et al. 2019b). However, the latest cohort report by Mandilaras et al. demonstrated that these mutations have no impact on a first platinum-free interval or OS (Mandilaras et al. 2019). To date, the prognostic impact of loss or gain of functions of *TP53* in OC is still conflicting. Therapeutically, targeting the TP53 pathway was also investigated in early clinical trials for OC. A phase II trial (NCT01164995) that investigated AZD1775 (a WEE1 kinase inhibitor developed by Merck®) given orally in combination with carboplatin in patients with *TP53*-mutated resistant or refractory OC to first-line chemotherapy showed encouraging signs of efficacy (Leijen et al. 2016). The toxicity profile was manageable and was mainly represented by fatigue, nausea, thrombocytopenia, diarrhea, and vomiting. In the 21 evaluated patients for efficacy, the overall response was 43% including one

patient that had a prolonged complete response. In addition, median PFS and OS were 5.3 and 12.6 months, respectively, in this difficult-to-treat population (Leijen et al. 2016). More recently, Oza et al. conducted a double-blind phase II trial (NCT01357161) to investigate the efficacy of oral adavosertib (AZD1775) or placebo in association with carboplatin and paclitaxel in OC patients with platinum-sensitive disease and enriched with mutated *TP53* (Oza et al. 2020). The addition of adavosertib to chemotherapy was found to improve PFS (HR: 0.63; 95% CI: 0.38–1.06); $p = 0.08$, meeting the predefined significance threshold <0.2 (Oza et al. 2020). More recently, the clinical activity of adavosertib in combination with gemcitabine in platinum-resistant or refractory OC was investigated in a randomized and placebo-controlled phase II trial (NCT02151292) (Lheureux et al. 2021). Median PFS in women treated with adavosertib and gemcitabine was significantly superior compared to gemcitabine monotherapy (HR: 0.55; 95% CI: 0.35–0.90, $p = 0.015$). Regarding OS, the experimental arm median OS was 11.4 months compared to 7.2 months in the control group treated with gemcitabine (HR: 0.56; 95% CI: 0.35–0.91, $p = 0.017$). However, despite this hope for this setting with poor outcomes, this study results introduced clinically significant adverse events (Lheureux et al. 2021). These works highlight the important role of *TP53* in OC and may be a promising targetable pathway for drug discovery in this cancer.

3.2.4.2 Retinoblastoma Protein Signaling

Historically, the retinoblastoma gene (*RB1*) was initially discovered in the 80th and was the first isolated human tumor suppressor gene (Lee et al. 1987). *RB1* gene is located at chromosome 13 (13q14.2) and is a key player in the control processes of cell-cycle progression in cooperation with other tumor suppressors such as *BRCA* and *TP53* (Di Fiore et al. 2013). Notable functions including cell-cycle arrest, cell death, genomic stability, differentiation, and a plethora of other cellular roles are regulated by this triplet of anti-oncogenes (Dick and Rubin 2013; Manning and Dyson 2012). Negative regulators of RB1 function by phosphorylation encompass cyclin D, CDK4, and CDK6 and allow G1/S transition by activation of the E2F family of transcription factors (transcribe a range of genes required for S phase) which therefore enable mitogenic release (reviewed in detail by Sherr and McCormick 2002; Dick and Rubin 2013).

RB1 loss is not only implicated in the development of retinoblastoma but is also related to the initiation and progression of several pediatric and adult cancers such as OC (Li et al. 1991; Takenaka et al. 2015; Stover et al. 2016; Jia and Zhao 2019). In addition to germline and somatic alterations of *RB1* observed in many cancers, a previous analysis of three case-control studies suggested that single nucleotide polymorphisms in three common variants of this gene may be also associated with an increased risk to develop invasive OC (Braem et al. 2011; Song et al. 2006). Data from the TCGA study found that *RB1* expression is deregulated in 67% of high-grade serous OC cases (The Cancer Genome Atlas Research Network 2011). A recent report using NGS found a prevalence of 29% of copy number variation of *RB1* gene in recurrent OC (Du et al. 2018) but there is still a lack of sequencing studies focusing on the prevalence of its genetic alterations in primary tumors. To date, most

OC genome sequencing projects focused only on the prognostic value of *RB1* for chemoresistance and survival outcomes (Garsed et al. 2018; Du et al. 2018; Patch et al. 2015; Takenaka et al. 2015; Milea et al. 2014). Gene breakage or homozygous deletion in *RB1* in OC was found recently to be associated with exceptional response to platinum-based treatment mainly in patients with improved PFS (Garsed et al. 2018). Gene breakage is a type of genetic alteration due to high levels of replication stress and causes a defect in DNA repair mechanisms which may explain possible sensitivity to various treatments. This previous study further assessed RB1 protein loss based on immunohistochemistry in a cohort of 313 OC patients including 91 exceptional responders and found a significant association with long PFS (35%, $p < 0.001$) as compared with unselected OC cases (Garsed et al. 2018). Moreover, Kaplan-Meier survival analysis suggested that exceptional responders to treatment with RB1 protein loss had better survival when their tumors harbor HRR deficiency ($p = 0.03$) (Garsed et al. 2018) which is consistent with a previous large cohort of high-grade serous OC (Milea et al. 2014).

3.2.5 Activating Invasion and Metastasis

Metastasis is a fatal hallmark of cancer. Patients with advanced cancer die often because of metastatic disease. This inevitable and organotropic process, particularly in OC, involves a complex interaction between intrinsic tumor characteristics and surrounding stroma (Welch and Hurst 2019). In OC, neoplastic progression into the peritoneal cavity was widely considered to be different as compared with other solid cancers. In fact, OC cells metastasize through a route using passive spread known as trans-coelomic dissemination (Barbolina 2018; Tan et al. 2006) in which multicellular spheroids adhere to mesothelial cells in the peritoneal cavity to build secondary metastatic sites. However, recent findings also suggest that hematogenous dissemination into the omentum can be also seen via circulating tumor cells (Yeung et al. 2015; Pradeep et al. 2014). Peritoneal metastases in OC are responsible for poor patients' prognosis. Various molecular signaling pathways involved in epithelial-to-mesenchymal transition (EMT), angiogenesis, and motility were defined and investigated to understand metastasis and offer therapeutic interventions and biomarkers to predict outcomes.

3.2.5.1 Cadherins

Cadherins family of cell-surface glycoproteins are involved in the calcium-dependent cell–cell adhesion that sustains the integrity of epithelial cells and tissue architecture and are found in most mammalian tissues (Gloushankova et al. 2017; Shamir and Ewald 2015). Cadherins constitute with other proteins (such as integrins and cytoskeleton proteins) molecular complexes known as adherens junctions that mediate intercellular adhesive interactions involved in various cell functions including adhesion (Klezovitch and Vasioukhin 2015), polarity (Ebnet et al. 2018), mechanotransduction (Leckband and de Rooij 2014), trafficking and migration (Collins and Nelson 2015; Brüser and Bogdan 2017), as well as communication

with extracellular matrix (ECM) (Ferreira et al. 2015). Deregulation of cadherin signaling by mutations, loss, methylation, damage or by other signaling pathways such as FGF2 plays a central role in cancer progression by promoting EMT which is a key characteristic of epithelial tumor cell invasion into the surrounding microenvironment and spread to distant organs (Sawada et al. 2008; Gheldof and Berx 2013; Lau et al. 2013; Wang et al. 2016b; Kourtidis et al. 2017; Wong et al. 2018). In addition, cadherin also forms a complex with β-catenin and supports its canonical oncogenic cell growth activity (Shahbazi and Perez-Moreno 2015). Cadherin molecules can be divided into type I [E-encoded by *CDH1* gene and N-encoded by *CDH2* gene] and are found in tissues with a high degree of intercellular cohesion such as human epithelia and type II expressed in cells with motility features (Pal et al. 2018). There are also other cadherins with potential impact on cancer progression such as VE and FAT cadherins and are reviewed elsewhere (Ashaie and Chowdhury 2016; Zhang et al. 2016b). In ovarian tissues, it was previously suggested that fallopian tube epithelia express more likely E-cadherin while ovarian surface epithelium (derived from mesoderm) expresses N-cadherin (Qiu et al. 2017; Adler et al. 2015; Koensgen et al. 2010; Hudson et al. 2008; Ahmed et al. 2007). However, cadherin expression is considered heterogeneous (Klymenko et al. 2017a) and it is admitted that well-differentiated OC express E-cadherin, while advanced and metastatic tumors display N-cadherin upregulation, a concept known as cadherin switching that favors metastasis (Patel et al. 2003; Hazan et al. 2004; Cheung et al. 2010) and is observed during EMT involved in intraperitoneal seeding of OC cells (Klymenko et al. 2017b; van Baal et al. 2018). In OC, other altered cadherins were also investigated such as P-cadherin which was previously found to facilitate the dissemination of tumor cell aggregates into the peritoneum (Usui et al. 2014) (for review, see: Vieira and Paredes 2015; Roggiani et al. 2016). The loss of cell–cell adhesion by cadherin alterations is therefore implicated in malignant transformation and invasive behaviors of OC as suggested by several latest studies (Chmelarova et al. 2018; Chen et al. 2017; Teng et al. 2015; Du et al. 2014; Huang et al. 2014b; Wang et al. 2014; Wakahashi et al. 2013). Importantly, downregulation of cadherins is regarded as an essential event in OC progression and aggressiveness and predicts poor outcomes (Yu et al. 2017; Peng et al. 2012). Based on immunohistochemistry and tissue microarray, Takai et al. analyzed tumor samples from 174 primary tumors and 34 metastases from OC patients for EMT markers (E-cadherin and its inhibitor Snail) and their associations with outcomes (Takai et al. 2014). Patients with EMT-positive markers (reduced E-cadherin and nuclear Snail expression) were likely to have peritoneal dissemination than those with negative status ($p < 0.05$) (Takai et al. 2014). Remarkably, in multivariate analysis, EMT-positive status was significantly associated with PFS ($p < 0.05$) and OS ($p < 0.01$) (Takai et al. 2014). Moreover, another report assessed the prognostic value of E-cadherin expression in advanced-stage high-grade serious OC patients ($n = 98$) treated with platinum-based chemotherapy and found that positive E-cadherin by immunostaining predicts better outcomes (Miše et al. 2015). Positive E-cadherin tumors were found significantly associated with improved response to first-line platinum-based treatment ($p < 0.001$) as well as better PFS and OS ($p < 0.001$ for both) (Miše et al. 2015). In

addition, positive E-cadherin expression predicts drug sensitivity to platinum ($p < 0.001$) and improved OS ($p = 0.01$) in multivariate analysis (Miše et al. 2015). Notably, a recent analysis from the Japanese Gynecologic Oncology Group (JGOG) (3016A1 study) of 201 high-grade serous OC cases showed that patients with mesenchymal transition phenotype have the worst prognosis (PFS: 1.4 years and OS: 3.6 years) (Murakami et al. 2019). A similar conclusion was drawn by a recent meta-analysis that included 1720 OC patients and found that reduced E-cadherin expression correlates with poor OS (pooled HR: 1.74, 95% CI: 1.40–2.17) and PFS (HR: 1.45, 95% CI: 1.12–1.86) (Yu et al. 2017). However, important heterogeneity ($I^2_{\text{statistic}} = 57.0\%, p = 0.003$) among studies enrolled for OS analysis was noted and may be explained by the difference in E-cadherin detection methods that were used by studies and their related cut-off point variations (Yu et al. 2017).

In an attempt to target this signaling axis, various therapeutic interventions were investigated (Wong et al. 2018; Mrozik et al. 2018) but their use in clinical research is still at the beginning. In OC, Bialucha et al. examined the anticancer activity of an antibody-drug conjugate HKT288 targeting tumor-associated antigen cadherin 6 (Bialucha et al. 2017). First-in-human HKT288 is an immunoconjugate consisting of a human monoclonal antibody against cadherin 6 conjugated to a maytansine-based cytotoxic agent developed by Novartis and was tested in a phase I trial for OC and renal carcinoma (NCT02947152) (currently terminated). Importantly, HKT288 showed durable anticancer activity in xenografts derived from ovarian and renal cancer patients (Bialucha et al. 2017). Of note, cadherin 6 is responsible for cancer metastatic behavior (Gugnoni et al. 2017) and correlates with poor prognosis (Ma et al. 2018b). Hence, drugging this EMT pathway merits further evaluation in OC.

3.2.5.2 ZEB1 and ZEB2 Axis

ZEB (zinc finger E-box-binding homeobox) 1 and 2 are transcription factors with pleiotropic roles especially in regulating the EMT process via mechanisms involving cell plasticity (Zhang et al. 2019b; Caramel et al. 2018; Krebs et al. 2017). ZEB DNA-binding proteins family promotes metastasis by repressing epithelial markers such as E-cadherins and activating mesenchymal cell programs (Simeone et al. 2018; Fardi et al. 2019; Zhang et al. 2019b). In addition, invasiveness of OC is enhanced when ZEB proteins are upregulated by various factors such as placental growth factor (PLGF) (Song et al. 2016), MAGI1-IT1 long non-coding RNA (Gao et al. 2019), TGF-β (Rafehi et al. 2016), and miR-429 (Chen et al. 2011). Various reports have indicated that high expression of these ZEB1/2 markers provides important prognostic information in OC (Yoshihara et al. 2009; Prislei et al. 2015; Wu et al. 2016; Yan et al. 2017; Sakata et al. 2017; Zhang et al. 2018). Previously and based on gene expression profiling of 43 OC tissues, Yoshihara et al. showed that high ZEB2 expression is an independent factor of poor PFS (HR: 1.37; 95% CI: 1.07–1.78, $p = 0.014$) and OS (HR: 1.53; 95% CI: 1.05–2.22, $p = 0.027$) on Cox multivariate analysis (Yoshihara et al. 2009). Later, another report that enrolled a cohort of 143 OC patients found that high ZEB2 mRNA expression is significantly correlated with poor survival outcomes as compared to patients with low ZEB2

mRNA expression (PFS: 16 vs 23 months, $p = 0.035$, OS: 42 vs 70 months, $p = 0.002$) (Prislei et al. 2015). Recently, a retrospective study from Yan et al. aimed to examine ZEB2 expression as a prognostic biomarker in OC based on tissue samples from 64 epithelial tumors, 36 benign tumors, and 28 normal specimens (Yan et al. 2017). Positive expression of ZEB2 was significantly increased in OC as compared to benign tumors and associated with differentiated histology and FIGO stage as well ($p = 0.002$ for both) (Yan et al. 2017). Furthermore, patients with positive expression of ZEB2 had worse OS ($p = 0.002$) (Yan et al. 2017). However, this prognostic significance disappeared in Cox multivariate analysis (HR: 1.496; 95% CI: 0.567–3.948, $p = 0.416$) (Yan et al. 2017).

In addition to its prognostic value, ZEB1 was found recently to mediate chemoresistance to platinum in OC cells by downregulating solute carrier family 3 member 2 (SLC3A2) (Cui et al. 2018). SLC3A2 is a cell-surface transporter and transmembrane glycoprotein involved in intracellular calcium levels control and is mainly expressed in rapidly proliferating cells (Fotiadis et al. 2013). Also, SLC3A2 was found to induce migration and invasion (Wang et al. 2017a). ZEB1 downregulates SLC3A2, and thus may likely induce dormancy and senescence of tumor cells which are known hallmarks of resistance to anticancer therapy (Yeh and Ramaswamy 2015; Endo and Inoue 2019). However, this concept is not discussed deeply yet in the current literature. Therapeutically, Sakata et al. demonstrated based on an in vitro and in vivo study that ZEB1 inhibition restored sensitivity to paclitaxel in resistant OC cells (Sakata et al. 2017). Similarly, suppression of ZEB1 in other cancers displayed potent anticancer properties in resistant cells (Peng et al. 2019; Ren et al. 2013). This signaling axis has an important link with EMT and OC patients' outcomes and there is growing evidence supporting the role of ZEB1/ZEB2 axis in other malignant cellular processes such as stemness, senescence, and cell death (Caramel et al. 2018). Therefore, additional studies are needed to better understand this signaling pathway in cell biology in general and particularly in cancer.

3.2.5.3 EpCAM

Epithelial cell adhesion molecule (EpCAM, also known as CD326) is a cell–cell adhesion glycoprotein involved in various cellular pathways including cell integrity, proliferation, signaling, and migration (Yahyazadeh Mashhadi et al. 2019; Schnell et al. 2013). EpCAM was reported to be highly expressed in various tumors of epithelial origin (Spizzo et al. 2011; for review, see: Herreros-Pomares et al. 2018). Of note, in vitro assessment found that this marker promotes invasion during the EMT process especially in cancer cells with non-mesenchymal phenotype (Martowicz et al. 2012). Phenotypic immunostaining of EpCAM in human tumors suggests stable or high expression in tumor-associated stem cells, effusions, and metastases (Patriarca et al. 2012). Moreover, germline *EPCAM* deletion in colorectal tissues causes *MSH2* epigenetic silencing which predisposes to Lynch syndrome (Pathak et al. 2019; Tutlewska et al. 2013). The presence of this molecule on circulating tumor cells is becoming a potential candidate for real-time profiling of human cancers (de Wit et al. 2019; Loeian et al. 2019) including OC (Van

Berckelaer et al. 2016) based on liquid biopsy approaches (Grover et al. 2014). Highly expressed EpCAM in OC stages is well documented. Previously, a retrospective study detected EpCAM in all OC subtypes and FIGO stages (Köbel et al. 2008). Furthermore, this can also be seen in recurrent ovarian tumors and metastases (Bellone et al. 2009). Clinical impact and prognostic value of EpCAM overexpression in OC were investigated in three recent studies and suggest favorable outcomes (Battista et al. 2014; Woopen et al. 2014; Tayama et al. 2017). Battista et al. evaluated the expression of EpCAM in a cohort of 117 OC and found a significant independent prognostic value for this biomarker in terms of disease-specific survival (HR: 0.408, 95% CI: 0.197–0.846; $p = 0.016$) on multivariate analysis (Battista et al. 2014). Similarly, another German report that enrolled tissue samples from 74 OC patients mostly with advanced FIGO stages found that overexpressed EpCAM is significantly associated with improved PFS ($p = 0.040$) and better response to chemotherapy ($p = 0.048$) (Woopen et al. 2014). In addition, EpCAM was found to predict OS ($p = 0.022$) (Woopen et al. 2014). Findings from a recent large Japanese study by Tayama et al. ($n = 168$) confirmed these data (Tayama et al. 2017). Kaplan-Meier curves of OS stratified by EpCAM expression found significant difference between high and low groups (HR: 2.17; 95% CI: 1.22–3.88; $p = 0.008$) (Tayama et al. 2017). However, these cohorts of OC patients that assessed EpCAM as a prognostic biomarker were retrospective in their design and exploratory in their nature and therefore, their findings must be interpreted with caution.

Therapeutically, EpCAM is a potential target for anticancer therapy that was investigated using trifunctional bispecific antibodies such as catumaxomab (Removab®) (Krishnamurthy and Jimeno 2018; Frampton 2012) and small-molecule inhibitors (Tretter et al. 2018) particularly for malignant ascites in peritoneal carcinomatosis (Knödler et al. 2018). Catumaxomab was developed by Neovii Biotech® (a German pharmaceutical company) and evaluated in phase II/III prospective trial (NCT00836654) that randomized 258 patients ($n = 129$ for OC) to receive catumaxomab combined with paracentesis against control of patients treated with paracentesis alone for recurrent malignant ascites (Heiss et al. 2010). Modest clinically meaningful improvement was reached in terms of puncture-free survival which was longer in the group treated with catumaxomab as compared to the control arm (median 46 vs 11 days; $p < 0.0001$) as well as in terms of median time to next paracentesis (77 vs 13 days; $p < 0.0001$) (Heiss et al. 2010). Moreover, catumaxomab was found to improve ascites symptoms and quality of life of OC patients with a chemotherapy-refractory setting in a single-arm open-label multicenter US phase II trial ($n = 32$; NCT00326885) (Berek et al. 2014). In platinum-resistant disease, this drug has slight anticancer activity as suggested by a phase IIa of the AGO trialists (NCT00189345) (Baumann et al. 2011). Catumaxomab given as an intraperitoneal infusion was approved by the US FDA and the EMA in Europe in early 2009 but withdrawn later for marketing since 2014 for insolvency concerns (https://neovii.com/neovii-completes-marketing-authorisation-withdrawal-of-removab-in-the-european-union/?cn-reloaded=1. Accessed 19/06/2019).

3.2.6 Enabling Replicative Immortality

In physiological conditions, mutant cells are suppressed by a blockade of their proliferation and eliminated by immunity. On some occasions, these cells can be immortal by additional (epi)genetic events that progress their phenotype into highly malignant cells that in turn can induce senescence and escape from tumor suppression (Moiseeva et al. 2020). The viable state of cancer cell senescence (also called cytostasis or dormancy) classically presents as a growth arrest but with the retained proliferative ability for survival, a well-known cancer condition called cellular plasticity (Damen et al. 2020). Accordingly, dormant/proliferative cancer cells have unlimited replicative potential. Telomere dysfunction and oncogenic and exogenic-induced stresses are the principal causes that stimulate cell senescence (Yaswen et al. 2015). Notably, the presence of senescent cells in cancer clones is associated with recurrent disease, metastatic dissemination, and poor outcomes (Damen et al. 2020). This hallmark is less investigated in OC for therapeutic approaches. However, its involvement in tumorigenesis and prognosis seems to be important. After front-line chemotherapy, OC cells can escape and survive to repopulate the initial tumors (Telleria 2013). This repopulation phenomenon encompasses transient cells with a senescent phenotype that drive relapse (Telleria 2013). Recently, Lam et al. demonstrated that signaling mechanisms of chemoresistance in OC and dormancy are linked (Lam et al. 2020). Chemoresistant OC cells had an enhanced survival by senescence (Lam et al. 2020). Telomere shortening in OC, which is regulated by telomerase—a prominent enzymatic activity of cancer cells, is involved in genomic instability that introduces additional mutations. During this event, end-to-end fusions in chromosomes were observed and can induce genome instability and bypass host cellular protection. Telomere shortening was remarkably noticed in serous tubal intraepithelial carcinomas, a precursor of high-grade serous OC (Kuhn et al. 2010). Moreover, this alteration was also observed in tubo-ovarian dysplastic lesions (Chen et al. 2013). This suggests that telomere shortening occurs earlier during ovarian tumorigenesis and is a selective mechanism of cancer cell immortality. The use of telomerase by tumor cells to maintain their telomere length and integrity has been an attractive druggable target. In addition, the pharmacological elimination of dormant cells has also been investigated using the so-called senolytic/senostatic drugs (Wyld et al. 2020). In this perspective, preclinical combinatorial approaches using these drugs and the standard OC chemotherapy were investigated (Meng et al. 2012; Stamelos et al. 2013; Wyld et al. 2020). Targeted inhibition of telomerase activity in OC using BIBR1532 and carboplatin was found to block the formation of spheroid-forming cells in vitro (Meng et al. 2012). Moreover, the preclinical use of navitoclax, an orally bioavailable Bcl-2 inhibitor directed against senescent cells, demonstrated an improved efficacy against OC cells when combined with paclitaxel-carboplatin therapy (Stamelos et al. 2013). Of note, the combination of paclitaxel and navitoclax was also previously shown to have a synergistic effect against OC cells (Wong et al. 2012). In OC patients, the high expression of Bcl-x(L) which induces senescence mediated chemoresistance and the use of these drugs reduced resistant cells (Wong

et al. 2012). Clinically, this approach was investigated in a phase II trial (MONAVI-1/NCT02591095) using the single-agent navitoclax in 47 women with platinum-resistant/refractory recurrent OC. The preliminary findings of this trial in 44 patients assessable for efficacy showed a long response in 11 subjects treated with chemotherapy after navitoclax in addition to 12 patients that had high response (Brachet et al. 2017). This suggests that this agent may reverse platinum-resistance in this difficult-to-treat population (McMullen et al. 2020). However, the findings of the blockade of this hallmark in OC which are mainly based on few preclinical studies are not convincing yet. Telomere shortening not only drives tumor cell senescence but is also involved in genome instability (Bär and Thum 2017). The model of "*too little of it can kill you but too much of it can kill you too*" enlightens well the difficulty of targeting this hallmark in cancer and the timing of its inhibition seems to be crucial (Bär and Thum 2017). As the mechanisms of replicative immortality interfere with those of "evading growth suppressors," the previous chapter discussing TP53 and RB pathways adds more details on this subject. For further reading, see: Książek (2020), Sikora et al. (2020), Saleh et al. (2020), and Moiseeva et al. (2020).

3.2.7 Inducing Angiogenesis

Without doubt, this hallmark accounts for the most relevant achievements and the most potential exploited compounds in cancer. Pathologic angiogenesis has a principal role in the growth and metastasis of solid tumors. This process is biologically supported by a network of pathways and growth factors dominated by vascular endothelial growth factor (VEGF) (Apte et al. 2019). Tumor hypoxia is a central regulator of VEGF expression through HIF and other hypoxia-related factors and genes such as platelet-derived growth factor (PDGF) and oncogenic mutations that synchronize VEGF-related signaling pathways (Apte et al. 2019). The VEGF/VEGF-R1/R2 canonical signaling induces vascular permeability, cell proliferation, migration, and survival via the activation of several kinases. An important number of studies demonstrated that VEGF expression has a prognostic value in OC. Previously, pooled data from a meta-analysis of 19 studies showed that VEGF overexpression is associated with reduced OS in OC (Hui and Meng 2015). Moreover, another meta-analysis of 16 studies also demonstrated that serum and tissue expression of VEGF is an independent predictor of poor PFS in OC (Yu et al. 2013).

Blockade of angiogenesis in OC resulted in promising findings. Bevacizumab is a neutralizing anti-VEGF monoclonal antibody approved for treating OC. Bevacizumab was investigated in several phase III trials for OC including ICON-7 (Perren et al. 2011; Oza et al. 2015a), GOG-0213 (Coleman et al. 2017a, b), GOG-0218 (Burger et al. 2011; Tewari et al. 2019), OCEANS (Aghajanian et al. 2012), and AURELIA (Pujade-Lauraine et al. 2014) for patients with newly diagnosed or recurrent disease. The FDA and EMA approvals of this anticancer drug were based on the promising findings of these landmark trials

particularly GOG-0218. This phase III trial was designed to show the superiority of adding bevacizumab to standard chemotherapy in the front-line setting. The investigators tested this hypothesis using three-arm placebo-controlled study that compared standard chemotherapy alone, chemotherapy plus bevacizumab, and chemotherapy plus bevacizumab followed by bevacizumab as maintenance in a population of 1873 women (Burger et al. 2011). The results of this study showed an increase in PFS by 4 months (but not in OS) in the arm adding bevacizumab to the standard carboplatin and paclitaxel treatment of advanced OC (Burger et al. 2011). Similarly, ICON-7 was a phase III trial that explored the benefits of bevacizumab in combination with the standard of care (Perren et al. 2011). This trial randomly assigned 1528 patients with OC to receive bevacizumab in association with carboplatin and paclitaxel or chemotherapy alone. PFS was also improved in this trial favoring the addition of bevacizumab to the standard of care (HR: 0.81; 95% CI: 0.70–0.94; $p = 0.004$) (Peeren et al. 2011).

In recurrent disease, OCEANS was a phase III ($n = 484$) placebo-controlled study that explored the addition of bevacizumab to carboplatin and gemcitabine as compared to this doublet alone in the platinum-sensitive setting (Aghajanian et al. 2012). Median PFS was superior in the bevacizumab arm (12.4 vs 8.4 months; HR: 0.484; 95% CI: 0.388–0.605; $p < 0.0001$) (Aghajanian et al. 2012). In the GOG-0213 phase III trial ($n = 674$) that was powered for OS, a clinically meaningful difference of OS by 5 months was noticed in the bevacizumab group as compared to chemotherapy alone (Coleman et al. 2017a, b). In addition, the investigators confirmed the benefits of bevacizumab plus gemcitabine and carboplatin concerning the PFS (Coleman et al. 2017a, b). In the platinum-resistant setting, the efficacy of bevacizumab in combination with non-platinum chemotherapy was explored in the AURELIA phase III trial ($n = 361$) (Pujade-Lauraine et al. 2014). This study showed an improvement in median PFS and ORR in the bevacizumab-containing arm (6.7 months vs 3.4 months and 27.3% and 11.8%, respectively) (Pujade-Lauraine et al. 2014). Based on these data, bevacizumab was also approved for the treatment of both platinum-sensitive and resistant recurrent OC, but not for refractory setting.

Cediranib is another antiangiogenic drug that was investigated in OC (Orbegoso et al. 2017). This molecule is an oral antiangiogenic vascular endothelial growth factor receptor 1–3 (VEGFR1–3) inhibitor. The efficacy of cediranib was explored in women with relapsed platinum-sensitive OC in the ICON-6 phase III trial ($n = 486$) (Lederman et al. 2016). PFS was improved in the group of patients treated with cediranib given with chemotherapy and continued as a maintenance treatment but with added adverse events including voice changes, diarrhea, neutropenia, and hypothyroidism which were the most common causes of treatment discontinuation (Lederman et al. 2016). In a randomized phase II study, cediranib was given in association with olaparib in comparison with olaparib alone in a population of 90 patients with platinum-sensitive OC (Liu et al. 2019a). Median PFS was doubled in the intention-to-treat population of the combination group (16.5 vs 8.2 months, HR: 0.5, $p = 0.007$) and also in the subgroup with wild-type/unknown germline *BRCA* status (23.7 vs 5.7 months, $p = 0.002$) (Liu et al. 2019a). These encouraging results provided the rationale to investigate the combination of cediranib and

olaparib in the ongoing ICON-9 phase III trial which will randomize 618 women with relapsed platinum-sensitive OC following a response to platinum-based chemotherapy to receive this association or olaparib alone as maintenance treatment (Elyashiv et al. 2021). PFS and OS are co-primary endpoints of this clinical trial and it is estimated to be completed in 2024 (Elyashiv et al. 2021).

Pazopanib, an oral multikinase inhibitor of VEGFR and also platelet-derived growth factor receptor (PDGFR), was investigated in OC in the AGO-OVAR16 phase III trial (du Bois et al. 2014). This study randomized 940 women with advanced OC who did not progress after first-line platinum-taxane chemotherapy to receive pazopanib or placebo as maintenance treatment (1:1). The hazard ratio for progression or death was 0.77 (95% CI: 0.64–0.91; $p = 0.0021$) with a median PFS of 17.9 months in pazopanib arm versus 12.3 months in patients treated with placebo. An interim analysis in 35.6% of patients did not show a significant difference in terms of survival (du Bois et al. 2014). Similarly, no improvements in median OS were noticed (Vergote et al. 2019a). Nintedanib is another tyrosine kinase inhibitor of VEGFR that has been studied for the standard first-line in advanced OC (du Bois et al. 2016). In this perspective, AGO-OVAR 12 phase III explored the efficacy of the combination of standard paclitaxel and carboplatin with nintedanib versus the doublet and placebo for newly diagnosed advanced OC. In this study, 1366 women were randomly assigned to receive one of the two combinations in a 2:1 fashion. The nintedanib group has statistically significantly increased median PFS as compared to the control (17.2 vs 16.6 months, HR: 0.84; 95% CI: 0.72–0.98, $p = 0.024$) but without a clinically meaningful improved PFS (0.6 months benefit). In addition, this combinatorial regimen was associated with more gastrointestinal adverse events (du Bois et al. 2016). This big clinical trial for chemonaïve OC patients is a good example of overpowered negative clinical trials in which statistical difference has no value over clinical significance. Other angiogenic targets such as angiopoietins 1 and 2 and Tie2 receptor were also explored for therapeutic strategies. Trebananib is an inhibitor of this pathway that was studied in phase III trials for OC. TRINOVA-1, TRINOVA-2, and TRINOVA-3 were randomized phase III clinical trials that studied the combination of trebananib with standard chemotherapy or single agents, paclitaxel and PLD for first-line and recurrent settings but without providing clinically meaningful improvements in median PFS (Monk et al. 2014; Marth et al. 2017; Vergote et al. 2019b). The exploration of antiangiogenics in OC is also being studied in other ongoing phase III trials. Other details on combinatorial synergistic approaches particularly immune-checkpoint blockade can be found in Sect. 2.9 (*Avoiding Immune Destruction*).

3.2.8 Resisting Cell Death

Classically, the regulation of cell death encompasses two major circuits, the extrinsic pathway that receives extracellular signals through death receptors and the intrinsic program that engages p53 after DNA damage. Basically, the activation of cell death

leads to progressive activation of caspases that causes proteolysis. However, cancer cells resist natural programmed cell death to avoid their elimination by host defense mechanisms. The deregulated machinery of apoptosis in cancer involves several strategies to avoid inducing sensors particularly "*TP53* loss", which suppresses critical damages for cells by activating intracellular signaling of death (Hanahan and Weinberg 2011). Accumulating evidence also demonstrated that cancer cells escape from cell death by increasing the expression of major negative regulators such as Bcl-2 and its relative Bcl-xL or downregulating multiple pro-apoptotic signals (Bax, Bim, and Puma). Also, additional mechanisms allow cancer cells to resist using diverse secondary pathways gained during tumor evolution (for scoping reviews on this topic, see elsewhere: Singh et al. 2019; Carneiro and El-Deiry 2020). Other forms of regulated cell death beyond apoptosis have recently emerged and merit recommended reading elsewhere (Wang et al. 2020; Galluzzi et al. 2017, 2018). In OC, mutated *TP53* is a well-known signature of early events of ovarian carcinogenesis (Kuhn et al. 2012). *TP53* mutations are believed to drive platinum-resistance and were also found to predict disease-free survival (Zhang et al. 2014; Seagle et al. 2015). The value of other cell death-related proteins in OC outcomes seems to be limited. On the one hand, the high expression of the pro-apoptotic Bax was found to prolong survival and predicted platinum sensitivity in OC (Yigit et al. 2012). Regarding Bcl-2, data from the large Danish MALOVA cohort showed that this marker may not be of clinical importance for the prognosis of OC patients (Høgdall et al. 2010). On the other hand, the pro-survival proteins (Bcl-xL and Mcl-1) were found to drive chemotherapy resistance in high-grade serous OC (Stover et al. 2019). Therapeutically, the use of agents that physically interfere with anti-apoptotic proteins via BH3 motifs seems to be a promising approach for cell death induction (so-called BH3 mimetics) (Ashkenazi et al. 2017). The efficacy of these agents was investigated in several preclinical studies. Previously, Simonin et al. showed that Bcl-xL and Mcl-1 cooperate to protect OC cells against oncogenic stress and cell death induced by chemotherapy (Simonin et al. 2009). These findings were later confirmed suggesting that their concomitant inhibition may be effective in OC (Brotin et al. 2010; Lincet et al. 2013). The exploitation of calcium signaling via calmodulin inhibition in combination with the BH3 mimetic ABT-737 was found to induce apoptosis by sensitizing OC cells (Bonnefond et al. 2015). A human pilot study by the team of *Stéphanie Lheureux* was conducted to explore predictive biomarkers of ABT-737 in patients with high-grade serous OC (NCT01440504) (Lheureux et al. 2015). Relevant markers of response were established to select patients for clinical trial design, and this includes Bim, Mcl-1, and phospho-Erk1/2 (Lheureux et al. 2015).

This has provided a rationale for investigating other antagonists to disrupt this pathway. The association of the Bcl-2 selective inhibitor WEHI-539 and the BH3 mimetic ABT-737 showed synergistic effects in potentiating the anticancer activity of carboplatin in vitro using various OC cells by inducing caspase 3/7 and PARP cleavage (Abed et al. 2016). Similarly, the combination of a PARP inhibitor (BMN-673) and BH3 mimetic ABT-263 also showed synergistic cytotoxic effects against OC cells by increasing the expression of Bim, a pro-apoptotic protein

(Yokoyama et al. 2017). Recently, Iavarone et al. explored the therapeutic blockade of MEK/ERK signaling based on cobimetinib (GDC-0973) combined to ABT-263 using patient-derived xenograft models of high-grade serous OC (Iavarone et al. 2019). The results of this report showed greater inhibition of tumor growth as compared to the single agent. Moreover, baseline levels of pro-apoptotic protein BIM and/or pERK were predictors of drug response suggesting their potential value as biomarkers (Iavarone et al. 2019). More recently, a strategy using drug repurposing of naftopidil to increase the expression of BH3-only proteins including Bim, Puma, and Noxa resulted in sensitizing patient-derived organoid models from OC patients to ABT-737 and the MEK inhibitor trametinib (Florent et al. 2020a). Of note, naftopidil is an α_1-adrenergic receptor antagonist used in benign prostatic hyperplasia management (reviewed by Florent et al. 2020b). The area of preclinical research on BH3 mimetics as single agents or in combination with other targeted therapeutics in OC seems to be highly active. To the best of our knowledge, there is only one BH3 mimetic that has been investigated in a clinical trial for OC (NCT02591095). MONAVI-1 was a French open-label phase II trial that studied navitoclax (ABT-263) given daily in a population of OC patients with platinum-resistant disease. Early signs of efficacy of this monotherapy were revealed in 11 patients that were treated with chemotherapy; therefore, confirming that this BH3 mimetic is a potent sensitizer (Brachet et al. 2017). More details on this hallmark in OC can be found in Sects. 2.4 and 2.6 (*Evading Growth Suppressors* and *Enabling Replicative Immortality*).

3.2.9 Avoiding Immune Destruction

Escape from host mechanisms of defense involving immune surveillance is an emerging hallmark of cancer (Hanahan and Weinberg 2011). Tumor cells avoid immunological killing by overexpressing immune-checkpoints such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) (Fig. 3.1), infiltration of immunosuppressive cells such as regulatory T lymphocytes (T^{reg}), and disruption of antigen processing and presentation machinery (Tang et al. 2020). As in other cancers, the tumor microenvironment of OC contains various cellular components of clinical value including tumor-infiltrating cells (TILs), tumor associated macrophages (TAMs), tumor associated neutrophils (TANs), cancer-associated fibroblasts (CAFs), and a variety of other cells (Macpherson et al. 2020). The prognostic value of these immune suppressive infiltrates as biomarkers was extensively studied in OC (Macpherson et al. 2020). A recent meta-analysis of 19 studies ($n = 6004$) pooled data of TILs in high-grade serous OC and demonstrated a significant association with OS and PFS (Hao et al. 2020). Indeed, intratumor and stromal TILs were favorably correlated to survival outcomes in this setting. Hence, these updated results confirmed the previous findings of Hwang's meta-analysis and other earlier TILs studies (Hwang et al. 2012; Webb et al. 2016; James et al. 2017; Wang et al. 2017b; Buderath et al. 2019). Recent additional reports on this topic also showed the benefits of high TILs in women with high-grade

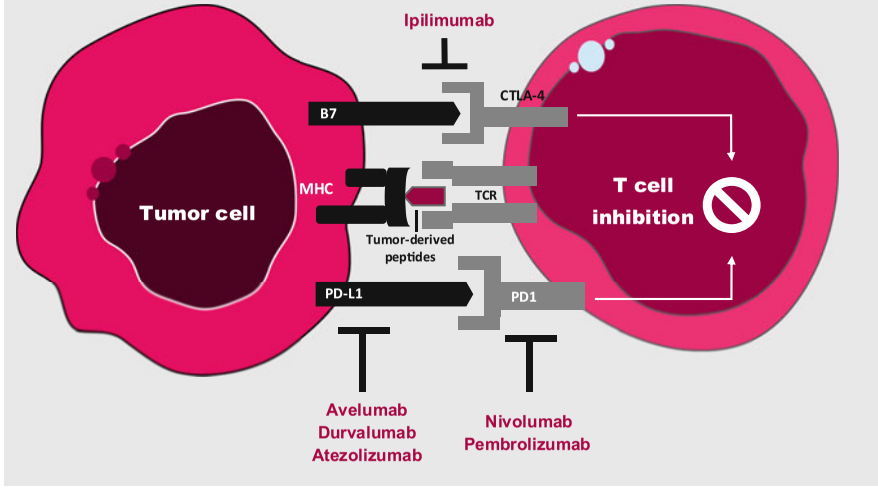

Fig. 3.1 Overview of immune-checkpoint blockade used in ovarian cancer clinical trials. Abbreviations: *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *MHC* major histocompatibility complex, *PD1* programmed death 1, *PD-L1* programmed death-ligand 1, *TCR* T cell receptor

serous OC. Martin de la Fuente et al. reported that patients with higher CD3, PD-L1, and PD-1 had significantly longer OS (Martin de la Fuente et al. 2020). Moreover, high expression of TILs was also found to have a positive impact on survival in OC (Martin de la Fuente et al. 2020). TILs in OC are most prevalent in tumors with high-grade histology (Chen et al. 2020). Improved PFS and immune response in OC patients with positive PD-L1 was also seen in advanced FIGO stages (Chen et al. 2020). OCs have frequently deficient homologous recombination systems with or without *BRCA* mutations. This allows tumors a notable expression of neo-antigens which in turn are marked indicators of an immune response in solid cancers (Fumet et al. 2020; Cormedi et al. 2020) and OC (Strickland et al. 2016; Le Saux et al. 2020). Therefore, these data are of important significance for investigating immunotherapy in this setting. The recent introduction of immune-oncology in clinical practice has revolutionized our current management of cancer. The advent of immune-checkpoint inhibitors (ICIs) and their predictive biomarkers for patients' selection has deeply changed outcomes in some cancers previously known to be aggressive (El Bairi et al. 2020; Keenan et al. 2019; Ribas and Wolchok 2018). Stunning successes with some cancers such as melanomas (Pasquali et al. 2018), metastatic colorectal cancer with microsatellite instability (André et al. 2020), and lung cancer (Almutairi et al. 2019), little benefits have been reported in OC (Le Saux et al. 2020). The therapeutic arsenal using immune-checkpoint blockade is a recent development in the design of novel clinical trials for OC using combinatorial approaches (Le Saux et al. 2020). OC is classically regarded as a "cold tumor" characterized by decreased levels of TILs (Le Saux et al. 2020). Therefore, response to ICIs in OC has been commonly reported to be low. Initial phase I/II studies that were conducted to investigate ICIs in OC have shown modest improvement in outcomes.

Experience with pembrolizumab (an anti-programmed death-1 (PD-1) monoclonal antibody) in phase I clinical trials as monotherapy for solid cancers (KEYNOTE-028/NCT02054806) demonstrated a durable antitumor response with a manageable safety and toxicity profile in patients with advanced PD-L1-positive OC (Varga et al. 2019). Following these early signs of efficacy, a two-cohort phase II study was conducted in patients with recurrent and advanced OC (KEYNOTE-100/NCT02674061). Cohort A included 285 patients that received 1–3 lines of therapy and cohort B ($n = 91$) received 4–6 lines of treatments (Matulonis et al. 2019). Pembrolizumab as a single agent at a dose of 200 mg was given every 3 weeks for both cohorts. ORR and disease control rate in cohort A were 7.4% and 37.2%, respectively, and 9.9% and 37.4% in cohort B. Notably, a higher response was observed in patients with a combined positive score (CPS) ≥ 1 (10% vs. 4.1% for CPS < 1). In addition, PFS in both cohorts was 2.1 months. The toxicity profile in this study was consistent with the previous experience with this agent (Matulonis et al. 2019). As expected, modest response was demonstrated for this novel monotherapy in this setting. However, a historical case report showed a complete response in an OC patient treated with pembrolizumab alone and harboring *PD-L1* gene structural variations (Bellone et al. 2018). The authors observed a notable complete response in a patient with recurrent advanced chemoresistant high-grade serous OC that progressed on all standard therapies. Whole exome sequencing of the

surgical specimens showed a low tumor mutational load/megabase with a remarkable structural variation of *PD-L1* gene causing unusual PD-L1 surface expression. This was markedly associated with high infiltration of CD4 and CD8 TILs, macrophages, and B lymphocytes suggesting immune escape (Bellone et al. 2018). To test the hypothesis that PARP inhibitors may increase the expression of PD-L1 (Jiao et al. 2017; Sato et al. 2017); and therefore the response to pembrolizumab, the TOPACIO/KEYNOTE-162 phase I/II trial (NCT02657889) investigated this approach in patients with platinum-resistant disease (Konstantinopoulos et al. 2019). This study was a single-arm and open-label and used pembrolizumab in combination with oral niraparib (200 mg daily for both) every 3 weeks. ORR and disease control rates were 18% and 65%, respectively. Moreover, three complete responses and eight partial responses were noticed regardless of prior bevacizumab exposure or *BRCA* status (Konstantinopoulos et al. 2019). Recently, the biomarker analysis of this study identified *PD-L1 and PD-L2* amplification as determinants of exceptional response in some patients of this trial (Färkkilä et al. 2020). In another phase II non-comparative trial (NCT02865811; $n = 23$), Lee et al. showed that the combination of pembrolizumab with PLD has a manageable toxicity profile and provided a preliminary evidence of its clinical activity including 26.1% of ORR in the population of patients with platinum-resistant OC (Lee et al. 2020). Moreover, the combination of pembrolizumab with metronomic cyclophosphamide and bevacizumab in another phase II trial (NCT02853318; $n = 40$) also demonstrated clinical benefits in OC patients with recurrent disease including >12 months of durable response in 25% of the treatment population that encompassed mainly platinum-resistant women (Zsiros et al. 2020). However, despite promising, these phase II trials were non-randomized and no comparator was added to their design and therefore, these early signs of efficacy should be interpreted with caution. The ongoing study registered on the US ClinicalTrials database shows more than 70 clinical trials using pembrolizumab used as monotherapy or in combination with other anticancer drugs for OC (www.clinicaltrials.gov, accessed 14/01/2020). The MK-7339-001/KEYLYNK-001/ENGOT-ov43/GOG-3036 is an ongoing phase III trial that may provide definitive and strong evidence for the future use of this agent in OC (NCT03740165). This study randomizes 1086 OC patients with advanced disease to receive the standard carboplatin-paclitaxel with or without pembrolizumab followed by maintenance therapy with the PARP inhibitor olaparib or placebo in the first-line setting. The study uses PFS and OS as primary endpoints and it is expected to be completed in August 2025.

The anti-PD-L1 durvalumab was investigated in OC as a combination with other therapeutics including PARP inhibitors and vaccines. A proof-of-concept phase II trial (NCT02484404; $n = 35$) aimed to assess the efficacy of durvalumab given every 4 weeks in combination with oral olaparib in recurrent and predominantly platinum-resistant OC (Lampert et al. 2020). The ORR was 14% and the disease control rate reached 71%. Moreover, this combination was found to increase the infiltration of TILs and IFNγ/TNFα release, which both are indicators of

immunomodulatory response. Moreover, patients with increased IFNγ had superior PFS (HR: 0.37, 95% CI: 0.16–0.87, $p = 0.023$ (Lampert et al. 2020). Durvalumab was also investigated in combination with the folate receptor alpha vaccine TPIV200 in patients with advanced platinum-resistant OC (Zamarin et al. 2020a). The investigators found an increased T cell response to vaccine peptides and prolonged median OS in one patient (21 months) in addition to stable disease in nine patients (Zamarin et al. 2020a). To test the hypothesis that PARP inhibitors create neo-antigens that may upregulate PD-L1 expression, MEDIOLA phase II trial (NCT02734004) was initiated. The initial results of this study that investigated the doublet olaparib and durvalumab and the triplet olaparib, durvalumab, and bevacizumab in non-germline *BRCA*-mutated platinum-sensitive and relapsed OC were recently presented at ESMO 2020 virtual meeting (Drew et al. 2020). Remarkably, ORR and PFS were 77.4% and 14.7 months, respectively, in the cohort treated with the triplet combination as compared to 31.3% of ORR and 5.5 months of PFS with the doublet (Drew et al. 2020). These encouraging results may be supported by the ongoing DUO-O phase III trial investigating the triplet approach ($n = 1254$; NCT03737643) in advanced OC. This is a large randomized multicenter phase III that was designed to evaluate the efficacy of durvalumab combined with the standard platinum-based chemotherapy and bevacizumab followed by durvalumab and bevacizumab as maintenance therapy or durvalumab, bevacizumab, and olaparib. PFS is the primary endpoint of this clinical trial, which is expected to provide preliminary results in November 2025.

Avelumab is another anti-PD-L1 that was investigated in the landmark JAVELIN studies for OC. The phase Ib (NCT01772004) part of this multicohort trial that investigated avelumab in OC was an open-label single-arm study that enrolled 125 participants with recurrent or refractory disease who had received platinum-based chemotherapy (Disis et al. 2019). Avelumab was given at a dose of 10 mg/kg every 14 days until progression assessed by RECIST version 1.1, unacceptable toxicities, or withdrawal from enrollment. After a median follow-up of 26.6 months, confirmed ORR was noticed in 12 patients with 1 and 11 complete and partial responses, respectively. 1-year PFS rate was 10.2% and median OS reached 11.2 months (Disis et al. 2019). The mature data of JAVELIN Ovarian 200 phase III trial (NCT02580058) were discouraging (Pujade-Lauraine et al. 2019). This study randomized 566 OC patients with platinum-resistant or refractory disease to receive avelumab as monotherapy or avelumab + PLD as compared to PLD alone (1:1:1 ratio) (Pujade-Lauraine et al. 2018). No significant differences between the three arms in terms of PFS and OS in the intention-to-treat population were noticed (Pujade-Lauraine et al. 2019). Similarly, the JAVELIN Ovarian 100 (NCT02718417) phase III trial that evaluated avelumab combined with/or following carboplatin-based chemotherapy versus chemotherapy alone in untreated OC patients did not meet its primary endpoint (Ledermann et al. 2020). This trial was stopped due to futility of efficacy at a planned interim analysis.

The ICIs nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) were also investigated in OC for both platinum-resistant and sensitive settings. A first phase II clinical trial enrolled 20 patients with platinum-resistant OC to receive intravenous nivolumab every 2 weeks as a monotherapy until disease progression (Hamanishi et al. 2015). The investigators found severe adverse events in two patients and ORR was 15%. Median PFS and OS were 3.5 and 20 months, respectively (Hamanishi et al. 2015). Nivolumab given every 2 weeks was also studied in combination with bevacizumab in a single-arm phase II trial (NCT02873962) (Liu et al. 2019c). This association is believed to have synergistic effects by modulating the tumor microenvironment to turn OC into a "hot tumor" (Tamura et al. 2019). Patients with platinum-sensitive OC seem to benefit much more from this combination as compared to those with platinum-resistance (ORR: 40% vs 16.7%) (Liu et al. 2019c). In another phase II study (NCT02498600), nivolumab was also studied in combination with ipilimumab as compared to nivolumab alone for OC as a dual blockade strategy (Zamarin et al. 2020b). This study included 100 OC patients with recurrent or persistent disease that were randomly allocated to receive monotherapy every 2 weeks or induction double blockade every 3 weeks followed by maintenance monotherapy with nivolumab. The median PFS was doubled in the combination as compared to nivolumab alone (3.9 vs 2 months, respectively, HR: 0.53; 95% CI: 0.34–0.82) (Zamarin et al. 2020b). As in other clinical trials, PD-L1 status didn't predict response to these agents. Therefore, other predictive biomarkers are needed for patients' selection in this setting. A phase III randomized and placebo-controlled four-arm trial (NCT03522246/ATHENA/GOG-3020/ENGOT-ov45) is currently exploring the activity of nivolumab in combination with rucaparib after front-line platinum-based chemotherapy in 1000 newly diagnosed OC patients (Westin et al. 2019). This multicenter study is expected to release its early findings in 2024. Promisingly, this type of combination involving a prior exposure to chemotherapy may be successful. It was recently demonstrated that neoadjuvant chemotherapy boosts local immunity in high-grade serous OC (Jiménez-Sánchez et al. 2020; Mesnage et al. 2017). Moreover, blockade of CTLA-4 within the intact tumor microenvironment in OC was demonstrated to induce tumor-reactive CD8+ tumor-infiltrating lymphocytes (Friese et al. 2020). This may improve the effectiveness of combined strategies after this initial modality.

Atezolizumab is an immune-checkpoint inhibitor of PD-L1 that is currently studied in treating OC (Palaia et al. 2020). A multicenter phase I trial ($n = 12$; NCT01375842) that enrolled women with recurrent epithelial OC evaluated the safety and tolerability profile of atezolizumab used as a single agent (Liu et al. 2019b). Long response duration was observed in two patients only and no new safety signals were identified for atezolizumab (Liu et al. 2019b). Atezolizumab was also investigated in OC in combination with bevacizumab in another phase I trial ($n = 20$; NCT01633970) for platinum-resistant disease (Moroney et al. 2020). ORR was 15% and disease control rate was 55%. Median PFS and OS were 4.9 and 10.2 months, respectively. The prior exposure to treatments and PD-L1 status did not affect

response to this combination (Moroney et al. 2020). In preclinical animal models, this combination was found to attenuate resistance to cisplatin by a synergestic suppression of epithelial to mesenchymal transition (Zhang et al. 2019c). To the best of our knowledge, no published findings of phase II trials using this agent in OC are available. All currently ongoing phase II studies on atezolizumab in OC are still in progress at the time of this chapter writing. This makes the ongoing phase III trials on this immune-checkpoint inhibitor in OC questionable in terms of the rationale for conducting large randomized and controlled trials. In this regard, IMagyn050/GOG 3015/ENGOT-OV39 is a large phase III trial (NCT03038100) that will randomize newly diagnosed advanced OC patients to receive either front-line atezolizumab combined with paclitaxel, carboplatin, and bevacizumab or placebo combined with the previous triplet (Moore and Pignata 2019). This trial is expected to enroll 1300 patients and PFS and OS are its co-primary endpoints in the intention-to-treat population and in the subpopulation of patients with positive PD-L1 (Moore and Pignata 2019). The preliminary findings of this study were presented at the ESMO 2020 Virtual Congress and demonstrated that the addition of atezolizumab to the standard of care did not improve PFS in this setting (Moore et al. 2020). The AGO-OVAR 2.29/ENGOT-ov34 is another ongoing phase III (NCT03353831) designed to investigate the clinical activity of atezolizumab combined with non-platinum chemotherapy and bevacizumab (standard of care) versus standard of care plus placebo in platinum-resistant OC (Harter et al. 2020). The estimated sample size of this trial is 664 patients and OS and PFS are its co-primary endpoints and it is currently recruiting patients. In platinum-sensitive OC, the Spanish randomized and controlled phase III ANITA trial (NCT03598270; ENGOT-Ov41/GEICO 69-O) is recruiting patients to receive atezolizumab + platinum-based chemotherapy followed by maintenance by niraparib + atezolizumab (experimental arm) versus a control arm consisting of platinum-based chemotherapy + placebo followed by maintenance by niraparib + placebo (González-Martín et al. 2020). With a sample size of 414 patients and PFS as a primary endpoint, the authors expect to demonstrate a benefit in terms of PFS per RECIST v1.1 criteria with a HR of 0.7 (power: 80%, two-sided p-value $<5\%$) (González-Martín et al. 2020). Atezolizumab is also being studied in the ATALANTE randomized and controlled phase III trial in platinum-sensitive and relapsed OC ($n = 405$, ENGOT-ov29/NCT02891824) (Kurtz et al. 2018). The investigators will compare the efficacy of adding atezolizumab to chemotherapy in combination with bevacizumab as compared to chemotherapy and bevacizumab alone in 2:1 ratio. The primary endpoint is RECIST v1.1-based PFS and the first results are estimated to be released in September 2023. Finally, the use of ICIs as monotherapies in OC didn't show clinically meaningful improvements in OC. However, combinatorial approaches using antiangiogenics or PARP inhibitors with ICIs seem to be promising. These associations are believed to induce an angiogenic tumor access by TILs. Presently, a promising escalating strategy using first-line platinum-based chemotherapy combined with ICIs and antiangiogenics followed by maintenance regimen with ICIs, antiangiogenics, and PARPi is being

studied in several phase III trials and is believed to improve survival outcomes in OC.

The clinical evaluation of other immunotherapeutic strategies such as the Toll-like receptor 8 (TLR8) agonist motolimod (NCT01666444) (Monk et al. 2017), the IDO1 inhibitor epacadostat (NCT01685255) (Kristeleit et al. 2017), and the Vigil® DNA engineered immunotherapy (Oh et al. 2016) was not successful in delivering improved outcomes to OC patients.

3.2.10 Deregulating Cellular Energetics

During neoplastic transformation, the deregulated control of the cell cycle involves an adjustment of energetic metabolism to fuel the tumorigenic process (Hanahan and Weinberg 2011). The use of glucose is a characteristic of normal cells, however; the previous works of the German Nobel laureate *Otto Heinrich Warburg* (1883–1970) showed that cancer cells have atypical energy metabolism (Warburg 1930, 1956). Accordingly, even in the presence of oxygen, tumor metabolism is reprogrammed to be dependent of glycolysis and thus the concept of "aerobic glycolysis or Warburg effect" (nicely reviewed elsewhere: Pascal et al. 2020; Scheid et al. 2021; Urbano 2021). This metabolic switch is partially covered by upregulation of glucose membrane transporters such as GLUT-1 which in turn is associated with mutated anti-oncogenes and activated oncogenes such as *Myc* and *RAS* (Hanahan and Weinberg 2011). During hypoxia, tumor cells accentuate their energetic needs based on glycolysis reliance by increasing the levels of hypoxia-inducible factor (HIF)-α (Hanahan and Weinberg 2011). Together, this suggests that this hallmark is essential for angiogenesis and invasion; and consequently the aggressive cancer phenotype (Icard et al. 2018). A previous report showed that GLUT-1 expression is correlated with tumor proliferation and microvessel density, in addition to suboptimal debulking in patients overexpressing this marker and Ki-67 (OR: 3.8, $p = 0.01$) (Semaan et al. 2011). Moreover, GLUT-1 was found associated with tumor cell mitosis (Kim et al. 2012) and its overexpression predicted reduced OS and shorter DFS in epithelial OC (Cantuaria et al. 2001; Cho et al. 2013). In addition, HIF-α in OC, which is released as a homeostatic response to hypoxia, promotes vasculogenic mimicry to induce epithelial to mesenchymal transition (Du et al. 2014). Also, HIF-α expression was found associated with metastasis and reduced 5-year survival and poor OS (Shen et al. 2017; Jin et al. 2014a; Braicu et al. 2014; Shimogai et al. 2008). Notably, several authors have investigated the Warburg effect in OC as a source for energy supply (Zhang et al. 2018; Ma et al. 2018a; Shang et al. 2017b; Jin et al. 2014b). Some of these preclinical studies have also provided potential pharmacological inhibitors of aerobic glycolysis in OC such as ginsenoside (Lu et al. 2020; Zhou et al. 2018), ABT737 (a BH3 mimetic) (Dong et al. 2020), ivermectin (Li et al. 2020), and berberine (Li et al. 2021). One clinical trial has attempted to investigate

an inhibitor of these pathways in OC. This was a phase II trial (NCT01652079) that enrolled 63 patients with recurrent platinum-resistant ovarian, fallopian tube, or peritoneal cancer to receive the anti-HIF-1α investigational nanoparticle-drug conjugate CRLX101 (camptothecin as the active molecule) in combination with bevacizumab. The latest available results of this two-stage trial and its preceding preclinical study showed that this combination is synergistic with durable inhibition of HIF-1α (Pham et al. 2015; Krasner et al. 2014, 2015, 2016). Very recently, the combination of EP0057 (formerly CRLX101) with weekly paclitaxel for recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer in a phase Ib/II trial (NCT02389985/$n = 30$) demonstrated an ORR of 31.6% in women with prior treatment with bevacizumab and one complete response (Duska et al. 2020). To the best of our knowledge, this study was terminated after the company decision.

3.3 Conclusion

With the emergence of data from large-scale sequencing projects, novel targets were discovered for OC. These actionable molecular alterations enabled enlargement of the current therapeutic arsenal against this aggressive cancer. Moreover, various biomarkers were also explored and seem to be promising for predicting prognosis and therapy response. There is a considerable move to exploit the hallmarks of cancer in improving outcomes and designing novel clinical trials for OC (Fig. 3.2). *Genome Instability, Inducing Angiogenesis, Avoiding Immune Destruction, and Sustaining Proliferative Signaling* were the most influencing hallmarks for the development of landmark phase III trials for OC. This list (Table 3.1) is expected to be extended in the future with newly launched phase III clinical studies which may supply the currently available treatments of OC with additional therapeutic approaches particularly targeted agents. Some signaling pathways that have a notable role in ovarian carcinogenesis were not discussed in this chapter because of the word limit and are illustrated elsewhere in other reviews (for further reading, see Box 3.1).

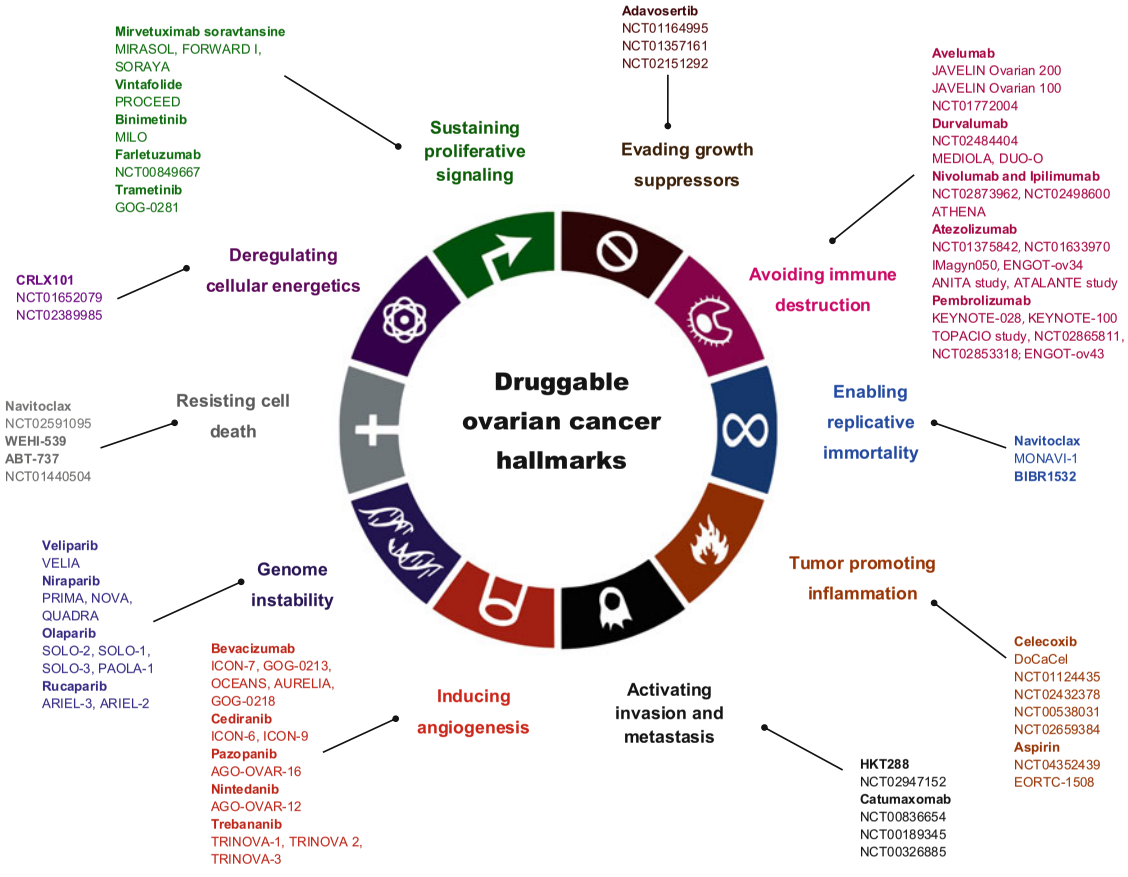

Fig. 3.2 Selected clinical studies using the hallmarks of ovarian cancer for drug development

Table 3.1 Selected phase III trials developed based on the concepts of "Cancer Hallmarks" in ovarian cancer

Cancer hallmarks	Trial name or NCT	Sample size	Anticancer drug	Disease setting	Study status
Genome instability	NOVA	553	Niraparib	Maintenance for recurrent platinum-sensitive	Completed
	SOLO-2	295	Olaparib		
	ARIEL-3	564	Rucaparib		
	SOLO-1	391	Olaparib	Maintenance in newly diagnosed	
	PAOLA-1	806			
	VELIA	1140	Veliparib	First-line and maintenance	
	PRIMA	733	Niraparib	First-line	
	SOLO-3	266	Olaparib	Recurrent platinum-sensitive	
Inducing angiogenesis	ICON-7	1528	Bevacizumab	First-line	Completed
	AURELIA	361		Recurrent platinum-resistant	
	GOG-0218	1873		First-line	
	GOG-0213	674		Recurrent platinum-sensitive	
	OCEANS	484			
	ICON-6	486	Cediranib		
	ICON-9	618			Ongoing
	TRINOVA-1	919	Trebananib	Recurrent	Completed
	TRINOVA-2	223		Recurrent partially platinum-sensitive or resistant	
	TRINOVA-3	1164		First-line	
	AGO-OVAR-12	1366	Nintedanib		
	AGO-OVAR-16	940	Pazopanib	First-line maintenance	

(continued)

Table 3.1 (continued)

Cancer hallmarks	Trial name or NCT	Sample size	Anticancer drug	Disease setting	Study status
Avoiding immune destruction	GOG-3036	1086	Pembrolizumab	First-line	Ongoing
	DUO-O	1254	Durvalumab		
	JAVELIN Ovarian 200	566	Avelumab	Recurrent platinum-resistant	Completed
	JAVELIN Ovarian 100	998		First-line	
	GOG-3020	1000	Nivolumab	First-line	Ongoing
	IMagyn050	1030	Atezolizumab		
	AGO-OVAR 2.29	664		Recurrent platinum-resistant	
	ANITA	414			
	ATALANTE	405		Recurrent platinum-sensitive	
Sustaining proliferative signaling	GOG-0281	260	Trametinib	Recurrent low-grade serous OC	Ongoing
	MIRASOL	430	Mirvetuximab soravtansine	Recurrent platinum-resistant	
	PROCEED	640	Vintafolide		Suspended
	SORAYA	110	Mirvetuximab soravtansine		Ongoing
	FORWARD I	333			Completed
	NCT00849667	1100	Farletuzumab	Recurrent platinum-sensitive	
	MILO	360	Binimetinib	Recurrent or persistent low-grade serous OC	

Box 3.1 Recommended reading of particular interest

Citation	DOI or PMID
Bogani G, et al. *Immunotherapy for platinum-resistant ovarian cancer*. Gynecol Oncol. 2020;158(2):484–488.	https://doi.org/10.1016/j.ygyno.2020.05.681
Madariaga A, et al. *Manage wisely: poly (ADP-ribose) polymerase inhibitor (PARPi) treatment and adverse events*. Int J Gynecol Cancer. 2020;30(7):903–915.	https://doi.org/10.1136/ijgc-2020-001288
Kuroki L, Guntupalli SR. *Treatment of epithelial ovarian cancer*. BMJ. 2020;371:m3773.	https://doi.org/10.1136/bmj.m3773
Moore KN, et al. *PARP inhibition in recurrent ovarian cancer*. Clin Adv Hematol Oncol. 2020;18(10):647–655.	33201871
Moore KN, et al. *PARP inhibition as frontline therapy in ovarian cancer*. Clin Adv Hematol Oncol. 2020;18(9):550–556.	33006584
Pujade-Lauraine E, et al. *Management of Platinum-Resistant, Relapsed Epithelial Ovarian Cancer and New Drug Perspectives.* J Clin Oncol. 2019;37(27):2437–2448.	https://doi.org/10.1200/JCO.19.00194
Pignata S, et al. *Treatment of recurrent ovarian cancer*. Ann Oncol. 2017;28(suppl_8):viii51–viii56.	https://doi.org/10.1093/annonc/mdx441
Keenan TE, et al. *Genomic correlates of response to immune checkpoint blockade.* Nat Med. 2019;25(3):389–402.	https://doi.org/10.1038/s41591-019-0382-x
Lord CJ, Ashworth A. *BRCAness revisited*. Nat Rev Cancer. 2016;16(2):110–20.	https://doi.org/10.1038/nrc.2015.21
Byrum AK, et al. *Defining and Modulating 'BRCAness'*. Trends Cell Biol. 2019;29(9):740–751.	https://doi.org/10.1016/j.tcb.2019.06.005
Hoppenot C, et al. *Who are the long-term survivors of high grade serous ovarian cancer?* Gynecol Oncol. 2018;148(1):204–212.	https://doi.org/10.1016/j.ygyno.2017.10.032
Chartron E, et al. *Targeting homologous repair deficiency in breast and ovarian cancers: Biological pathways, preclinical and clinical data.* Crit Rev Oncol Hematol. 2019;133:58–73.	https://doi.org/10.1016/j.critrevonc.2018.10.012

Acknowledgment and Conflicts of Interest KE is an editor in Springer Nature Journals and a previous editor for a Springer book (https://link.springer.com/book/10.1007/978-3-030-53821-7). Other authors: none.

Authors' Contribution KE wrote the first draft and coordinated the development of the chapter and shared a preliminary content discussion. OA revised the manuscript and SA supervised the chapter writing. The final draft was reviewed and approved by all the authors. The contents of the chapter reflect the authors' perspectives and not of their institutions of affiliation.

References

Abdel-Rahman O, ElHalawani H, Ahmed H (2016) Doublet BRAF/MEK inhibition versus single-agent BRAF inhibition in the management of BRAF-mutant advanced melanoma, biological rationale and meta-analysis of published data. Clin Transl Oncol 18(8):848–858. https://doi.org/10.1007/s12094-015-1438-0

Abed MN, Abdullah MI, Richardson A (2016) Antagonism of Bcl-XL is necessary for synergy between carboplatin and BH3 mimetics in ovarian cancer cells. J Ovarian Res 9:25. https://doi.org/10.1186/s13048-016-0234-y

Adler E, Mhawech-Fauceglia P, Gayther SA, Lawrenson K (2015) PAX8 expression in ovarian surface epithelial cells. Hum Pathol 46(7):948–956

Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR (2012) OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 30(17):2039–2045. https://doi.org/10.1200/JCO.2012.42.0505

Aguilera A, García-Muse T (2013) Causes of genome instability. Annu Rev Genet 47:1–32. https://doi.org/10.1146/annurev-genet-111212-133232

Ahmed N, Thompson EW, Quinn MA (2007) Epithelial-mesenchymal interconversions in normal ovarian surface epithelium and ovarian carcinomas: an exception to the norm. J Cell Physiol 213 (3):581–588

Ahn JH, Kim TJ, Lee JH, Choi JH (2017) Mutant p53 stimulates cell invasion through an interaction with Rad21 in human ovarian cancer cells. Sci Rep 7(1):9076. https://doi.org/10.1038/s41598-017-08880-4

Almutairi AR, Alkhatib N, Martin J, Babiker HM, Garland LL, McBride A, Abraham I (2019) Comparative efficacy and safety of immunotherapies targeting the PD-1/PD-L1 pathway for previously treated advanced non-small cell lung cancer: a Bayesian network meta-analysis. Crit Rev Oncol Hematol 142:16–25. https://doi.org/10.1016/j.critrevonc.2019.07.004

Andrade RC, Dos Santos AC, de Aguirre Neto JC et al (2017) TP53 and CDKN1A mutation analysis in families with Li-Fraumeni and Li-Fraumeni like syndromes. Fam Cancer 16 (2):243–248. https://doi.org/10.1007/s10689-016-9935-z

André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardiere C, Rivera F, Elez E, Bendell J, Le DT, Yoshino T, Van Cutsem E, Yang P, Farooqui MZH, Marinello P, Diaz LA Jr, KEYNOTE-177 Investigators (2020) Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med 383(23):2207–2218. https://doi.org/10.1056/NEJMoa2017699

Apte RS, Chen DS, Ferrara N (2019) VEGF in signaling and disease: beyond discovery and development. Cell 176(6):1248–1264. https://doi.org/10.1016/j.cell.2019.01.021

Armstrong DK, White AJ, Weil SC et al (2013) Farletuzumab (a monoclonal antibody against folate receptor alpha) in relapsed platinum-sensitive ovarian cancer. Gynecol Oncol 129(3):452–458. https://doi.org/10.1016/j.ygyno.2013.03.002

Arteaga CL, Engelman JA (2014) ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell 25(3):282–303

Ashaie MA, Chowdhury EH (2016) Cadherins: the superfamily critically involved in breast cancer. Curr Pharm Des 22(5):616–638

Ashkenazi A, Fairbrother WJ, Leverson JD, Souers AJ (2017) From basic apoptosis discoveries to advanced selective BCL-2 family inhibitors. Nat Rev Drug Discov 16(4):273–284. https://doi.org/10.1038/nrd.2016.253

Assaraf YG, Leamon CP, Reddy JA (2014) The folate receptor as a rational therapeutic target for personalized cancer treatment. Drug Resist Updat 17(4–6):89–95. https://doi.org/10.1016/j.drup.2014.10.002

Aubrey BJ, Strasser A, Kelly GL (2016) Tumor-suppressor functions of the TP53 pathway. Cold Spring Harb Perspect Med 6(5):a026062. https://doi.org/10.1101/cshperspect.a026062

Au-Yeung G, Lang F, Azar WJ et al (2016) Selective targeting of cyclin E1-amplified high-grade serous ovarian cancer by cyclin-dependent kinase 2 and AKT inhibition. Clin Cancer Res 23 (7):1862–1874

Ayhan A, Kuhn E, Wu RC et al (2017) CCNE1 copy-number gain and overexpression identify ovarian clear cell carcinoma with a poor prognosis. Mod Pathol 30(2):297–303. https://doi.org/10.1038/modpathol.2016.160

Aziz AUR, Farid S, Qin K, Wang H, Liu B (2018a) PIM kinases and their relevance to the PI3K/AKT/mTOR pathway in the regulation of ovarian cancer. Biomolecules 8(1):7. https://doi.org/10.3390/biom8010007

Aziz D, Etemadmoghadam D, Caldon CE et al (2018b) 19q12 amplified and non-amplified subsets of high grade serous ovarian cancer with overexpression of cyclin E1 differ in their molecular drivers and clinical outcomes. Gynecol Oncol 151(2):327–336. https://doi.org/10.1016/j.ygyno.2018.08.039

Bahar-Shany K, Brand H, Sapoznik S et al (2014) Exposure of fallopian tube epithelium to follicular fluid mimics carcinogenic changes in precursor lesions of serous papillary carcinoma. Gynecol Oncol 132(2):322–327. https://doi.org/10.1016/j.ygyno.2013.12.015

Bakkar RM, Xie SS, Urbauer DL et al (2015) Intact PTEN expression by immunohistochemistry is associated with decreased survival in advanced stage ovarian/primary peritoneal high-grade serous carcinoma. Int J Gynecol Pathol 34(6):497–506. https://doi.org/10.1097/PGP.0000000000000205

Bär C, Thum T (2017) Changing direction: from therapeutic telomerase inhibition to activation? Circ Res 120(9):1393–1395. https://doi.org/10.1161/CIRCRESAHA.116.310316

Barbolina MV (2018) Molecular mechanisms regulating organ-specific metastases in epithelial ovarian carcinoma. Cancers (Basel) 10(11):444. https://doi.org/10.3390/cancers10110444

Battista MJ, Cotarelo C, Jakobi S et al (2014) Overexpression of epithelial cell adhesion molecule protein is associated with favorable prognosis in an unselected cohort of ovarian cancer patients. J Cancer Res Clin Oncol 140(7):1097–1102. https://doi.org/10.1007/s00432-014-1672-9

Baumann K, Pfisterer J, Wimberger P et al (2011) Intraperitoneal treatment with the trifunctional bispecific antibody Catumaxomab in patients with platinum-resistant epithelial ovarian cancer: a phase IIa study of the AGO Study Group. Gynecol Oncol 123(1):27–32. https://doi.org/10.1016/j.ygyno.2011.06.004

Bayard Q, Meunier L, Peneau C et al (2018) Cyclin A2/E1 activation defines a hepatocellular carcinoma subclass with a rearrangement signature of replication stress. Nat Commun 9 (1):5235. https://doi.org/10.1038/s41467-018-07552-9

Beck A, Goetsch L, Dumontet C et al (2017) Strategies and challenges for the next generation of antibody-drug conjugates. Nat Rev Drug Discov 16(5):315–337. https://doi.org/10.1038/nrd.2016.268

Bedard PL, Tabernero J, Janku F et al (2015) A phase Ib dose-escalation study of the oral pan-PI3K inhibitor buparlisib (BKM120) in combination with the oral MEK1/2 inhibitor trametinib (GSK1120212) in patients with selected advanced solid tumors. Clin Cancer Res 21 (4):730–738. https://doi.org/10.1158/1078-0432.CCR-14-1814

Behbakht K, Sill MW, Darcy KM et al (2011) Phase II trial of the mTOR inhibitor, temsirolimus and evaluation of circulating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary peritoneal malignancies: a Gynecologic Oncology Group study. Gynecol Oncol 123(1):19–26

Bellone S, Siegel ER, Cocco E et al (2009) Overexpression of epithelial cell adhesion molecule in primary, metastatic, and recurrent/chemotherapy-resistant epithelial ovarian cancer: implications for epithelial cell adhesion molecule-specific immunotherapy. Int J Gynecol Cancer 19(5):860–866. https://doi.org/10.1111/IGC.0b013e3181a8331f

Bellone S, Buza N, Choi J, Zammataro L, Gay L, Elvin J, Rimm DL, Liu Y, Ratner ES, Schwartz PE, Santin AD (2018) Exceptional response to pembrolizumab in a metastatic, chemotherapy/radiation-resistant ovarian cancer patient harboring a PD-L1-genetic rearrangement. Clin Cancer Res 24(14):3282–3291. https://doi.org/10.1158/1078-0432.CCR-17-1805

Berek JS, Edwards RP, Parker LP et al (2014) Catumaxomab for the treatment of malignant ascites in patients with chemotherapy-refractory ovarian cancer: a phase II study. Int J Gynecol Cancer 24(9):1583–1589. https://doi.org/10.1097/IGC.0000000000000286

Bergamini A, Ferrero S, Leone Roberti Maggiore U et al (2016) Folate receptor alpha antagonists in preclinical and early stage clinical development for the treatment of epithelial ovarian cancer. Expert Opin Investig Drugs 25(12):1405–1412

Bernardini MQ, Baba T, Lee PS et al (2010) Expression signatures of TP53 mutations in serous ovarian cancers. BMC Cancer 10:237. https://doi.org/10.1186/1471-2407-10-237

Bialucha CU, Collins SD, Li X et al (2017) Discovery and optimization of HKT288, a cadherin-6-targeting ADC for the treatment of ovarian and renal cancers. Cancer Discov 7(9):1030–1045. https://doi.org/10.1158/2159-8290.CD-16-1414

Bielski CM, Zehir A, Penson AV et al (2018) Genome doubling shapes the evolution and prognosis of advanced cancers. Nat Genet 50(8):1189–1195

Bilanges B, Posor Y, Vanhaesebroeck B (2019) PI3K isoforms in cell signalling and vesicle trafficking. Nat Rev Mol Cell Biol 20(9):515–534. https://doi.org/10.1038/s41580-019-0129-z

Boers-Sonderen MJ, de Geus-Oei LF, Desar IM et al (2014) Temsirolimus and pegylated liposomal doxorubicin (PLD) combination therapy in breast, endometrial, and ovarian cancer: phase Ib results and prediction of clinical outcome with FDG-PET/CT. Target Oncol 9(4):339–347. https://doi.org/10.1007/s11523-014-0309-x

Bonnefond ML, Lambert B, Giffard F, Abeilard E, Brotin E, Louis MH, Gueye MS, Gauduchon P, Poulain L, N'Diaye M (2015) Calcium signals inhibition sensitizes ovarian carcinoma cells to anti-Bcl-xL strategies through Mcl-1 down-regulation. Apoptosis 20(4):535–550. https://doi.org/10.1007/s10495-015-1095-3

Bouaoun L, Sonkin D, Ardin M et al (2016) TP53 variations in human cancers: new lessons from the IARC TP53 database and genomics data. Hum Mutat 37(9):865–876. https://doi.org/10.1002/humu.23035

Brachet PE, Fabbro M, Leary A et al (2017) A gineco phase II study of navitoclax (abt 263) in women with platinum resistant/refractory recurrent ovarian cancer (roc). Ann Oncol 28. https://doi.org/10.1093/annonc/mdy285.179

Braem MG, Schouten LJ, Peeters PH et al (2011) Genetic susceptibility to sporadic ovarian cancer: a systematic review. Biochim Biophys Acta 1816(2):132–146. https://doi.org/10.1016/j.bbcan.2011.05.002

Braicu EI, Luketina H, Richter R, Cacsire Castillo-Tong D, Lambrechts S, Mahner S, Concin N, Mentze M, Zeillinger R, Vergote I, Sehouli J (2014) HIF1α is an independent prognostic factor for overall survival in advanced primary epithelial ovarian cancer – a study of the OVCAD Consortium. Onco Targets Ther 7:1563–1569. https://doi.org/10.2147/OTT.S65373

Bregar AJ, Growdon WB (2016) Emerging strategies for targeting PI3K in gynecologic cancer. Gynecol Oncol 140(2):333–344. https://doi.org/10.1016/j.ygyno.2015.09.083

Brosh R, Rotter V (2009) When mutants gain new powers: news from the mutant p53 field. Nat Rev Cancer 9(10):701–713. https://doi.org/10.1038/nrc2693

Brotin E, Meryet-Figuière M, Simonin K, Duval RE, Villedieu M, Leroy-Dudal J, Saison-Behmoaras E, Gauduchon P, Denoyelle C, Poulain L (2010) Bcl-XL and MCL-1 constitute pertinent targets in ovarian carcinoma and their concomitant inhibition is sufficient to induce apoptosis. Int J Cancer 126(4):885–895. https://doi.org/10.1002/ijc.24787

Brüser L, Bogdan S (2017) Adherens junctions on the move-membrane trafficking of e-cadherin. Cold Spring Harb Perspect Biol 9(3):a029140. https://doi.org/10.1101/cshperspect.a029140

Buderath P, Mairinger F, Mairinger E, Böhm K, Mach P, Schmid KW, Kimmig R, Kasimir-Bauer S, Bankfalvi A, Westerwick D, Hager T (2019) Prognostic significance of PD-1 and PD-L1 positive tumor-infiltrating immune cells in ovarian carcinoma. Int J Gynecol Cancer 29(9):1389–1395. https://doi.org/10.1136/ijgc-2019-000609

Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente M, Birrer MJ, Liang SX, Gynecologic Oncology Group (2011)

Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365 (26):2473–2483. https://doi.org/10.1056/NEJMoa1104390

Cai J, Xu L, Tang H et al (2014) The role of the PTEN/PI3K/Akt pathway on prognosis in epithelial ovarian cancer: a meta-analysis. Oncologist 19(5):528–535

Cai L, Michelakos T, Ferrone CR et al (2017) Expression status of folate receptor alpha is a predictor of survival in pancreatic ductal adenocarcinoma. Oncotarget 8(23):37646–37656

Cancer Genome Atlas Research Network (2011) Integrated genomic analyses of ovarian carcinoma. Nature 474(7353):609–615. https://doi.org/10.1038/nature10166

Cantuaria G, Fagotti A, Ferrandina G, Magalhaes A, Nadji M, Angioli R, Penalver M, Mancuso S, Scambia G (2001) GLUT-1 expression in ovarian carcinoma: association with survival and response to chemotherapy. Cancer 92(5):1144–1150. https://doi.org/10.1002/1097-0142(20010901)92:5<1144::aid-cncr1432>3.0.co;2-t

Caramel J, Ligier M, Puisieux A (2018) Pleiotropic roles for ZEB1 in cancer. Cancer Res 78 (1):30–35. https://doi.org/10.1158/0008-5472.CAN-17-2476

Carneiro BA, El-Deiry WS (2020) Targeting apoptosis in cancer therapy. Nat Rev Clin Oncol 17 (7):395–417. https://doi.org/10.1038/s41571-020-0341-y

Castro MP, Whitcomb BP, Zajchowski DA, Coleman RL (2015) Successful use of next generation genomic sequencing (NGS)-directed therapy of clear cell carcinoma of the ovary (CCCO) with trametinib and metformin in a patient with chemotherapy-refractory disease. Gynecol Oncol Res Pract 2:4. https://doi.org/10.1186/s40661-015-0013-2

Chen J, Wang L, Matyunina LV, Hill CG, McDonald JF (2011) Overexpression of miR-429 induces mesenchymal-to-epithelial transition (MET) in metastatic ovarian cancer cells. Gynecol Oncol 121(1):200–205. https://doi.org/10.1016/j.ygyno.2010.12.339

Chen YL, Chang MC, Huang CY et al (2012) Serous ovarian carcinoma patients with high alpha-folate receptor had reducing survival and cytotoxic chemo-response. Mol Oncol 6(3):360–369

Chen C, Li J, Yao G, Chambers SK, Zheng W (2013) Tubal origin of ovarian low-grade serous carcinoma. Am J Clin Exp Obstet Gynecol 1(1):13–36

Chen Y, Wang DD, Wu YP et al (2017) MDM2 promotes epithelial-mesenchymal transition and metastasis of ovarian cancer SKOV3 cells. Br J Cancer 117(8):1192–1201

Chen H, Molberg K, Strickland AL, Castrillon DH, Carrick K, Jiang Q, Niu S, Rivera-Colon G, Gwin K, Hinson S, Lea J, Miller DS, Zheng W, Lucas E (2020) PD-L1 expression and CD8+ tumor-infiltrating lymphocytes in different types of tubo-ovarian carcinoma and their prognostic value in high-grade serous carcinoma. Am J Surg Pathol 44(8):1050–1060. https://doi.org/10.1097/PAS.0000000000001503

Cheung LW, Leung PC, Wong AS (2010) Cadherin switching and activation of p120 catenin signaling are mediators of gonadotropin-releasing hormone to promote tumor cell migration and invasion in ovarian cancer. Oncogene 29(16):2427–2440. https://doi.org/10.1038/onc.2009.523

Chien J, Sicotte H, Fan JB et al (2015) TP53 mutations, tetraploidy and homologous recombination repair defects in early stage high-grade serous ovarian cancer. Nucleic Acids Res 43 (14):6945–6958

Chmelarova M, Baranova I, Ruszova E et al (2018) Importance of cadherins methylation in ovarian cancer: a next generation sequencing approach. Pathol Oncol Res. https://doi.org/10.1007/s12253-018-0500-y

Cho H, Lee YS, Kim J, Chung JY, Kim JH (2013) Overexpression of glucose transporter-1 (GLUT-1) predicts poor prognosis in epithelial ovarian cancer. Cancer Invest 31(9):607–615. https://doi.org/10.3109/07357907.2013.849722

Chui MH, Wang Y, Wu RC et al (2014) Loss of ALDH1A1 expression is an early event in the pathogenesis of ovarian high-grade serous carcinoma. Mod Pathol 28(3):437–445

Cibula D, Zikan M, Dusek L et al (2011) Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis. Expert Rev Anticancer Ther 11(8):1197–1207. https://doi.org/10.1586/era.11.38

Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, Kim BG, Fujiwara K, Tewari KS, O'Malley DM, Davidson SA, Rubin SC, Di Silvestro P, Basen-Engquist K,

Huang H, Chan JK, Spirtos NM, Ashfaq R, Mannel RS (2017a) Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 18(6):779–791. https://doi.org/10.1016/S1470-2045(17)30279-6

Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp A, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Garcia-Donas J, Swisher EM, Floquet A, Konecny GE, McNeish IA, Scott CL, Cameron T, Maloney L, Isaacson J, Goble S, Grace C, Harding TC, Raponi M, Sun J, Lin KK, Giordano H, Ledermann JA, ARIEL3 Investigators (2017b) Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebocontrolled, phase 3 trial. Lancet 390(10106):1949–1961. https://doi.org/10.1016/S01406736(17)32440-6. Epub 2017 Sep 12. Erratum in: Lancet. 2017 Oct 28;390 (10106):1948

Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, Okamoto A, Moore KN, Efrat Ben-Baruch N, Werner TL, Cloven NG, Oaknin A, Di Silvestro PA, Morgan MA, Nam JH, Leath CA III, Nicum S, Hagemann AR, Littell RD, Cella D, Baron-Hay S, Garcia-Donas J, Mizuno M, Bell-McGuinn K, Sullivan DM, Bach BA, Bhattacharya S, Ratajczak CK, Ansell PJ, Dinh MH, Aghajanian C, Bookman MA (2019) Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med 381 (25):2403–2415. https://doi.org/10.1056/NEJMoa1909707

Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, et al. (2008) Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 371 (9609):303–314. https://doi.org/10.1016/S0140-6736(08)60167-1

Collins C, Nelson WJ (2015) Running with neighbors: coordinating cell migration and cell-cell adhesion. Curr Opin Cell Biol 36:62–70

Colon-Otero G, Weroha SJ, Foster NR et al (2017) Phase 2 trial of everolimus and letrozole in relapsed estrogen receptor-positive high-grade ovarian cancers. Gynecol Oncol 146(1):64–68. https://doi.org/10.1016/j.ygyno.2017.04.020

Cormedi MCV, Van Allen EM, Colli LM (2020) Predicting immunotherapy response through genomics. Curr Opin Genet Dev 66:1–9. https://doi.org/10.1016/j.gde.2020.11.004

Cossa G, Lanzi C, Cassinelli G et al (2014) Differential outcome of MEK1/2 inhibitor-platinum combinations in platinum-sensitive and -resistant ovarian carcinoma cells. Cancer Lett 347 (2):212–224. https://doi.org/10.1016/j.canlet.2014.02.016

Cui Y, Qin L, Tian D et al (2018) ZEB1 promotes chemoresistance to cisplatin in ovarian cancer cells by suppressing SLC3A2. Chemotherapy 63(5):262–271. https://doi.org/10.1159/000493864

Damen MPF, van Rheenen J, Scheele CLGJ (2020) Targeting dormant tumor cells to prevent cancer recurrence. FEBS J. https://doi.org/10.1111/febs.15626

De Luca A, Maiello MR, D'Alessio A et al (2012) The RAS/RAF/MEK/ERK and the PI3K/AKT signalling pathways: role in cancer pathogenesis and implications for therapeutic approaches. Expert Opin Ther Targets 16(Suppl 2):S17–S27. https://doi.org/10.1517/14728222.2011.639361

De Palma M, Hanahan D (2012) The biology of personalized cancer medicine: facing individual complexities underlying hallmark capabilities. Mol Oncol 6(2):111–127. https://doi.org/10.1016/j.molonc.2012.01.011

De Picciotto N, Cacheux W, Roth A et al (2016) Ovarian cancer: status of homologous recombination pathway as a predictor of drug response. Crit Rev Oncol 101:50–59. https://doi.org/10.1016/j.critrevonc.2016.02.014

de Wit S, Rossi E, Weber S et al (2019) Single tube liquid biopsy for advanced non-small cell lung cancer. Int J Cancer 144(12):3127–3137. https://doi.org/10.1002/ijc.32056

DeFazio A, Moujaber T, Etemadmoghadam D, Kennedy C, Chiew YE, Balleine RL et al (2016) Abstract A25: brafv600E mutations in serous ovarian cancer and response to the BRAF inhibitor, dabrafenib. Clin Cancer Res 22:a25. https://doi.org/10.1158/1557-3265.OVCA15-A25

Della Pepa C, Tonini G, Santini D et al (2015) Low Grade Serous Ovarian Carcinoma: from the molecular characterization to the best therapeutic strategy. Cancer Treat Rev 41(2):136–143. https://doi.org/10.1016/j.ctrv.2014.12.003

Demir L, Yigit S, Sadullahoglu C et al (2014) Hormone receptor, HER2/NEU and EGFR expression in ovarian carcinoma–is here a prognostic phenotype? Asian Pac J Cancer Prev 15 (22):9739–9745

Deng L, Feng DQ, Ling B (2020) Cyclooxygenase-2 promotes ovarian cancer cell migration and cisplatin resistance via regulating epithelial mesenchymal transition. J Zhejiang Univ Sci B 21 (4):315–326. https://doi.org/10.1631/jzus.B1900445

Despierre E et al (2015) Epidermal growth factor receptor (EGFR) pathway biomarkers in the randomized phase III trial of erlotinib versus observation in ovarian cancer patients with no evidence of disease progression after first-line platinum-based chemotherapy. Target Oncol 10 (4):583–596

Dhillon S (2016) Dabrafenib plus trametinib: a review in advanced melanoma with a BRAF (V600) mutation. Target Oncol 11(3):417–428. https://doi.org/10.1007/s11523-016-0443-8

Di Fiore R, D'Anneo A, Tesoriere G et al (2013) RB1 in cancer: different mechanisms of RB1 inactivation and alterations of pRb pathway in tumorigenesis. J Cell Physiol 228(8):1676–1687. https://doi.org/10.1002/jcp.24329

Diakos CI, Charles KA, McMillan DC et al (2014) Cancer-related inflammation and treatment effectiveness. Lancet Oncol 15(11):e493–e503. https://doi.org/10.1016/S1470-2045(14)70263-3

Dick FA, Rubin SM (2013) Molecular mechanisms underlying RB protein function. Nat Rev Mol Cell Biol 14(5):297–306

Disis ML, Taylor MH, Kelly K et al (2019) Efficacy and safety of avelumab for patients with recurrent or refractory ovarian cancer: phase 1b results from the JAVELIN solid tumor trial. JAMA Oncol 5(3):393–401. https://doi.org/10.1001/jamaoncol.2018.6258

Dong D, Dong Y, Fu J, Lu S, Yuan C, Xia M, Sun L (2020) Bcl2 inhibitor ABT737 reverses the Warburg effect via the Sirt3-HIF1α axis to promote oxidative stress-induced apoptosis in ovarian cancer cells. Life Sci 255:117846. https://doi.org/10.1016/j.lfs.2020.117846

Drew Y, Penson RT, O'Malley DM et al (2020) Phase II study of olaparib (O) plus durvalumab (D) and bevacizumab (B) (MEDIOLA): initial results in patients (pts) with non-germline BRCA-mutated (non-gBRCAm) platinum sensitive relapsed (PSR) ovarian cancer (OC) [ESMO abstract 814MO]. Ann Oncol 31(Suppl 4):S615–S616

du Bois A, Floquet A, Kim JW, Rau J, del Campo JM, Friedlander M, Pignata S, Fujiwara K, Vergote I, Colombo N, Mirza MR, Monk BJ, Kimmig R, Ray-Coquard I, Zang R, Diaz-Padilla I, Baumann KH, Mouret-Reynier MA, Kim JH, Kurzeder C, Lesoin A, Vasey P, Marth C, Canzler U, Scambia G, Shimada M, Calvert P, Pujade-Lauraine E, Kim BG, Herzog TJ, Mitrica I, Schade-Brittinger C, Wang Q, Crescenzo R, Harter P (2014) Incorporation of pazopanib in maintenance therapy of ovarian cancer. J Clin Oncol 32(30):3374–3382. https://doi.org/10.1200/JCO.2014.55.7348

du Bois A, Kristensen G, Ray-Coquard I, Reuss A, Pignata S, Colombo N, Denison U, Vergote I, Del Campo JM, Ottevanger P, Heubner M, Minarik T, Sevin E, de Gregorio N, Bidziński M, Pfisterer J, Malander S, Hilpert F, Mirza MR, Scambia G, Meier W, Nicoletto MO, Bjørge L, Lortholary A, Sailer MO, Merger M, Harter P, AGO Study Group led Gynecologic Cancer Intergroup/European Network of Gynaecologic Oncology Trials Groups Intergroup Consortium (2016) Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 17(1):78–89. https://doi.org/10.1016/S1470-2045(15)00366-6

Du J, Sun B, Zhao X, Gu Q, Dong X, Mo J, Sun T, Wang J, Sun R, Liu Y (2014) Hypoxia promotes vasculogenic mimicry formation by inducing epithelial-mesenchymal transition in ovarian carcinoma. Gynecol Oncol 133(3):575–583. https://doi.org/10.1016/j.ygyno.2014.02.034

Du ZH, Bi FF, Wang L, Yang Q (2018) Next-generation sequencing unravels extensive genetic alteration in recurrent ovarian cancer and unique genetic changes in drug-resistant recurrent ovarian cancer. Mol Genet Genomic Med 6(4):638–647. https://doi.org/10.1002/mgg3.414

Duska LR, Krasner CN, O'Malley DM, Hays JL, Modesitt SC, Mathews CA, Moore KN, Thaker PH, Miller A, Purdy C, Zamboni WC, Lucas AT, Supko JG, Schilder RJ (2020) A phase Ib/II and pharmacokinetic study of EP0057 (formerly CRLX101) in combination with weekly paclitaxel in patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Gynecol Oncol. S0090-8258(20)34228-1. https://doi.org/10.1016/j.ygyno.2020.12.025

Ebnet K, Kummer D, Steinbacher T et al (2018) Regulation of cell polarity by cell adhesion receptors. Semin Cell Dev Biol 81:2–12. https://doi.org/10.1016/j.semcdb.2017.07.032

El Bairi K, Amrani M, Maleb A (2020) Gut microbiota, next-generation sequencing, immune-checkpoint inhibitors, and colorectal cancer: how hot is the link? In: El Bairi K (ed) Illuminating colorectal cancer genomics by next-generation sequencing. Springer, Cham. https://doi.org/10.1007/978-3-030-53821-7_5

El Bairi K, Al Jarroudi O, Afqir S (2021) Revisiting antibody-drug conjugates and their predictive biomarkers in platinum-resistant ovarian cancer. Semin Cancer Biol. S1044-579X(21)00081-X. https://doi.org/10.1016/j.semcancer.2021.03.031

Elyashiv O, Ledermann J, Parmar G, Farrelly L, Counsell N, Feeney A, El-Khouly F, Macdonald I, Neto A, Arthur-Darkwa E, Burnett E, Jayson GC, Mileshkin L, Gourley C, Nicum S (2021) ICON 9-an international phase III randomized study to evaluate the efficacy of maintenance therapy with olaparib and cediranib or olaparib alone in patients with relapsed platinum-sensitive ovarian cancer following a response to platinum-based chemotherapy. Int J Gynecol Cancer 31(1):134–138. https://doi.org/10.1136/ijgc-2020-002073

Emons G, Kurzeder C, Schmalfeldt B et al (2016) Temsirolimus in women with platinum-refractory/resistant ovarian cancer or advanced/recurrent endometrial carcinoma. A phase II study of the AGO-study group (AGO-GYN8). Gynecol Oncol 140(3):450–456. https://doi.org/10.1016/j.ygyno.2015.12.025

Endo H, Inoue M (2019) Dormancy in cancer. Cancer Sci 110(2):474–480. https://doi.org/10.1111/cas.13917

Etemadmoghadam D, de Fazio A, Beroukhim R, Mermel C, George J, Getz G, Tothill R, Okamoto A, Raeder MB, Harnett P, Lade S, Akslen LA, Tinker AV, Locandro B, Alsop K, Chiew YE, Traficante N, Fereday S, Johnson D, Fox S, Sellers W, Urashima M, Salvesen HB, Meyerson M, Bowtell D, AOCS Study Group (2009) Integrated genome-wide DNA copy number and expression analysis identifies distinct mechanisms of primary chemoresistance in ovarian carcinomas. Clin Cancer Res 15(4):1417–1427. https://doi.org/10.1158/1078-0432.CCR-08-1564

Etemadmoghadam D, George J, Cowin PA et al (2010) Amplicon-dependent CCNE1 expression is critical for clonogenic survival after cisplatin treatment and is correlated with 20q11 gain in ovarian cancer. PLoS One 5(11):e15498. https://doi.org/10.1371/journal.pone.0015498

Etemadmoghadam D, Au-Yeung G, Wall M et al (2013a) Resistance to CDK2 inhibitors is associated with selection of polyploid cells in CCNE1-amplified ovarian cancer. Clin Cancer Res 19(21):5960–5971. https://doi.org/10.1158/1078-0432.CCR-13-1337

Etemadmoghadam D, Weir BA, Au-Yeung G et al (2013b) Synthetic lethality between CCNE1 amplification and loss of BRCA1. Proc Natl Acad Sci U S A 110(48):19489–19494

Fardi M, Alivand M, Baradaran B, Farshdousti Hagh M, Solali S (2019) The crucial role of ZEB2: from development to epithelial-to-mesenchymal transition and cancer complexity. J Cell Physiol. https://doi.org/10.1002/jcp.28277

Färkkilä A, Gulhan DC, Casado J et al (2020) Immunogenomic profiling determines responses to combined PARP and PD-1 inhibition in ovarian cancer [published correction appears in Nat

Commun 2020;11(1):2543]. Nat Commun 11(1):1459. https://doi.org/10.1038/s41467-020-15315-8

Farley J, Brady WE, Vathipadiekal V et al (2013) Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 14(2):134–140

Fernández ML, DiMattia GE, Dawson A et al (2016) Differences in MEK inhibitor efficacy in molecularly characterized low-grade serous ovarian cancer cell lines. Am J Cancer Res 6 (10):2235–2251

Fernandez ML, Dawson A, Hoenisch J et al (2019) Markers of MEK inhibitor resistance in low-grade serous ovarian cancer: EGFR is a potential therapeutic target. Cancer Cell Int 19:10. https://doi.org/10.1186/s12935-019-0725-1

Ferreira AR, Felgueiras J, Fardilha M (2015) Signaling pathways in anchoring junctions of epithelial cells: cell-to-cell and cell-to-extracellular matrix interactions. J Recept Signal Transduct Res 35(1):67–75. https://doi.org/10.3109/10799893.2014.931426

Flesken-Nikitin A, Hwang CI, Cheng CY, Michurina TV, Enikolopov G, Nikitin AY (2013) Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche. Nature 495(7440):241–245

Florent R, Weiswald LB, Lambert B, Brotin E, Abeilard E, Louis MH, Babin G, Poulain L, N'Diaye M (2020a) Bim, Puma and Noxa upregulation by Naftopidil sensitizes ovarian cancer to the BH3-mimetic ABT-737 and the MEK inhibitor Trametinib. Cell Death Dis 11(5):380. https://doi.org/10.1038/s41419-020-2588-8

Florent R, Poulain L, N'Diaye M (2020b) Drug repositioning of the α1-adrenergic receptor antagonist naftopidil: a potential new anti-cancer drug? Int J Mol Sci 21(15):5339. https://doi.org/10.3390/ijms21155339

Fortner RT, Poole EM, Wentzensen NA et al (2018) Ovarian cancer risk factors by tumor aggressiveness: an analysis from the Ovarian Cancer Cohort Consortium. Int J Cancer. https://doi.org/10.1002/ijc.32075

Fotiadis D, Kanai Y, Palacín M (2013) The SLC3 and SLC7 families of amino acid transporters. Mol Aspects Med 34(2–3):139–158. https://doi.org/10.1016/j.mam.2012.10.007

Fowler M (2020) Mirvetuximab soravtansine combination yields encouraging response rates in ovarian cancer. Oncology (Williston Park) 34(7):250

Frampton JE (2012) Catumaxomab: in malignant ascites. Drugs 72(10):1399–1410. https://doi.org/10.2165/11209040-000000000-00000

Franzese E, Diana A, Centonze S et al (2020) PARP inhibitors in first-line therapy of ovarian cancer: are there any doubts? Front Oncol 10:782. https://doi.org/10.3389/fonc.2020.00782

Friese C, Harbst K, Borch TH, Westergaard MCW, Pedersen M, Kverneland A, Jönsson G, Donia M, Svane IM, Met Ö (2020) CTLA-4 blockade boosts the expansion of tumor-reactive CD8+ tumor-infiltrating lymphocytes in ovarian cancer. Sci Rep 10(1):3914. https://doi.org/10.1038/s41598-020-60738-4

Fruman DA, Rommel C (2014) PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov 13(2):140–156

Fu S, Hennessy BT, Ng CS et al (2012) Perifosine plus docetaxel in patients with platinum and taxane resistant or refractory high-grade epithelial ovarian cancer. Gynecol Oncol 126 (1):47–53. https://doi.org/10.1016/j.ygyno.2012.04.006

Fumet JD, Truntzer C, Yarchoan M, Ghiringhelli F (2020) Tumour mutational burden as a biomarker for immunotherapy: current data and emerging concepts. Eur J Cancer 131:40–50. https://doi.org/10.1016/j.ejca.2020.02.038

Galluzzi L, Kepp O, Chan FK, Kroemer G (2017) Necroptosis: mechanisms and relevance to disease. Annu Rev Pathol 12:103–130. https://doi.org/10.1146/annurev-pathol-052016-100247

Galluzzi L, Vitale I, Aaronson SA et al (2018) Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ 25 (3):486–541. https://doi.org/10.1038/s41418-017-0012-4

Gao H, Li X, Zhan G et al (2019) Long noncoding RNA MAGI1-IT1 promoted invasion and metastasis of epithelial ovarian cancer via the miR-200a/ZEB axis. Cell Cycle 18 (12):1393–1406. https://doi.org/10.1080/15384101.2019.1618121

Garsed DW, Alsop K, Fereday S et al (2018) Homologous recombination DNA repair pathway disruption and retinoblastoma protein loss are associated with exceptional survival in high-grade serous ovarian cancer. Clin Cancer Res 24(3):569–580. https://doi.org/10.1158/1078-0432.CCR-17-1621

Gershenson DM, Sun CC, Wong KK (2015) Impact of mutational status on survival in low-grade serous carcinoma of the ovary or peritoneum. Br J Cancer 113(9):1254–1258

Gewinner C, Wang ZC, Richardson A et al (2009) Evidence that inositol polyphosphate 4-phosphatase type II is a tumor suppressor that inhibits PI3K signaling. Cancer Cell 16 (2):115–125

Gheldof A, Berx G (2013) Cadherins and epithelial-to-mesenchymal transition. Prog Mol Biol Transl Sci 116:317–336. https://doi.org/10.1016/B978-0-12-394311-8.00014-5

Ghezelayagh TS, Pennington KP, Norquist BM et al (2020) Characterizing TP53 mutations in ovarian carcinomas with and without concurrent BRCA1 or BRCA2 mutations. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2020.12.007

Ghigo A, Morello F, Perino A et al (2012) Phosphoinositide 3-kinases in health and disease. Subcell Biochem 58:183–213. https://doi.org/10.1007/978-94-007-3012-0_6

Ginter PS, McIntire PJ, Cui X et al (2017) Folate receptor alpha expression is associated with increased risk of recurrence in triple-negative breast cancer. Clin Breast Cancer 17(7):544–549. https://doi.org/10.1016/j.clbc.2017.03.007

Gloushankova NA, Rubtsova SN, Zhitnyak IY (2017) Cadherin-mediated cell-cell interactions in normal and cancer cells. Tissue Barriers 5(3):e1356900

González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Pérez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, Monk BJ, PRIMA/ENGOT-OV26/GOG-3012 Investigators (2019) Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 381(25):2391–2402. https://doi.org/10.1056/NEJMoa1910962

González-Martín A, Sanchez Lorenzo L, Colombo N, dePont Christensen R, Heitz F, Meirovitz M, Selle F, van Gorp T, Alvarez N, Sanchez J, Marqués C (2020) A phase III, randomized, double blinded trial of platinum based chemotherapy with or without atezolizumab followed by niraparib maintenance with or without atezolizumab in patients with recurrent ovarian, tubal, or peritoneal cancer and platinum treatment free interval of more than 6 months: engot-Ov41/GEICO 69-O/ANITA Trial. Int J Gynecol Cancer. https://doi.org/10.1136/ijgc-2020-001633

Grisham RN, Iyer G, Garg K et al (2012) BRAF mutation is associated with early stage disease and improved outcome in patients with low-grade serous ovarian cancer. Cancer 119(3):548–554

Grisham RN, Moore KN, Gordon MS et al (2018) Phase Ib study of binimetinib with paclitaxel in patients with platinum-resistant ovarian cancer: final results, potential biomarkers, and extreme responders. Clin Cancer Res 24(22):5525–5533. https://doi.org/10.1158/1078-0432.CCR-18-0494

Grover PK, Cummins AG, Price TJ, Roberts-Thomson IC, Hardingham JE (2014) Circulating tumour cells: the evolving concept and the inadequacy of their enrichment by EpCAM-based methodology for basic and clinical cancer research. Ann Oncol 25(8):1506–1516. https://doi.org/10.1093/annonc/mdu018

Gruosso T, Garnier C, Abelanet S et al (2015) MAP3K8/TPL-2/COT is a potential predictive marker for MEK inhibitor treatment in high-grade serous ovarian carcinomas. Nat Commun 6:8583. https://doi.org/10.1038/ncomms9583

Gugnoni M, Sancisi V, Gandolfi G et al (2017) Cadherin-6 promotes EMT and cancer metastasis by restraining autophagy. Oncogene 36(5):667–677. https://doi.org/10.1038/onc.2016.237

Guha T, Malkin D (2017) Inherited TP53 mutations and the Li-Fraumeni syndrome. Cold Spring Harb Perspect Med 7(4). pii: a026187. https://doi.org/10.1101/cshperspect.a026187

Gupta R, Cristea M, Frankel P, Ruel C, Chen C, Wang Y, Morgan R, Leong L, Chow W, Koczywas M, Koehler S, Lim D, Luu T, Martel C, McNamara M, Somlo G, Twardowski P, Yen Y, Idorenyi A, Raechelle T, Carroll M, Chung V (2019) Randomized trial of oral cyclophosphamide versus oral cyclophosphamide with celecoxib for recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer. Cancer Treat Res Commun 21:100155. https://doi.org/10.1016/j.ctarc.2019.100155

Hainaut P, Pfeifer GP (2016) Somatic TP53 mutations in the era of genome sequencing. Cold Spring Harb Perspect Med 6(11):a026179. https://doi.org/10.1101/cshperspect.a026179

Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, Kanai M, Mori Y, Matsumoto S, Chikuma S, Matsumura N, Abiko K, Baba T, Yamaguchi K, Ueda A, Hosoe Y, Morita S, Yokode M, Shimizu A, Honjo T, Konishi I (2015) Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J Clin Oncol 33(34):4015–4022. https://doi.org/10.1200/JCO.2015.62.3397

Han C, Bellone S, Zammataro L, Schwartz PE, Santin AD (2018) Binimetinib (MEK162) in recurrent low-grade serous ovarian cancer resistant to chemotherapy and hormonal treatment. Gynecol Oncol Rep 25:41–44. https://doi.org/10.1016/j.gore.2018.05.011

Hanahan D, Coussens LM (2012) Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell 21(3):309–322. https://doi.org/10.1016/j.ccr.2012.02.022

Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1):57–70. https://doi.org/10.1016/s0092-8674(00)81683-9

Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 14:646–674. https://doi.org/10.1016/j.cell.2011.02.013

Hao J, Yu H, Zhang T, An R, Xue Y (2020) Prognostic impact of tumor-infiltrating lymphocytes in high grade serous ovarian cancer: a systematic review and meta-analysis. Ther Adv Med Oncol 12:1758835920967241. https://doi.org/10.1177/1758835920967241

Hao J, Liu Y, Zhang T, He J, Zhao H, An R, Xue Y (2021) Efficacy and safety of PARP inhibitors in the treatment of advanced ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials. Crit Rev Oncol Hematol 157:103145. https://doi.org/10.1016/j.critrevonc.2020.103145

Harter P, Pautier P, Van Nieuwenhuysen E, Reuss A, Redondo A, Lindemann K, Kurzeder C, Petru E, Heitz F, Sehouli J, Degregorio N, Wimberger P, Burges A, Cron N, Ledermann J, Lorusso D, Paoletti X, Marme F (2020) Atezolizumab in combination with bevacizumab and chemotherapy versus bevacizumab and chemotherapy in recurrent ovarian cancer – a randomized phase III trial (AGO-OVAR 2.29/ENGOT-ov34). Int J Gynecol Cancer 30(12):1997–2001. https://doi.org/10.1136/ijgc-2020-001572

Hasegawa K, Kagabu M, Mizuno M et al (2017) Phase II basket trial of perifosine monotherapy for recurrent gynecologic cancer with or without PIK3CA mutations. Invest New Drugs 35(6):800–812. https://doi.org/10.1007/s10637-017-0504-6

Havrilesky LJ, Moorman PG, Lowery WJ et al (2013) Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet Gynecol 122(1):139–147. https://doi.org/10.1097/AOG.0b013e318291c235

Hazan RB, Qiao R, Keren R, Badano I, Suyama K (2004) Cadherin switch in tumor progression. Ann N Y Acad Sci 1014:155–163. https://doi.org/10.1196/annals.1294.016

Heiss MM, Murawa P, Koralewski P et al (2010) The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial. Int J Cancer 127(9):2209–2221. https://doi.org/10.1002/ijc.25423

Herreros-Pomares A, Aguilar-Gallardo C, Calabuig-Fariñas S, Sirera R, Jantus-Lewintre E, Camps C (2018) EpCAM duality becomes this molecule in a new Dr. Jekyll and Mr. Hyde tale. Crit Rev Oncol Hematol 126:52–63. https://doi.org/10.1016/j.critrevonc.2018.03.006

Hew KE, Miller PC, El-Ashry D et al (2015) MAPK activation predicts poor outcome and the MEK inhibitor, selumetinib, reverses antiestrogen resistance in ER-positive high-grade serous ovarian cancer. Clin Cancer Res 22(4):935–947

Høgdall EV, Christensen L, Kjaer SK, Blaakaer J, Christensen IJ, Høgdall CK (2010) Limited prognostic value of tissue protein expression levels of BCl-2 in Danish ovarian cancer patients: from the Danish 'MALOVA' ovarian cancer study. APMIS 118(8):557–564. https://doi.org/10.1111/j.1600-0463.2010.02614.x

Hortobagyi GN, Stemmer SM, Burris HA et al (2016) Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 375(18):1738–1748

Huang LN, Wang DS, Chen YQ et al (2012) Meta-analysis for cyclin E in lung cancer survival. Clin Chim Acta 413(7-8):663–668. https://doi.org/10.1016/j.cca.2011.12.020

Huang TB, Yan Y, Guo ZF et al (2014a) Aspirin use and the risk of prostate cancer: a metaanalysis of 24 epidemiologic studies. Int Urol Nephrol 46(9):1715–1728. https://doi.org/10.1007/s11255-014-0703-4

Huang HN, Huang WC, Lin CH et al (2014b) Chromosome 20q13.2 ZNF217 locus amplification correlates with decreased E-cadherin expression in ovarian clear cell carcinoma with PI3K-Akt pathway alterations. Hum Pathol 45(11):2318–2325. https://doi.org/10.1016/j.humpath.2014.07.020

Huang HS, Chu SC, Hsu CF et al (2015) Mutagenic, surviving and tumorigenic effects of follicular fluid in the context of p53 loss: initiation of fimbria carcinogenesis. Carcinogenesis 36 (11):1419–1428. https://doi.org/10.1093/carcin/bgv132

Hudson LG, Zeineldin R, Stack MS (2008) Phenotypic plasticity of neoplastic ovarian epithelium: unique cadherin profiles in tumor progression. Clin Exp Metastasis 25(6):643–655

Hui G, Meng M (2015) Prognostic value of vascular endothelial growth factor expression in women with ovarian cancer: a meta-analysis. J BUON 20(3):870–878

Hwang WT, Adams SF, Tahirovic E, Hagemann IS, Coukos G (2012) Prognostic significance of tumor-infiltrating T cells in ovarian cancer: a meta-analysis. Gynecol Oncol 124(2):192–198. https://doi.org/10.1016/j.ygyno.2011.09.039

Iavarone C, Zervantonakis IK, Selfors LM, Palakurthi S, Liu JF, Drapkin R, Matulonis UA, Hallberg D, Velculescu VE, Leverson JD, Sampath D, Mills GB, Brugge JS (2019) Combined MEK and BCL-2/XL inhibition is effective in high-grade serous ovarian cancer patient-derived xenograft models and BIM levels are predictive of responsiveness. Mol Cancer Ther 18 (3):642–655. https://doi.org/10.1158/1535-7163.MCT-18-0413

Icard P, Shulman S, Farhat D, Steyaert JM, Alifano M, Lincet H (2018) How the Warburg effect supports aggressiveness and drug resistance of cancer cells? Drug Resist Updat 38:1–11. https://doi.org/10.1016/j.drup.2018.03.001

Iyengar M, O'Hayer P, Cole A et al (2018) CDK4/6 inhibition as maintenance and combination therapy for high grade serous ovarian cancer. Oncotarget 9(21):15658–15672. https://doi.org/10.18632/oncotarget.24585

James FR, Jiminez-Linan M, Alsop J, Mack M, Song H, Brenton JD, Pharoah PDP, Ali HR (2017) Association between tumour infiltrating lymphocytes, histotype and clinical outcome in epithelial ovarian cancer. BMC Cancer 17(1):657. https://doi.org/10.1186/s12885-017-3585-x

Jia P, Zhao Z (2019) Characterization of tumor-suppressor gene inactivation events in 33 cancer types. Cell Rep 26(2):496–506.e3. https://doi.org/10.1016/j.celrep.2018.12.066

Jiao S, Xia W, Yamaguchi H, Wei Y, Chen MK, Hsu JM, Hsu JL, Yu WH, Du Y, Lee HH, Li CW, Chou CK, Lim SO, Chang SS, Litton J, Arun B, Hortobagyi GN, Hung MC (2017) PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 23(14):3711–3720. https://doi.org/10.1158/1078-0432.CCR-16-3215

Jiménez-Sánchez A, Cybulska P, Mager KL, Koplev S, Cast O, Couturier DL, Memon D, Selenica P, Nikolovski I, Mazaheri Y, Bykov Y, Geyer FC, Macintyre G, Gavarró LM, Drews RM, Gill MB, Papanastasiou AD, Sosa RE, Soslow RA, Walther T, Shen R, Chi DS, Park KJ, Hollmann T, Reis-Filho JS, Markowetz F, Beltrao P, Vargas HA, Zamarin D, Brenton JD, Snyder A, Weigelt B, Sala E, Miller ML (2020) Unraveling tumor-immune heterogeneity in

advanced ovarian cancer uncovers immunogenic effect of chemotherapy. Nat Genet 52 (6):582–593. https://doi.org/10.1038/s41588-020-0630-5

Jin Y, Wang H, Liang X, Ma J, Wang Y (2014a) Pathological and prognostic significance of hypoxia-inducible factor 1α expression in epithelial ovarian cancer: a meta-analysis. Tumour Biol 35(8):8149–8159. https://doi.org/10.1007/s13277-014-2059-x

Jin Z, Gu J, Xin X, Li Y, Wang H (2014b) Expression of hexokinase 2 in epithelial ovarian tumors and its clinical significance in serous ovarian cancer. Eur J Gynaecol Oncol 35(5):519–524

Kaldawy A, Segev Y, Lavie O et al (2016) Low-grade serous ovarian cancer: a review. Gynecol Oncol 143(2):433–438. https://doi.org/10.1016/j.ygyno.2016.08.320

Kalli KR, Block MS, Kasi PM et al (2018) Folate receptor alpha peptide vaccine generates immunity in breast and ovarian cancer patients. Clin Cancer Res 24(13):3014–3025. https://doi.org/10.1158/1078-0432.CCR-17-2499

Kang HJ, Chun SM, Kim KR, Sohn I, Sung CO (2013) Clinical relevance of gain-of-function mutations of p53 in high-grade serous ovarian carcinoma. PLoS One 8(8):e72609. https://doi.org/10.1371/journal.pone.0072609

Kanska J, Zakhour M, Taylor-Harding B et al (2016) Cyclin E as a potential therapeutic target in high grade serous ovarian cancer. Gynecol Oncol 143(1):152–158. https://doi.org/10.1016/j.ygyno.2016.07.111

Karnezis AN, Cho KR, Gilks CB et al (2017) The disparate origins of ovarian cancers: pathogenesis and prevention strategies. Nat Rev Cancer 17(1):65–74. https://doi.org/10.1038/nrc.2016.113

Karst AM, Jones PM, Vena N, Ligon AH, Liu JF, Hirsch MS, Etemadmoghadam D, Bowtell DD, Drapkin R (2014) Cyclin E1 deregulation occurs early in secretory cell transformation to promote formation of fallopian tube-derived high-grade serous ovarian cancers. Cancer Res 74(4):1141–1152. https://doi.org/10.1158/0008-5472.CAN-13-2247

Kassem L, Abdel-Rahman O (2016) Targeting mTOR pathway in gynecological malignancies: biological rationale and systematic review of published data. Crit Rev Oncol Hematol 108:1–12. https://doi.org/10.1016/j.critrevonc.2016.10.003

Katagiri A, Nakayama K, Rahman MT et al (2010) MEK inhibition suppresses cell invasion and migration in ovarian cancers with activation of ERK1/2. Exp Ther Med 1(4):591–596

Kato N, Sato Y, Kamataki A et al (2018) PIK3CA hotspot mutations and cyclooxygenase-2-expression in ovarian clear cell carcinomas: a close association with stromal features. Hum Pathol. https://doi.org/10.1016/j.humpath.2018.11.013

Kawanishi S, Ohnishi S, Ma N, Hiraku Y, Murata M (2017) Crosstalk between DNA damage and inflammation in the multiple steps of carcinogenesis. Int J Mol Sci 18(8):1808. https://doi.org/10.3390/ijms18081808

Keenan TE, Burke KP, Van Allen EM (2019) Genomic correlates of response to immune checkpoint blockade. Nat Med 25(3):389–402. https://doi.org/10.1038/s41591-019-0382-x

Kelly RJ (2018) Dabrafenib and trametinib for the treatment of non-small cell lung cancer. Expert Rev Anticancer Ther 18(11):1063–1068. https://doi.org/10.1080/14737140.2018.1521272

Khan AQ, Kuttikrishnan S, Siveen KS et al (2018) RAS-mediated oncogenic signaling pathways in human malignancies. Semin Cancer Biol. pii: s1044-579X(18)30002-6. https://doi.org/10.1016/j.semcancer.2018.03.001

Kim K, Park WY, Kim JY et al (2012) Prognostic relevance of the expression of CA IX, GLUT-1, and VEGF in ovarian epithelial cancers. Korean J Pathol 46(6):532–540. https://doi.org/10.4132/KoreanJPathol.2012.46.6.532

Klezovitch O, Vasioukhin V (2015) Cadherin signaling: keeping cells in touch. F1000Res 4 (F1000ulty Rev):550. https://doi.org/10.12688/f1000research.6445.1

Klotz DM, Wimberger P (2017) Cells of origin of ovarian cancer: ovarian surface epithelium or fallopian tube? Arch Gynecol Obstet 296(6):1055–1062. https://doi.org/10.1007/s00404-017-4529-z

Klymenko Y, Johnson J, Bos B, Lombard R, Campbell L, Loughran E, Stack MS (2017a) Heterogeneous cadherin expression and multicellular aggregate dynamics in ovarian cancer dissemination. Neoplasia 19(7):549–563. https://doi.org/10.1016/j.neo.2017.04.002

Klymenko Y, Kim O, Loughran E, Yang J, Lombard R, Alber M, Stack MS (2017b) Cadherin composition and multicellular aggregate invasion in organotypic models of epithelial ovarian cancer intraperitoneal metastasis. Oncogene 36(42):5840–5851. https://doi.org/10.1038/onc.2017.171

Knödler M, Körfer J, Kunzmann V et al (2018) Randomised phase II trial to investigate catumaxomab (anti-EpCAM × anti-CD3) for treatment of peritoneal carcinomatosis in patients with gastric cancer. Br J Cancer 119(3):296–302. https://doi.org/10.1038/s41416-018-0150-6

Kobayashi H, Ogawa K, Kawahara N et al (2017) Sequential molecular changes and dynamic oxidative stress in high-grade serous ovarian carcinogenesis. Free Radic Res 51(9–10):755–764. https://doi.org/10.1080/10715762.2017.1383605

Köbel M, Kalloger SE, Boyd N et al (2008) Ovarian carcinoma subtypes are different diseases: implications for biomarker studies. PLoS Med 5(12):e232. https://doi.org/10.1371/journal.pmed.0050232

Köbel M, Reuss A, du Bois A et al (2010) The biological and clinical value of p53 expression in pelvic high-grade serous carcinomas. J Pathol 222(2):191–198. https://doi.org/10.1002/path.2744

Koensgen D, Freitag C, Klaman I et al (2010) Expression and localization of E-cadherin in epithelial ovarian cancer. Anticancer Res 30(7):2525–2530

Konstantinopoulos PA, Barry WT, Birrer M, Westin SN, Cadoo KA, Shapiro GI, Mayer EL, O'Cearbhaill RE, Coleman RL, Kochupurakkal B, Whalen C, Curtis J, Farooq S, Luo W, Eismann J, Buss MK, Aghajanian C, Mills GB, Palakurthi S, Kirschmeier P, Liu J, Cantley LC, Kaufmann SH, Swisher EM, D'Andrea AD, Winer E, Wulf GM, Matulonis UA (2019) Olaparib and α-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial. Lancet Oncol 20(4):570–580. https://doi.org/10.1016/S1470-2045(18)30905-7

Kourtidis A, Lu R, Pence LJ, Anastasiadis PZ (2017) A central role for cadherin signaling in cancer. Exp Cell Res 358(1):78–85

Krasner CN, Birrer MJ, Berlin ST, Horowitz NS, Buss MK, Eliasof S et al (2014) Phase II clinical trial evaluating CRLX101 in recurrent ovarian, tubal, and peritoneal cancer. J Clin Oncol 32 (Suppl 5):abstr 5581

Krasner CN, Birrer MJ, Berlin ST et al (2015) Targeting VEGFRi resistance through HIF-1á suppression: phase II clinical trial evaluating CRLX101 as monotherapy and in combination with bevacizumab in recurrent platinum resistant ovarian cancer. J Clin Oncol 33(Suppl 15): abstr 5614. https://doi.org/10.1200/jco.2015.33.15_suppl.tps5614

Krasner C, Birrer M, Peters C et al (2016) Abstract CT090: phase II trial of the NDC CRLX101 in combination with bevacizumab in patients with platinum-resistant ovarian cancer (PROC). Cancer Res 76:CT090. https://doi.org/10.1158/1538-7445.AM2016-CT090

Krebs AM, Mitschke J, Lasierra Losada M et al (2017) The EMT-activator Zeb1 is a key factor for cell plasticity and promotes metastasis in pancreatic cancer. Nat Cell Biol 19(5):518–529. https://doi.org/10.1038/ncb3513

Krishnamurthy A, Jimeno A (2018) Bispecific antibodies for cancer therapy: a review. Pharmacol Ther 185:122–134. https://doi.org/10.1016/j.pharmthera.2017.12.002

Kristeleit R, Davidenko I, Shirinkin V, El-Khouly F, Bondarenko I, Goodheart MJ, Gorbunova V, Penning CA, Shi JG, Liu X, Newton RC, Zhao Y, Maleski J, Leopold L, Schilder RJ (2017) A randomised, open-label, phase 2 study of the IDO1 inhibitor epacadostat (INCB024360) versus tamoxifen as therapy for biochemically recurrent (CA-125 relapse)-only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer. Gynecol Oncol 146 (3):484–490. https://doi.org/10.1016/j.ygyno.2017.07.005

Kroeger PT, Drapkin R (2016) Pathogenesis and heterogeneity of ovarian cancer. Curr Opin Obstet Gynecol 29(1):26–34

Kruk J, Aboul-Enein HY (2017) Reactive oxygen and nitrogen species in carcinogenesis: implications of oxidative stress on the progression and development of several cancer types. Mini Rev Med Chem 17(11):904–919. https://doi.org/10.2174/1389557517666170228115324

Książek K (2020) Where does cellular senescence belong in the pathophysiology of ovarian cancer? Semin Cancer Biol. S1044-579X(20)30260-1. https://doi.org/10.1016/j.semcancer.2020.11.021

Kuhn E, Meeker A, Wang TL, Sehdev AS, Kurman RJ, Shih IM (2010) Shortened telomeres in serous tubal intraepithelial carcinoma: an early event in ovarian high-grade serous carcinogenesis. Am J Surg Pathol 34(6):829–836. https://doi.org/10.1097/PAS.0b013e3181dcede7

Kuhn E, Kurman RJ, Vang R, Sehdev AS, Han G, Soslow R, Wang TL, Shih IM (2012) TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma–evidence supporting the clonal relationship of the two lesions. J Pathol 226 (3):421–426. https://doi.org/10.1002/path.3023

Kuhn E, Bahadirli-Talbott A, Shih IM (2014) Frequent CCNE1 amplification in endometrial intraepithelial carcinoma and uterine serous carcinoma. Mod Pathol 27(7):1014–1019. https://doi.org/10.1038/modpathol.2013.209

Kuhn E, Wang TL, Doberstein K et al (2016) CCNE1 amplification and centrosome number abnormality in serous tubal intraepithelial carcinoma: further evidence supporting its role as a precursor of ovarian high-grade serous carcinoma. Mod Pathol 29(10):1254–1261. https://doi.org/10.1038/modpathol.2016.101

Kurtz J, Marth C, Oaknin A, Asselain B, Baumann K, Cibula D et al (2018) ATALANTE (ENGOT-ov29): a randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab. J Clin Oncol 36(Suppl):abstr TPS5607

Kuznetsova AY, Seget K, Moeller GK et al (2015) Chromosomal instability, tolerance of mitotic errors and multidrug resistance are promoted by tetraploidization in human cells. Cell Cycle 14 (17):2810–2820

Kyriakopoulos CE, Braden AM, Kolesar JM et al (2016) A phase I study of tivantinib in combination with temsirolimus in patients with advanced solid tumors. Invest New Drugs 35 (3):290–297

Labidi-Galy SI, Papp E, Hallberg D et al (2017) High grade serous ovarian carcinomas originate in the fallopian tube. Nat Commun 8(1):1093. https://doi.org/10.1038/s41467-017-00962-1

Lam T, Aguirre-Ghiso JA, Geller MA, Aksan A, Azarin SM (2020) Immobilization rapidly selects for chemoresistant ovarian cancer cells with enhanced ability to enter dormancy. Biotechnol Bioeng 117(10):3066–3080. https://doi.org/10.1002/bit.27479

Lambert AW, Pattabiraman DR, Weinberg RA (2017) Emerging biological principles of metastasis. Cell 168(4):670–691. https://doi.org/10.1016/j.cell.2016.11.037

Lampert EJ, Zimmer A, Padget M, Cimino-Mathews A, Nair JR, Liu Y, Swisher EM, Hodge JW, Nixon AB, Nichols E, Bagheri MH, Levy E, Radke MR, Lipkowitz S, Annunziata CM, Taube JM, Steinberg SM, Lee JM (2020) Combination of PARP inhibitor olaparib, and PD-L1 inhibitor durvalumab, in recurrent ovarian cancer: a proof-of-concept phase II study. Clin Cancer Res 26(16):4268–4279. https://doi.org/10.1158/1078-0432.CCR-20-0056

Laplante M, Sabatini DM (2012) mTOR signaling in growth control and disease. Cell 149(2):274–293. https://doi.org/10.1016/j.cell.2012.03.017

Lau MT, So WK, Leung PC (2013) Fibroblast growth factor 2 induces E-cadherin down-regulation via PI3K/Akt/mTOR and MAPK/ERK signaling in ovarian cancer cells. PLoS One 8(3):e59083

Le Page C, Amuzu S, Rahimi K, Gotlieb W, Ragoussis J, Tonin PN (2020) Lessons learned from understanding chemotherapy resistance in epithelial tubo-ovarian carcinoma from BRCA1and BRCA2mutation carriers. Semin Cancer Biol. S1044-579X(20)30177-2. https://doi.org/10.1016/j.semcancer.2020.08.005

Le Saux O, Ray-Coquard I, Labidi-Galy SI (2020) Challenges for immunotherapy for the treatment of platinum resistant ovarian cancer. Semin Cancer Biol. S1044-579X(20)30193-0. https://doi.org/10.1016/j.semcancer.2020.08.017

Leckband DE, de Rooij J (2014) Cadherin adhesion and mechanotransduction. Annu Rev Cell Dev Biol 30:291–315. https://doi.org/10.1146/annurev-cellbio-100913-013212

Ledermann JA, Canevari S, Thigpen T (2015) Targeting the folate receptor: diagnostic and therapeutic approaches to personalize cancer treatments. Ann Oncol 26(10):2034–2043. https://doi.org/10.1093/annonc/mdv250

Ledermann JA, Embleton AC, Raja F, Perren TJ, Jayson GC, GJS R, Kaye SB, Hirte H, Eisenhauer E, Vaughan M, Friedlander M, González-Martín A, Stark D, Clark E, Farrelly L, Swart AM, Cook A, Kaplan RS, MKB P, ICON6 collaborators (2016) Cediranib in patients with relapsed platinum sensitive ovarian cancer (ICON6): a randomised, double-blind, placebocontrolled phase 3 trial. Lancet 387(10023):1066–1074. https://doi.org/10.1016/S0140-6736(15)01167-8. Erratum in: Lancet. 2016 Apr23;387(10029):1722

Ledermann JA, Colombo N, Oza M et al (2020) Avelumab in combination with and/or following chemotherapy vs chemotherapy alone in patients with previously untreated epithelial ovarian cancer: results from the phase 3 javelin ovarian 100 trial. Society of Gynecologic Oncology Annual Meeting on Women's Cancer. LBA 25, Scientific Plenary. https://doi.org/10.1016/j.ygyno.2020.06.025

Lee EK, Matulonis UA (2020) Emerging drugs for the treatment of ovarian cancer: a focused review of PARP inhibitors. Expert Opin Emerg Drugs 25(2):165–188. https://doi.org/10.1080/14728214.2020.1773791

Lee WH, Bookstein R, Hong F et al (1987) Human retinoblastoma susceptibility gene: cloning, identification, and sequence. Science 235(4794):1394–1399

Lee JG, Ahn JH, Jin Kim T, Ho Lee J, Choi JH (2015) Mutant p53 promotes ovarian cancer cell adhesion to mesothelial cells via integrin β4 and Akt signals. Sci Rep 5:12642. https://doi.org/10.1038/srep12642

Lee EK, Xiong N, Cheng SC, Barry WT, Penson RT, Konstantinopoulos PA, Hoffman MA, Horowitz N, Dizon DS, Stover EH, Wright AA, Campos SM, Krasner C, Morrissey S, Whalen C, Quinn R, Matulonis UA, Liu JF (2020) Combined pembrolizumab and pegylated liposomal doxorubicin in platinum resistant ovarian cancer: a phase 2 clinical trial. Gynecol Oncol 159(1):72–78. https://doi.org/10.1016/j.ygyno.2020.07.028

Legge F, Paglia A, D'Asta M et al (2011) Phase II study of the combination carboplatin plus celecoxib in heavily pre-treated recurrent ovarian cancer patients. BMC Cancer 11:214. https://doi.org/10.1186/1471-2407-11-214

Leijen S, van Geel RM, Sonke GS, de Jong D, Rosenberg EH, Marchetti S, Pluim D, van Werkhoven E, Rose S, Lee MA, Freshwater T, Beijnen JH, Schellens JH (2016) Phase II study of WEE1 inhibitor AZD1775s carboplatin in patients with TP53-mutated ovarian cancer refractory or resistant to first-line therapy within 3 months. J Clin Oncol 34(36):4354–4361. https://doi.org/10.1200/JCO.2016.67.5942

Leroy B, Anderson M, Soussi T (2014) TP53 mutations in human cancer: database reassessment and prospects for the next decade. Hum Mutat 35(6):672–688. https://doi.org/10.1002/humu.22552

Lheureux S, N'Diaye M, Blanc-Fournier C, Dugué AE, Clarisse B, Dutoit S, Giffard F, Abeilard E, Briand M, Labiche A, Grellard JM, Crouet H, Martin S, Joly F, Poulain L (2015) Identification of predictive factors of response to the BH3-mimetic molecule ABT-737: an ex vivo experiment in human serous ovarian carcinoma. Int J Cancer 136(5):E340–E350. https://doi.org/10.1002/ijc.29104

Lheureux S, Cristea MC, Bruce JP, Garg S, Cabanero M, Mantia-Smaldone G, Olawaiye AB, Ellard SL, Weberpals JI, Wahner Hendrickson AE, Fleming GF, Welch S, Dhani NC, Stockley T, Rath P, Karakasis K, Jones GN, Jenkins S, Rodriguez-Canales J, Tracy M, Tan Q, Bowering V, Udagani S, Wang L, Kunos CA, Chen E, Pugh TJ, Oza AM (2021) Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 397(10271):281–292. https://doi.org/10.1016/S0140-6736(20)32554-X

Li H, Zhang R (2013) Role of EZH2 in epithelial ovarian cancer: from biological insights to therapeutic target. Front Oncol 3:47. https://doi.org/10.3389/fonc.2013.00047

Li SB, Schwartz PE, Lee WH et al (1991) Allele loss at the retinoblastoma locus in human ovarian cancer. J Natl Cancer Inst 83(9):637–640

Li W, Xu XL, Zhang J, Cai JH, Tang YX (2012) Effects of cyclooxygenase inhibitors on survival time in ovarian cancer xenograft-bearing mice. Oncol Lett 4(6):1269–1273. https://doi.org/10.3892/ol.2012.929

Li H, Zeng J, Shen K (2014) PI3K/AKT/mTOR signaling pathway as a therapeutic target for ovarian cancer. Arch Gynecol Obstet 290(6):1067–1078. https://doi.org/10.1007/s00404-014-3377-3

Li C, Bonazzoli E, Bellone S et al (2019a) Mutational landscape of primary, metastatic, and recurrent ovarian cancer reveals c-MYC gains as potential target for BET inhibitors. Proc Natl Acad Sci U S A 116(2):619–624. https://doi.org/10.1073/pnas.1814027116

Li VD, Li KH, Li JT (2019b) TP53 mutations as potential prognostic markers for specific cancers: analysis of data from The Cancer Genome Atlas and the International Agency for Research on Cancer TP53 Database. J Cancer Res Clin Oncol 145(3):625–636. https://doi.org/10.1007/s00432-018-2817-z

Li N, Li H, Wang Y, Cao L, Zhan X (2020) Quantitative proteomics revealed energy metabolism pathway alterations in human epithelial ovarian carcinoma and their regulation by the antiparasite drug ivermectin: data interpretation in the context of 3P medicine. EPMA J 11(4):661–694. https://doi.org/10.1007/s13167-020-00224-z

Li J, Zou Y, Pei M, Zhang Y, Jiang Y (2021) Berberine inhibits the Warburg effect through TET3/miR-145/HK2 pathways in ovarian cancer cells. J Cancer 12(1):207–216. https://doi.org/10.7150/jca.48896

Lin Q, Liu W, Xu S, Shang H, Li J, Guo Y, Tong J (2021) PARP inhibitors as maintenance therapy in newly diagnosed advanced ovarian cancer: a meta-analysis. BJOG 128(3):485–493. https://doi.org/10.1111/1471-0528.16411

Lincet H, Kafara P, Giffard F, Abeilard-Lemoisson E, Duval M, Louis MH, Poulain L, Icard P (2013) Inhibition of Mcl-1 expression by citrate enhances the effect of Bcl-xL inhibitors on human ovarian carcinoma cells. J Ovarian Res 6(1):72. https://doi.org/10.1186/1757-2215-6-72

Liu F, Yang X, Geng M, Huang M (2018) Targeting ERK, an Achilles' Heel of the MAPK pathway, in cancer therapy. Acta Pharm Sin B 8(4):552–562

Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, Rimel BJ, Buss MK, Nattam SR, Hurteau J, Luo W, Curtis J, Whalen C, Kohn EC, Ivy SP, Matulonis UA (2019a) Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. Ann Oncol 30(4):551–557. https://doi.org/10.1093/annonc/mdz018

Liu JF, Gordon M, Veneris J, Braiteh F, Balmanoukian A, Eder JP, Oaknin A, Hamilton E, Wang Y, Sarkar I, Molinero L, Fassò M, O'Hear C, Lin YG, Emens LA (2019b) Safety, clinical activity and biomarker assessments of atezolizumab from a Phase I study in advanced/recurrent ovarian and uterine cancers. Gynecol Oncol 154(2):314–322. https://doi.org/10.1016/j.ygyno.2019.05.021

Liu JF, Herold C, Gray KP et al (2019c) Assessment of combined nivolumab and bevacizumab in relapsed ovarian cancer: a phase 2 clinical trial [published online ahead of print, 2019]. JAMA Oncol 5(12):1731–1738. https://doi.org/10.1001/jamaoncol.2019.3343

Loeian MS, Mehdi Aghaei S, Farhadi F et al (2019) Liquid biopsy using the nanotube-CTC-chip: capture of invasive CTCs with high purity using preferential adherence in breast cancer patients. Lab Chip 19(11):1899–1915. https://doi.org/10.1039/c9lc00274j

Long GV, Hauschild A, Santinami M et al (2017a) Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 377(19):1813–1823. https://doi.org/10.1056/NEJMoa1708539

Long GV, Flaherty KT, Stroyakovskiy D et al (2017b) Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol 28(7):1631–1639

Lord CJ, Ashworth A (2012) The DNA damage response and cancer therapy. Nature 481:287. https://doi.org/10.1038/nature10760

LoRusso PM (2016) Inhibition of the PI3K/AKT/mTOR pathway in solid tumors. J Clin Oncol 34 (31):3803–3815. https://doi.org/10.1200/JCO.2014.59.0018

Lu J, Chen H, He F, You Y, Feng Z, Chen W, Li X, Zhao L (2020) Ginsenoside 20(S)-Rg3 upregulates HIF-1α-targeting miR-519a-5p to inhibit the Warburg effect in ovarian cancer cells. Clin Exp Pharmacol Physiol 47(8):1455–1463. https://doi.org/10.1111/1440-1681.13321

Lundgren C, Ahlin C, Holmberg L et al (2015) Cyclin E1 is a strong prognostic marker for death from lymph node negative breast cancer. A population-based case-control study. Acta Oncol 54 (4):538–544. https://doi.org/10.3109/0284186X.2014.965274

Luo H, Xu X, Ye M, Sheng B, Zhu X (2018) The prognostic value of HER2 in ovarian cancer: a meta-analysis of observational studies. PLoS One 13(1):e0191972. https://doi.org/10.1371/journal.pone.0191972

Luther C, Swami U, Zhang J et al (2019) Advanced stage melanoma therapies: detailing the present and exploring the future. Crit Rev Oncol Hematol 133:99–111. https://doi.org/10.1016/j.critrevonc.2018.11.002

Ma Y, Wang W, Idowu MO et al (2018a) Ovarian cancer relies on glucose transporter 1 to fuel glycolysis and growth: anti-tumor activity of BAY-876. Cancers (Basel) 11(1):33. https://doi.org/10.3390/cancers11010033

Ma C, Zhao JZ, Lin RT et al (2018b) Combined overexpression of cadherin 6, cadherin 11 and cluster of differentiation 44 is associated with lymph node metastasis and poor prognosis in oral squamous cell carcinoma. Oncol Lett 15(6):9498–9506

Mabuchi S, Kuroda H, Takahashi R et al (2015) The PI3K/AKT/mTOR pathway as a therapeutic target in ovarian cancer. Gynecol Oncol 137(1):173–179. https://doi.org/10.1016/j.ygyno.2015.02.003

Macpherson AM, Barry SC, Ricciardelli C, Oehler MK (2020) Epithelial ovarian cancer and the immune system: biology, interactions, challenges and potential advances for immunotherapy. J Clin Med 9(9):2967. https://doi.org/10.3390/jcm9092967

Mandilaras V, Garg S, Cabanero M, Tan Q, Pastrello C, Burnier J, Karakasis K, Wang L, Dhani NC, Butler MO, Bedard PL, Siu LL, Clarke B, Shaw PA, Stockley T, Jurisica I, Oza AM, Lheureux S (2019) TP53 mutations in high grade serous ovarian cancer and impact on clinical outcomes: a comparison of next generation sequencing and bioinformatics analyses. Int J Gynecol Cancer. https://doi.org/10.1136/ijgc-2018-000087

Manning AL, Dyson NJ (2012) RB: mitotic implications of a tumour suppressor. Nat Rev Cancer 12(3):220–226. https://doi.org/10.1038/nrc3216

Marth C, Vergote I, Scambia G, Oberaigner W, Clamp A, Berger R, Kurzeder C, Colombo N, Vuylsteke P, Lorusso D, Hall M, Renard V, Pignata S, Kristeleit R, Altintas S, Rustin G, Wenham RM, Mirza MR, Fong PC, Oza A, Monk BJ, Ma H, Vogl FD, Bach BA (2017) ENGOT-ov-6/TRINOVA-2: randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. Eur J Cancer 70:111–121. https://doi.org/10.1016/j.ejca.2016.09.004

Martin de la Fuente L, Westbom-Fremer S, Arildsen NS, Hartman L, Malander S, Kannisto P, Måsbäck A, Hedenfalk I (2020) PD-1/PD-L1 expression and tumor-infiltrating lymphocytes are prognostically favorable in advanced high-grade serous ovarian carcinoma. Virchows Arch 477 (1):83–91. https://doi.org/10.1007/s00428-020-02751-6

Martin LP, Konner JA, Moore KN et al (2017) Characterization of folate receptor alpha (FRα) expression in archival tumor and biopsy samples from relapsed epithelial ovarian cancer patients: a phase I expansion study of the FRα-targeting antibody-drug conjugate mirvetuximab soravtansine. Gynecol Oncol 147(2):402–407. https://doi.org/10.1016/j.ygyno.2017.08.015

Martins FC, Santiago ID, Trinh A et al (2014) Combined image and genomic analysis of high-grade serous ovarian cancer reveals PTEN loss as a common driver event and prognostic classifier. Genome Biol 15(12):526. https://doi.org/10.1186/s13059-014-0526-8

Martowicz A, Spizzo G, Gastl G, Untergasser G (2012) Phenotype-dependent effects of EpCAM expression on growth and invasion of human breast cancer cell lines. BMC Cancer 12:501. https://doi.org/10.1186/1471-2407-12-501

Mattmann ME, Stoops SL, Lindsley CW (2011) Inhibition of Akt with small molecules and biologics: historical perspective and current status of the patent landscape. Expert Opin Ther Pat 21(9):1309–1338

Matulonis UA, Wulf GM, Barry WT et al (2016) Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer. Ann Oncol 28 (3):512–518

Matulonis UA, Moore KN, Martin LP et al (2018) Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), with pembrolizumab in platinum-resistant ovarian cancer (PROC): initial results of an expansion cohort from FORWARD II, a phase Ib study. Ann Oncol 29. https://doi.org/10.1093/annonc/mdy285.157

Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I, Raspagliesi F, Sonke GS, Birrer M, Provencher DM, Sehouli J, Colombo N, González-Martín A, Oaknin A, Ottevanger PB, Rudaitis V, Katchar K, Wu H, Keefe S, Ruman J, Ledermann JA (2019) Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol 30(7):1080–1087. https://doi.org/10.1093/annonc/mdz135

McAlpine JN, Porter H, Köbel M et al (2012) BRCA1 and BRCA2 mutations correlate with TP53 abnormalities and presence of immune cell infiltrates in ovarian high-grade serous carcinoma. Mod Pathol 25(5):740–750. https://doi.org/10.1038/modpathol.2011.211

McCormick A, Earp E, Leeson C et al (2016) Phosphatase and tensin homolog is a potential target for ovarian cancer sensitization to cytotoxic agents. Int J Gynecol Cancer 26(4):632–639. https://doi.org/10.1097/IGC.0000000000000657

McLachlan J, Gore M, Banerjee S (2016a) Targeting the mitogen-activated protein kinase pathway in low-grade serous carcinoma of the ovary. Pharmacogenomics 17(12):1353–1363. https://doi.org/10.2217/pgs.16.24

McLachlan J, Lima JP, Dumas L, Banerjee S (2016b) Targeted agents and combinations in ovarian cancer: where are we now? Expert Rev Anticancer Ther 16(4):441–454. https://doi.org/10.1586/14737140.2016.1162101

McMullen M, Madariaga A, Lheureux S (2020) New approaches for targeting platinum-resistant ovarian cancer. Semin Cancer Biol. S1044-579X(20)30186-3. https://doi.org/10.1016/j.semcancer.2020.08.013

Mendivil AA, Tung PK, Bohart R, Bechtol K, Goldstein BH (2018) Dramatic clinical response following dabrafenib and trametinib therapy in a heavily pretreated low grade serous ovarian carcinoma patient with a BRAF V600E mutation. Gynecol Oncol Rep 26:41–44. https://doi.org/10.1016/j.gore.2018.09.002

Meng E, Taylor B, Ray A, Shevde LA, Rocconi RP (2012) Targeted inhibition of telomerase activity combined with chemotherapy demonstrates synergy in eliminating ovarian cancer spheroid-forming cells. Gynecol Oncol 124(3):598–605. https://doi.org/10.1016/j.ygyno.2011.11.018

Mesnage SJL, Auguste A, Genestie C, Dunant A, Pain E, Drusch F, Gouy S, Morice P, Bentivegna E, Lhomme C, Pautier P, Michels J, Le Formal A, Cheaib B, Adam J, Leary AF (2017) Neoadjuvant chemotherapy (NACT) increases immune infiltration and programmed death-ligand 1 (PD-L1) expression in epithelial ovarian cancer (EOC). Ann Oncol 28 (3):651–657. https://doi.org/10.1093/annonc/mdw625

Milea A, George SH, Matevski D et al (2014) Retinoblastoma pathway deregulatory mechanisms determine clinical outcome in high-grade serous ovarian carcinoma. Mod Pathol 27 (7):991–1001. https://doi.org/10.1038/modpathol.2013.218

Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M, Ledermann JA, Lorusso D, Vergote I, Ben-Baruch NE, Marth C, Mądry R, Christensen RD, Berek JS,

Dørum A, Tinker AV, du Bois A, González-Martín A, Follana P, Benigno B, Rosenberg P, Gilbert L, Rimel BJ, Buscema J, Balser JP, Agarwal S, Matulonis UA, ENGOT-OV16/NOVA Investigators (2016) Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 375(22):2154–2164. https://doi.org/10.1056/NEJMoa1611310

Mirza MR, Pignata S, Ledermann JA (2018) Latest clinical evidence and further development of PARP inhibitors in ovarian cancer. Ann Oncol 29(6):1366–1376. https://doi.org/10.1093/annonc/mdy174

Mirza MR, Coleman RL, González-Martín A, Moore KN, Colombo N, Ray-Coquard I, Pignata S (2020) The forefront of ovarian cancer therapy: update on PARP inhibitors. Ann Oncol 31 (9):1148–1159. https://doi.org/10.1016/j.annonc.2020.06.004

Miše BP, Telesmanić VD, Tomić S et al (2015) Correlation between E-cadherin immunoexpression and efficacy of first line platinum-based chemotherapy in advanced high grade serous ovarian cancer. Pathol Oncol Res 21(2):347–356. https://doi.org/10.1007/s12253-014-9827-1

Mitsudomi T, Yatabe Y (2010) Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. FEBS J 277(2):301–308. https://doi.org/10.1111/j.1742-4658.2009.07448.x

Mittal K, Donthamsetty S, Kaur R et al (2017) Multinucleated polyploidy drives resistance to Docetaxel chemotherapy in prostate cancer. Br J Cancer 116(9):1186–1194

Moiseeva O, Guillon J, Ferbeyre G (2020) Senescence: a program in the road to cell elimination and cancer. Semin Cancer Biol. S1044-579X(20)30277-7. https://doi.org/10.1016/j.semcancer.2020.12.017

Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, Oaknin A, Ray-Coquard I, Provencher DM, Karlan BY, Lhommé C, Richardson G, Rincón DG, Coleman RL, Herzog TJ, Marth C, Brize A, Fabbro M, Redondo A, Bamias A, Tassoudji M, Navale L, Warner DJ, Oza AM (2014) Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 15 (8):799–808. https://doi.org/10.1016/S1470-2045(14)70244-X

Monk BJ, Brady MF, Aghajanian C, Lankes HA, Rizack T, Leach J, Fowler JM, Higgins R, Hanjani P, Morgan M, Edwards R, Bradley W, Kolevska T, Foukas P, Swisher EM, Anderson KS, Gottardo R, Bryan JK, Newkirk M, Manjarrez KL, Mannel RS, Hershberg RM, Coukos G (2017) A phase 2, randomized, double-blind, placebo-controlled study of chemo-immunotherapy combination using motolimod with pegylated liposomal doxorubicin in recurrent or persistent ovarian cancer: a Gynecologic Oncology Group partners study. Ann Oncol 28 (5):996–1004. https://doi.org/10.1093/annonc/mdx049

Moore KN, Pignata S (2019) Trials in progress: imagyn050/GOG 3015/ENGOT-OV39. A Phase III, multicenter, randomized study of atezolizumab versus placebo administered in combination with paclitaxel, carboplatin, and bevacizumab to patients with newly-diagnosed stage III or stage IV ovarian, fallopian tube, or primary peritoneal cancer. Int J Gynecol Cancer. https://doi.org/10.1136/ijgc-2018-000071

Moore KN, Borghaei H, O'Malley DM et al (2017) Phase 1 dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor α-targeting antibody-drug conjugate, in patients with solid tumors. Cancer 123(16):3080–3087. https://doi.org/10.1002/cncr.30736

Moore KN, Martin LP, O'Malley DM et al (2018a) A review of mirvetuximab soravtansine in the treatment of platinum-resistant ovarian cancer. Future Oncol 14(2):123–136. https://doi.org/10.2217/fon-2017-0379

Moore KN, O'Malley DM, Vergote I et al (2018b) Safety and activity findings from a phase 1b escalation study of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with carboplatin in patients with platinum-sensitive ovarian cancer. Gynecol Oncol 151(1):46–52. https://doi.org/10.1016/j.ygyno.2018.07.017

Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, Gourley C, Banerjee S, Oza A, González-Martín A, Aghajanian C, Bradley W, Mathews C, Liu J, Lowe ES, Bloomfield R, DiSilvestro P (2018c) Maintenance

olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 379 (26):2495–2505. https://doi.org/10.1056/NEJMoa1810858

Moore KN, Secord AA, Geller MA, Miller DS, Cloven N, Fleming GF, Wahner Hendrickson AE, Azodi M, DiSilvestro P, Oza AM, Cristea M, Berek JS, Chan JK, Rimel BJ, Matei DE, Li Y, Sun K, Luptakova K, Matulonis UA, Monk BJ (2019a) Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 20(5):636–648. https://doi.org/10.1016/S1470-2045(19)30029-4

Moore KN, Oza AM, Colombo N et al (2019b) FORWARD I (GOG 3011): a Phase III study of mirvetuximab soravtansine, a folate receptor alpha (FRa)-targeting antibody-drug conjugate (ADC), versus chemotherapy in patients (pts) with platinum-resistant ovarian cancer (PROC). Ann Oncol 30(Suppl 5):v403–v434. https://doi.org/10.1093/annonc/mdz250

Moore KN, Bookman M, Sehouli J (2020) LBA31 primary results from IMagyn050/GOG 3015/ENGOT-OV39, a double-blind placebo (pbo)-controlled randomised phase III trial of bevacizumab (bev)-containing therapy ± atezolizumab (atezo) for newly diagnosed stage III/IV ovarian cancer (OC). Ann Oncol. https://doi.org/10.1016/j.annonc.2020.08.2261

Moroney JW, Powderly J, Lieu CH, Bendell JC, Eckhardt SG, Chang CW, Molinero L, Spahn J, Williams P, Lin YG, Hodi FS (2020) Safety and clinical activity of atezolizumab plus bevacizumab in patients with ovarian cancer: a phase Ib study. Clin Cancer Res 26 (21):5631–5637. https://doi.org/10.1158/1078-0432.CCR-20-0477

Morrison J, Thoma C, Goodall RJ et al (2018) Epidermal growth factor receptor blockers for the treatment of ovarian cancer. Cochrane Database Syst Rev 10:CD007927. https://doi.org/10.1002/14651858.CD007927

Morse CB, Toukatly MN, Kilgore MR, Agnew KJ, Bernards SS, Norquist BM, Pennington KP, Garcia RL, Liao JB, Swisher EM (2019) Tumor infiltrating lymphocytes and homologous recombination deficiency are independently associated with improved survival in ovarian carcinoma. Gynecol Oncol 153(2):217–222. https://doi.org/10.1016/j.ygyno.2019.02.011

Moujaber T, Etemadmoghadam D, Kennedy CJ et al (2018) BRAF mutations in low-grade serous ovarian cancer and response to BRAF inhibition. JCO Precis Oncol 2:1–14. https://doi.org/10.1200/PO.17.00221

Mrozik KM, Blaschuk OW, Cheong CM et al (2018) N-cadherin in cancer metastasis, its emerging role in haematological malignancies and potential as a therapeutic target in cancer. BMC Cancer 18:939. https://doi.org/10.1186/s12885-018-4845-0

Murakami R, Matsumura N, Brown JB et al (2017) Exome sequencing landscape analysis in ovarian clear cell carcinoma shed light on key chromosomal regions and mutation gene networks. Am J Pathol 187(10):2246–2258. https://doi.org/10.1016/j.ajpath.2017.06.012

Murakami R, Matsumura N, Michimae H et al (2019) The mesenchymal transition subtype more responsive to dose dense taxane chemotherapy combined with carboplatin than to conventional taxane and carboplatin chemotherapy in high grade serous ovarian carcinoma: a survey of Japanese Gynecologic Oncology Group study (JGOG3016A1). Gynecol Oncol 153 (2):312–319. https://doi.org/10.1016/j.ygyno.2019.02.010

Nadkarni NJ, Geest KD, Neff T et al (2013) Microvessel density and p53 mutations in advanced-stage epithelial ovarian cancer. Cancer Lett 331(1):99–104. https://doi.org/10.1016/j.canlet.2012.12.016

Nakayama N, Nakayama K, Shamima Y et al (2010) Gene amplification CCNE1 is related to poor survival and potential therapeutic target in ovarian cancer. Cancer 116(11):2621–2634. https://doi.org/10.1002/cncr.24987

Naumann RW, Coleman RL, Burger RA et al (2013) PRECEDENT: a randomized phase II trial comparing vintafolide (EC145) and pegylated liposomal doxorubicin (PLD) in combination versus PLD alone in patients with platinum-resistant ovarian cancer. J Clin Oncol 31 (35):4400–4406. https://doi.org/10.1200/JCO.2013.49.7685

O'Malley DM, Matulonis UA, Birrer MJ, Castro CM, Gilbert L, Vergote I, Martin LP, Mantia-Smaldone GM, Martin AG, Bratos R, Penson RT, Malek K, Moore KN (2020) Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate

(ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. Gynecol Oncol 157(2):379–385. https://doi.org/10.1016/j.ygyno.2020.01.037

Oh J, Barve M, Matthews CM, Koon EC, Heffernan TP, Fine B, Grosen E, Bergman MK, Fleming EL, DeMars LR, West L, Spitz DL, Goodman H, Hancock KC, Wallraven G, Kumar P, Bognar E, Manning L, Pappen BO, Adams N, Senzer N, Nemunaitis J (2016) Phase II study of Vigil® DNA engineered immunotherapy as maintenance in advanced stage ovarian cancer. Gynecol Oncol 143(3):504–510. https://doi.org/10.1016/j.ygyno.2016.09.018

Orbegoso C, Marquina G, George A, Banerjee S (2017) The role of Cediranib in ovarian cancer. Expert Opin Pharmacother 18(15):1637–1648. https://doi.org/10.1080/14656566.2017.1383384

Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Park-Simon TW, Rustin G, Joly F, Mirza MR, Plante M, Quinn M, Poveda A, Jayson GC, Stark D, Swart AM, Farrelly L, Kaplan R, Parmar MK, Perren TJ, ICON7 Trial Investigators (2015a) Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol 16(8):928–936. https://doi.org/10.1016/S1470-2045(15)00086-8

Oza AM, Vergote IB, Gilbert LG, Lucy P, Ghatage A, Lisyankaya S et al (2015b) A randomized double-blind phase III trial comparing vintafolide (EC145) and pegylated liposomal doxorubicin (PLD/Doxil®/Caelyx®) in combination versus PLD in participants with platinum-resistant ovarian cancer (PROCEED) (NCT01170650). Gynecol Oncol 137:5–6. https://doi.org/10.1016/j.ygyno.2015.01.010

Oza AM, Estevez-Diz M, Grischke EM, Hall M, Marmé F, Provencher D, Uyar D, Weberpals JI, Wenham RM, Laing N, Tracy M, Freshwater T, Lee MA, Liu J, Qiu J, Rose S, Rubin EH, Moore K (2020) A biomarker-enriched, randomized phase II trial of adavosertib (AZD1775) plus paclitaxel and carboplatin for women with platinum-sensitive TP53-mutant ovarian cancer. Clin Cancer Res 26(18):4767–4776. https://doi.org/10.1158/1078-0432.CCR-20-0219

Pal M, Bhattacharya S, Kalyan G et al (2018) Cadherin profiling for therapeutic interventions in Epithelial Mesenchymal Transition (EMT) and tumorigenesis. Exp Cell Res 368(2):137–146. https://doi.org/10.1016/j.yexcr.2018.04.014

Palaia I, Tomao F, Sassu CM, Musacchio L, Benedetti Panici P (2020) Immunotherapy for ovarian cancer: recent advances and combination therapeutic approaches. Onco Targets Ther 13:6109–6129. https://doi.org/10.2147/OTT.S205950

Papa S, Choy PM, Bubici C (2018) The ERK and JNK pathways in the regulation of metabolic reprogramming. Oncogene. https://doi.org/10.1038/s41388-018-0582-8

Pascale RM, Calvisi DF, Simile MM, Feo CF, Feo F (2020) The Warburg effect 97 years after its discovery. Cancers (Basel) 12(10):2819. https://doi.org/10.3390/cancers12102819

Pasquali S, Hadjinicolaou AV, Chiarion Sileni V, Rossi CR, Mocellin S (2018) Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev 2(2):CD011123. https://doi.org/10.1002/14651858.CD011123.pub2

Patch AM, Christie EL, Etemadmoghadam D et al (2015) Whole-genome characterization of chemoresistant ovarian cancer. Nature 521(7553):489–494. https://doi.org/10.1038/nature14410

Patel IS, Madan P, Getsios S et al (2003) Cadherin switching in ovarian cancer progression. Int J Cancer 106(2):172–177

Pathak SJ, Mueller JL, Okamoto K et al (2019) EPCAM mutation update: variants associated with congenital tufting enteropathy and Lynch syndrome. Hum Mutat 40(2):142–161. https://doi.org/10.1002/humu.23688

Patriarca C, Macchi RM, Marschner AK, Mellstedt H (2012) Epithelial cell adhesion molecule expression (CD326) in cancer: a short review. Cancer Treat Rev 38(1):68–75. https://doi.org/10.1016/j.ctrv.2011.04.002

Pearce CL, Templeman C, Rossing MA et al (2012) Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol 13(4):385–394

Peng HL, He L, Zhao X (2012) Association of reduced immunohistochemical expression of E-cadherin with a poor ovarian cancer prognosis--results of a meta-analysis. Asian Pac J Cancer Prev 13(5):2003–2007

Peng DH, Kundu ST, Fradette JJ et al (2019) ZEB1 suppression sensitizes KRAS mutant cancers to MEK inhibition by an IL17RD-dependent mechanism. Sci Transl Med 11(483):eaaq1238. https://doi.org/10.1126/scitranslmed.aaq1238

Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA III, Bidziński M, Kim JW, Nam JH, Madry R, Hernández C, Mora PAR, Ryu SY, Milenkova T, Lowe ES, Barker L, Scambia G (2020) Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. J Clin Oncol 38(11):1164–1174. https://doi.org/10.1200/JCO.19.02745

Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Kurzeder C, du Bois A, Sehouli J, Kimmig R, Stähle A, Collinson F, Essapen S, Gourley C, Lortholary A, Selle F, Mirza MR, Leminen A, Plante M, Stark D, Qian W, Parmar MK, Oza AM, ICON7 Investigators (2011) A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 365(26):2484–2496. https://doi.org/10.1056/NEJMoa1103799. Erratum in: N Engl J Med 2012;366(3):284

Petersen S, Wilson AJ, Hirst J, Roby KF, Fadare O, Crispens MA, Beeghly-Fadiel A, Khabele D (2020) CCNE1 and BRD4 co-amplification in high-grade serous ovarian cancer is associated with poor clinical outcomes. Gynecol Oncol 157(2):405–410. https://doi.org/10.1016/j.ygyno.2020.01.038

Pétigny-Lechartier C, Duboc C, Jebahi A et al (2017) The mTORC1/2 inhibitor AZD8055engthens the efficiency of the MEK inhibitor trametinib to reduce the Mcl-1/[Bim and Puma] ratio and to sensitize ovarian carcinoma cells to ABT-737. Mol Cancer Ther 16(1):102–115. https://doi.org/10.1158/1535-7163.MCT-16-0342

Petrillo M et al (2016) Targeting the hallmarks of ovarian cancer: the big picture. Gynecol Oncol 142:176–183

Pham E, Birrer MJ, Eliasof S, Garmey EG, Lazarus D, Lee CR, Man S, Matulonis UA, Peters CG, Xu P, Krasner C, Kerbel RS (2015) Translational impact of nanoparticle-drug conjugate CRLX101 with or without bevacizumab in advanced ovarian cancer. Clin Cancer Res 21(4):808–818. https://doi.org/10.1158/1078-0432.CCR-14-28102868

Piha-Paul SA, Wheler JJ, Fu S et al (2014) Advanced gynecologic malignancies treated with a combination of the VEGF inhibitor bevacizumab and the mTOR inhibitor temsirolimus. Oncotarget 5(7):1846–1855

Pils D, Bachmayr-Heyda A, Auer K et al (2014) Cyclin E1 (CCNE1) as independent positive prognostic factor in advanced stage serous ovarian cancer patients – a study of the OVCAD consortium. Eur J Cancer 50(1):99–110. https://doi.org/10.1016/j.ejca.2013.09.011

Poveda A, Floquet A, Ledermann JA et al (2020) Final overall survival results from SOLO2/ENGOT-ov21: a phase III trial assessing maintenance olaparib in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation. ASCO20 Virtual Scientific Program. Abstract 6002. Presented at press briefing on May 12, 2020

Pradeep S, Kim SW, Wu SY et al (2014) Hematogenous metastasis of ovarian cancer: rethinking mode of spread. Cancer Cell 26(1):77–91. https://doi.org/10.1016/j.ccr.2014.05.002

Prat J, D'Angelo E, Espinosa I (2018) Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics. Hum Pathol 80:11–27. https://doi.org/10.1016/j.humpath.2018.06.018

Prislei S, Martinelli E, Zannoni GF et al (2015) Role and prognostic significance of the epithelial-mesenchymal transition factor ZEB2 in ovarian cancer. Oncotarget 6(22):18966–18979. https://doi.org/10.18632/oncotarget.3943

Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D, Ray-Coquard I (2014) Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 32 (13):1302–1308. https://doi.org/10.1200/JCO.2013.51.4489

Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, Korach J, Huzarski T, Poveda A, Pignata S, Friedlander M, Colombo N, Harter P, Fujiwara K, Ray-Coquard I, Banerjee S, Liu J, Lowe ES, Bloomfield R, Pautier P, SOLO2/ENGOT-Ov21 Investigators (2017) Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 18(9):1274–1284. https://doi.org/10.1016/S1470-2045(17)30469-2. Epub 2017. Erratum in: Lancet Oncol 2017;18(9):e510

Pujade-Lauraine E, Fujiwara K, Dychter SS, Devgan G, Monk BJ (2018) Avelumab (anti-PD-L1) in platinum-resistant/refractory ovarian cancer: javelin Ovarian 200 Phase III study design. Future Oncol 14(21):2103–2113. https://doi.org/10.2217/fon-2018-0070

Pujade-Lauraine E, Fujiwara K, Ledermann JAL et al (2019) Avelumab alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase III JAVELIN Ovarian 200 trial. Soc Gynecol Oncol Annual Meeting. (LBA1). https://www.sgo50.org/wp-content/uploads/2019/03/SGO-2019-Late-Breaking-Abstracts.pdf. Accessed 16 Jan 2021

Qiao Y, Yang T, Gan Y et al (2018) Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. BMC Cancer 18(1):288. https://doi.org/10.1186/s12885-018-4156-5

Qiu C, Lu N, Wang X et al (2017) Gene expression profiles of ovarian low-grade serous carcinoma resemble those of fallopian tube epithelium. Gynecol Oncol 147(3):634–641. https://doi.org/10.1016/j.ygyno.2017.09.029

Rafehi S, Ramos Valdes Y, Bertrand M et al (2016) TGFβ signaling regulates epithelial-mesenchymal plasticity in ovarian cancer ascites-derived spheroids. Endocr Relat Cancer 23 (3):147–159. https://doi.org/10.1530/ERC-15-0383

Rahman M, Nakayama K, Rahman MT et al (2012) Clinicopathologic and biological analysis of PIK3CA mutation in ovarian clear cell carcinoma. Hum Pathol 43(12):2197–2206. https://doi.org/10.1016/j.humpath.2012.03.011

Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, Fujiwara K, Vergote I, Colombo N, Mäenpää J, Selle F, Sehouli J, Lorusso D, Guerra Alía EM, Reinthaller A, Nagao S, Lefeuvre-Plesse C, Canzler U, Scambia G, Lortholary A, Marmé F, Combe P, de Gregorio N, Rodrigues M, Buderath P, Dubot C, Burges A, You B, Pujade-Lauraine E, Harter P, PAOLA-1 Investigators (2019) Olaparib plus Bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med 381(25):2416–2428. https://doi.org/10.1056/NEJMoa1911361

Rechsteiner M, Zimmermann AK, Wild PJ et al (2013) TP53 mutations are common in all subtypes of epithelial ovarian cancer and occur concomitantly with KRAS mutations in the mucinous type. Exp Mol Pathol 95(2):235–241. https://doi.org/10.1016/j.yexmp.2013.08.004

Ren J, Chen Y, Song H, Chen L, Wang R (2013) Inhibition of ZEB1 reverses EMT and chemoresistance in docetaxel-resistant human lung adenocarcinoma cell line. J Cell Biochem 114(6):1395–1403. https://doi.org/10.1002/jcb.24481

Ren YA, Mullany LK, Liu Z, Herron AJ, Wong KK, Richards JS (2016) Mutant p53 promotes epithelial ovarian cancer by regulating tumor differentiation, metastasis, and responsiveness to steroid hormones. Cancer Res 76(8):2206–2218

Reyes HD, Thiel KW, Carlson MJ et al (2014) Comprehensive profiling of EGFR/HER receptors for personalized treatment of gynecologic cancers. Mol Diagn Ther 18(2):137–151. https://doi.org/10.1007/s40291-013-0070-3

Reyners AK, de Munck L, Erdkamp FL et al (2012) A randomized phase II study investigating the addition of the specific COX-2 inhibitor celecoxib to docetaxel plus carboplatin as first-line

chemotherapy for stage IC to IV epithelial ovarian cancer, Fallopian tube or primary peritoneal carcinomas: the DoCaCel study. Ann Oncol 23(11):2896–2902. https://doi.org/10.1093/annonc/mds107

Ribas A, Wolchok JD (2018) Cancer immunotherapy using checkpoint blockade. Science 359 (6382):1350–1355. https://doi.org/10.1126/science.aar4060

Rizzo A, Napoli A, Roggiani F, Tomassetti A, Bagnoli M, Mezzanzanica D (2018) One-carbon metabolism: biological players in epithelial ovarian cancer. Int J Mol Sci 19(7):2092. https://doi.org/10.3390/ijms19072092

Roggiani F, Mezzanzanica D, Rea K, Tomassetti A (2016) Guidance of signaling activations by cadherins and integrins in epithelial ovarian cancer cells. Int J Mol Sci 17(9):1387. https://doi.org/10.3390/ijms17091387

Rubinsak LA, Cohen C, Khanna N et al (2018) Folate receptor alpha expression in platinum resistant/refractory ovarian carcinomas and primary endocervical adenocarcinomas. Appl Immunohistochem Mol Morphol 26(8):567–572. https://doi.org/10.1097/PAI.0000000000000476

Ruscito I, Bellati F, Ray-Coquard I, Mirza MR, du Bois A, Gasparri ML, Costanzi F, De Marco MP, Nuti M, Caserta D, Pignata S, Dorigo O, Sehouli J, Braicu EI (2020) Incorporating parp-inhibitors in primary and recurrent ovarian cancer: a meta-analysis of 12 phase II/III randomized controlled trials. Cancer Treat Rev 87:102040. https://doi.org/10.1016/j.ctrv.2020.102040

Russell SE, McCluggage WG (2004) A multistep model for ovarian tumorigenesis: the value of mutation analysis in the KRAS and BRAF genes. J Pathol 203(2):617–619

Russo A, Czarnecki AA, Dean M et al (2018) PTEN loss in the fallopian tube induces hyperplasia and ovarian tumor formation. Oncogene 37(15):1976–1990. https://doi.org/10.1038/s41388-017-0097-8

Sakata J, Kajiyama H, Suzuki S et al (2017) Impact of positive ZEB1 expression in patients with epithelial ovarian carcinoma as an oncologic outcome-predicting indicator. Oncol Lett 14 (4):4287–4293. https://doi.org/10.3892/ol.2017.6658

Saleh T, Carpenter VJ, Bloukh S, Gewirtz DA (2020) Targeting tumor cell senescence and polyploidy as potential therapeutic strategies. Semin Cancer Biol. S1044-579X(20)30270-4. https://doi.org/10.1016/j.semcancer.2020.12.010

Salmena L, Shaw P, Fans I et al (2015) Prognostic value of INPP4B protein immunohistochemistry in ovarian cancer. Eur J Gynaecol Oncol 36(3):260–267

Sarker D, Ang JE, Baird R et al (2014) First-in-human phase I study of pictilisib (GDC-0941), a potent pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, in patients with advanced solid tumors. Clin Cancer Res 21(1):77–86

Sato H, Niimi A, Yasuhara T, Permata TBM, Hagiwara Y, Isono M, Nuryadi E, Sekine R, Oike T, Kakoti S, Yoshimoto Y, Held KD, Suzuki Y, Kono K, Miyagawa K, Nakano T, Shibata A (2017) DNA double-strand break repair pathway regulates PD-L1 expression in cancer cells. Nat Commun 8(1):1751. https://doi.org/10.1038/s41467-017-01883-9

Sawada K, Mitra AK, Radjabi AR et al (2008) Loss of E-cadherin promotes ovarian cancer metastasis via alpha 5-integrin, which is a therapeutic target. Cancer Res 68(7):2329–2339

Scaranti M, Cojocaru E, Banerjee S, Banerji U (2020) Exploiting the folate receptor α in oncology. Nat Rev Clin Oncol 17(6):349–359. https://doi.org/10.1038/s41571-020-0339-5

Scheid AD, Beadnell TC, Welch DR (2021) Roles of mitochondria in the hallmarks of metastasis. Br J Cancer 124(1):124–135. https://doi.org/10.1038/s41416-020-01125-8

Schnell U, Cirulli V, Giepmans BN (2013) EpCAM: structure and function in health and disease. Biochim Biophys Acta 1828(8):1989–2001. https://doi.org/10.1016/j.bbamem.2013.04.018

Seagle BL, Yang CP, Eng KH, Dandapani M, Odunsi-Akanji O, Goldberg GL, Odunsi K, Horwitz SB, Shahabi S (2015) TP53 hot spot mutations in ovarian cancer: selective resistance to microtubule stabilizers in vitro and differential survival outcomes from The Cancer Genome Atlas. Gynecol Oncol 138(1):159–164. https://doi.org/10.1016/j.ygyno.2015.04.039

Semaan A, Munkarah AR, Arabi H, Bandyopadhyay S, Seward S, Kumar S, Qazi A, Hussein Y, Morris RT, Ali-Fehmi R (2011) Expression of GLUT-1 in epithelial ovarian carcinoma:

correlation with tumor cell proliferation, angiogenesis, survival and ability to predict optimal cytoreduction. Gynecol Oncol 121(1):181–186. https://doi.org/10.1016/j.ygyno.2010.11.019
Shahbazi MN, Perez-Moreno M (2015) Connections between cadherin-catenin proteins, spindle misorientation, and cancer. Tissue Barriers 3(3):e1045684. https://doi.org/10.1080/21688370.2015.1045684
Shamir ER, Ewald AJ (2015) Adhesion in mammary development: novel roles for E-cadherin in individual and collective cell migration. Curr Top Dev Biol 112:353–382
Shang AQ, Wu J, Bi F et al (2017a) Relationship between HER2 and JAK/STAT-SOCS3 signaling pathway and clinicopathological features and prognosis of ovarian cancer. Cancer Biol Ther 18 (5):314–322
Shang Y, He J, Wang Y, Feng Q, Zhang Y, Guo J, Li J, Li S, Wang Y, Yan G, Ren F, Shi Y, Xu J, Zeps N, Zhai Y, He D, Chang Z (2017b) CHIP/Stub1 regulates the Warburg effect by promoting degradation of PKM2 in ovarian carcinoma. Oncogene 36(29):4191–4200. https://doi.org/10.1038/onc.2017.31
Shen W, Li HL, Liu L, Cheng JX (2017) Expression levels of PTEN, HIF-1α, and VEGF as prognostic factors in ovarian cancer. Eur Rev Med Pharmacol Sci 21(11):2596–2603
Sheppard KE, Cullinane C, Hannan KM et al (2013) Synergistic inhibition of ovarian cancer cell growth by combining selective PI3K/mTOR and RAS/ERK pathway inhibitors. Eur J Cancer 49 (18):3936–3944. https://doi.org/10.1016/j.ejca.2013.08.007
Sherr CJ, McCormick F (2002) The RB and p53 pathways in cancer. Cancer Cell 2(2):103–112
Shibuya Y, Tokunaga H, Saito S et al (2018) Identification of somatic genetic alterations in ovarian clear cell carcinoma with next generation sequencing. Genes Chromosomes Cancer 57 (2):51–60. https://doi.org/10.1002/gcc.22507
Shimogai R, Kigawa J, Itamochi H, Iba T, Kanamori Y, Oishi T, Shimada M, Sato S, Kawaguchi W, Sato S, Terakawa N (2008) Expression of hypoxia-inducible factor 1alpha gene affects the outcome in patients with ovarian cancer. Int J Gynecol Cancer 18 (3):499–505. https://doi.org/10.1111/j.1525-1438.2007.01055.x
Sigismund S, Avanzato D, Lanzetti L (2017) Emerging functions of the EGFR in cancer. Mol Oncol 12(1):3–20
Sikora E, Czarnecka-Herok J, Bojko A, Sunderland P (2020) Therapy-induced polyploidization and senescence: coincidence or interconnection? Semin Cancer Biol. S1044-579X(20)30253-4. https://doi.org/10.1016/j.semcancer.2020.11.015
Silwal-Pandit L, Langerød A, Børresen-Dale AL (2017) TP53 mutations in breast and ovarian cancer. Cold Spring Harb Perspect Med 7(1):a026252. https://doi.org/10.1101/cshperspect.a026252
Simeone P, Trerotola M, Franck J et al (2018) The multiverse nature of epithelial to mesenchymal transition. Semin Cancer Biol. S1044-579X(18)30086-5. https://doi.org/10.1016/j.semcancer.2018.11.004
Simonin K, Brotin E, Dufort S, Dutoit S, Goux D, N'diaye M, Denoyelle C, Gauduchon P, Poulain L (2009) Mcl-1 is an important determinant of the apoptotic response to the BH3-mimetic molecule HA14-1 in cisplatin-resistant ovarian carcinoma cells. Mol Cancer Ther 8 (11):3162–3170. https://doi.org/10.1158/1535-7163.MCT-09-0493
Simpkins F, Jang K, Yoon H et al (2018) Dual Src and MEK inhibition decreases ovarian cancer growth and targets tumor initiating stem-like cells. Clin Cancer Res 24(19):4874–4886. https://doi.org/10.1158/1078-0432.CCR-17-3697
Singer G, Oldt R III, Cohen Y et al (2003) Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. J Natl Cancer Inst 95(6):484–486
Singh R, Letai A, Sarosiek K (2019) Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. Nat Rev Mol Cell Biol 20(3):175–193. https://doi.org/10.1038/s41580-018-0089-8
Skírnisdóttir I, Seidal T (2011) Prognostic impact of concomitant p53 and PTEN on outcome in early stage (FIGO I-II) epithelial ovarian cancer. Int J Gynecol Cancer 21(6):1024–1031. https://doi.org/10.1097/IGC.0b013e31821dc906

Song H, Ramus SJ, Shadforth D et al (2006) Common variants in RB1 gene and risk of invasive ovarian cancer. Cancer Res 66(20):10220–10226

Song H, Kwan SY, Izaguirre DI et al (2013) PAX2 expression in ovarian cancer. Int J Mol Sci 14 (3):6090–6105. https://doi.org/10.3390/ijms14036090

Song N, Liu H, Ma X, Zhang S (2016) Placental growth factor promotes ovarian cancer cell invasion via ZEB2. Cell Physiol Biochem 38(1):351–358. https://doi.org/10.1159/000438635

Sonntag R, Giebeler N, Nevzorova YA et al (2018) Cyclin E1 and cyclin-dependent kinase 2 are critical for initiation, but not for progression of hepatocellular carcinoma. Proc Natl Acad Sci U S A 115(37):9282–9287. https://doi.org/10.1073/pnas.1807155115

Soong TR, Dinulescu DM, Xian W et al (2018) Frontiers in the pathology and pathogenesis of ovarian cancer: cancer precursors and "precursor escape". Hematol Oncol Clin North Am 32 (6):915–928. https://doi.org/10.1016/j.hoc.2018.07.013

Soong TR, Howitt BE, Horowitz N et al (2019) The fallopian tube, "precursor escape" and narrowing the knowledge gap to the origins of high-grade serous carcinoma. Gynecol Oncol 152(2):426–433. https://doi.org/10.1016/j.ygyno.2018.11.033

Soussi T (2010) The history of p53. A perfect example of the drawbacks of scientific paradigms. EMBO Rep 11(11):822–826

Spizzo G, Fong D, Wurm M et al (2011) EpCAM expression in primary tumour tissues and metastases: an immunohistochemical analysis. J Clin Pathol 64(5):415–420. https://doi.org/10.1136/jcp.2011.090274

Spreafico A, Oza AM, Clarke BA et al (2017) Genotype-matched treatment for patients with advanced type I epithelial ovarian cancer (EOC). Gynecol Oncol 144(2):250–255. https://doi.org/10.1016/j.ygyno.2016.12.002

Stamelos VA, Robinson E, Redman CW, Richardson A (2013) Navitoclax augments the activity of carboplatin and paclitaxel combinations in ovarian cancer cells. Gynecol Oncol 128 (2):377–382. https://doi.org/10.1016/j.ygyno.2012.11.019

Stewart D, Cristea M (2019) Antibody-drug conjugates for ovarian cancer: current clinical development. Curr Opin Obstet Gynecol 31(1):18–23. https://doi.org/10.1097/GCO.0000000000000515

Stewart ML, Tamayo P, Wilson AJ et al (2015) KRAS genomic status predicts the sensitivity of ovarian cancer cells to decitabine. Cancer Res 75(14):2897–2906

Stover EH, Howitt B, Lindeman NI et al (2016) Somatic mutations and copy number variations in cancer-associated genes in 695 ovarian cancer patients. [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016-20; New Orleans, LA. Philadelphia (PA): aacr. Cancer Res 76(14 Suppl):Abstract nr 95

Stover EH, Baco MB, Cohen O, Li YY, Christie EL, Bagul M, Goodale A, Lee Y, Pantel S, Rees MG, Wei G, Presser AG, Gelbard MK, Zhang W, Zervantonakis IK, Bhola PD, Ryan J, Guerriero JL, Montero J, Liang FJ, Cherniack AD, Piccioni F, Matulonis UA, Bowtell DDL, Sarosiek KA, Letai A, Garraway LA, Johannessen CM, Meyerson M (2019) Pooled genomic screens identify anti-apoptotic genes as targetable mediators of chemotherapy resistance in ovarian cancer. Mol Cancer Res 17(11):2281–2293. https://doi.org/10.1158/1541-7786.MCR-18-1243

Strickland KC, Howitt BE, Shukla SA, Rodig S, Ritterhouse LL, Liu JF, Garber JE, Chowdhury D, Wu CJ, D'Andrea AD, Matulonis UA, Konstantinopoulos PA (2016) Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. Oncotarget 7 (12):13587–13598. https://doi.org/10.18632/oncotarget.7277

Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, Konecny GE, Coleman RL, Tinker AV, O'Malley DM, Kristeleit RS, Ma L, Bell-McGuinn K, Brenton JD, Cragun JM, Oaknin A, Ray-Coquard I, Harrell MI, Mann E, Kaufmann SH, Floquet A, Leary A, Harding TC, Goble S, Maloney L, Isaacson J, Allen AR, Rolfe L, Yelensky R, Raponi M, McNeish IA (2017) Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an

international, multicentre, open-label, phase 2 trial. Lancet Oncol 18(1):75–87. https://doi.org/10.1016/S1470-2045(16)30559-9

Takai M, Terai Y, Kawaguchi H et al (2014) The EMT (epithelial-mesenchymal-transition)-related protein expression indicates the metastatic status and prognosis in patients with ovarian cancer. J Ovarian Res 7:76. https://doi.org/10.1186/1757-2215-7-76

Takekuma M, Wong KK, Coleman RL (2016) A long-term surviving patient with recurrent low-grade serous ovarian carcinoma treated with the MEK1/2 inhibitor, selumetinib. Gynecol Oncol Res Pract 3:5. https://doi.org/10.1186/s40661-016-0026-5

Takenaka M, Saito M, Iwakawa R et al (2015) Profiling of actionable gene alterations in ovarian cancer by targeted deep sequencing. Int J Oncol 46(6):2389–2398. https://doi.org/10.3892/ijo.2015.2951

Tamura R, Tanaka T, Akasaki Y, Murayama Y, Yoshida K, Sasaki H (2019) The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: perspectives for therapeutic implications. Med Oncol 37(1):2. https://doi.org/10.1007/s12032-019-1329-2

Tan DS, Agarwal R, Kaye SB (2006) Mechanisms of transcoelomic metastasis in ovarian cancer. Lancet Oncol 7(11):925–934. https://doi.org/10.1016/S1470-2045(06)70939-1

Tang S, Ning Q, Yang L, Mo Z, Tang S (2020) Mechanisms of immune escape in the cancer immune cycle. Int Immunopharmacol 86:106700. https://doi.org/10.1016/j.intimp.2020.106700

Taniguchi K, Karin M (2018) NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol 18(5):309–324. https://doi.org/10.1038/nri.2017.142

Tayama S, Motohara T, Narantuya D et al (2017) The impact of EpCAM expression on response to chemotherapy and clinical outcomes in patients with epithelial ovarian cancer. Oncotarget 8 (27):44312–44325. https://doi.org/10.18632/oncotarget.17871

Telleria CM (2013) Repopulation of ovarian cancer cells after chemotherapy. Cancer Growth Metastasis 6:15–21. https://doi.org/10.4137/CGM.S11333

Temkin SM, Yamada SD, Fleming GF (2010) A phase I study of weekly temsirolimus and topotecan in the treatment of advanced and/or recurrent gynecologic malignancies. Gynecol Oncol 117(3):473–476. https://doi.org/10.1016/j.ygyno.2010.02.022

Teng L, Peng S et al (2015) Conditioned media from human ovarian cancer endothelial progenitor cells induces ovarian cancer cell migration by activating epithelial-to-mesenchymal transition. Cancer Gene Ther 22(11):518–523. https://doi.org/10.1038/cgt.2015.45

Teplinsky E, Muggia F (2015) EGFR and HER2: is there a role in ovarian cancer? Translat Cancer Res 4(1):107–117. https://doi.org/10.3978/j.issn.2218-676X.2015.01.01

Tew WP, Sill MW, Walker JL et al (2018) Randomized phase II trial of bevacizumab plus everolimus versus bevacizumab alone for recurrent or persistent ovarian, fallopian tube or peritoneal carcinoma: an NRG oncology/gynecologic oncology group study. Gynecol Oncol 151(2):257–263. https://doi.org/10.1016/j.ygyno.2018.08.027

Tewari KS, Burger RA, Enserro D, Norquist BM, Swisher EM, Brady MF, Bookman MA, Fleming GF, Huang H, Homesley HD, Fowler JM, Greer BE, Boente M, Liang SX, Ye C, Bais C, Randall LM, Chan JK, Ferriss JS, Coleman RL, Aghajanian C, Herzog TJ, DiSaia PJ, Copeland LJ, Mannel RS, Birrer MJ, Monk BJ (2019) Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. J Clin Oncol 37(26):2317–2328. https://doi.org/10.1200/JCO.19.01009

Tomao F, Bardhi E, Di Pinto A, Sassu CM, Biagioli E, Petrella MC, Palaia I, Muzii L, Colombo N, Panici PB (2019) Parp inhibitors as maintenance treatment in platinum sensitive recurrent ovarian cancer: an updated meta-analysis of randomized clinical trials according to BRCA mutational status. Cancer Treat Rev 80:101909. https://doi.org/10.1016/j.ctrv.2019.101909

Topatana W, Juengpanich S, Li S, Cao J, Hu J, Lee J, Suliyanto K, Ma D, Zhang B, Chen M, Cai X (2020) Advances in synthetic lethality for cancer therapy: cellular mechanism and clinical translation. J Hematol Oncol 13(1):118. https://doi.org/10.1186/s13045-020-00956-5

Trabert B, Poole EM, White E et al (2018) Analgesic use and ovarian cancer risk: an analysis in the ovarian cancer cohort consortium. J Natl Cancer Inst. https://doi.org/10.1093/jnci/djy100

Tretter JY, Schorpp K, Luxenburger E et al (2018) A high-content screen for small-molecule regulators of epithelial cell-adhesion molecule (EpCAM) cleavage yields a robust inhibitor. J Biol Chem 293(23):8994–9005. https://doi.org/10.1074/jbc.RA118.002776

Turashvili G, Grisham RN, Chiang S et al (2018) BRAFV600E mutations and immunohistochemical expression of VE1 protein in low-grade serous neoplasms of the ovary. Histopathology 73 (3):438–443. https://doi.org/10.1111/his.13651

Tutlewska K, Lubinski J, Kurzawski G (2013) Germline deletions in the EPCAM gene as a cause of Lynch syndrome – literature review. Hered Cancer Clin Pract 11(1):9. https://doi.org/10.1186/1897-4287-11-9

Urbano AM (2021) Otto Warburg: the journey towards the seminal discovery of tumor cell bioenergetic reprogramming. Biochim Biophys Acta Mol Basis Dis 1867(1):165965. https://doi.org/10.1016/j.bbadis.2020.165965

Usui A, Ko SY, Barengo N, Naora H (2014) P-cadherin promotes ovarian cancer dissemination through tumor cell aggregation and tumor-peritoneum interactions. Mol Cancer Res 12 (4):504–513

van Baal JOAM, van Noorden CJF, Nieuwland R et al (2018) Development of peritoneal carcinomatosis in epithelial ovarian cancer: a review. J Histochem Cytochem 66(2):67–83

Van Berckelaer C, Brouwers AJ, Peeters DJ et al (2016) Current and future role of circulating tumor cells in patients with epithelial ovarian cancer. Eur J Surg Oncol 42(12):1772–1779. https://doi.org/10.1016/j.ejso.2016.05.010

Vanhaesebroeck B, Guillermet-Guibert J, Graupera M et al (2010) The emerging mechanisms of isoform-specific PI3K signalling. Nat Rev Mol Cell Biol 11(5):329–341. https://doi.org/10.1038/nrm2882

Varga A, Piha-Paul S, Ott PA, Mehnert JM, Berton-Rigaud D, Morosky A, Yang P, Ruman J, Matei D (2019) Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: analysis of KEYNOTE-028. Gynecol Oncol 152(2):243–250. https://doi.org/10.1016/j.ygyno.2018.11.017

Veneris JT, Matulonis UA, Liu JF, Konstantinopoulos PA (2020) Choosing wisely: selecting PARP inhibitor combinations to promote anti-tumor immune responses beyond BRCA mutations. Gynecol Oncol 156(2):488–497. https://doi.org/10.1016/j.ygyno.2019.09.021

Verdoodt F, Dehlendorff C, Friis S et al (2018) Non-aspirin NSAID use and ovarian cancer mortality. Gynecol Oncol 150(2):331–337. https://doi.org/10.1016/j.ygyno.2018.06.018

Vergote I, Armstrong D, Scambia G et al (2016) A randomized, double-blind, placebo-controlled, phase III study to assess efficacy and safety of weekly farletuzumab in combination with carboplatin and taxane in patients with ovarian cancer in first platinum-sensitive relapse. J Clin Oncol 34(19):2271–2278. https://doi.org/10.1200/JCO.2015.63.2596

Vergote I, du Bois A, Floquet A, Rau J, Kim JW, Del Campo JM, Friedlander M, Pignata S, Fujiwara K, Colombo N, Mirza MR, Monk BJ, Tsibulak I, Calvert PM, Herzog TJ, Hanker LC, Meunier J, Lee JY, Bologna A, Carrasco-Alfonso MJ, Harter P (2019a) Overall survival results of AGO-OVAR16: a phase 3 study of maintenance pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced ovarian cancer. Gynecol Oncol 155(2):186–191. https://doi.org/10.1016/j.ygyno.2019.08.024

Vergote I, Scambia G, O'Malley DM, Van Calster B, Park SY, Del Campo JM, Meier W, Bamias A, Colombo N, Wenham RM, Covens A, Marth C, Raza Mirza M, Kroep JR, Ma H, Pickett CA, Monk BJ, TRINOVA-3/ENGOT-ov2/GOG-3001 Investigators (2019b) Trebananib or placebo plus carboplatin and paclitaxel as first-line treatment for advanced ovarian cancer (TRINOVA-3/ENGOT-ov2/GOG-3001): a randomised, double-blind, phase 3 trial. Lancet Oncol 20(6):862–876. https://doi.org/10.1016/S1470-2045(19)30178-0

Verma S, Bartlett CH, Schnell P et al (2016) Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2-negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3). Oncologist 21(10):1165–1175

Vieira AF, Paredes J (2015) P-cadherin and the journey to cancer metastasis. Mol Cancer 14:178. https://doi.org/10.1186/s12943-015-0448-4

Vijayakumaran R, Tan KH, Miranda PJ, Haupt S, Haupt Y (2015) Regulation of mutant p53 protein expression. Front Oncol 5:284. https://doi.org/10.3389/fonc.2015.00284

Wakahashi S, Sudo T, Oka N et al (2013) VAV1 represses E-cadherin expression through the transactivation of Snail and Slug: a potential mechanism for aberrant epithelial to mesenchymal transition in human epithelial ovarian cancer. Transl Res 162(3):181–190. https://doi.org/10.1016/j.trsl.2013.06.005

Wang Y, Ma J, Shen H et al (2014) Reactive oxygen species promote ovarian cancer progression via the HIF-1α/LOX/E-cadherin pathway. Oncol Rep 32(5):2150–2158

Wang Y, Zhang FC, Wang YJ (2015) The efficacy and safety of non-steroidal anti-inflammatory drugs in preventing the recurrence of colorectal adenoma: a meta-analysis and systematic review of randomized trials. Colorectal Dis 17(3):188–196. https://doi.org/10.1111/codi.12838

Wang D, Li C, Zhang Y et al (2016a) Combined inhibition of PI3K and PARP is effective in the treatment of ovarian cancer cells with wild-type PIK3CA genes. Gynecol Oncol 142 (3):548–556

Wang Q, Wang B, Zhang YM, Wang W (2016b) The association between CDH1 promoter methylation and patients with ovarian cancer: a systematic meta-analysis. J Ovarian Res 9:23. https://doi.org/10.1186/s13048-016-0231-1

Wang S, Han H, Hu Y et al (2017a) SLC3A2, antigen of mAb 3G9, promotes migration and invasion by upregulating of mucins in gastric cancer. Oncotarget. 8(51):88586–88598. https://doi.org/10.18632/oncotarget.19529

Wang Q, Lou W, Di W, Wu X (2017b) Prognostic value of tumor PD-L1 expression combined with CD8+ tumor infiltrating lymphocytes in high grade serous ovarian cancer. Int Immunopharmacol 52:7–14. https://doi.org/10.1016/j.intimp.2017.08.017

Wang YP, Wang QY, Li CH, Li XW (2018) COX-2 inhibition by celecoxib in epithelial ovarian cancer attenuates E-cadherin suppression through reduced Snail nuclear translocation. Chem Biol Interact 292:24–29. https://doi.org/10.1016/j.cbi.2018.06.020

Wang Y, Wei Z, Pan K, Li J, Chen Q (2020) The function and mechanism of ferroptosis in cancer. Apoptosis 25(11–12):786–798. https://doi.org/10.1007/s10495-020-01638-w

Warburg O (1930) The metabolism of tumours: investigations from the Kaiser Wilhelm Institute for Biology, Berlin-Dahlem. Arnold Constable, London

Warburg O (1956) On respiratory impairment in cancer cells. Science 124(3215):269–270

Webb JR, Milne K, Kroeger DR, Nelson BH (2016) PD-L1 expression is associated with tumor-infiltrating T cells and favorable prognosis in high-grade serous ovarian cancer. Gynecol Oncol 141(2):293–302. https://doi.org/10.1016/j.ygyno.2016.03.008

Welch DR, Hurst DR (2019) Defining the hallmarks of metastasis. Cancer Res 79(12):3011–3027. https://doi.org/10.1158/0008-5472.CAN-19-0458

Wendel JRH, Wang X, Hawkins SM (2018) The endometriotic tumor microenvironment in ovarian cancer. Cancers (Basel) 10(8):261. https://doi.org/10.3390/cancers10080261

Westin SN, Kristeleit RS, Coleman RL et al (2019) Abstract CT158: athena (GOG-3020/ENGOT-ov45): a randomized, double-blind, placebo-controlled, Phase III study of rucaparib + nivolumab following front-line platinum-based chemotherapy in ovarian cancer. Cancer Res 79:CT158

Wojnarowicz PM, Oros KK, Quinn MC et al (2012) The genomic landscape of TP53 and p53 annotated high grade ovarian serous carcinomas from a defined founder population associated with patient outcome. PLoS One 7(9):e45484

Wong KK, Tsang YT, Deavers MT et al (2010) BRAF mutation is rare in advanced-stage low-grade ovarian serous carcinomas. Am J Pathol 177(4):1611–1617

Wong M, Tan N, Zha J, Peale FV, Yue P, Fairbrother WJ, Belmont LD (2012) Navitoclax (ABT-263) reduces Bcl-x(L)-mediated chemoresistance in ovarian cancer models. Mol Cancer Ther 11(4):1026–1035. https://doi.org/10.1158/1535-7163.MCT-11-0693

Wong KK, Izaguirre DI, Kwan SY et al (2013) Poor survival with wild-type TP53 ovarian cancer? Gynecol Oncol 130(3):565–569

Wong SHM, Fang CM, Chuah LH et al (2018) E-cadherin: its dysregulation in carcinogenesis and clinical implications. Crit Rev Oncol Hematol 121:11–22. https://doi.org/10.1016/j.critrevonc.2017.11.010

Wood DJ, Endicott JA (2018) Structural insights into the functional diversity of the CDK-cyclin family. Open Biol 8(9):180112

Woopen H, Pietzner K, Richter R et al (2014) Overexpression of the epithelial cell adhesion molecule is associated with a more favorable prognosis and response to platinum-based chemotherapy in ovarian cancer. J Gynecol Oncol 25(3):221–228. https://doi.org/10.3802/jgo.2014.25.3.221

Wu DI, Liu L, Ren C et al (2016) Epithelial-mesenchymal interconversions and the regulatory function of the ZEB family during the development and progression of ovarian cancer. Oncol Lett 11(2):1463–1468. https://doi.org/10.3892/ol.2016.4092

Wyld L, Bellantuono I, Tchkonia T, Morgan J, Turner O, Foss F, George J, Danson S, Kirkland JL (2020) Senescence and cancer: a review of clinical implications of senescence and senotherapies. Cancers (Basel) 12(8):2134. https://doi.org/10.3390/cancers12082134

Xu Y, Bi R, Xiao Y et al (2017) Low frequency of BRAF and KRAS mutations in Chinese patients with low-grade serous carcinoma of the ovary. Diagn Pathol 12(1):87. https://doi.org/10.1186/s13000-017-0679-3

Xu Y, Zhang Q, Miao C et al (2019) CCNG1 (Cyclin G1) regulation by mutant-P53 via induction of Notch3 expression promotes high-grade serous ovarian cancer (HGSOC) tumorigenesis and progression. Cancer Med 8(1):351–362

Yahyazadeh Mashhadi SM, Kazemimanesh M, Arashkia A et al (2019) Shedding light on the EpCAM: an overview. J Cell Physiol 234(8):12569–12580. https://doi.org/10.1002/jcp.28132

Yan Z, Tian X, Wang R et al (2017) Title prognosis significance of ZEB2 and TGF-β1 as well as other clinical characteristics in epithelial ovarian cancer. Int J Gynecol Cancer 27(7):1343–1349. https://doi.org/10.1097/IGC.0000000000001037

Yang SYC, Lheureux S, Karakasis K et al (2018) Landscape of genomic alterations in high-grade serous ovarian cancer from exceptional long- and short-term survivors. Genome Med 10(1):81. https://doi.org/10.1186/s13073-018-0590-x

Yaswen P, MacKenzie KL, Keith WN, Hentosh P, Rodier F, Zhu J, Firestone GL, Matheu A, Carnero A, Bilsland A, Sundin T, Honoki K, Fujii H, Georgakilas AG, Amedei A, Amin A, Helferich B, Boosani CS, Guha G, Ciriolo MR, Chen S, Mohammed SI, Azmi AS, Bhakta D, Halicka D, Niccolai E, Aquilano K, Ashraf SS, Nowsheen S, Yang X (2015) Therapeutic targeting of replicative immortality. Semin Cancer Biol 35(Suppl):S104–S128. https://doi.org/10.1016/j.semcancer.2015.03.007

Yeh AC, Ramaswamy S (2015) Mechanisms of cancer cell dormancy–another hallmark of cancer? Cancer Res 75(23):5014–5022. https://doi.org/10.1158/0008-5472.CAN-15-1370

Yeku O, Zamarin D, Gallagher J, Aghajanian C, Konner J (2018) A phase II trial of TPIV200 (a polypeptide vaccine against folate receptor alpha) plus durvalumab (anti-PD-L1 antibody) in patients with platinum-resistant ovarian cancer. Gynecol Oncol 149(Suppl):56–57. https://doi.org/10.1016/j.ygyno.2018.04.124

Yeung TL, Leung CS, Yip KP, Au Yeung CL, Wong ST, Mok SC (2015) Cellular and molecular processes in ovarian cancer metastasis. A review in the theme: cell and molecular processes in cancer metastasis. Am J Physiol Cell Physiol 309(7):C444–C456. https://doi.org/10.1152/ajpcell.00188.2015

Yigit S, Demir L, Tarhan MO, Cabuk FK, Ellidokuz H, Erten C, Somali I, Dirican A, Cakalagaoglu F (2012) The clinicopathological significance of Bax and Bcl-2 protein expression with tumor infiltrating lymphocytes in ovarian carcinoma. Neoplasma 59(5):475–485. https://doi.org/10.4149/neo_2012_061

Yokoyama T, Kohn EC, Brill E, Lee JM (2017) Apoptosis is augmented in high-grade serous ovarian cancer by the combined inhibition of Bcl-2/Bcl-xL and PARP. Int J Oncol 50 (4):1064–1074. https://doi.org/10.3892/ijo.2017.3914

Yoshihara K, Tajima A, Komata D et al (2009) Gene expression profiling of advanced-stage serous ovarian cancers distinguishes novel subclasses and implicates ZEB2 in tumor progression and prognosis. Cancer Sci 100(8):1421–1428. https://doi.org/10.1111/j.1349-7006.2009.01204.x

Yu L, Deng L, Li J, Zhang Y, Hu L (2013) The prognostic value of vascular endothelial growth factor in ovarian cancer: a systematic review and meta-analysis. Gynecol Oncol 128 (2):391–396. https://doi.org/10.1016/j.ygyno.2012.11.002

Yu L, Hua X, Yang Y et al (2017) An updated meta-analysis of the prognostic value of decreased E-cadherin expression in ovarian cancer. Oncotarget 8(46):81176–81185. https://doi.org/10.18632/oncotarget.20885

Zamarin D, Walderich S, Holland A, Zhou Q, Iasonos AE, Torrisi JM, Merghoub T, Chesebrough LF, Mcdonnell AS, Gallagher JM, Li Y, Hollmann TJ, Grisham RN, Erskine CL, Block MS, Knutson KL, O'Cearbhaill RE, Aghajanian C, Konner JA (2020a) Safety, immunogenicity, and clinical efficacy of durvalumab in combination with folate receptor alpha vaccine TPIV200 in patients with advanced ovarian cancer: a phase II trial. J Immunother Cancer 8(1):e000829. https://doi.org/10.1136/jitc-2020-000829

Zamarin D, Burger RA, Sill MW, Powell DJ Jr, Lankes HA, Feldman MD, Zivanovic O, Gunderson C, Ko E, Mathews C, Sharma S, Hagemann AR, Khleif S, Aghajanian C (2020b) Randomized phase II trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: an NRG oncology study. J Clin Oncol 38(16):1814–1823. https://doi.org/10.1200/JCO.19.02059

Zannoni GF, Improta G, Chiarello G et al (2014) Mutational status of KRAS, NRAS, and BRAF in primary clear cell ovarian carcinoma. Virchows Arch 465(2):193–198. https://doi.org/10.1007/s00428-014-1599-1

Zannoni GF, Improta G, Pettinato A et al (2016) Molecular status of PI3KCA, KRAS and BRAF in ovarian clear cell carcinoma: an analysis of 63 patients. J Clin Pathol 69(12):1088–1092. https://doi.org/10.1136/jclinpath-2016-203776

Zhang GN, Liu H, Huang JM, Wang L, Zhao JS, Li C, Mi K, Zhu Y, Cheng J, Zha X (2014) TP53 K351N mutation-associated platinum resistance after neoadjuvant chemotherapy in patients with advanced ovarian cancer. Gynecol Oncol 132(3):752–757. https://doi.org/10.1016/j.ygyno.2014.01.028

Zhang D, Bai B, Xi Y et al (2016a) Can aspirin reduce the risk of endometrial cancer? A systematic review and meta-analysis of observational studies. Int J Gynecol Cancer 26(6):1111–1120. https://doi.org/10.1097/IGC.0000000000000731

Zhang X, Liu J, Liang X et al (2016b) History and progression of Fat cadherins in health and disease. Onco Targets Ther 9:7337–7343. https://doi.org/10.2147/OTT.S111176

Zhang M, Zhuang G, Sun X et al (2017) TP53 mutation-mediated genomic instability induces the evolution of chemoresistance and recurrence in epithelial ovarian cancer. Diagn Pathol 12 (1):16. https://doi.org/10.1186/s13000-017-0605-8

Zhang B, Wang L, Zhao X, Wei Y, Zhang Y (2018) Identification of candidate genes associated with chemotherapy resistance in ovarian cancer. Ann Clin Lab Sci 48(5):573–579

Zhang X, Yan K, Deng L, Liang J, Liang H, Feng D, Ling B (2019a) Cyclooxygenase 2 promotes proliferation and invasion in ovarian cancer cells via the PGE2/NF-κB pathway. Cell Transplant 28(1 Suppl):1S–13S. https://doi.org/10.1177/0963689719890597

Zhang Y, Xu L, Li A, Han X (2019b) The roles of ZEB1 in tumorigenic progression and epigenetic modifications. Biomed Pharmacother 110:400–408. https://doi.org/10.1016/j.biopha.2018.11.112

Zhang L, Chen Y, Li F, Bao L, Liu W (2019c) Atezolizumab and bevacizumab attenuate cisplatin resistant ovarian cancer cells progression synergistically via suppressing epithelial-mesenchymal transition. Front Immunol 10:867. https://doi.org/10.3389/fimmu.2019.00867

Zhao R, Diop-Bove N, Visentin M, Goldman ID (2011) Mechanisms of membrane transport of folates into cells and across epithelia. Annu Rev Nutr 31:177–201

Zhao H, Wang J, Zhang Y et al (2018) Prognostic values of CCNE1 amplification and overexpression in cancer patients: a systematic review and meta-analysis. J Cancer 9 (13):2397–2407. https://doi.org/10.7150/jca.24179

Zhou Y, Zheng X, Lu J, Chen W, Li X, Zhao L (2018) Ginsenoside 20(S)-Rg3 inhibits the Warburg effect via modulating DNMT3A/MiR-532-3p/HK2 pathway in ovarian cancer cells. Cell Physiol Biochem 45(6):2548–2559. https://doi.org/10.1159/000488273

Zsiros E, Lynam S, Attwood KM, Wang C, Chilakapati S, Gomez EC, Liu S, Akers S, Lele S, Frederick PJ, Odunsi K (2020) Efficacy and safety of pembrolizumab in combination with bevacizumab and oral metronomic cyclophosphamide in the treatment of recurrent ovarian cancer: a phase 2 nonrandomized clinical trial. JAMA Oncol 7:e205945. https://doi.org/10.1001/jamaoncol.2020.5945